EASD 2025 VIENNA
#EASD2025

Proteomic analysis of skeletal muscle supporting muscle growth and metabolic improvement effect by HM17321 in diet induced obesity mouse model

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Hanmi

Presenter Disclosure

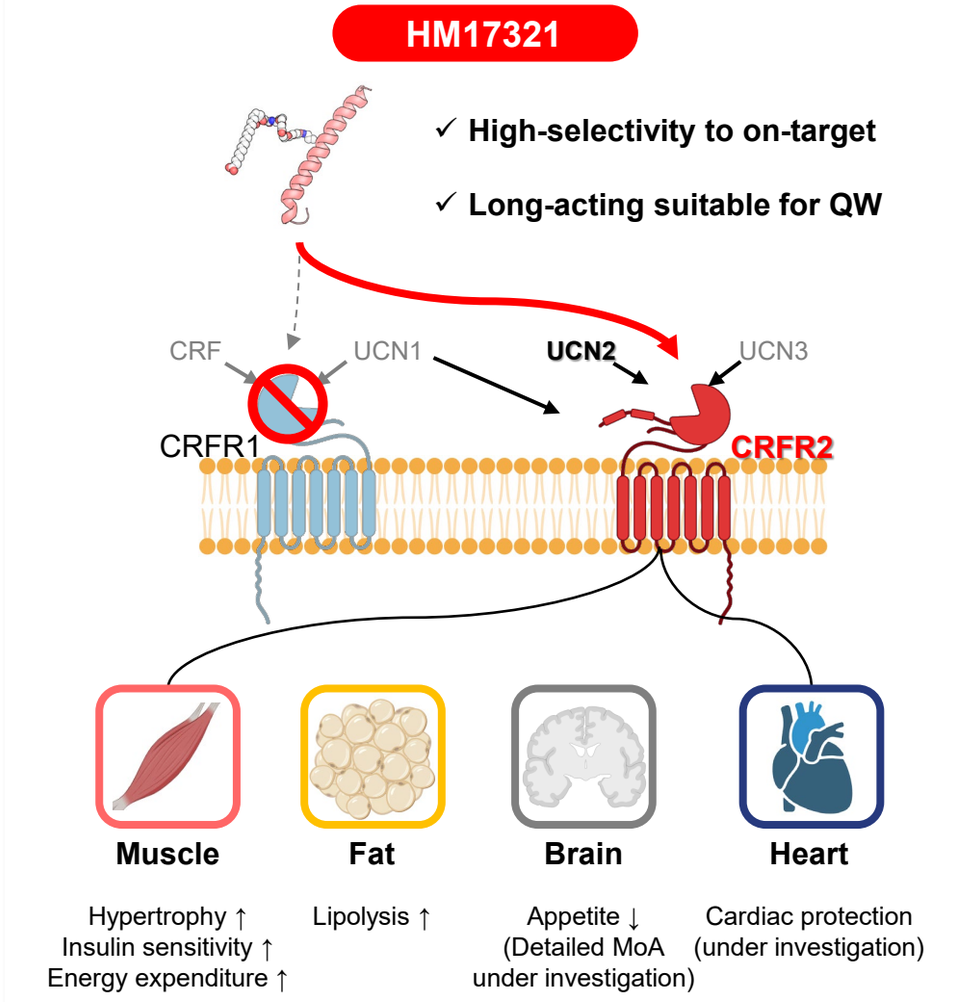
Haemin Chon, MD., Ph.D.

Employee of Hanmi Pharm. Co., Ltd.

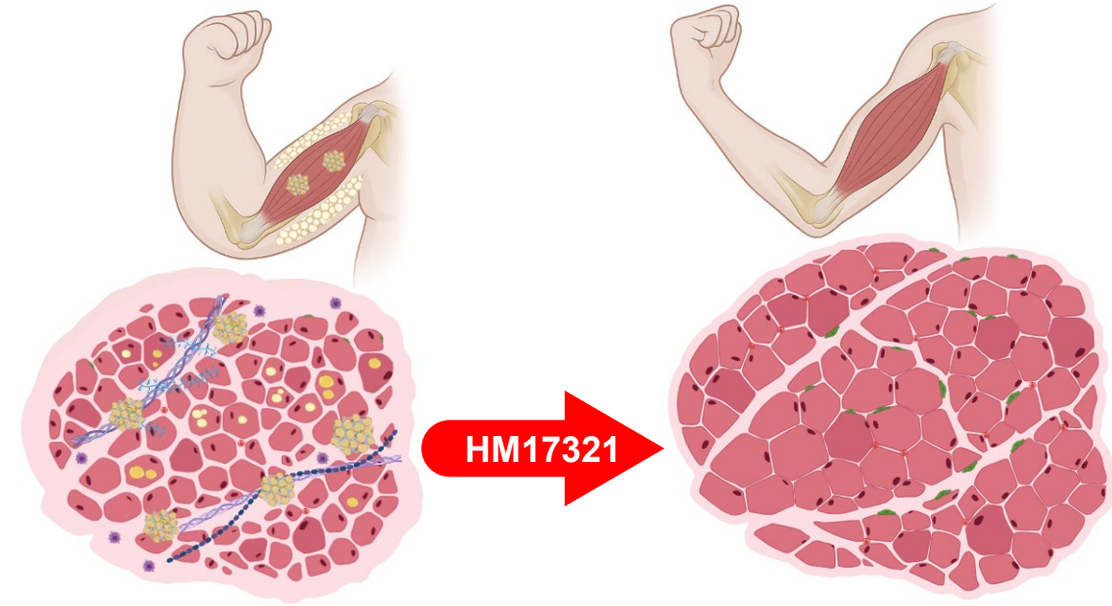
Vice President of Clinical Translational Research Team

A Novel Long-acting CRFR2 Selective and UCN2 Analog

Information of HM17321



Body Recomposition: Burn Fat & Build Muscle



✓ **Pathophysiological changes in muscle**

Muscle fiber CSA*	➔	**UP**
Capillary density	➔	**UP**
Satellite cell number	➔	**UP**
MΦ infiltration	➔	**DOWN**
Inter- /Intramuscular fat	➔	**DOWN**
ECM deposition	➔	**DOWN**

*CSA: Cross-sectional area

Lee *et al*., Discovery and Nonclinical Characterization of a Novel CRFR2 Selective and Biased UCN2 Analog, HM17321, for High Quality Weight Management. Poster presented at: ObesityWeek; San Antonio, TX, USA. November 2024.
Lee *et al*., A Novel CRFR2 Selective UCN2 Analog, HM17321, Facilitates Weight Loss and Improves Body Composition across Animal Models of Obesity. Poster presented at: American Diabetes Association (ADA); Chicago, IL, USA. June 2025.
Lee *et al*., A Novel CRFR2-Selective UCN2 Analog, HM17321, Improves Glycemic Control across Multiple Preclinical Models. Poster presented at: American Diabetes Association (ADA); Chicago, IL, USA. June 2025.

In Vivo Efficacy Study and Proteomic Analysis

Experimental scheme

DIO mice ♂
C57BL/6N, n=6/group
(16 weeks HFD)

D0 — D14 — D28

Drug treatment (S.C, Q2D)

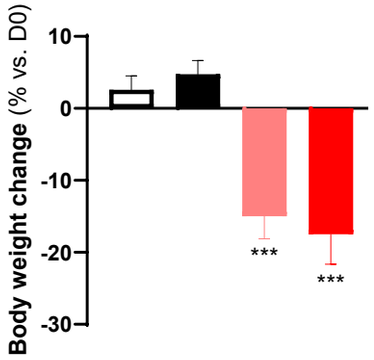
Tibialis anterior muscle

Mesenteric fat

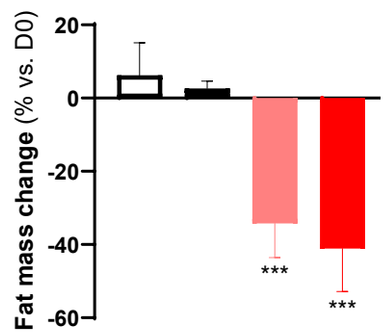
LC-MS based proteomics

Bioinformatics analysis

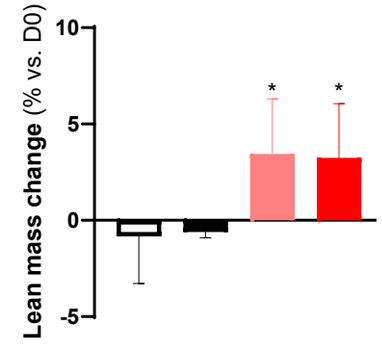
Body weight change



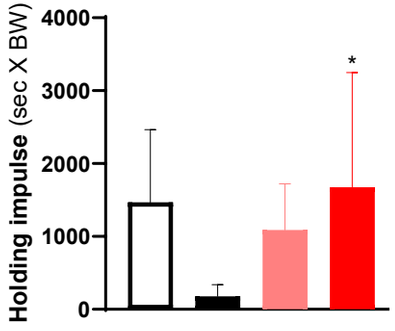
Fat mass change



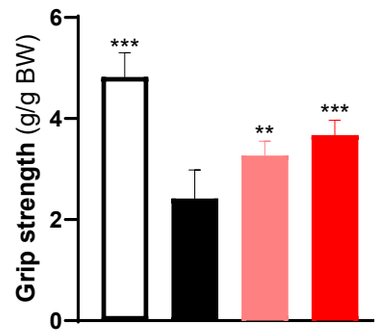
Lean mass change

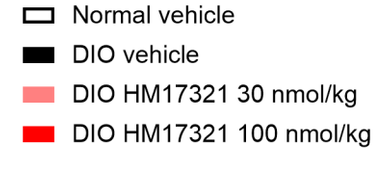


Wire hang



Grip strength





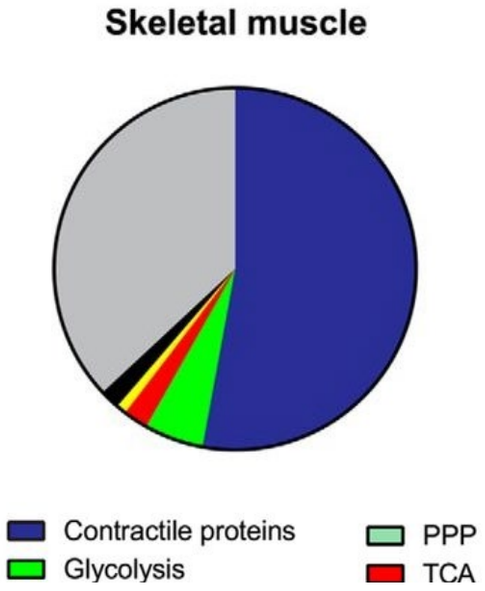
HM17321 improves weight loss quality by reducing fat mass, increasing lean mass, and enhancing muscle function

Proteomic analysis was conducted on skeletal muscle and adipose tissue to investigate the underlying mechanism of HM17321

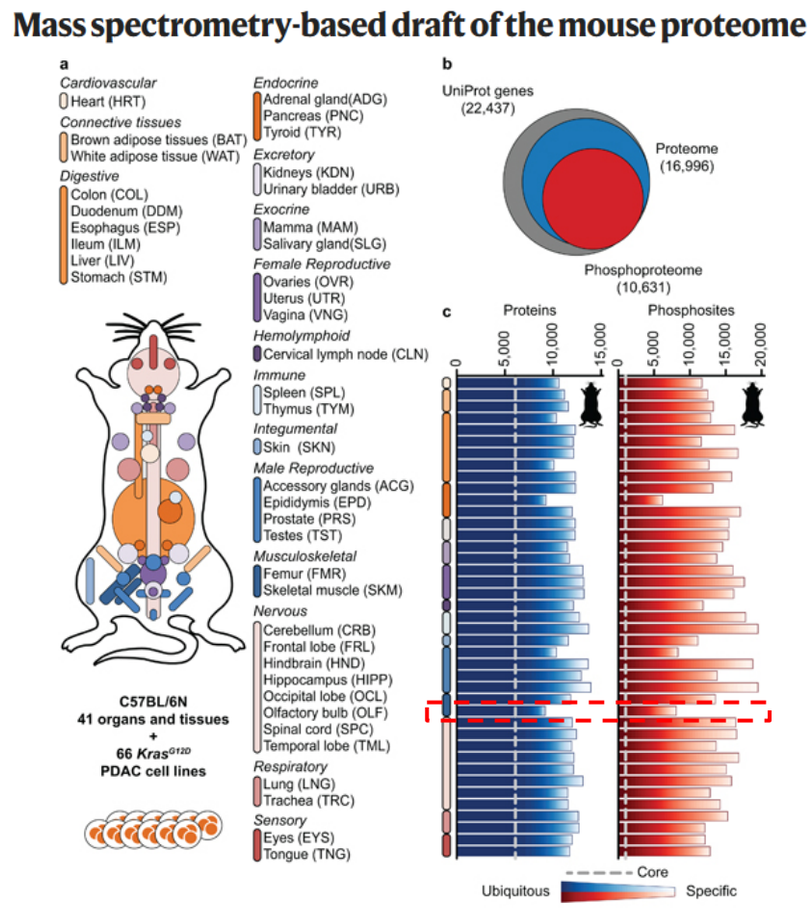
*~*** p<0.05~0.001 vs. DIO, vehicle by One-way ANOVA

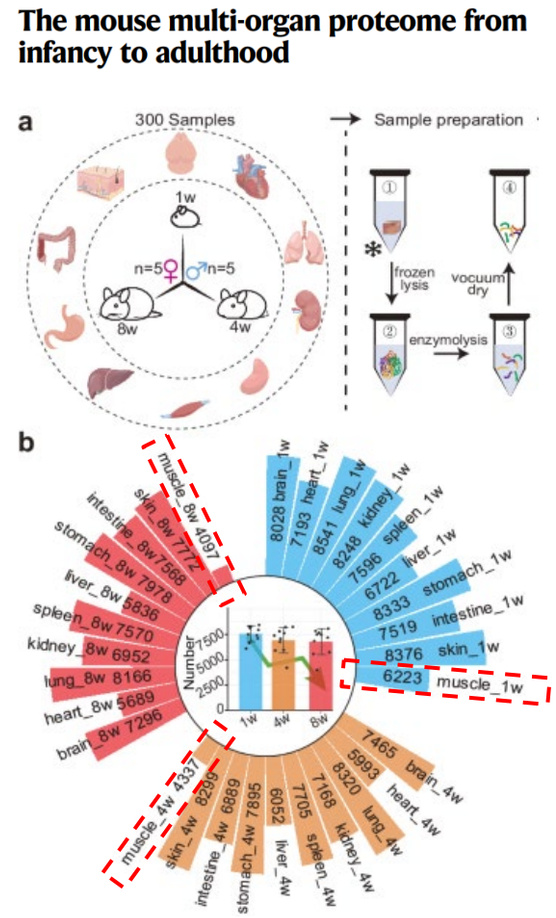
Challenges in Skeletal Muscle Proteomics

Dynamic range issue



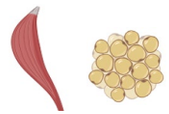
Limited proteome coverage



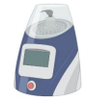


Deep Proteome Coverage for Deeper Insights

Method optimization by Bertis's ProteoID system

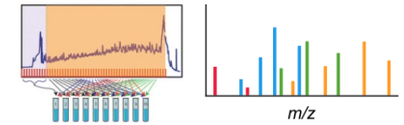


Sample collection



Tissue homogenization

Enzyme digestion



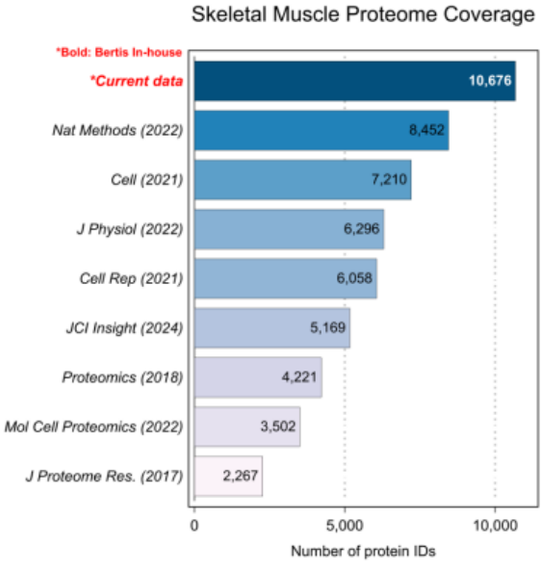
LC-DIA-MS/MS (Orbitrap Astral)

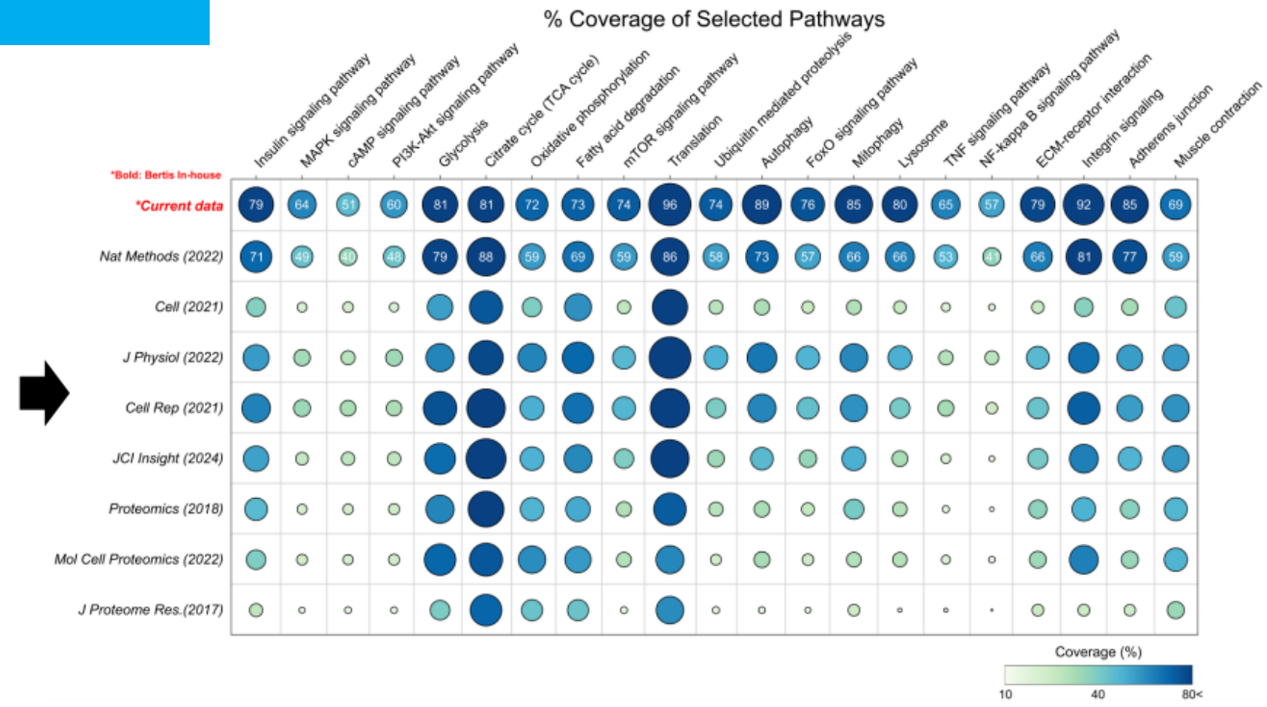
Database search (DIA-NN)

Systems biology

Core Technology ProteoID Mass Spectrometry BERTIS

Deep Proteome Coverage

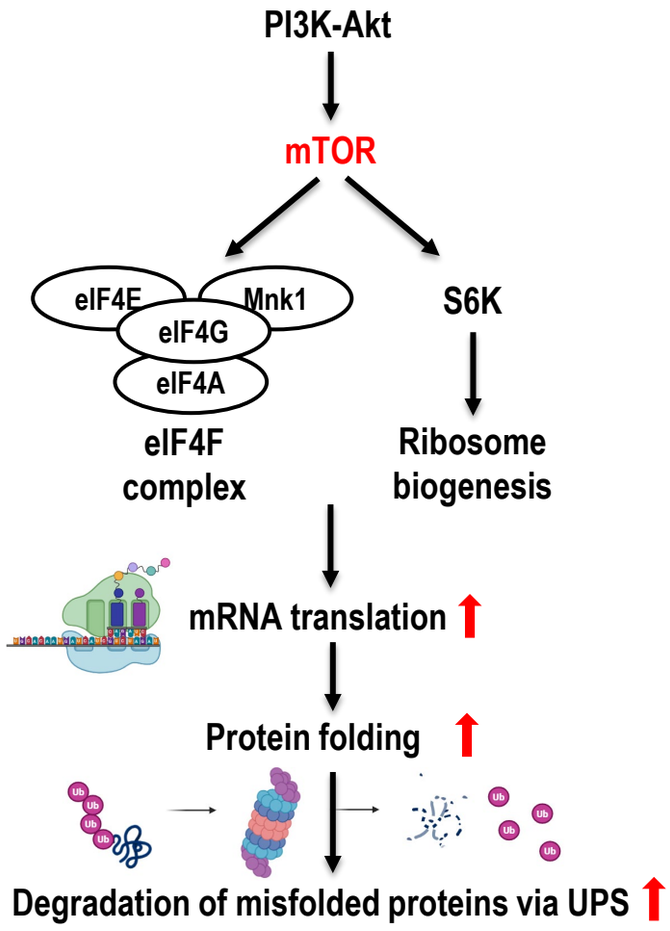




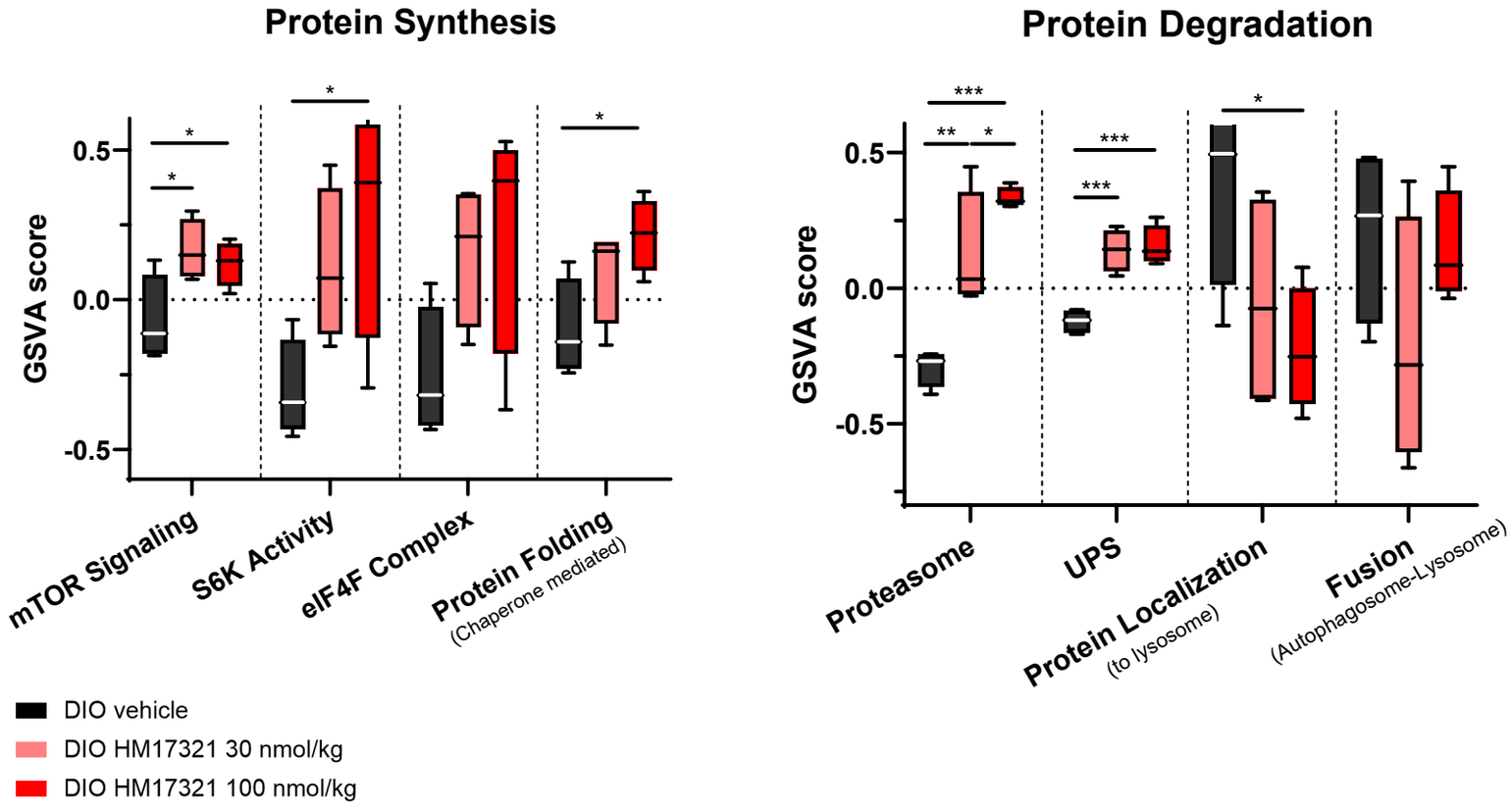
Enhancement of Protein Production Through mTOR activation

Skeletal muscle proteomics revealed that HM17321 induces mTOR signaling, promoting increased protein synthesis and processing

mTOR active



Enhanced protein turnover



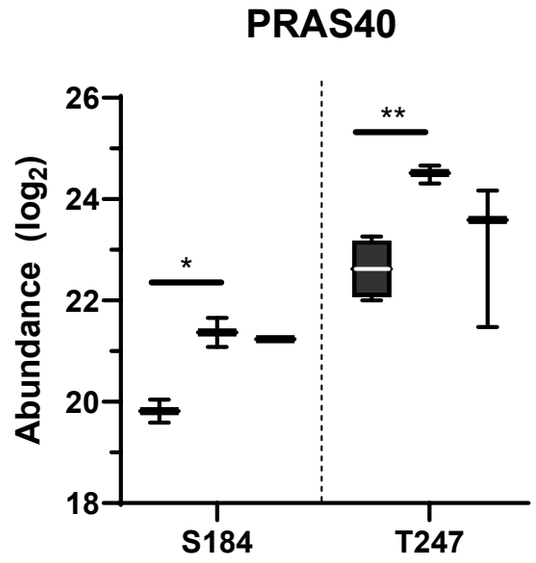
* : p-value < 0.1; ** : p-value < 0.01; *** : p-value < 0.001

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

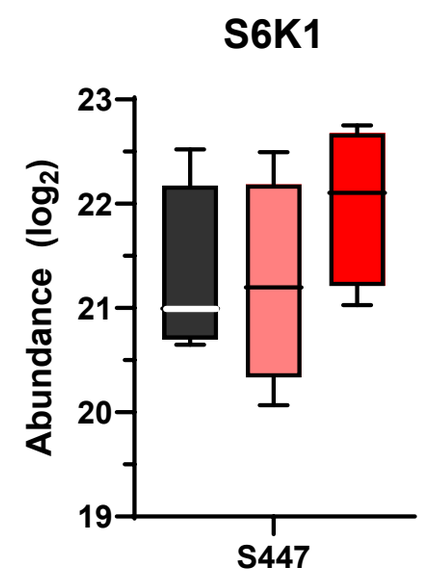
Phosphoproteomic Insights into the Regulation of Translation Initiation

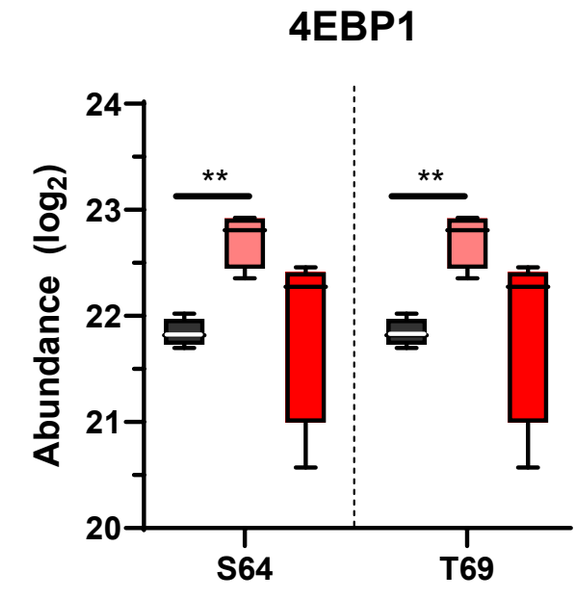
Skeletal muscle phospho-proteomics indicated activation of the mTORC1 by identifying increased phosphorylation of its regulator, PRAS40, and its downstream targets, S6K1 and 4EBP1

mTORC1 negative regulator



mTORC1 downstream targets



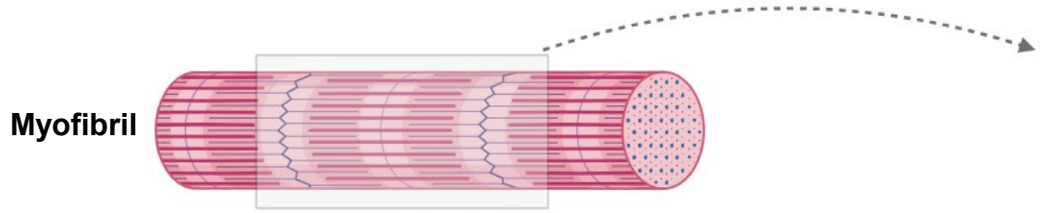


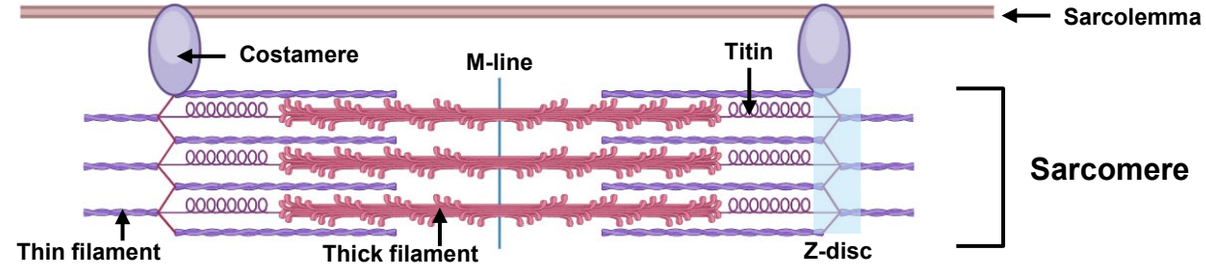
DIO vehicle
DIO HM17321 30 nmol/kg
DIO HM17321 100 nmol/kg

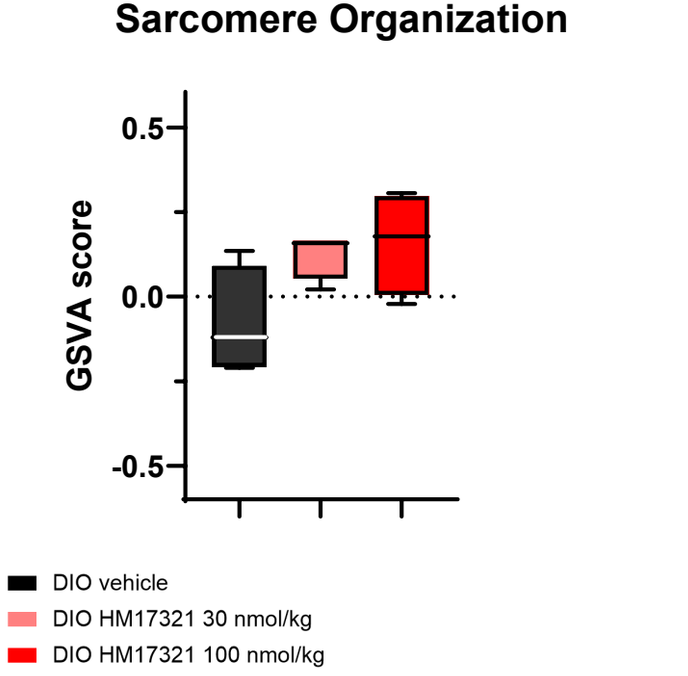
* : p-value < 0.1; ** : p-value < 0.01; *** : p-value < 0.001

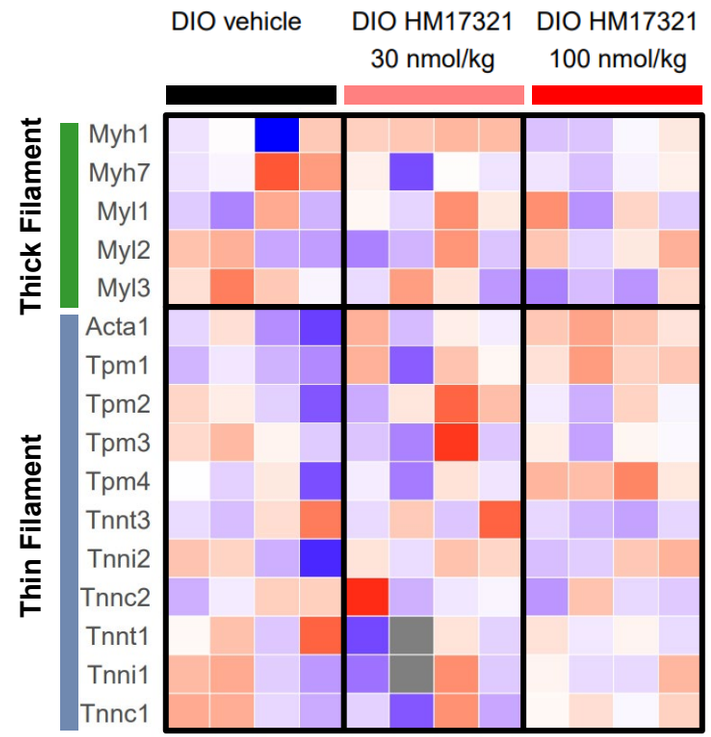
Upregulation of Sarcomere Proteins

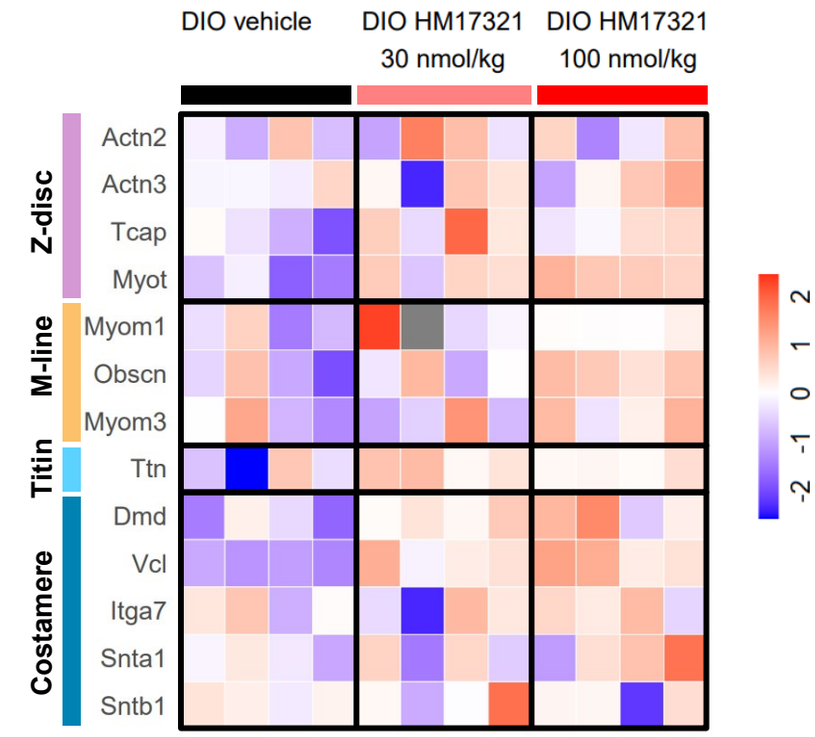
Skeletal muscle proteomics revealed that HM17321 induces sarcomere organization with upregulating sarcomere-related proteins









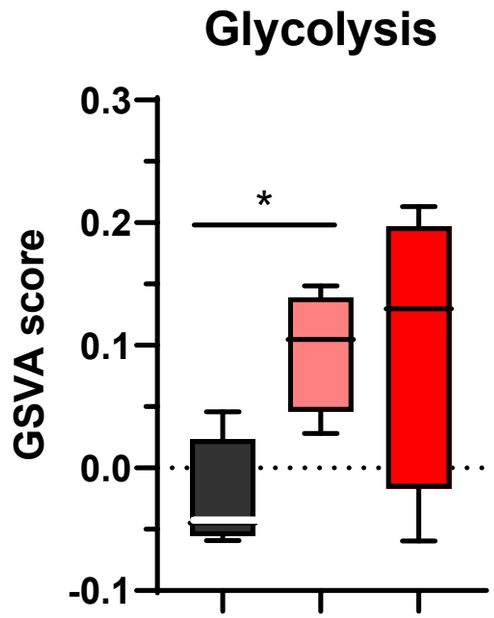


GSVA: gene set variational analysis

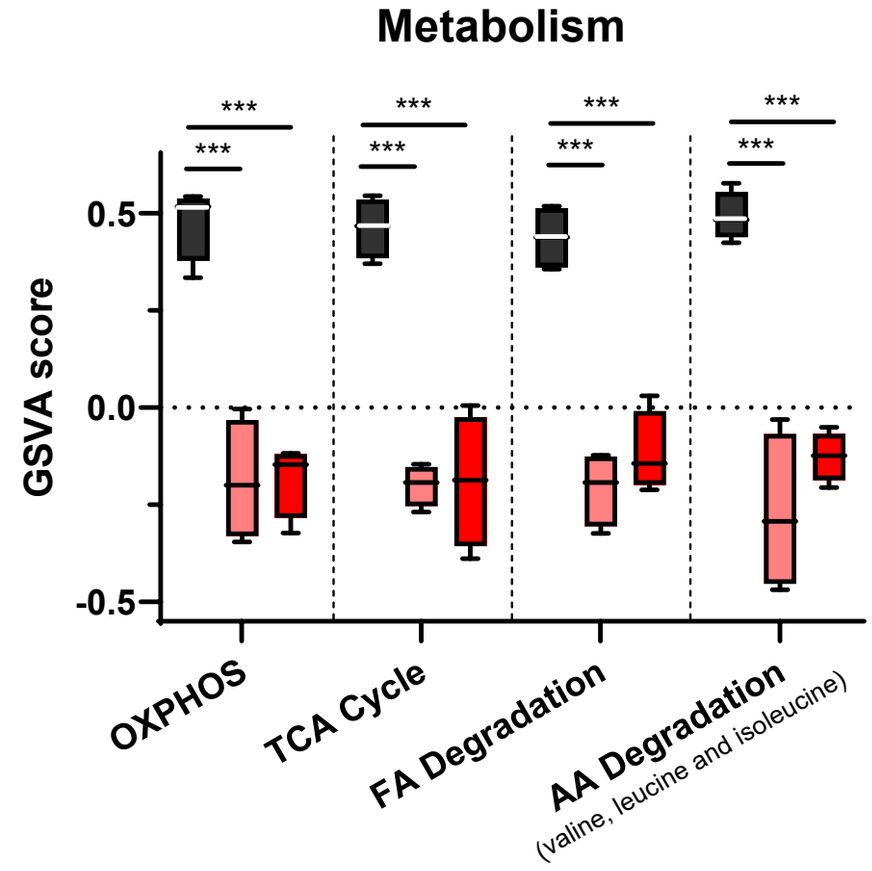
Metabolic Adaptation Toward Glycolytic Energy Metabolism

Metabolic adaptation was characterized by increased glucose utilization through glycolysis, coupled with a decrease in other energy metabolism

Glycolytic energy metabolism



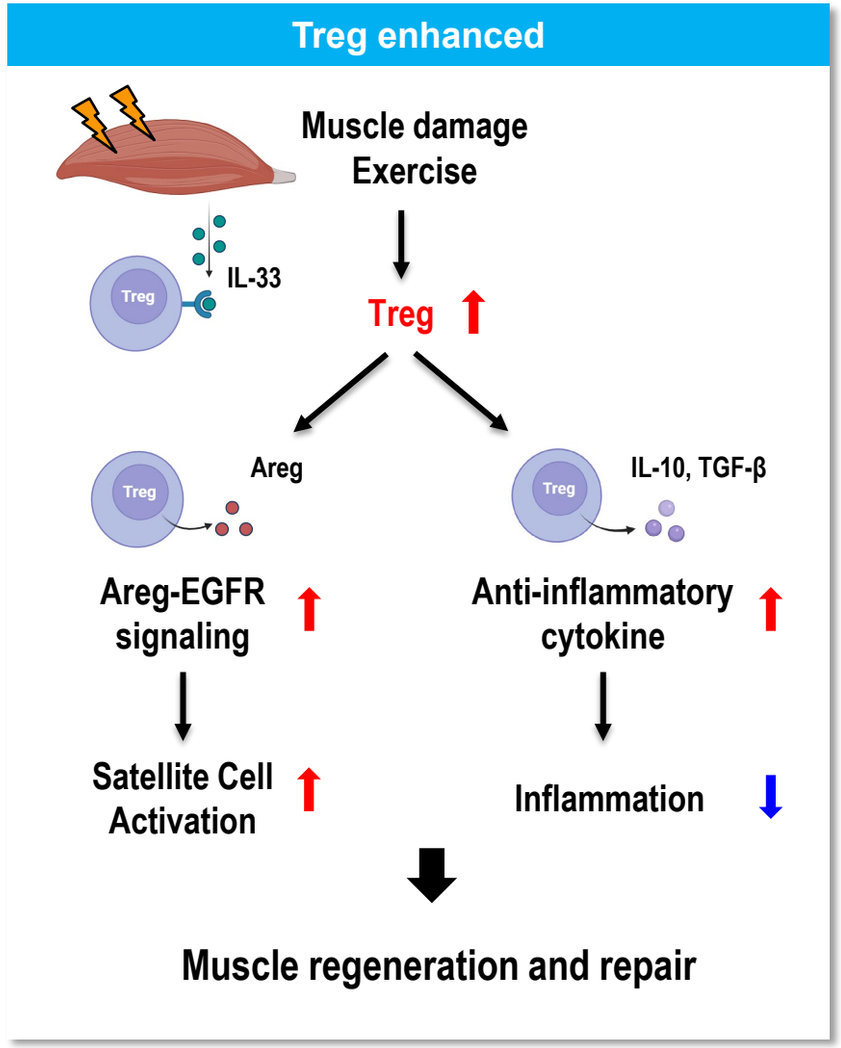
Oxidative energy metabolism

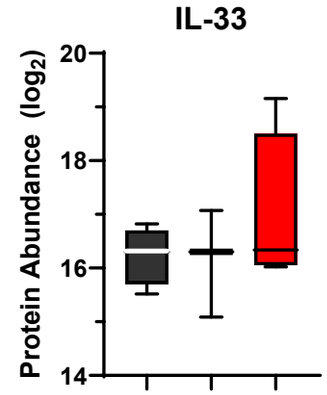


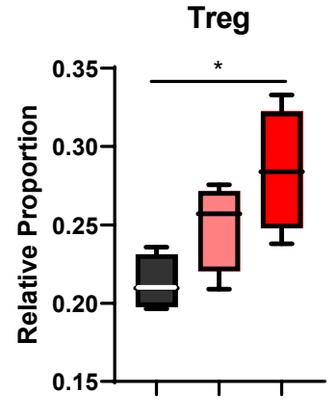
* : p-value < 0.1; ** : p-value < 0.01; *** : p-value < 0.001 AA: amino acid; FA: fatty acid; GSVA: gene set variational analysis; OXPHOS: oxidative phosphorylation

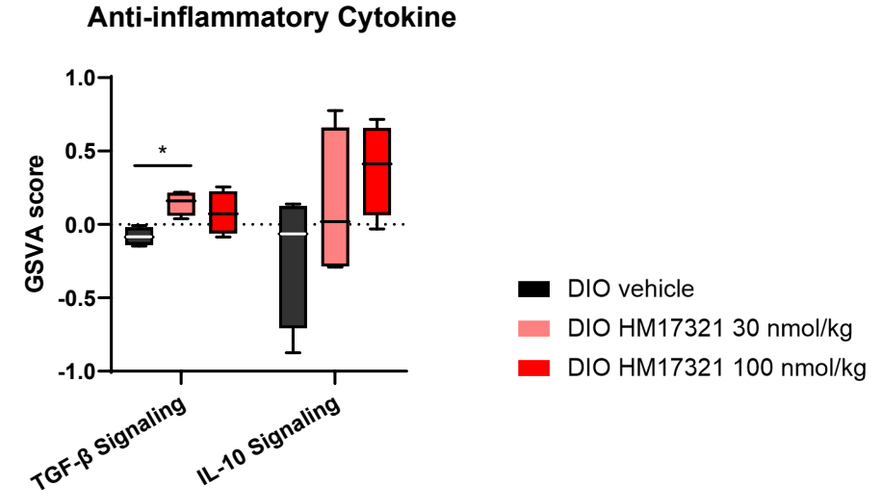
Regulatory T Cell Mediated Satellite Cell Activation

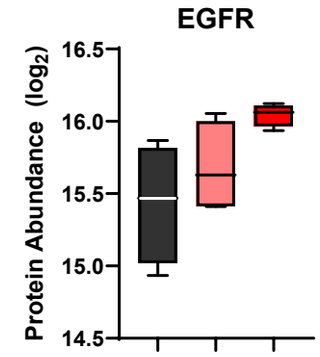
Skeletal muscle proteomics revealed that HM17321 induces regulatory T cell (Treg) mediated muscle regeneration and repair

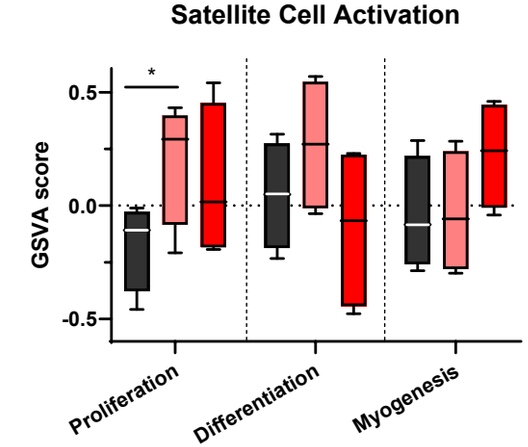








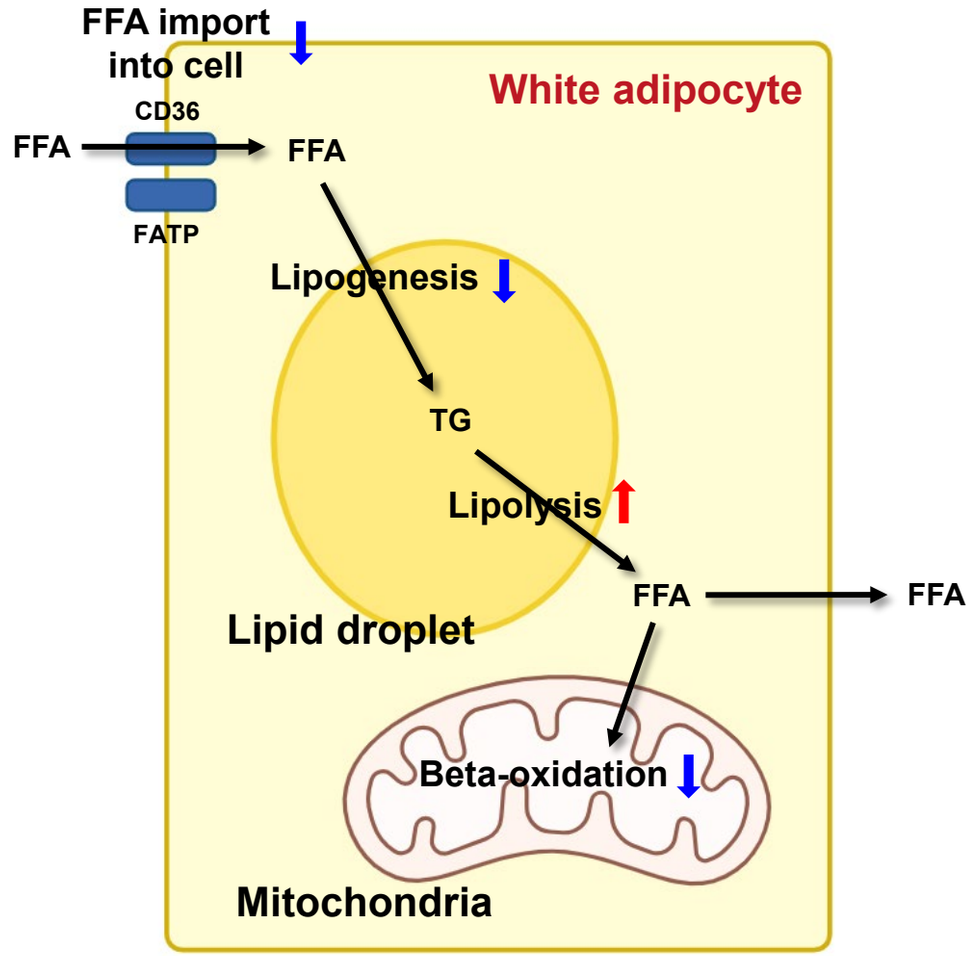


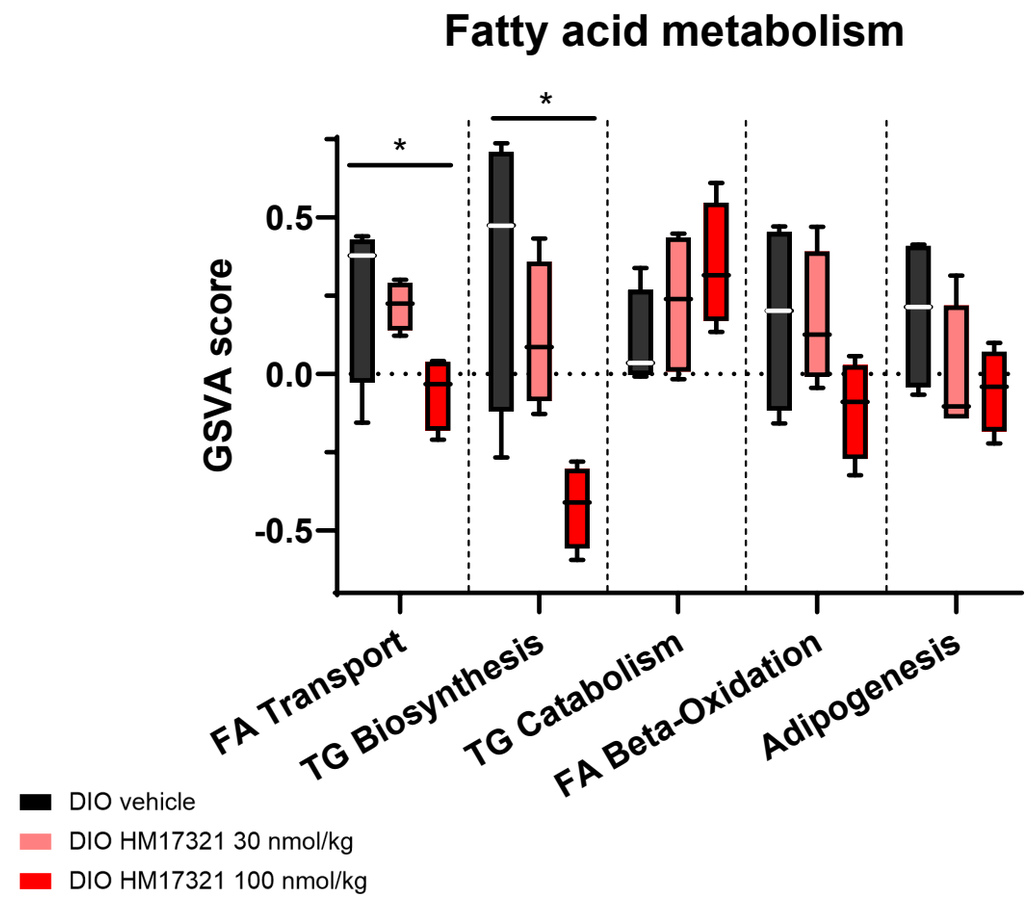


* : p-value < 0.1; ** : p-value < 0.01; *** : p-value < 0.001 Areg: amphiregulin; GSVA: gene set variational analysis; Treg: regulatory T cell

Fat Mass Reduction in White Adipose Tissue

Adipose tissue proteomics revealed that HM17321 reduces fatty acid (FA) uptake and triglyceride (TG) synthesis, while increasing lipolysis, collectively leading to reduction in TG level





* : p-value < 0.1; ** : p-value < 0.01; *** : p-value < 0.001 FA: fatty acid; FFA: free fatty acid; GSVA: gene set variational analysis; TG: triglyceride

Expression of UCP1 by HM17321 in Adipose Tissue

Experimental scheme

DIO mice ♂
C57BL/6N, n=6/group
(19 weeks HFD)

D0 — D22 — D42

Drug treatment (S.C, Q2D→QW)

* Administration interval changed on D22

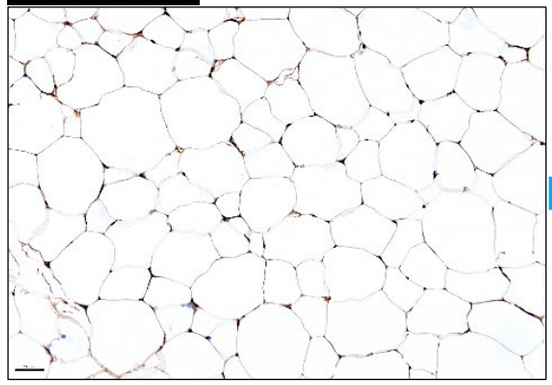
WAT from inguinal fat

BAT from interscapular fat

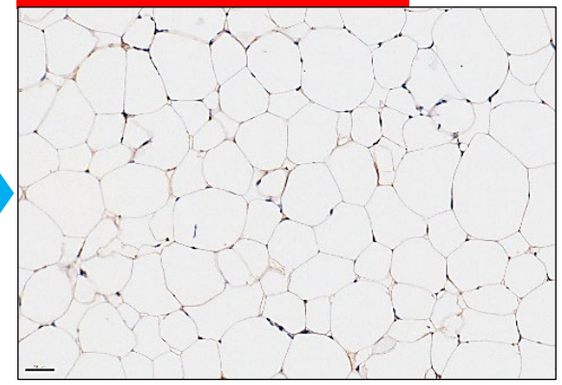
UCP1 expression is selectively upregulated in BAT, a tissue-specific fat consumption through active thermogenesis

White adipose tissue (WAT)

DIO vehicle

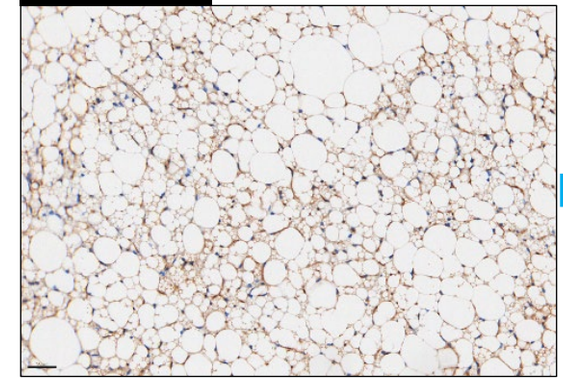


DIO HM17321 100 nmol/kg

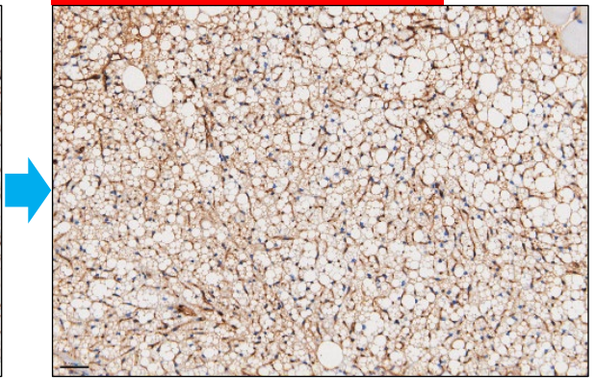


Brown adipose tissue (BAT)

DIO vehicle



DIO HM17321 100 nmol/kg

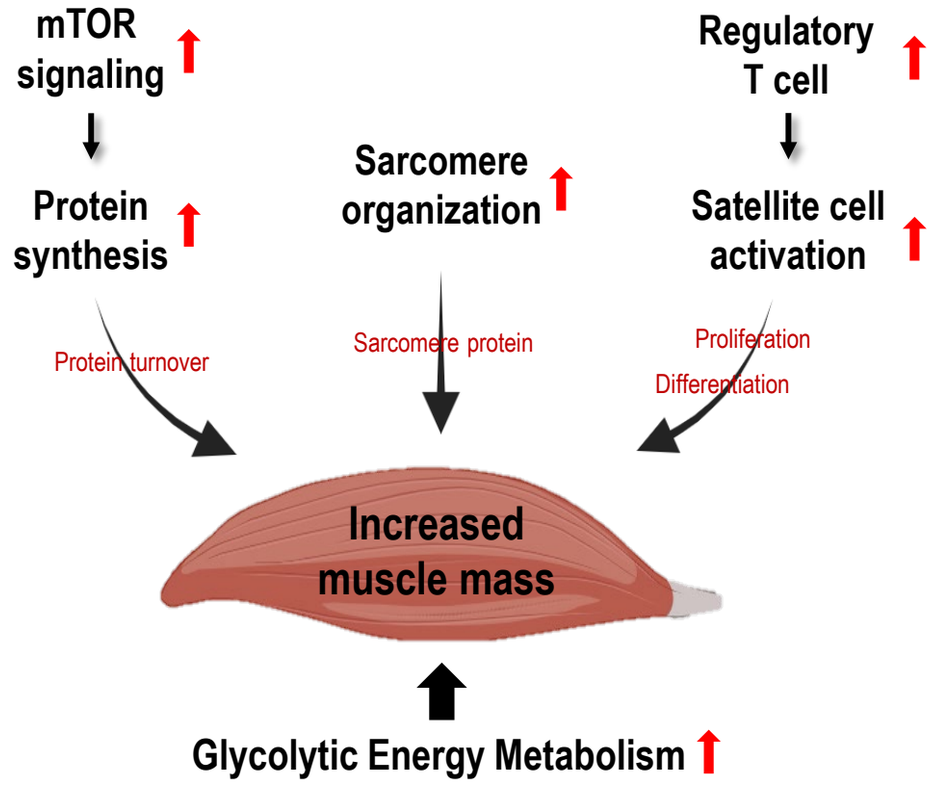


Summary

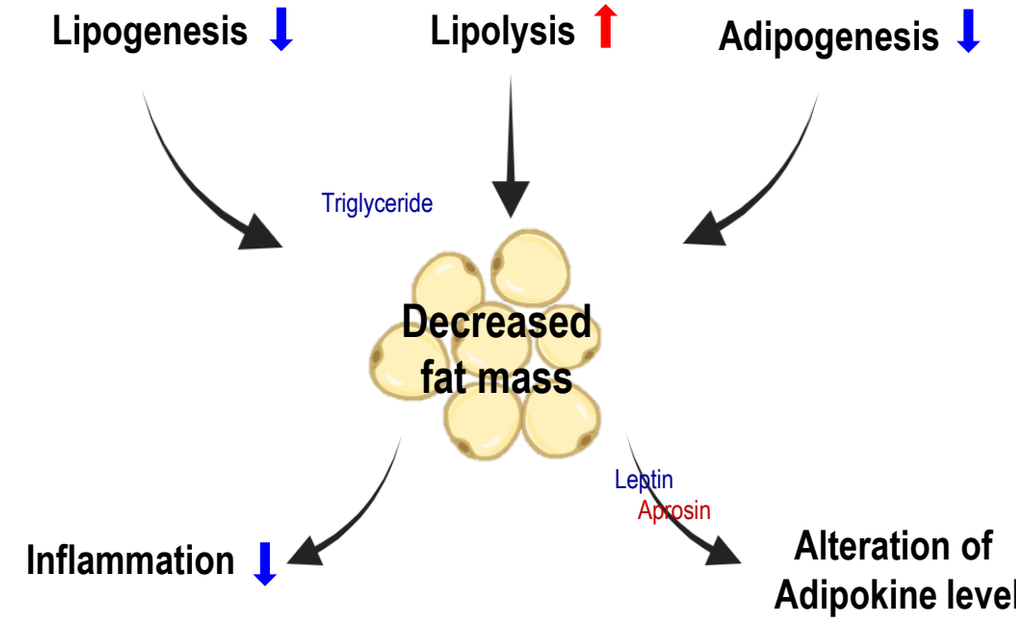
Mimics the effects of resistance exercise

HM17321

Muscle hypertrophic effect



Fat mass reduction effect



Conclusion

- HM17321 demonstrated robust, high-quality weight loss in DIO mice by selectively reducing fat mass and increasing lean mass.
- Analysis of skeletal muscle (Tibialis anterior) proteomics revealed that HM17321 mimics the effect of resistance exercise, enhancing muscle growth and glycolytic metabolism.
- Analysis of white adipose tissue (mesenteric fat) proteomics 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, with the potential to mitigate metabolic risks of obese patients.
- IND submission is forthcoming, with Phase 1 clinical trial initiation planned by year-end.

Please note poster presentation reporting more information about HM17321: P669, P730, P869

Also, you can find posters of Hanmi's other obesity assets:
HM15275 (long-acting GLP1/GIP/Glucagon agonist) – P765, oral GLP-1 – LBA47

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