

Investigating the Mechanisms of HM17321-Induced Fat Loss and Lean Mass Preservation for Clinical Application

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Introduction

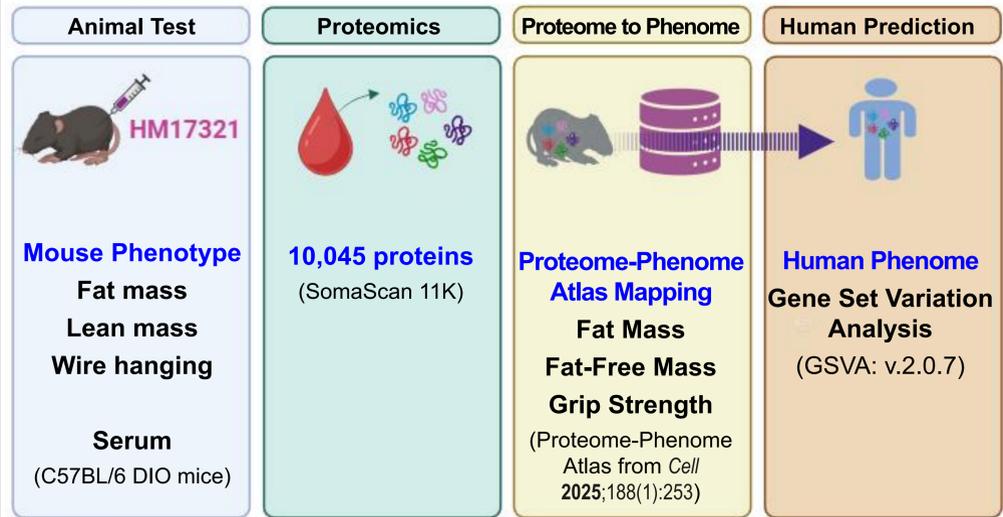
Effective obesity management requires not only fat reduction but also preservation of lean body mass and functional capacity. Although GLP-1 receptor agonists have transformed obesity treatment, concerns remain regarding muscle loss and weight regain after discontinuation. Thus, strategies that improve the quality of weight loss by maintaining lean mass are urgently needed. Urocortin-2, a selective CRF2R agonist, is being investigated to address these limitations. However, translating preclinical findings into clinically relevant human outcomes remains challenging.

Advances in **blood proteomics** and resources like the **Human Proteome-Phenome Atlas (PPA)** now enable cross-species translation using the **Proteome-to-Phenome (P2P) approach**. This allows evaluation of whether proteomic changes in animals reflect clinically meaningful endpoints, such as body composition and muscle function in humans.

In this study, we applied P2P analysis to assess whether treatment with **HM17321, a long-acting selective CRF2R agonist**, in a mouse model of diet-induced obesity leads to proteomic signatures associated with **fat loss, lean mass preservation, and muscle function enhancement**—key translational outcomes of interest in human obesity management. This approach highlights **the potential of integrating preclinical proteomics with human phenome resources** to de-risk early drug development and inform clinical translation.

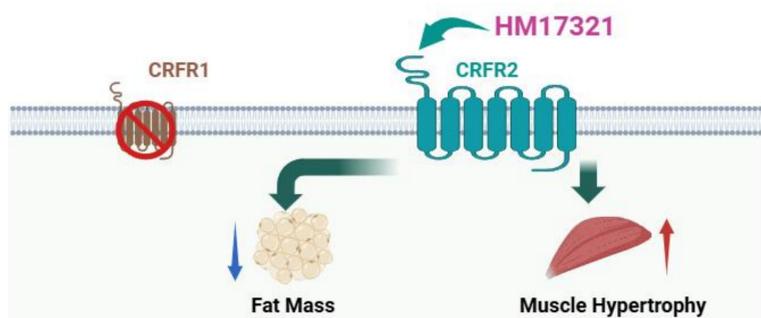
Method

Scheme of Proteome-to-Phenome Translation of HM17321 Effects

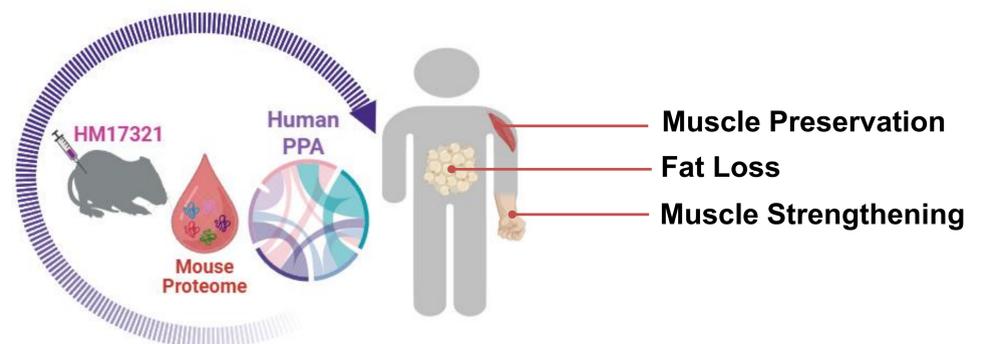


HM17321, The next generation obesity drugs

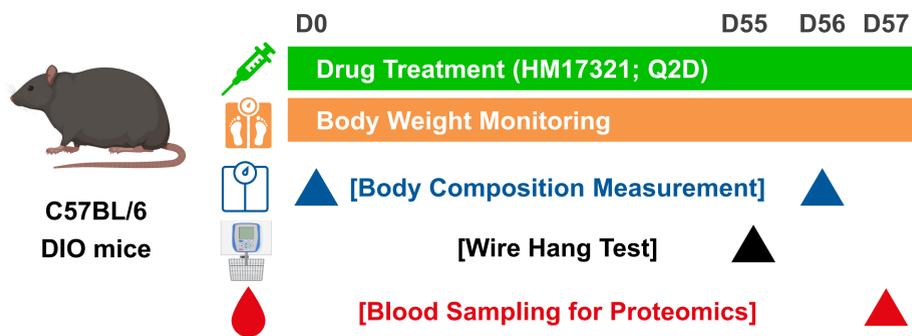
- **HM17321**, a long-acting selective CRF2R agonist, has an effect of increasing muscle mass while simultaneously reducing fat mass.



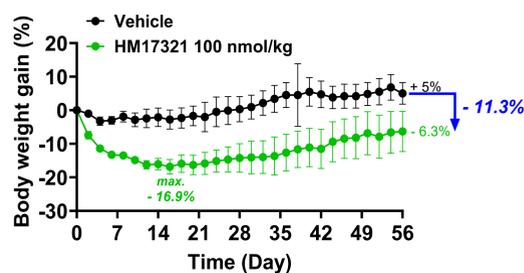
HM17321 reflects the human proteome-phenome association in Mice



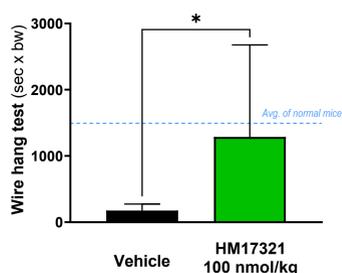
HM17321 promotes fat loss, lean mass gain, and improved muscle function



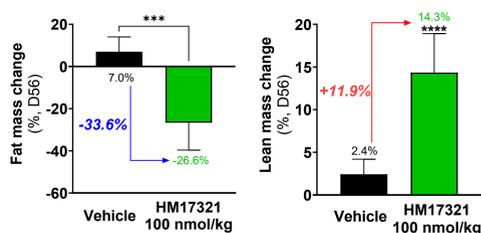
A. Body Weight Change over Time



C. Changes in Wire Hang Test



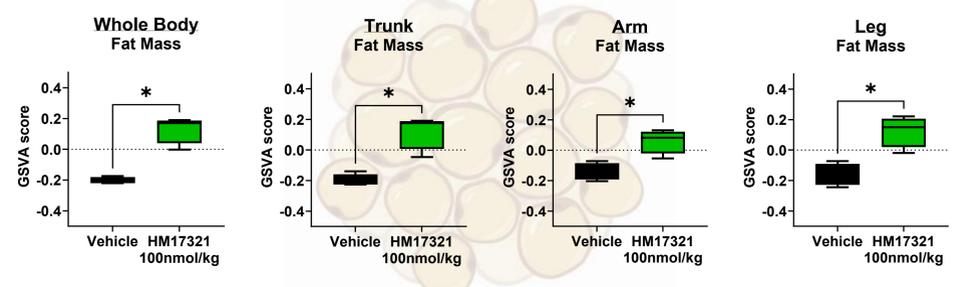
B. Changes in Body Composition (Fat / Lean Mass)



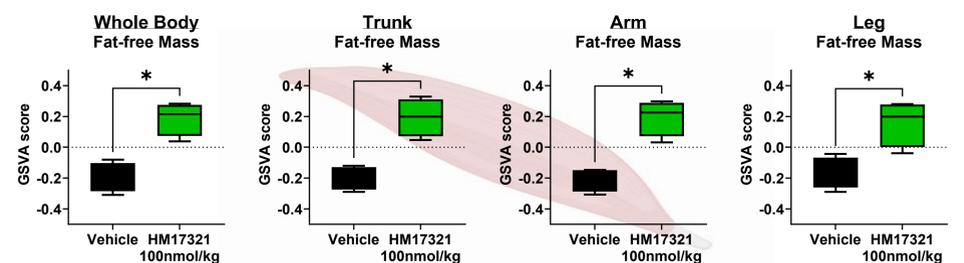
- In DIO mice, HM17321 reduced body weight compared to vehicle.
- HM17321 significantly promoted fat loss and lean mass gain.
- HM17321 increased muscular function.

Mean ± SD *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. Vehicle, t-test (One-tailed)

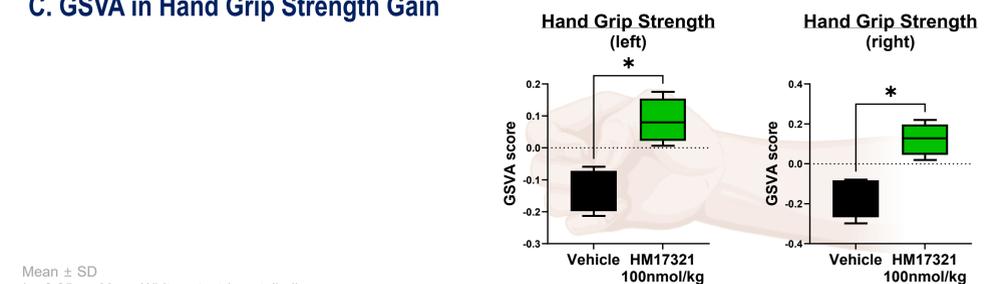
A. GSVA in Fat Mass Loss



B. GSVA in Fat-Free Mass Gain



C. GSVA in Hand Grip Strength Gain



Mean ± SD *p<0.05 vs. Mann-Whitney test (one-tailed)

Concluding Remarks

- In DIO mice, HM17321 upregulated serum proteins associated with fat mass loss, as predicted by the human proteome-phenome atlas, suggesting a potential anti-obesity effects via adipose tissue modulation in humans.
- HM17321 increased circulating proteins linked to fat free mass gain and grip strength, indicating a predicted enhancement of skeletal muscle mass and function in human.
- A Phase 1 clinical trial is planned for Q4 2025 to validate these effects in humans.

References

1. Lautherbach, N., Gonçalves, D. A., et al. *Molecular Metabolism* 2022;60:101492
2. Borg, M. L., Massart, J., et al. *Diabetes* 2019;68(7):1403-1414.
3. Deng, Y. T., You, J., et al. *Cell* 2025;188(1):253-271.
4. The graphical representations were generated with BioRender.com

