Circulating proteomics analysis reveals potential beneficial effects of HM17321 on muscle and bone

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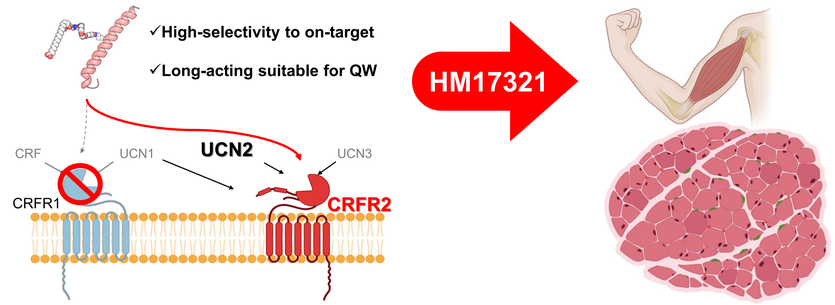
Abstract

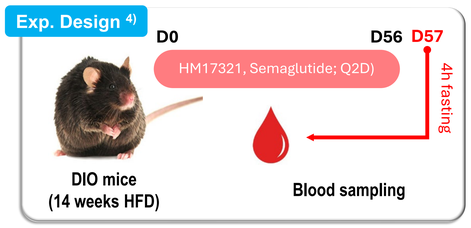
Background and aims: The weight reduction achieved through anti-obesity pharmacotherapy is not exclusively attributed to fat mass loss but is often accompanied by a reduction in fat-free mass. A novel CRFR2 selective and biased urocortin-2 analog (UCN2), HM17321 (HM), has been developed and exhibited successful fat mass reduction with simultaneous increase in lean mass in diet-induced obesity (DIO) mice. In this study, we examined natural hormonal axes, myogenesis and bone health pathways, and cardiac safety pathways leveraging blood proteomics.

Results: Influence of HPA axis by HM is excluded with unaltered level of CRH and POMC by HM. Contribution of male gonadotropin in HM was denied supported by unaltered FSH and LH level with only 8 % decrease of GnRH. In pathway analysis, protein sets explaining muscle hypertrophy were upregulated by HM. In addition, HM showed increased expression of proteins related to bone development and bone growth, while vehicle and Sema vice versa. Cardiac markers and protein signature representing cardiomyopathy were stable with either HM or semaglutide.

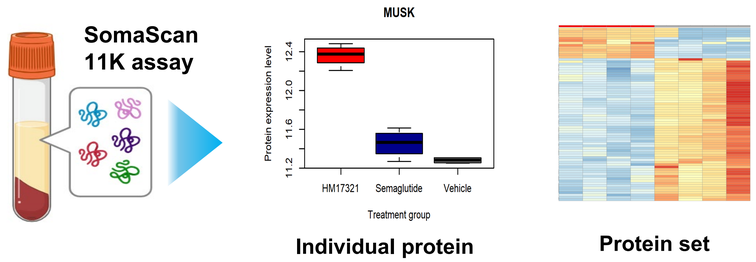
Conclusion: HM has demonstrated superior weight loss quality by promoting fat reduction while increasing lean mass, particularly skeletal muscle, in a DIO mouse model. Serum proteomics have supported the beneficial effects on weight loss quality of HM while excluding possible side effects possibly related with HPA and gonadotropin axis. These results suggest that HM not only facilitates effective obesity management but also preserves musculoskeletal health, highlighting its potential as a promising therapeutic strategy for improving body composition and metabolic outcomes.

Introduction



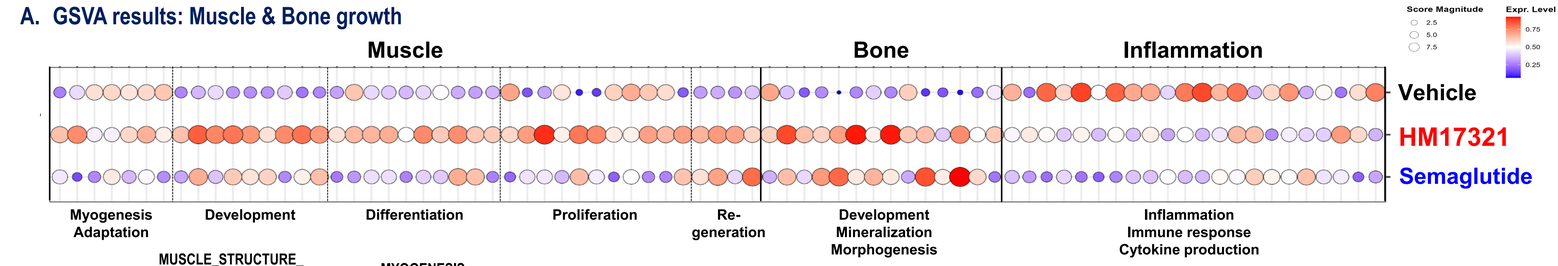


- ✓**Proteome analysis in serum samples**
- ✓**Differentially abundance protein**
- ✓**Gene Set Variation Analysis (GSVA)**
  HPA axis, androgen loop,
  Muscle-, bone-, inflammation pathways
  Cardiac safety evaluation

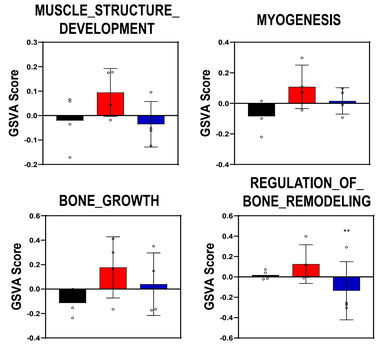


Mechanism of Action in Muscle and Bone

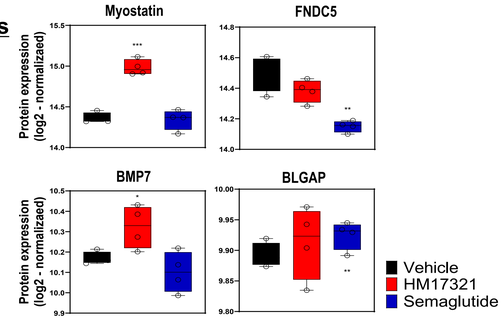
A. GSVA results: Muscle & Bone growth



Pathways



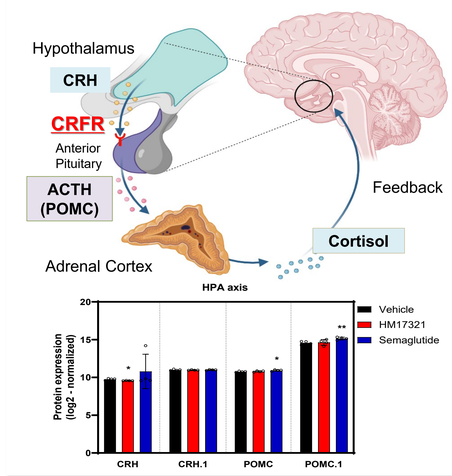
Genes



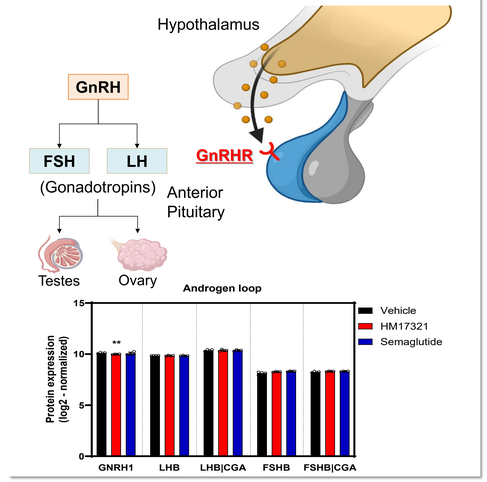
- HM17321 induced up-regulation of pathways related with muscle hypertrophy such as; myogenesis, muscle development, satellite cell differentiation, satellite cell proliferation, and muscle regeneration
- Pathways related with bone health, such as bone growth, remodeling, and development were up-regulated by HM17321.
- Multiple sets of pathway revealing systemic inflammation was generally down-regulated with either HM17321 or semaglutide.

Impacts in hormonal axis and Cardiovascular Risks

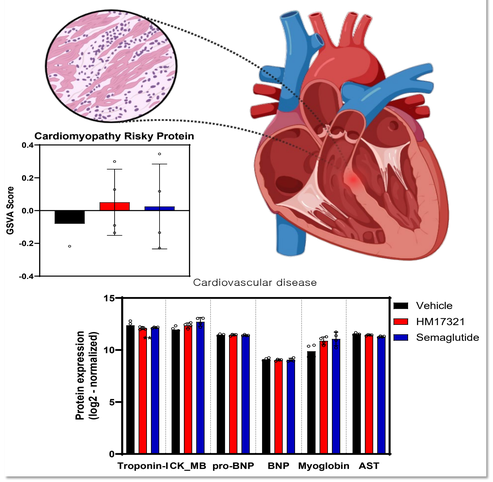
A. HPA (Hypothalamic – Pituitary – Adrenal) axis



B. Androgen Loop



C. Cardiovascular Risk



Concluding Remarks

- HM17321's **robust, high-quality weight loss** in DIO mice were validated by enrichment of muscle hypertrophy related protein sets in blood proteomics
- HM17321 **activated pathways related with bone health** while **suppressing systemic inflammation protein sets**
- HM17321 treatment **did not induce CRFR1-mediated corticotrophic action**, and **androgen agonism was not associated** with the mechanism of action underlying HM17321's pharmacological effects.
- HM17321 treatment **did not exhibit an increased risk of cardiovascular disease** in comparison to the vehicle.
- Please also note Hanmi's additional presentations: P-819, P-669, P-226 (HM17321), LBA-47 (oral GLP-1), P-765 (HM15275)

References

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