A Novel CRFR2 Selective UCN2 Analog, HM17321, Enhances Favorable Body Recomposition, Energy Expenditure and Metabolic Health in DIO Mice

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Abstract

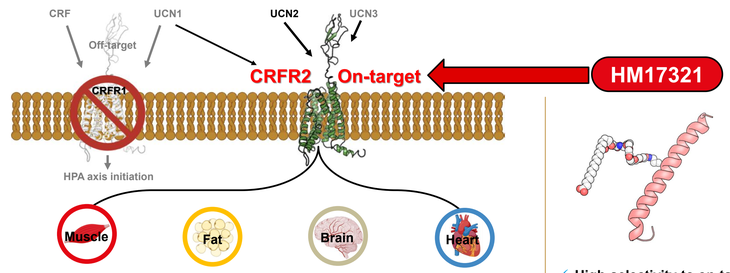
Introduction and Objective: Incretin-based therapies effectively promote weight loss but also cause inevitable lean mass loss, compromising weight loss quality (WLQ). Urocortin-2 (UCN2) has been known to have potential for enhancing lipolysis and muscle hypertrophy, offering a strategy to improve WLQ in obesity. To optimize receptor signaling and achieve these outcomes alongside weight loss, a novel corticotropin-releasing factor receptor-2 (CRFR2) selective UCN2 analog, HM17321, was designed using a structure-based approach. The present study evaluates the potential effects of HM17321 on body composition and energy expenditure in DIO mice.

Results: HM17321 markedly reduced body weight compared to the pair-fed group, suggesting the presence of additional weight loss mechanisms beyond food intake inhibition. Despite a significant reduction in food intake, HM17321 led to a favorable body recomposition, with a continued increase in lean mass and a sustained reduction in fat mass. Notably, while Sema-induced weight loss (both fat and lean mass loss) was accompanied by a decrease in energy expenditure, HM17321 significantly increased energy expenditure with achieving similar weight loss. Importantly, unlike Sema, HM17321 significantly increased absolute muscle weights while reducing skeletal muscle lipid deposition. Mechanistically, HM17321 exhibited a potent lipolytic effect in both 3T3-L1 adipocytes and human visceral white adipocytes, while also promoting differentiation and inducing hypertrophy in both C2C12 myoblasts and human skeletal muscle cells, suggesting its direct effects on adipose tissue catabolism and skeletal muscle anabolism.

Conclusion: HM17321 promotes favorable body recomposition and this directly contribute to the increase in basal metabolic rate. HM17321 improved overall metabolic health, reinforcing its potential as a next-generation therapeutic for obesity and metabolic disorders.

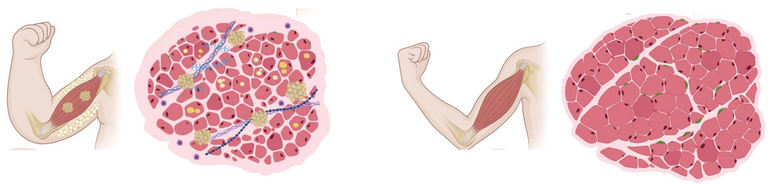
Background

CRF2 Receptor Expression & Expected Effects of UCN2 Analog



- ✓ High-selectivity to on-target
- ✓ Long-acting suitable for QW

Body Recomposition: Burn Fat & Build Muscle



Pathophysiological Changes in Muscle under Obesity

Interstitial space (⚪): ↑
- MΦ infiltration: ↑
- Mt function: ↓
- Capillary density: ↓
- Satellite cell number: ↓
- ECM deposition: ↑
- Intramuscular fat: ↑
- Intermuscular fat: ↑

→ pseudo-hypertrophy

HM17321

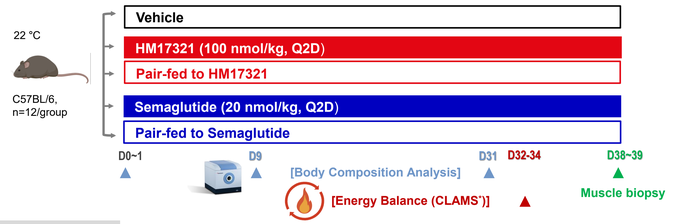
- ✓ Muscle fiber CSA*: ↑
- ✓ Muscular fat: ↓
- ✓ MΦ infiltration: ↓
- ✓ Mt function: ↑
- ✓ Capillary density: ↑
- ✓ Satellite cell number: ↑
- ✓ ECM deposition: ↓

*CSA: Cross-sectional area

Study Design

***In vivo* study**

Diet-induced obesity (DIO) mice, ♂ 19W (60kcal% HFD for 13 weeks)



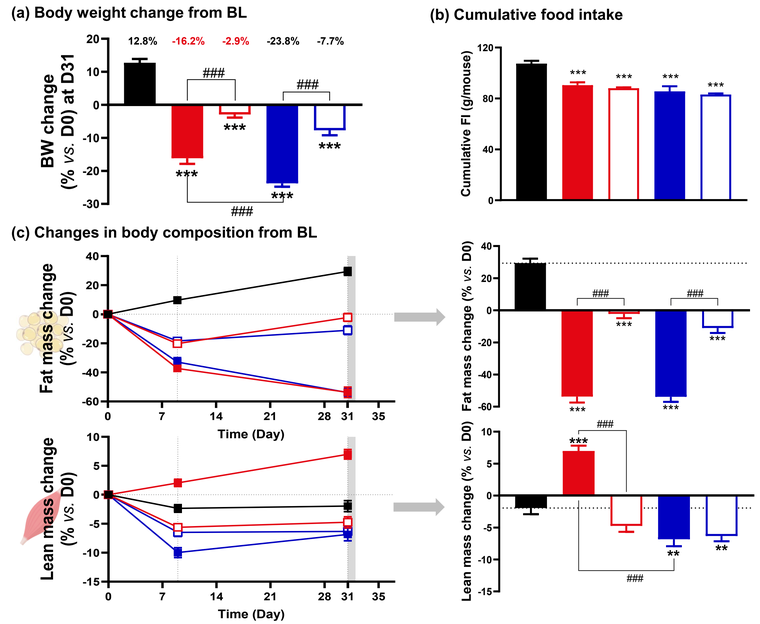
***In vitro* studies**

Study 1. Primary Human White Preadipocytes (HWP): Adipogenesis and Lipolysis

Study 2. Primary Human Skeletal Muscle Cells (HSkMC): Myogenesis and Intramyocellular lipids

Weight loss and Body Recomposition in DIO mice

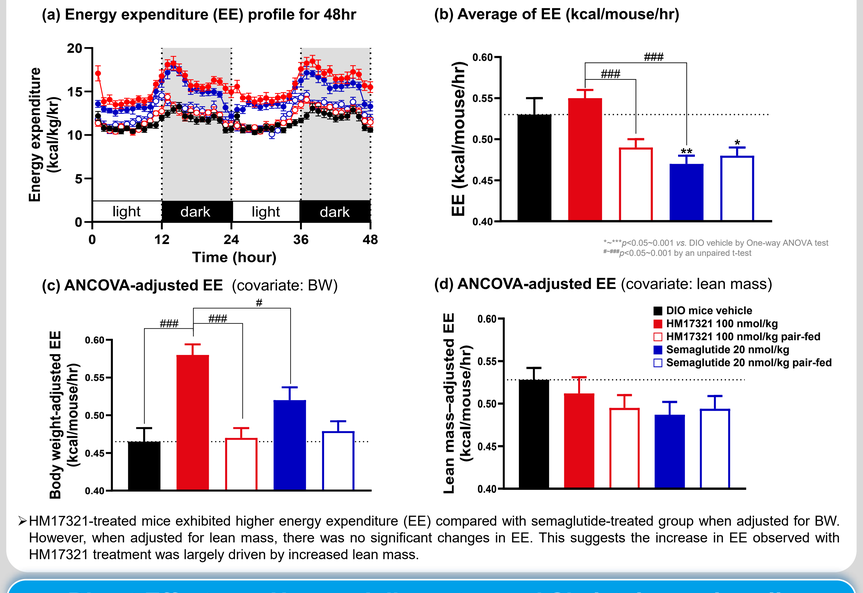
Figure 1. Effect of HM17321 on body composition and skeletal muscle weight in DIO mice



➢ In DIO mice, HM17321 enhanced weight loss quality by reducing fat and promoting lean mass gain, unlike Sema which leads to lean mass loss. HM17321 significantly increased skeletal muscle mass. Both the HM17321 and semaglutide significantly decreased the intramuscular TG levels, however, the reduction was greater in the HM17321 group compared to semaglutide.

Body Recomposition-driven Energy Expenditure increase

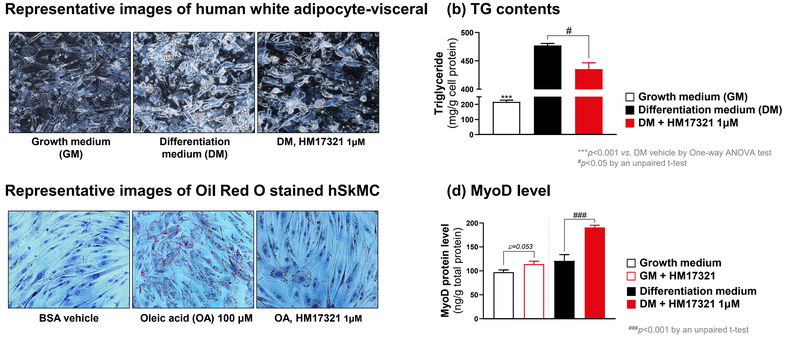
Figure 2. Effect of HM17321 on skeletal muscle in DIO mice



➢ HM17321-treated mice exhibited higher energy expenditure (EE) compared with semaglutide-treated group when adjusted for BW. However, when adjusted for lean mass, there was no significant changes in EE. This suggests the increase in EE observed with HM17321 treatment was largely driven by increased lean mass.

Direct Effects on Human Adipocytes and Skeletal muscle cells

Figure 3. Effects of HM17321 on human adipocytes and skeletal muscle cells



➢ HM17321 promoted lipolysis in differentiated human visceral adipocytes by reducing TG levels.
➢ HM17321 enhanced myogenic differentiation in human skeletal muscle cells by decreasing intramuscular lipid and increasing MyoD expression.

Concluding Remarks

- HM17321 demonstrated robust, **high-quality weight loss** in DIO mice by selectively reducing fat mass and increasing lean mass, with elevated energy expenditure even after body weight adjustment.
- *In vitro* MoA studies using human cells confirmed that HM17321 promotes lipolysis in adipocytes and enhances differentiation in skeletal muscle cells.
- Collectively, these findings highlight the potential of HM17321 as a metabolically driven anti-obesity therapy that delivers durable and high-qualfity weight loss.
- **Please note Hanmi's additional posters on our obesity pipeline:**
  HM17321, a UCN2 analog (P-226, P-739, P-819) / Oral GLP-1 RA (LBA-47)
  HM15275, a GLP-1/GIP/Glucagon triple agonist (P-765)