Overcoming Muscle Loss in Obesity Treatment: HM17321 Promoted High-Quality Weight Loss and Improved Metabolic Health

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Poster
P-105

Abstract

Background: Incretin-based therapies are effective in managing obesity, but are limited by muscle loss, which compromises their overall benefits by diminishing the metabolic and functional advantages conferred by muscle. Urocortin-2 (UCN2) has been proposed to promote muscle hypertrophy and lipolysis, which may contribute to improved weight loss quality (WLQ) and whole-body metabolism through the preservation of lean mass. HM17321, a rationally designed UCN2 analog, was developed to overcome the limitations of existing therapies. Here, we provide the nonclinical evidence supporting the potential of HM17321 to enable high quality weight management and associated metabolic improvement.

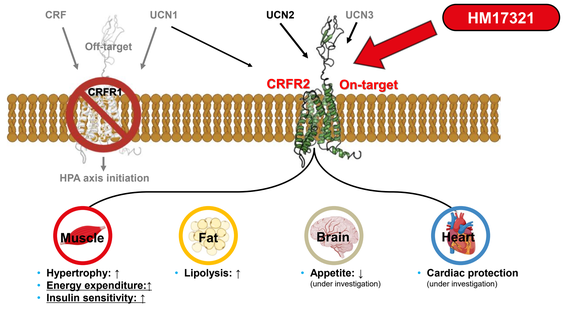
Methods: DIO mice were utilized to evaluate the therapeutic effects of HM17321 on body weight (BW), body composition and energy expenditure, followed by muscle tissue analysis. To assess glycemic control efficacy, intraperitoneal glucose tolerance tests (ipGTT) and insulin tolerance tests (ITT) were conducted after both single and chronic administrations. Semaglutide (Sema) was used as a comparative control. C2C12 cells were utilized to investigate the underlying mechanism of HM17321 on glycemic regulation.

Results: In DIO mice, HM17321 led to a significant BW reduction. Notably, despite comparable BW loss, HM17321 induced greater fat mass loss and significantly increased lean mass, unlike Sema. This was accompanied by enhanced energy expenditure, suggesting that the increase of lean mass by HM17321 contributed to a more favorable shift in energy balance. For glycemic control, chronic administration of HM17321 significantly lowered blood glucose levels during ipGTT (p<0.01~0.001 vs. DIO vehicle) and ITT (p<0.001 vs. DIO vehicle), consistent with improvements in body composition. Interestingly, a single administration of HM17321 also reduced blood glucose levels during ipGTT, indicating a direct improvement in insulin sensitivity, independent of body re-composition. This direct effect was further supported by increased glucose uptake in C2C12 cells treated with HM17321.

Conclusion: HM17321 demonstrated a unique profile by achieving high-quality weight loss through favorable body re-composition, especially characterized by increased lean mass. In addition, HM17321 provided metabolic benefits such as enhanced energy expenditure and improved glycemic control, supporting the fact that HM17321 enhances not only muscle mass, but also its metabolic functionality. These findings position HM17321 as a promising next-generation therapeutic candidate for obesity and related metabolic disorders, with the potential to be used in combination with incretin-based therapies.

Background

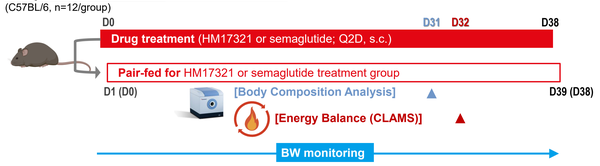
HM17321: A Novel Long-acting CRFR2 Selective UCN2 Analog



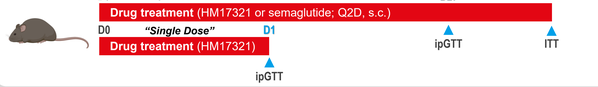
: HM17321 was rationally designed to selectively activate CRFR2, which leads to muscle gain followed by increased energy expenditure and enhancing glucose utilization

Methods: Overview of *In Vivo* Studies

Study 1. DIO mice, ♂ 19W *6-week-old, HFD for 13 weeks*
(C57BL/6, n=12/group)

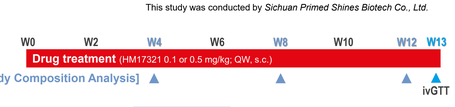


Study 2. DIO mice, ♂ 24W *6-week-old, HFD for 18 weeks*
(C57BL/6, n=6/group)



Study 3. Obese Monkey (mean BW: 18.0 kg), ♂ 10 ~ 18 yrs
(Rhesus, n=6~7/group)

This study was conducted by *Sichuan Primed Shines Biotech Co., Ltd.*



Baseline characteristics

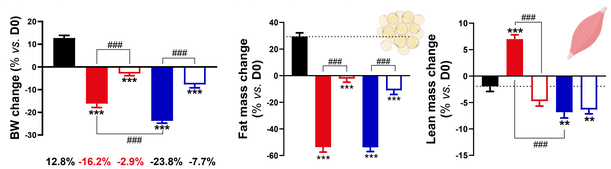
Age (years)	10~18
Body weight (kg)	18.0
Body fat contents (%)	42.8
BMI (kg/m^2)	49.3
Fasting blood glucose (mg/dL)	84.6

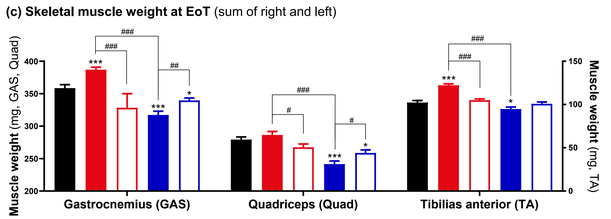
Obese monkey, Vehicle, QW, s.c. (n = 6)
Obese monkey, HM17321 2.5* → 0.1 mg/kg, QW, s.c. (n = 7)
Obese monkey, HM17321 0.5 mg/kg, QW, s.c. (n = 7)

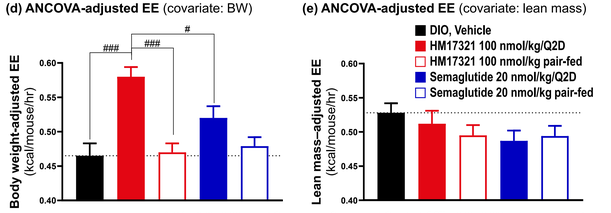
**The initial dose of 2.5 mg/kg was reduced to 0.1 mg/kg after the 1st dosing*

Body Recomposition and Increased Energy Expenditure

Figure 1. Effects of HM17321 on BW, Body composition and Energy expenditure in DIO mice





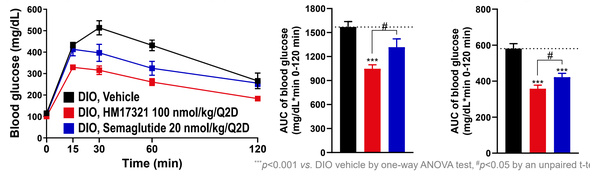


*~***p<0.05~0.001 *vs.* DIO vehicle by One-way ANOVA test, #~###p<0.05~0.001 by an unpaired t-test

➢ In DIO mice, HM17321 significantly reduced BW and fat mass compared to both the vehicle and pair-fed groups. Notably, HM17321 promoted lean mass gain and significantly increased skeletal muscle mass, unlike Sema which caused muscle loss. The higher energy expenditure (EE) observed with HM17321 disappeared after lean mass correction, indicating that the elevated EE was mainly driven by muscle gain.

Chronic Glycemic Control and Insulin Sensitivity in DIO Mice

Figure 2. Effects of HM17321 on glycemic control in DIO mice

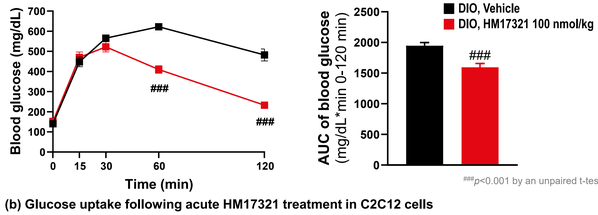


***p<0.001 *vs.* DIO vehicle by one-way ANOVA test, #p<0.05 by an unpaired t-test

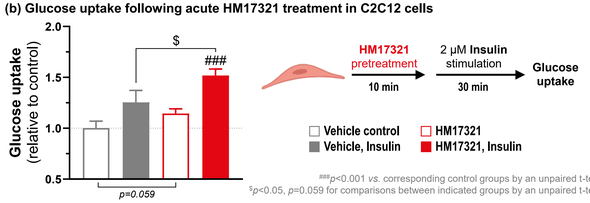
➢ In DIO mice, HM17321 showed greater glycemic control efficacy than Sema. This improvement appeared to result from both favorable body recomposition (fat loss and lean gain) and a direct metabolic effect linked to enhanced muscle function, including improved glucose uptake and utilization.

Acute Glycemic Regulation: *In Vivo* and *In Vitro* Evidence

Figure 3. Direct effects of HM17321 on glucose utilization



###p<0.001 by an unpaired t-test

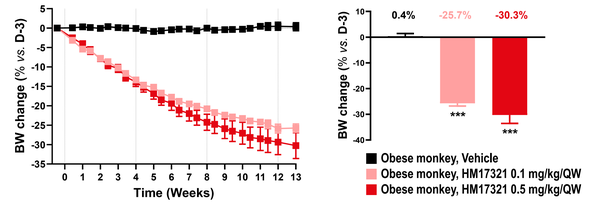


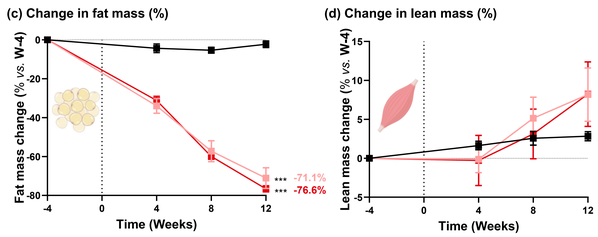
###p<0.001 *vs.* corresponding control groups by an unpaired t-test
$$p<0.05, p=0.059 for comparisons between indicated groups by an unpaired t-test

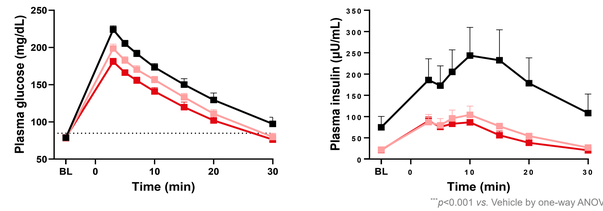
➢ Interestingly, HM17321 single administration enhanced glycemic control efficacy in DIO mice.
➢ Mechanistically, HM17321 increased glucose uptake under both basal and insulin-stimulated conditions, suggesting that HM17321 directly modulates glucose metabolism.

Fat-driven Weight Loss & Metabolic Improvement in Obese NHP

Figure 4. Effects of HM17321 on body recomposition and glycemic control in obese monkeys







***p<0.001 *vs.* Vehicle by one-way ANOVA test

➢ In obese monkey, HM17321 significantly induced body weight loss primarily driven by a reduction in fat mass, while lean mass was increased. This favorable body recomposition, together with the direct metabolic actions of HM17321, contributed to improved glycemic control as evidenced by reduced plasma glucose and insulin levels during ivGTT.

Concluding Remarks

- HM17321 consistently induced lean mass gain in both DIO mice and obese primates, which led to increased energy expenditure and ultimately contributed to improved metabolic outcomes.
- This cascade, **LM gain → elevated EE & enhanced glycemic control**, highlights HM17321's distinct mechanism of action compared to existing incretin-based drugs.
- Furthermore, an acute exposure of HM17321 significantly enhanced glucose utilization in both *in vivo* and *in vitro* studies, underscoring its potential for direct glycemic regulation independent of muscle hypertrophy.
- Collectively, these findings position HM17321 as a promising candidate for treating obesity and metabolic disorders through high-quality weight loss and improved glucose metabolism.
- P1 IND application has been approved to the U.S. FDA.
- **Hanmi's posters in ObesityWeek® 2025**
  - HM15275: Phase 1 trial: Safety, PK and PD in obese subjects (P-218)
  - HM17321: AI-based discovery (P-320)
    Blood & muscle proteomics for muscle preservation (P-571)

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