Discovery of HM17321: A Novel CRFR2 Selective UCN2 Analog for High-Quality Weight Loss

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Poster P-320

Abstract

Background: Current incretin-based anti-obesity medications showed remarkable weight-reduction efficacy, yet they are limited by lean mass loss. To address these issues, we explored the corticotropin-releasing factor (CRF) system, particularly CRFR2. CRFR2 regulates pathways affecting lipolysis, energy expenditure, and glucose uptake. We employed AI-based design approaches, providing comprehensive insights for harmoniously tuning multiple desired properties.

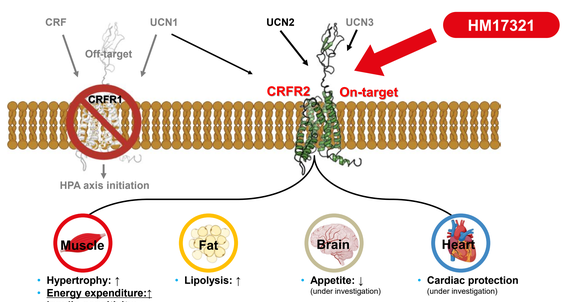
Methods: Using AI-based structure modeling and molecular dynamics simulations, we optimized the CRFR2-UCN2 complex structure. Novel UCN2 analogs were designed by integrating energetically favorable mutations and optimal amino acid compatibility with human-guided optimization. The candidates were evaluated by CRFR-mediated cAMP accumulation and β-arrestin recruitment assays. For *in vivo* efficacy studies, HM17321 was administered periodically, followed by body composition analysis.

Results: Through our systematic development approach, we designed multiple UCN2 analogs by applying three sequential strategies: (1) Enhancement of CRFR2 activity, (2) Reduction of CRFR1 activity and CRFR2 desensitization, and (3) Fine-modulation between aforementioned properties. This stepwise approach allowed us to integrate critical molecular features such as improved CRFR2 selectivity and G-protein biased agonism. This approach enabled the rapid identification of HM17321, which demonstrated significant fat mass loss and increased lean mass across animal models of obesity, indicating its potential for high-quality weight management.

Conclusions: HM17321, a novel long-acting, CRFR2-selective, and biased UCN2 analog, demonstrates significant potential as next-generation obesity and related metabolic disease medication. This seamless integration of computational tools and biological knowledge highlights the significant impact of collaborative approaches in driving progress in drug development.

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

Step-wise Design Strategy

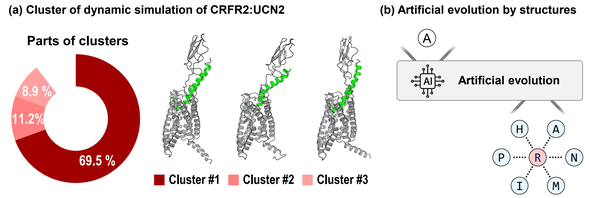
Tabel 1. Step-wise design strategy for hanmi's novel CRFR2 agonist

Design Generation	Purpose	Goal of Analog Design			
		Long-acting	CRFR2 Activity†	CRFR1 Activity†	CRFR2 Desensitization‡
1st Generation	Enhancement of on-target effects	↑	↑	n.a.	n.a.
	Reduction of off-target effects and receptor desensitization	↑	↑	↓	↓
2nd Generation	Fine-modulation of properties	↑	↑↑	↓↓	↓↓

† cAMP accumulation activity by CRFR2 or CRFR1
‡ β-arrestin recruitment by CRFR2
'↑' and '↓' denote increase and decrease of the corresponding effects. The number of arrows indicated the strength of enhancement or reduction of the activities.
'n.a.' denotes 'not applied' meaning that the strategy is not applied in the stage.

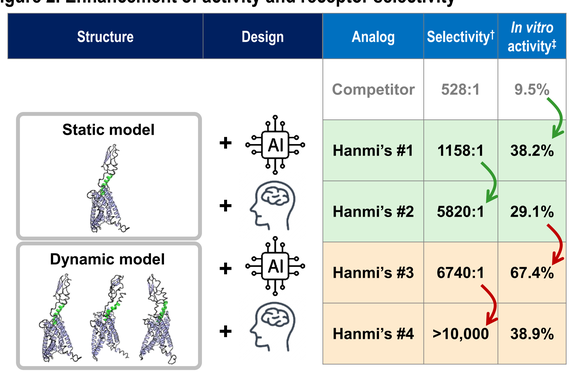
Design from *In Silico* Structure Model (1st Generation)

Figure 1. Simulation of dynamic CRFR2:UCN2 complex structure



Artificial evolution was performed to search the optimal residue changes for the desired properties, using AI-based affinity calculation method.

Figure 2. Enhancement of activity and receptor selectivity

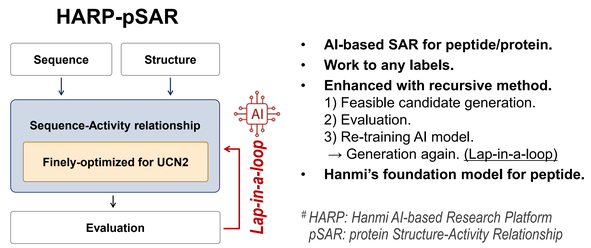


† "Selectivity" means the ratio of "*in vitro* activity" toward CRFR2 and CRFR1.
‡ "*In vitro* activity' were calculated as relative activity compared to native peptide, such as hUCN1 and hUCN2, using EC_{50} value.

➢ In combination of dynamic structure model of CRFR2:UCN2 and AI-based sequence design with human intervention could generate the novel UCN2 analog as super-selective CRFR2 agonist.

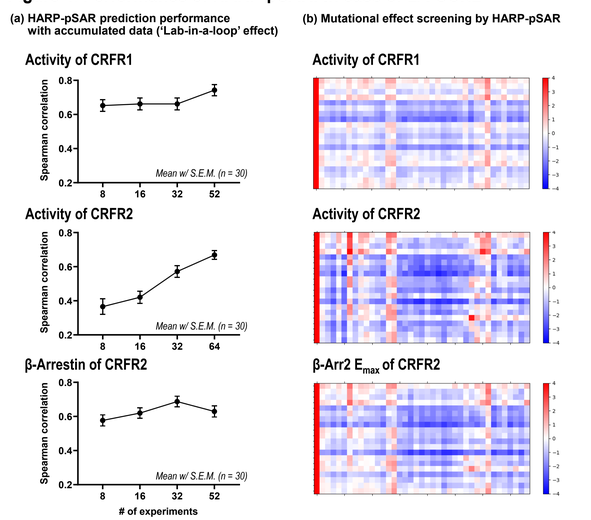
Design by AI-based SAR Strategy (2nd Generation)

Figure 3. Recursive design of peptide using HARP-pSAR#



HARP: Hanmi AI-based Research Platform pSAR: protein Structure-Activity Relationship

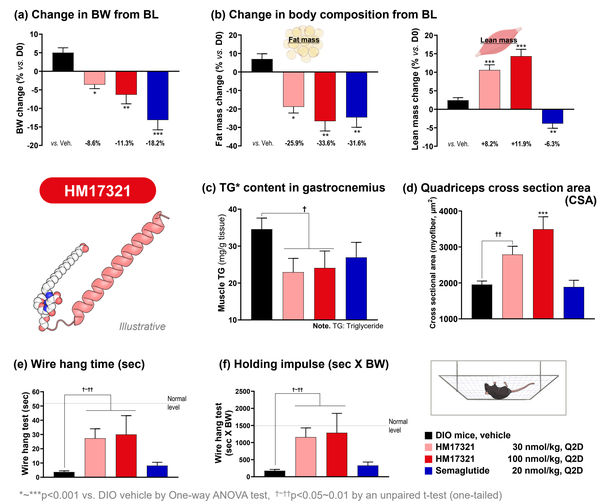
Figure 4. Performance of HARP-pSAR: In case of LA-UCN2



➢ As 'lap-in-a-loop' goes on, HAPR-pSAR could generate more desired molecules, which makes drug development faster than ever and less experiments to discover the potent lead molecule.

In Vivo Efficacy: Fat Mass Reduction & Lean Mass Increase

Figure 5. *In vivo* efficacy of the designed LA-UCN2 candidates



*~***p<0.001 vs. DIO vehicle by One-way ANOVA test, †~††p<0.05~0.01 by an unpaired t-test (one-tailed)

➢ In DIO mice, HM17321 dose dependently decreased BW and fat mass. Moreover, HM17321 effectively increased the holding impulse, relatively reduced in obese mice, indicating HM17321 contributed to improvements in muscle strength and function. These results demonstrate HM17321 could not only reduce BW and fat mass, but also enhance muscle function, improving WLQ (Weight-loss quality).

Concluding Remarks

- HM17321, the most potent of LA-UCN2 analog, was evaluated to show the desired *in vivo* efficacy: Selectively reducing fat mass and increasing lean mass, with increased muscle strength and function.
- *In silico* static and dynamic structure models of CRFR2:UCN2 complex were utilized to engineer its native peptide properties for enhanced agonistic activity and receptor selectivity.
- HARP-pSAR (Hanmi's AI platform) utilized *in vitro* activity results exclusively, to generate HM17321 with super-selectivity and super-agonistic activity toward human.
- 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: Muscle preservation and blood glycemic control (P-105)
    Blood & muscle proteomics for muscle preservation (P-571)

References

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2. Abraham *et al., SoftwareX*. 2015; 1–2 19–25.
3. Lee *et al., ObesityWeek* 2024 poster-504.