HM17321, a CRFR2-Selective UCN2 Analog, Prevents Muscle Loss and Functional Decline in Sarcopenic Mice

Dahae Lee, Yohan Kim, Hyunjoo Kwon, Eunjin Park, Jeong A Kim, Jung Kuk Kim, Sungmin Bae, Sang Hyun Lee and In Young Choi
R&D Division, Hanmi Pharm. Co., Ltd., Gyeonggi-do, Republic of Korea

Hanmi

Poster
1783-P

Introduction

Introduction and Objective: Sarcopenia is characterized by progressive deterioration of skeletal muscle mass, structural integrity and function. Senescence-accelerated mouse-prone 8 (SAMP8) mice represent accelerated aging model that recapitulates key features of sarcopenia. HM17321 is a CRFR2-selective UCN2 analog with established metabolic benefits and emerging relevance to improvement of skeletal muscle mass and function. This study evaluated the effects of HM17321 on aging-associated sarcopenia in SAMP8 mice and its efficacy across complementary models of muscle atrophy.

Methods: Male SAMP8 mice were subcutaneously administrated with HM17321 for 4 months, with senescence-resistant SAMR1 mice as age-matched controls. Body composition, neuromuscular function and aging-associated phenotypes were longitudinally assessed. Skeletal muscle atrophy was evaluated by histological analysis. The efficacy of HM17321 against muscle wasting was further assessed in a dexamethasone-induced muscle atrophy model.

Results: Relative to SAMR1 mice, SAMP8 mice exhibited accelerated degeneration of skeletal muscle mass and function. HM17321 treatment broadly ameliorated these age-associated deficits, increasing lean mass (up to +7.9% point vs. SAMP8 vehicle) while reducing fat mass (up to –23.0% point), accompanied by marked improvements in muscle performance, including grip strength and holding impulse, and alleviation of kyphosis and hindlimb clasping. These improvements were supported by preserved muscle architecture, with maintained myofiber cross-sectional area and laminin expression, and reduced MuRF1 in the gastrocnemius muscle. Consistently, in a dexamethasone-induced muscle atrophy model, HM17321 mitigated functional impairment more effectively than bimagrumab, supporting its protective effect on skeletal muscle under catabolic conditions.

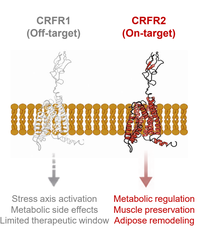
Conclusion: HM17321 attenuated sarcopenia across multiple etiologies by preserving muscle mass, function, and structural integrity. These findings support the potential of HM17321 as a therapeutic approach for sarcopenia.

Background

HM17321, a novel long-acting CRFR2-selective UCN2 analog, is designed to mitigate age-associated decline in muscle mass and functional deterioration through selective CRFR2 signaling.

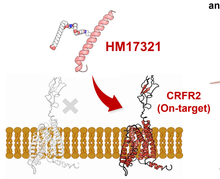
CRFR system and aging

UCN2–CRFR2 signaling supports metabolic and muscle homeostasis



HM17321

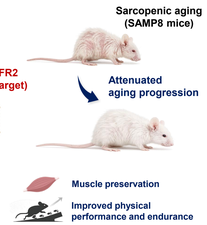
Selective CRFR2 activation by HM17321



High selectivity for CRFR2 over CRFR1
Bias toward beneficial signaling
Long-acting exposure

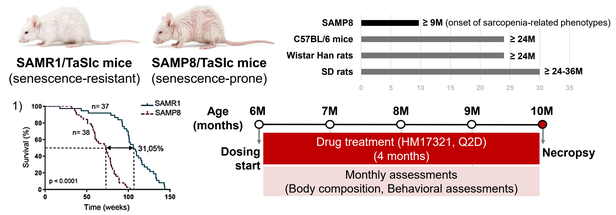
Therapeutic potential

HM17321 may preserve muscle and physical function during aging

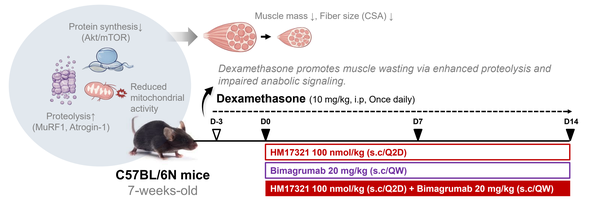


Study Design

Study 1.
Senescence-accelerated sarcopenia model [SAMP8]

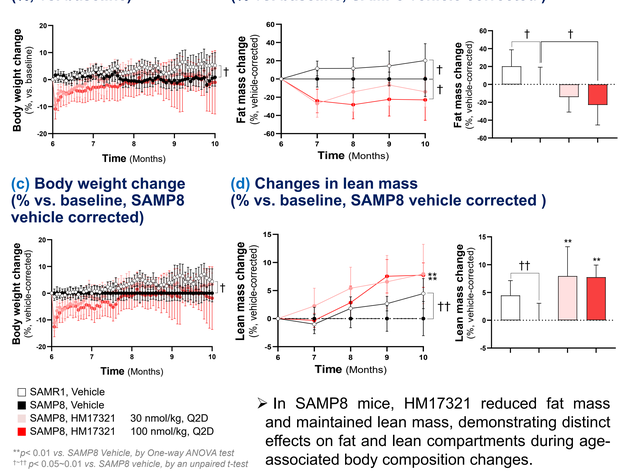


Study 2.
Glucocorticoid-induced muscle atrophy model [DEX-induced mice]



Improved Lean-to-Fat Composition in Aged SAMP8 Mice

Figure 1. Body Composition Changes in SAMP8 Mice

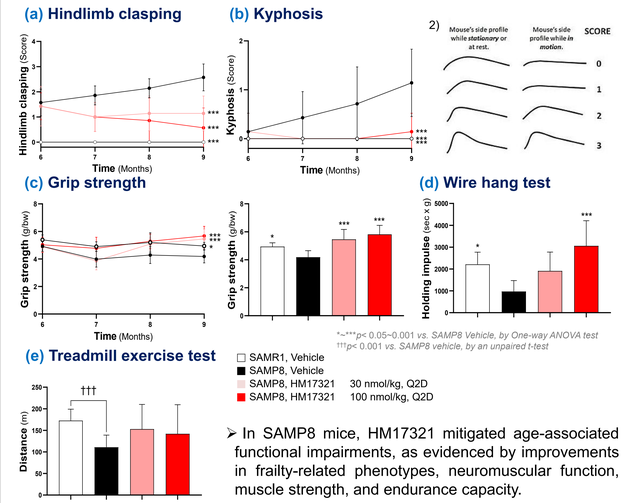


**p< 0.01 vs. SAMP8 Vehicle, by One-way ANOVA test
†-†† p< 0.05~0.01 vs. SAMP8 vehicle, by an unpaired t-test

➢ In SAMP8 mice, HM17321 reduced fat mass and maintained lean mass, demonstrating distinct effects on fat and lean compartments during age-associated body composition changes.

Attenuation of Age-Associated Functional Decline

Figure 2. Functional Assessments in SAMP8 Mice

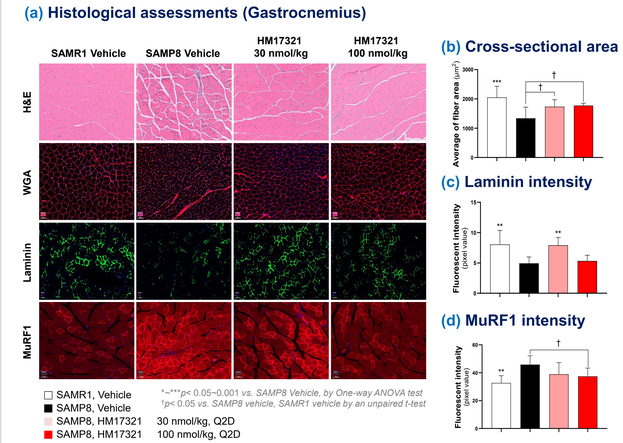


*-***p< 0.05~0.001 vs. SAMP8 Vehicle, by One-way ANOVA test
†††p< 0.001 vs. SAMP8 vehicle, by an unpaired t-test

➢ In SAMP8 mice, HM17321 mitigated age-associated functional impairments, as evidenced by improvements in frailty-related phenotypes, neuromuscular function, muscle strength, and endurance capacity.

Preservation of Skeletal Muscle Integrity

Figure 3. Skeletal Muscle Integrity in SAMP8 Mice

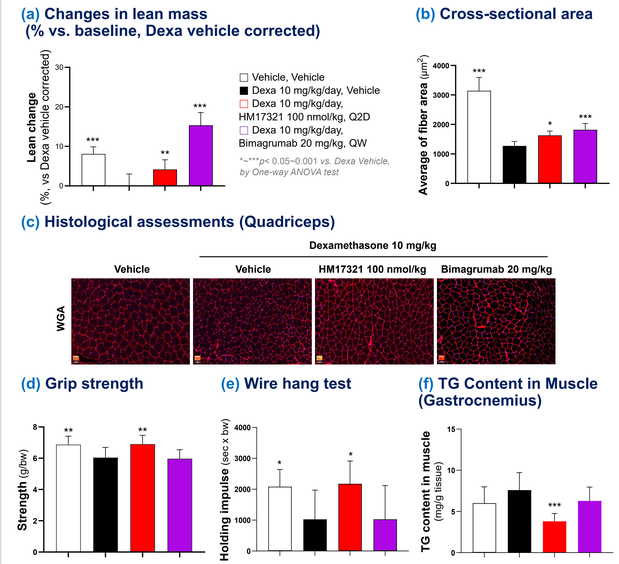


*-***p< 0.05~0.001 vs. SAMP8 Vehicle, by One-way ANOVA test
†p< 0.05 vs. SAMP8 vehicle, SAMR1 vehicle by an unpaired t-test

➢ In SAMP8 mice, HM17321 preserved skeletal muscle integrity and demonstrated beneficial effects on muscle integrity by enhancing myofiber size and modulating the expression of atrophy-associated markers.

Attenuation of Glucocorticoid-Induced Skeletal Muscle Decline

Figure 4. Skeletal Muscle Mass and Function in a DEX-Induced Muscle Atrophy Model



➢ HM17321 preserved myofiber size, improved muscle function, and reduced intramuscular TG accumulation under glucocorticoid-induced atrophy, suggesting its potential to improve muscle quality beyond lean mass preservation.

Concluding Remarks

- HM17321 demonstrated consistent muscle protecting efficacy across distinct muscle atrophy models, improving both muscle mass and functional performance.
- In SAMP8 mice, HM17321 ameliorated age-related muscle decline by improving muscle function and frailty-related phenotypes, while preserving skeletal muscle integrity by modulating atrophy-associated markers.
- Under dexamethasone-induced catabolic stress, HM17321 preserved lean mass and myofiber size, improved muscle function, and reduced intramuscular TG accumulation.
- Collectively, these findings support HM17321-mediated selective CRFR2 activation as a differentiated therapeutic strategy for enhancing skeletal muscle resilience under aging- and catabolic stress-associated conditions.
- Please also note Hanmi's additional presentations on our pipeline:
  HM17321, a UCN2 analog: 1803-P | 2537-P | 2538-P | 2579-P | 2872-LB | 3078-LB
  HM500197, a peptide-based MSTN inhibitor: 3073-LB

References

1) Aging (Albany NY). 2023 May 23;15(11):4600-4624.
2) Biol Open. 2022 Apr 15;11(4):bio059052.