Evaluation of GLP1R/GIPR Dual-Target Drugs AMG133 and Tirzepatide in DIO Humanized GIPR Mice

WuXi Biology

Hao Qi, Siyuan Yao, Na Liu, Lanlan Shao, Yusen Zha, Zhongxiang Li, Ying Li, Qingyang Gu, *In Vivo* Pharmacology Unit, WuXi Biology, WuXi AppTec

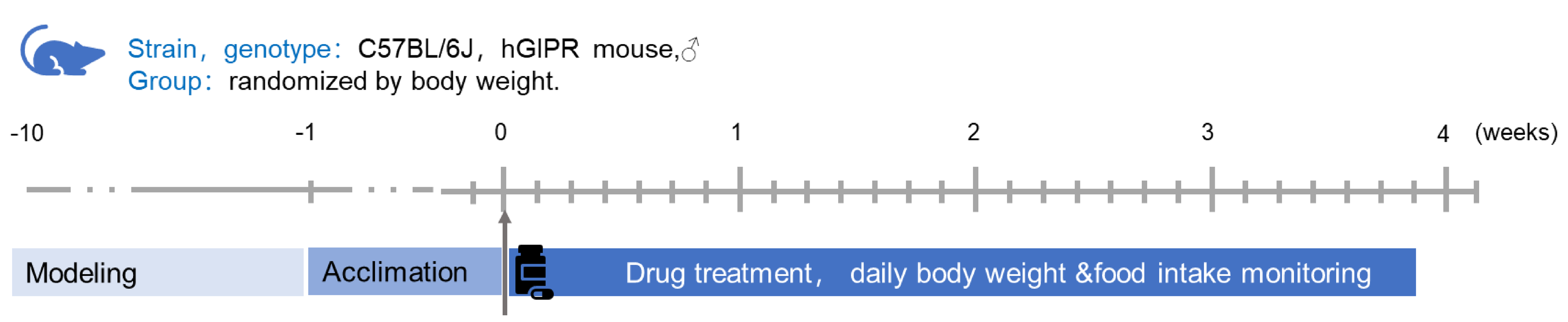
Introduction

Multi-target drugs targeting GLP1R/GIPR/GCGR have shown superior efficacy compared to single-target GLP1R drugs.

Compared with GLP1R, the sequence homology between murine and human GIPR is limited. and studies have explicitly reported that dual-target GLP1R/GIPR drugs exert their effects primarily through GLP1R in wild-type DIO mice, with GIPR not functioning effectively.

To overcome this limitation and improve the translational relevance of preclinical efficacy assessments, we employed GIPR-humanized mice, in which the murine GIPR gene is replaced with its human counterpart. Using this model, we evaluated the weight loss efficacy of tirzepatide and AMG133, both of which exhibited significantly enhanced anti-obesity effects in GIPR-humanized mice compared to wild-type DIO mice. These findings suggest that GIPR-humanized mice provide a more suitable platform for evaluating the therapeutic potential of dual GLP-1R/GIPR agonists in obesity treatment.

Experimental Design



#	Group
1	Control-Vehicle
2	HFD-Vehicle
3	HFD-AMG133
4	HFD-hGIPR-AMG133
5	HFD-Tirzepatide
6	HFD-hGIPR-Tirzepatide

Readouts
Body weight
Body composition
Fat mass
Fasting blood glucose
OGTT
……

Results

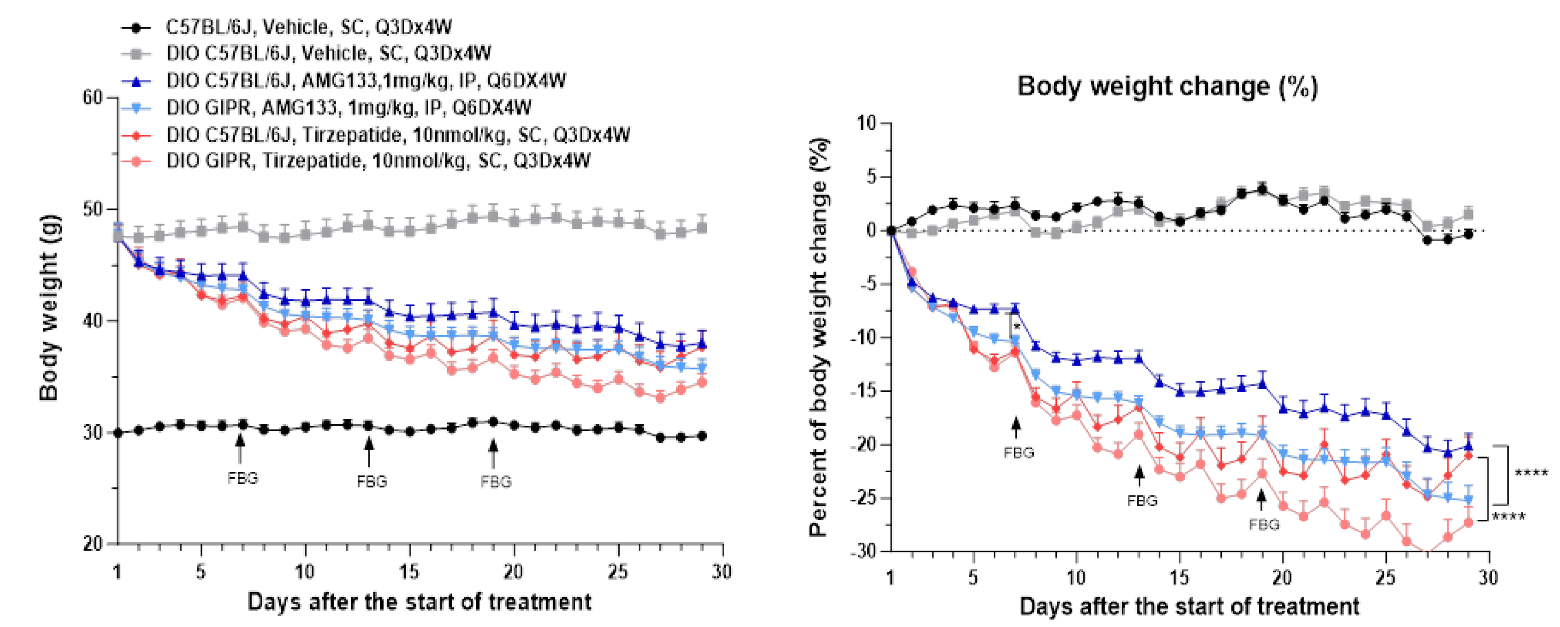


Figure 1. Both AMG133 and Tirzepatide have shown better weight loss efficacy in GIPR-humanized mice.
(Both AMG133 (1mpk, Q6D) and Tirzepatide (10mpk, Q3D) treatments achieved greater weight loss in DIO-GIPR humanized mice compared to wild-type DIO mice (AMG133: DIO-WT vs DIO-GIPR = 20.10% ± 1.13% vs 25.24% ± 1.42%; Tirzepatide: DIO-WT vs DIO-GIPR = 21.03% ± 1.76% vs 27.28% ± 1.50%). Data are presented as mean ± SEM. Statistical analysis was performed by one-way ANOVA followed by Dunnett's post hoc test. **** $p < 0.0001$. n = 10.

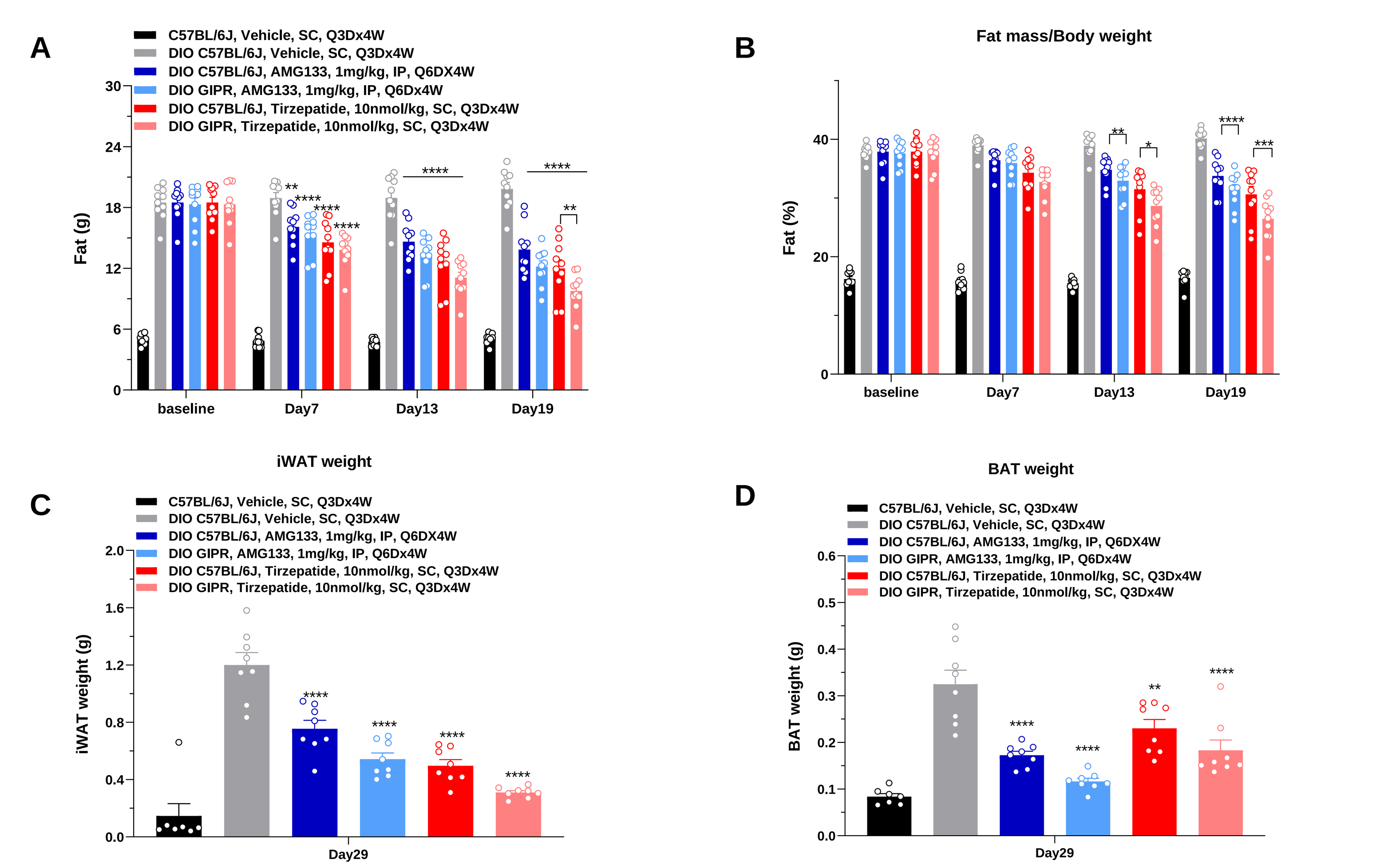


Figure 2. Both AMG133 and Tirzepatide have shown better fat loss efficacy in GIPR-humanized mice.
(A) and (B): Fat mass and fat ratio of wild-type DIO mice and DIO-GIPR humanized mice were measured by Brucker's LF50 before and after treatments. (C) and (D):Inguinal white adipose tissue (iWAT) and brown adipose tissue (BAT) were collected and weighed at the termination. Data are presented as mean ± SEM. Statistical analysis was performed by one-way ANOVA followed by Dunnett's post hoc test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. n = 10.

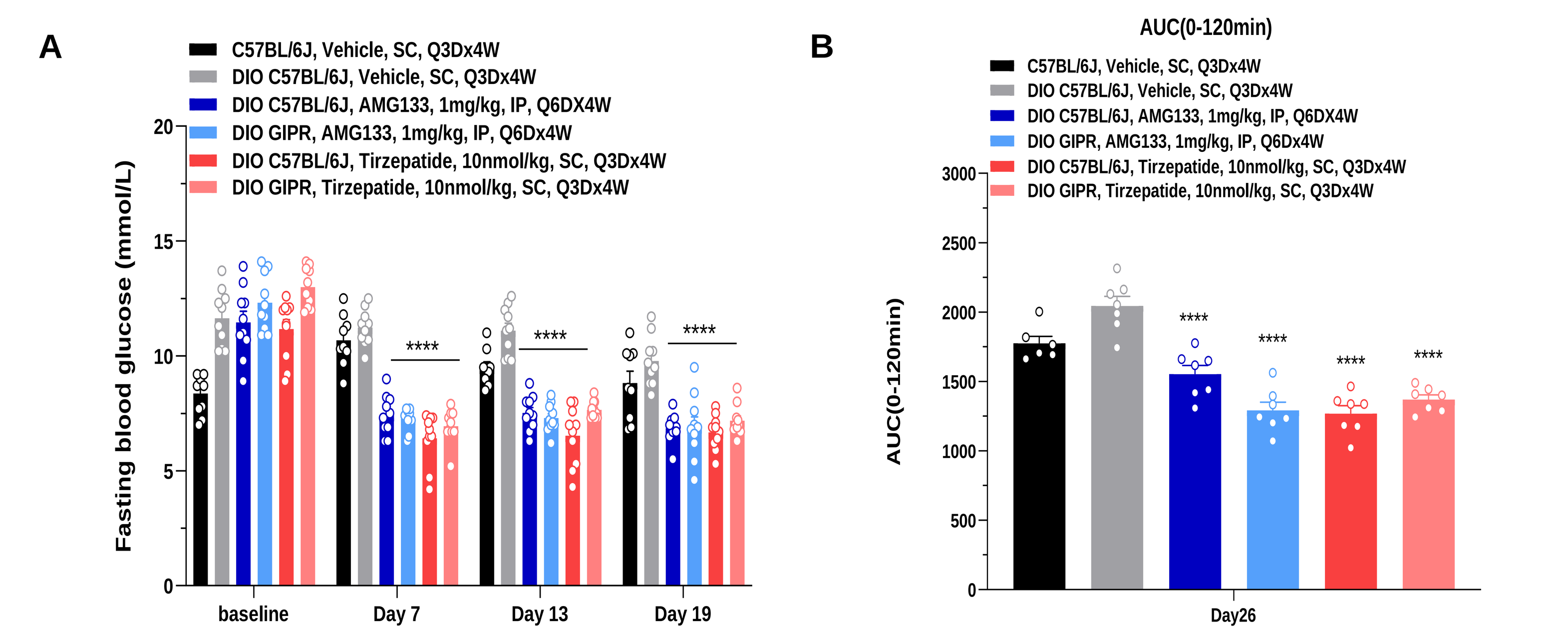


Figure 3. AMG133 has shown better glucose-lowering efficacy in GIPR-humanized mice.
Upon administration of AMG133 and Tirzepatide, a significant reduction in fasting blood glucose levels was observed in both wild-type DIO mice and DIO-GIPR humanized mice. However, no significant intergroup differences were noted (A). In the oral glucose tolerance test (OGTT), AMG133 exhibited a superior efficacy in ameliorating glucose intolerance in DIO-GIPR humanized mice (B). Data are presented as mean ± SEM. Statistical analysis was performed by one-way ANOVA followed by Dunnett's post hoc test. **** $p < 0.0001$. n = 10.

Conclusions

- Humanizing the GIPR in mice allows for a more accurate reflection of the in vivo regulatory effects of AMG133 and Tirzepatide on GIPR.
- Both AMG133 and Tirzepatide have demonstrated superior efficacy in reducing body weight and fat in DIO-GIPR humanized mice.
- AMG133 exhibited a superior efficacy in ameliorating glucose intolerance in DIO-GIPR humanized mice.
- Compared to wild-type DIO mice, DIO-GIPR humanized mice are better suited for the in vivo pharmacological evaluation of dual-target GLP1R/GIPR drugs.

References

1. Kimberley El, Jonathan D. Douros, Francis S. Willard. et al. The incretin co-agonist tirzepatide requires GIPR for hormone secretion from human islets. *Nature Metabolism* Volume 5 | June 2023 | 945–954

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Business contact: mahnaz_arjomand@wuxiapptec.com (US)
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Business contact: fumio_itoh@wuxiapptec.com (Japan)
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