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Efficacy of Semaglutide and Related Drugs in Animal Models of Various Diseases

Yishuang Wei, Xingjuan Wang, Ping Chen, Lingling Chang, Danyi Zhu, Chenlin Su, Ming Ding, Yunhan Qiu, Liang Xiang, Beilei Cai, Runan Yin, Xin Li, Jeff Duan, Deming Xu

Department of Disease Pharmacology, PharmaLegacy Laboratory (Shanghai) Co. Ltd., Shanghai, P.R. China

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INTRODUCTION

The glucagon-like peptide-1 (GLP-1) and the agonists of its receptor (GLP-1R) have become the focal point in recent years, due to its novel mechanism, significant clinical efficacies and broad potential in treating diseases, from diabetes, obesity to possibly Alzheimer's disease.

AIM

We are interested in testing the agonists of GLP-1R, dual and triple agonists in animals model corresponding to related clinical indications. In particular, we want to determine how symptoms in animal models respond to various treatment, and find out whether these models could shed new insights to the mechanism of action in treating various diseases.

METHODS

We selected the following animal models for efficacy studies:

- High-fat diet induced obesity (DIO) in mice
- Spontaneous obese cynomolgus monkeys
- DIO in transgenic hGLP-1R mice
- Mouse db/db model for diabetes
- Mouse MASH model induced by CDAHFD
- Heart failure model in mice induced by HFD + L-NAME
- Alcohol preferences model in mice

Time-course of body weight changes, fat and lean mass, blood biomarkers for lipid and glucose metabolism were closely monitored. Glucose tolerance test was used in diabetes model, and histopathology and RNA seq were employed in the MASH model. Cardial functional tests (echocardiography etc.) were used in the hear failure model.

PharmaLegacy's animal care and use program is fully accredited by AAALAC. All the experiments described in this poster were approved by PharmaLegacy IACUC, and were performed in accordance with the relevant laws, regulations, ethical and industry standards.

RESULTS

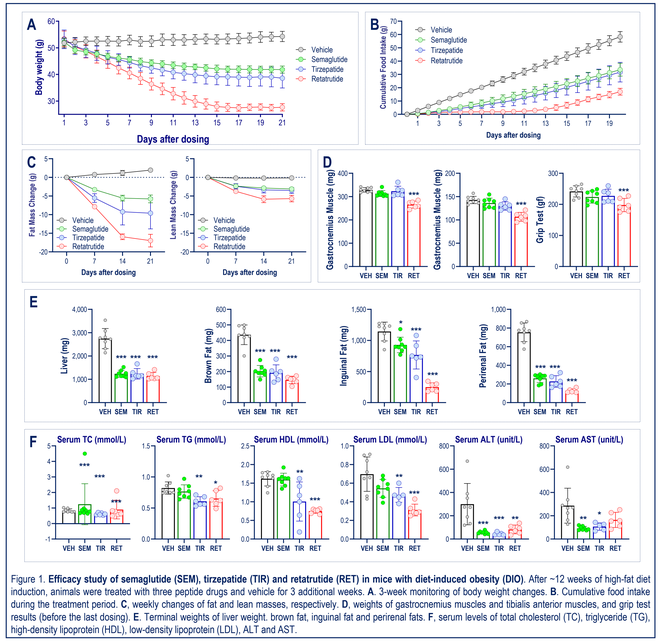


Figure 1. **Efficacy study of semaglutide (SEM), tirzepatide (TIR) and retatrutide (RET) in mice with diet-induced obesity (DIO)**. After ~12 weeks of high-fat diet induction, animals were treated with three peptide drugs and vehicle for 3 additional weeks. **A**. 3-week monitoring of body weight changes. **B**. Cumulative food intake during the treatment period. **C**. weekly changes of fat and lean masses, respectively. **D**. weights of gastrocnemius muscles and tibialis anterior muscles, and grip test results (before the last dosing). **E**. Terminal weights of liver weight, brown fat, inguinal fat and perirenal fats. **F**, serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), ALT and AST.

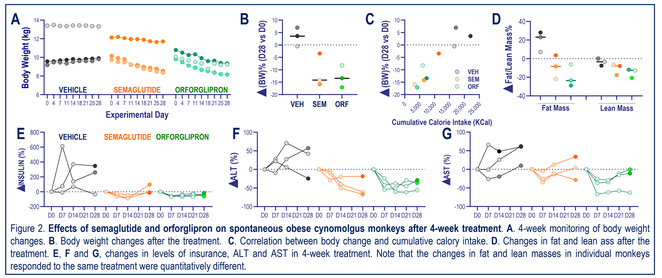


Figure 2. **Effects of semaglutide and orforglipron on spontaneous obese cynomolgus monkeys after 4-week treatment**. **A**. 4-week monitoring of body weight changes. **B**. Body weight changes after the treatment. **C**. Correlation between body change and cumulative calory intake. **D**. Changes in fat and lean ass after the treatment. **E**, **F** and **G**. changes in levels of insurance, ALT and AST in 4-week treatment. Note that the changes in fat and lean masses in individual monkeys responded to the same treatment were quantitatively different.

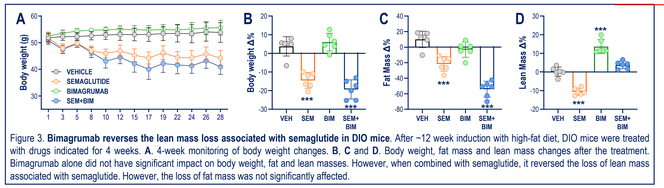


Figure 3. **Bimagrumab reverses the lean mass loss associated with semaglutide in DIO mice**. After ~12 week induction with high-fat diet, DIO mice were treated with drugs indicated for 4 weeks. **A**. 4-week monitoring of body weight changes. **B**, **C** and **D**. Body weight, fat mass and lean mass changes after the treatment. Bimagrumab alone did not have significant impact on body weight, fat and lean masses. However, when combined with semaglutide, it reversed the loss of lean mass associated with semaglutide. However, the loss of fat mass was not significantly affected.

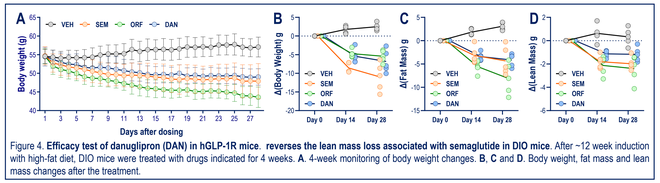


Figure 4. **Efficacy test of danuglipron (DAN) in hGLP-1R mice**. **reverses the lean mass loss associated with semaglutide in DIO mice**. After ~12 week induction with high-fat diet, DIO mice were treated with drugs indicated for 4 weeks. **A**. 4-week monitoring of body weight changes. **B**, **C** and **D**. Body weight, fat mass and lean mass changes after the treatment.

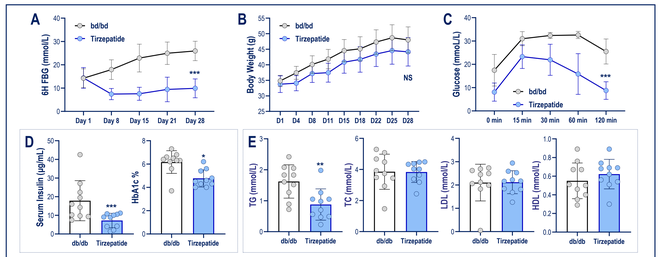


Figure 5. **Efficacy test of tirzepatide on diabetes in *db/db* mice**. Diabetic bd/bd mice were treated with tirzepatide for 4 weeks. **A**. Weekly fasting blood glucose (after 6 hour fasting). **B**. Body weight monitoring, note that the different the model and treatment was not significant on Day 28. **C**. Oral glucose tolerance test on Day 27, **D**. Serum levels of insulin and HbA1c on Day 28. **E**. Serum levels of TG, TC, LDL and HDL. Note that tirzepatide reduced serum TG only.

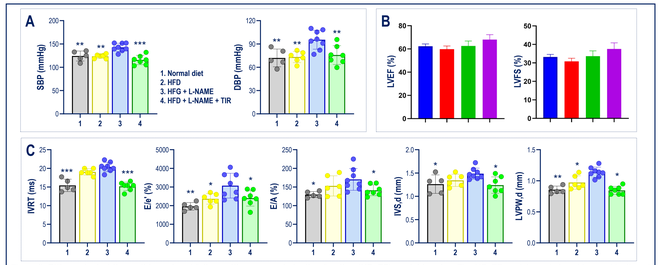


Figure 6. **Efficacy test of tirzepatide on heart failure with preserved ejection fraction (HFpEF) model in mice**. The HFpEF model was induced by combination of high-fat diet (HFD) and L-NAME (N-nitro-L-arginine methyl ester), and treated with tirzepatide. Blood pressures were measured on Day 57 (**A**, SBP and DBP, systolic and diastolic blood pressures). Cardial functions were determined by echocardiography. Note that the systolic functions (**B**, LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shorting) were preserved in the model and not affected by tirzepatide. The diastolic functions (**C**) were impaired and restored by tirzepatide.

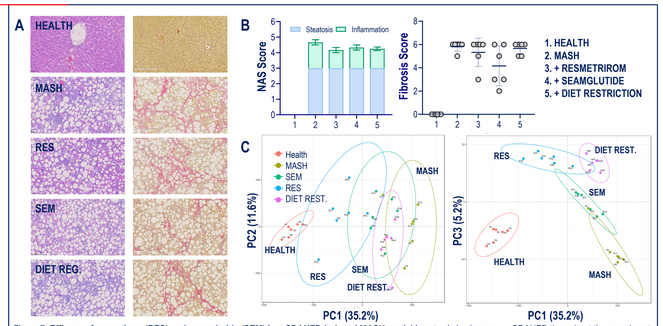


Figure 7. **Efficacy of resmetirom (RES) and semaglutide (SEM) in a CDAHFD-induced MASH model in rats**. Animals were on CDAHFD throughout the experiment, and resmetirom and semaglutide were administered from 5th to 8th weeks. In the last group (diet regimen, DIET REST.), animals were given restricted amount of diet based on the food consumption of SEM group. **A**. Histopathology of liver stained with HE (*left*) and Sirius red (*right*). Note that; ballooning is not observed in this model. **B**. Results of histopathology analysis, NAS (NALD Activity Score, *top*) and fibrosis score (*bottom*); **C**. Principal Component (PC) Analysis of RNA transcription profiling by RNA-seq.

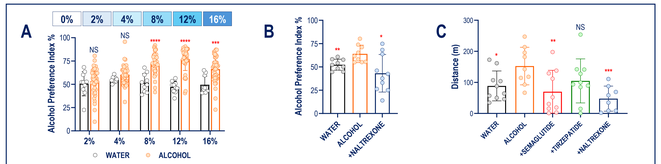


Figure 8. **Effects of semaglutide and tirzepatide on alcohol preference in C57BL/6J mice**. **A**. Alcohol preference test. Animals were given two-bottom choice with one containing increase alcohol (0% to 16%, each concentration lasted for 4 days). Their alcohol preference index were determined (volume of alcohol consumed relative to total fluid intake). **B**. Validation of alcohol preference test with naltrexone. C. Effects of semaglutide and tirzepatide (dosed in the 16% period) on alcohol preference in comparison with naltrexone, as determined by locomotive activity (distance traveled during the test period).

CONCLUSIONS

- In DIO mice and spontaneous obese cynomolgus monkeys, GLP-1 receptor agonists (semaglutide and orforglipron), GLP-1/GIP dual agonist (tirzepatide) and GLP-1/GIP/glucagon triple agonist (retatrutide) are efficacious in weight loss, accompanied by losses of both fat and lean masses. Bimagrumab reverses the lean mass loss associated with semaglutide.
- Tirzepatide is efficacious in treatment of diabetes in mouse bd/bd model, and systolic failure in mouse model induced by HFD+L-NAME.
- In a mouse model of MASH (CDAFHD), the effects of semaglutide are, at least in part, associated with reduced food intake.
- Semaglutide reverses alcohol preference in C57BL/6J mice.

CONTACTS

- Business Contact: Aimee.Duan@pharmalegacy.com
- Scientific Contact: Deming.Xu@pharmalegacy.com