Monoclonal Antibodies (mAbs) to Glucose-Dependent Insulinotropic Polypeptide (GIP) to Prevent and Treat Obesity in Wild-Type (WT) and Leptin-Deficient (*ob/ob*) Mice

M. Michael Wolfe[1], Patrick H. Griffin[2], Sireesh Appajosyula[2], Michael O. Boylan[1]
[1]Case Western Reserve University, Cleveland, Ohio, US; [2]9 Meters Biopharma, Raleigh, North Carolina, US

A0596

Introduction

- Glucose-dependent insulinotropic peptide (GIP) was initially isolated from porcine small intestine in 1969 and was named "gastric inhibitory polypeptide" for its ability to inhibit acid secretion.
- In addition to its gastric inhibitory effects, subsequent investigation demonstrated that in the presence of glucose, GIP enhanced insulin release by pancreatic islet β-cells. It was, therefore, suggested that GIP may function as an "incretin," a proposed enteric factor that stimulates insulin release and that plays a physiological role in maintaining glucose homeostasis.
- GIP is also insulin mimetic and thereby plays a critical role in promoting nutrient uptake and storage. A recent study demonstrated that GIP promotes fat accumulation in humans. All of these metabolic properties support the notion that GIP represents a major factor contributing to the development of insulin resistance and obesity.

Aims

- The aims of this study were to investigate whether GIP mAb will prevent weight gain in wild-type (wt) mice, promote weight loss in wt mice, and to determine the effects of this mAb in preventing weight gain in ob/ob mice, a model of extreme hyperphagia.

Methods

- Phosphate-buffered saline (PBS) or GIP mAbs (50 mg/kg BW/week) were injected intraperitoneally (ip) to wt C57BL/6 mice fed a 60% high-fat diet (HFD).
- At the end of 12 weeks, mice that received PBS were divided into two groups and were fed a 40% HFD for 5 weeks; one received PBS, and the other was administered GIP mAbs (50 mg/kg BW) ip per week. Both body weight and food consumption were measured weekly.
- In a separate study, PBS or GIP mAbs (60 mg/kg BW/week) were injected ip to ob/ob mice fed normal mouse chow for 8 weeks, and body weight and food consumption were measured weekly.

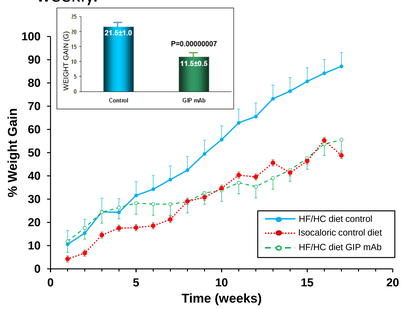


Fig. 1. Effects of GIP mAbs on weight gain in wt mice fed a HFD.

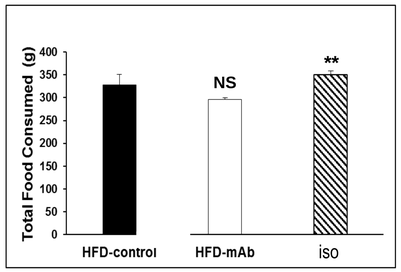
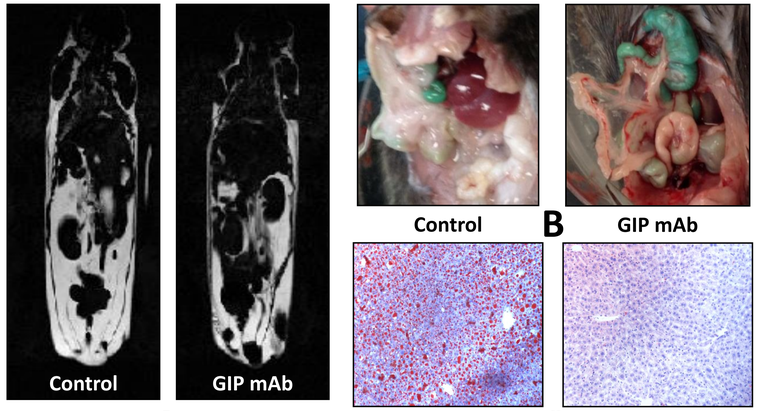


Fig. 2. Food consumption in wt mice fed a HFD or a control diet.



	HFD-Control	HFD-GIP mAb
Omental fat	9.3 g	2.7 g*
Hepatic fat	0.31 g	0.15 g**
Subcut. Fat	20.1 g	10.2 g*
Lean body wt.	16.5 g	22.8 g*

*P<0.001, **P<0.03

D

Fig. 3. Representative (A) MRI of wt mice fed a HFD; white areas represent accumulation of omental fat; (B) Representative post-necropsy laparotomy showing omental fat in mice fed a HFD with and without GIP mAbs; (C) Hepatic fat (stained red with Oil Red O) of wt mice fed a HFD with and without GIP mAbs; (D) Quantification of fat deposition in wt mice fed a HFD with and without GIP mAbs.

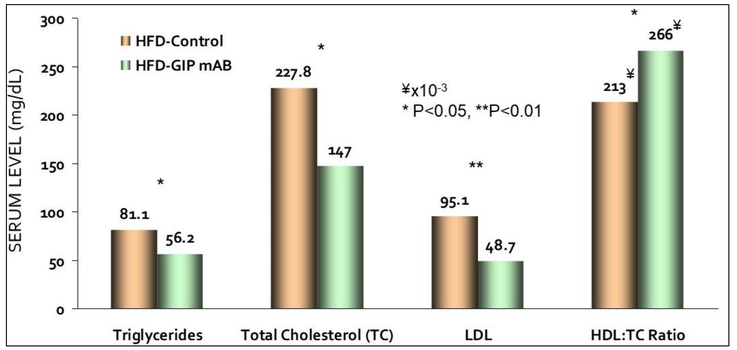


Fig. 4. Effect of GIP mAbs on atherogenic lipids in wt mice fed a HFD.

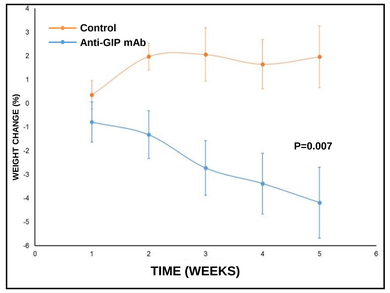


Fig. 5. Reversal of weight in wt mice fed a 40% HFD, treated with GIP mAbs.

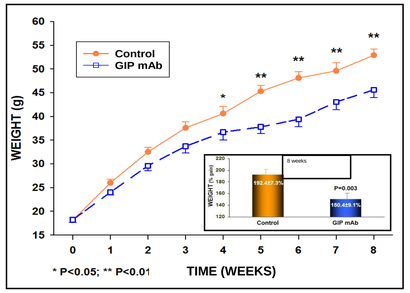


Fig. 6. Effects of GIP mAbs on weight gain in hyperphagic, leptin-deficient (*ob/ob*) mice fed normal mouse chow.

Results

- Wild-type mice treated with PBS gained significantly more than mice injected with GIP mAbs. (Fig. 1). No difference in food consumed was detected between the 2 groups (Fig. 2).
- MRI demonstrated that GIP mAb-treated mice had significantly less subcut. (P<0.001), omental (P<0.001), and liver fat (P<0.03) than controls (Fig. 3). Mice treated with GIP mAbs also had a significantly improved lipid profile (Fig. 4). Finally, basal hyperinsulinemia and the IP glucose tolerance test normalized in GIP mAb-treated mice, consistent with the reversal of pre-diabetes (Data not shown).
- In the second portion of the study, wt mice fed a 40% HFD and PBS continued to gain weight (+2.1±0.9%), while mice administered GIP mAbs lost 4.1±1.4% BW (P<0.01) (Fig. 5).
- ob/ob mice in both groups fed normal mouse chow consumed similar amounts of food, and significant differences in weight were detected by week 4. At the end of 8 weeks, the group administered PBS and GIP mAbs gained 250.4±9.1% and 192.4±7.3%, respectively, a reduction of 21.9% in the latter group (P<0.01)(Fig.6).

Summary and Conclusion

- A specific GIP mAb effectively attenuates weight gain in mice fed a HFD while decreasing fat deposition and lipid profile.
- In addition, GIP mAbs can effectively produce consistent, linear weight loss in obese wt mice without affecting food consumption.
- Finally, GIP mAbs can prevent weight gain in hyperphagic mice without any effect on food consumption.
- The results of these studies support the hypothesis that a reduction in GIP signaling using specific GIP mAbs decreases body weight and improves the lipid profile without suppressing food intake. GIP mAbs might thereby provide a novel, effective method for the treatment and prevention of obesity.

Poster presented at the American College of Gastroenterology (ACG) Annual Meeting, October 21 – 26, 2022, Charlotte, North Carolina, US