Supplemental Figure Legends

Supplemental Figure 1. Wild type C57BL/6 mice were fed Lean (3.0 kcal/g, 12.7% from fat and 58.5% from carbohydrate) or high fat (HF; 5.1 kcal/g, 61.6% from fat and 20.3% from carbohydrate) diets starting at 4 weeks of age. Guanylin was quantified by immunoblot analysis in proximal and distal colon at 16 weeks of age. Results represent the mean ± SEM of at least 5 mice. *, p<0.05; **, p<0.01.

Supplemental Figure 2. Wild type C57BL/6 mice were fed Lean (3.0 kcal/g, 12.7% from fat and 58.5% from carbohydrate) or high fat (HF; 5.1 kcal/g, 61.6% from fat and 20.3% from carbohydrate) diets starting at 4 weeks of age. GUCY2C was quantified by qRT-PCR in proximal and distal colon at 20 weeks of age. Results represent the mean ± SEM of at least 4 mice.

Supplemental Figure 3. Wild type C57BL/6 mice were fed Lean (3.0 kcal/g, 12.7% from fat and 58.5% from carbohydrate), high carbohydrate (HC; 3.8 kcal/g, 10.2% from fat and 71.8% from carbohydrate) or high fat (HF; 5.1 kcal/g, 61.6% from fat and 20.3% from carbohydrate) diets starting at 4 weeks of age. (A) Daily caloric intake in mice at 12 wks of age. (B) Body weight at 20 wks of age (16 wks on diet). Only HF, but not HC, diet induced the obese phenotype in mice.

Supplemental Figure 4. (A-C) Wild type C57BL/6 mice were fed Lean or HF diets for 20 wks starting at 4 wks of age. (A) Daily caloric intake in mice at 24 wks of age demonstrating that all mice on a HF diet consumed equivalent excess daily calories. (B) Body weights at 24 wks of age (20 wks on diets) reveal that some mice on a HF diet resist developing obesity (HF-R). (C) Guanylin (GUCA2A) mRNA expression was reduced by a HF diet equally in mice sensitive and resistant to obesity.
**Supplemental Figure 5.** Balb/c mice were fed Lean or HF diets starting at 4 wks of age. (A) Daily calorie intake at 16 wks of age (12 wks on diet) revealed that mice on a HF diet consumed excess calories. (B) Body weight at 16 wks of age revealed that Balb/c mice resist the obese phenotype, and mice on a HF diet have weights that are comparable to those on a Lean diet. (C) Relative guanylin protein expression in mice quantified by immunoblot analysis and normalized to villin1 revealed that consumption of excess calories, in the absence of obesity, was associated with suppression of guanylin expression.

**Supplemental Figure 6.** (A-B) Mice deficient in leptin (ob/ob) were hyperphagic on a Lean diet. Wild type C57BL/6 mice on an ad lib Lean diet served as controls and the caloric intake of this group (~9 kcal/day/mouse) was used to define the daily calorie restriction for ob/ob mice. Both dietary cohorts [calorie-restricted (9 kcal lean diet per day) and ad lib] of ob/ob mice were obese at study initiation. (A) Daily caloric intake in mice at 6 wks of age demonstrating that ob/ob mice on caloric restriction consumed the same daily calories as wild type mice on an ad lib diet. (B) Growth curve from 6-12 wks of age demonstrating that ob/ob on a calorie-restricted maintained body weights in the obese (>40 g) range. (C) Although ob/ob mice on a restricted diet are obese, they express higher levels of guanylin mRNA compared to ob/ob mice on an ad lib diet consuming excess daily calories.

**Supplemental Figure 7.** (A-B) Wild type C57BL/6 mice were fed Lean or HF diets starting at 4 wks of age. At 20 wks, mice in the HF-reversed cohort were switched to a Lean diet (HF-Lean), and diets continued for another 4 wks before sample collection. (A) Body weights at 24 wks demonstrated that while mice switched from a HF to a Lean diet maintained a lower weight than those on a continuous HF diet, the HF-Lean cohort maintained weights that were, on
average, obese (~40 g). (B) Relative guanylin (GUCA2A) mRNA expression in mice analyzed by RT-PCR and normalized to villin1 revealed that switching mice from a HF to a Lean diet reconstituted guanylin mRNA expression.
Supplemental Figure 1
Supplemental Figure 2
Supplemental Figure 3

A

B

Lean HC HF

Lean HC HF

kcal / day

weight (g)

***

***

n.s.

***

***
Supplemental Figure 4
Supplemental Figure 5

A. Energy intake (kcal/day) significantly differs between Lean and HF groups (**). 

B. Weight (g) does not show a significant difference between Lean and HF groups (n.s.). 

C. Guanylin protein expression is significantly lower in the HF group compared to the Lean group (**).
Supplemental Figure 6
Supplemental Table 1. Mouse diet calorie and nutrient content.

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<tr>
<th>Calorie Content</th>
<th>Lean</th>
<th>High Carbohydrate</th>
<th>High Fat</th>
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<tr>
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<tr>
<td>Carbohydrate (% energy)</td>
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<td>Energy (kcal/g)</td>
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