**Supplemental Figure Legends**

**Supplemental Figure 1. Relative guanylin expression in proximal (PC) and distal (DC) colons of mice on lean or high fat (HF) diets.** 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. Relative GUCY2C expression in proximal (PC) and distal (DC) colons of mice on lean or high fat (HF) diets.** 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. Daily calorie intake and body weights in mice on lean, high carbohydrate (HC), or high fat (HF) diets.** 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.** **Daily calorie intake, body weights, and guanylin expression in wild type and obesity-resistant (HF-R) C57BL/6 mice on lean or high fat (HF) diets.** (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.** **Daily calorie intake, body weights, and guanylin expression in Balb/c mice on lean or high fat (HF) diets.** 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.** **Daily calorie intake, body weights, and guanylin expression in *Ob/Ob* mice on ad libitum or calorie-restricted diets.** (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 calorie 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.** B**ody weights and guanylin expression in C57BL/6 mice on a lean or high fat (HF) diet, or switched from a high fat to a lean diet (HF-Lean).** (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.