GUT MICROBIOTA CONTRIBUTES TO THE BENEFICIAL METABOLIC EFFECTS OF GELESIS HYDROGEL TECHNOLOGY

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INTRODUCTION

- Gelesis' Oral superabsorbent hydrogels (OSH) are crosslinked cellulose-based materials that expand upon hydration in gastrointestinal tract and are engineered to mimic the mechanical properties of masticated vegetables[1, 2].
- One OSH prototype, denoted Gel-B, was tested in both preventative and treatment settings in murine models of diet-induced obesity[3, 4].
- Gel-B administration blunted weight gain, reversed gut atrophy, improved metabolic parameters (glucose and insulin tolerance tests; GTT and ITT) and restored barrier function[3, 4].
- In tandem with these metabolic improvements, Gel-B (2% and 4%) induced several changes to the fecal microbiota[5], including:
  - Restoration of the Bacteriodetes:Firmicutes ratio
  - Decrease in Actinobacteria
  - Increase in Verrucomicrobia (exclusively *Akkermansia muciniphila)*

OBJECTIVE

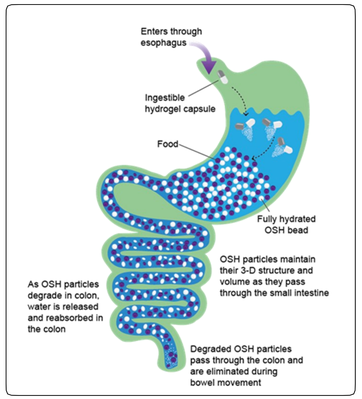
- In this study, we employed intestinal microbiota transfer to investigate the functional role of the gut microbiota to partially explain the protective metabolic effects associated with Gel-B administration.

METHODS

- Metabolic disease was induced in two cohorts of male C57BL6/J mice (termed **Donors** and **Recipients**) via consumption of a high fat, high cholesterol diet (HFHCC; 39.6% fat, 1% cholesterol, 42g/L fructose/glucose *ad lib*) for 10 weeks.
- After 10 weeks induction, Donors either continued HFHCC (n=8) or were treated with HFHCC+Gel-B (2 and 4%; n=8 per group) for 6 additional weeks.
- Fecal samples were processed from Donors every other day during weeks 2-6 of treatment. These samples were homogenized in PBS (100 mg feces/1mL PBS) and centrifuged at 500g for 3 min to remove debris.
- After 12 weeks induction, Recipients received intestinal microbiota transfer via 200µL gavage from HFHCC (n=8) or HFHCC+Gel-B (2 and 4%; n=8 per group) Donors every other day for 4 weeks.
- Change in body weight was measured weekly, and glucose and insulin tolerance tests (GTT and ITT) were performed one week prior to sacrifice.

Figure 1. Oral superabsorbent hydrogels (OSH) are released in the stomach where they expand and mix with a meal. OSH retain their structure as they pass through the gastrointestinal tract and are degraded in the colon. In this experiment, the OSH Gel-B was pre-mixed into animal diets at 2% and 4%.

Figure modified from Aronne *et al*. (2021)[1].



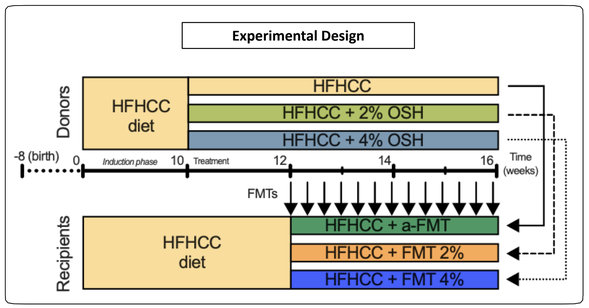


Figure 2. Intestinal microbiota was collected from Donor fecal samples obtained after two weeks treatment with either 2% Gel-B, 4% Gel-B, or untreated control HFHCC diet.

RESULTS

- At 4 weeks, HFHCC-corrected % body weight difference in Recipients was -10.8% and -9.6% for the 2% Gel-B-derived IMT (p=0.02), and 4% Gel-B-derived IMT (p= 0.02) respectively (Figure 3).
- Glucose excursions, $AUC_{0\text{-}2h}$ from GTT, were significantly reduced in both Recipient groups (Figure 4; p=0.01 for both 2% and 4% Gel-B-derived IMT). The $AUC_{0\text{-}2h}$ from ITT were significantly increased in the 4% Gel-B-derived IMT Recipients (p=0.04) and trended for the 2% Gel-B-derived IMT group (p=0.13).

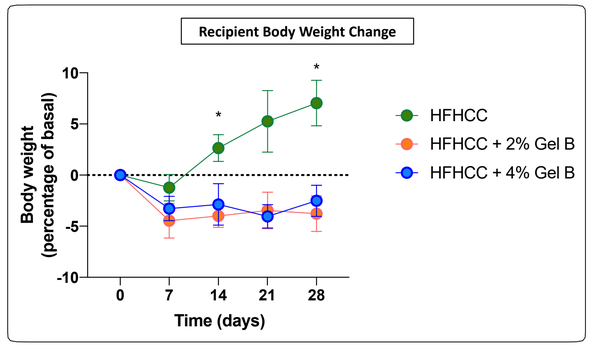


Figure 3. Weight gain over 4 weeks in animals receiving IMT. Recipients HFHCC-derived microbiota continued to gain weight, while recipients of Gel-B-derived microbiota lost weight (*p=0.02).

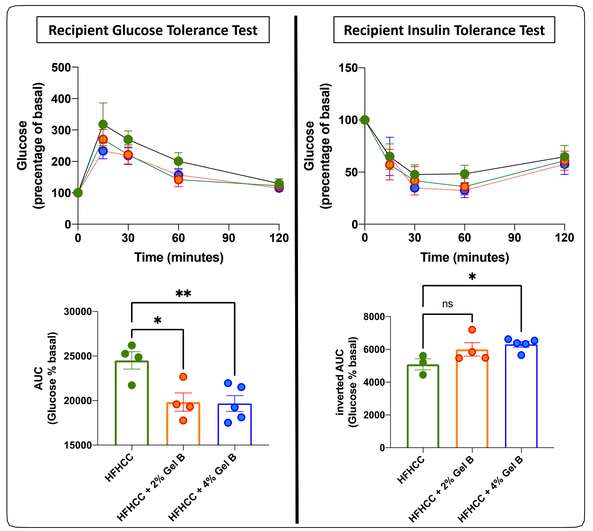


Figure 4. Glucose tolerance test (left panel) and insulin tolerance test (right panel) in animals receiving IMT. Glucose tolerance improved in both 2% and 4% IMT recipients (*p=0.01; **p=0.01), while insulin sensitivity improved in 4% IMT recipients (*p=0.04).

CONCLUSIONS

- **The beneficial metabolic effects associated with Gel-B treatment are, in part, explained by changes in the gut microbiota.**
- **Specifically, intestinal microbiota transplant from animals consuming Gel-B:**
  - **Induced weight loss compared to HFHCC microbiota recipients.**
  - **Improved measurements of both glucose tolerance and insulin sensitivity compared to HFHCC microbiota recipients.**
- **Gel-B induced changes to gut microbiota will be defined, and the durability of engraftment will be explored in future studies.**

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DISCLOSURES

M. Rescigno, A. Silvestri, A. Gil-Gomez : none. **E. Chiquette, B. Jones** are employed by Gelesis Inc and own stock options. **A. Sannino, C. Demitri** are employed by Gelesis S.r.l. and own stock options.

GELESIS