

# Oral Superabsorbent Hydrogel Expands *Akkermansia* and Drives Changes to the Gut Microbiota Associated with Metabolic Benefits in a Mouse Model of Diet Induced Obesity

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## INTRODUCTION

- Gelesis oral superabsorbent hydrogels (OSH) are cellulose-based structures that mimic 3D mechanical properties of masticated vegetables during digestive system transit (Figure 1)<sup>1,2</sup>.
- We previously developed a murine diet-induced obesity (DIO) model and observed improvement in several metabolic parameters after treatment with the OSH Gel-B<sup>2,3</sup>.
- In these studies, Gel-B administration blunted weight gain, reversed gut atrophy, improved metabolic parameters (glucose and insulin tolerance tests; GTT and ITT) and restored barrier function<sup>2,3</sup>.
- Additionally, Principal Coordinates Analysis (PCoA) revealed consistent changes to the microbiome associated with Gel-B (2% and 4%) consumption compared to controls<sup>2</sup>.

**Figure 1.** OSH particles expand and mix with ingested food in the stomach upon consumption. These particles retain their structure as they pass through the small intestine and are degraded in the colon prior to elimination. The OSH used in these experiments was not in pill form but was pre-mixed into the experimental diets.

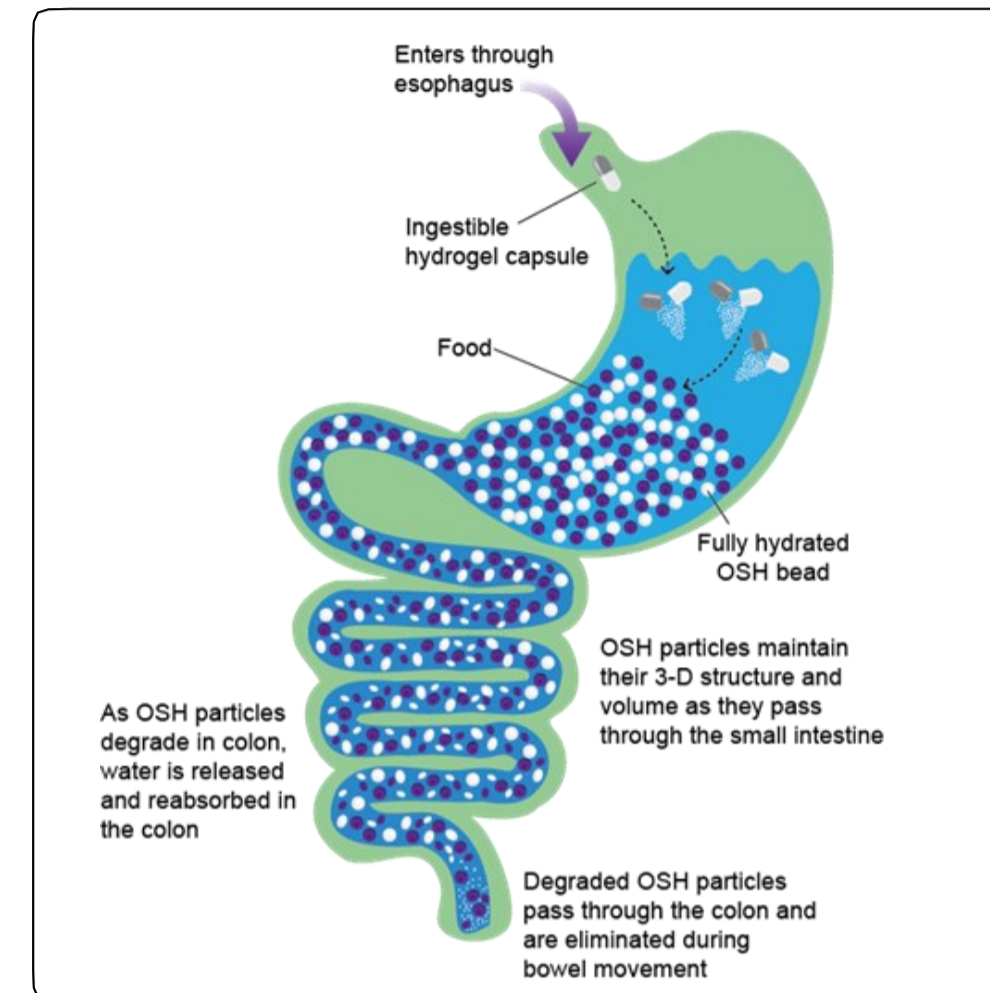


Figure modified from Reference 1 (Aronne *et al.* 2021)

## OBJECTIVE

- This study aimed to define the gut microbiota associated with observed metabolic improvement and uncover how Gel-B may be driving compositional changes to these communities.

## METHODS

### Animal Model

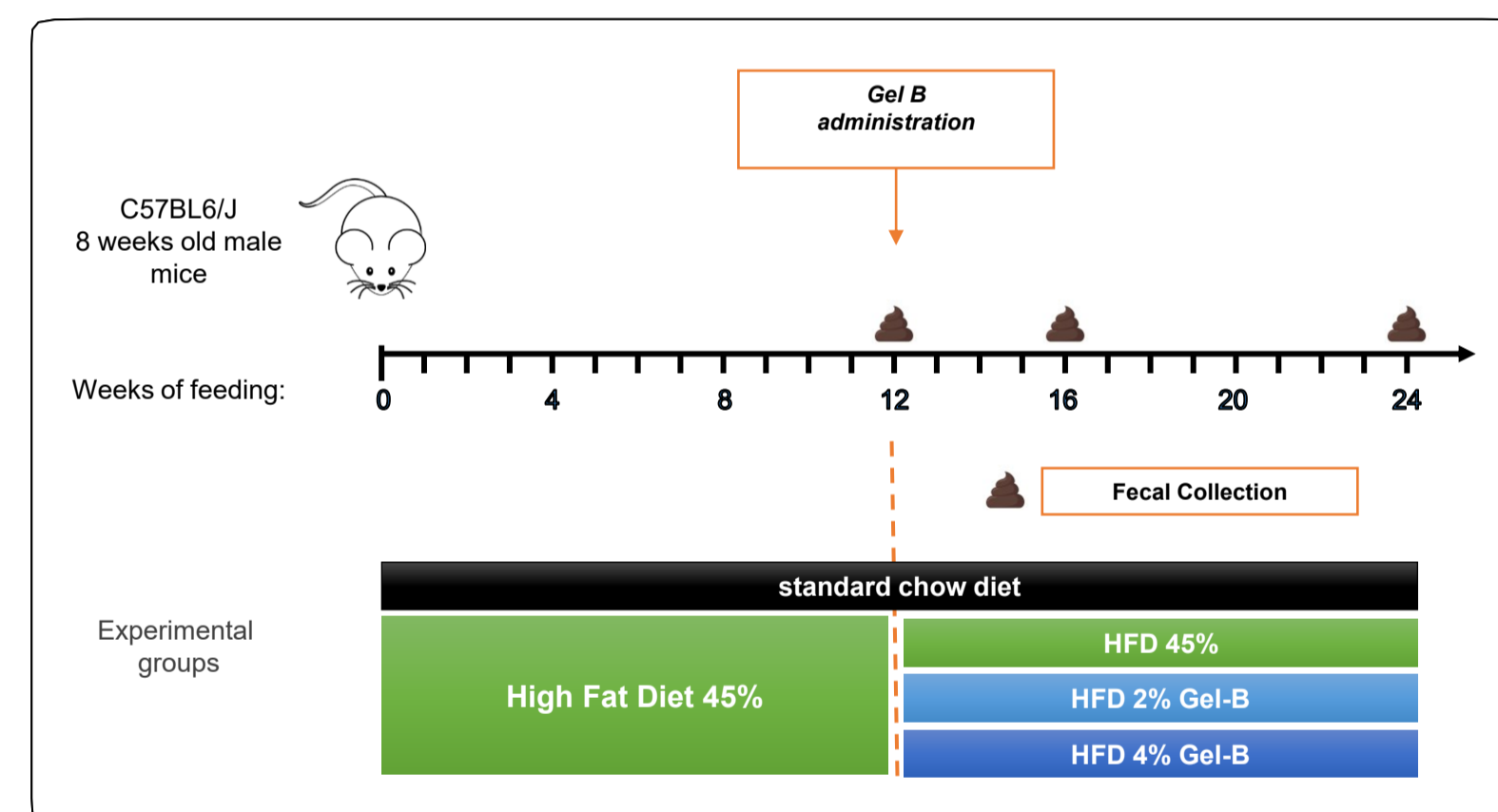
- Male C57BL/6J wild type mice were fed HFD (45% fat) for 12 weeks (Figure 2).
- From week 12 to 24, mice were treated with either HFD alone (n=20), HFD+Gel-B 2% (n=18) or 4% (n=18). A control group (n=21) remained on chow alone.
- Fecal samples were collected at experiment week 12 (treatment week 0), 16 (treatment week 4) and 24 (treatment week 12).

### Bioinformatic Pipeline

- Whole-genome shotgun sequencing was performed, and count tables were generated using the CosmosID Metagenomics Cloud.
- Statistical modeling was performed in R.

### *Akkermansia muciniphila* Growth Study

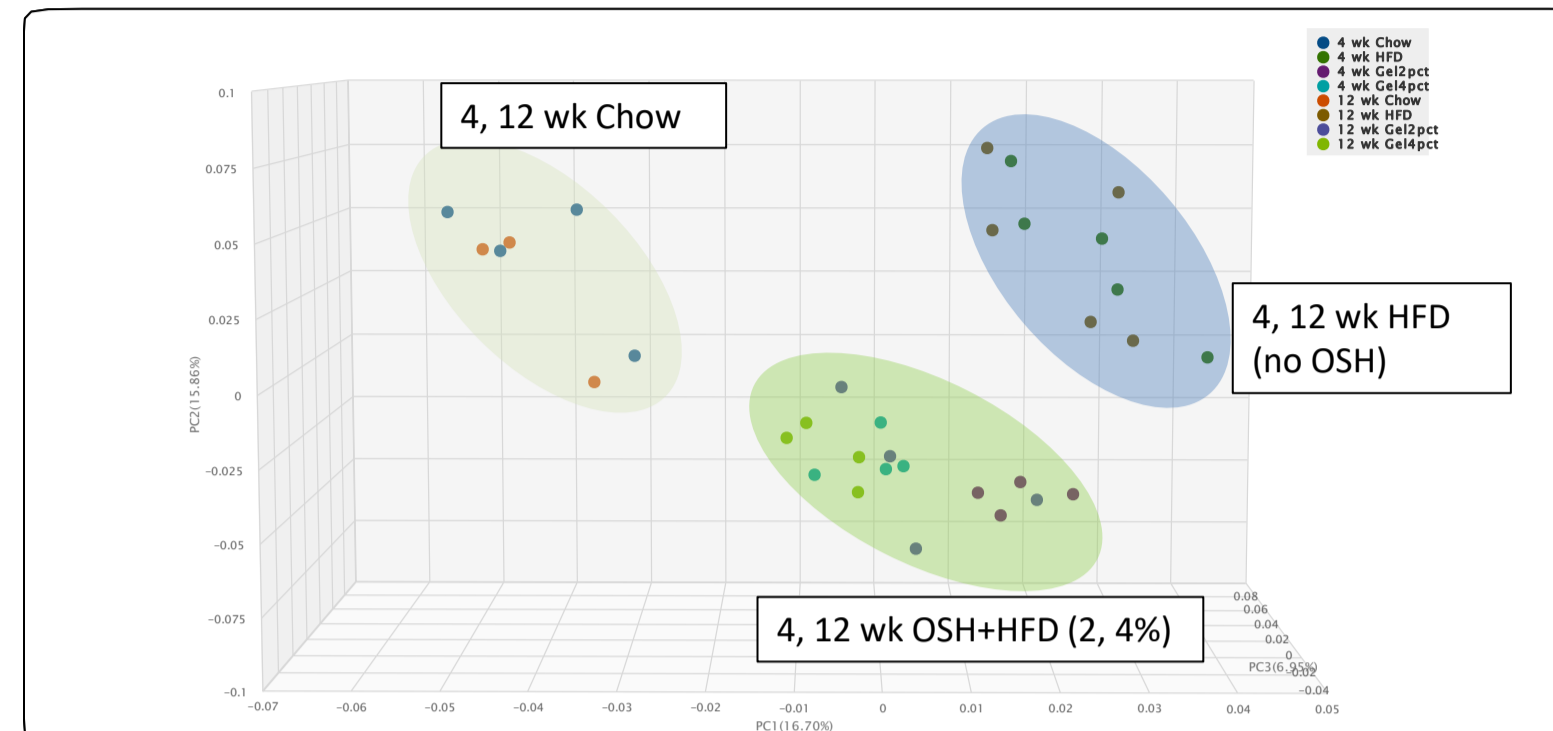
- Akkermansia muciniphila* was added to anaerobic culture broth (Thermo Scientific™ CM0957B) supplemented with 0.05% mucin and 4g/L glucose.
- Gel-B, CMC, citric acid, CMC+citric acid, or acrylic gel were added to culture medium, and OD600 was measured at 24, 48 and 72h.



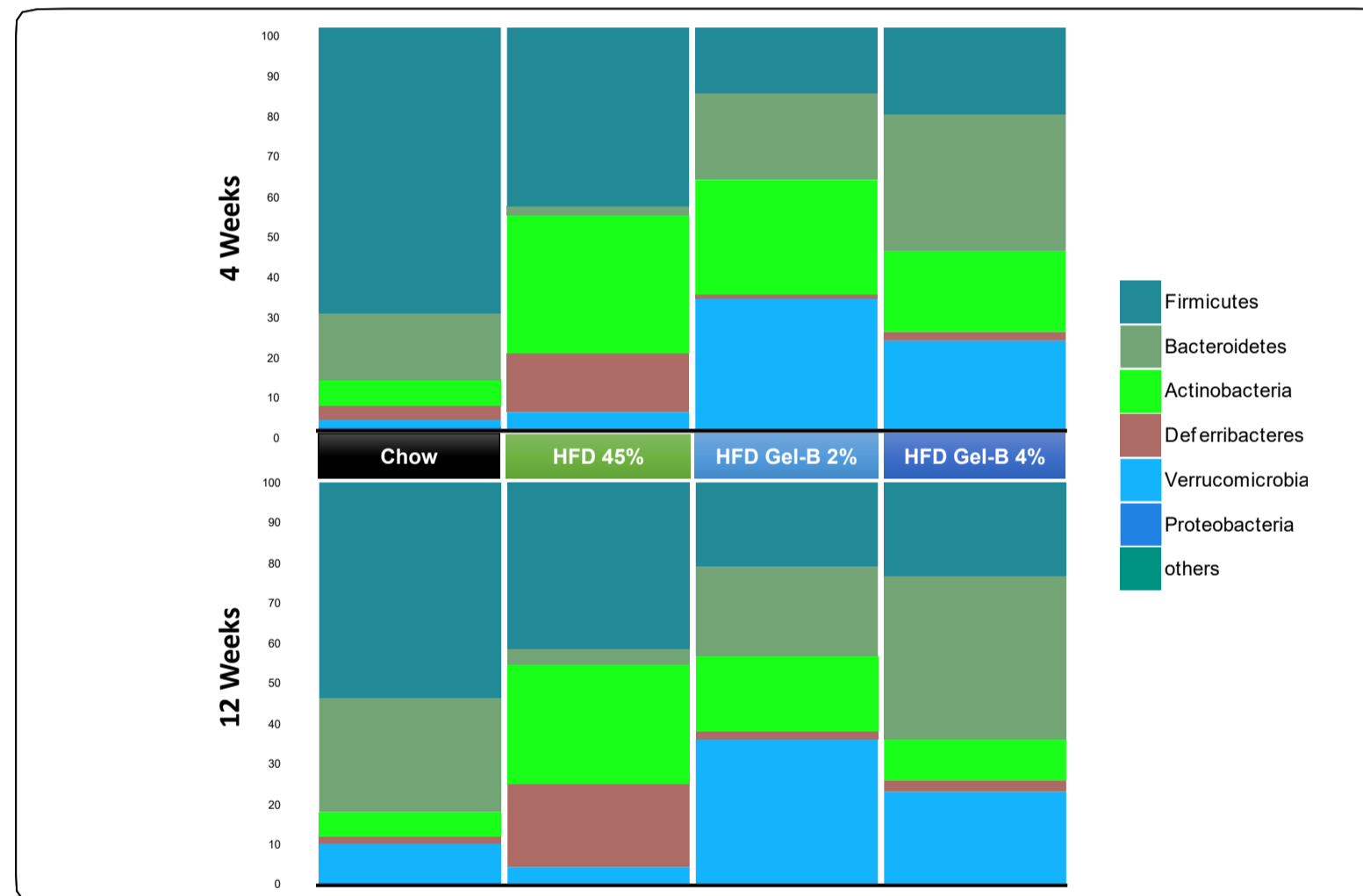
**Figure 2.** Experimental design. 12 weeks of HFD induced obesity in animals. Fecal samples were collected after 0, 4, and 12 weeks treatment.

## RESULTS

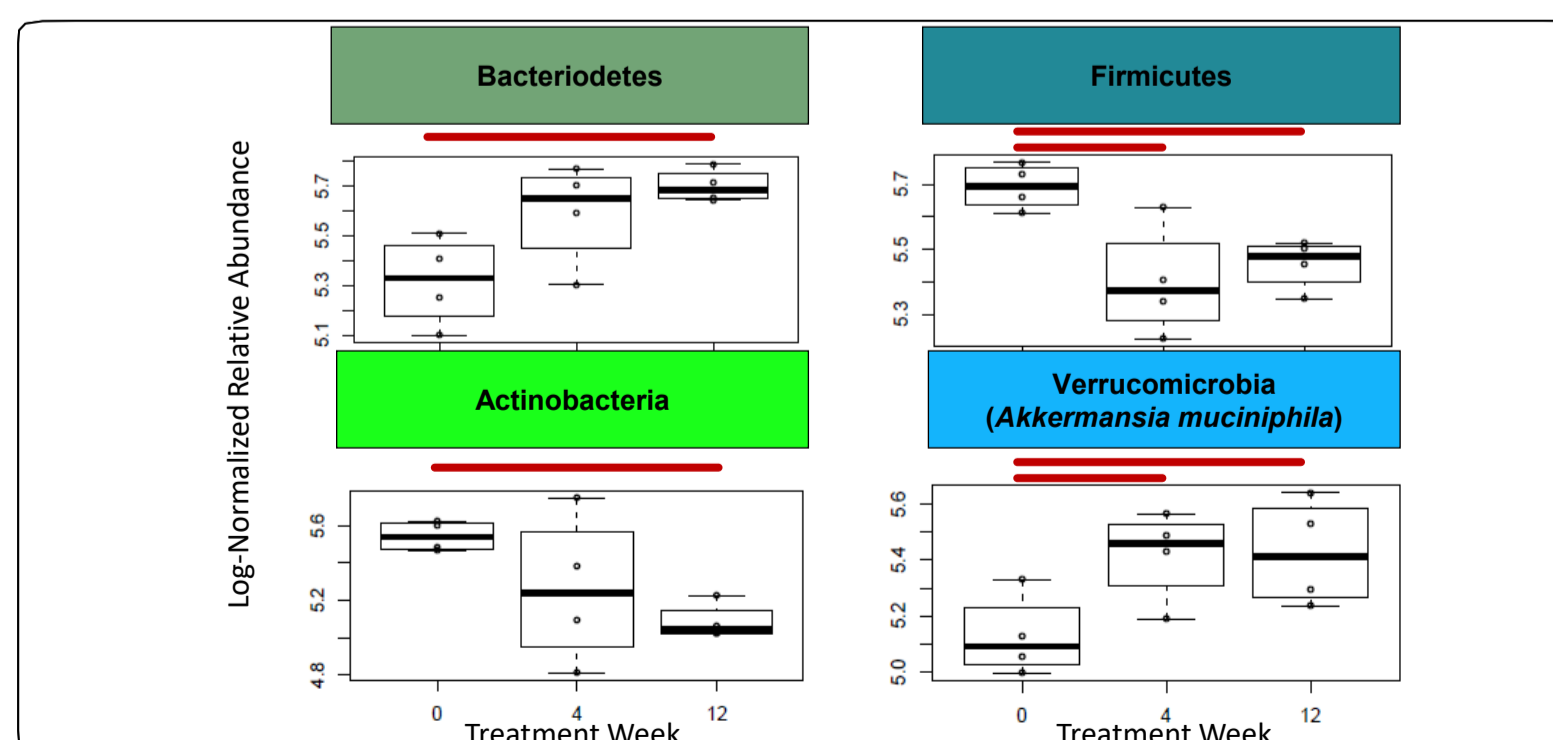
- On PCoA analysis, gut microbiota of the groups showed significant separation ( $p < 0.01$ ; ADONIS permutation; Figure 3)
- By 4 weeks, Phylum-level changes in the microbiome were observed in Gel-B compared to chow and HFD (Figure 4)
- At 12 weeks, relative to HFD, treatment of Gel-B 4% increased relative abundance of Bacteroidetes ( $p < 0.02$ ) and Verrucomicrobia (exclusively *Akkermansia muciniphila*;  $p = 0.05$ ), and decreased Firmicutes ( $p < 0.01$ ) and Actinobacteria ( $p < 0.01$ ) (Figure 5).
- Addition of Gel-B to growth media increased *Akkermansia muciniphila* growth over growth media alone ( $p < 0.01$ ); non-crosslinked Gel-B backbone did not increase AM growth ( $p < 0.01$ ) (Figure 6).



**Figure 3.** PCoA revealed grouping of the animals consuming chow (grey oval), HFD alone (blue oval) and 2, 4% OSH (green oval). Separation between groups was significant ( $p < 0.01$ ; ADONIS permutation).

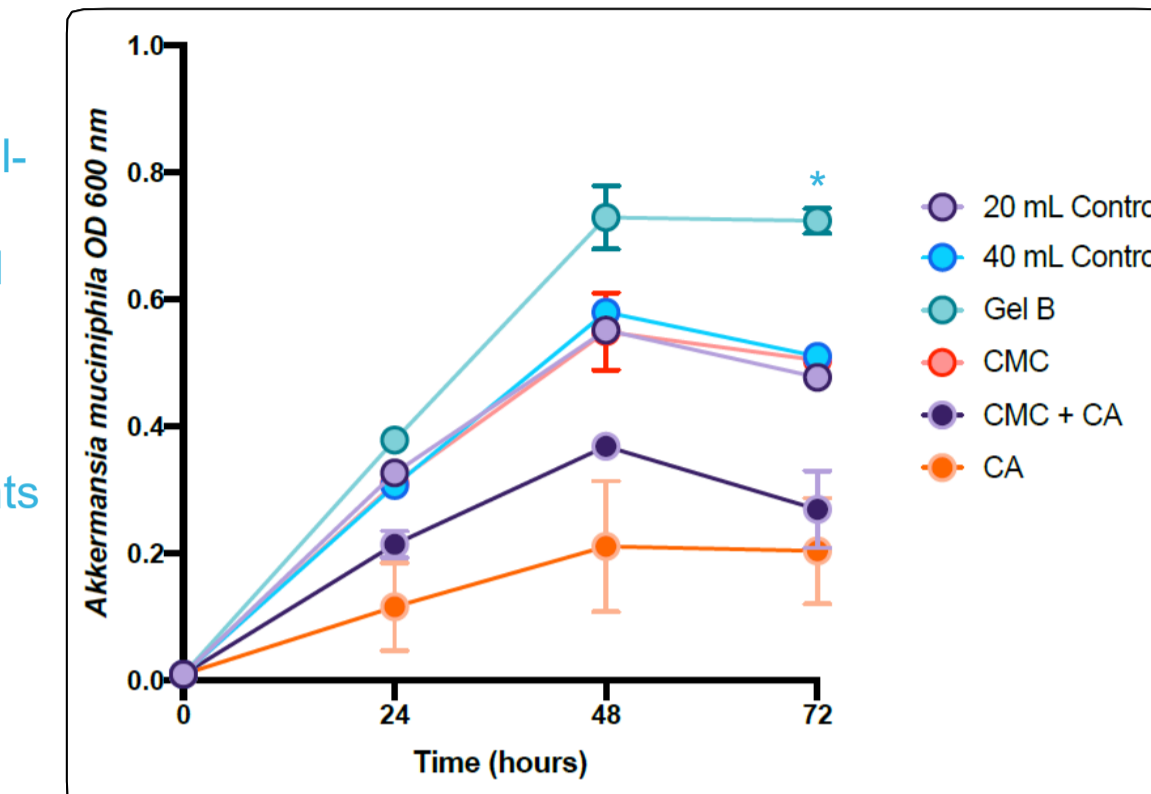


**Figure 4.** Phylum-level semi-quantitative differences in the fecal microbiota between study groups after 4 and 12 weeks of treatment. Quantitative analysis of several phyla of interest is shown in Figure 5.



**Figure 5.** Log-normalized relative abundance of several phyla of interest. Red bars indicate statistically significant changes with  $p < 0.05$ .

**Figure 6. A.** *mutiniphila* growth was increased in Gel-B supplemented media over standard growth media alone ( $*p < 0.01$  at 72h). Moreover, the individual components of Gel-B (CMC and CA - citric acid) did not.



## CONCLUSIONS

- Gel-B treatment induced changes to the gut microbiota in DIO mice that are associated with improved metabolic outcomes. Phylum-level changes include:
  - Restored the Bacteroidetes:Firmicutes ratio, increasing Bacteroidetes and decreasing Firmicutes
  - Decrease in Actinobacteria
  - Increase in Verrucomicrobia, driven exclusively by *Akkermansia muciniphila*
- Gel-B addition to *Akkermansia muciniphila* growth medium potentiated its expansion *in vitro*, while CMC fiber did not.
  - Further, uncrosslinked Gel-B components (CMC and citric acid) did not support growth, indicating that the 3D structure of Gel-B is required for this phenomenon.
- Looking forward, we plan to further explore the mechanisms by which the physical and mechanical properties of Gel-B influence microbiome community structure.

## REFERENCES

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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.

