The Impact of the Gut and Reproductive Tract Microbiomes on Endocrine Function and Female Infertility

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Background

- Females with chronic gastrointestinal-related immune disorders, such as inflammatory bowel disease (IBD), experience higher rates of infertility than females without these disorders.[1]
  - This has implications for the health and wellbeing of females desiring children.[2]
- Previous research has shown that IBD is accompanied by alterations in the gut microbiota.[3]
  - There is evidence that the gut microbiota impacts the function of the hypothalamic-pituitary-gonadal (HPG) axis.[4,5,6]
    - The HPG axis controls the rate of secretion of ovarian hormones.[7]

We hypothesize that changes in the gut microbiota, which is altered in chronic inflammatory states including IBD, is associated with changes in the activity of the HPG axis, leading to increased infertility in females.

Methods

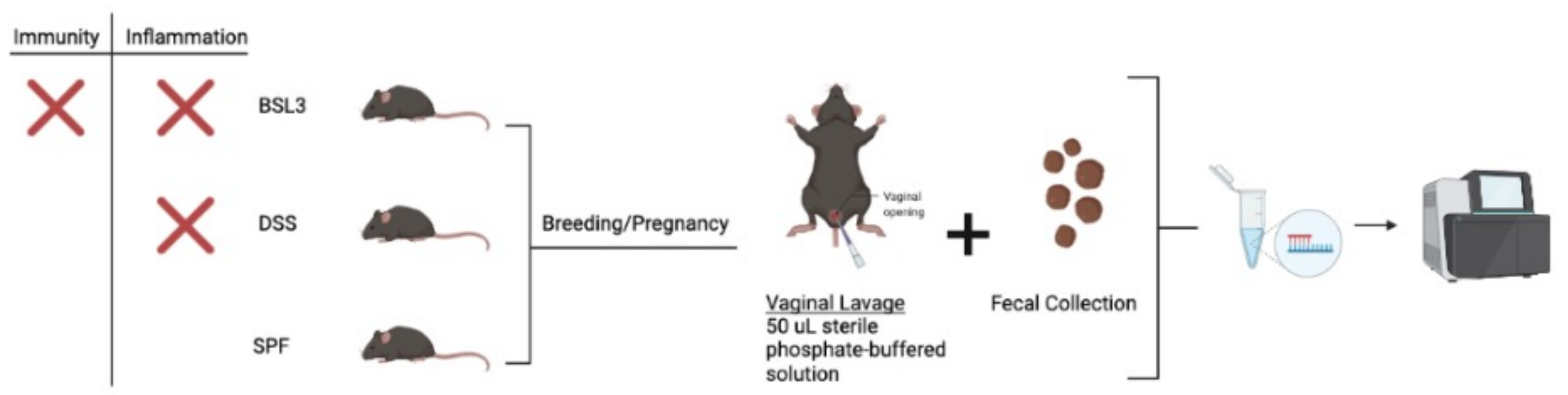

Figure 1: Murine model for the generation of specific-pathogen-free (SPF), intestinal inflammation (DSS), and human IBD (BSL3) mice. SPF mice served as a control in this model. SPF mice were cohoused with pet store mice for 60 days to generate BSL3 mice, reflecting the human immune system. Proper inflammatory induction in BSL3 mice was determined in Dr. Vaiva Vezys' laboratory. Dextran sulfate sodium (DSS) was administered intermittently to induce intestinal inflammation over a 55-day period. Female mice underwent daily estrus cycle assessment. Lavage and fecal samples were collected during the diestrus phase. Female mice also underwent peripheral blood collections to monitor hormonal fluctuations (progesterone, estradiol, LH, FSH, AMH), which were analyzed by Dr. Eugenia Schmidt's laboratory. Following delivery, pups were monitored for evidence of IBD, maternal mouse blood was collected, and organs were harvested for further analysis by Dr. Eugenia Schmidt's laboratory.

Analysis

- Microbiota characterized by Illumina next-generation amplicon sequencing of the 16S rRNA gene
- Amplicon sequenced data was processed and analyzed using MSI's package mothur
  - XLSTAT was used to analyze genera of different experimental groups

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Results

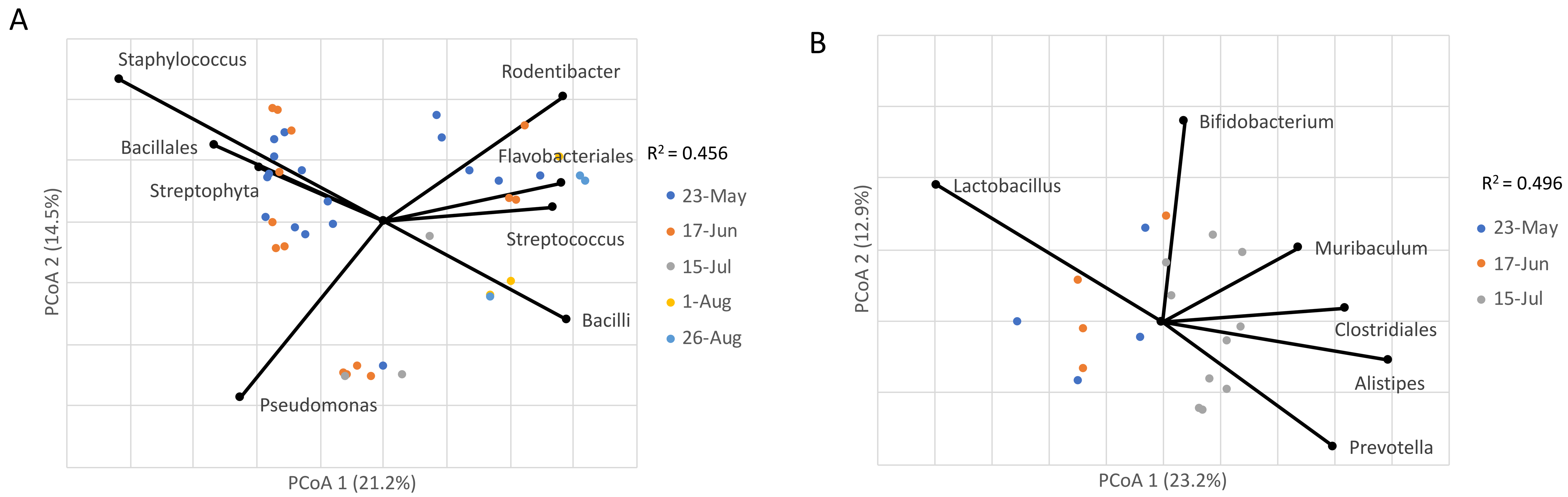

Figure 2: Principal coordinate analysis of Bray-Curtis dissimilarities in fecal and vaginal lavage communities across various timepoints. a) vaginal lavage microbial communities (ANOSIM p<0.001*, R-value=0.418) b) fecal microbial communities (ANOSIM p <0.001*, R-value=0.66) are shown. The most abundant genera that were significantly correlated with x-axis position (Spearman P < 0.05) are shown. R^2 values indicate the accuracy of the plot at summarizing differences in beta diversity.

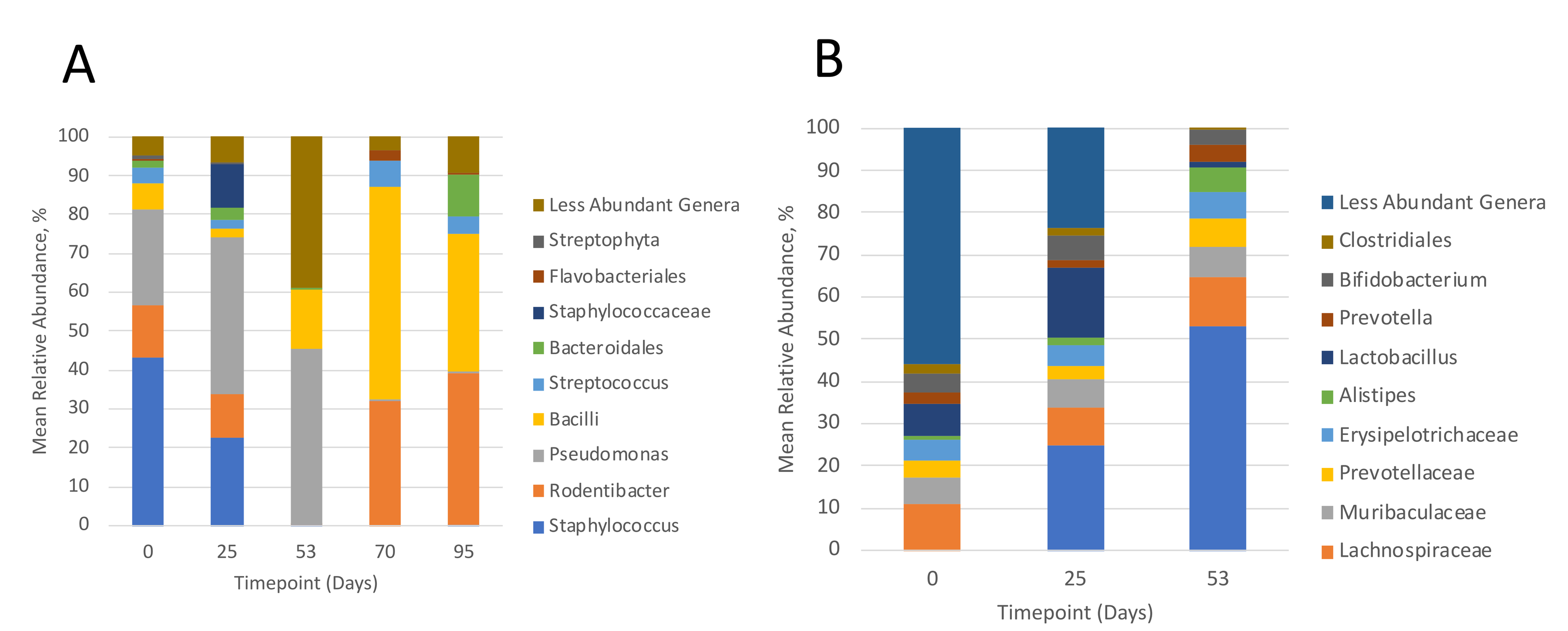

Figure 3: Mean relative abundances (%) of predominant genera that varied across timepoints. A) vaginal lavage microbial composition b) fecal microbial composition

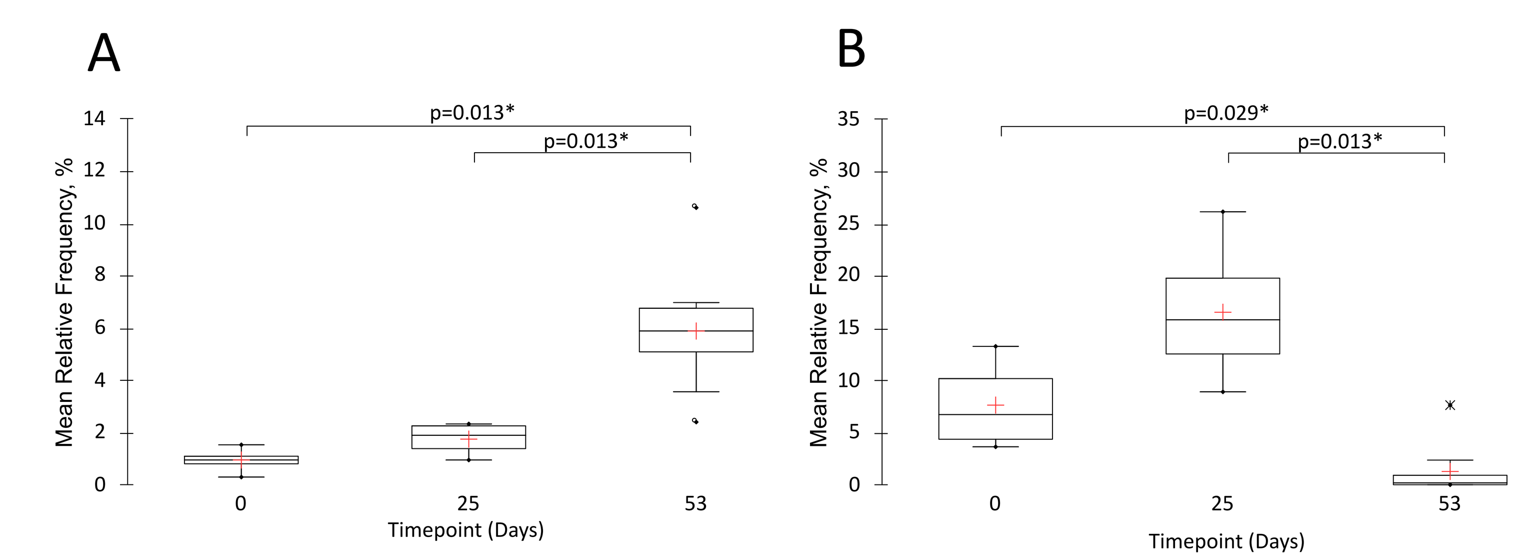

Figure 4: Abundances of predominant genera that varied significantly among timepoints by Kruskal-Wallis test. a) *Alistipes* (p=0.013) b) *Lactobacillus* (p=0.029)

Conclusions

- There was longitudinal variation in genera in the vaginal lavage samples and fecal samples from BSL-3 mice with directional variation among several genera.
- The relative abundance of *Alistipes* was significantly greater in fecal samples from BSL-3 mice with increased time. The relative abundance of *Lactobacillus* was significantly lower in fecal samples from BSL-3 mice with increasing time.
- Mean relative abundances of several genera reveal a shift toward increasing *Rodentibacter* and *Bacilli* abundance in vaginal lavage BSL-3 mice. There was a shift toward a decrease in the abundance of *Lactobacillus* in fecal samples from BSL-3 mice.
- Further examination of endpoint data is needed to confirm the effect of IBD on the gut and reproductive tract microbiota.
- Further analysis of hormonal fluctuations, pup IBD symptoms and weights, and maternal mouse organs is needed to correlate these findings with increased female infertility.