Microbiome and the Host Immune Response Signatures in the Gut Environment and their Influence on Colonization with *Candida*.

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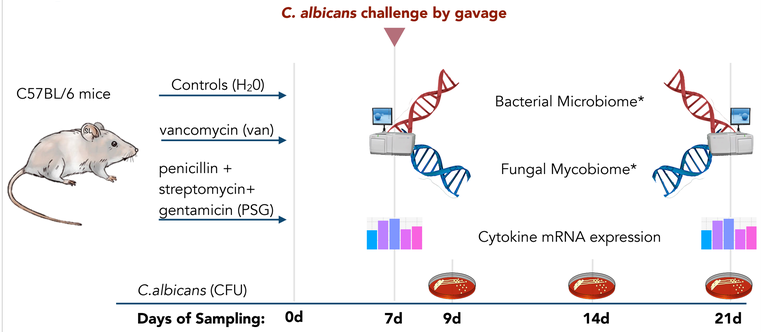
Motivation and Hypotheses

- Fungi and bacteria mutually influence each other by competing for nutrients and interacting through metabolites and quorum sensing molecules.
- Both contribute to gastrointestinal (GI) homeostasis through modulation of the host immune response.
- Host immune response can also modulate the composition of the bacterial and fungal flora.
- Unlike humans, mice are not normally colonized with *Candida albicans*, unless the resident GI flora is perturbed by the administration of oral antibiotics.
- We hypothesized that antibiotic induced changes in the bacterial and fungal microbiome and in the GI immune response influence *C. albicans* colonization.

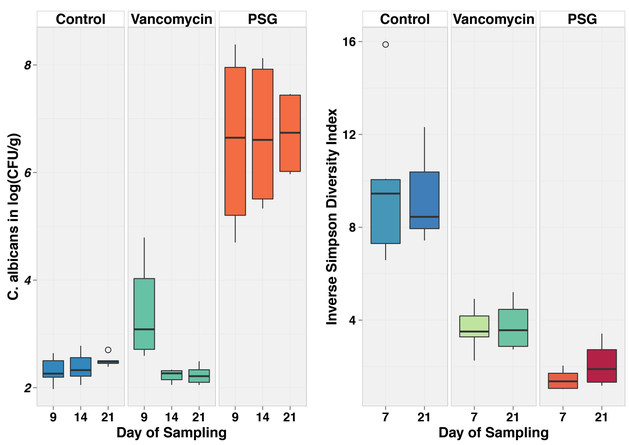
Experimental Methods



*454 pyrosequencing followed by taxonomic classification of the16S bacterial and ITS fungal amplicons with a tailored workflow.

Key Observations and Analyses

- PSG lead to persistent colonization with *C. albicans*.
- Vancomycin lead to transient colonization.
- Both reduced total microbiome diversity.



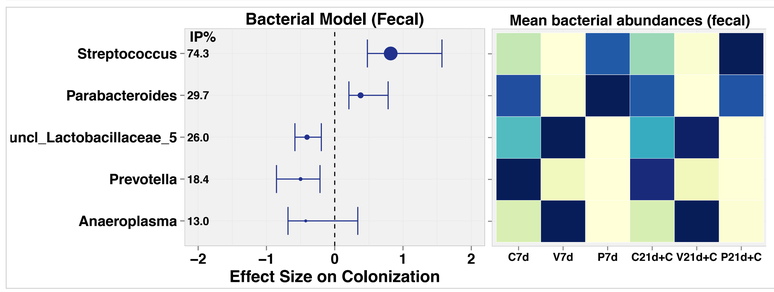
- We built Bayesian multivariable penalized regression models to examine the effect of the microbiome on *C. albicans* colonization and the host immune response at ileal and fecal sites.
- We report the model inclusion probability (IP) as % and effect sizes with their 95% confidence intervals as measures of statistical significance.

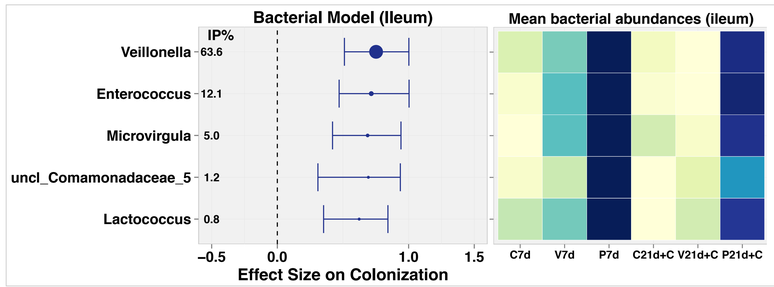
Microbiome Signatures

- **Bacterial Model**: PSG-induced changes in bacterial microbiome were significantly associated with increased *C. albicans* colonization. Changes associated with vancomycin were relatively protective against high levels of colonization

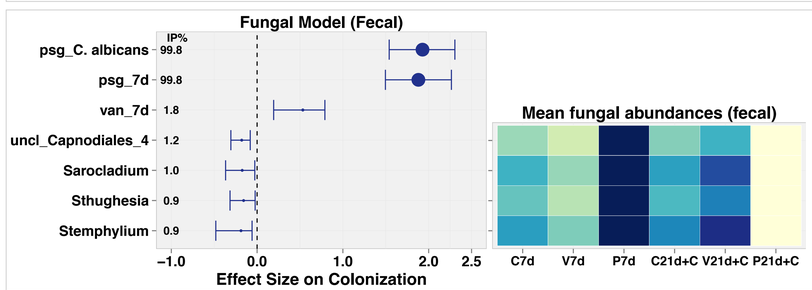
IP% and effect sizes with 95% CI | Mean Abundances

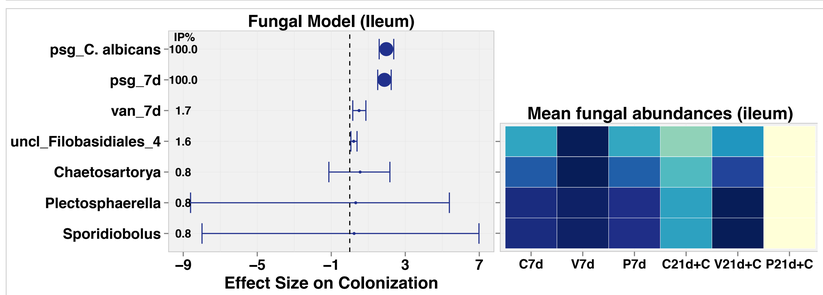
C7d, V7d, P7d: Controls, Vancomycin, PSG at 7days. C21d+C, V21d+C, P21d+C: Controls, Vancomycin, PSG at 21 days after *C.albicans* gavage





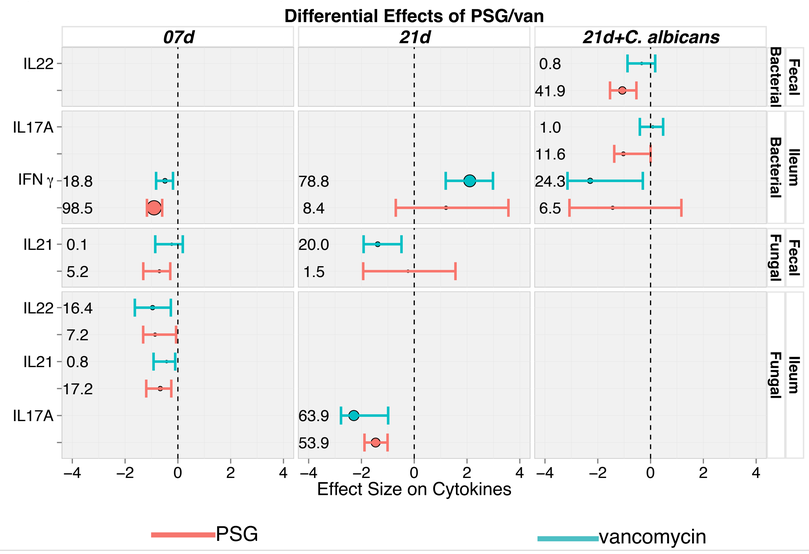
- **Fungal Model:** Fungal flora had minimal direct influence on *C. albicans* colonization while PSG at 7 days and PSG at 21 days after *Candida* gavage had significant effects.



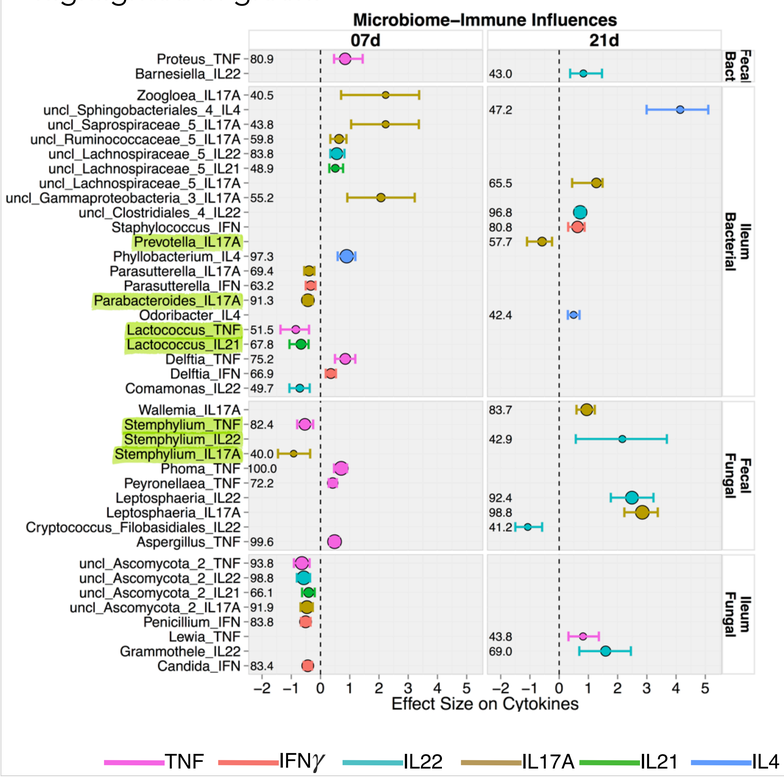


Host Immune Signatures

- PSG and vancomycin were dissimilar in their effects on host cytokines across time points. Compared to vancomycin, PSG significantly diminished IFNγ at 7 days (IP: 98.5% vs. 18.8%) and IL22 at 21 days with *C. albicans* (IP: 41.9% vs. 0.8%).



- A few microbes influential within the colonization models had significant effects on cytokines. These are highlighted in green.



Conclusions

- PSG has complex multi-pronged effects on the bacterial microbiome with significant effects on the host immune response. These predispose the host to *C. albicans* colonization through direct as well as indirect effects.
- In contrast, vancomycin has limited effects on both the bacterial microbiome and the cytokine axes.
- Antibiotic-shaped bacterial communities significantly influence the differential pattern of *C. albicans* colonization between PSG and vancomycin. Concurrent effects of the fungal flora and cytokines on colonization are weaker.
- Microbes most relevant to *C. albicans* colonization are not the top influences on cytokine mRNA levels.

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