Uncovering interactions between oral hormone contraceptives and human gut microbiota

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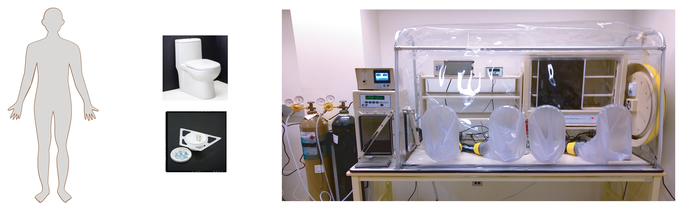
ABSTRACT

The effect of pharmaceuticals, including hormone-based contraceptives, on gut microbiota is both unclear and understudied. Our goal is to evaluate the bidirectional interactions between these drugs and gut microbiota. Specifically, we hypothesize that hormones influence the structure and function of gut microbial communities. Secondly, we predict that microbial community members can metabolize the contraceptive hormones administered in the most common prescriptions. Many progestins used in hormonal contraceptives are prodrugs that have to be metabolically activated by hepatic cytochromes P450s for activation. Along with the interactions of all the hormones and the gut microbiome, we aim to determine the capacity of gut microbiota to activate these prodrugs and whether the gut metagenome might encode microbial pathways that provide an alternative source of prodrug activation, something that is unknown at this point. In this study we use an in vitro culture system exposing gut microbiota to the most common hormones used in hormonal contraceptives. 16S rRNA gene amplification and sequencing will be used to determine the taxonomic effects of the hormones on the microbial communities. Functional assessment will be executed using metagenome prediction. Our preliminary data show changes in taxon abundances and diversity in the presence of hormones. Future work we will include chemical analysis of the hormone prodrugs and active metabolites from microbial communities exposed to only the prodrug.
This in-process project will provide information to the research community on the role of gut bacterial communities in women relying on orally delivered hormones for contraceptive or health purposes. It will also shed light on the potential that these bacterial communities might be influencing the metabolism of progestin prodrugs, something not currently known.

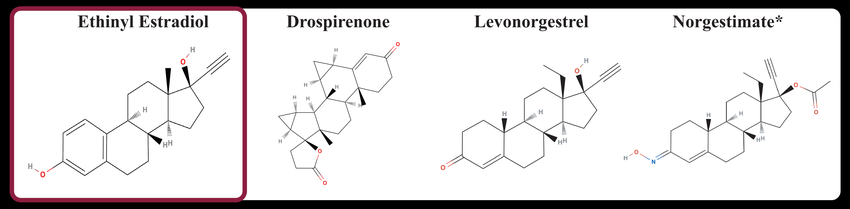
RESEARCH GOAL

Determine whether contraceptive hormones have an effect on bacterial community structure in the gut.

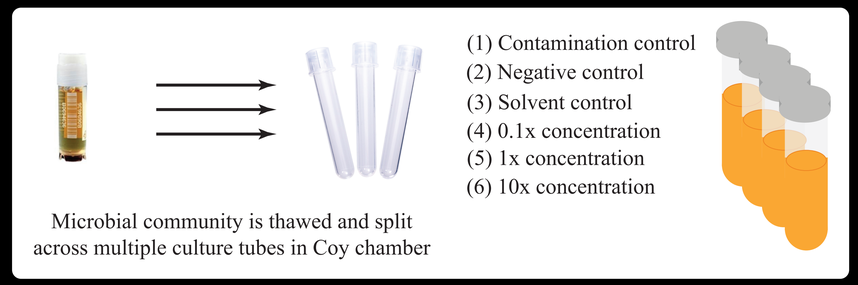
SAMPLE PREPARATION



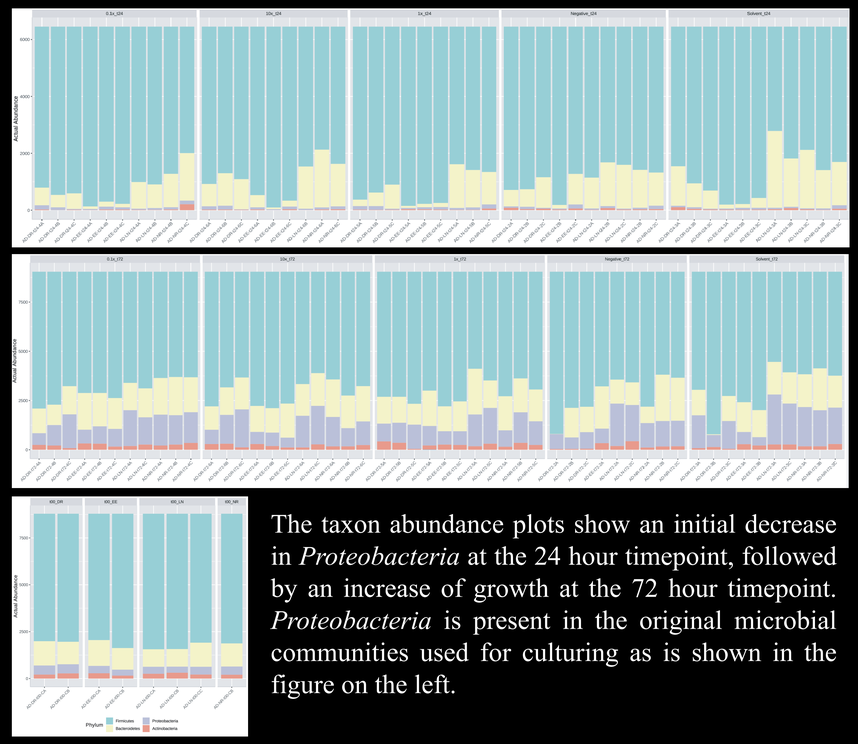
WHICH HORMONES HAVE BEEN TESTED?



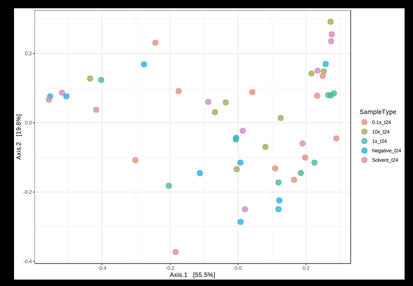
EXPERIMENTAL WORKFLOW

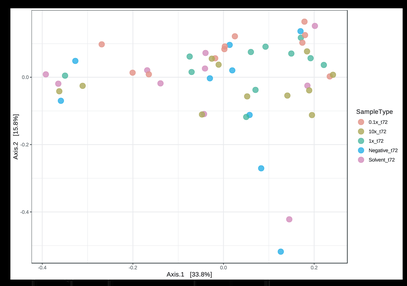


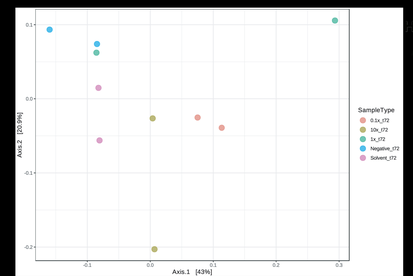
PRELIMINARY RESULTS



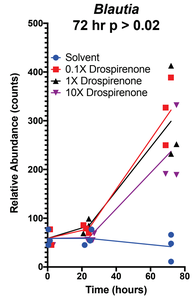
The taxon abundance plots show an initial decrease in *Proteobacteria* at the 24 hour timepoint, followed by an increase of growth at the 72 hour timepoint. *Proteobacteria* is present in the original microbial communities used for culturing as is shown in the figure on the left.







The only significant changes found in alpha diversity plots were due to passage of time, but not as a function of hormone exposure. However, in beta diversity plots a shift can be observed away from the control replicates, indicating the presence of hormone has an effect. Beta diversity plots for all hormones at 24 and 72 hours are shown below, and a plot for levonorgestrel at 72 hours is shown above.



Ethinyl Estradiol		Drospirenone	
Streptococcus	Decrease	*Paraclostridium*	Decrease
Enterococcus	Increase	*Blautia*	Increase
		Intestinimonas	Increase

Levonorgestrel		Norgestimate	
Intestinimonas	Decrease	*Lactococcus*	Decrease
Lachnoclostridium	Decrease	*Turicibacter*	Increase
Lactococcus	Decrease	*Weissella*	Increase
Blautia	Decrease		
Streptococcus	Increase		
Agathobacter	Increase		
Paraclostridium	Increase		

FUTURE WORK

As a continuation of this project we will test additional hormones on microbial communities from additional donors. We will test the combinatorial effects of estrogen and progestins when dosed simulataneously. Several presciption formulations of oral contraceptives contain iron in the form of ferrous fumarate. Further investigation into the role of iron in combination with contraceptive hormones will be addressed. Addtitionally, we will assess whether prodrugs have the same effect on taxon abundance and diversity as activated drugs and if we can chemically detect their presence.

ACKNOWLEDGEMENTS

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