

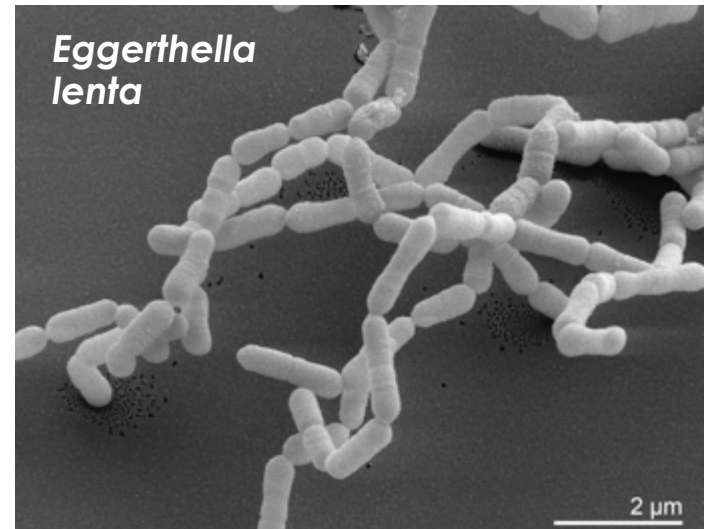
Moving towards a metagenomic basis of therapeutics



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NIH Microbiome Symposium: July 2013

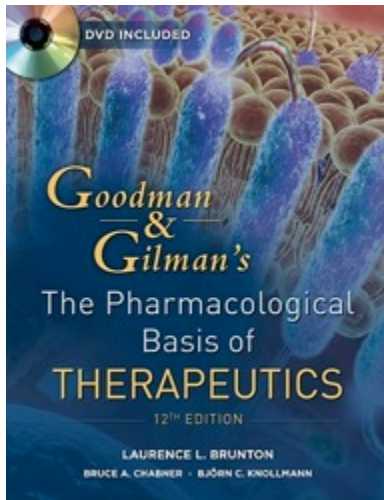


A brief footnote in the pharmacology textbooks



“The microflora residing in the GI tract can metabolize a variety of drugs, which can reduce the amount available for absorption. Hydrolysis of esters and amides, reduction of double bonds, and nitro and diazo groups, dehydroxylation, dealkylation, deamination, acetylation, and esterification are some of [the] metabolic reactions mediated by gut microflora.”

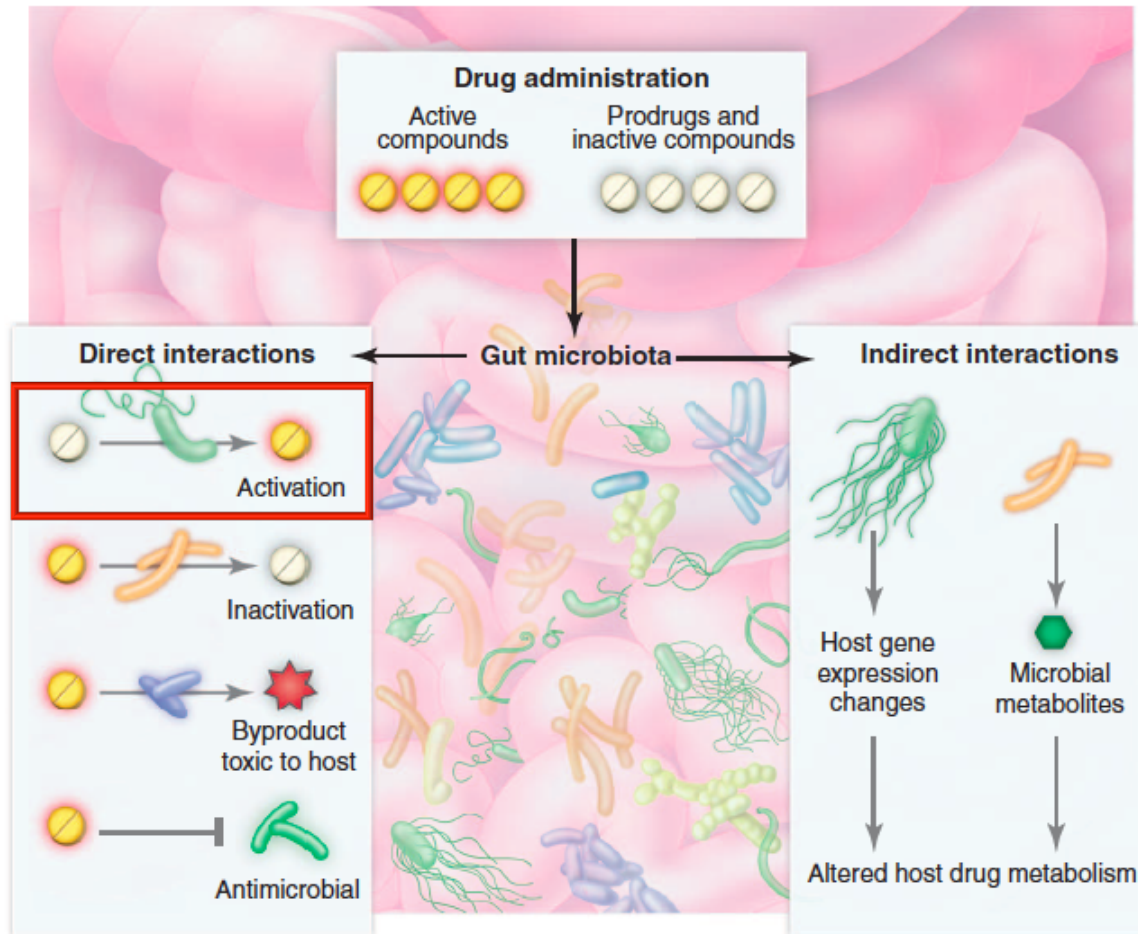
– Handbook of Essential Pharmacokinetics, Pharmacodynamics, and Drug Metabolism for Industrial Scientists



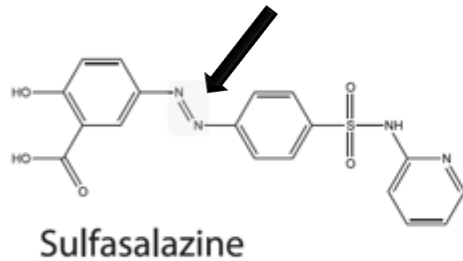
“Drugs in the GI tract may be metabolized by the enzymes of the intestinal flora...before they gain access to the general circulation”

– Goodman & Gilman's Pharmacological Basis of Therapeutics 12th edition

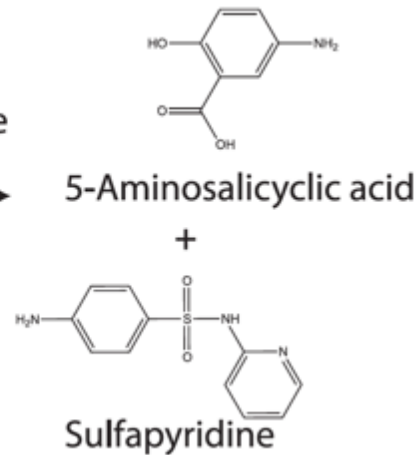
The gut microbiome influences drug metabolism



Microbial activation of drugs for IBD and arthritis



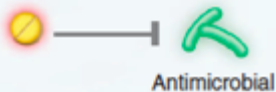
Azoreductase activity



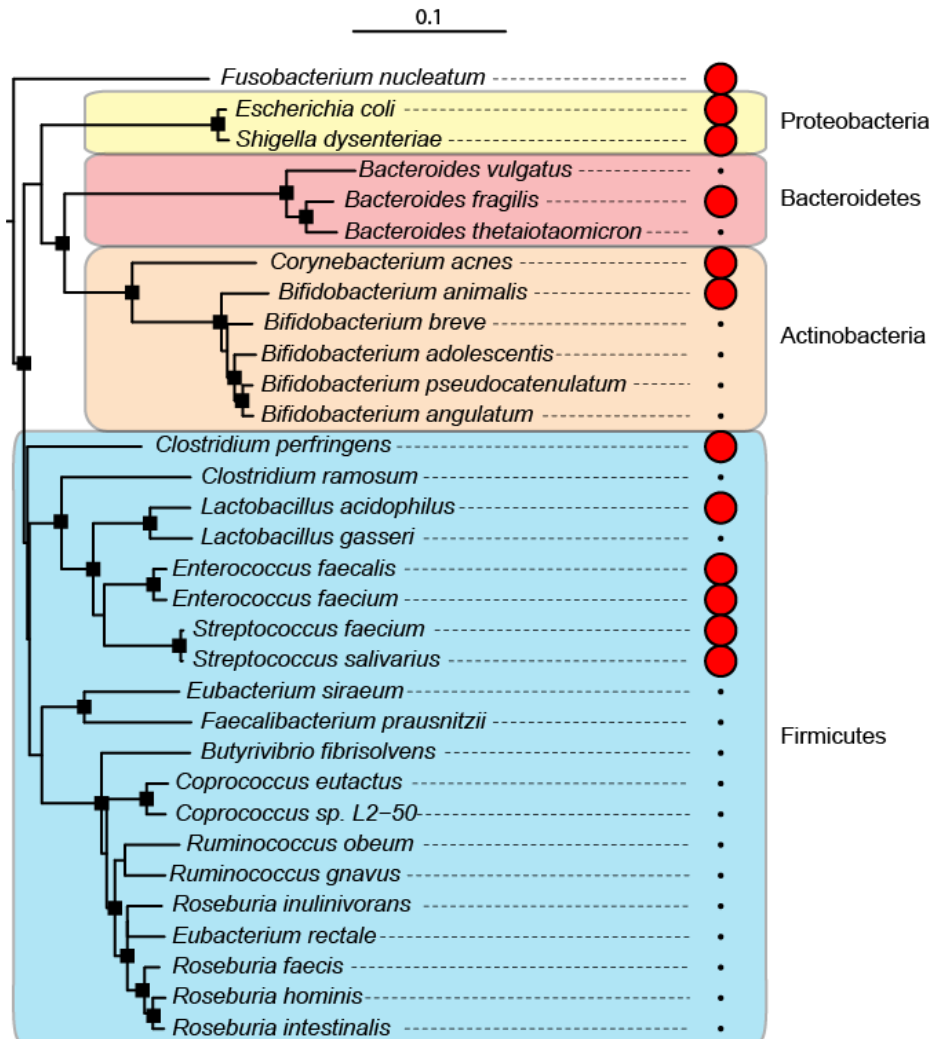
Anti-inflammatory effects

Side effects

Direct interactions

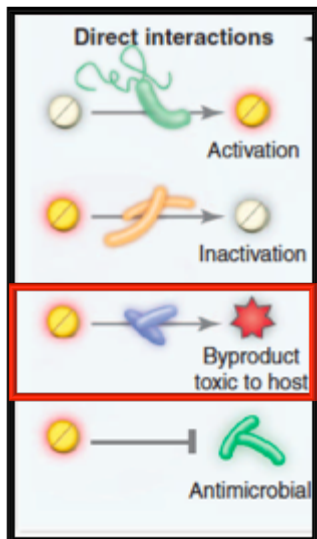
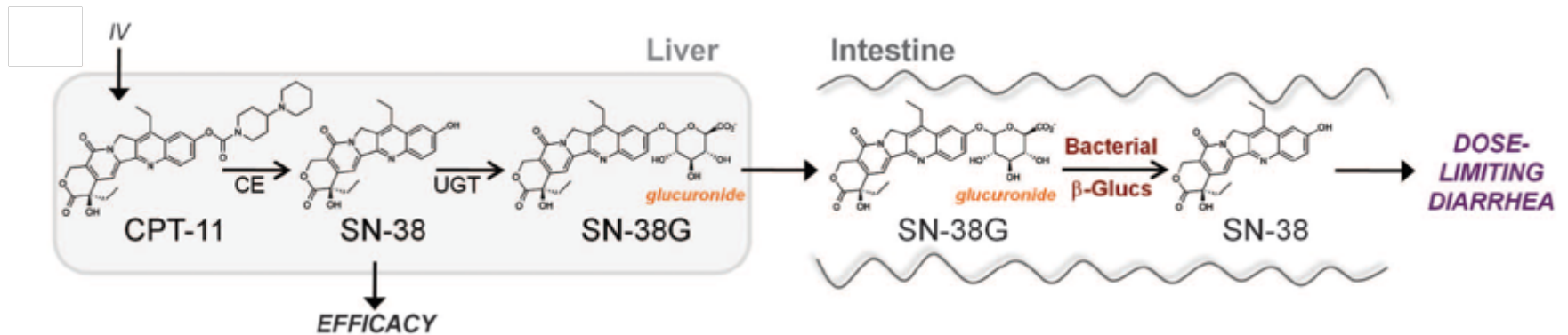


Azoreductases are widely distributed in the human gut microbiome



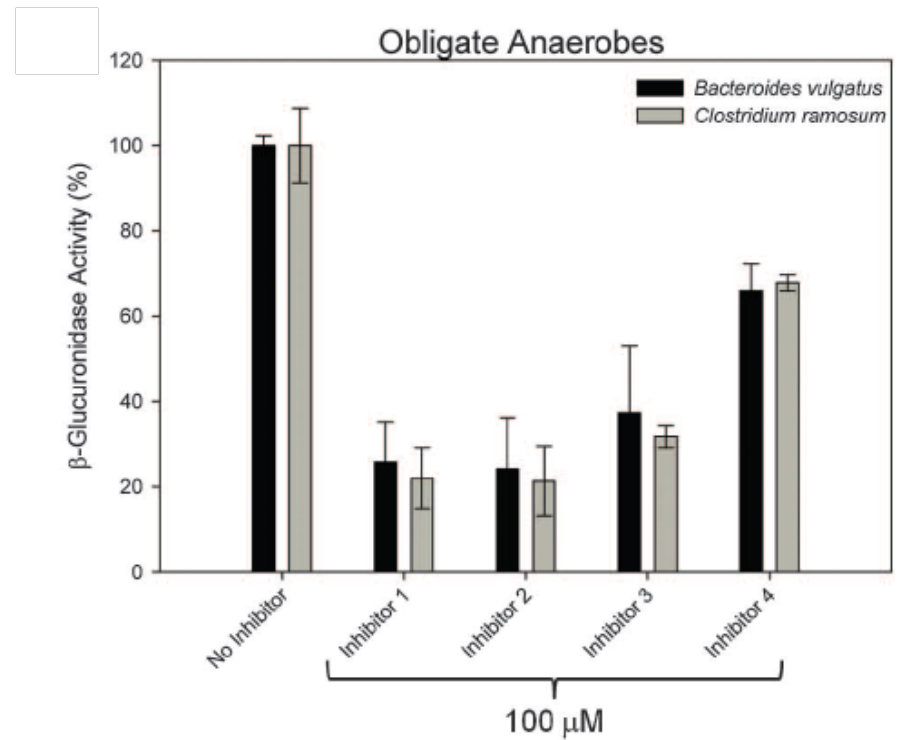
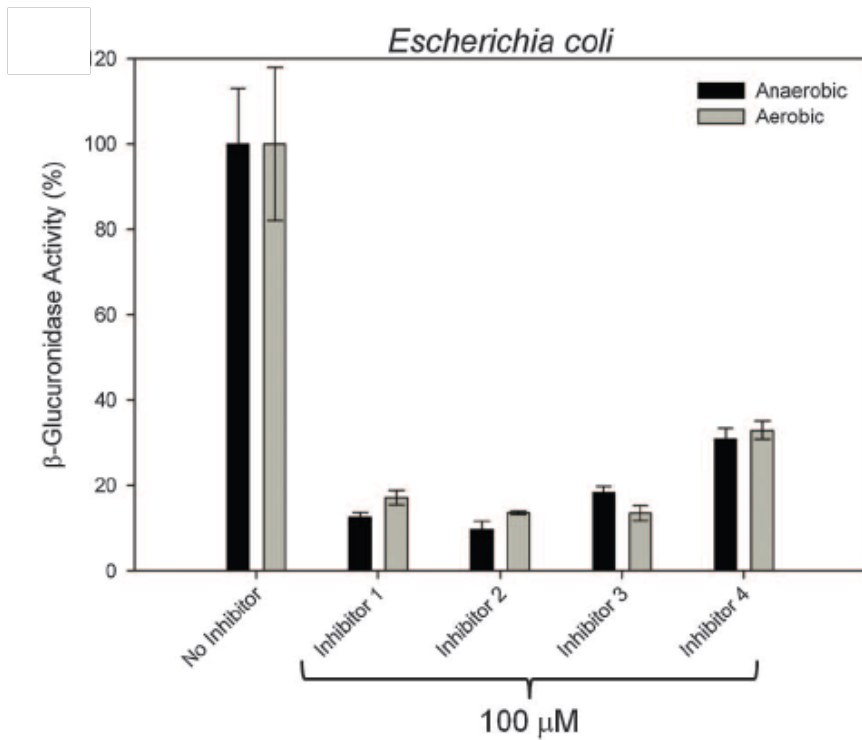
- Can exploit these enzymes to deliver compounds to the distal gut
- Do variations in azoreductase activity alter drug efficacy?

Gut microbes contribute to GI toxicity

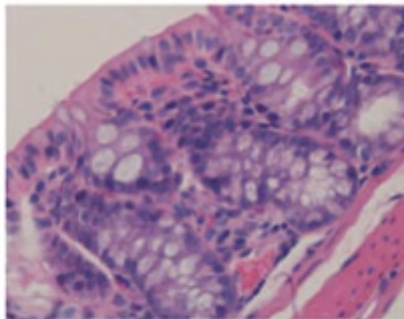
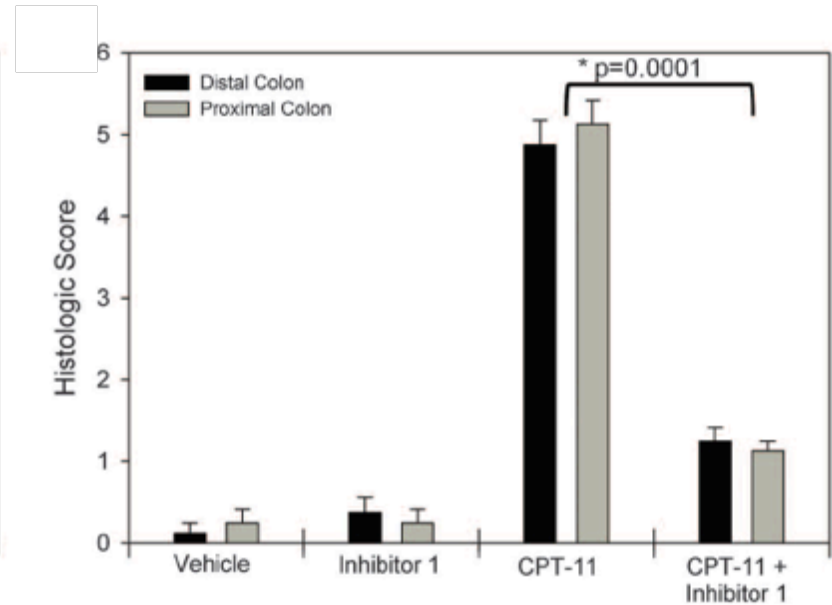
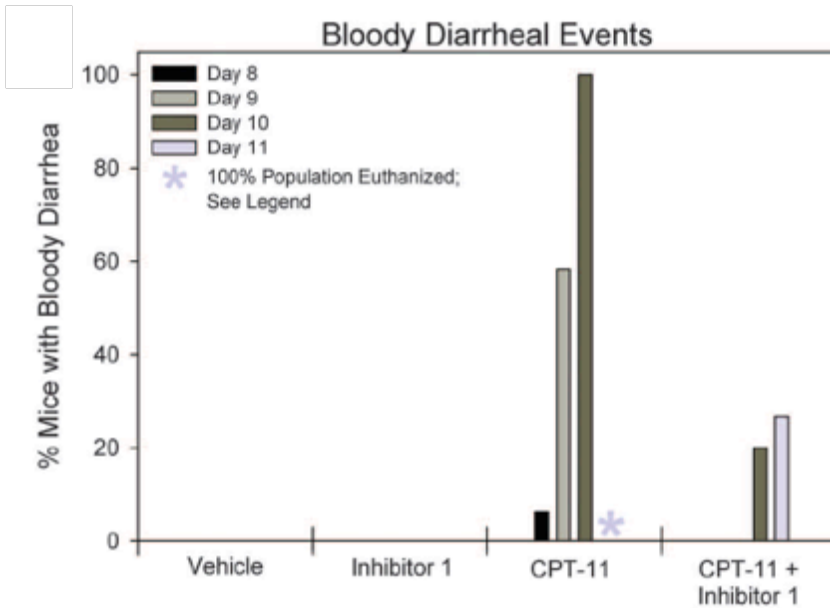


- Structure solved for *E. coli* beta-glucuronidase
- High-throughput screening found 4 small molecule inhibitors

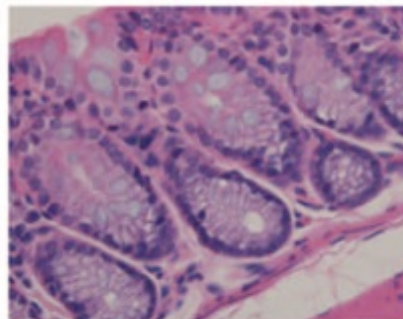
Inhibitors work on multiple bacterial species



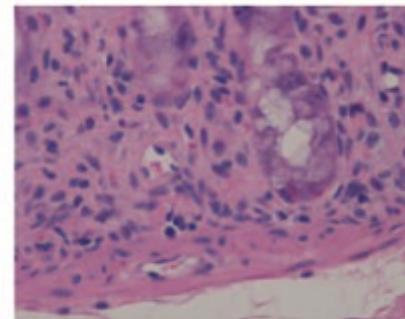
Inhibitor rescues GI side effects



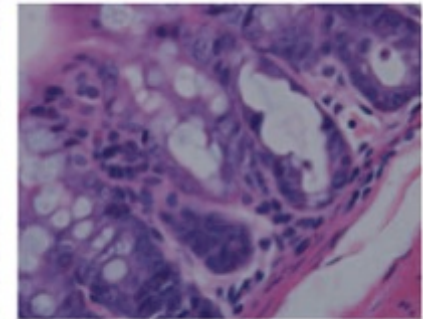
Vehicle



Inhibitor 1

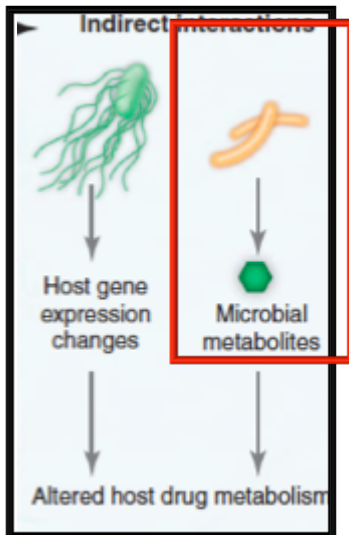
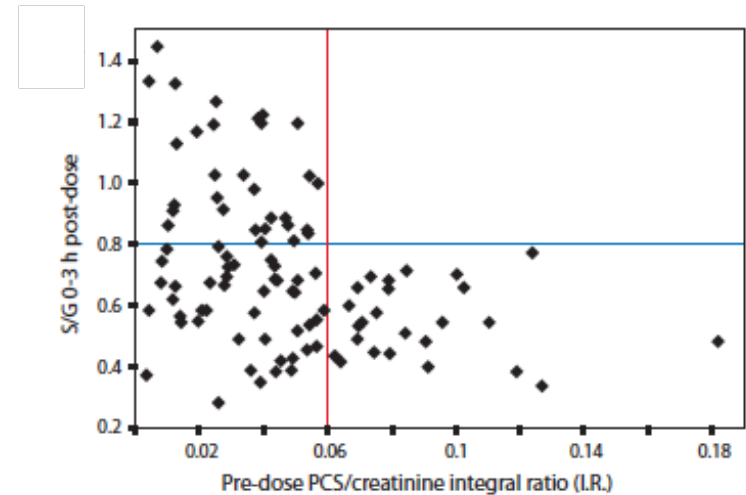
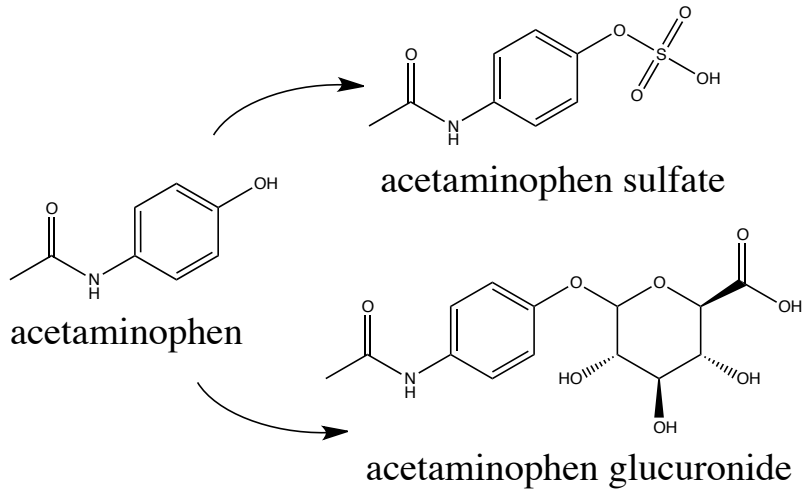


CPT-11



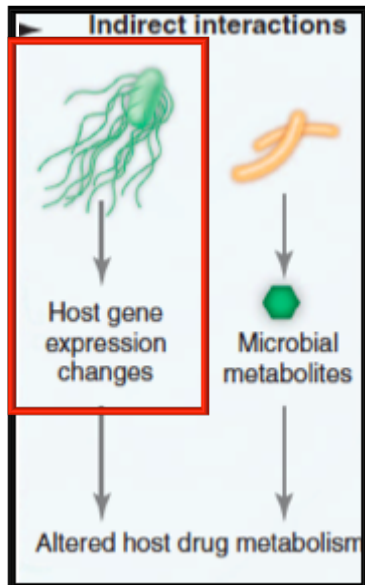
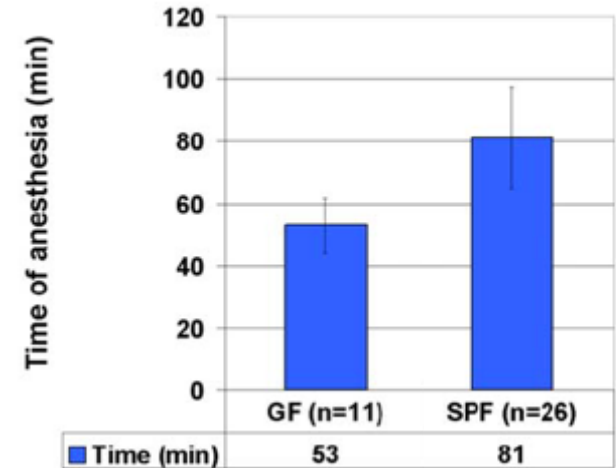
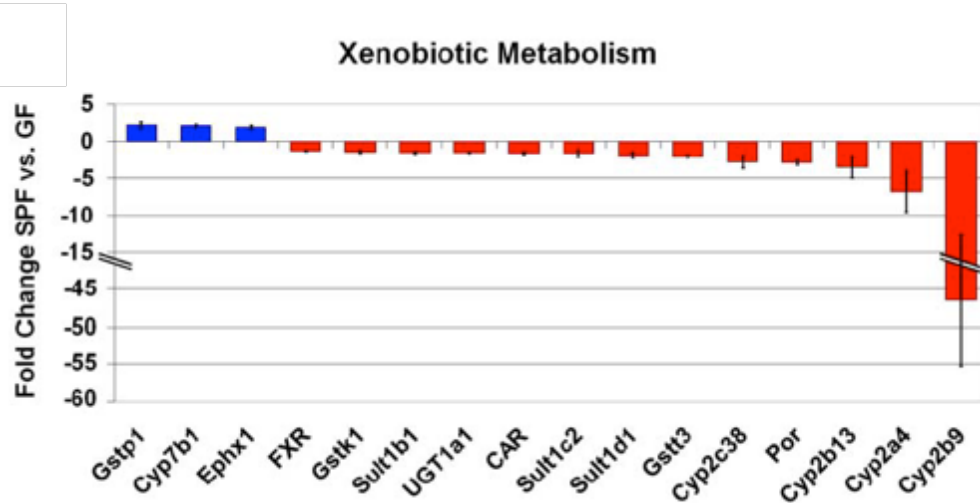
CPT-11 + Inhibitor 1

Can microbial metabolites interfere with host drug metabolism?



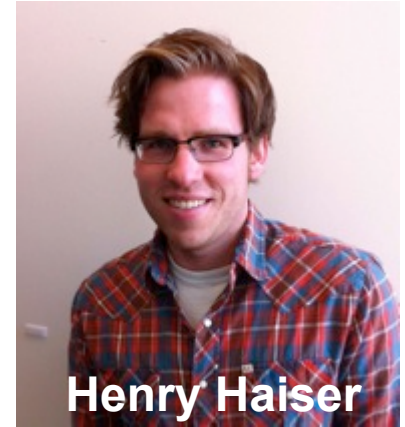
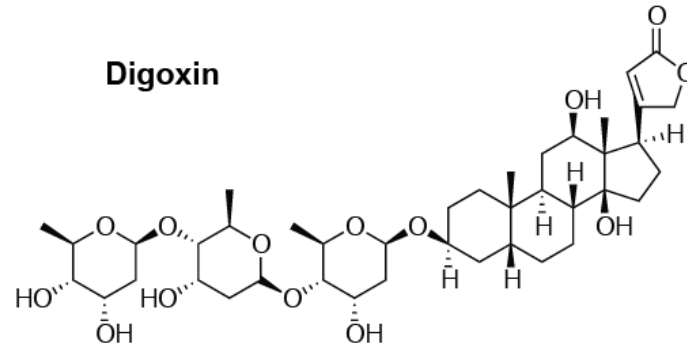
- p-cresol is associated with post-dose S/G ratio
- Competes for sulfonation
- Could impact toxicity by removing a major detoxification pathway

Microbial colonization alters host gene expression

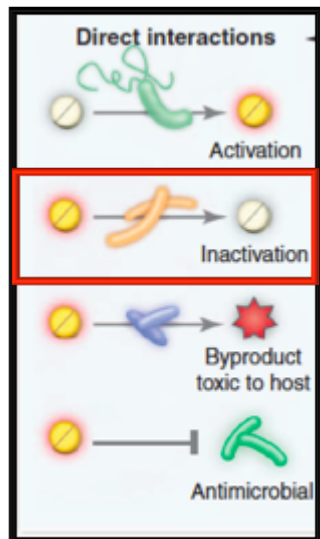


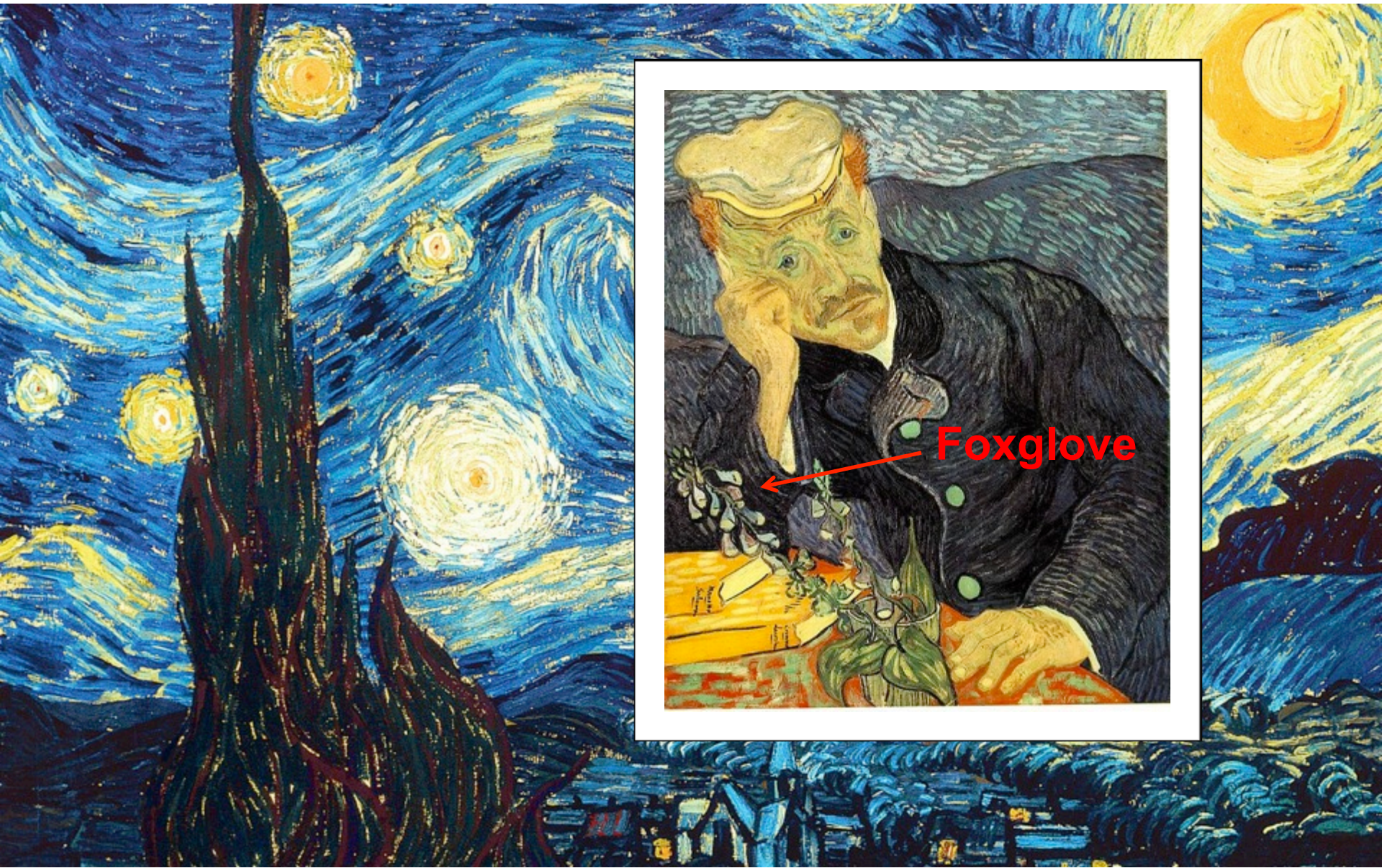
- Liver gene expression was altered in conventionally raised mice relative to germ-free
- Significant changes to the length of anaesthesia during treatment with barbituates

Focusing in on the cardiac glycosides

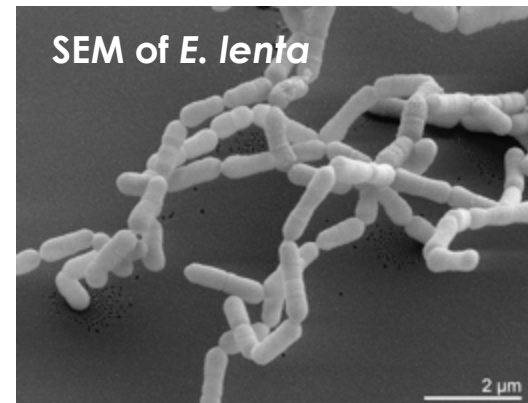
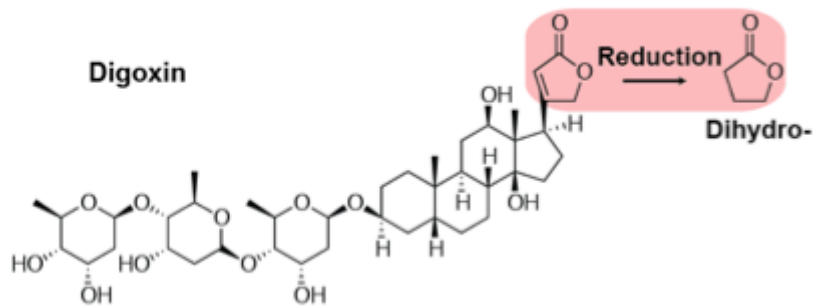


- Widely used drug for heart failure and arrhythmia
- Slows heart rate, increases force and velocity of contractions, via Na/K ATPase target
- Narrow therapeutic range: symptoms include blurred vision, GI problems (anorexia, nausea, diarrhea, vomiting), and cardiovascular dysfunction



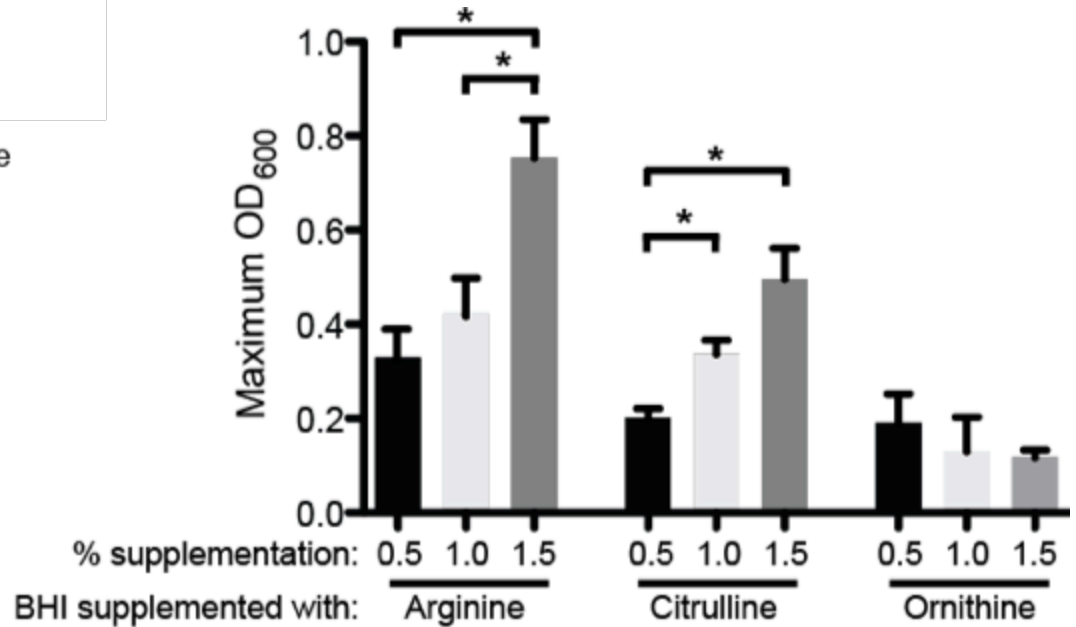
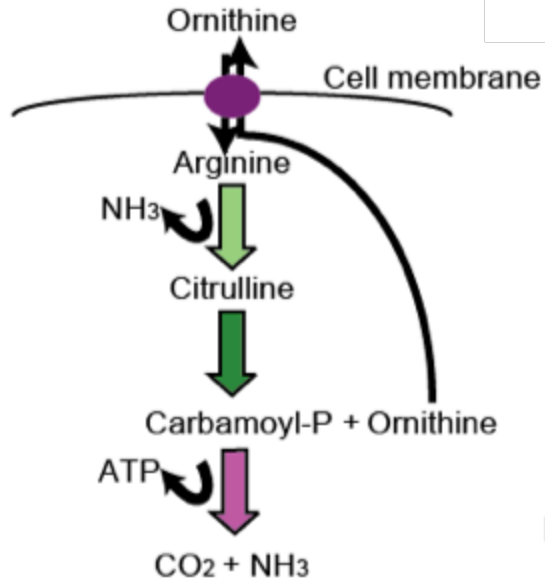


Eggerthella lenta inactivates digoxin

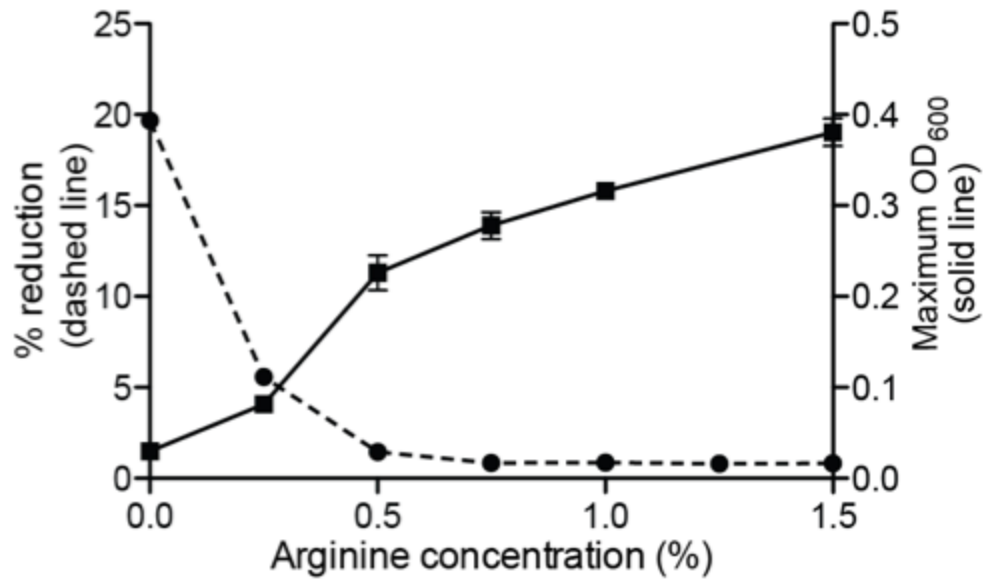


- Serum concentration elevated by antibiotics

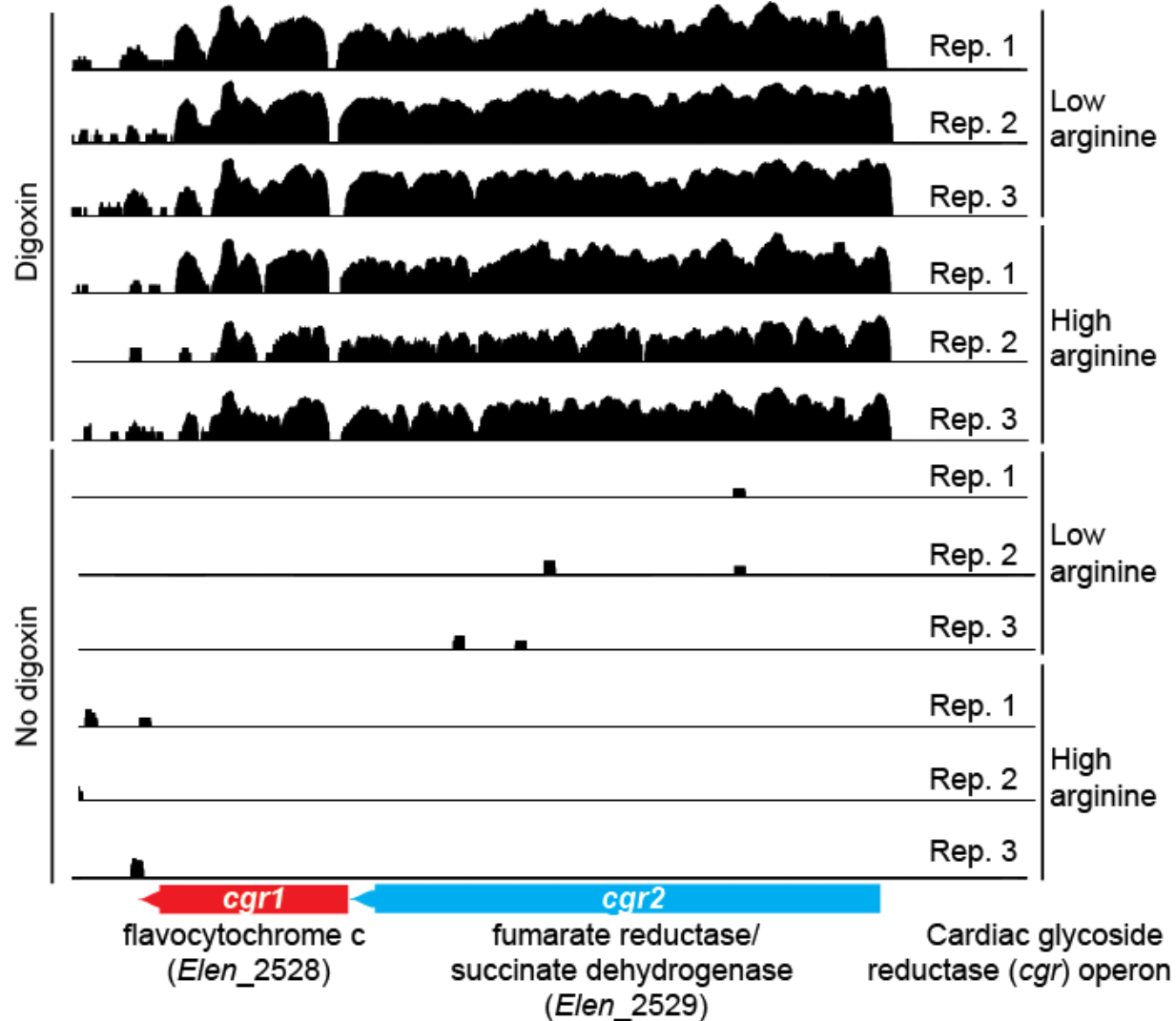
Eggerthella lenta lives for arginine



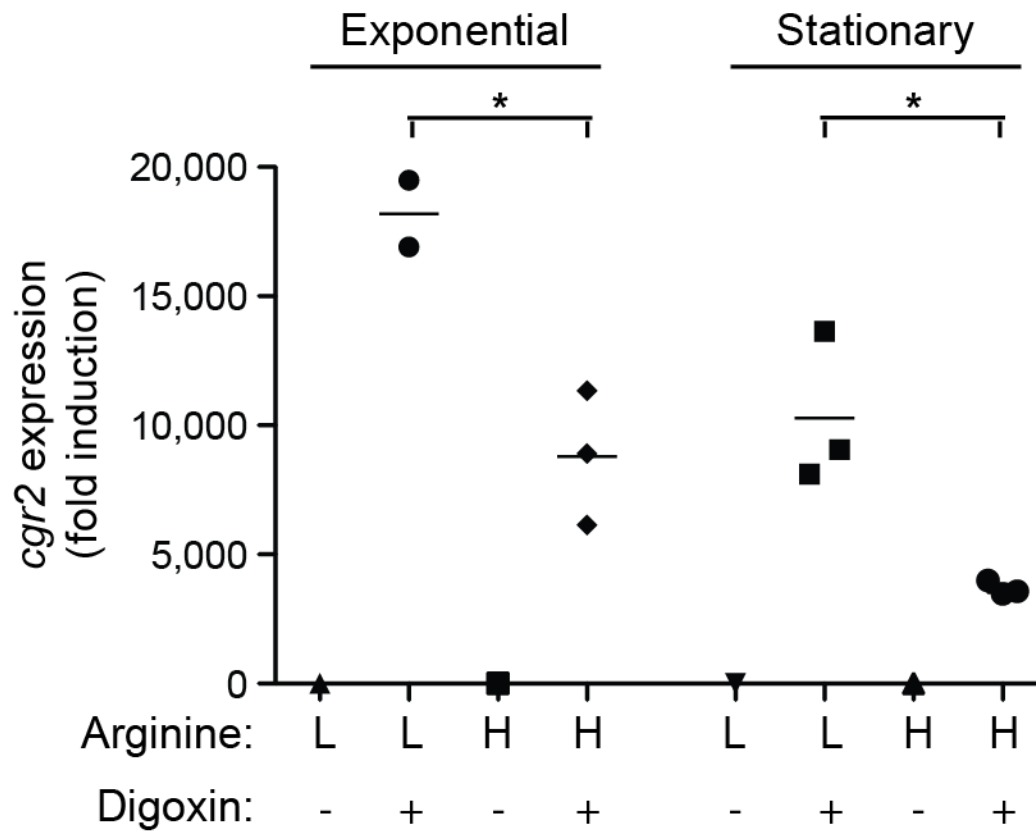
Arginine inhibits digoxin reduction



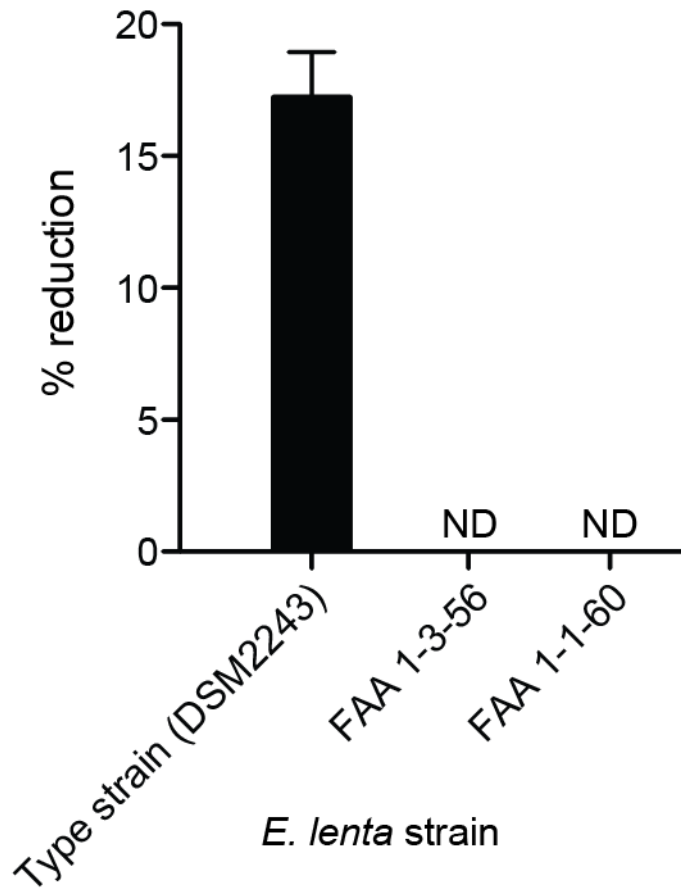
Up-regulation of a cytochrome operon by digoxin



cgr operon is expressed at higher levels in low arginine conditions

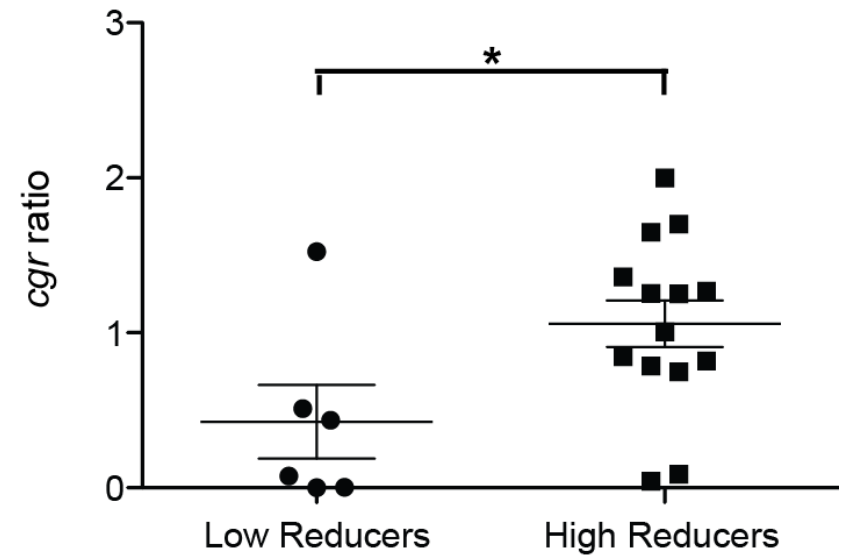
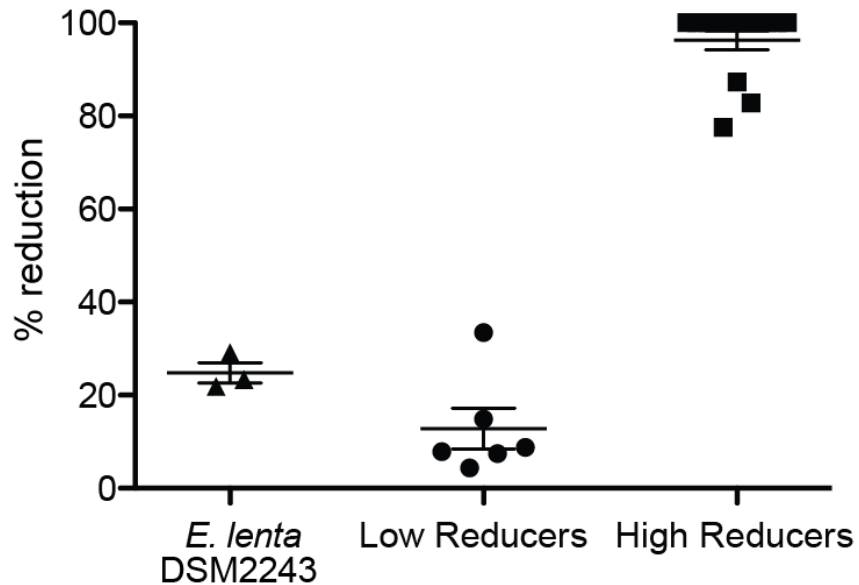


The *cgr* operon is unique to reducing strains



The ***cgr operon*** and two operons for sugar/small metabolite transport are missing from these two non-reducing strains

CGR ratio predicts digoxin reduction efficiency



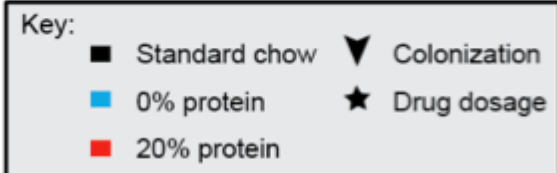
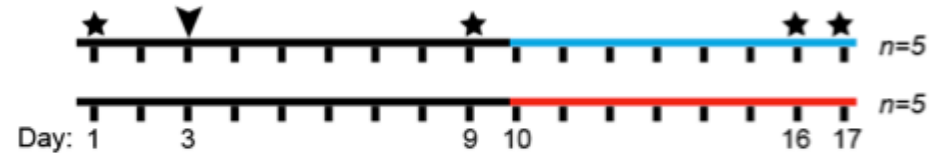
Does dietary protein inhibit digoxin reduction?

- Arginine blocks digoxin reduction *in vitro*
- Does this also occur *in vivo*?

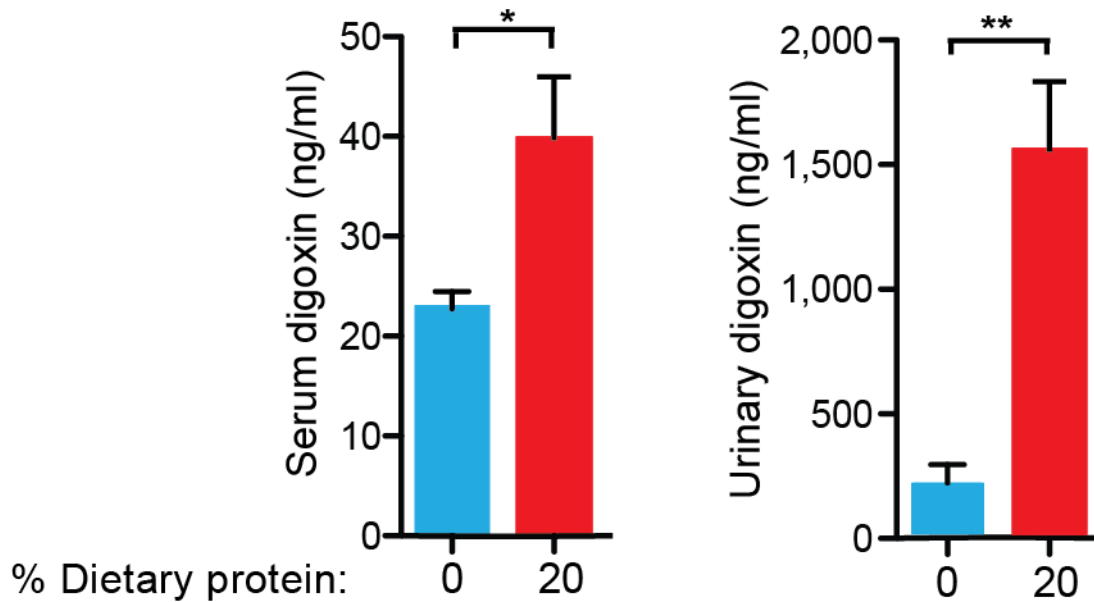
Germ-free isolators:



A) Type strain colonization- experimental design:



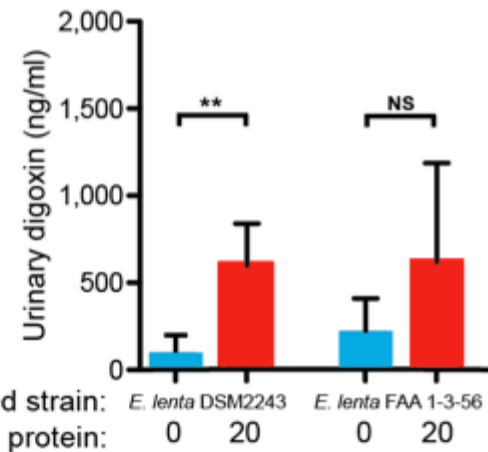
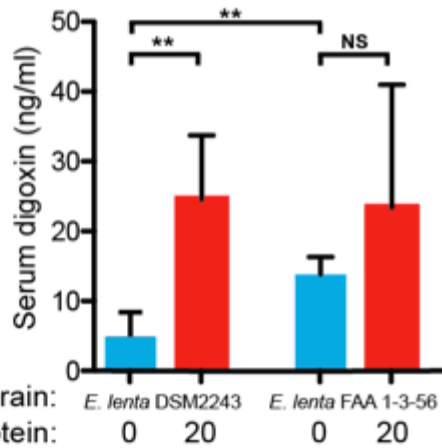
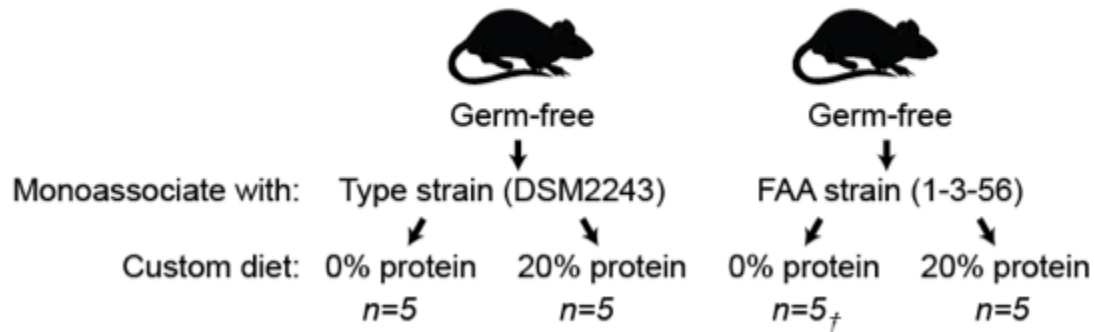
Serum and urine digoxin levels altered by diet



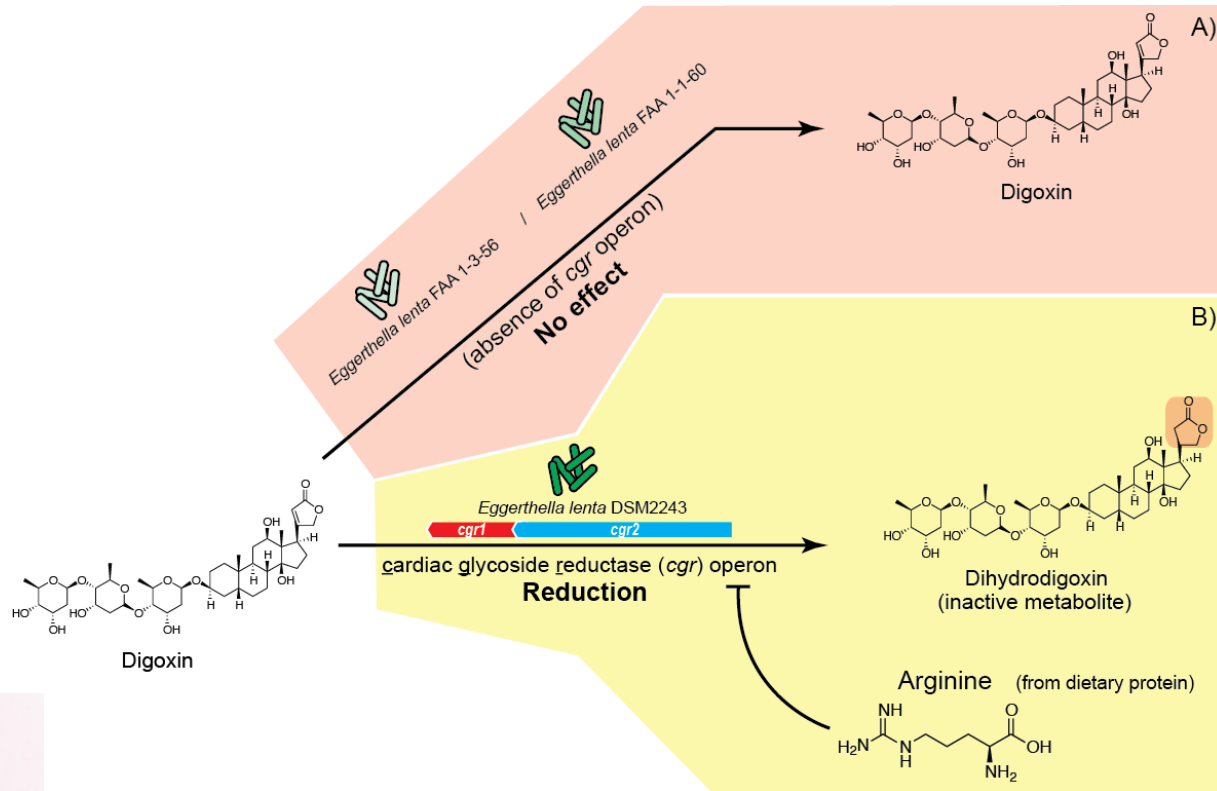
- Serum and urine collected 4 hours following digoxin administration
- ELISA assay used to quantitate digoxin levels

Diet only significantly alters digoxin levels when colonized with the type strain of *E.lenta*

Type/FAA strain colonization- experimental groups:



Model for digoxin inactivation by the human gut microbiome



See Poster P14

Haiser *et al.*, *Science* 341, 295-298 (2013)



Needs and gaps

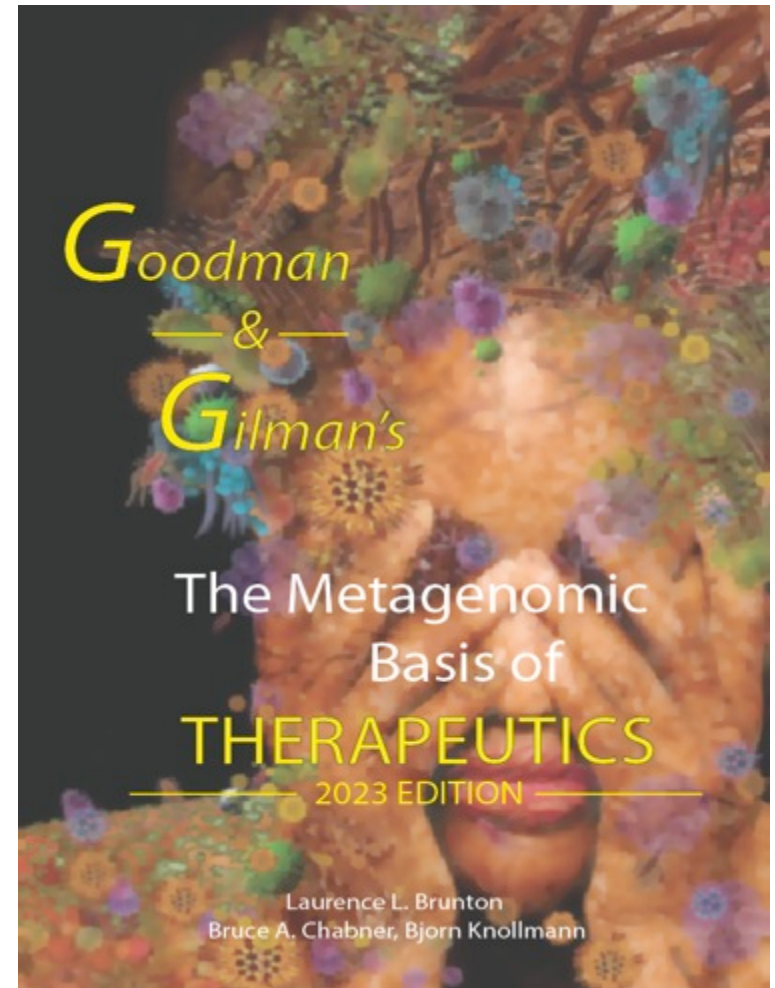
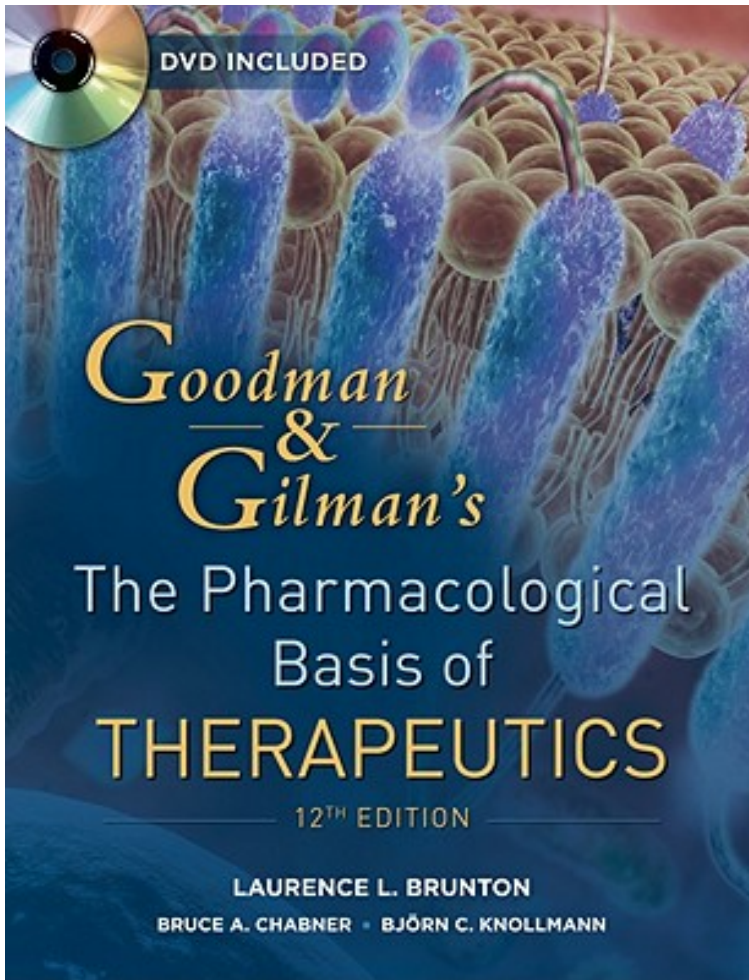


Need: gnotobiotics

Gaps:

1. Which bacterial taxa and metabolic pathways are involved?
2. How do microbial communities adapt to xenobiotics?
3. What are the relative contributions of host, microbial, and environmental factors to pharmacokinetics and dynamics?

The grand challenge



Acknowledgements



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for Systems Biology



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UNC Gnotobiotic Core

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KEYSTONE SYMPOSIA on Molecular and Cellular Biology

Exploiting and Understanding Chemical Biotransformations in the Human Microbiome (D1)

April 1-6, 2014 • Big Sky Resort • Big Sky, Montana, USA

Scientific Organizers: Peter J. Turnbaugh, Curtis Huttenhower and Michael A. Fischbach

Supported by the Directors' Fund

Abstract & Scholarship Deadline: / Late-Breaking Abstract Deadline: / Early Registration Deadline: