

Microbiome contributions to drug metabolism

Andy Goodman

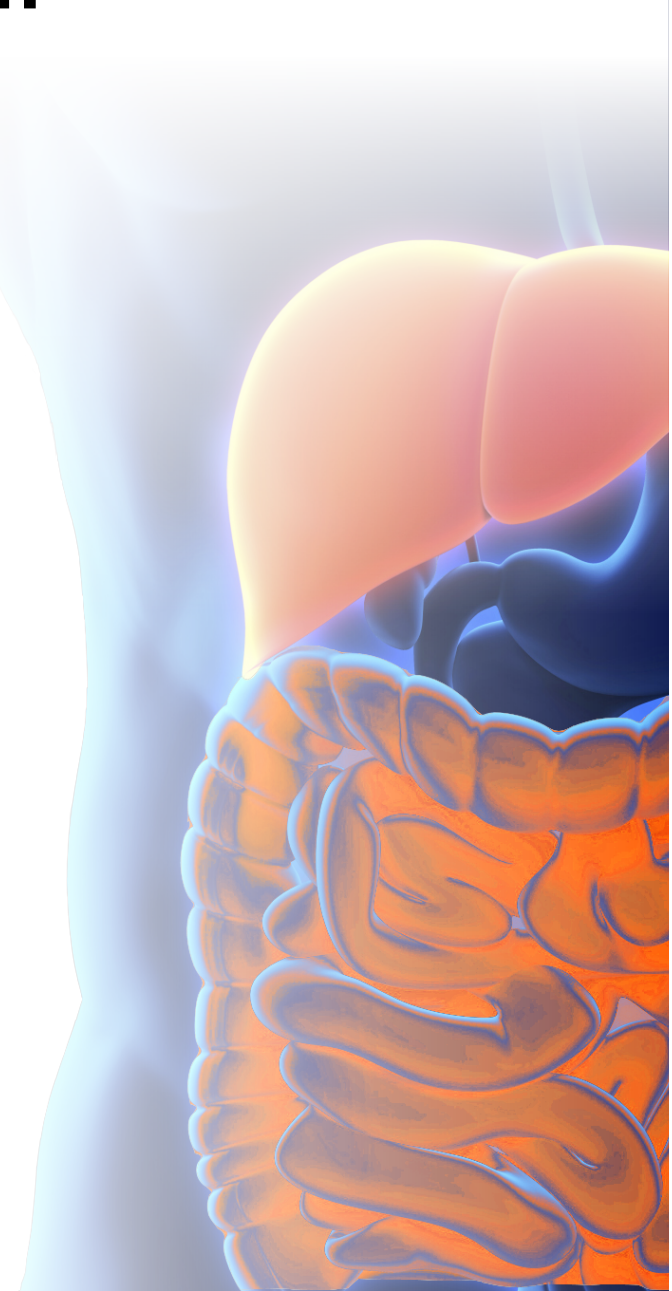
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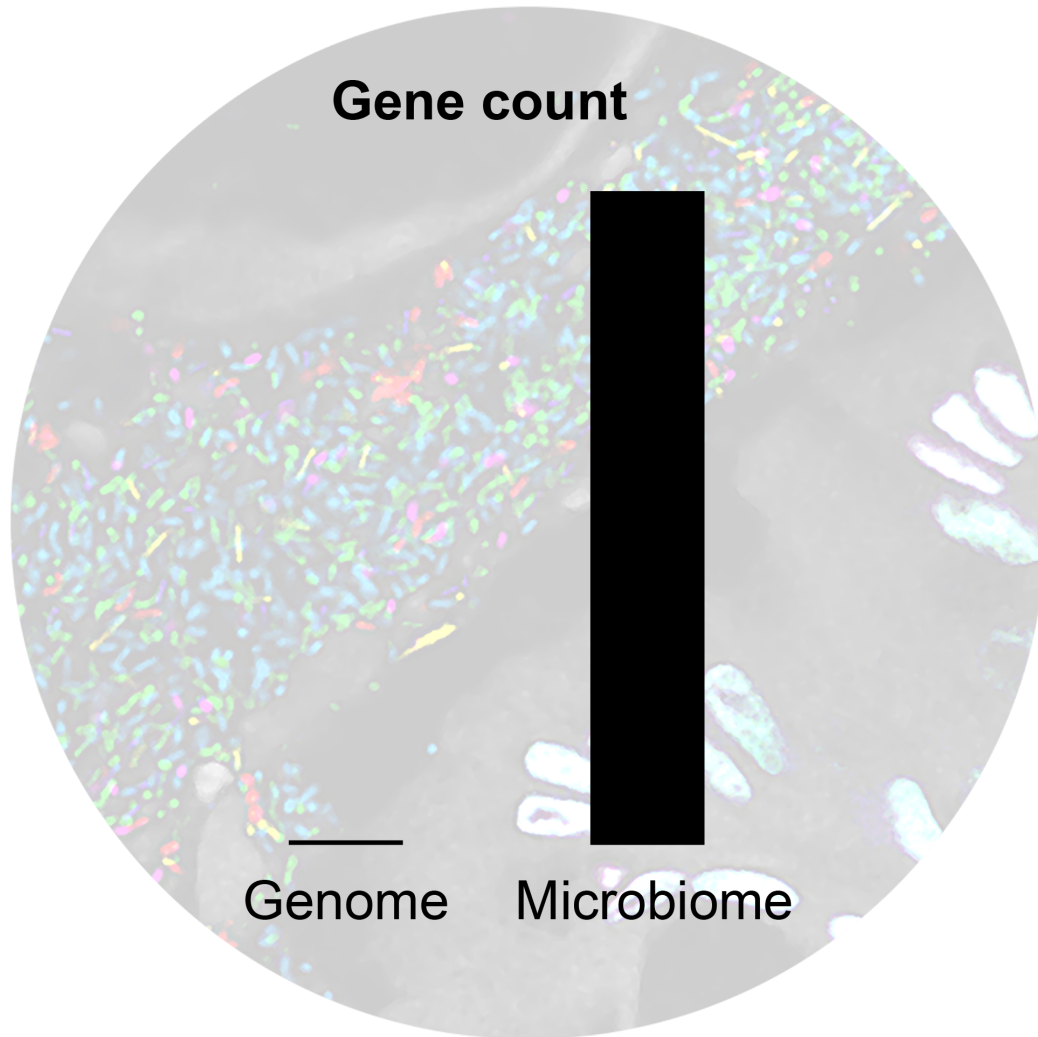
The team



The team

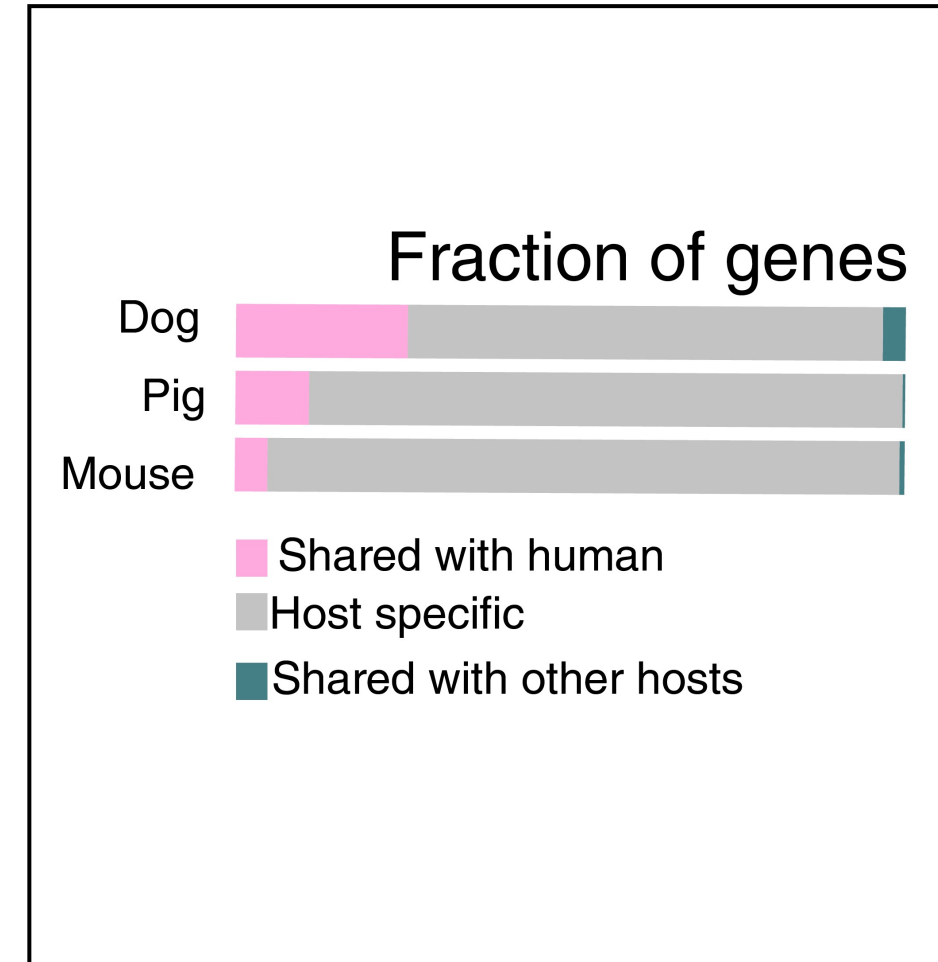
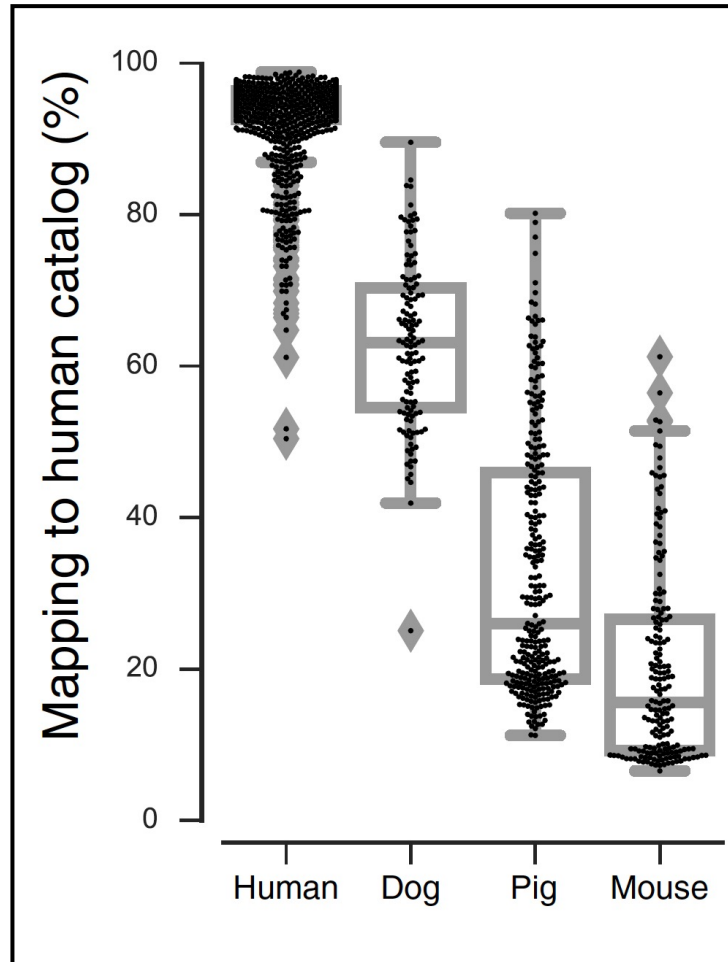
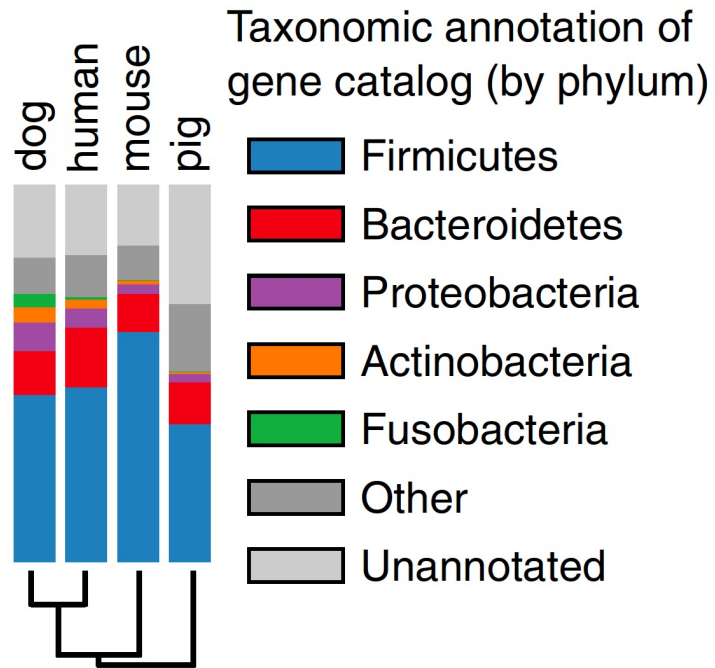


The microbiome is acquired from the environment and can dramatically change gene content over time

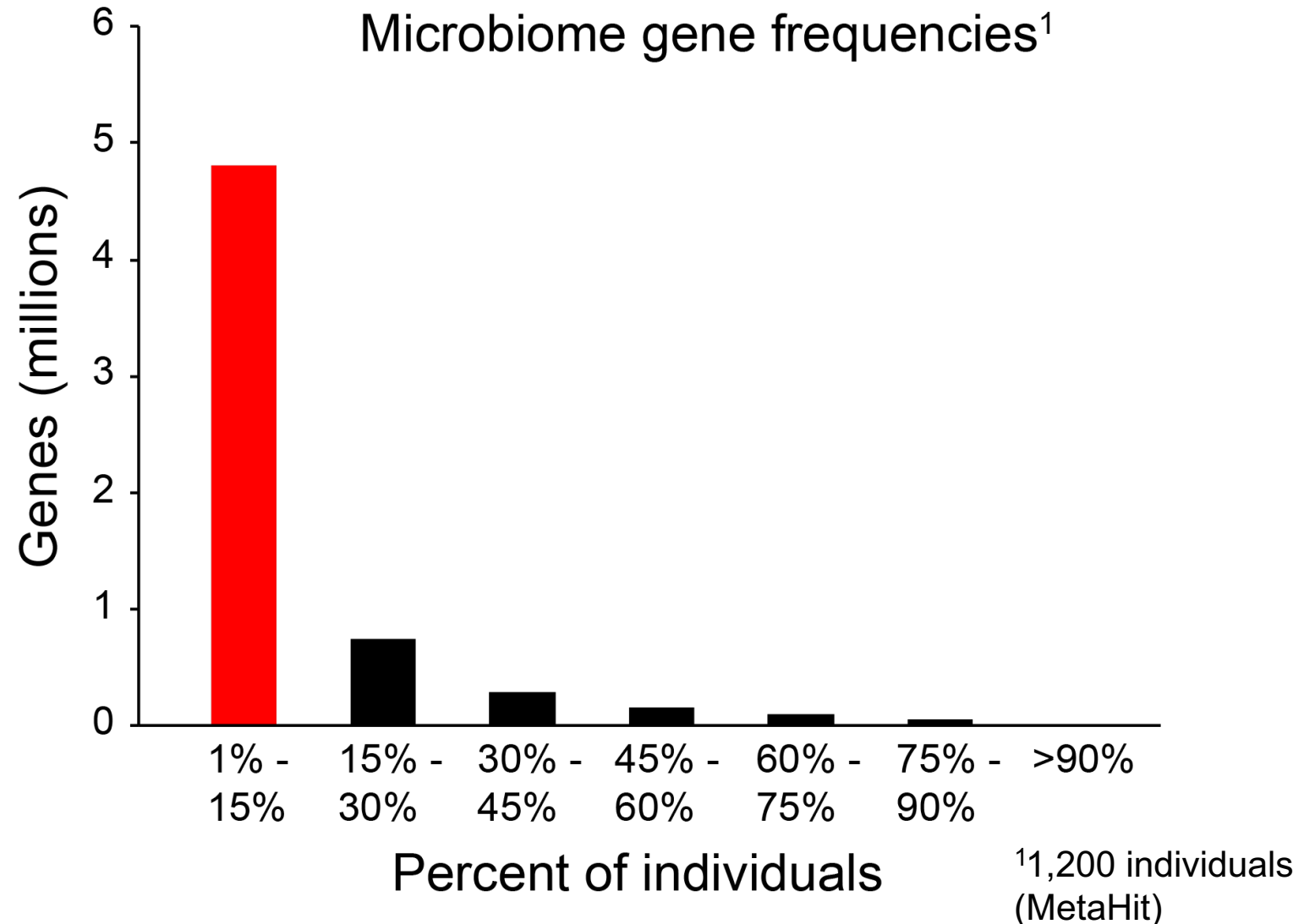


- Possibly the most therapeutically tractable organ in the body
- Possibly the least understood

Typical preclinical animal studies are not designed to measure microbiome impact on drug metabolism

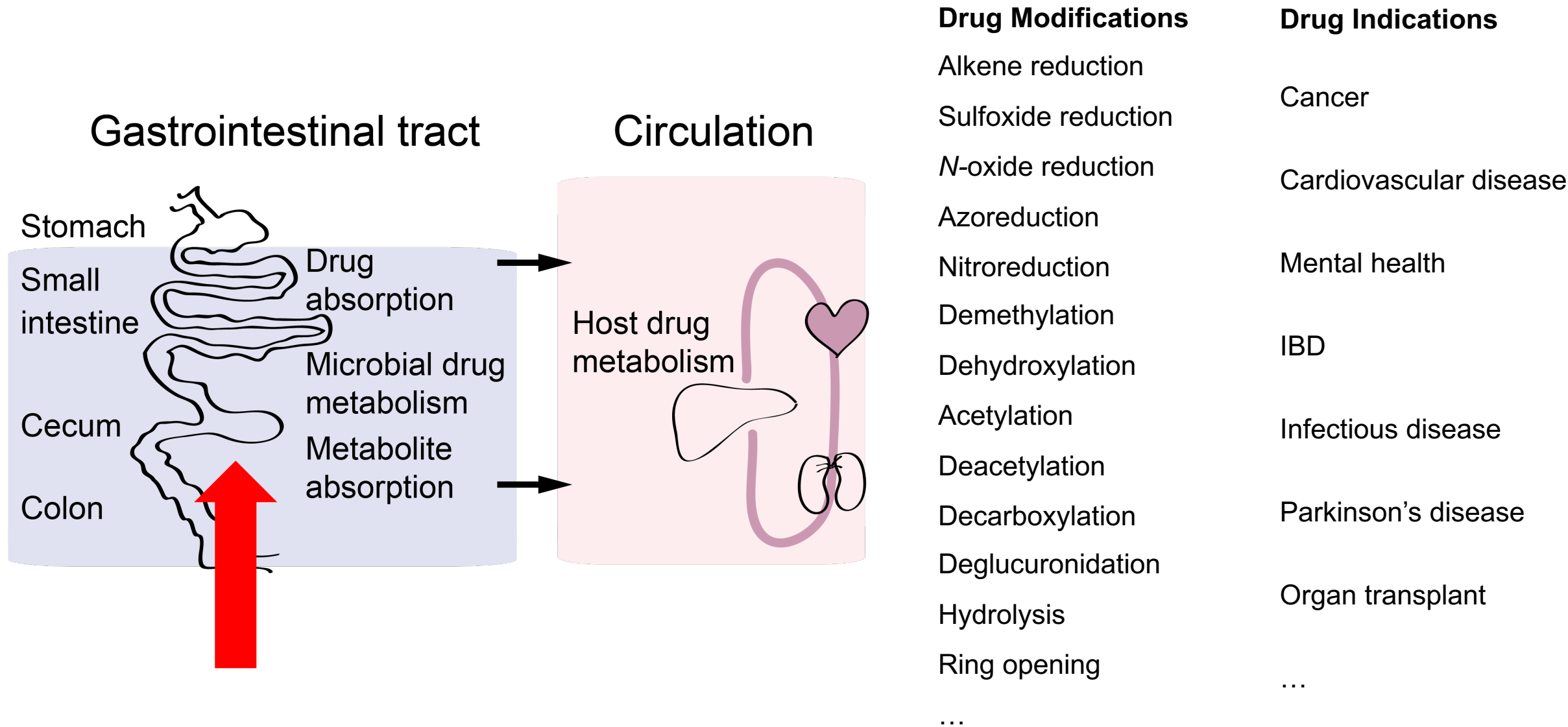


Human mass balance studies are also not designed to capture microbiome impacts

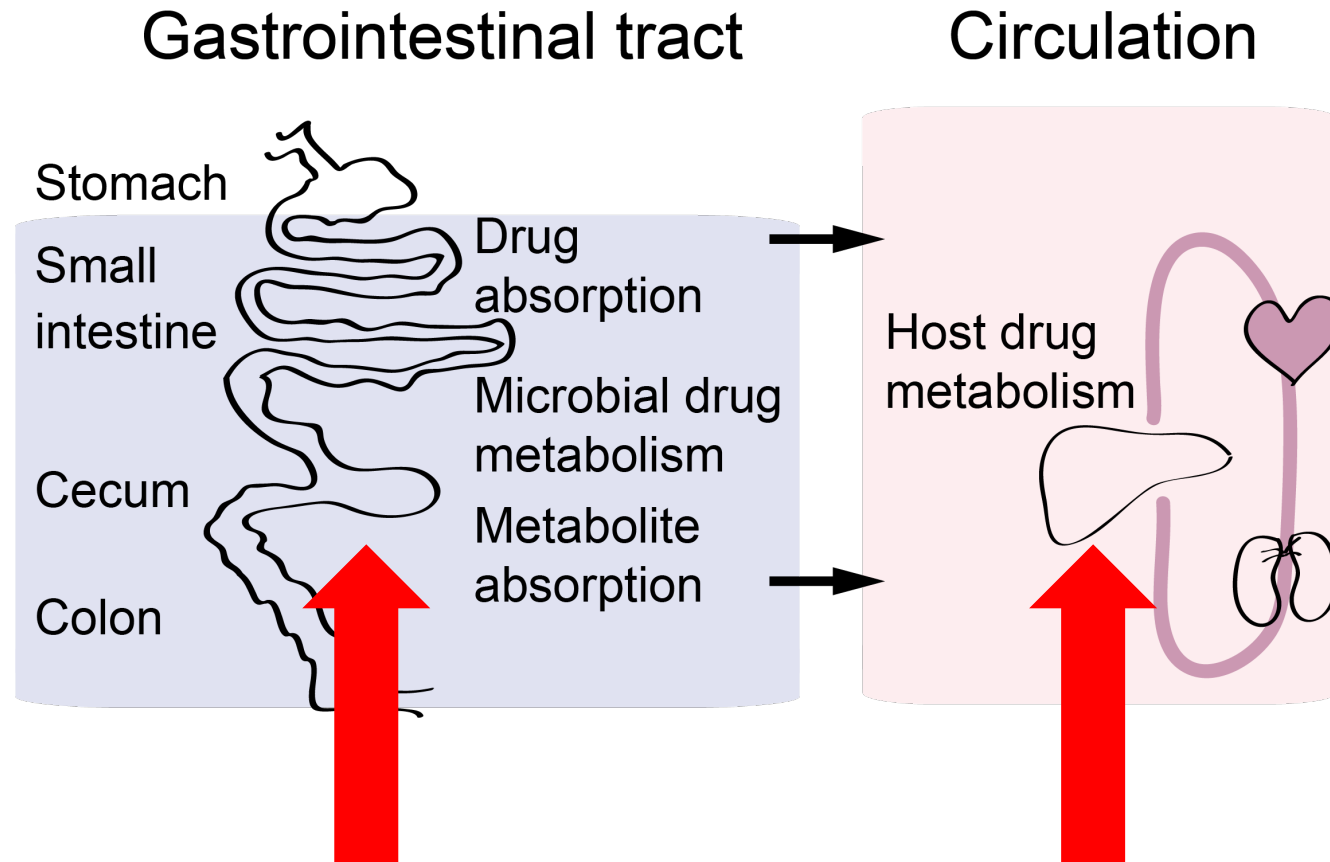


These studies also don't resolve *where* a drug metabolite is made

Anecdotal examples of microbiome-mediated drug metabolism



Drug metabolites produced by both liver and microbiome are challenging to identify



Site of metabolism will determine the impact of:

- Genetic variation (host and microbiome)
- Diet
- Liver and gut health
- Disease state
- Other drugs

How can we understand microbiome contributions to drug metabolism?

1. An outline of drug metabolism by human gut microbes and their genes

How can we understand microbiome contributions to drug metabolism?

1. An outline of drug metabolism by human gut microbes and their genes
2. Resolving host and microbiome contributions to shared drug metabolites

An outline of drug metabolism by human gut microbes and their genes

Are there rules that dictate whether and how a gut microbe will metabolize a drug?

Do gut microbes encode enzymes that metabolize many drugs?

We can begin to explore these questions by asking how a large number of drugs are metabolized by a large number of microbes

271 FDA-approved, oral drugs

ABACAVIR	BUDESONIDE	DEFLAZACORT	EZETIMIBE	LAMOTRIGINE	MILNACIPRAN	PAROXETINE	REPAGLINIDE	TERAZOSIN
ACEBUTOLOL	BUPROPION	DESVENLAFAXINE	FAMCICLOVIR	LETROZOLE	MYCOPHENOLATE	PENBUTOLOL	RESERPINE	TERBINAFINE
ACECAINIDE	BURAMATE	DEXAMETHASONE	FAMPROFAZONE	LEVAMISOLE	NADOLOL	PENTOXIFYLLINE	RILUZOLE	THIABENDAZOLE
ALFUZOSIN	BUSPIRONE	DEXTROMETHORPHAN	FEBUXOSTAT	LEVONORGESTREL	NAFRONYL OXALATE	PERGOLIDE	RIMANTADINE	THIOTHIXENE
ALMOTRIPTAN	CAMYLOFINE	DIACETAMATE	FENOFIBRATE	LINAGLIPTIN	NAFTOPIDIL	PERICIAZINE	RISPERIDONE	TIAPRIDE
ALPRENOLOL	CAPECITABINE	DICYCLOMINE	FENSPIRIDE	LOFEXIDINE	NALOXONE	PERINDOPRIL	RITONAVIR	TIMOLOL
AMANTADINE	CARBETAPENTANE	DIFLORASONE	FEXOFENADINE	LOPERAMIDE	NAPROXEN(+)	PHENACETIN	RIVASTIGMINE	TINIDAZOLE
AMINOGLUTETHIMIDE	CARBINOXAMINE	DIGITOXIN	FINASTERIDE	LOSARTAN	NATEGLINIDE	PHENAZOPYRIDINE	RIZATRIPTAN	TOLAZAMIDE
AMISULPRIDE	CARISOPRODOL	DIGOXIN	FLUCONAZOLE	LOVASTATIN	NEFAZODONE	PHENYTOIN	ROPINIROLE	TOPOTECAN
ANAGRELIDE	CARVEDILOL	DILTIAZEM	FLUOXETINE	LOXAPINE	NEFOPAM	PIDOTIMOD	ROSIGLITAZONE	TRANDOLAPRIL
ANASTROZOLE	CELECOXIB	DIPERODON	FLUPHENAZINE	MEBENDAZOLE	NEOSTIGMINE	PIMOZIDE	ROSUVASTATIN	TRANILAST
ANTAZOLINE	CETIRIZINE	DIPHENYLPYRALINE	FLUVOXAMINE	MEBHYDROLIN	NEVIRAPINE	PITAVASTATIN	ROXATIDINE	TRAZODONE
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76 genome-sequenced human gut bacterial isolates

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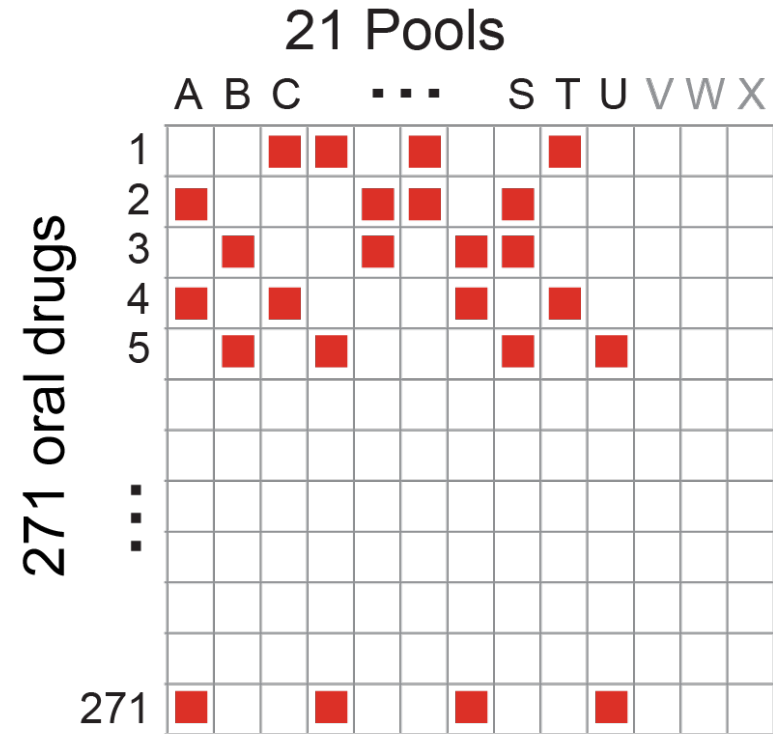
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Bacteroides fragilis HMW610
Bacteroides fragilis ATCC 43859
Bacteroides fragilis HMW615
Bacteroides fragilis DS-208
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Odoribacter splanchnicus
Parabacteroides distasonis ATCC 8503
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Alistipes indistinctus DSM 22520
Bacteroides finegoldii DSM 17565
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Bacteroides WH2
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Parabacteroides johnsonii DSM 18315
Bacteroides thetaiotaomicron 3731
Bacteroides thetaiotaomicron VPI-5482
Bacteroides thetaiotaomicron 7330
Bacteroides ovatus ATCC 8483
Bacteroides stercoris ATCC 43183
Bacteroides fragilis 3397 T10
Bacteroides eggerthii DSM 20697
Bacteroides caccae ATCC 43185
Escherichia coli K12
Proteus penneri ATCC 35198
Enterobacter cancerogenus ATCC 353
Edwardsiella tarda ATCC 23685
Providencia rettgeri DSM 1131
Providencia alcalifaciens DSM 30120
Providencia stuartii ATCC 25827
Salmonella typhimurium LT2

Ruminococcus gnavus ATCC 29149
Clostridium hathewayi DSM 13479
Marvinbryantia formatexigens DSM 14469
Eubacterium ventriosum ATCC 27560
Clostridium ramosum DSM 1402
Clostridium spiroforme DSM 1552
Dorea formicigenerans ATCC 27755
Clostridium bolteae ATCC BAA-613
Anaerostipes sp.
Ruminococcus lactaris ATCC 29176
Clostridium symbiosum ATCC 14940
Anaerotruncus colihominis DSM 17241
Anaerococcus hydrogenalis DSM 7454
Coprococcus comes ATCC 27758
Eubacterium rectale ATCC 33656
Subdoligranulum variabile DSM 15176
Blautia luti DSM 14534
Roseburia intestinalis L1-82
Eubacterium hallii DSM 3353
Clostridium asparagiforme DSM 15981
Clostridium scindens ATCC 35704
Enterococcus faecalis V583
Clostridium difficile 120
Clostridium sporogenes ATCC 15579
Eubacterium bifforme DSM 3989
Clostridium nexile DSM 1787
Blautia hansenii DSM 20583
Ruminococcus torques ATCC 27756
Lactobacillus reuteri CF48-3A
Collinsella aerofaciens ATCC 25986
Collinsella intestinalis DSM 13280
Bifidobacterium breve DSM 20213
Bifidobacterium adolescentis ATCC15
Bifidobacterium longum s. infantis
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Eggerthella lenta ATCC 25559
Akkermansia muciniphila ATCC BAA-8
Victivallis vadensis ATCC BAA-548

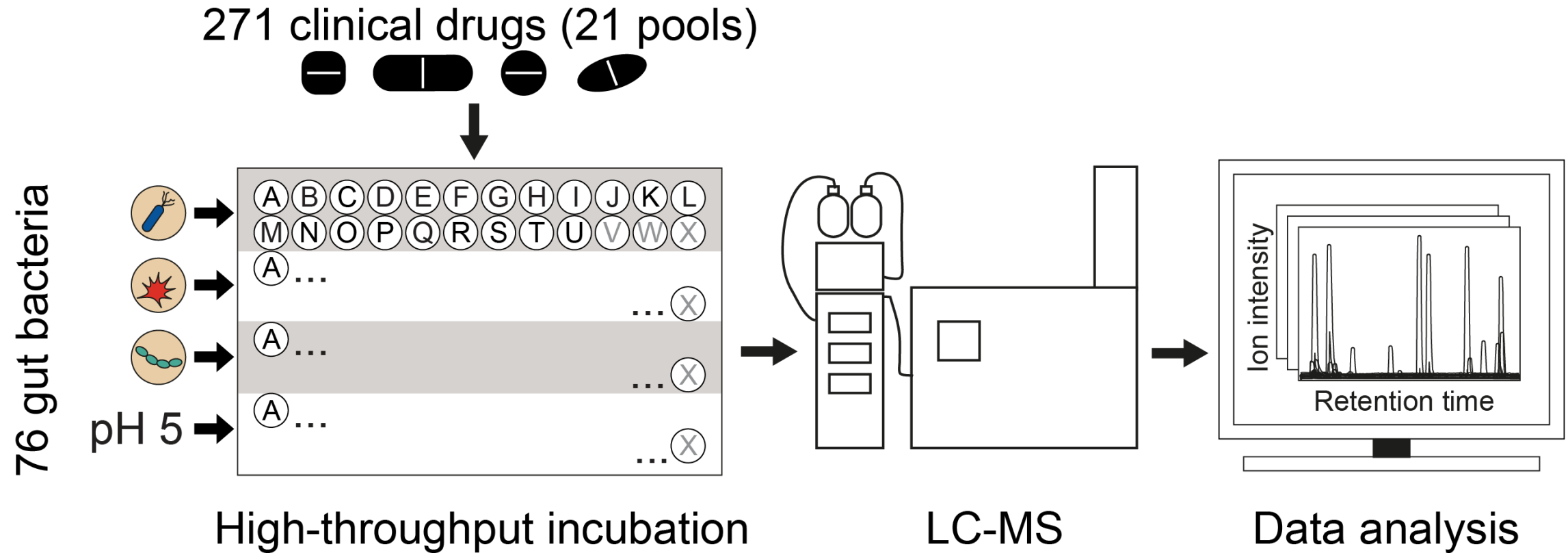
271 drugs, 76 bacterial strains, 2 timepoints, 4 replicates = 164,768 measurements

We assigned each drug to a subset of pools according to two simple rules

- Each drug is placed in 4 pools
- Any two drugs share at most 2 of their 4 assigned pools

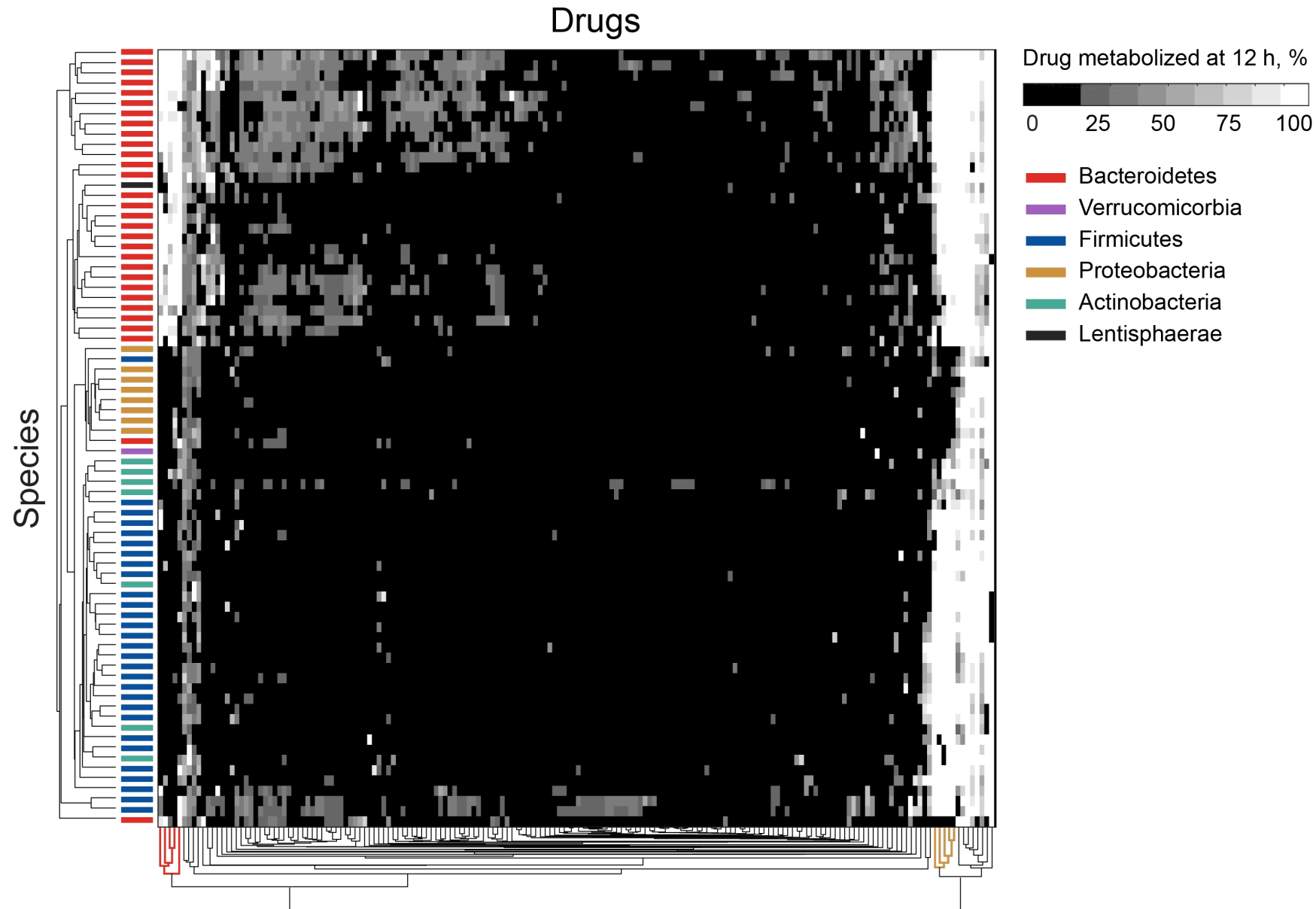


High-throughput measurement of drug metabolism by LC-MS

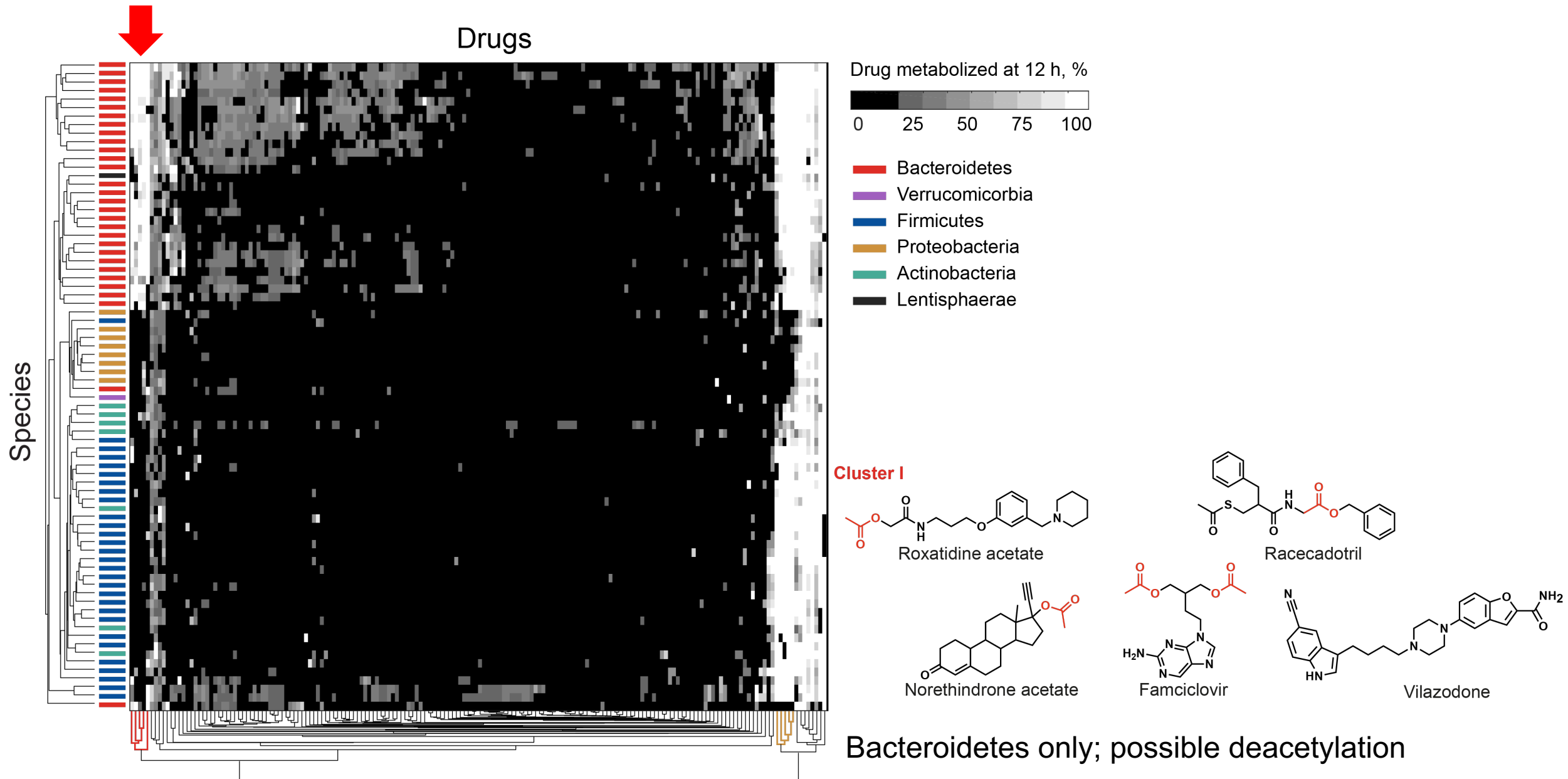


164,768 measurements from 19 96-well plates

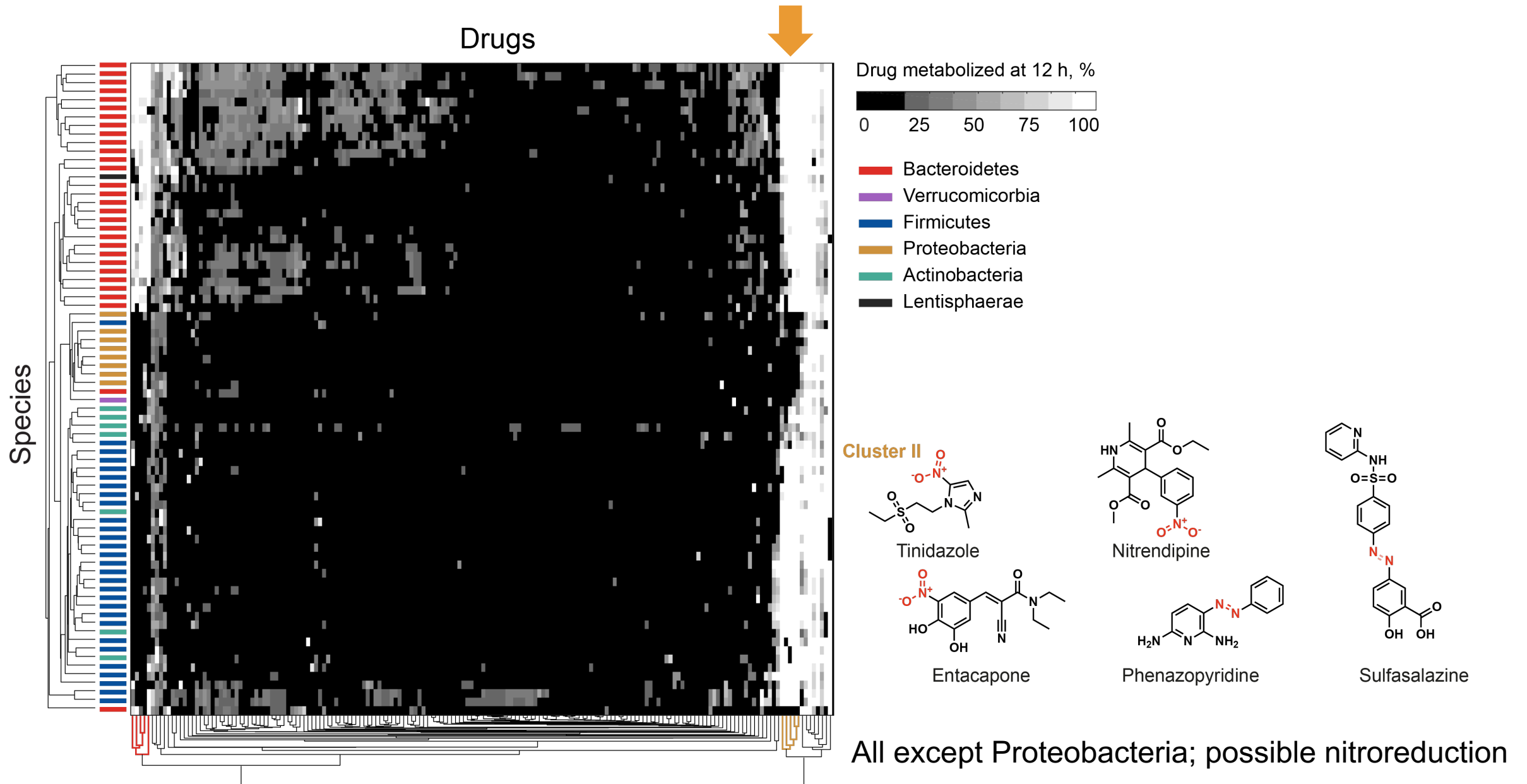
Related gut bacteria metabolize similar subsets of drugs



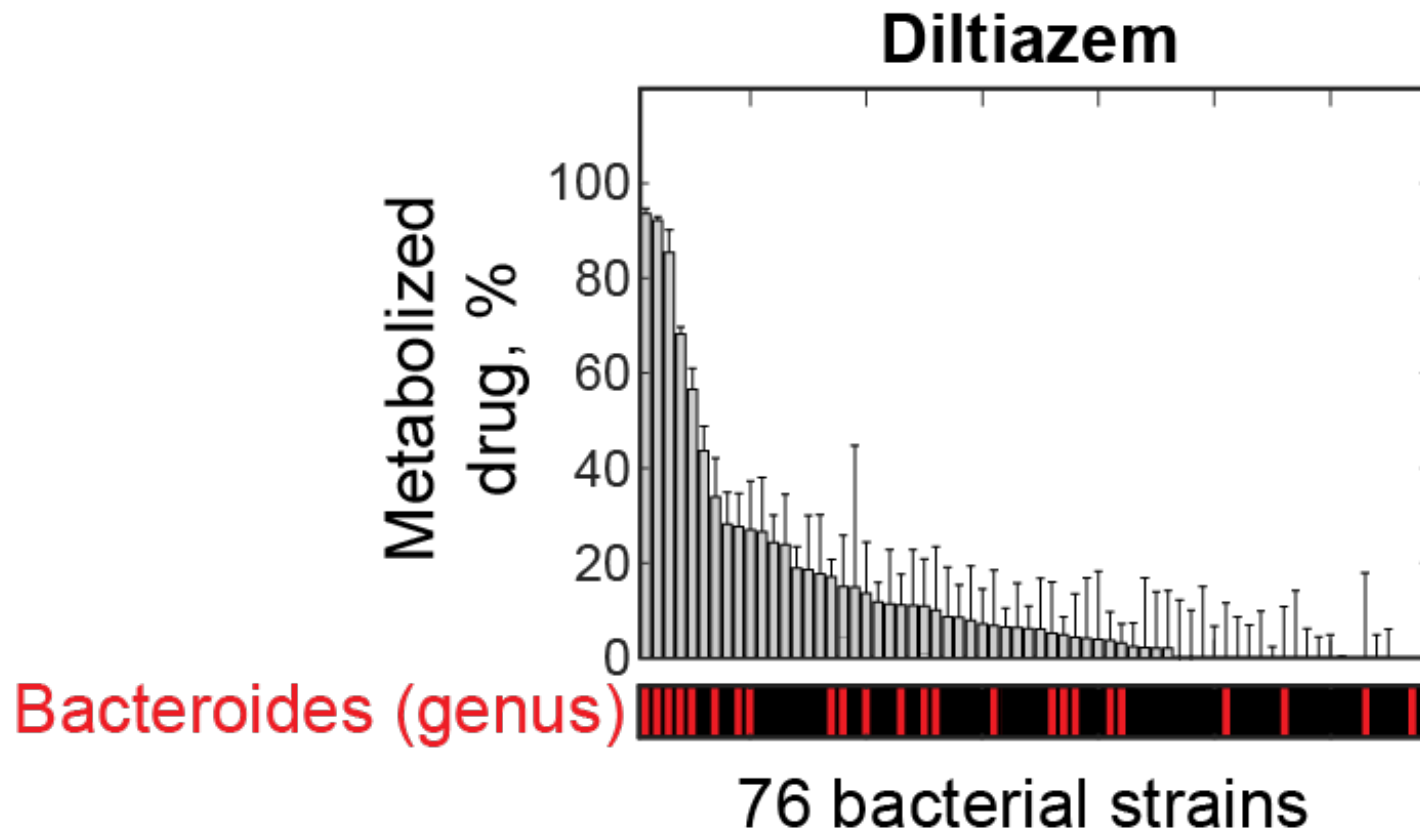
Some drugs with shared features cluster together



Some drugs with shared features cluster together

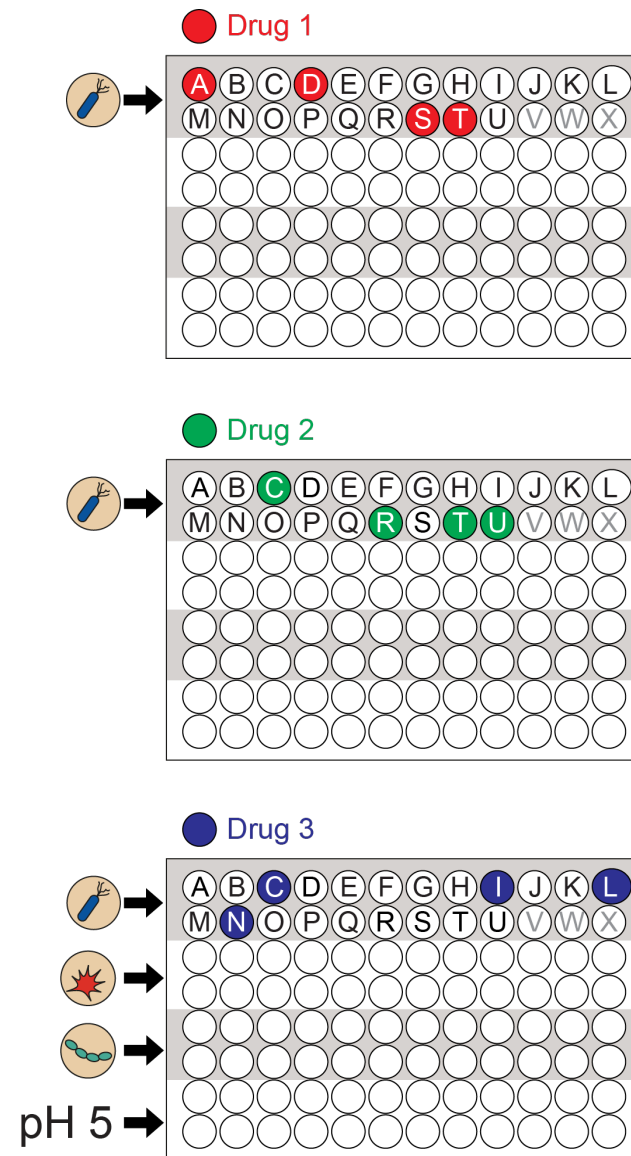


In many cases, genus (or species) identity does not predict drug-metabolizing activity

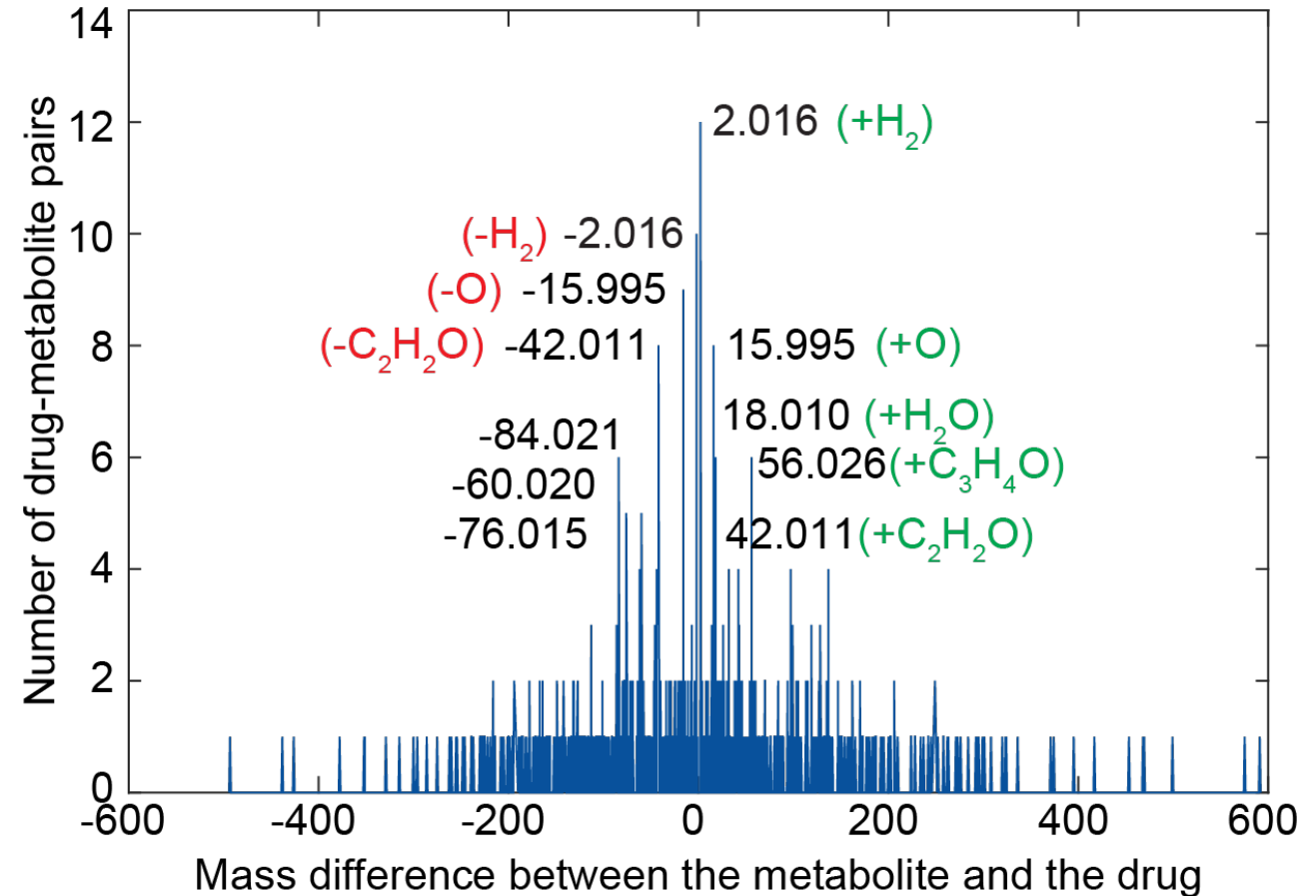
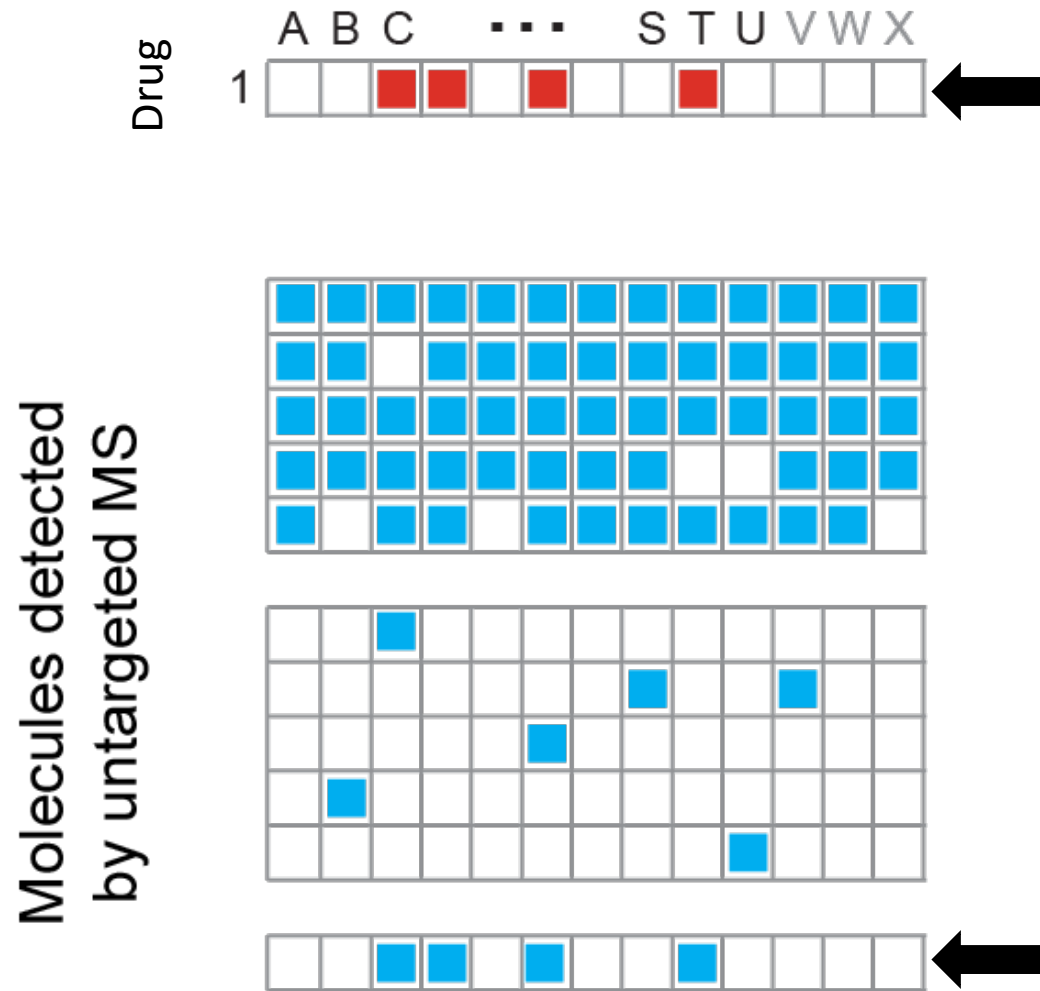


- What drug metabolites are formed?

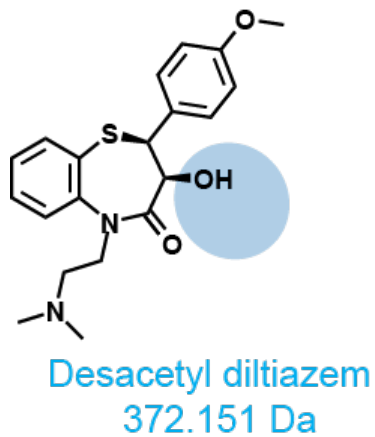
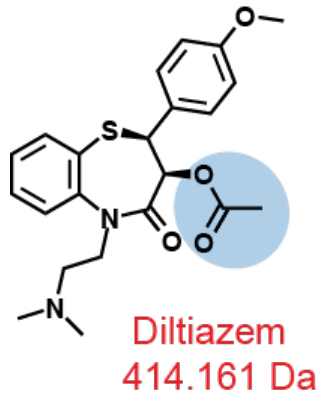
Molecules detected by untargeted MS



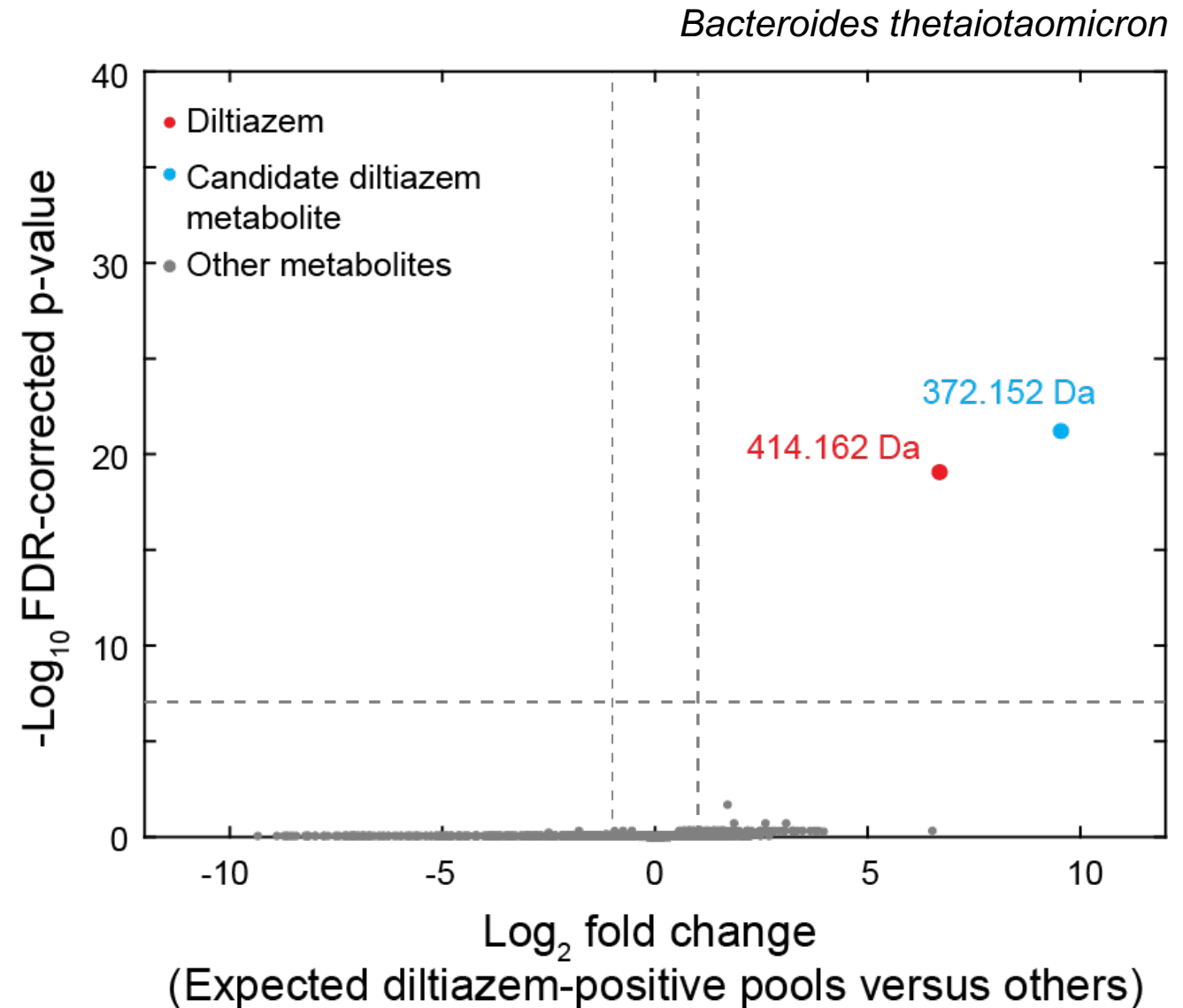
Gut microbes carry out the same modifications on multiple drugs



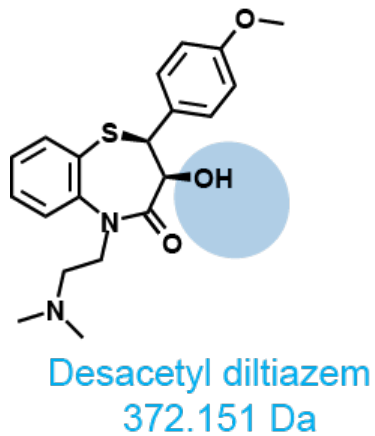
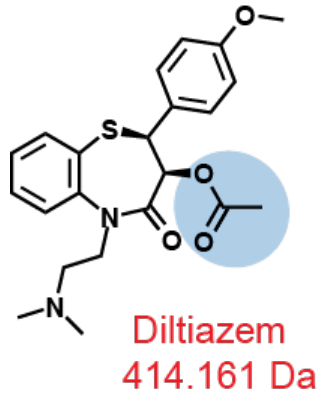
Two compounds are specifically present in diltiazem-containing pools



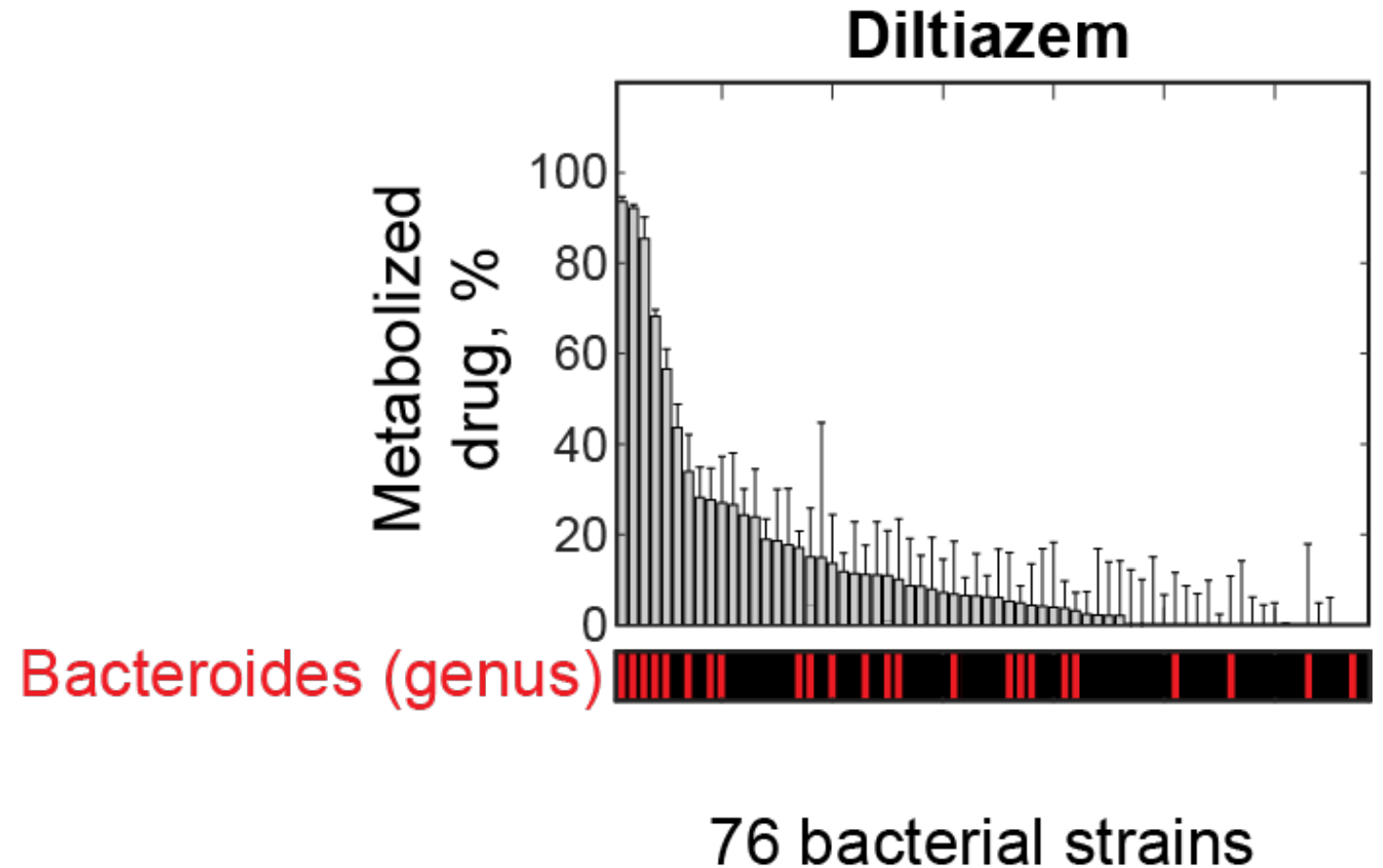
Mass shift: -42.01 Da



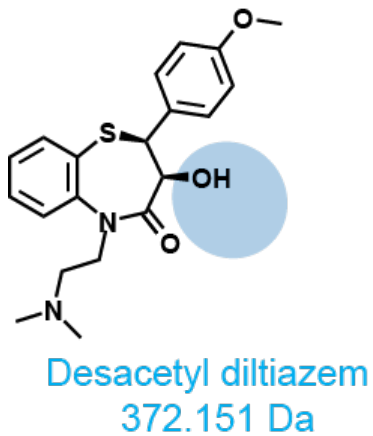
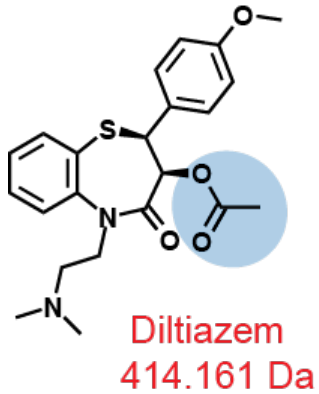
Even simple drug modifications can be restricted to select bacteria



Mass shift: -42.01 Da

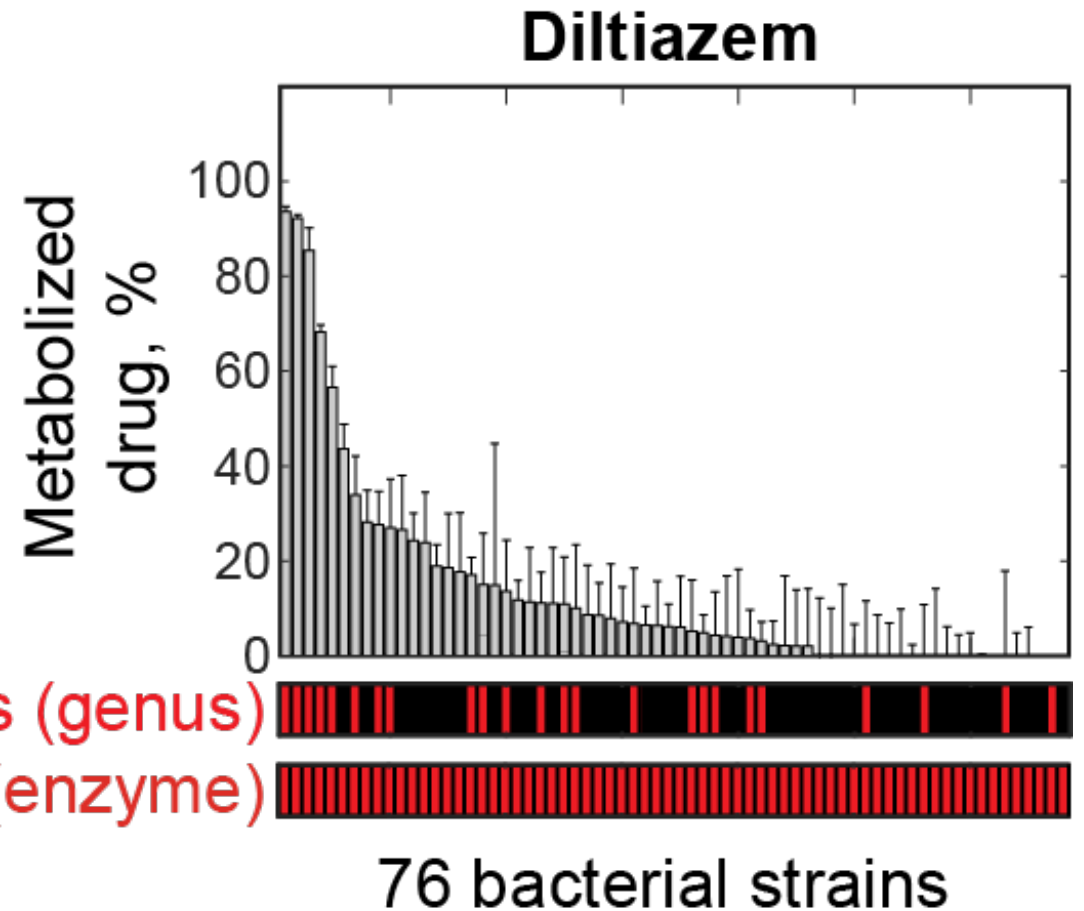


Genome annotation does not predict drug metabolism activity

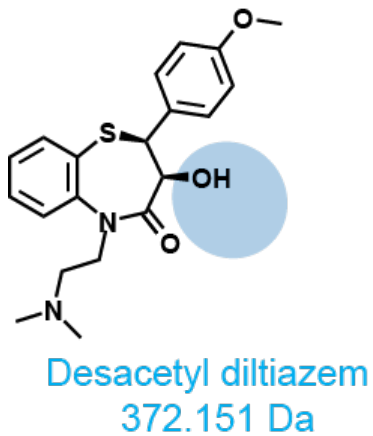
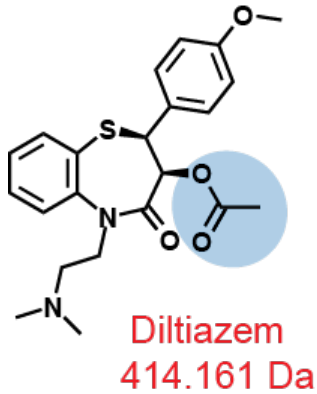


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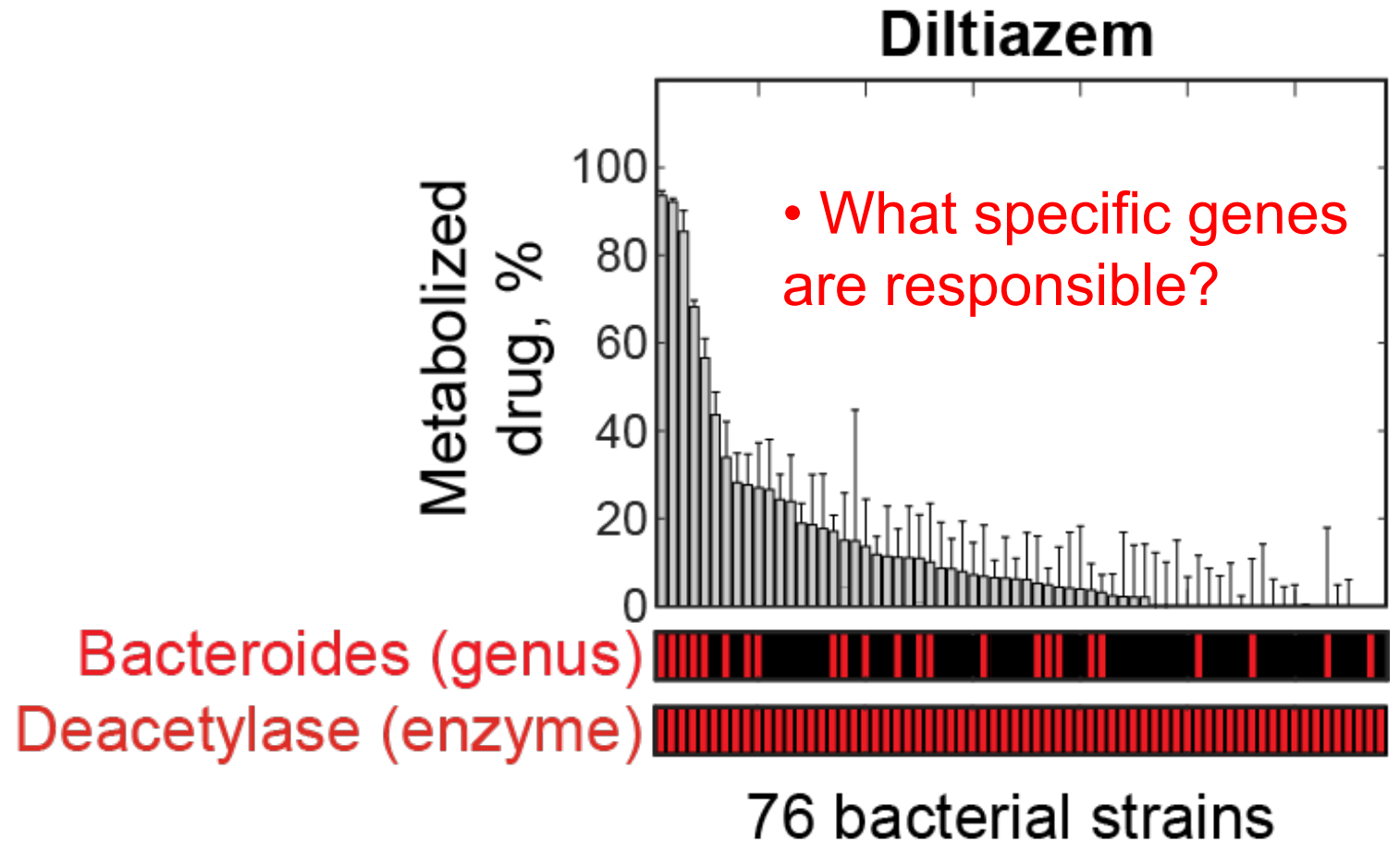
Bacteroides (genus)
Deacetylase (enzyme)



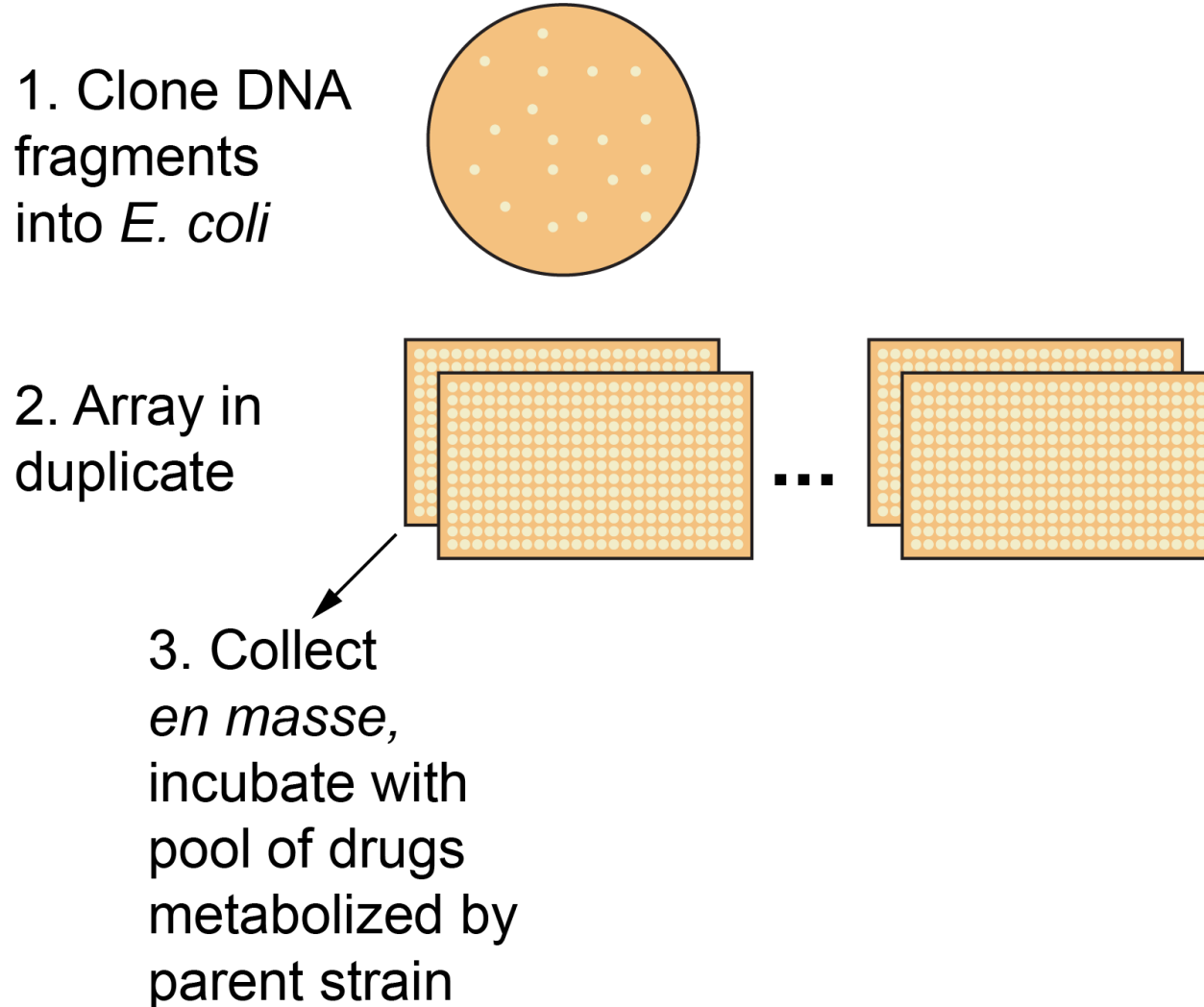
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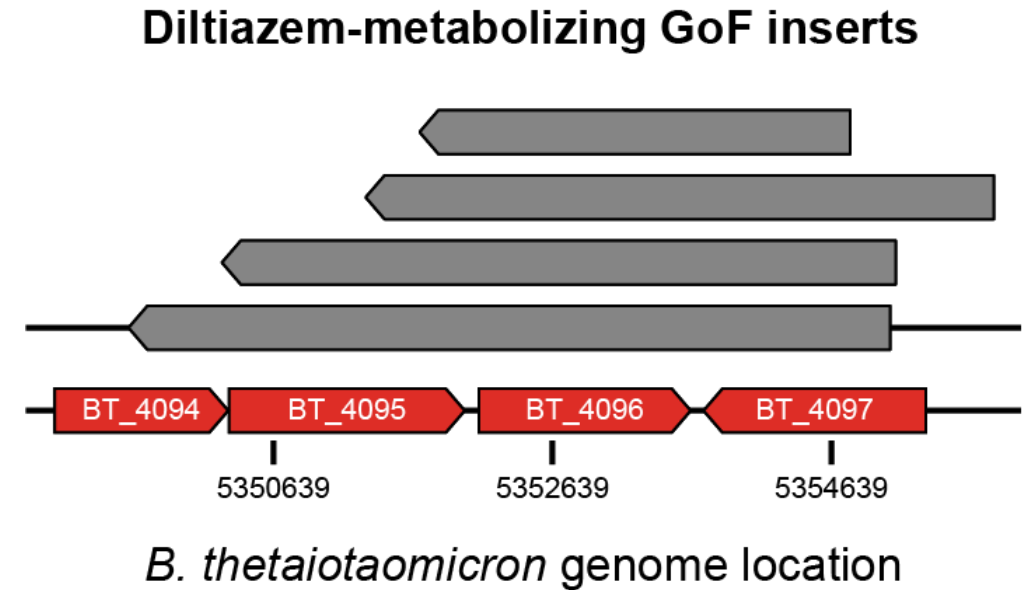
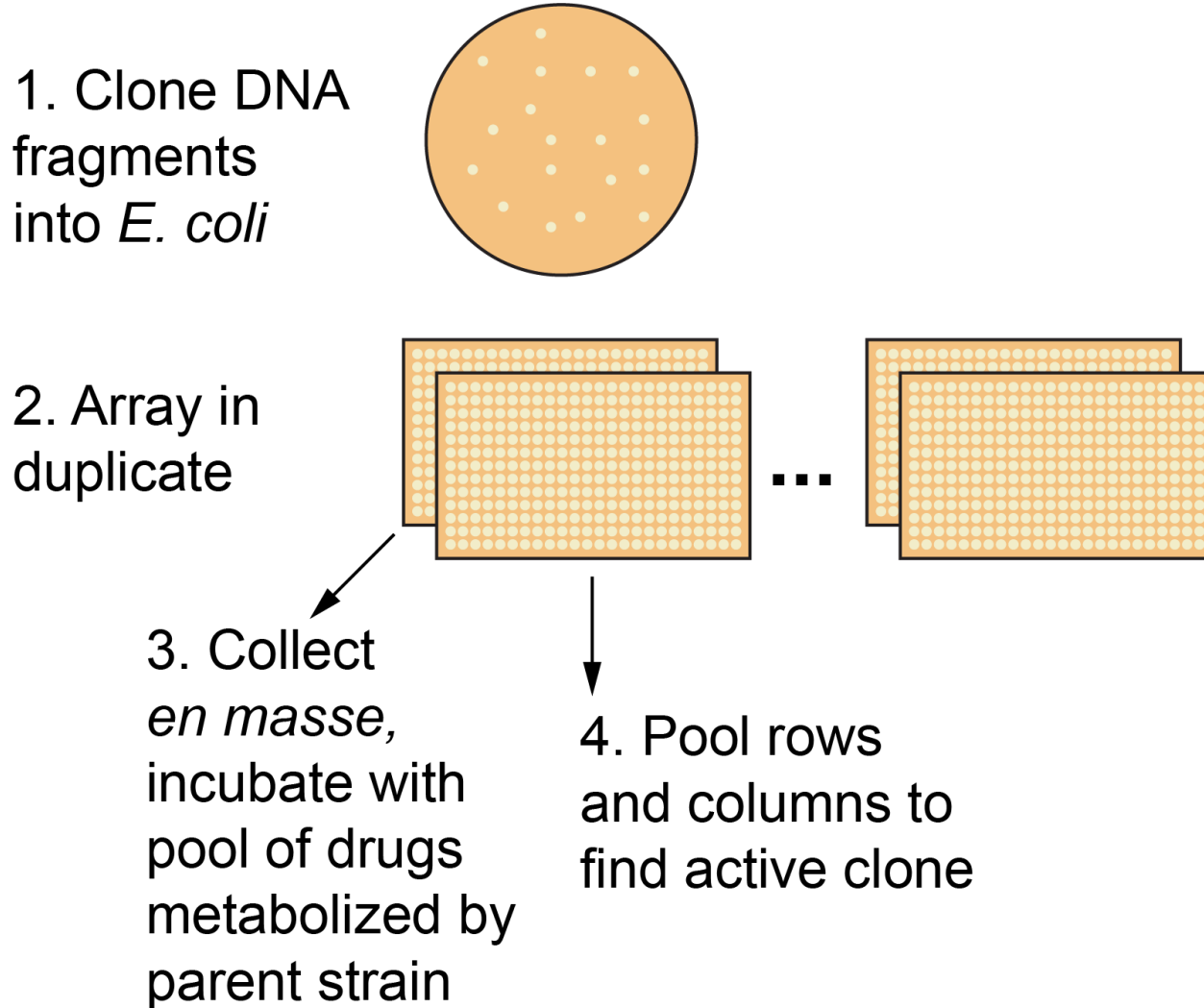
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A gain-of-function strategy for identifying drug metabolizing enzymes

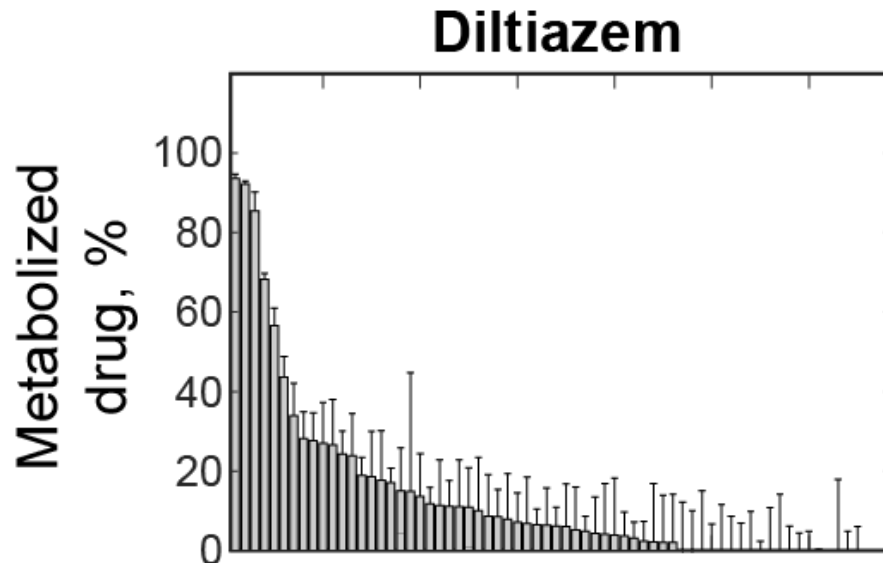





A gain-of-function strategy for identifying drug metabolizing enzymes

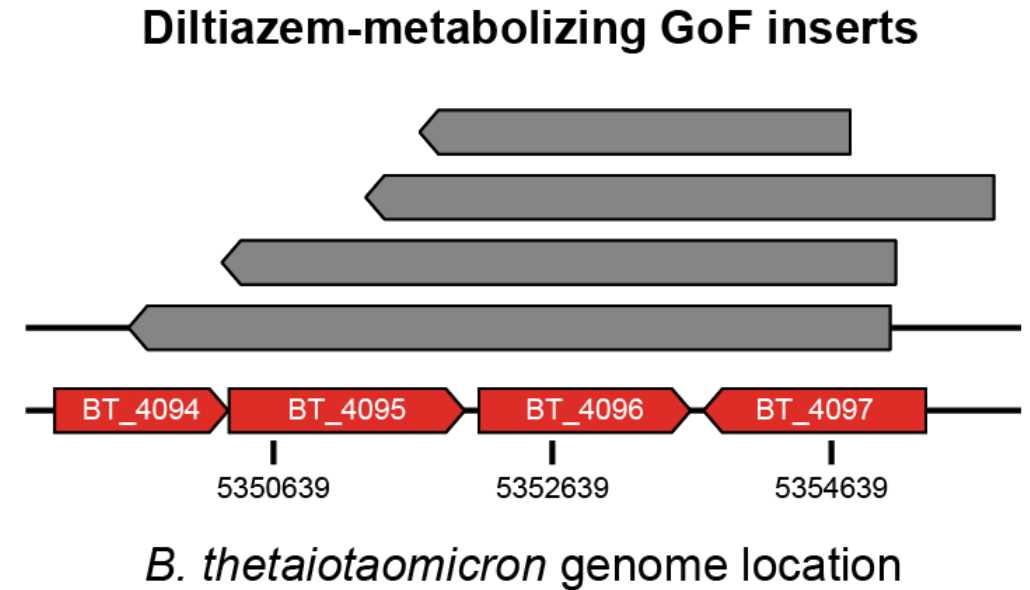


BT_4096 confirmed by targeted deletion and expression studies *in vitro* and in mice

Identified genes can explain drug-metabolizing activity across human gut species

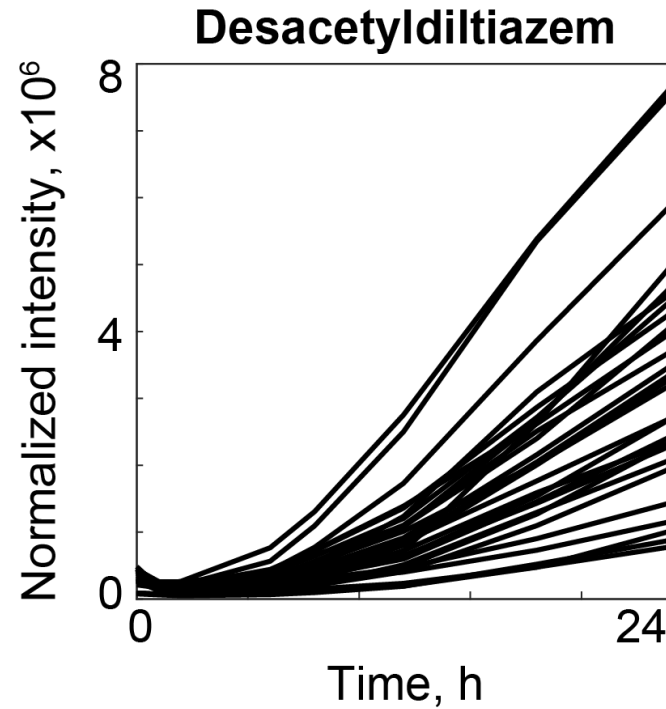
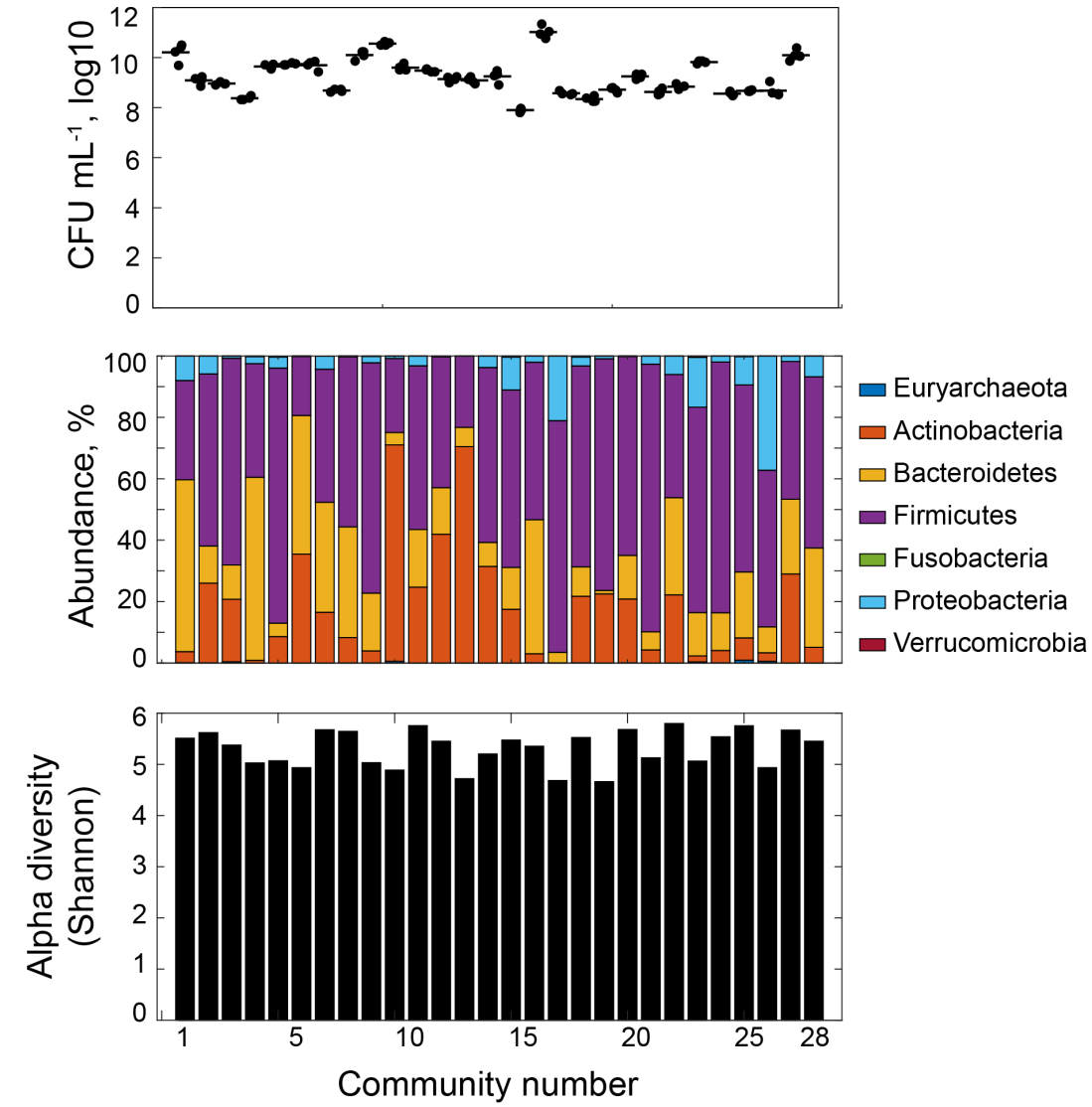


Bacteroides (genus) 
Deacetylase (enzyme) 
BT4096 (gene) 
76 bacterial strains

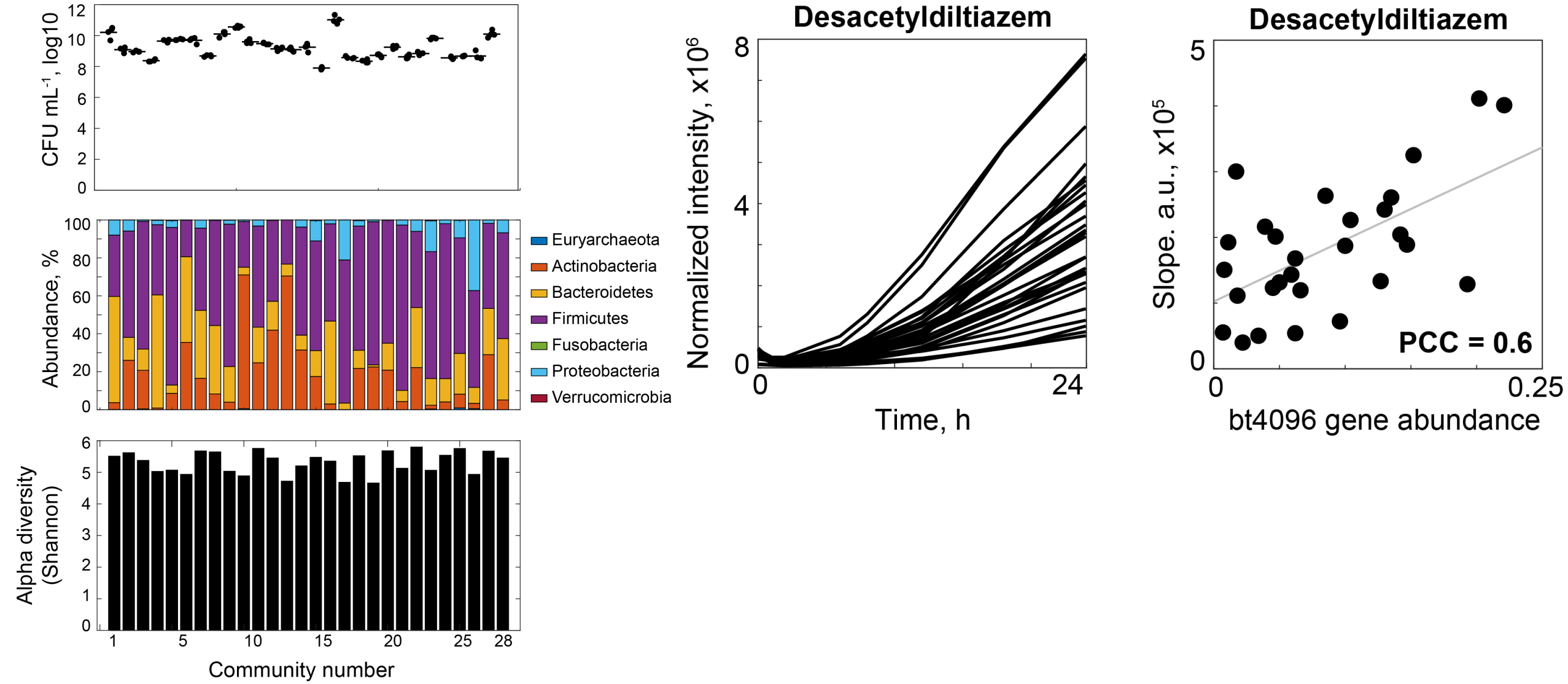


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Human gut communities exhibit variable diltiazem metabolism

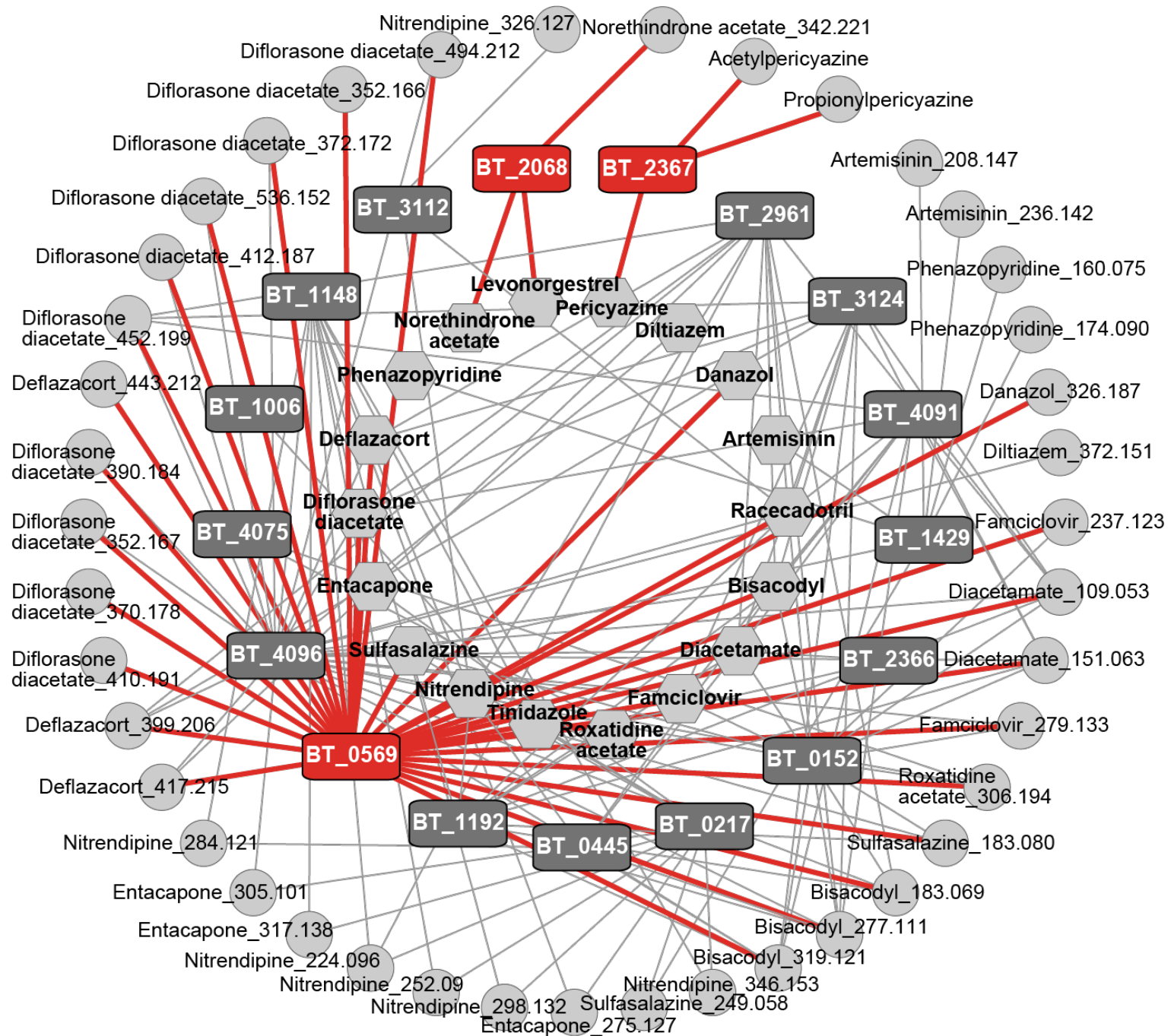


Identified genes help explain drug-metabolizing activity across human gut species and communities



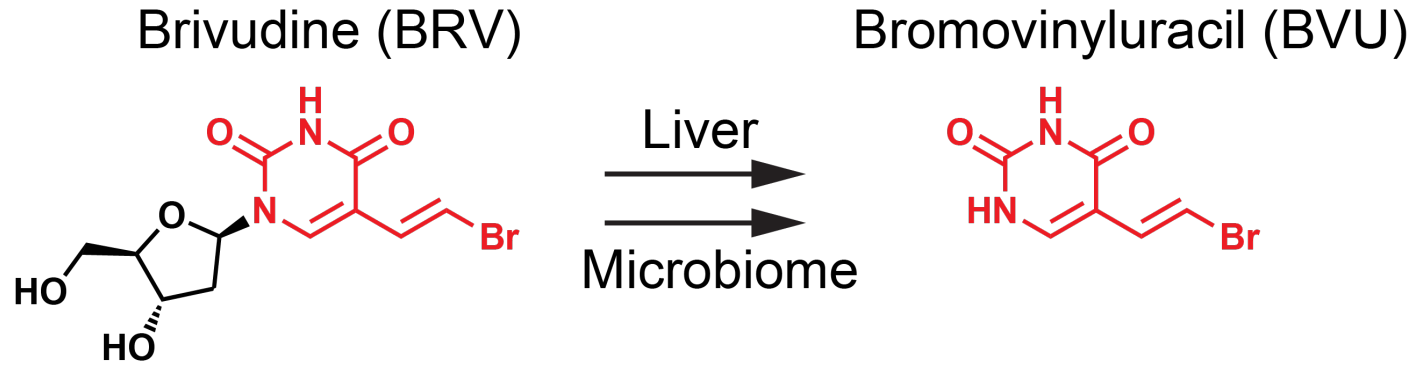
Gut microbes encode many drug-metabolizing enzymes

From 3 species, we found 30 microbiome-encoded enzymes that convert 20 drugs into 59 metabolites

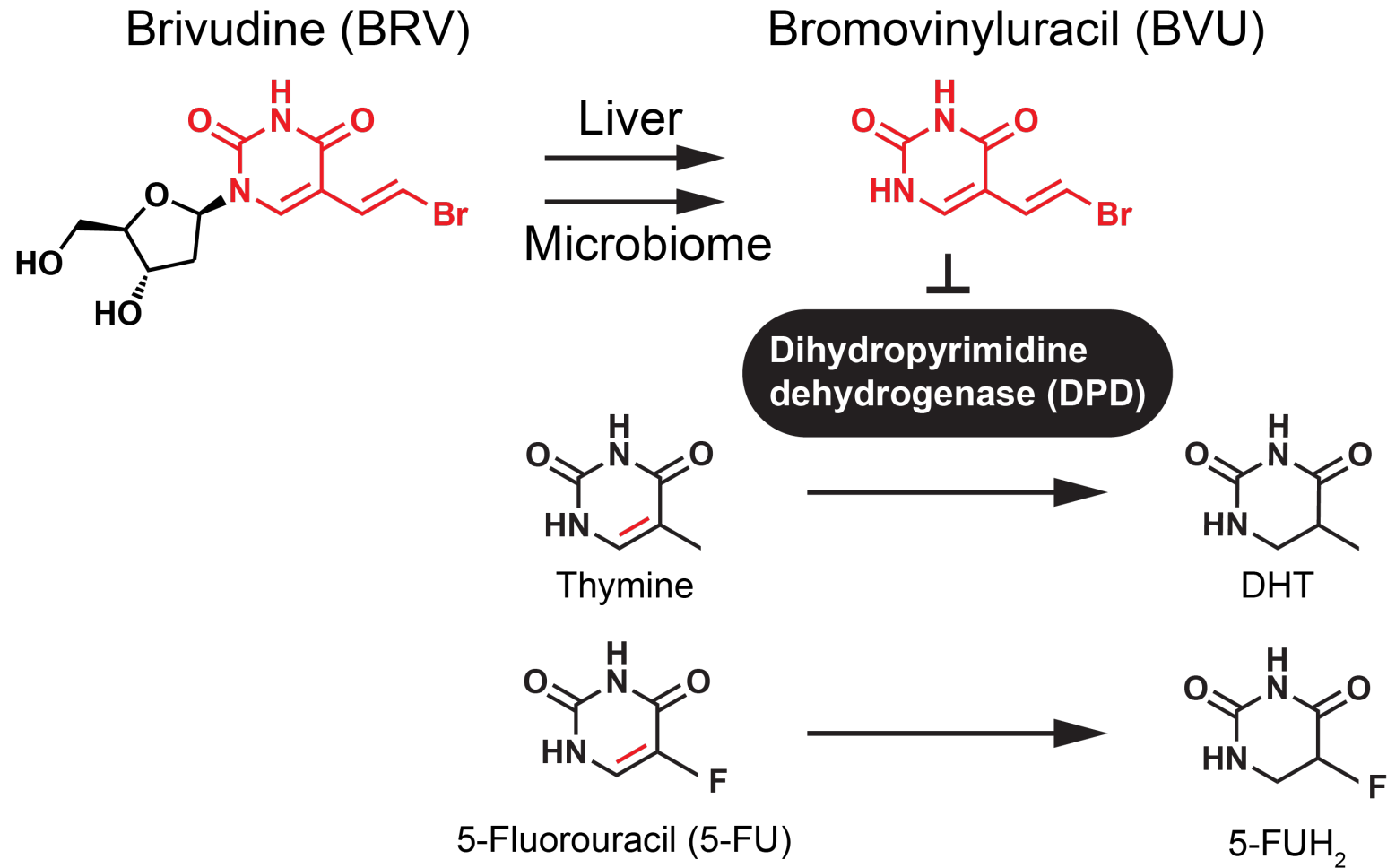


Could the microbiome contribute to the production of toxic drug metabolites if the liver has the same activity?

Could the microbiome contribute to the production of toxic drug metabolites if the liver has the same activity?

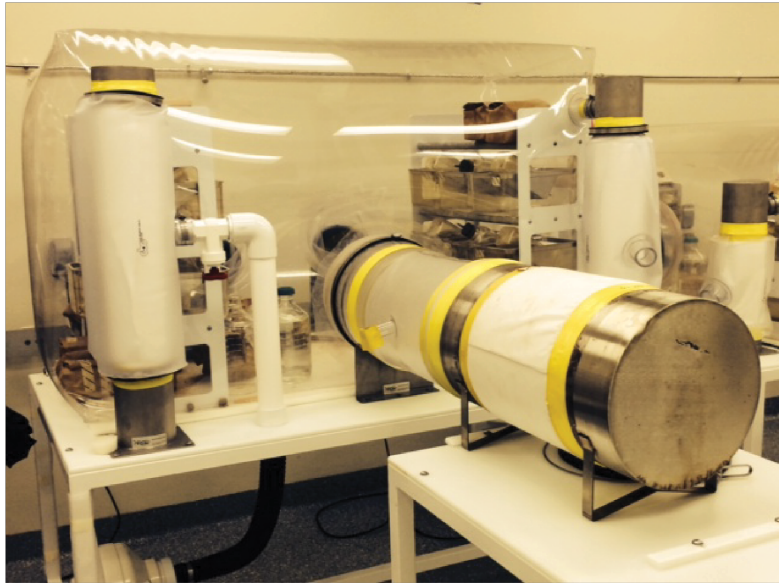


BVU is a toxic drug metabolite

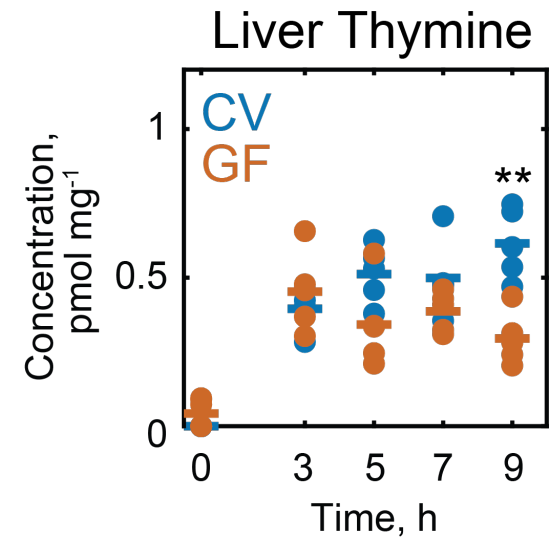
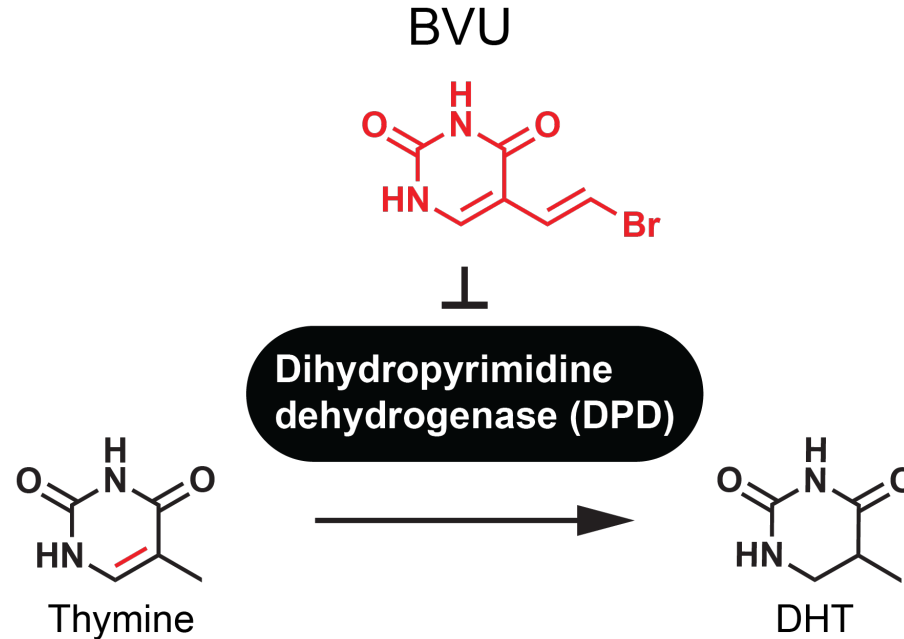


Germfree mice show reduced thymine accumulation in the liver after BRV administration

Gnotobiotic isolator

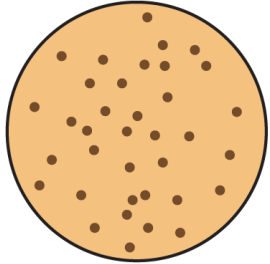


- Conventional (CV): complete flora
- Germfree (GF): no microbiome

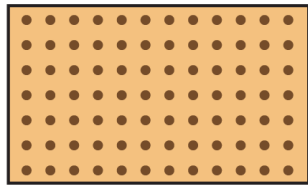


A loss-of-function strategy for identifying drug metabolizing enzymes

1. Mutagenize target strain

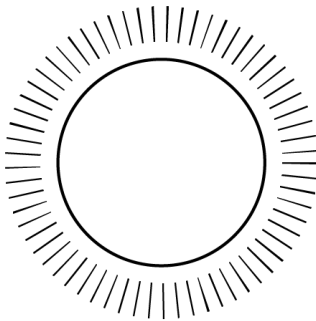


2. Map mutation sites



...
(x100)

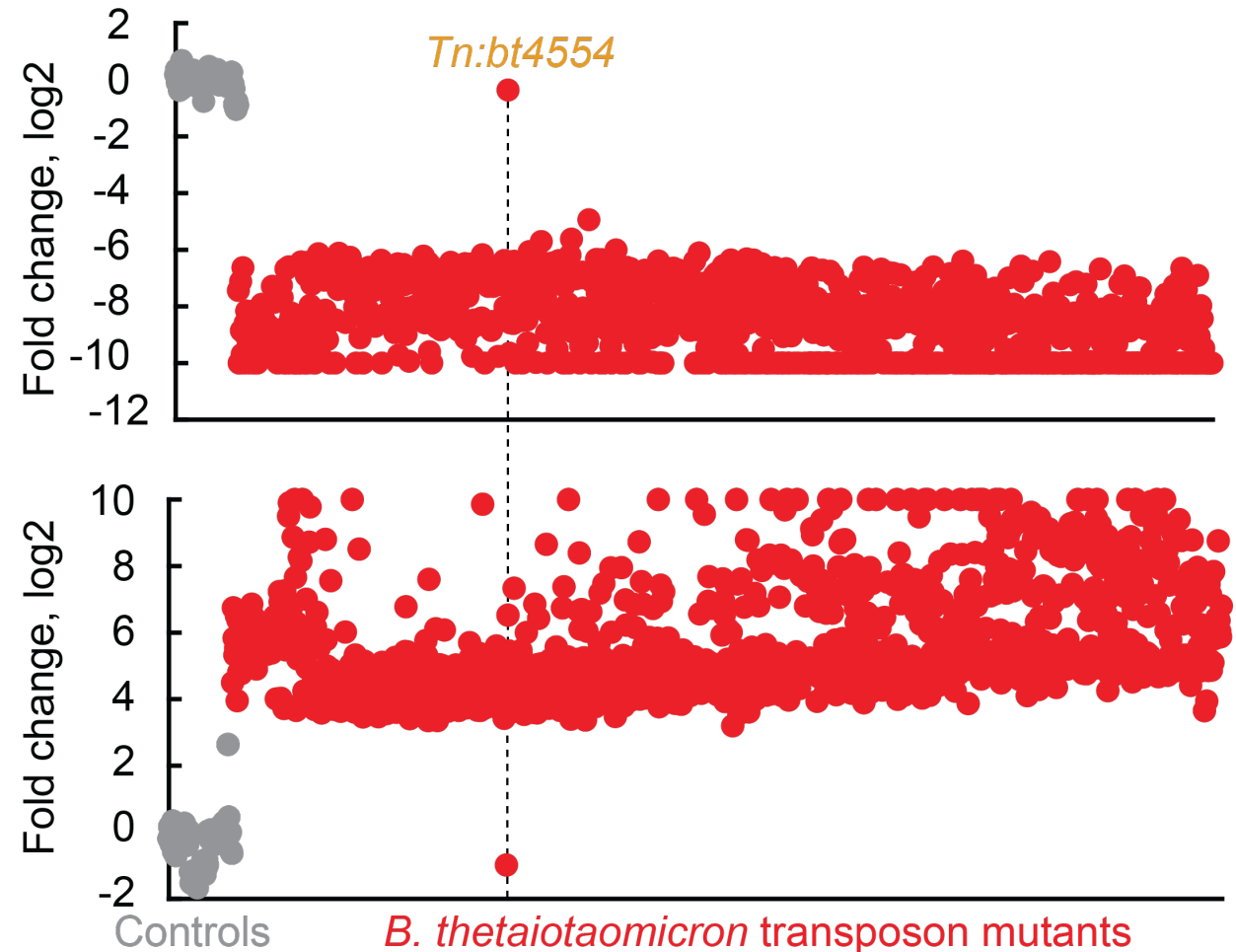
3. Assemble non-redundant library



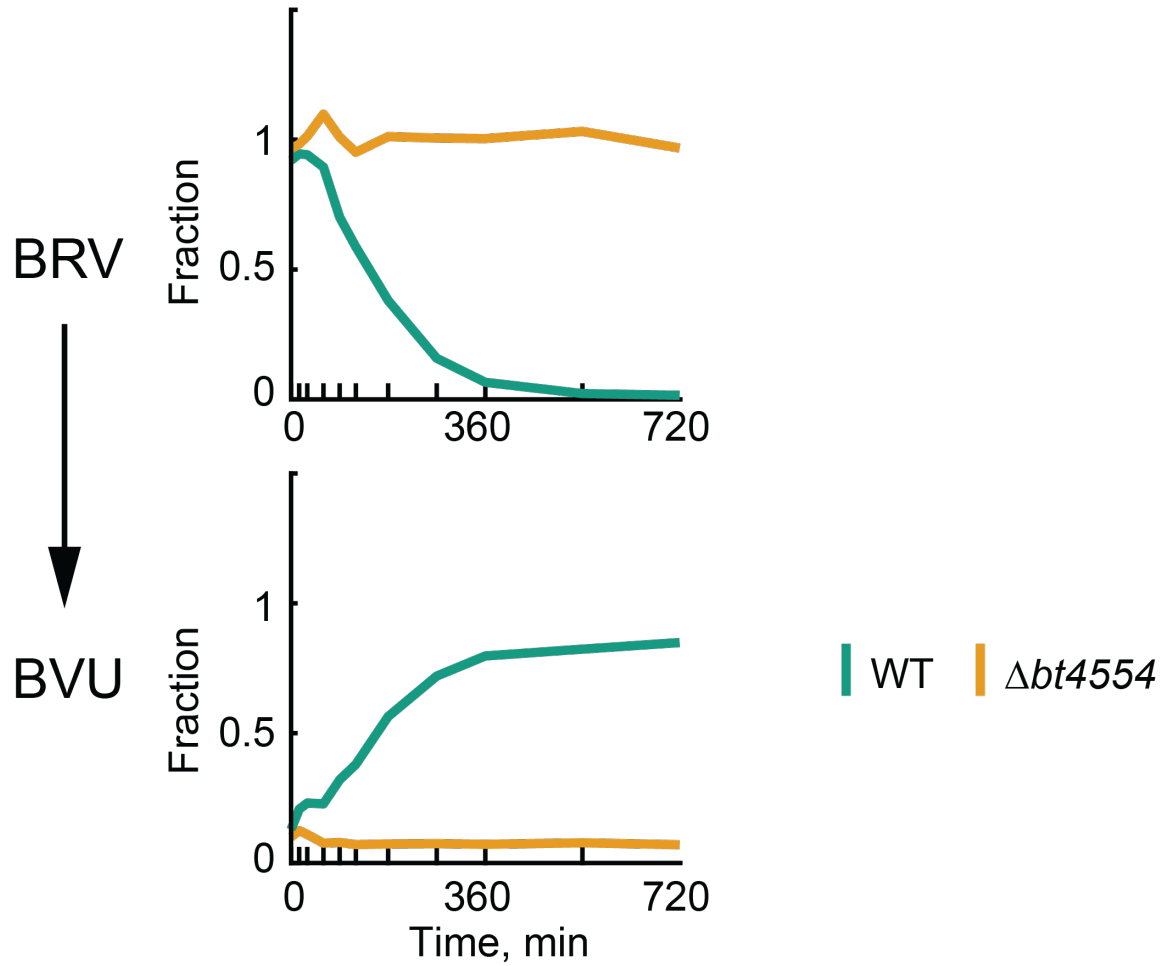
4. Incubate each mutant with drug pool

BRV

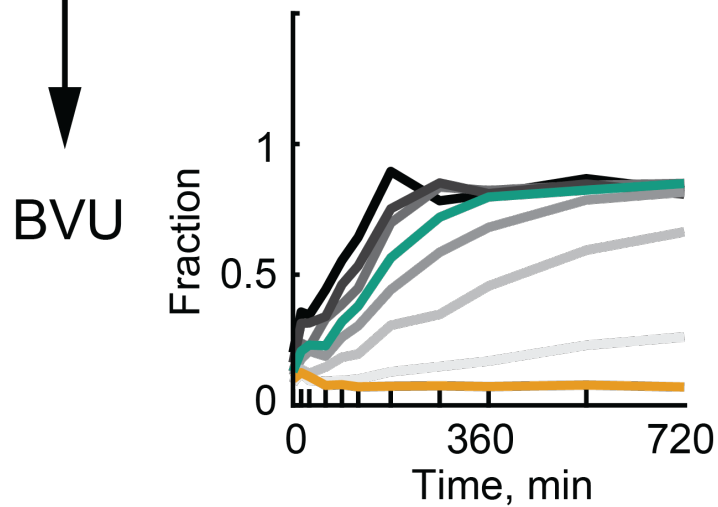
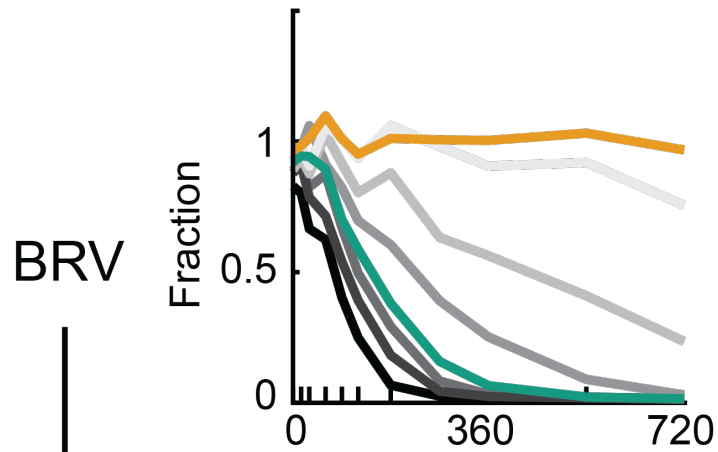
BVU



BT4554 is necessary, dose-limiting, and sufficient



BT4554 is necessary, dose-limiting, and sufficient



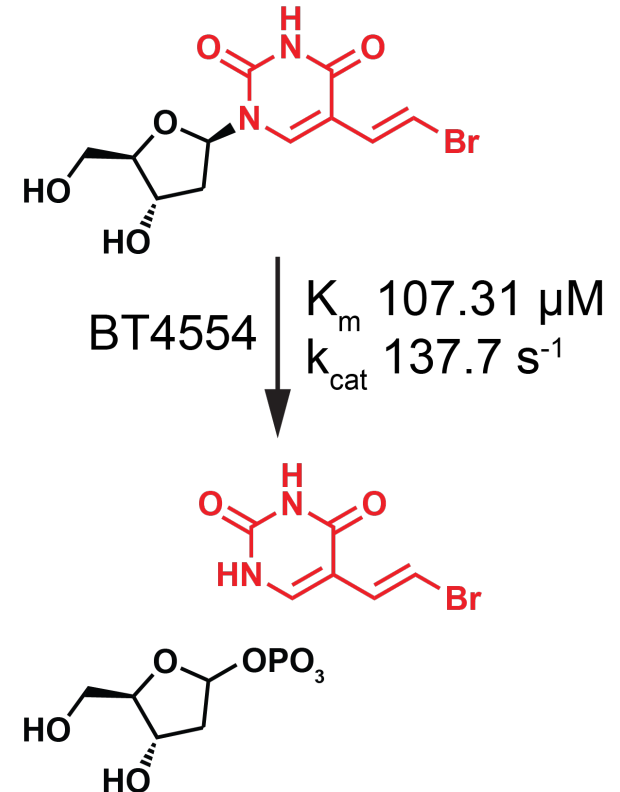
WT $\Delta bt4554$



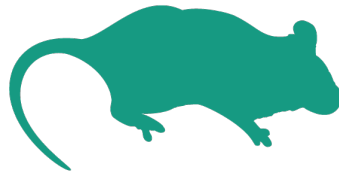
Brivudine (BRV)

Bromovinyluracil (BVU)

+
Deoxyribose
1-phosphate



Pharmacokinetics in mice that vary in a single microbiome-encoded enzyme



GN^{WT}

Host:

C57BL/6



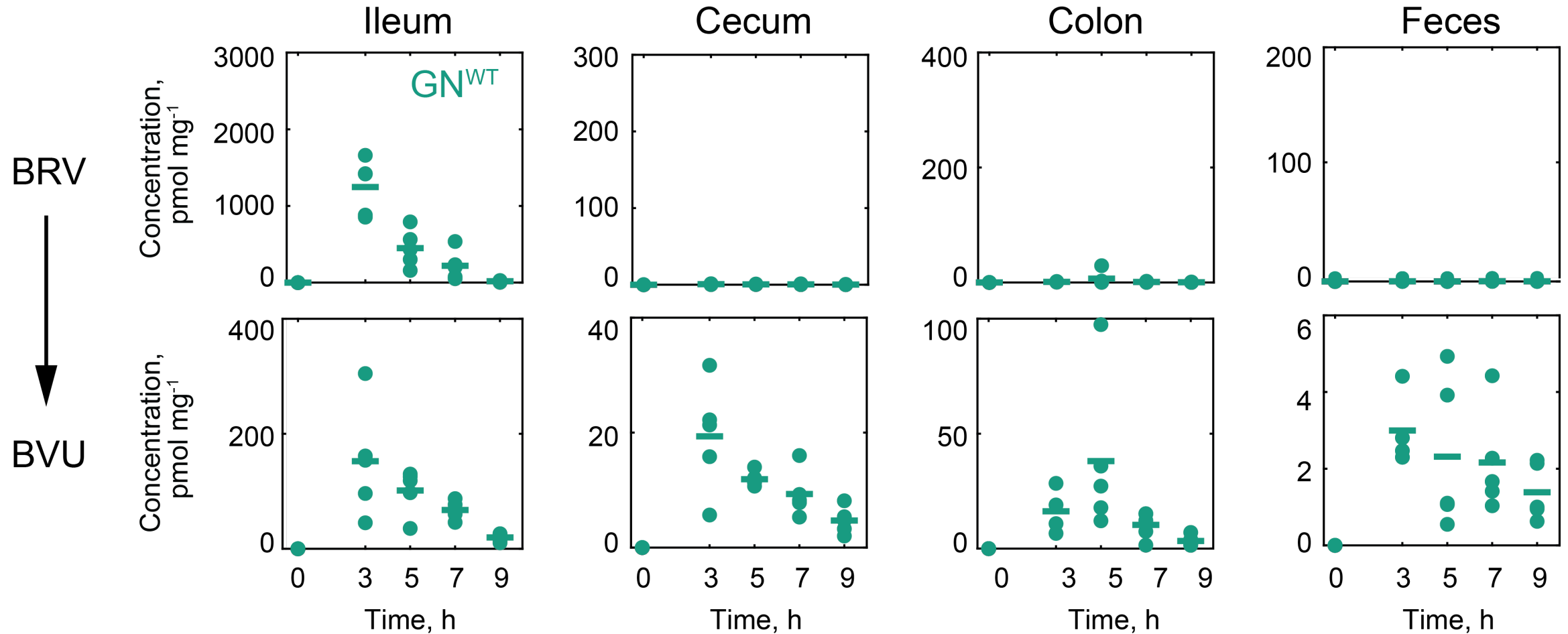
GN^{MUT}

Microbiota:

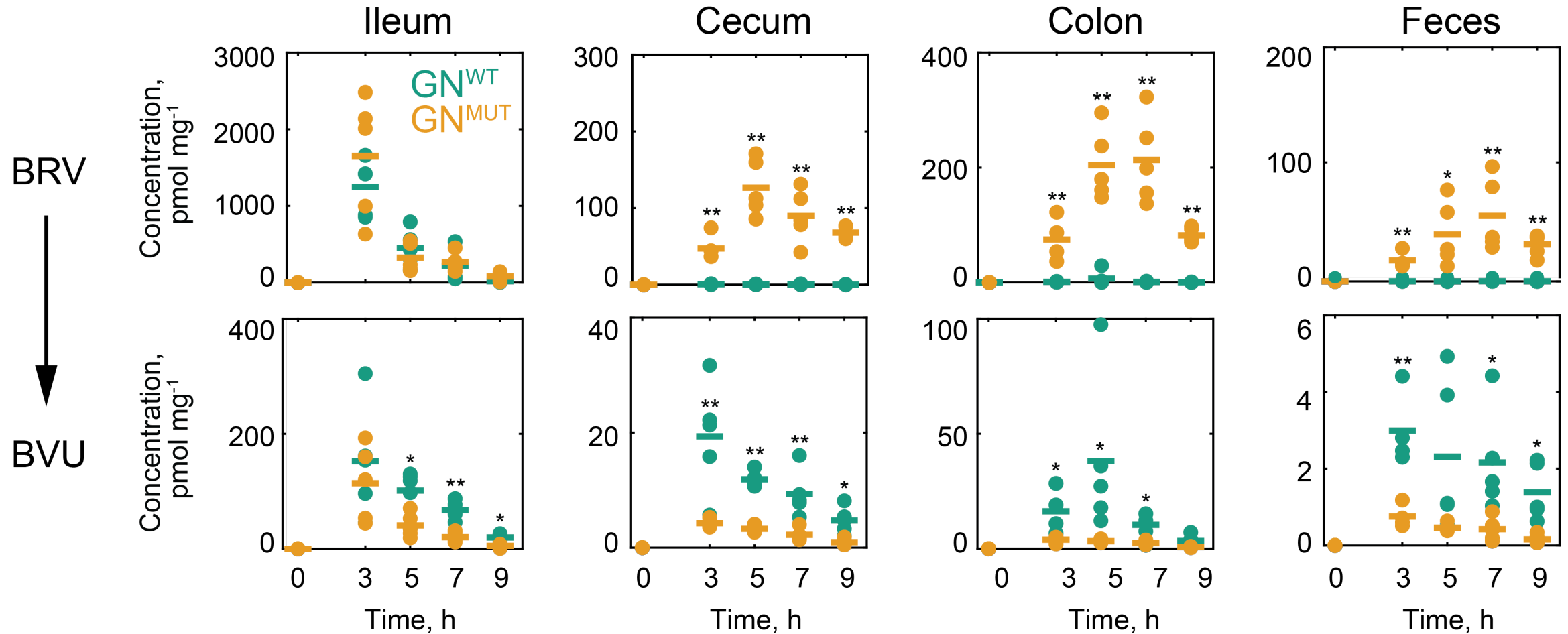
B. theta

B. theta
 $\Delta bt4554$

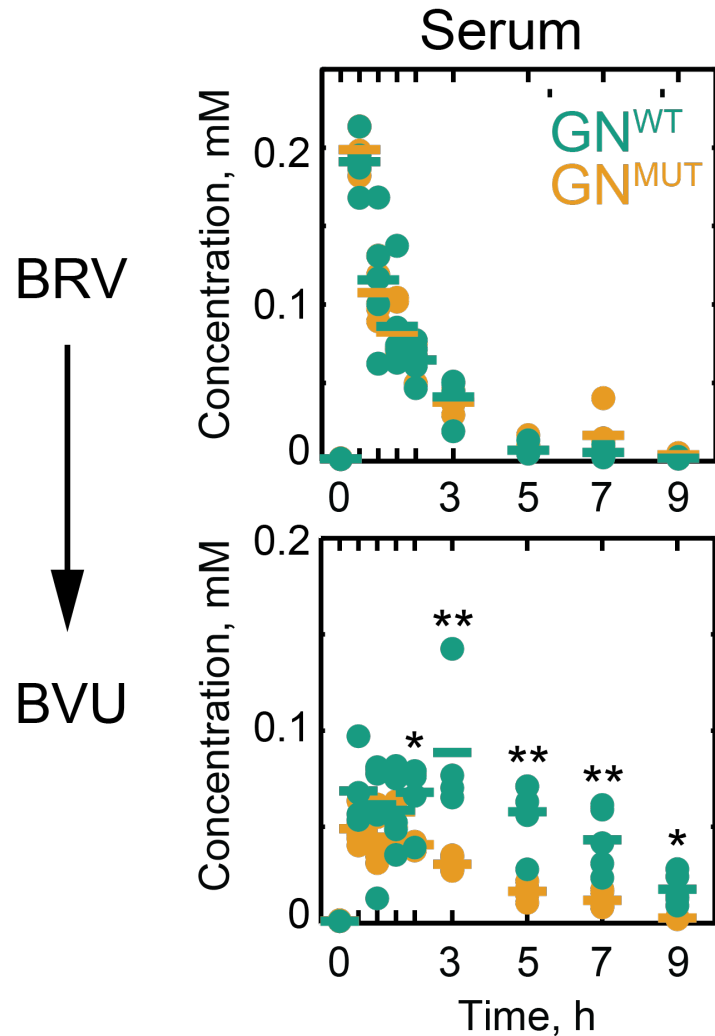
Pharmacokinetics in mice that vary in a single microbiome-encoded enzyme



Pharmacokinetics in mice that vary in a single microbiome-encoded enzyme



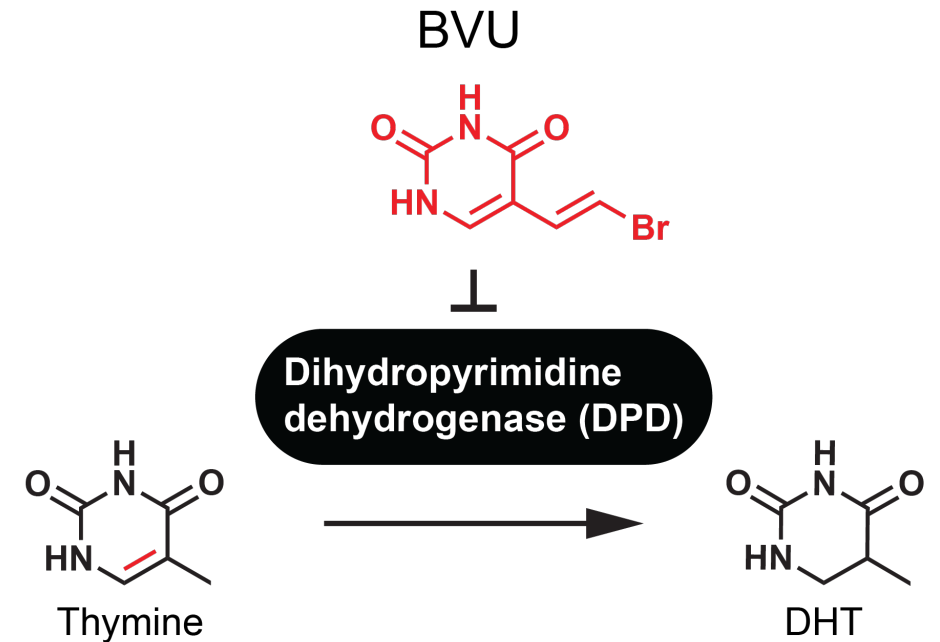
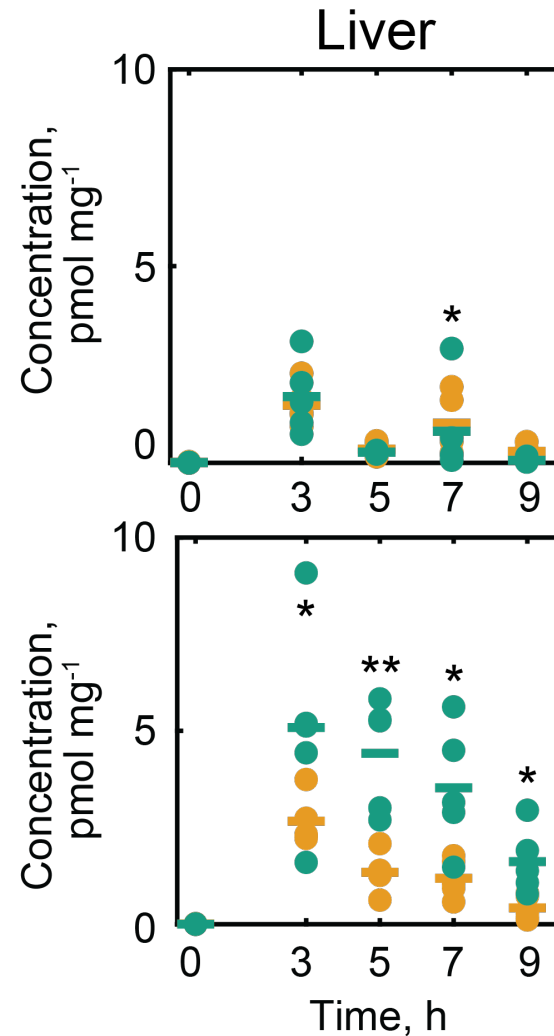
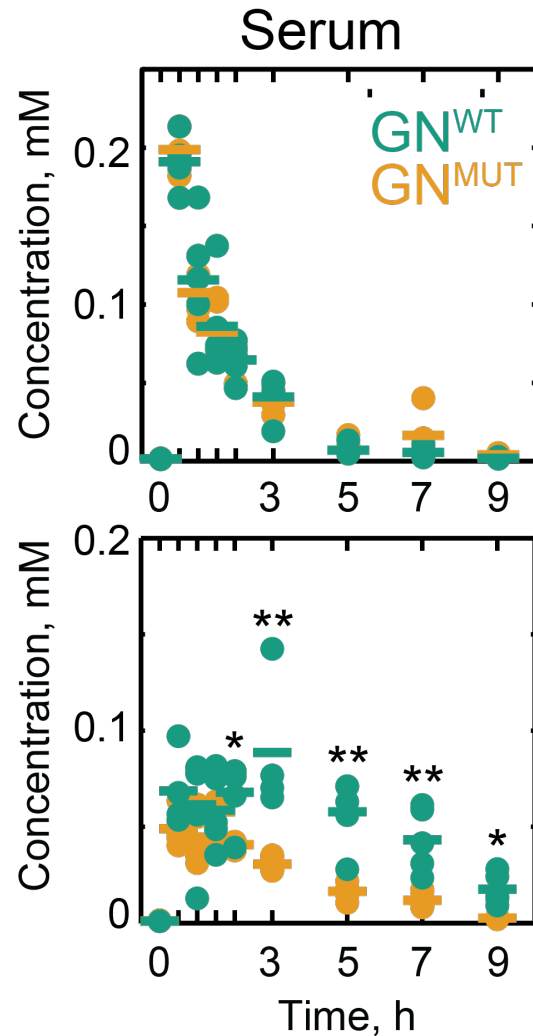
BVU is readily absorbed from the gut into systemic circulation



BVU is readily absorbed from the gut into systemic circulation

BRV

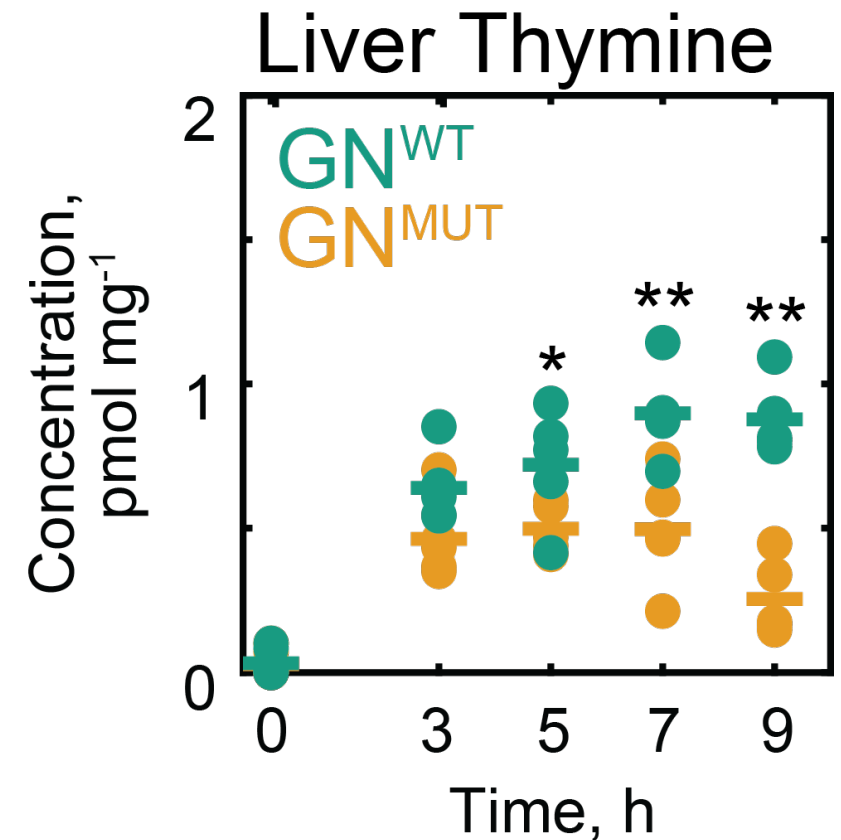
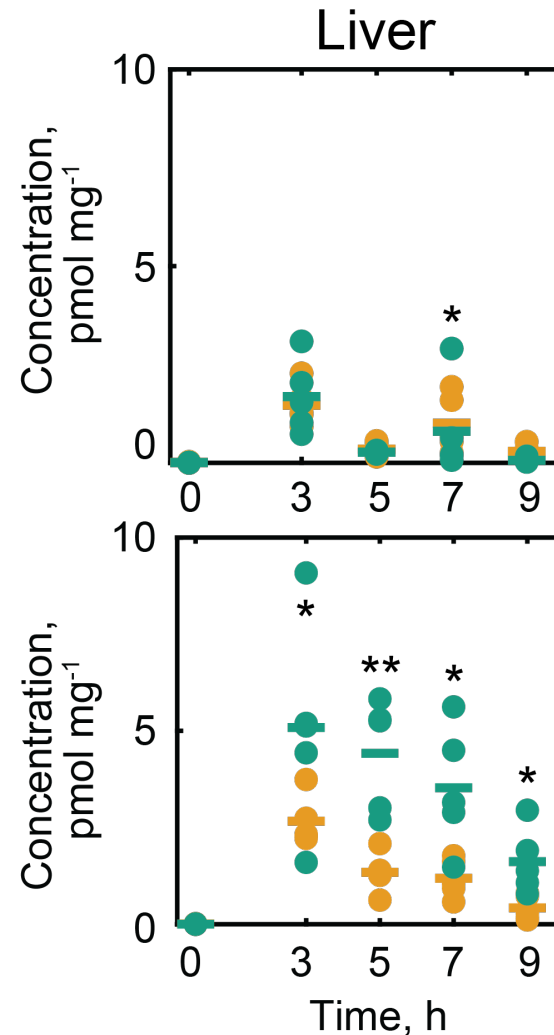
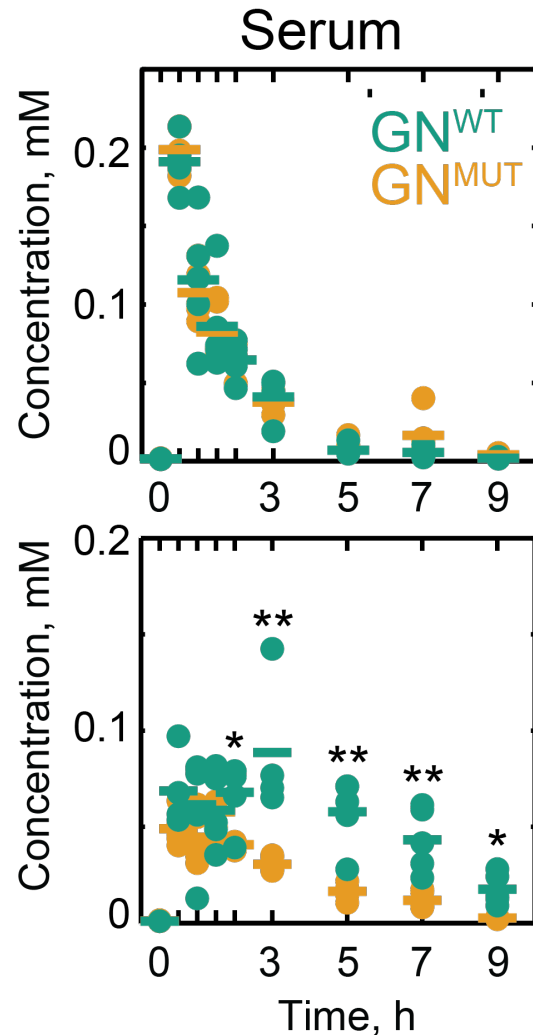
BVU



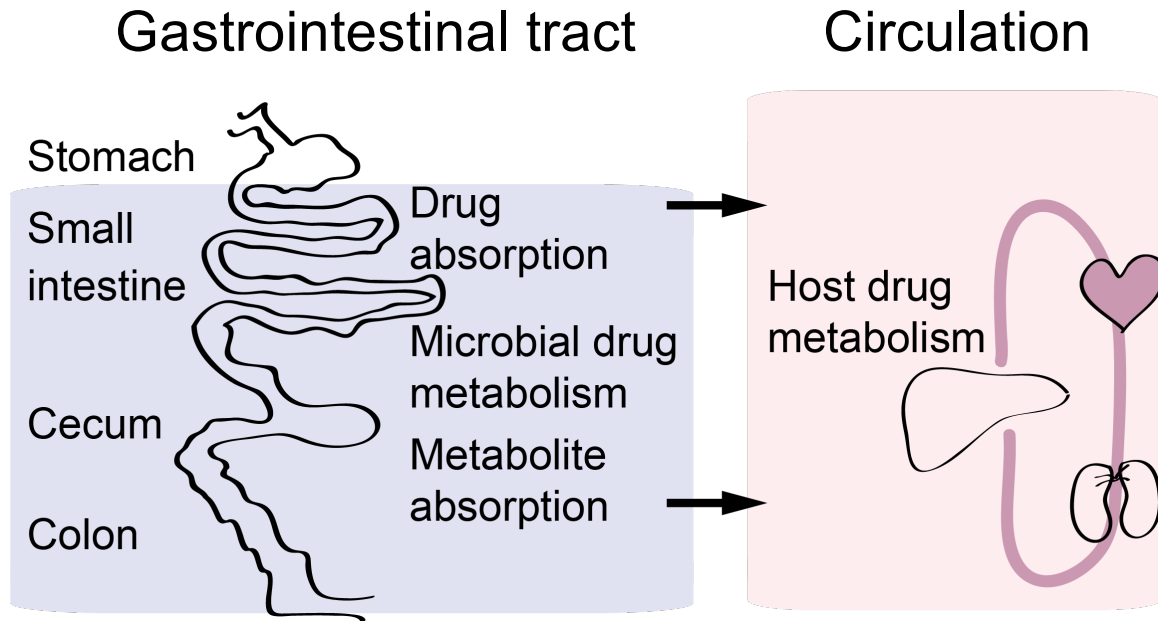
Drug metabolizing activity in the microbiome determines drug toxicity in the liver

BRV

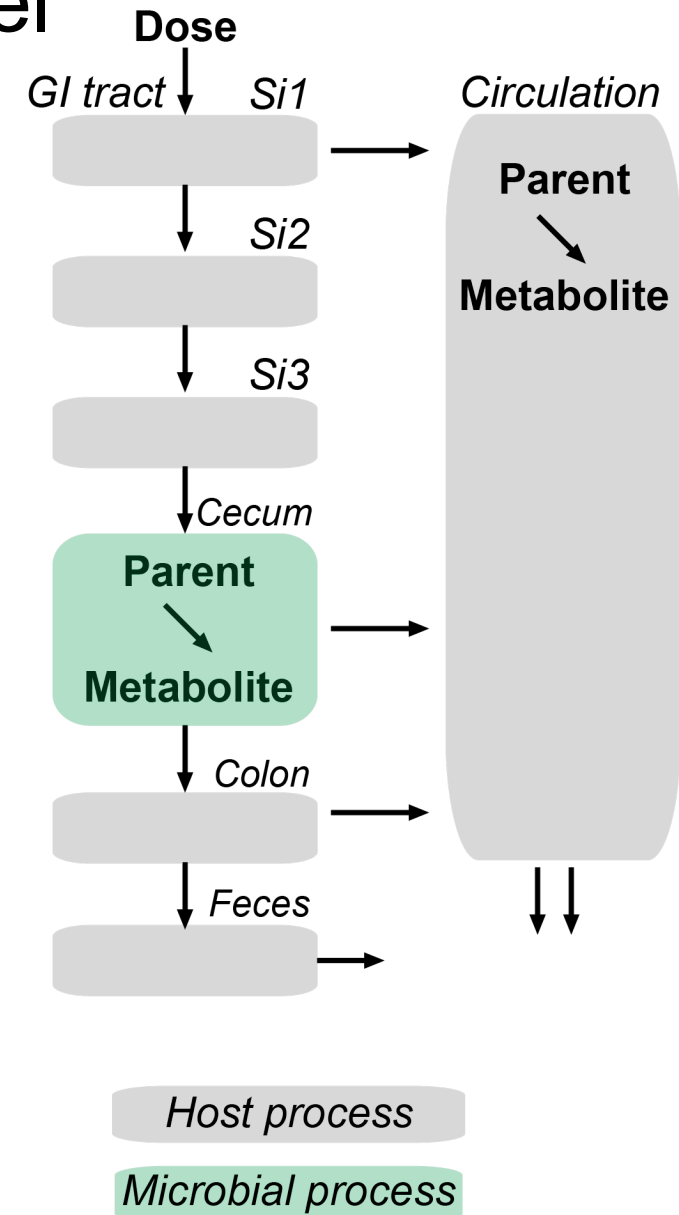
BVU



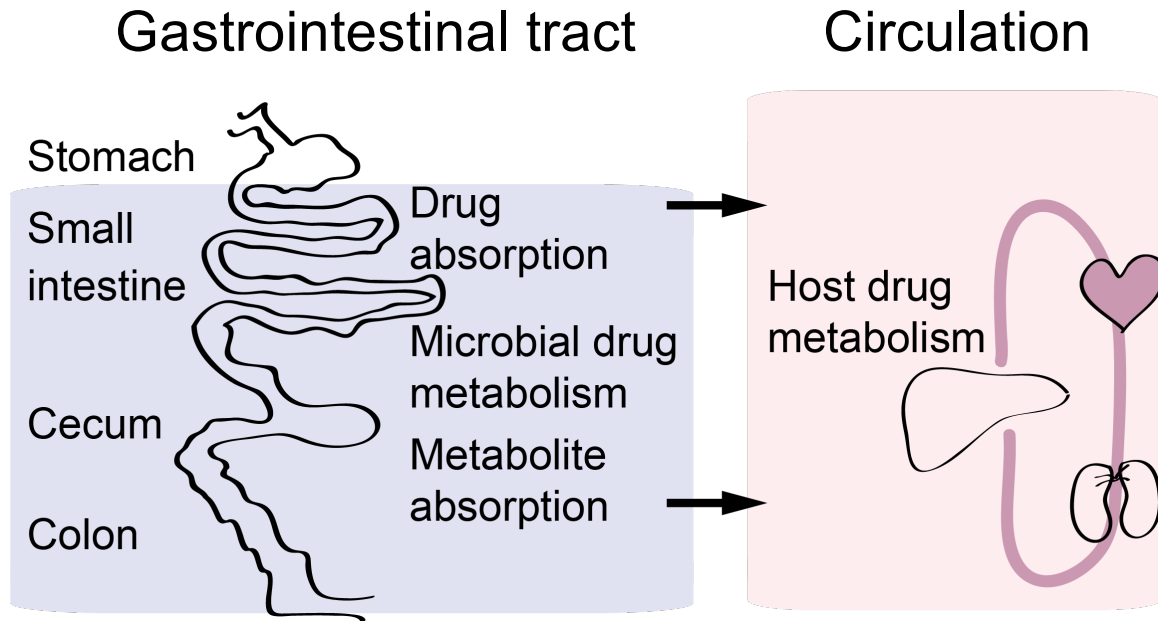
Physiology-based pharmacokinetic model of host-microbiome drug metabolism



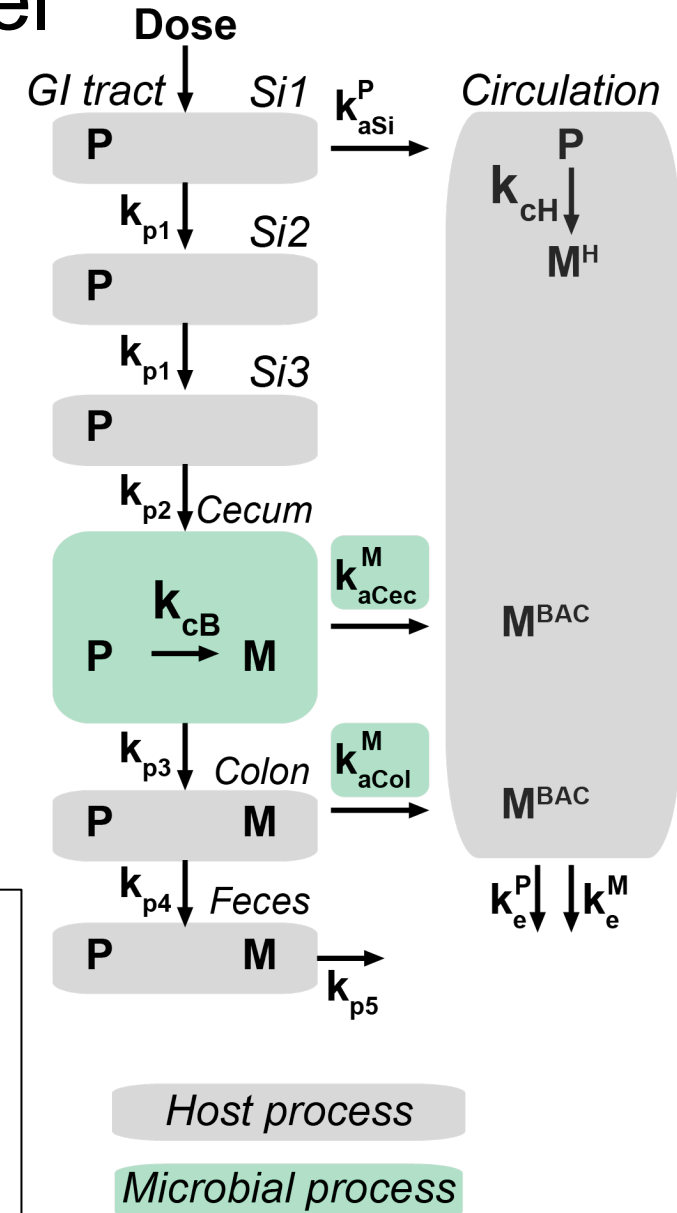
- Quantify microbiome contribution to serum drug metabolite exposure
- Estimate how different factors impact microbiome contribution



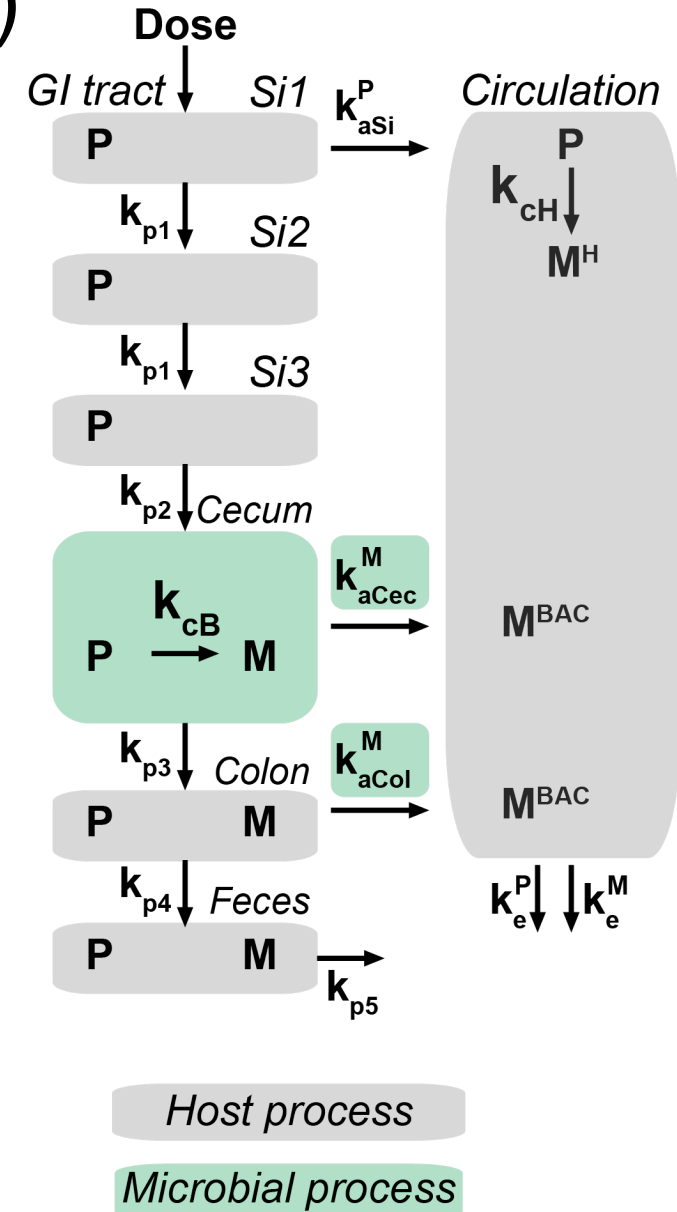
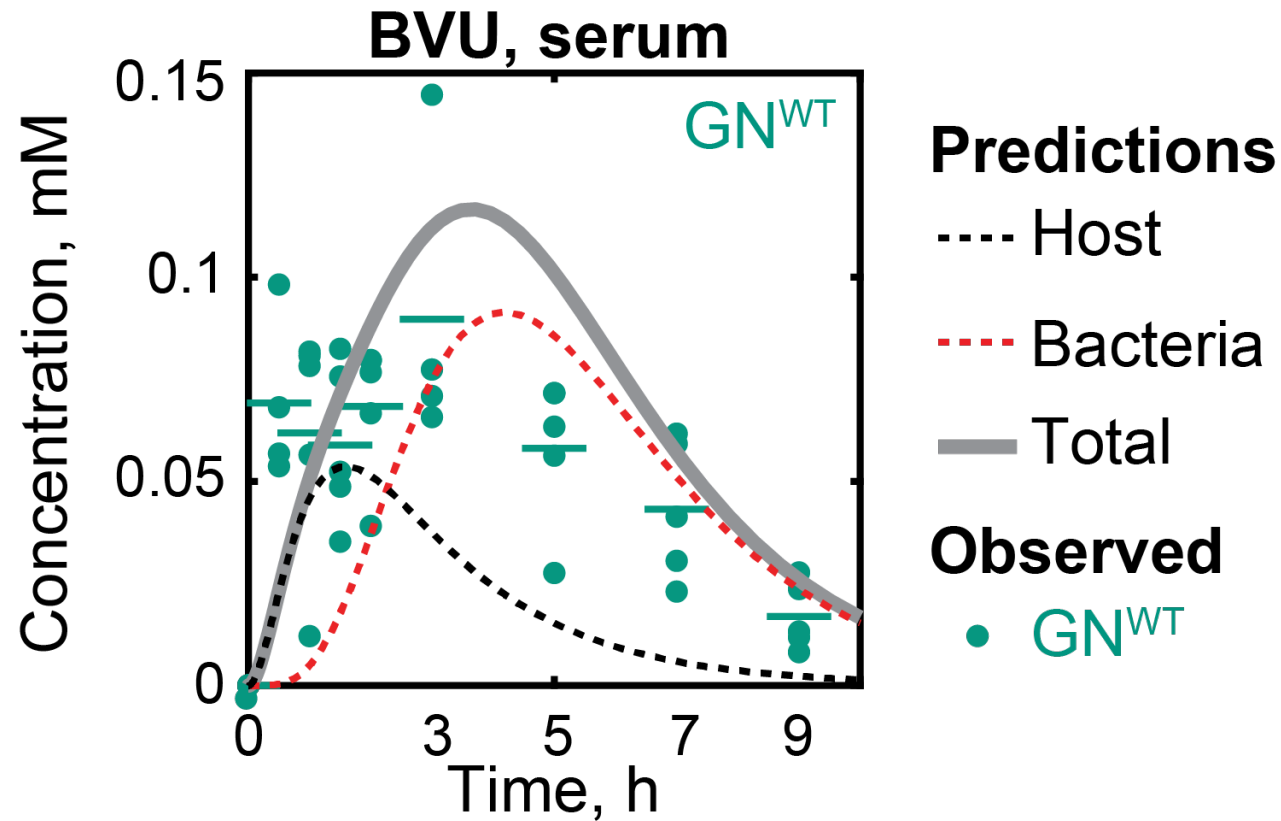
Physiology-based pharmacokinetic model of host-microbiome drug metabolism



P	Parent
M^H	Metabolite from host
M^{BAC}	Metabolite from microbiome
k_a	Absorption
k_p	Propagation (transit)
k_c	Conversion (metabolism)

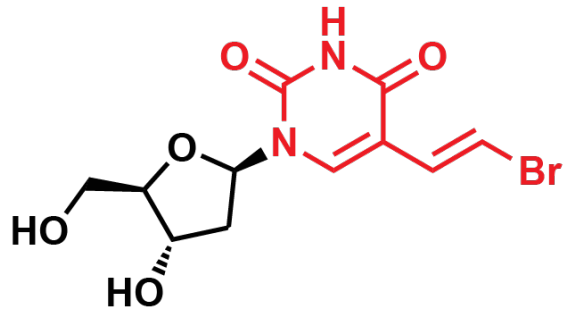


Evidence that the model is reasonable (I)

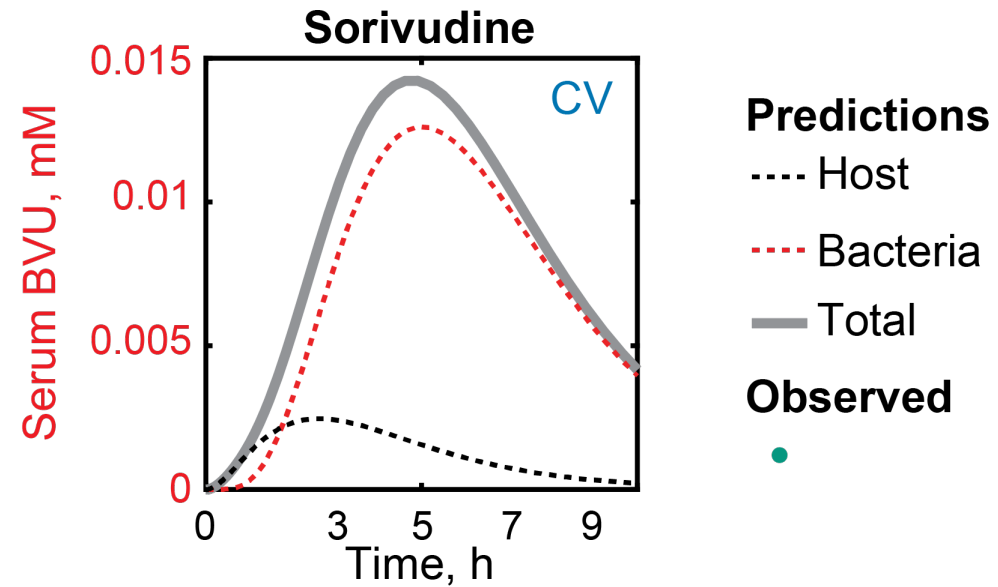
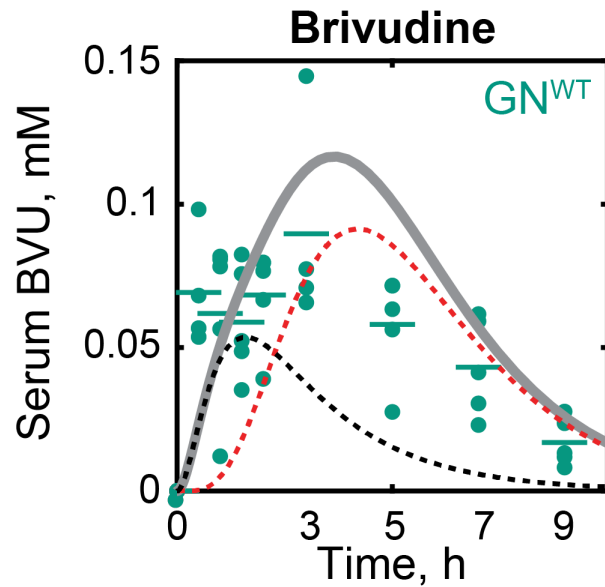
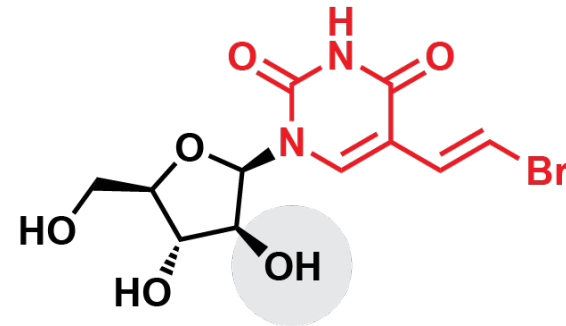


Evidence that the model is reasonable (II)

Brivudine (BRV)

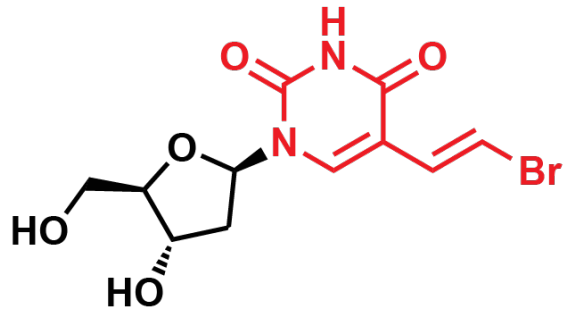


Sorivudine (SRV)

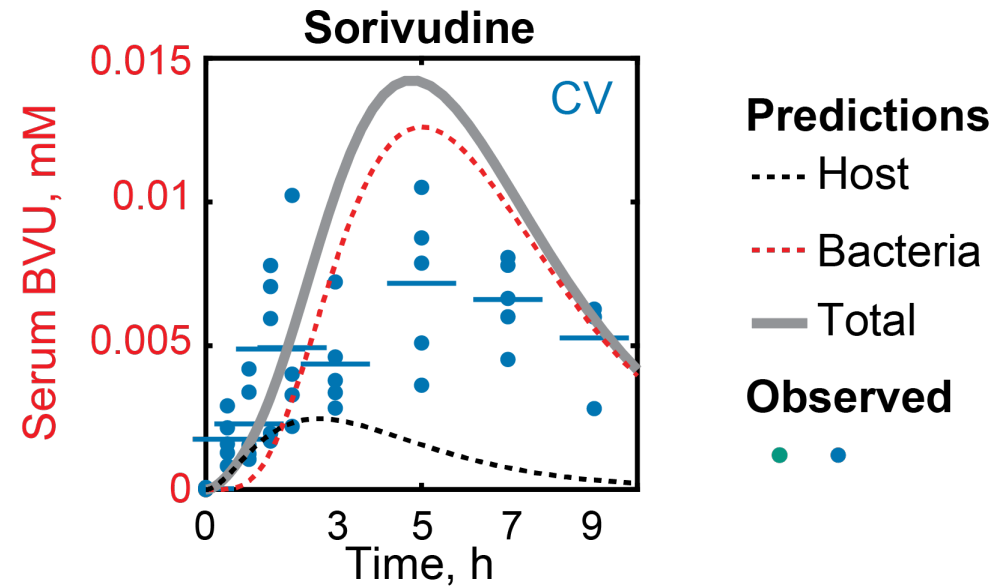
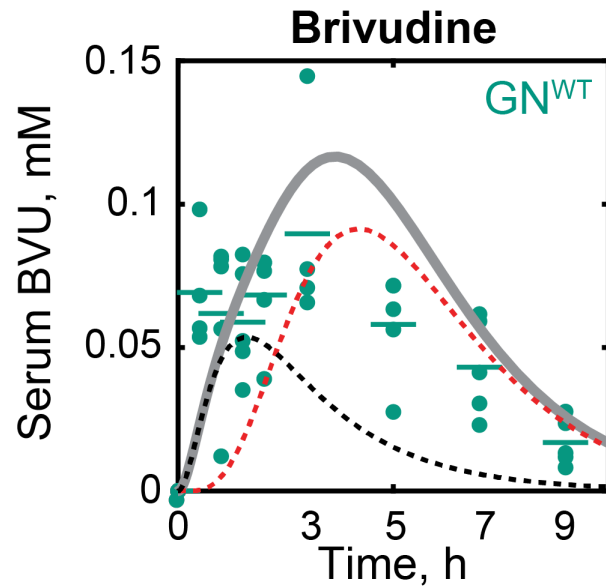
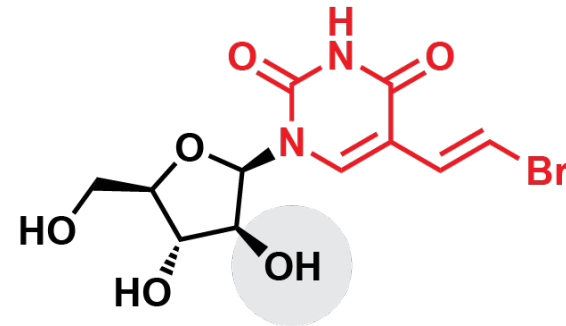


Evidence that the model is reasonable (II)

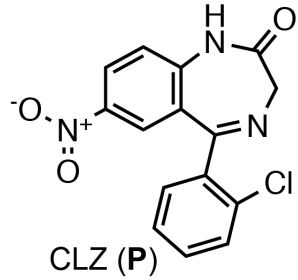
Brivudine (BRV)



Sorivudine (SRV)

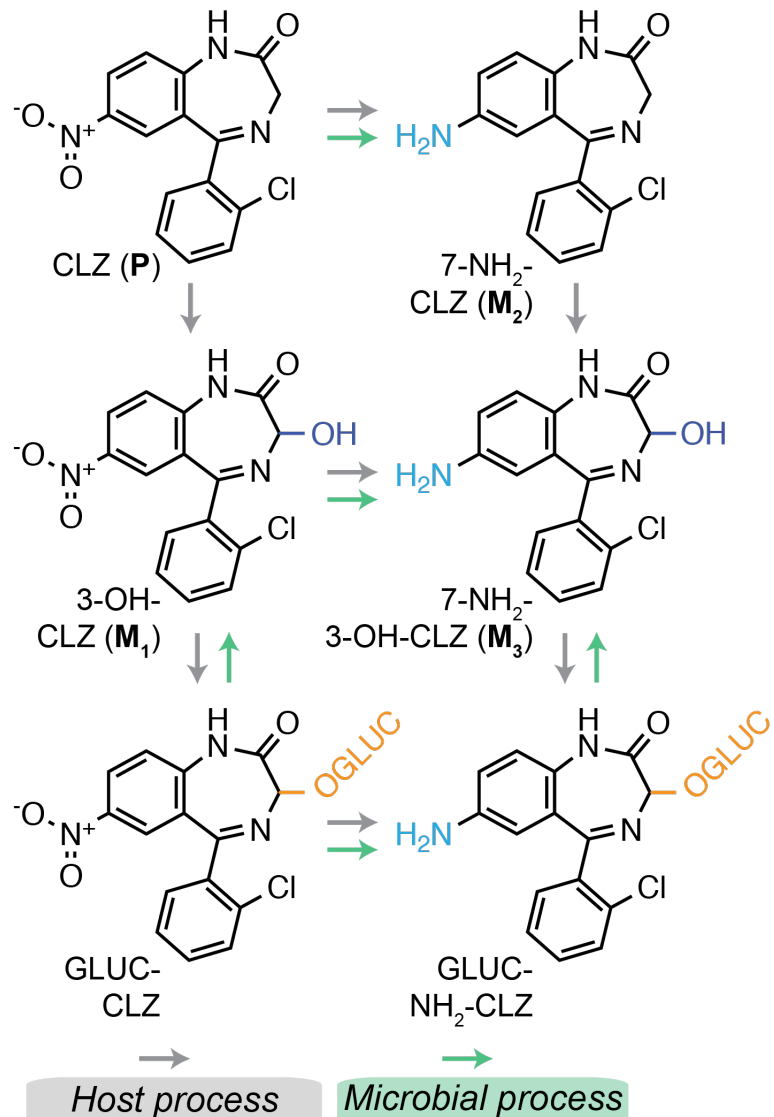


Evidence that the model is reasonable (III)

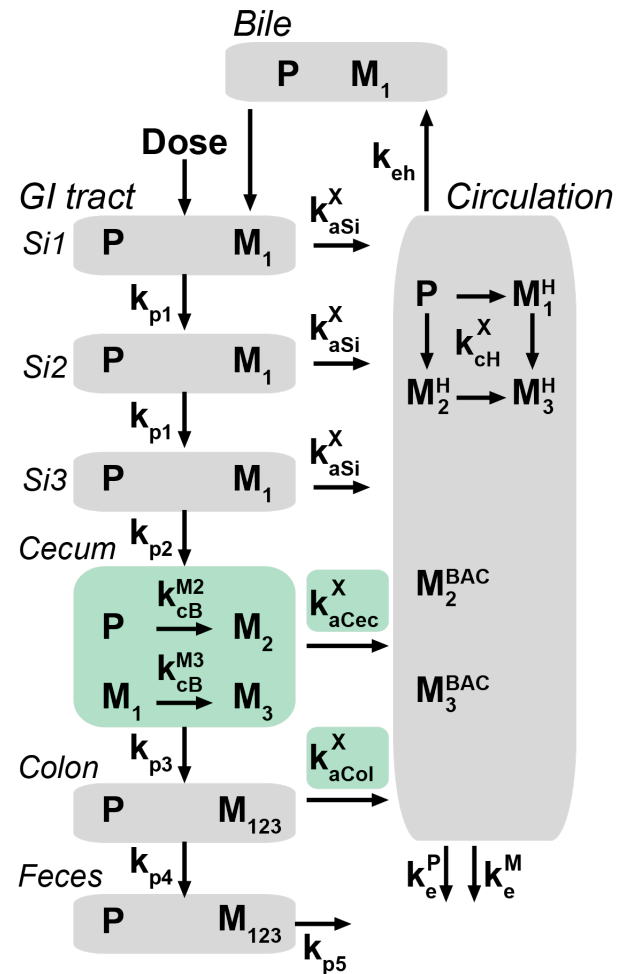
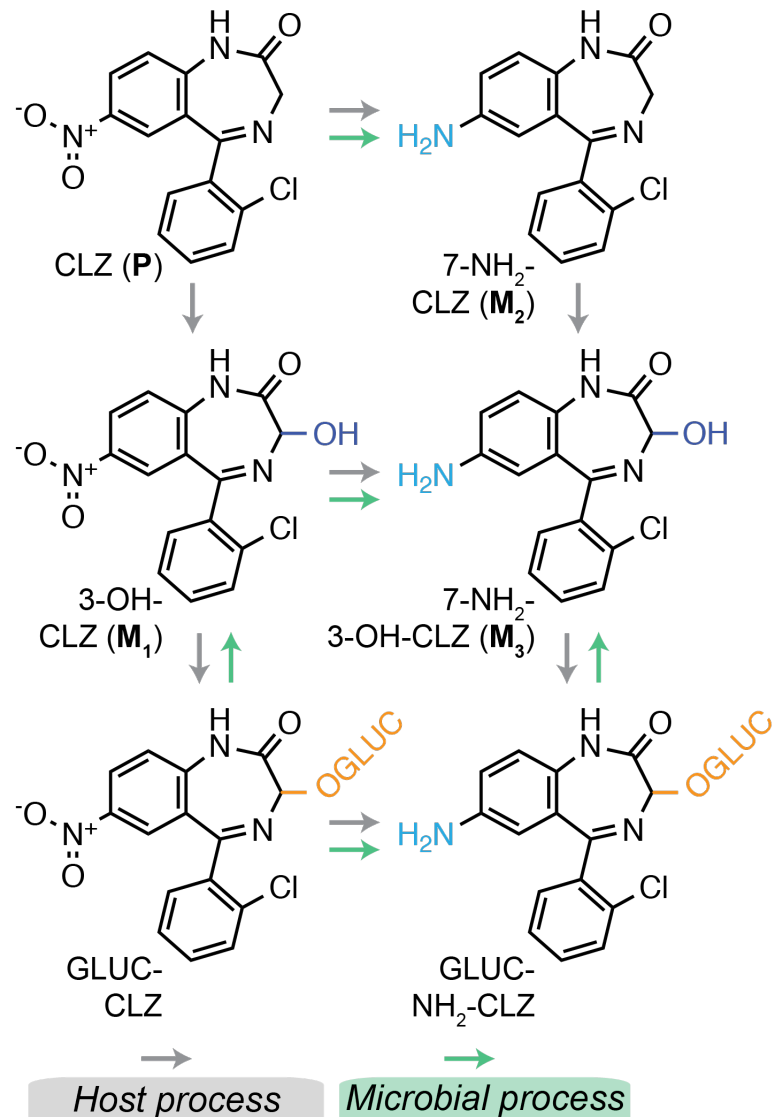


Clonazepam: anti-convulsant and anti-anxiety; nitro-reduced metabolites associated with toxicity

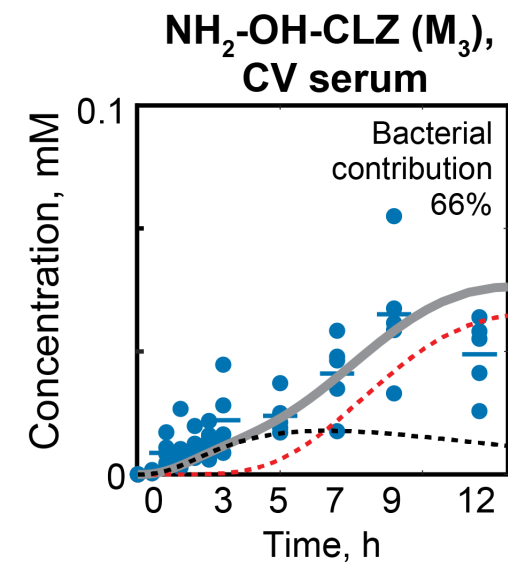
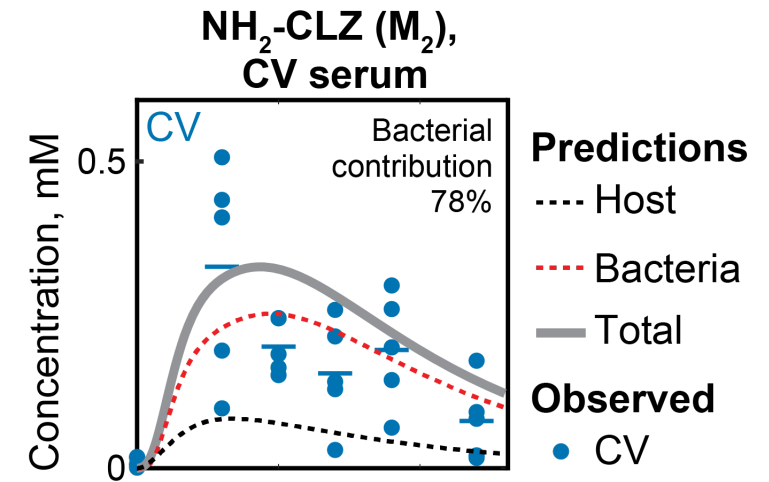
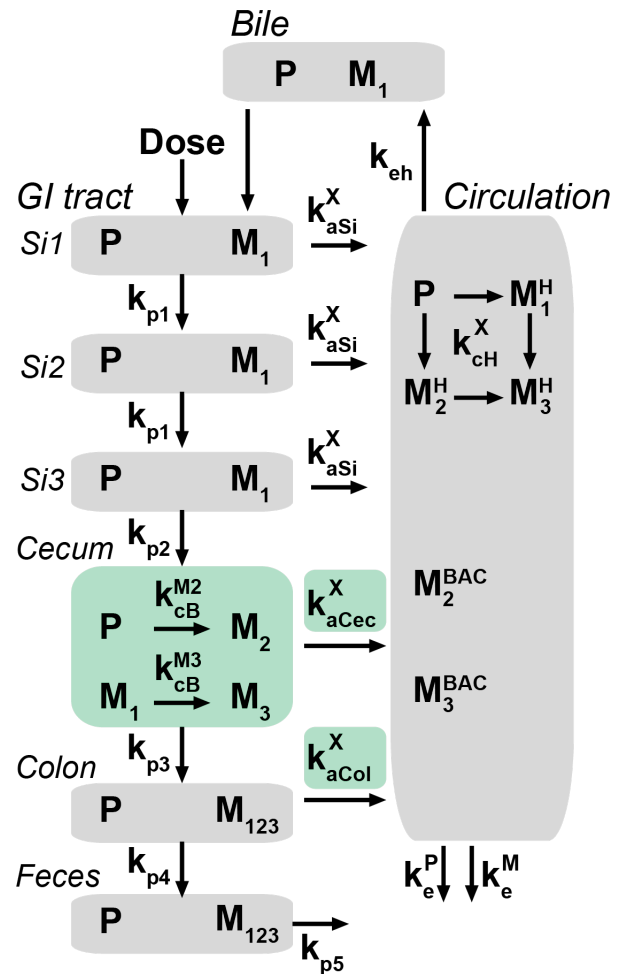
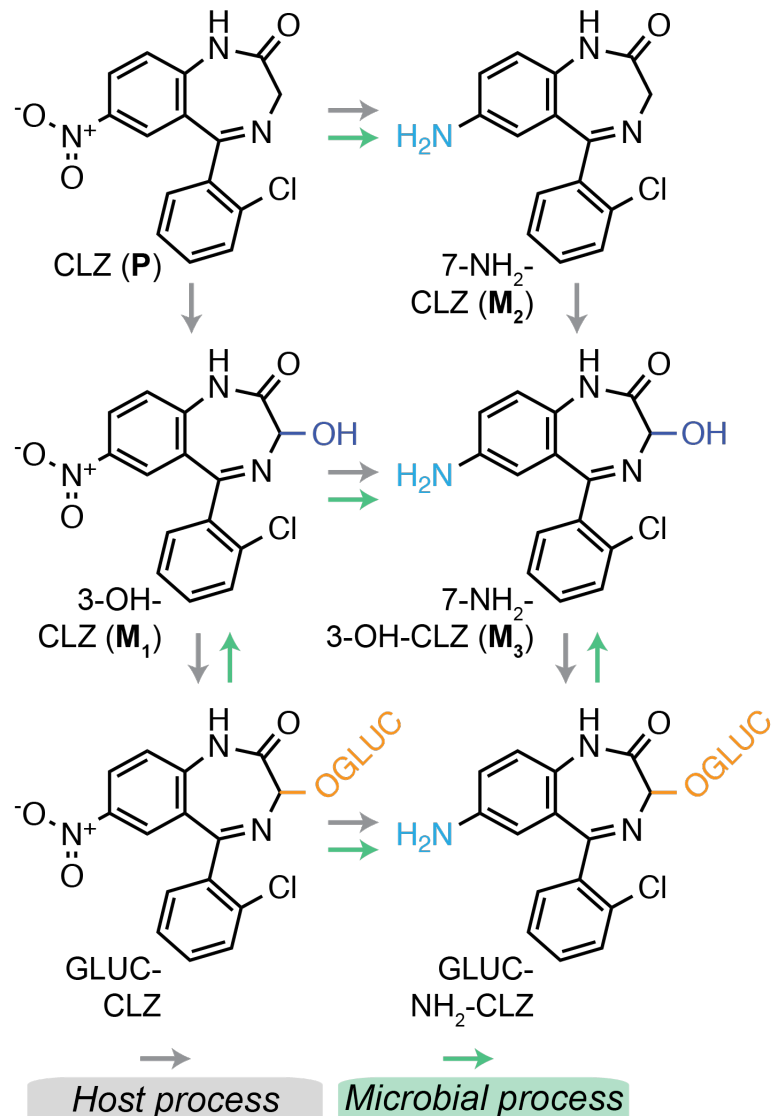
Clonazepam exhibits multiple metabolic routes and metabolites



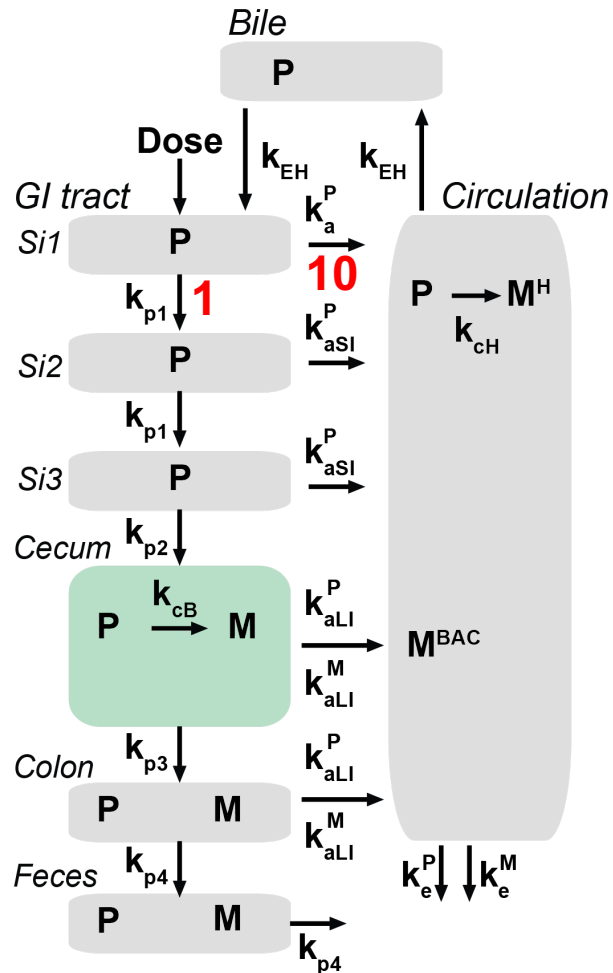
Clonazepam exhibits multiple metabolic routes and metabolites



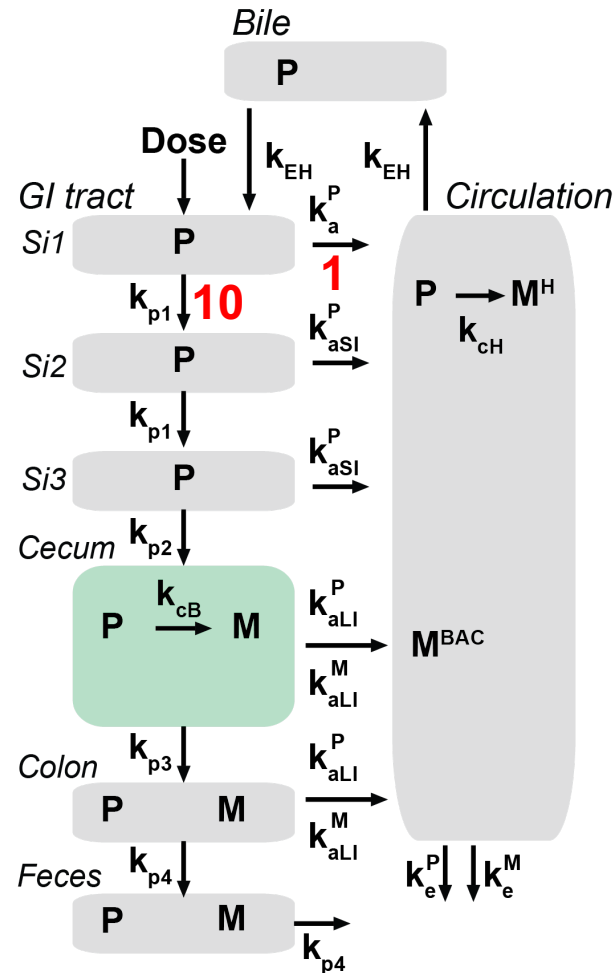
Evidence that the model is reasonable (III)



Are there conditions in which microbiome activity could impact well absorbed drugs?



Well absorbed drug

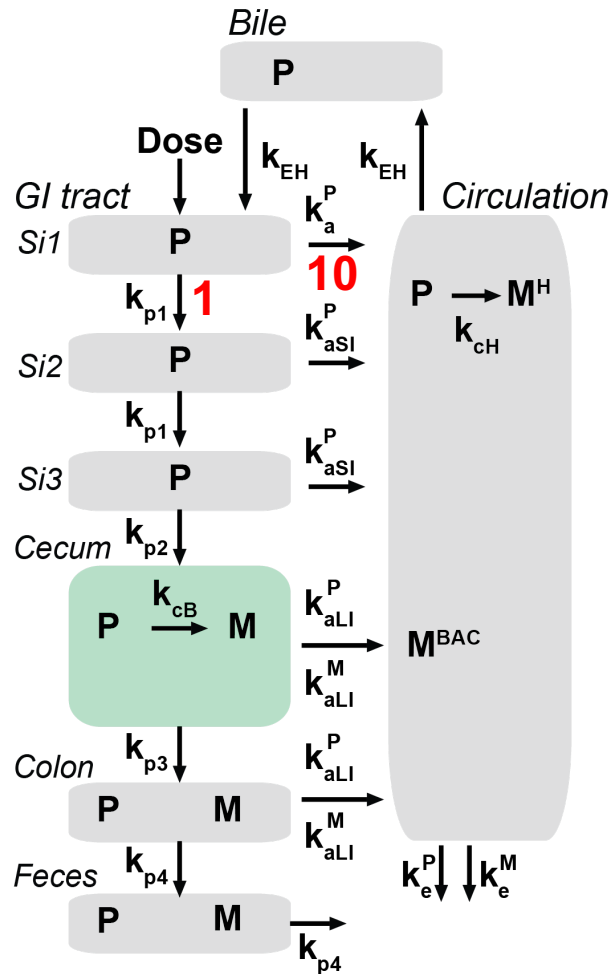


Poorly absorbed drug

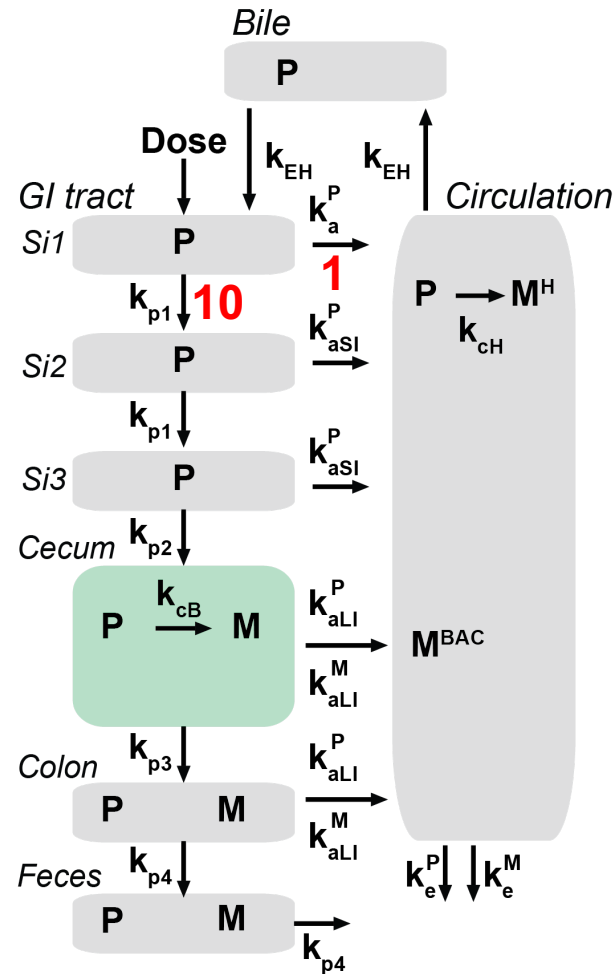
For each of 10,000 iterations:

1. Randomize all parameters except absorption
2. Predict microbiome contribution to serum metabolite exposure if drug is well absorbed
3. Predict microbiome contribution to serum metabolite exposure if drug is poorly absorbed

Are there conditions in which microbiome activity could impact well absorbed drugs?

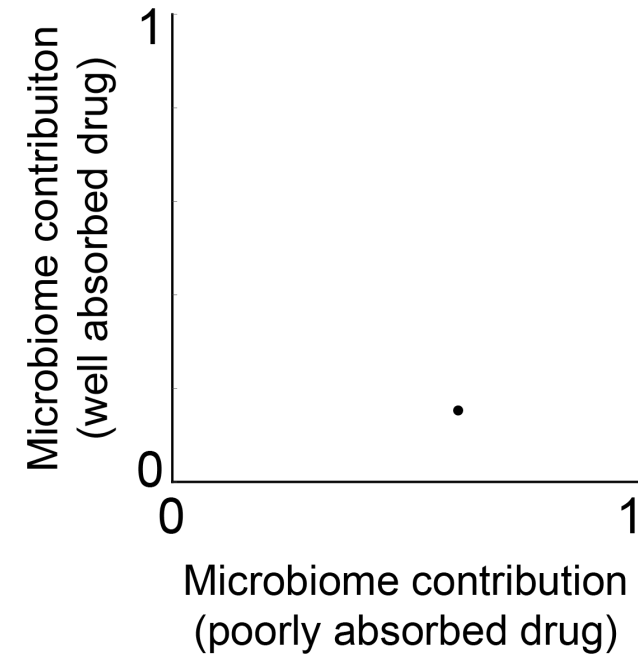


Well absorbed drug

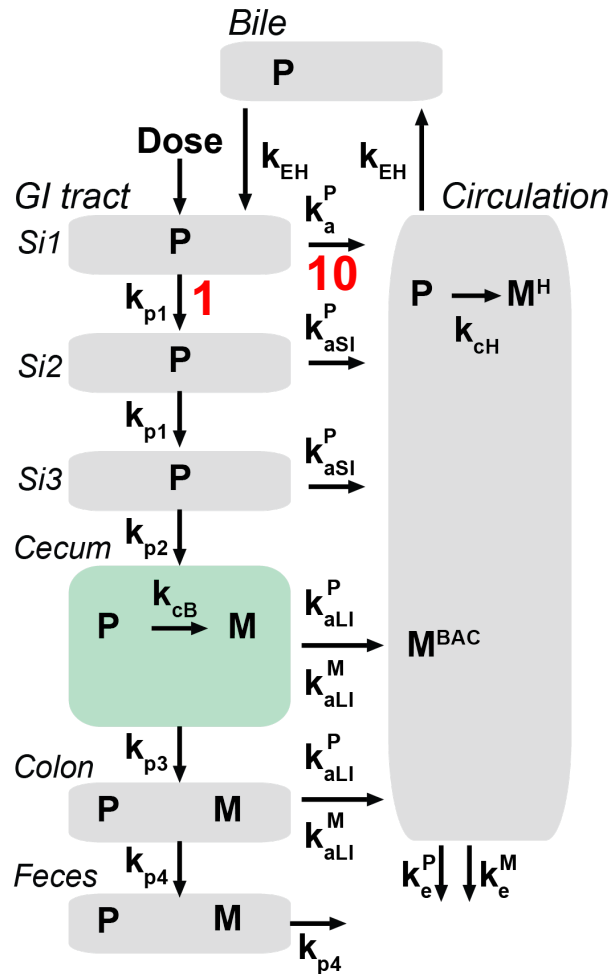


Poorly absorbed drug

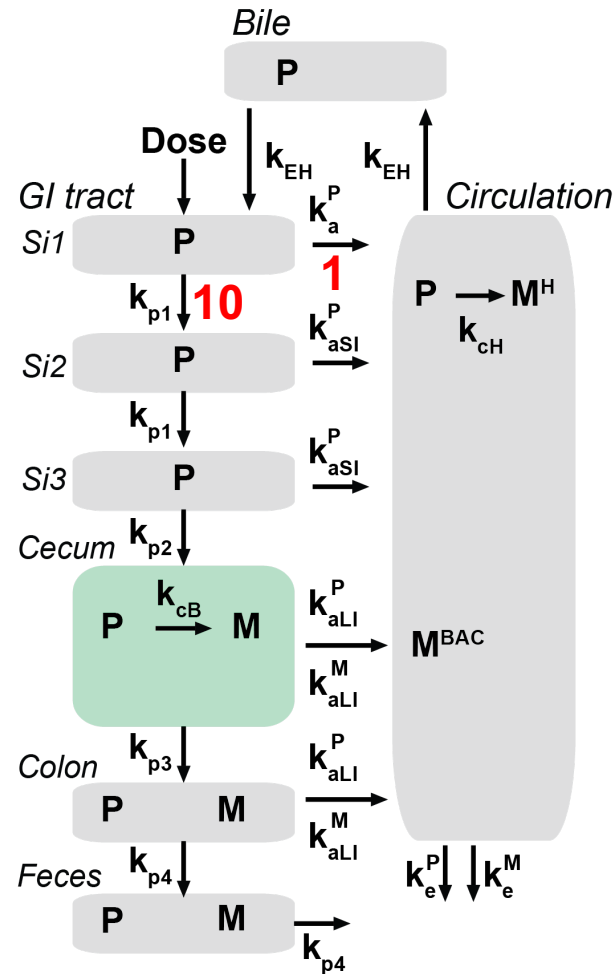
Microbiome contribution to serum metabolite exposure



Are there conditions in which microbiome activity could impact well absorbed drugs?

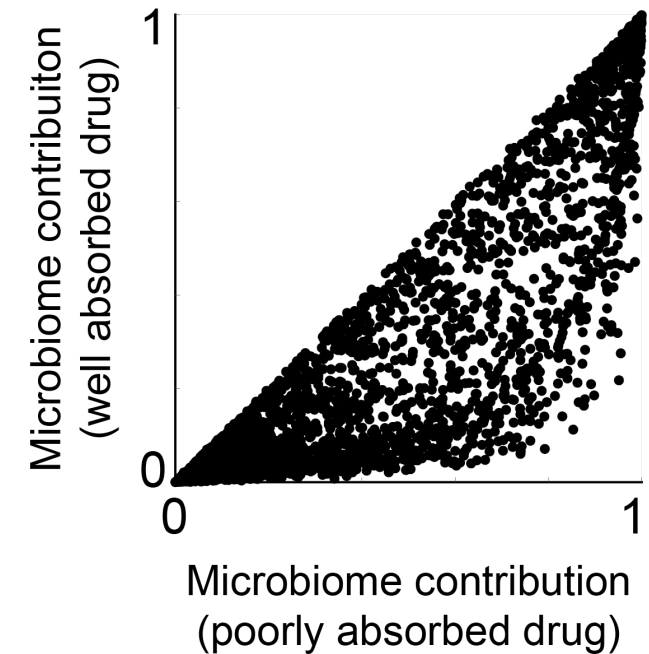


Well absorbed drug

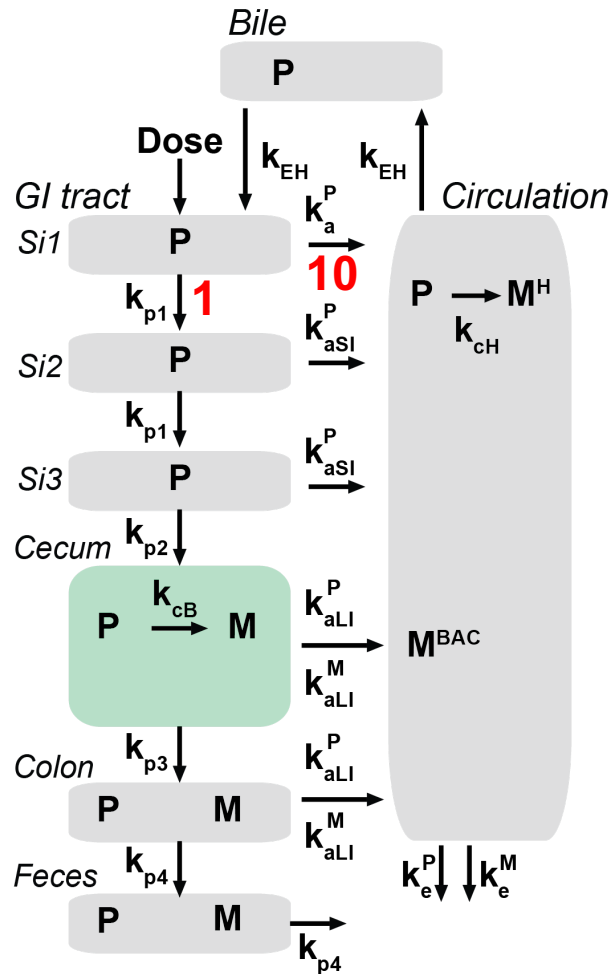


Poorly absorbed drug

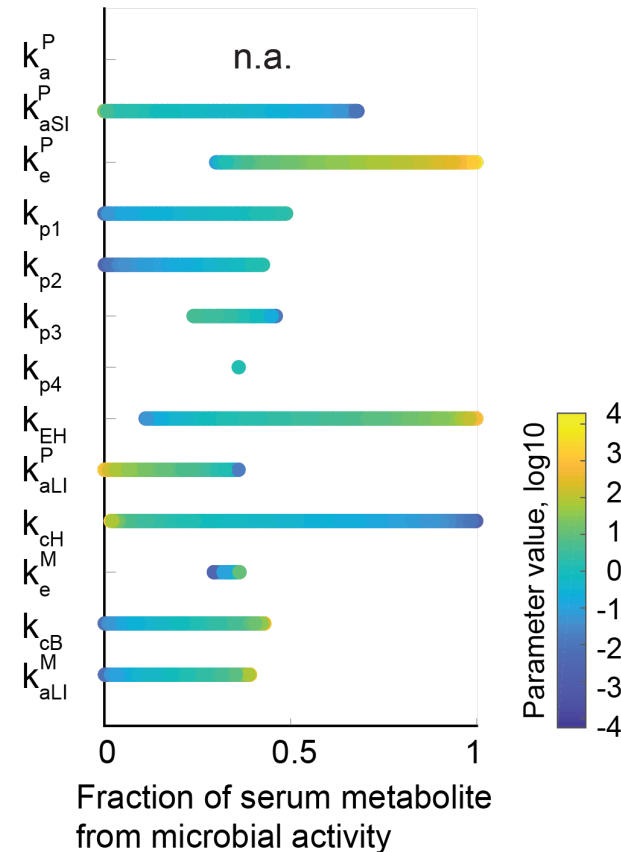
Microbiome contribution
to serum metabolite exposure



Local sensitivity analysis to identify contributing factors



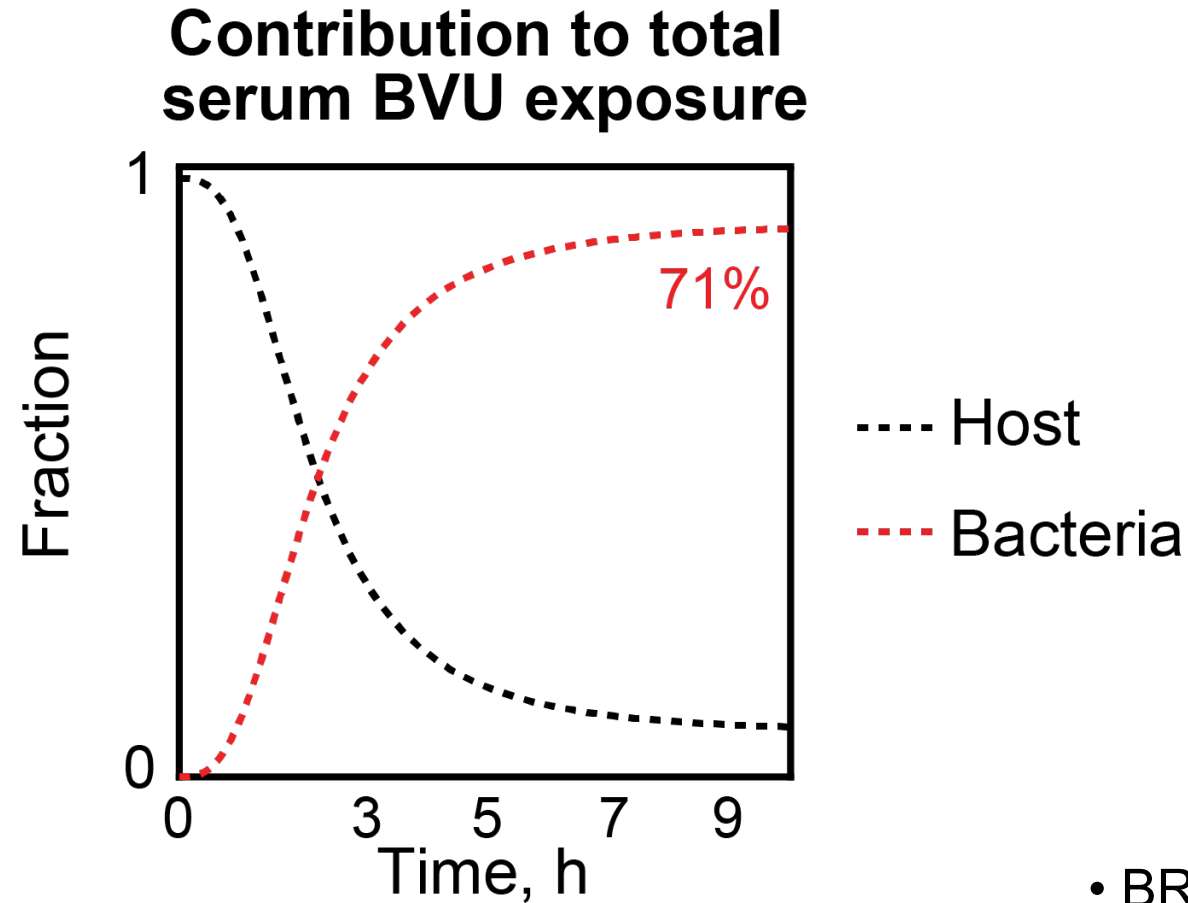
Well absorbed drug



Factors that favor a microbiome contribution to serum drug metabolite exposure (readily absorbed drug)

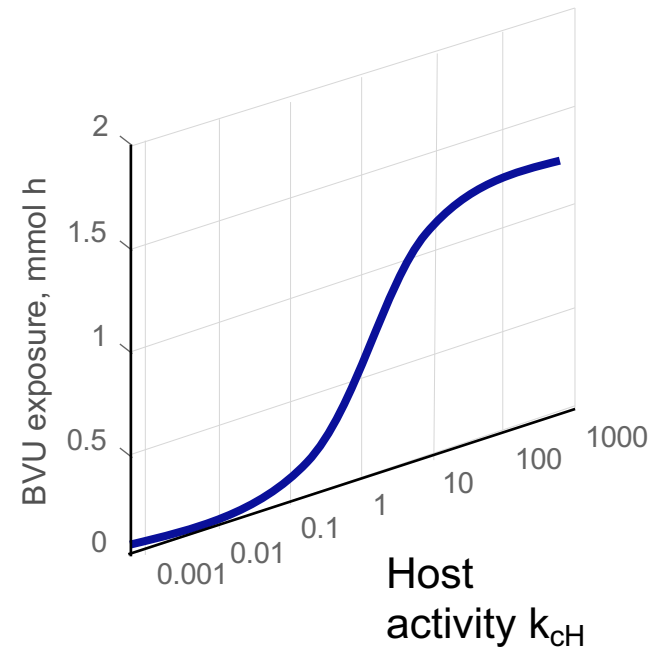
- Enterohepatic circulation (k_{EH})
- Rapid parent drug clearance (k_e^P)
- Reduced host metabolism (k_{cH})
- Reduced colonic transit (k_{p3})

Brivudine provides an example

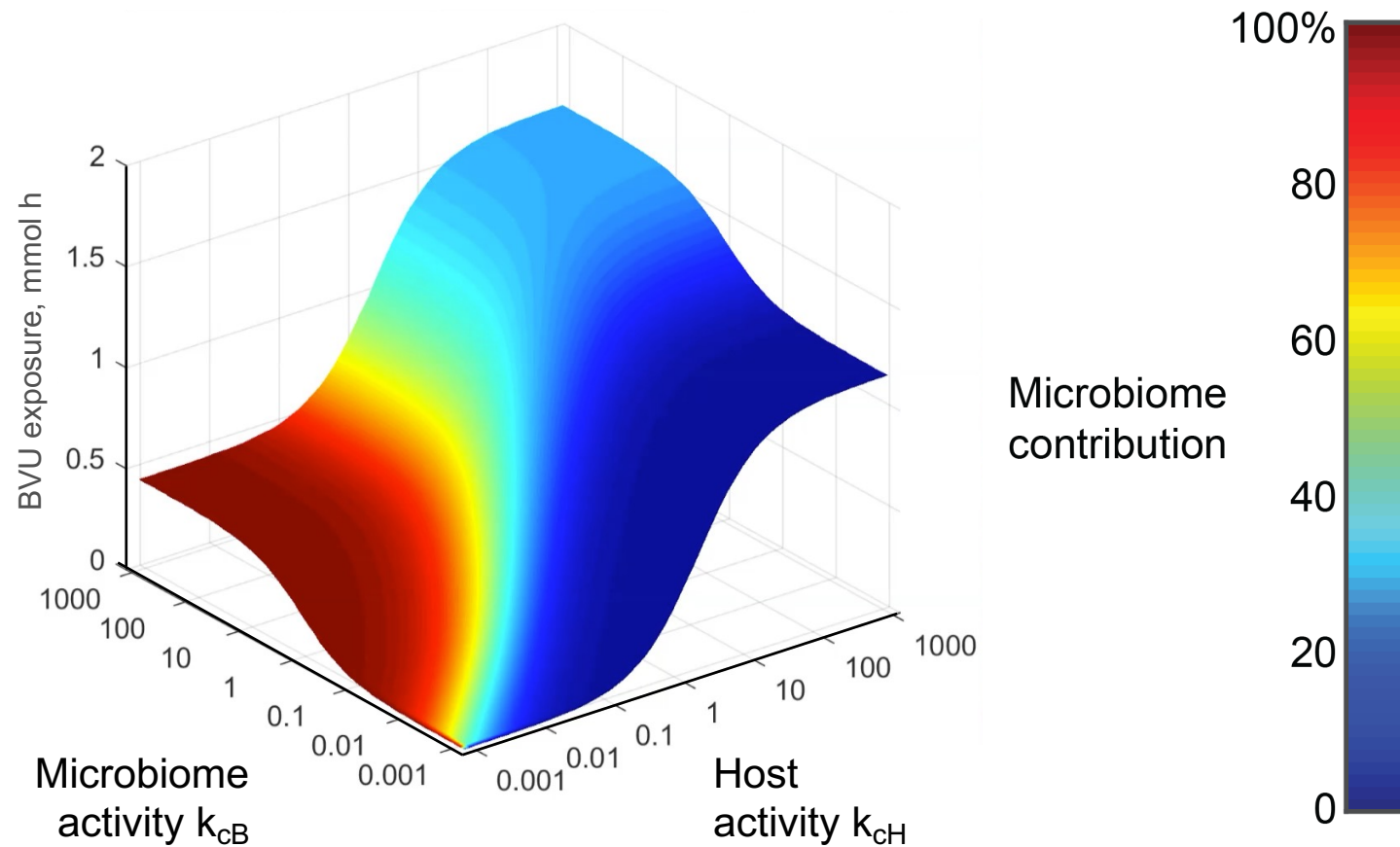


- BRV is fairly well absorbed (70% bioavailability)
- Liver extracts readily convert BRV to BVU
- Little BVU detected in feces

Pharmacogenomics

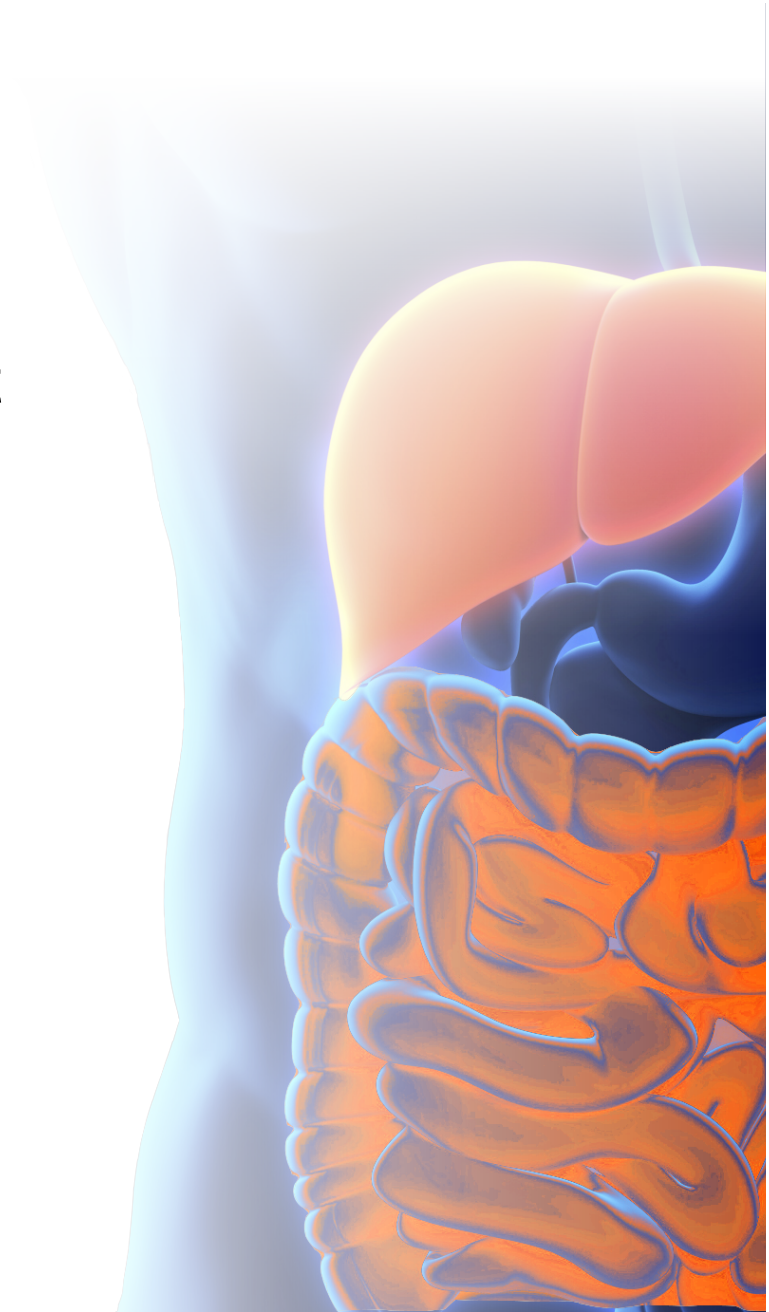


Pharmacogenomics of a host- and microbiome-metabolized drug



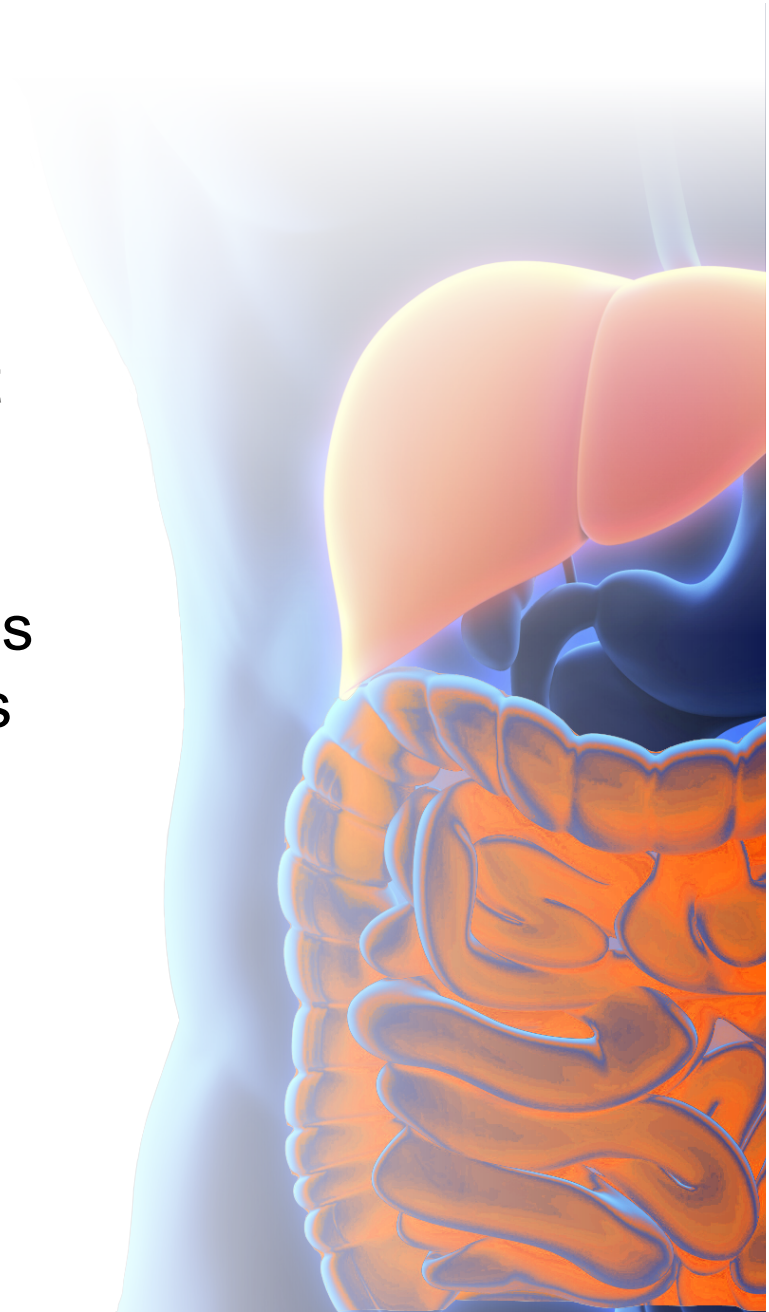
Summary

- Medical drugs serve as chemical tools to understand how gut microbes recognize and transform their environment



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- We're developing approaches to uncover these mechanisms in microbial communities, species, enzymes, and metabolites



Summary

- Medical drugs serve as chemical tools to understand how gut microbes recognize and transform their environment
- We're developing approaches to uncover these mechanisms in microbial communities, species, enzymes, and metabolites
- These approaches could impact how medical drugs are developed, tested in the appropriate patient cohorts during clinical trials, and administered

