香港中文大學
The Chinese University of Hong Kong

Impacts of gut microbiota on drug metabolism

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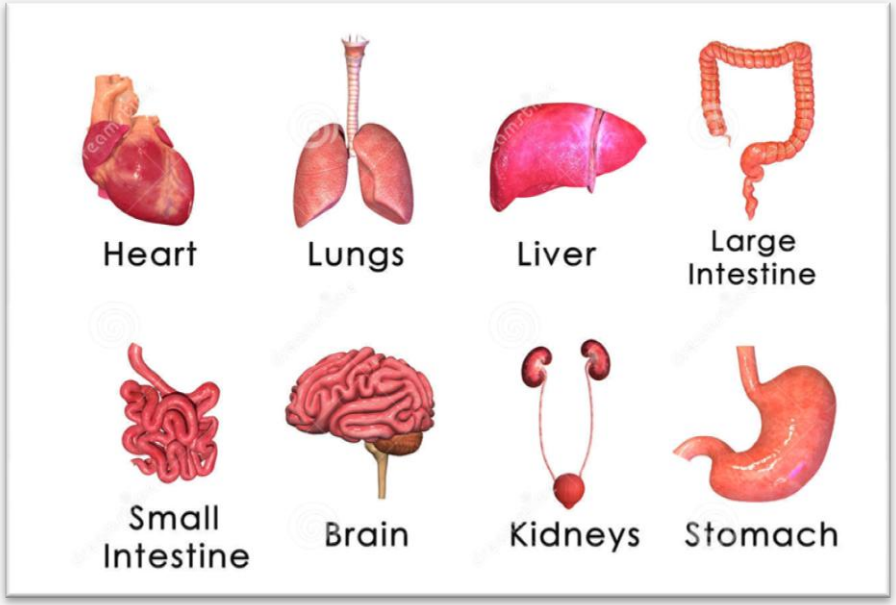
7-Dec-2017

Which body organ is the major site for drug metabolism?



Drug metabolism pathway

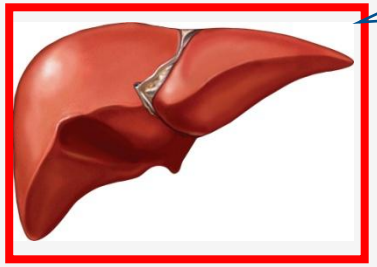
Mouth

GI

Portal vein

Billary excretion

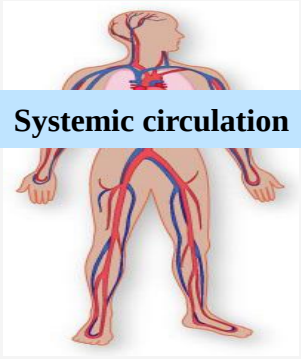
Liver



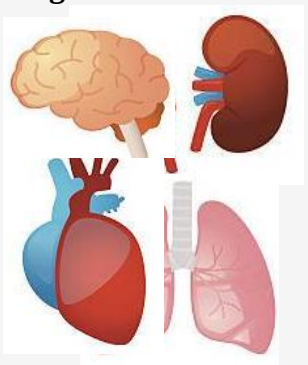
- **Chance**
- **Enzymes**

Sub-Q, IV, IM

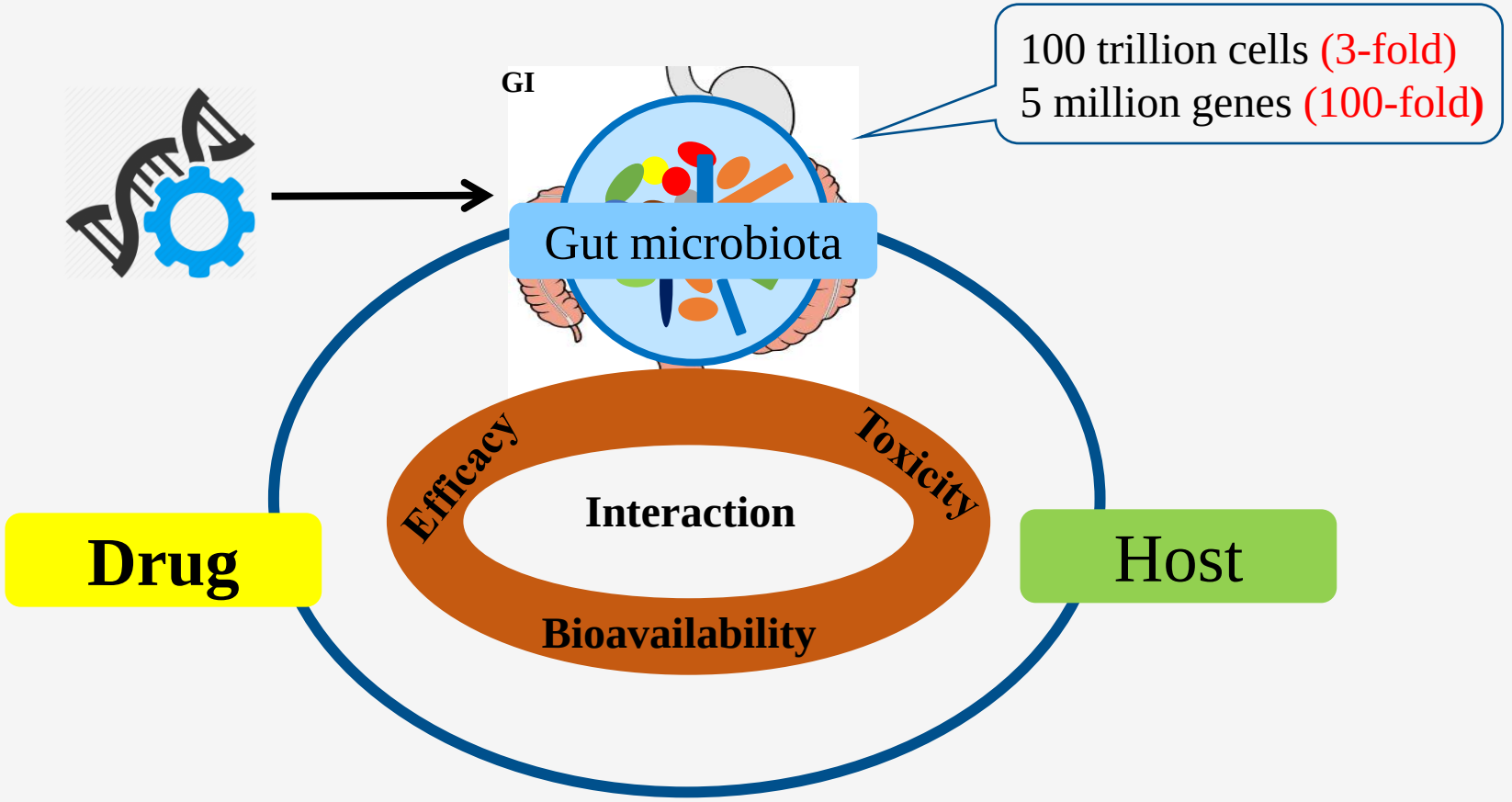
Systemic circulation



Organs



Gut microbiota-drug interaction



First discovery

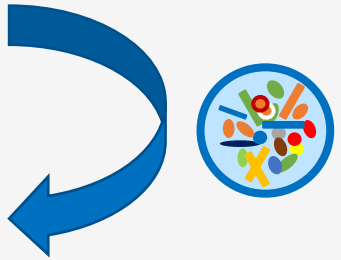
IS *p*-AMINOBENZENESULPHONAMIDE THE ACTIVE AGENT IN PRONTOSIL THERAPY ?

LANCET 1936

BY A. T. FULLER, Ph.D. Lond., F.I.C.

BIOCHEMIST, BERNHARD BARON MEMORIAL RESEARCH LABORATORIES, QUEEN CHARLOTTE'S HOSPITAL, LONDON

Prontosil (inactive *in vitro*)



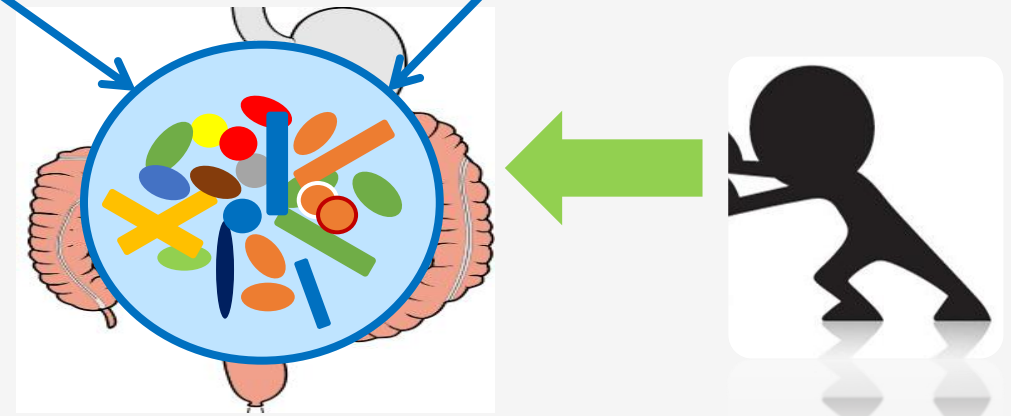
Prontosil (active *in vivo*)

Drug metabolism by gut microbiota (cont.)

Anti-bacterial, anti-cancer, anti-hypertension, anti-parkinson...

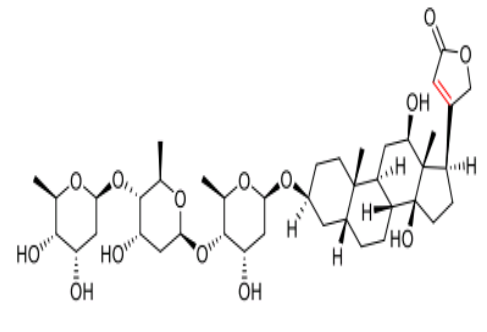
>50

5-Fluorouracil	Metronidazole	Sulfinpyrazone	Levamisole
Balsalazide	Misonidazole	Sulindac	Lovastatin
BILR 355	Neoprontosil	Zonisamide	Methotrexate
Chloramphenicol	Nitrazepam	zetirelin	Morphine 6-glucuronide
Clonazepam	Nizatidine	Benzylpenicillin	Phenacetin
Deleobuvir	Olsalazine	Calcitonin	Sennosides
Digoxin	Omeprazole	Chloramphenicol	Irinotecan
Eltrombopag	Potassium oxonate	Diclofenac glucuronide	Sodium picosulfate
Glyceryl trinitrate	Prontosil	Glycyrrhizin	Sorivudine
Indicine *N*-oxide	Ranitidine	Indomethacin glucuronide	Succinyl sulfathiazole
Levodopa	Risperidone	Insulin	5-Aminosalicylic acid
Loperamide *N*-oxide	Sennosides	Isosorbide dinitrate	Sulfapyridine
Methamphetamine	Sulfasalazine	Ketoprofen glucuronide	Flucytosine

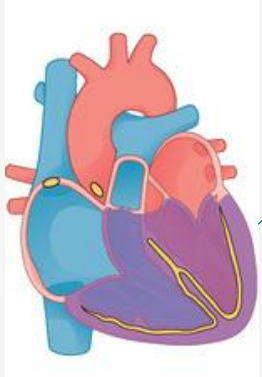


Digoxin

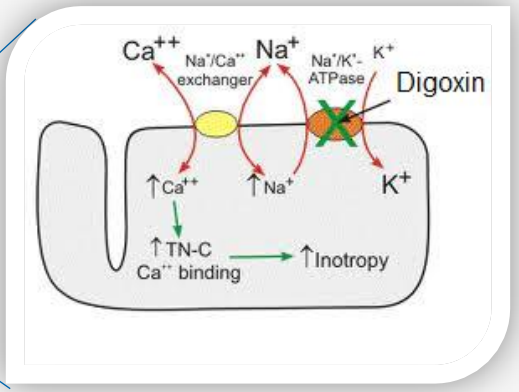
- **Digoxin:** derivatives of plants of genus *Digitalis*, has been widely used for hundreds of years to treat the heart failure and arrhythmia.
- **Mechanism:** inhibits the Na+/K+ATPase in cardiac myocytes , causing an influx of calcium and enhancing muscular contraction



Digoxin

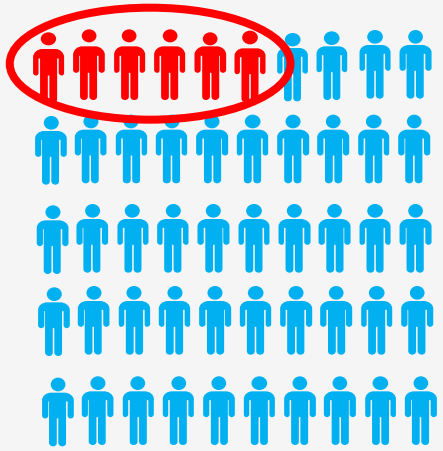


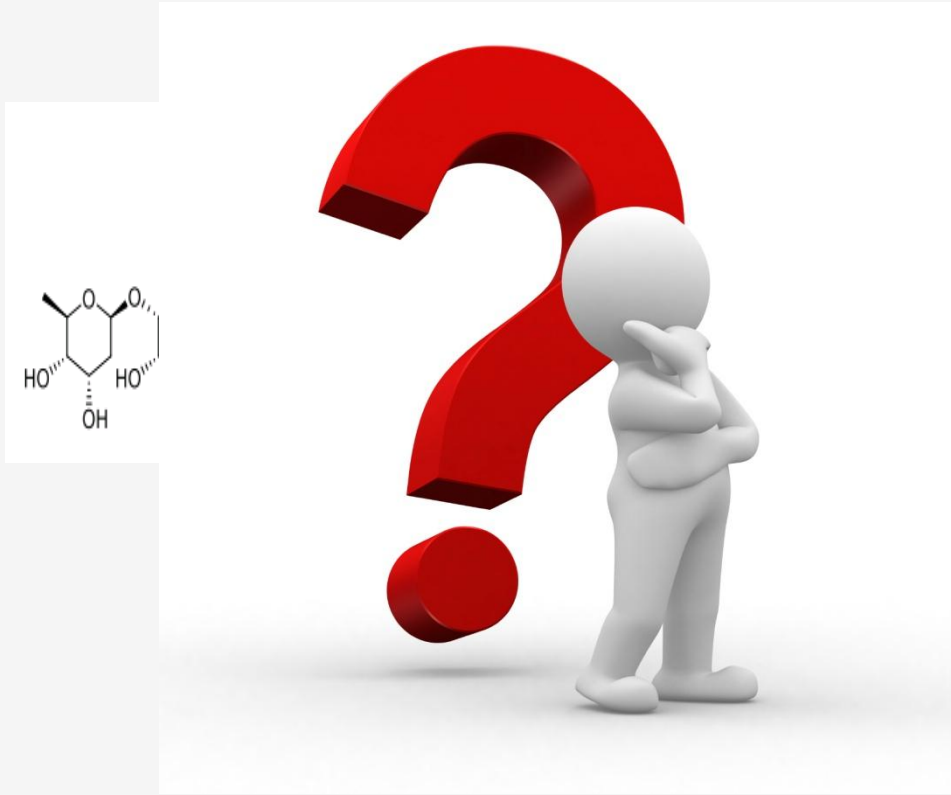
Heart failure

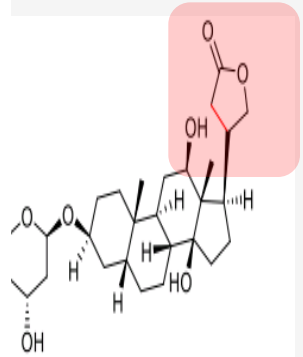


Digoxin inactivation

- **>10%** patients receiving digoxin therapy excreted the inactive metabolite, dihydrodigoxin.



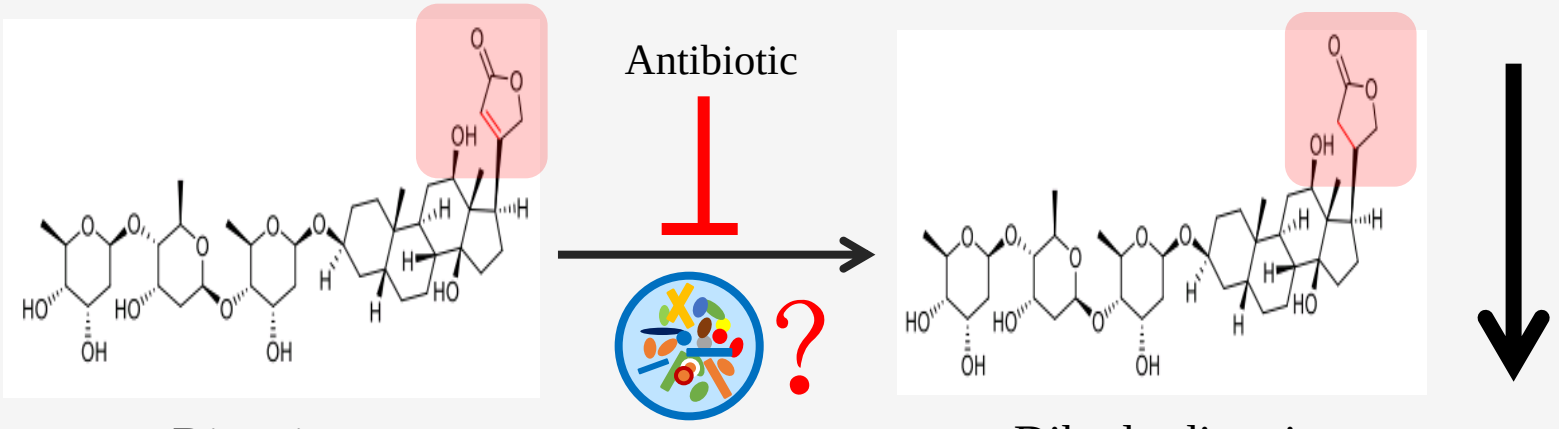




odigoxin
ctive)

Key finding

- Co-administration of antibiotic can decrease the dihydrodigoxin production, and increase the level of digoxin.



Digoxin
(**active**)

Dihydrodigoxin
(**inactive**)

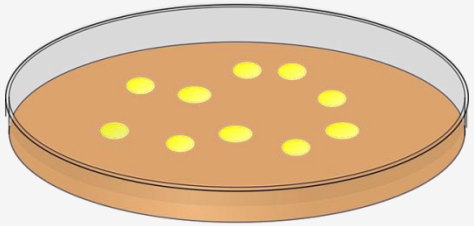
E. lenta is responsible for the inactivation

Digoxin-inactivating bacteria: identification in human gut flora

Saha JR, VP Butler Jr, HC Neu, J Lindenbaum
+ See all authors and affiliations

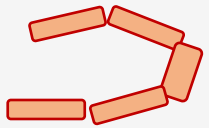
Science 1983

Science 15 Apr 1983:
Vol. 220, Issue 4594, pp. 325-327
DOI: 10.1126/science.6836275

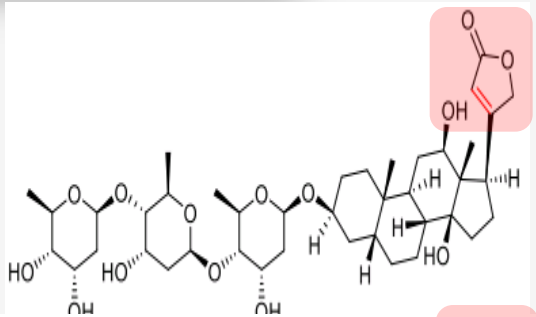


Culture-dependent

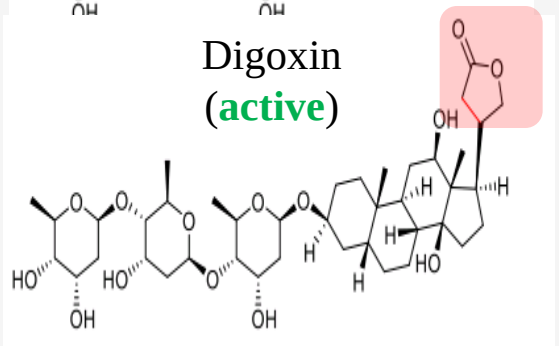
>400 colonies



Eggerthella lenta

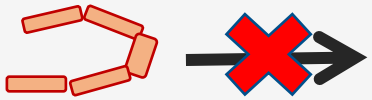


Digoxin
(**active**)



Dihydrodigoxin
(**inactive**)

E. lenta is not a biomarker for digoxin inactivation

Attemption:  digoxin inactivation

E. lenta

Puzzle: *E. lenta* was screened from patients who did not excrete dihydrodigoxin.

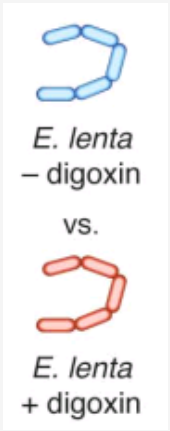
Cgr operon correlates with digoxin inactivation

Predicting and Manipulating Cardiac Drug Inactivation by the Human Gut Bacterium *Eggerthella lenta*

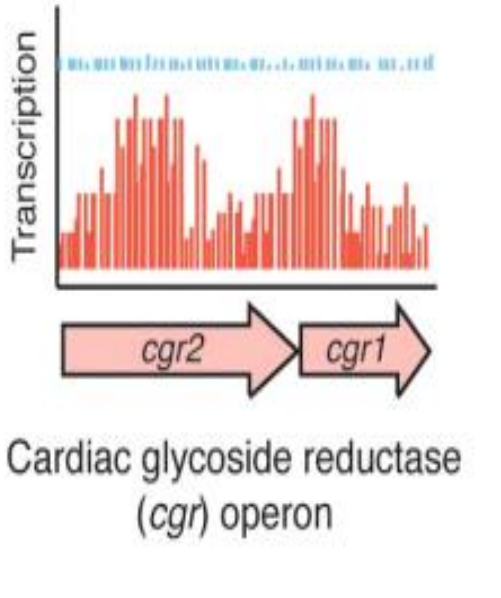
Henry J. Haiser[1], David B. Gootenberg[1], Kelly Chatman[1], Gopal Sirasani[2], Emily P. Balskus[2], Peter J...
+ See all authors and affiliations

Science 2013

Science 19 Jul 2013:
Vol. 341, Issue 6143, pp. 295-298
DOI: 10.1126/science.1235872

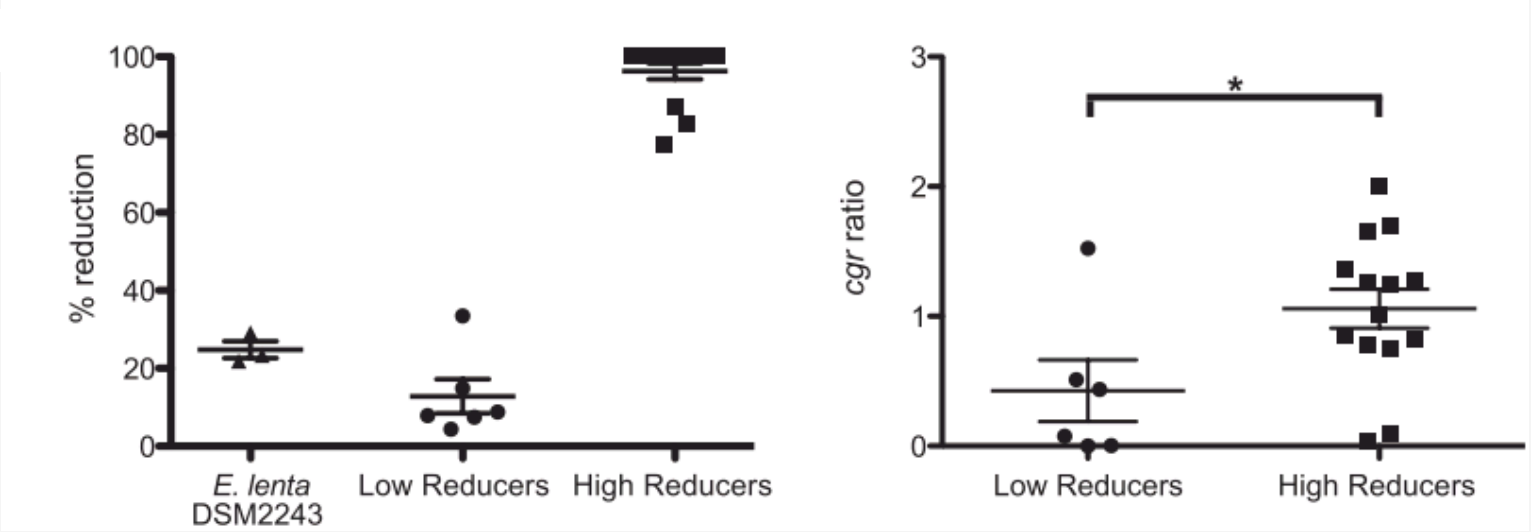


RNA-seq



>100 fold upregulated in the presence of digoxin

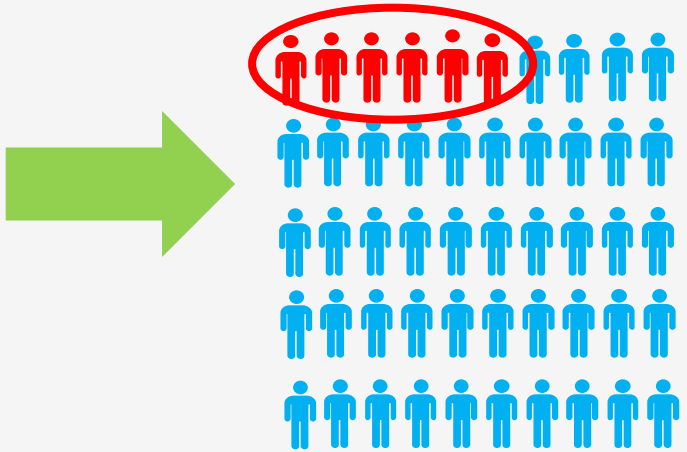
Cgr operon: predictor for digoxin inactivation



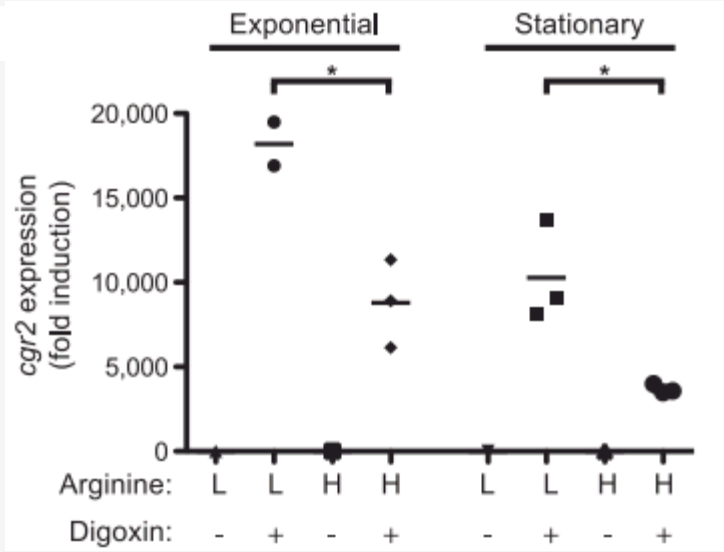
The abundance of the *cgr* operon relative to the *E. lenta* 16S ribosomal RNA (rRNA) gene (the "*cgr* ratio") in microbial community is measured using microbial community DNA from 20 unrelated healthy people by q-PCR.

Cgr operon → digoxin inactivation

What we can do?

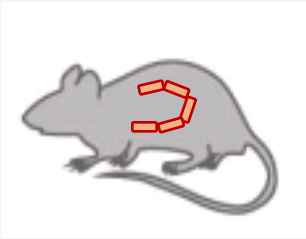


Dietary protein intervention

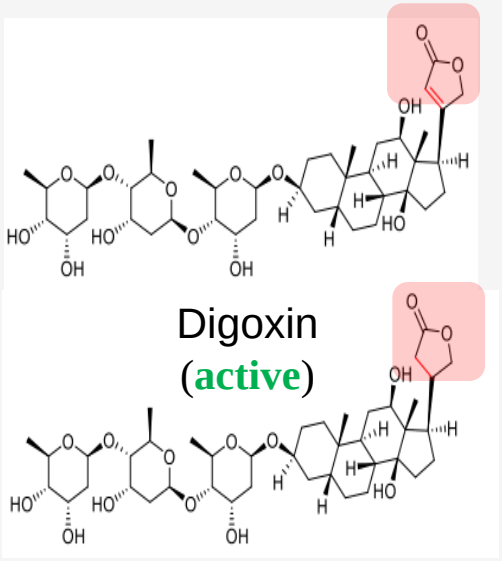


In vitro growth of *E. lenta* showed that, arginine can supress *cgr* operon expression.

Dietary protein: Arginine →



⊣ ***Cgr*** ⊣



Dietary intervention can increase the bioavailability of digoxin.

Gut microbiota elevates irinotecan toxicity

Injection

serum

CPT-11
(prodrug)

carboxylesterases
(host)

SN-38
(active)

Topoisomerase I

Diarrhea

Gut

SN-38
(active)

UGT-enzyme

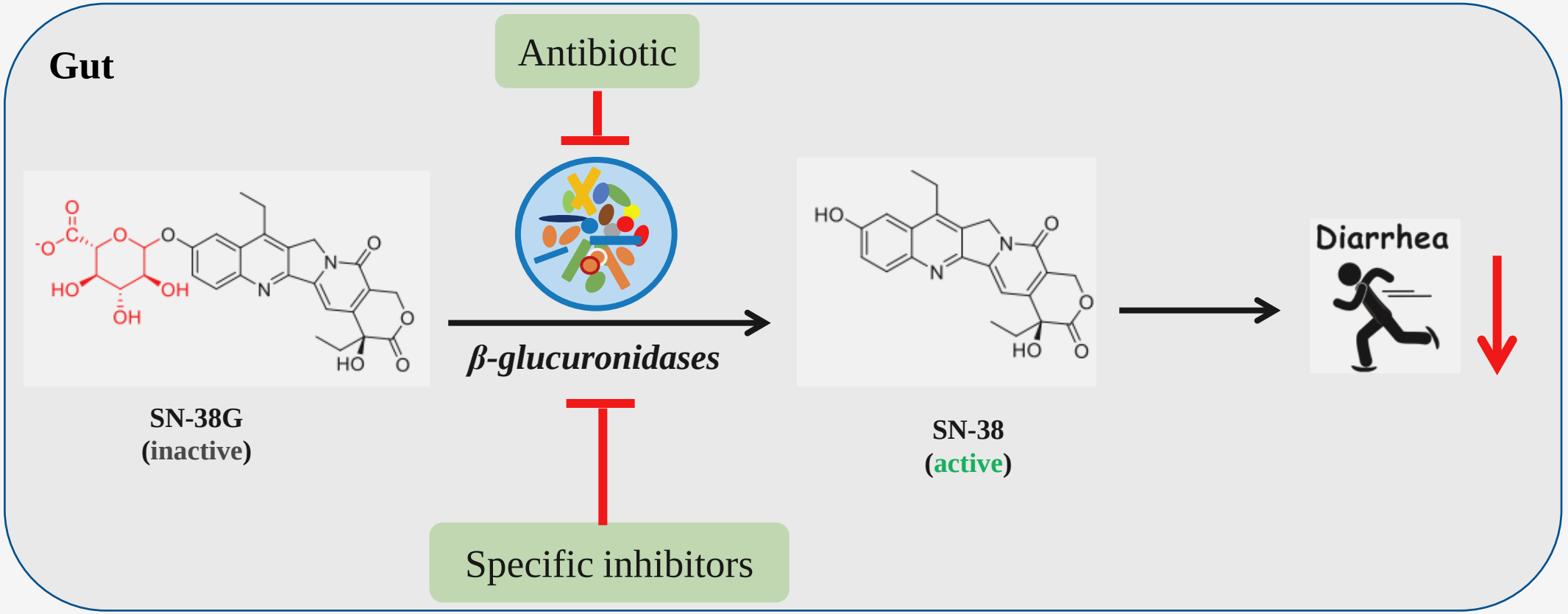
liver

SN-38G
(inactive)

Biliary duct

SN-38G
(inactive)

Solution for the elevated toxicity

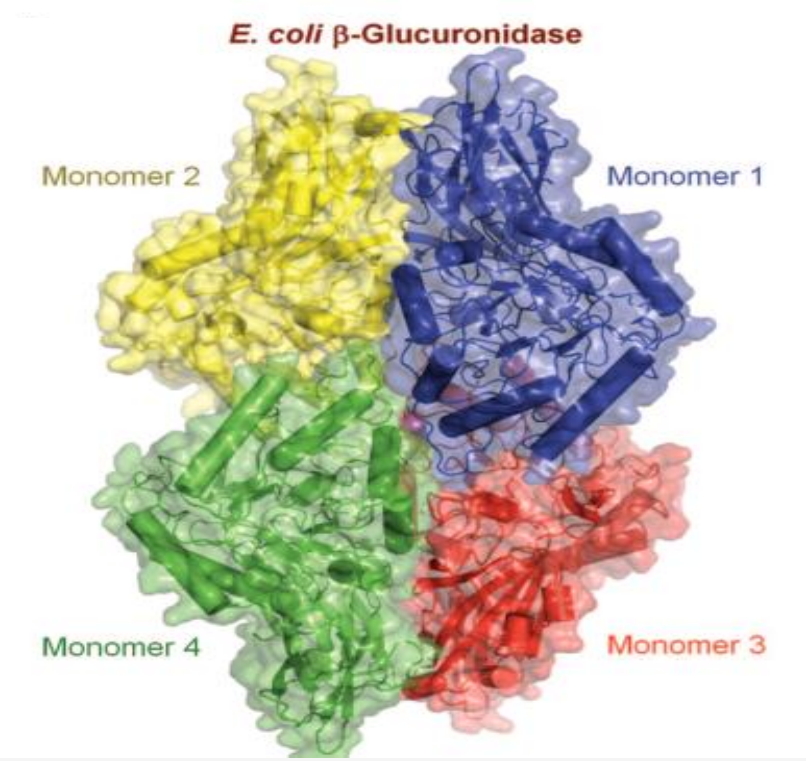


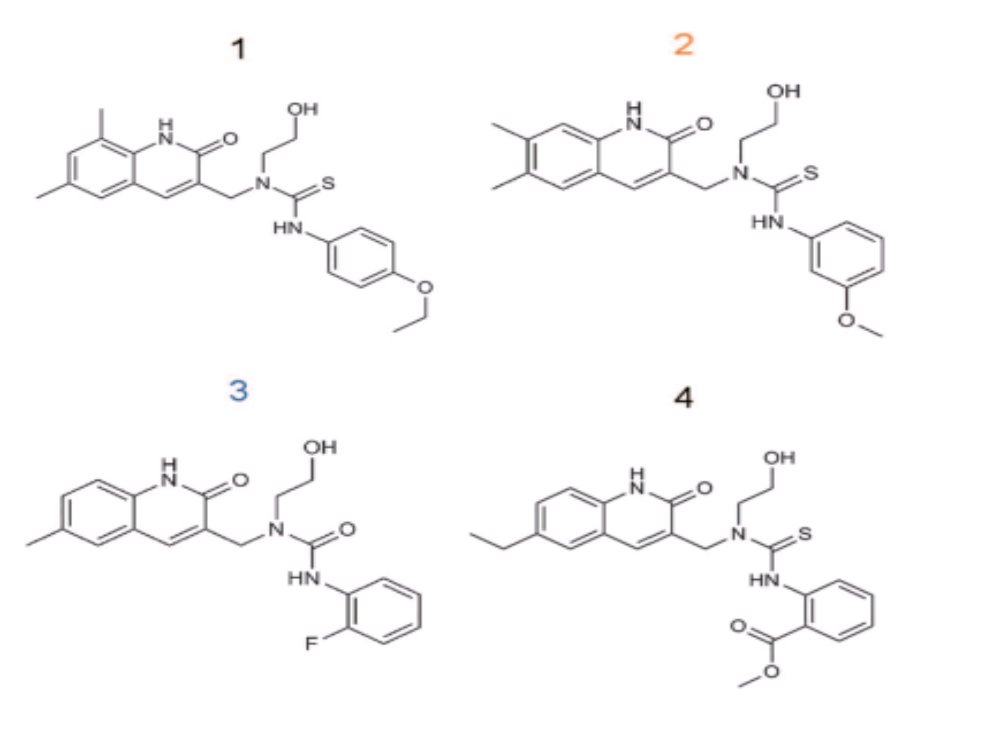
Inhibitors target gut bacterial enzyme

Alleviating Cancer Drug Toxicity by Inhibiting a Bacterial Enzyme

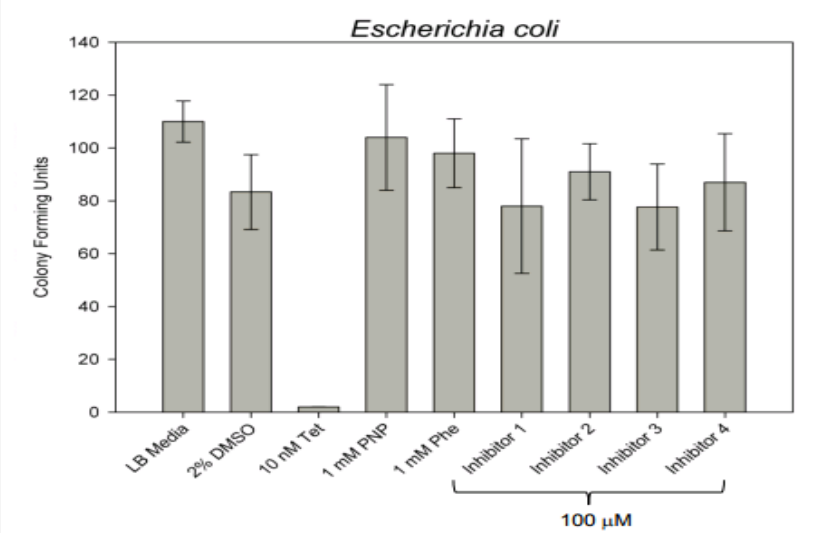
Bret D. Wallace[1], Hongwei Wang[2], Kimberly T. Lane[1], John E. Scott[3], Jillian Orans[1], Ja Seol Koo[4], Madhukumar Venkatesh[2], ...
+ See all authors and affiliations

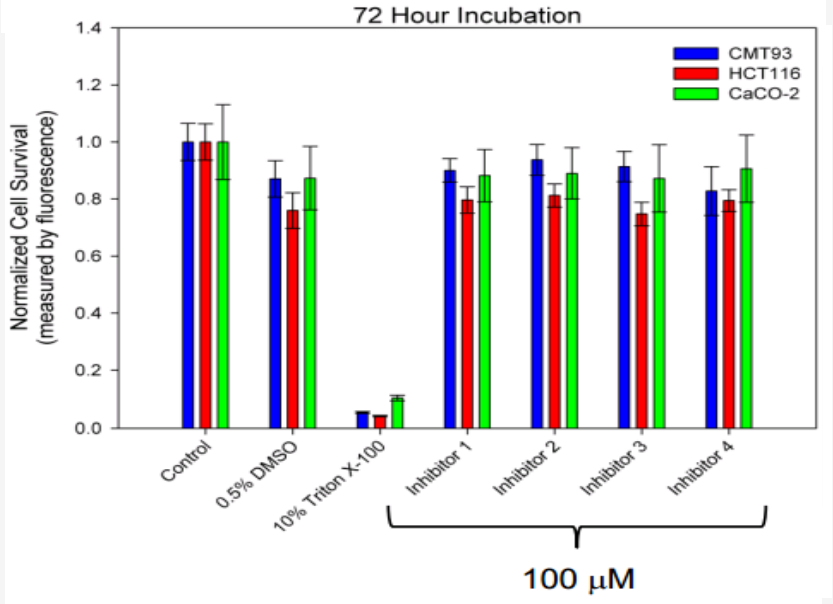
Science 05 Nov 2010:
Vol. 330, Issue 6005, pp. 831-835
DOI: 10.1126/science.1191175





Assessment for selectivity

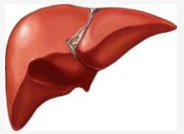




gut microbiota

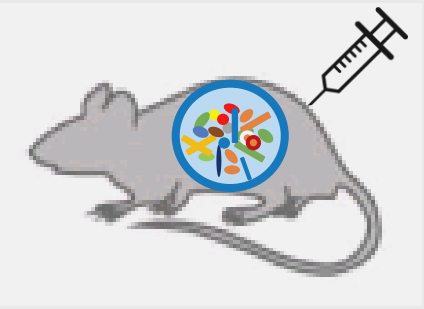
Inhibitors → 

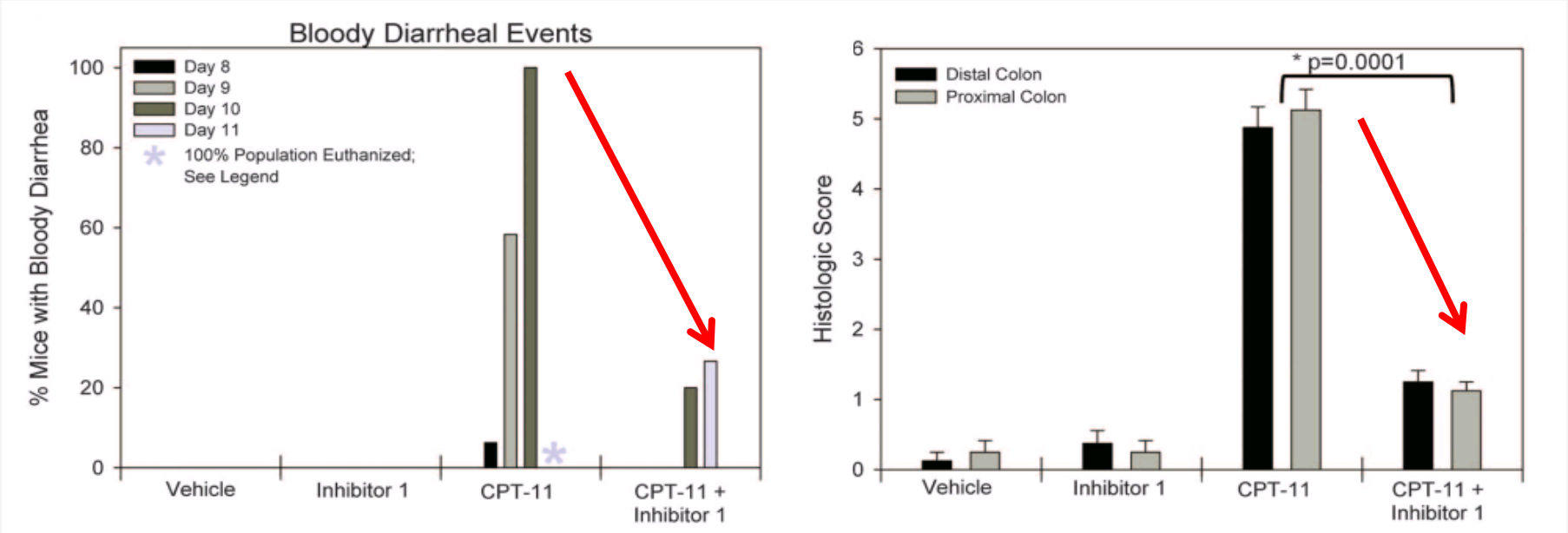
liver

Inhibitors → ✗ 

Inhibitors eliminate the toxicity caused by irinotecan

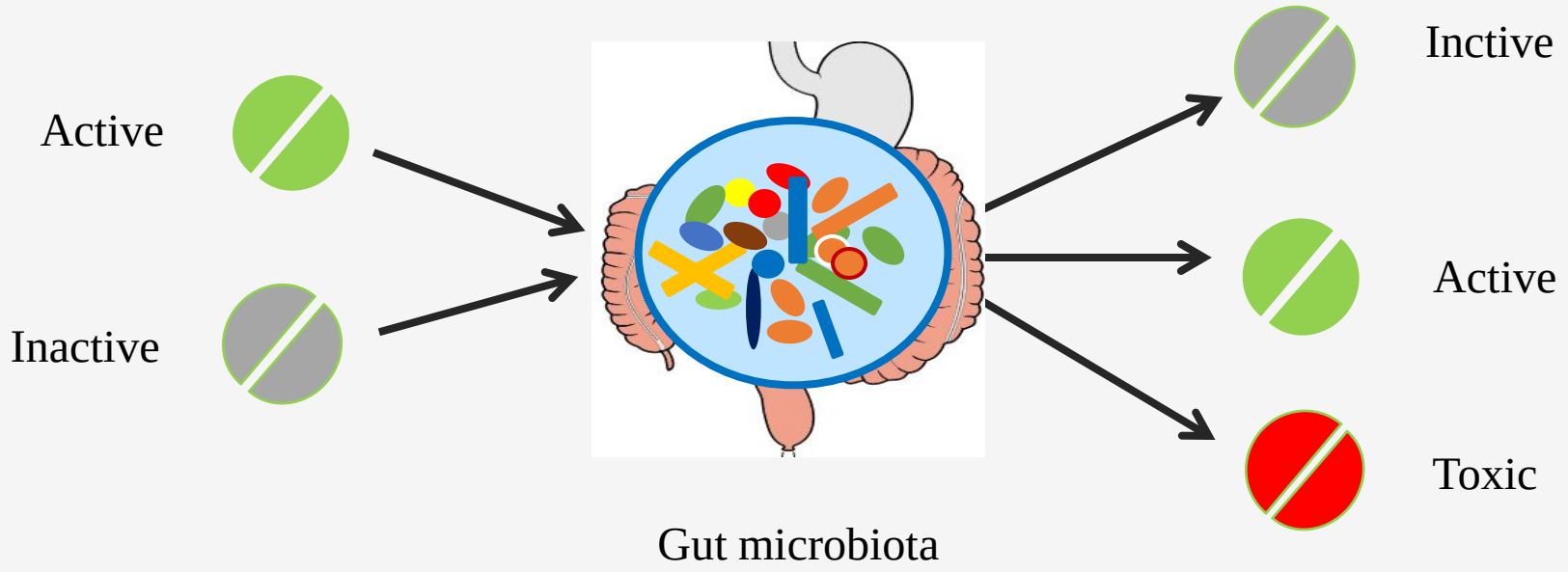
In vivo

Screened Inhibitor →  → Blood diarrheal events ↓
Histological damage



Summary

Which body organ is the major site for drug metabolism?



- Apart from the liver, the gut microbiota plays a critical role in drug metabolism.
- The gut microbiota is involved in prodrug activation, drug inactivation, and even drug toxicities elevation.

Future directions

- Study of the interaction between gut microbiota and drug metabolism could add a new dimension for personalized medicine.
- Manipulation of the gut microbiota with dietary intervention or developed drugs could be a novel approach to enhance the efficacy or decrease the toxicity of drugs.

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Thank you!