Gut Microbiome and drug interactions: Biopharmaceutical and oral bioavailability considerations

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Microbiome Ireland
Interfacing Food & Medicine

A TRADITION OF INDEPENDENT THINKING

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

The Gut Microbiome

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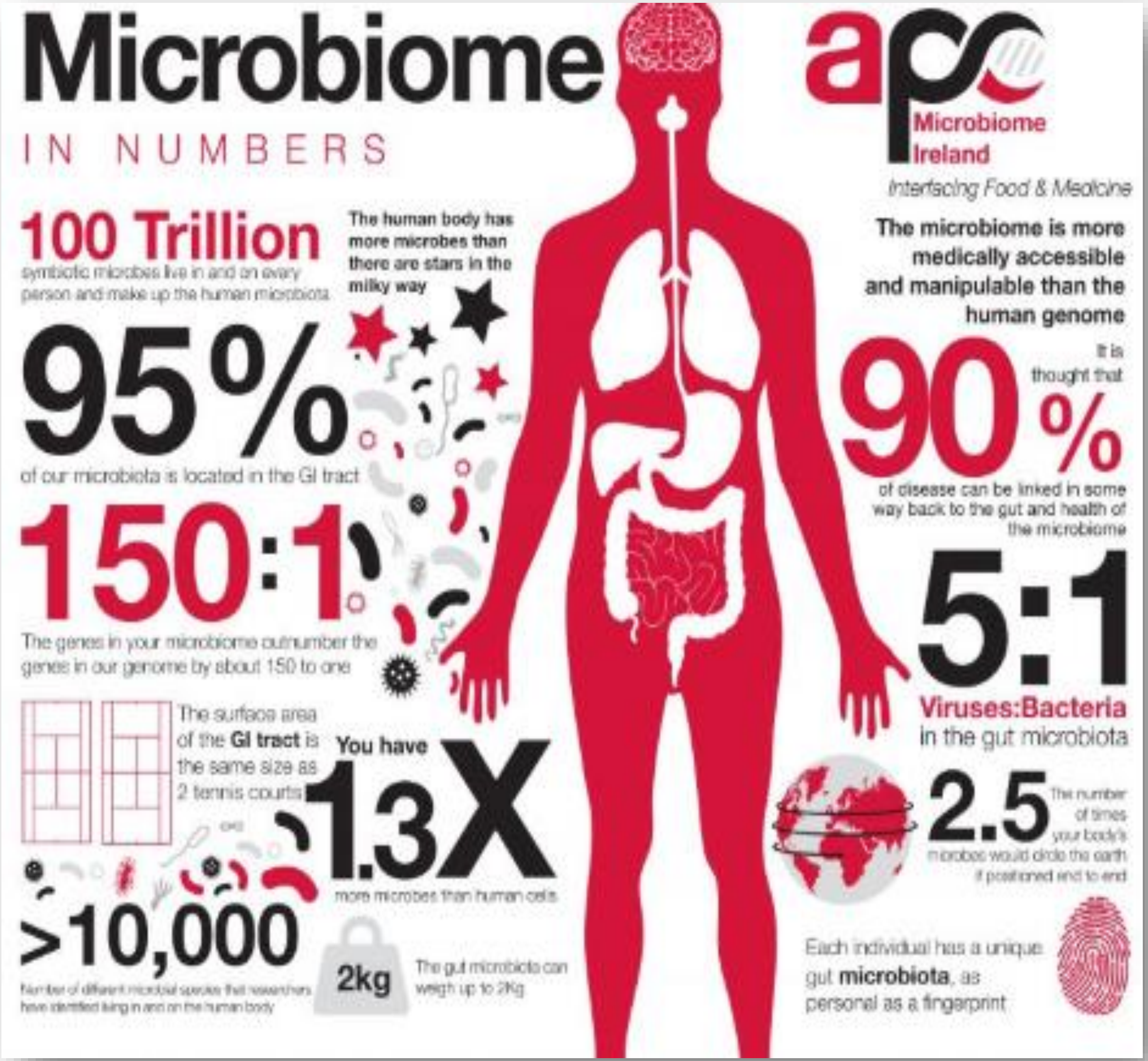

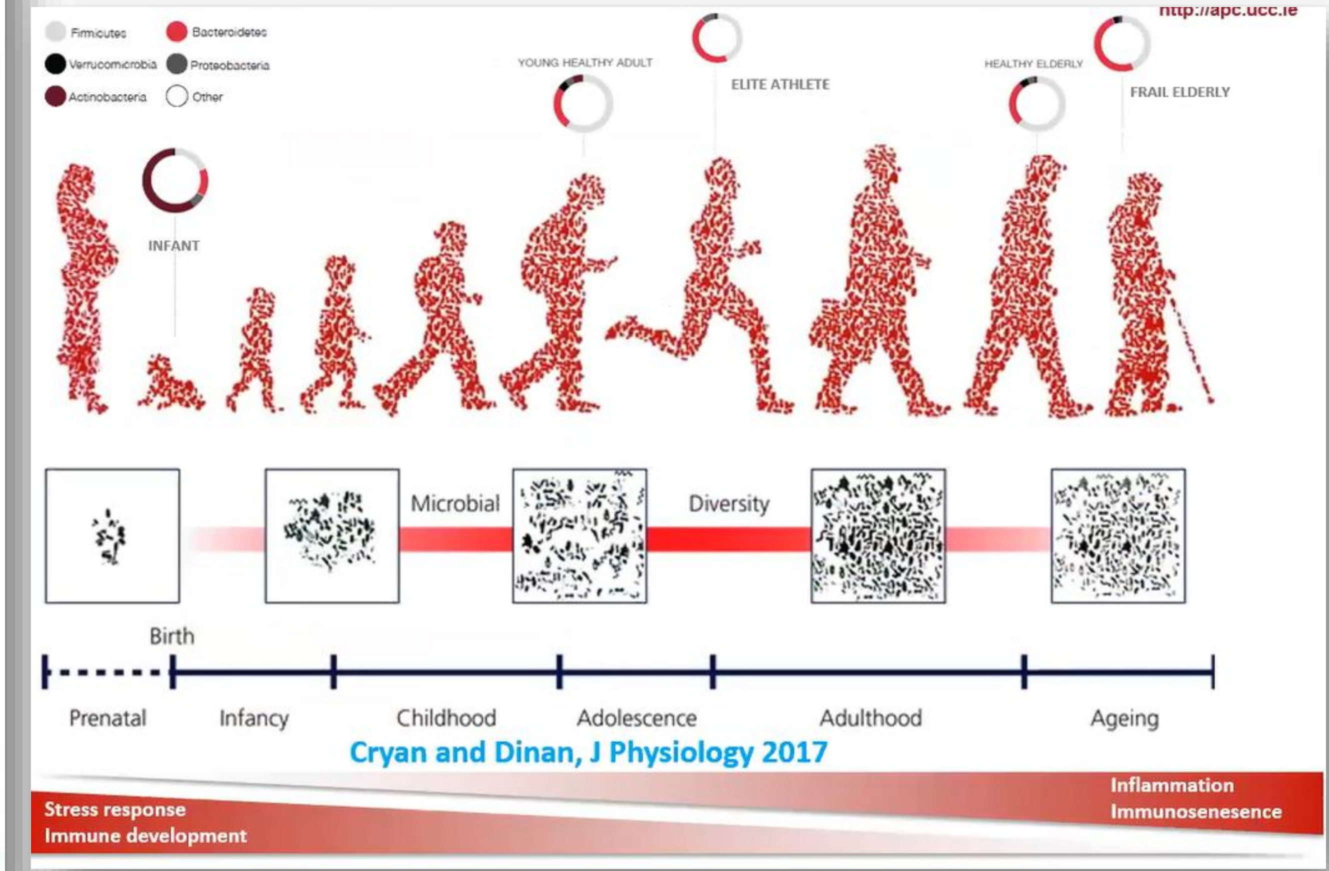

Cryan and Dinan, J Physiology 2017

Gut Microbiota – host interactions

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Cell Host Microbe. 2008 June 12; 3(6): 417–427. doi:10.1016/j.chom.2008.05.001.

Metagenomic Approaches for Defining the Pathogenesis of Inflammatory Bowel Diseases

Daniel A. Peterson[1,*], Dan
[1]Center for Genome Science
USA
[2]Department of Molecular, C
CO, 80309 USA

nature COMMUNICATIONS

Article | OPEN | Published: 04 December 2012

Symptomatic atherosclerosis is associated with an altered gut metagenome

Fredrik H. Karlsson, Frida Fåk, Intawat Nookaew, Valentina Tremaroli, Björn Fagerberg, Dina

REPORT

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. Turnbaugh[1,*]

tric Research 82 (2016) 109–118

available at ScienceDirect

iatric Research

evier.com/locate/psychires

ated gut microbiota induces

CrossMark

laine Patterson [a,c], Sahar El Aidy [a,d],
en Scott [a], Gerard Moloney [a],
Paul Ross [c], Catherine Stanton [c],
n [a,b,*]

reland

roningen, The Netherlands

OPEN

Citation: Transl Psychiatry (2013) **3**, e309; doi:10.1038/tp.2013.83

www.nature.com/tp

ORIGINAL ARTICLE

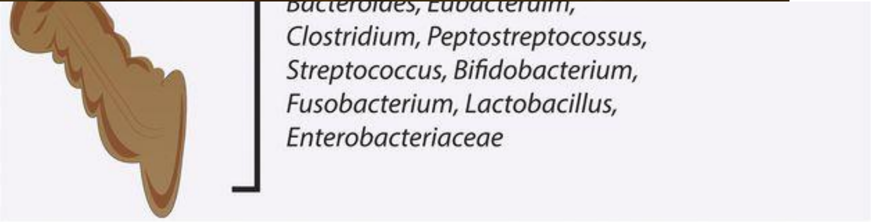
Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat

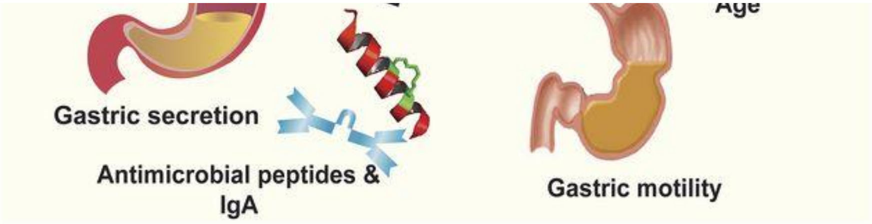
KJ Davey[1,2], PD Cotter[1,3], O O'Sullivan[1,3], F Crispie[3], TG Dinan[1,4], JF Cryan[1,5] and SM O'Mahony[1,5]

et *al.* 2018

Factors defining the Gut Microbiome

- Characteristics of



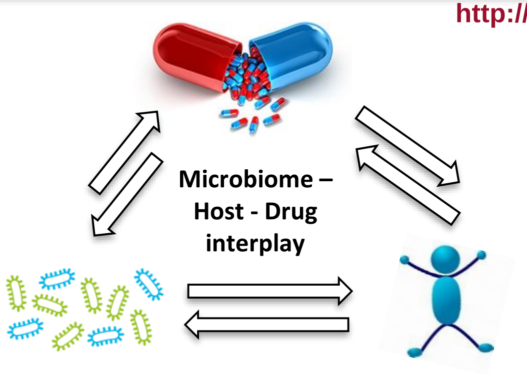



Tim Spector lost 1,300 species of gut microbes when he switched to a fast-food died for 10 days (Tim Spector)

- Drugs can modify Gut Microbiome

Deciphering Microbiome – Host - Drug interplay

"what the HOST does to the drug"



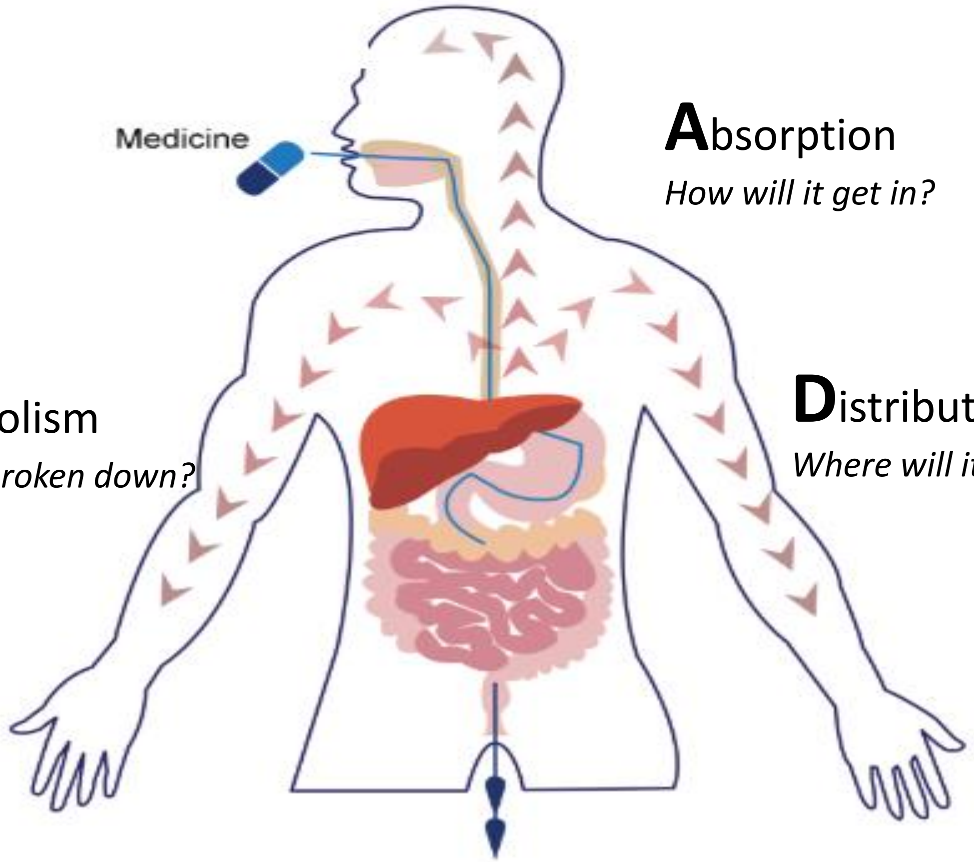
PK= ADME

Absorption
How will it get in?

Distribution
Where will it go?

Metabolism
How is it broken down?

Excretion
How does it leave?



Gut Microbiome?

Gut Microbiome – Host - Drug interactions

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DRUG-MICROBIOTA INTERACTIONS

Antibacterial effects e.g. sertraline

BJP British Journal of Pharmacology

British Journal of Pharmacology (2018) **175** 4415–4429 4415

Themed Section: When Pharmacology Meets the Microbiome: New Targets for Therapeutics?

REVIEW ARTICLE

Drug–gut microbiota interactions: implications for neuropharmacology

Correspondence Gerard Clarke, APC Microbiome Ireland, University College Cork, Cork, Ireland. E-mail: g.clarke@ucc.ie

Received 23 November 2017; **Revised** 4 April 2018; **Accepted** 17 April 2018

Jacinta Walsh[1,4], Brendan T Griffin[2,4], Gerard Clarke[3,4] and Niall P Hyland[1,4,5]

Metabolism by bacterial enzymes e.g. sulfasalazine

MICROBIOTA-DRUG INTERACTIONS

Walsh et al., 2018 (adapted)

Clinically relevant microbiome-mediated drug metabolism

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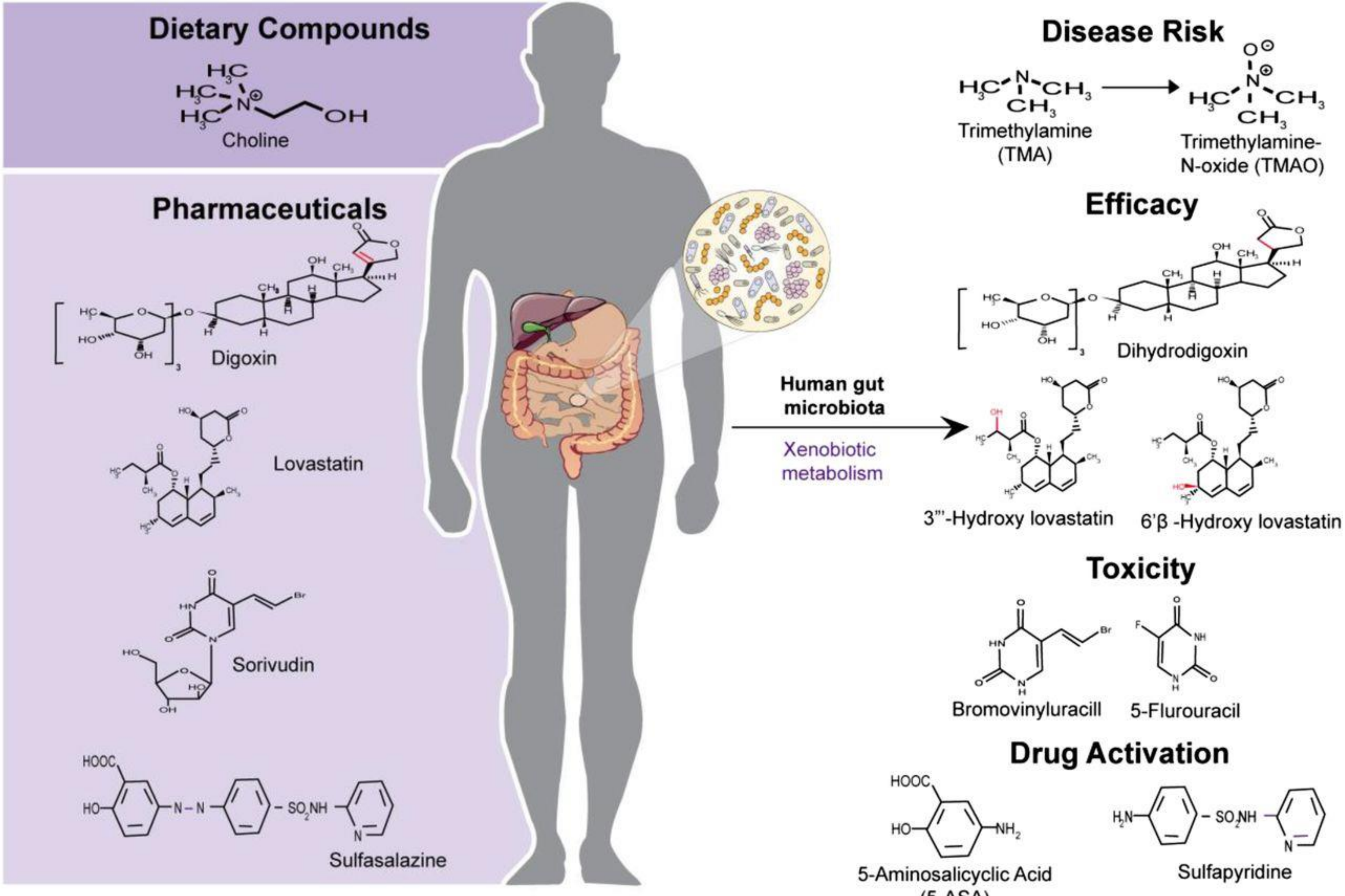
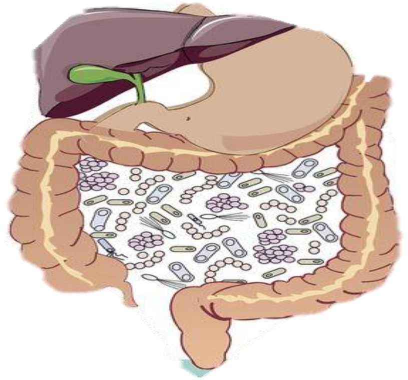


Gut Microbiota – Drug metabolic Interactions



*Clarke G, Sandhu KV, Griffin BT, Dinan TG, Cryan JF, **Hyland NP**. Gut Reactions: Breaking Down Xenobiotic-Microbiome Interactions. Pharmacol Rev. 2019 Apr;71(2):198-224.*

Gut microbiome-mediated drug metabolism

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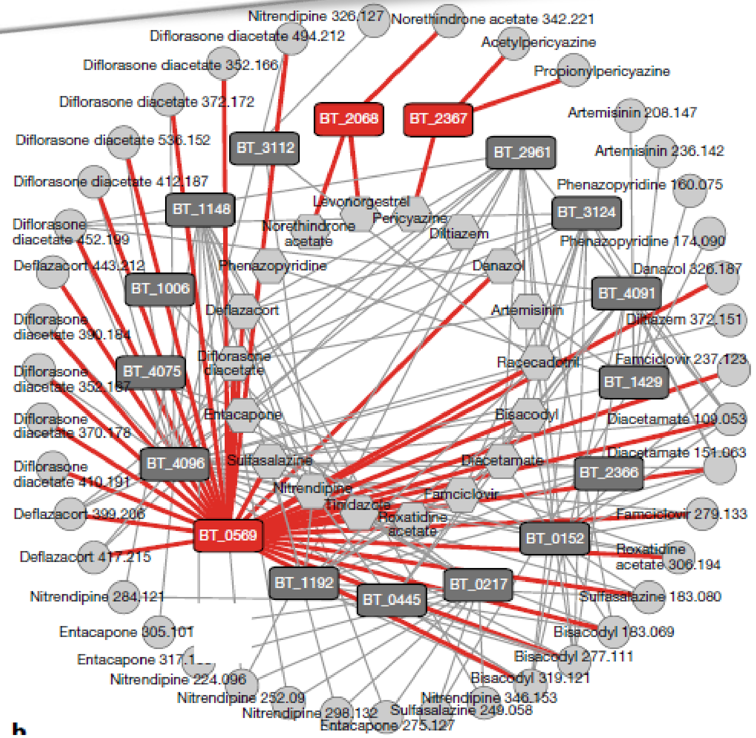
ARTICLE

https://doi.org/10.1038/s41586-019-1291-3

Mapping human microbiome drug metabolism by gut bacteria and their genes

Michael Zimmermann[1,3], Maria Zimmermann-Kogadeeva[1,3], Rebekka Wegmann[1,2] & Andrew L. Goodman[1*]



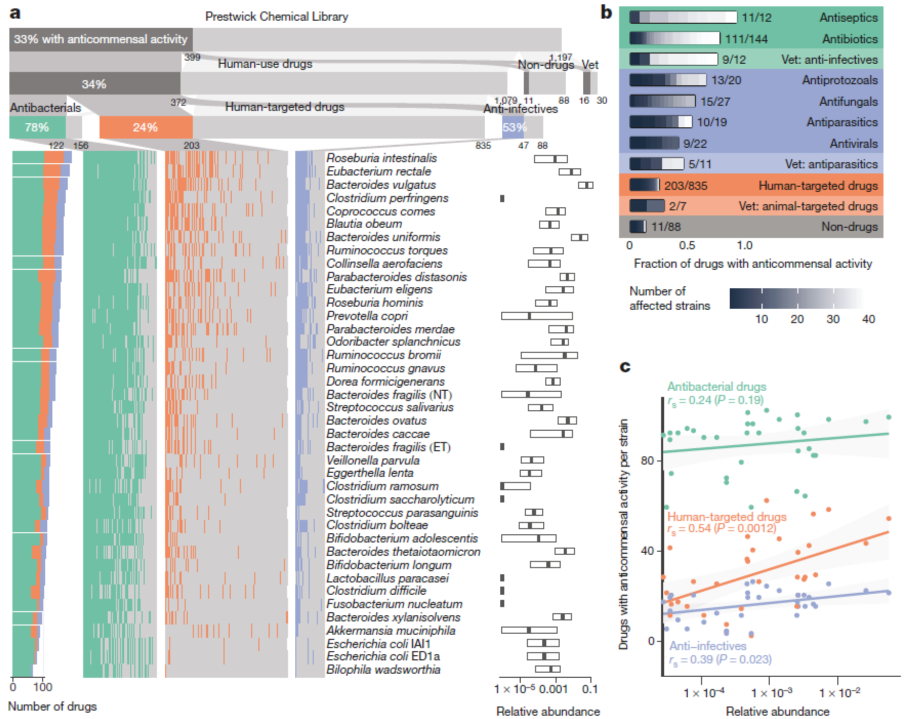
Of 271 orally administered drugs, 66% were susceptible to gut bacteria mediated metabolism

ARTICLE

doi:10.1038/nature25979

Extensive impact of non-antibiotic drugs on human gut bacteria

Lisa Maier[1*], Mihaela Pruteanu[1†*], Michael Kuhn[2*], Georg Zeller[2], Anja Telzerow[1], Exene Erin Anderson[1], Ana Rita Brochado[1], Keith Conrad Fernandez[1], Hitomi Dose[3], Hirotada Mori[3], Kiran Raosaheb Patil[2], Peer Bork[2,4,5,6] & Athanasios Typas[1,2]



Of more that 1,000 drugs screened, 24% of the drugs with human targets negatively impact growth of gut microbiome growth

Gut microbiome – excipient interactions

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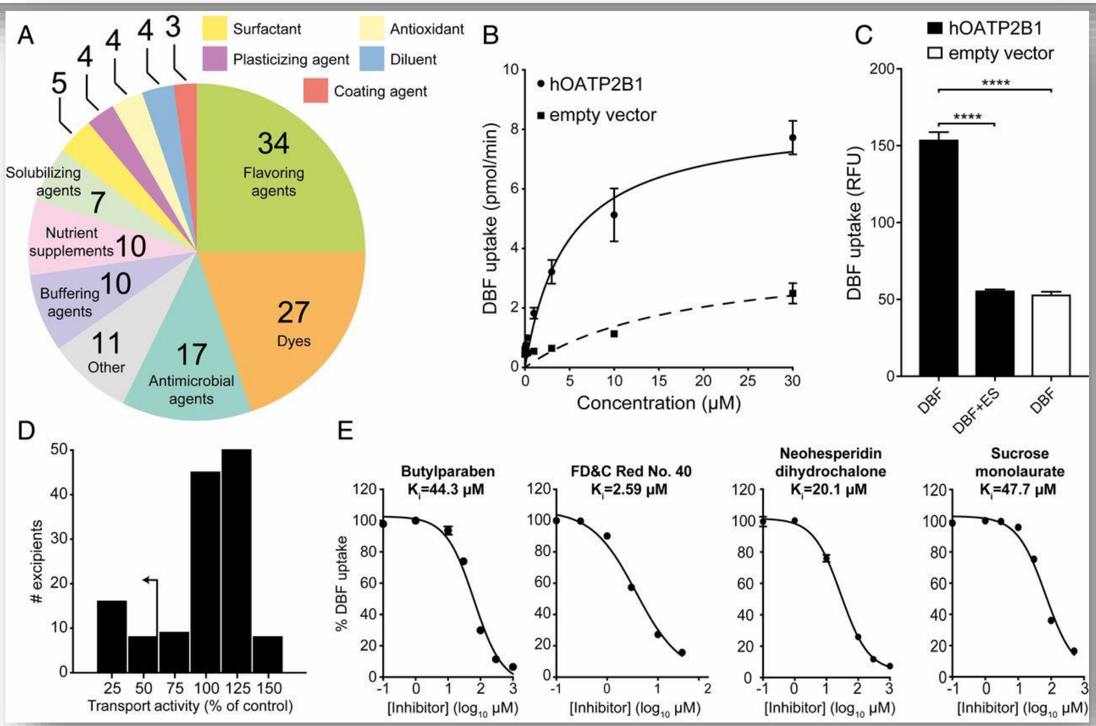
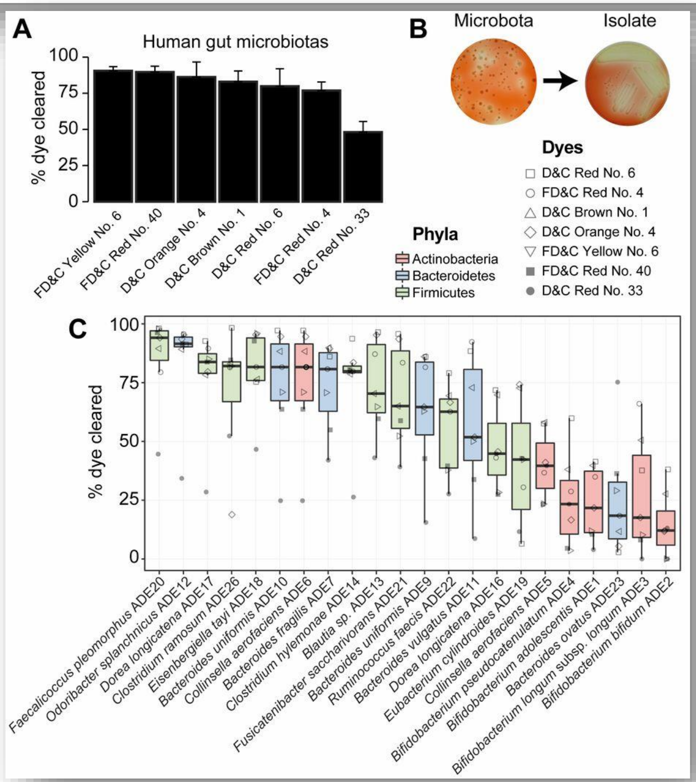
Bacterial metabolism rescues the inhibition of intestinal drug absorption by food and drug additives

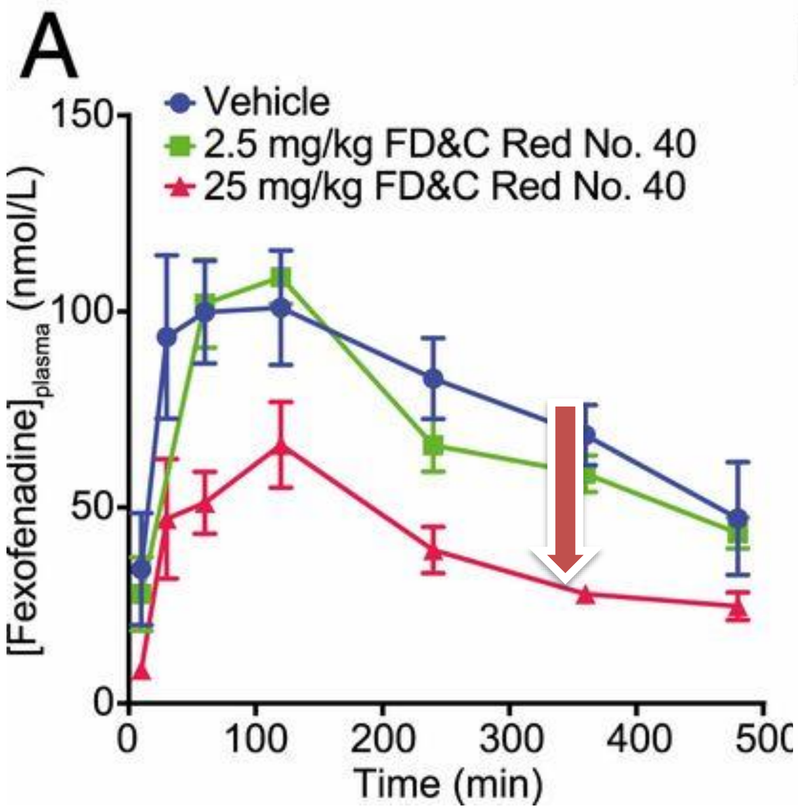
Ling Zou[a,1], Peter Spanogiannopoulos[b,1], Lindsey M. Pieper[b], Huan-Chieh Chien[a], Wenlong Cai[c], Natalia Khuri[d], Joshua Pottel[e,f], Bianca Vora[a], Zhanglin Ni[g], Eleftheria Tsakalozou[g], Wenjun Zhang[c,h], Brian K. Shoichet[e,f], Kathleen M. Giacomini[a,2], and Peter J. Turnbaugh[b,h,2]



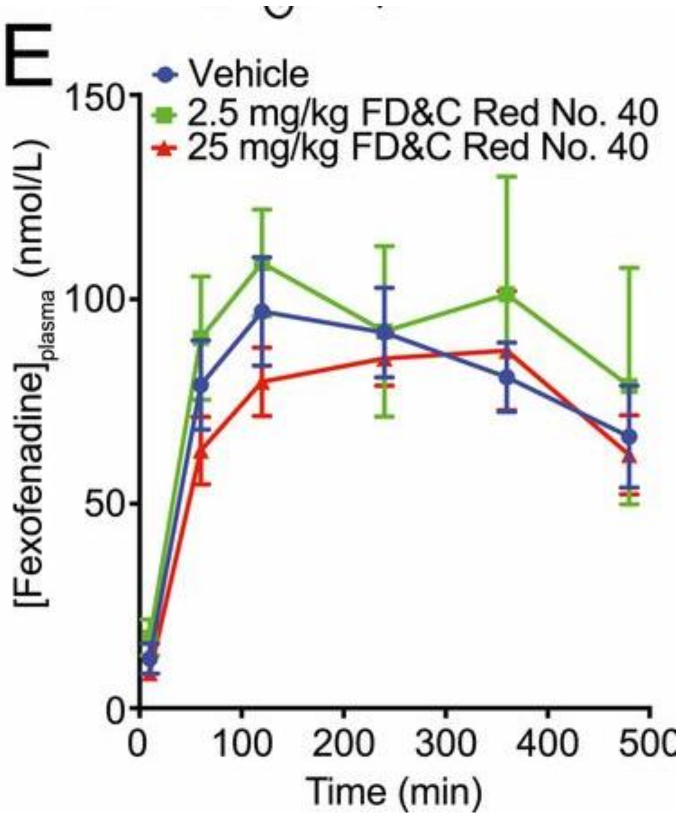


Ling Zou et al. PNAS 2020;117:27:16009-16018

Microbiome metabolism – impact on excipients effect



High dose Red azo dye reduces fexofenadine bioavailability – saturation of gut bacterial azoreductase activity



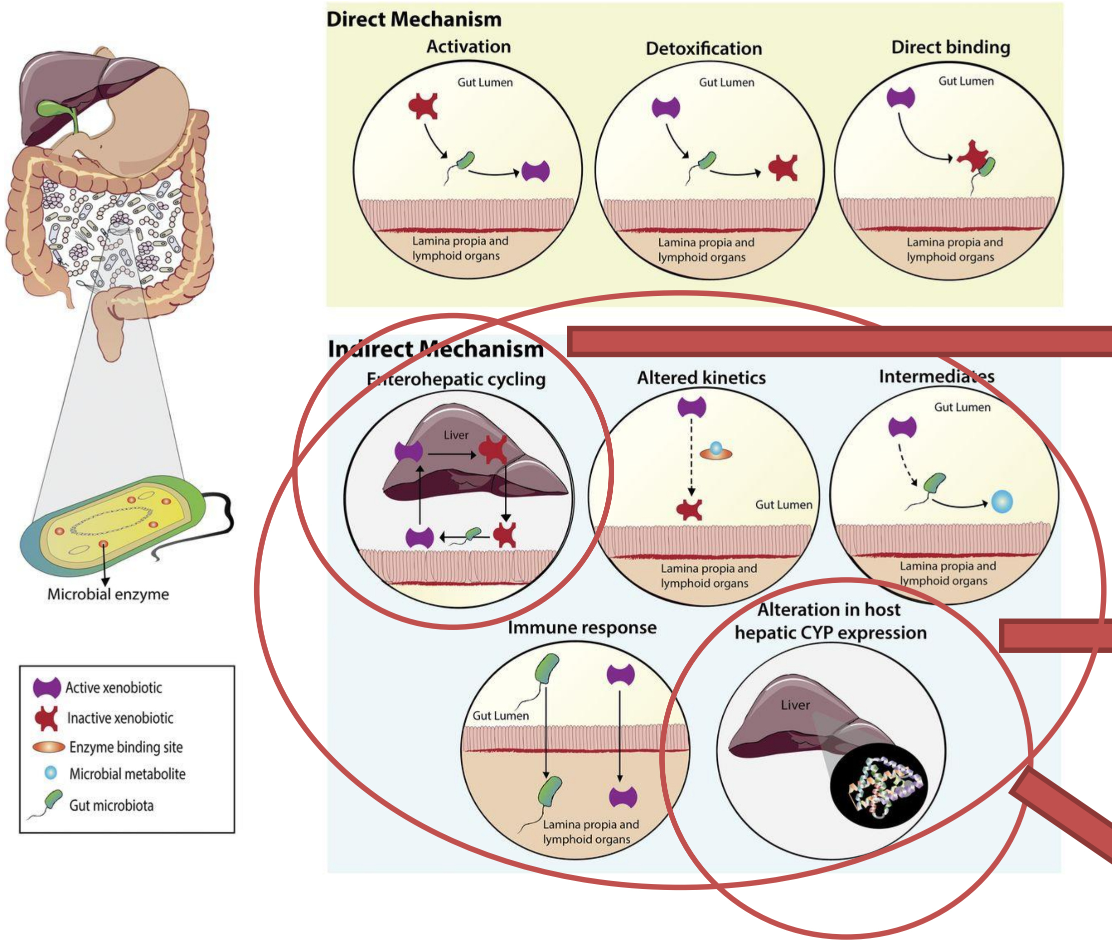
No impact in Germ free mice

Significance

Food and drug products are supplemented with small molecules called excipients that are assumed to be inert. In this study, we screened a collection of common oral excipients and identified 24 that inhibit intestinal drug transport, including the common excipient FD&C Red No. 40, which decreased drug absorption in mice. Excipient inhibitors were enriched for azo dyes, which human gut bacteria could metabolize, producing metabolites that no longer inhibit intestinal drug transporter activity. This work demonstrates the unintended consequences of oral excipients and a beneficial role for the gut microbiome in limiting these unfavorable effects.

Ling Zou et al. PNAS 2020;117:27:16009-16018

Understanding Microbiome – Host - Drug interactions



Clarke, Sandhu, Griffin, Dinan, Cryan & Hyland. Pharmacol Rev 2019;71:198-224

1. Alter Microbiome → Alter Phase II metabolism

2. Alter Microbiome → Alter Hepatic Genes?

3. Alter Microbiome → Alter Drug Pharmacokinetics?

Microbiome – Host metabolism interplay

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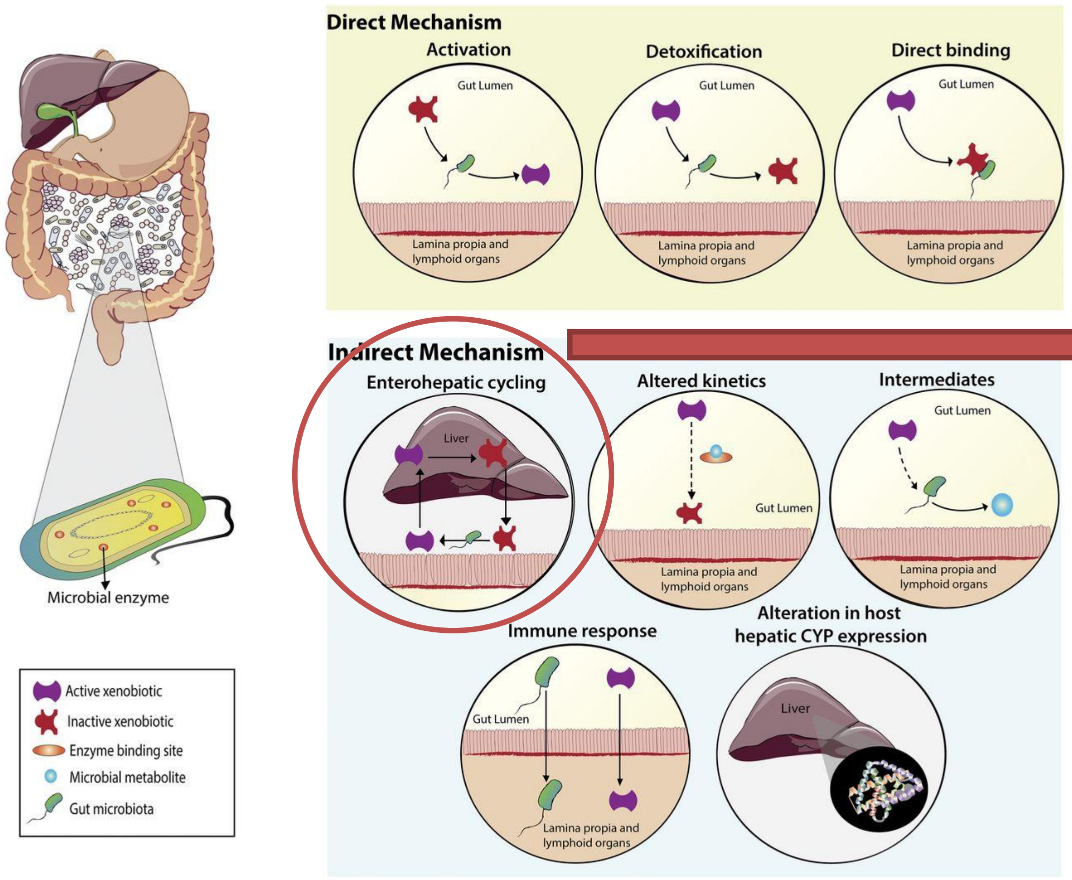

1. Alter Microbiome → Alter Phase II metabolism

Clarke, Sandhu, Griffin, Dinan, Cryan & Hyland. Pharmacol Rev 2019;71:198-224

Impact of Antibiotic Treatment on Faecal Enzymatic Activity

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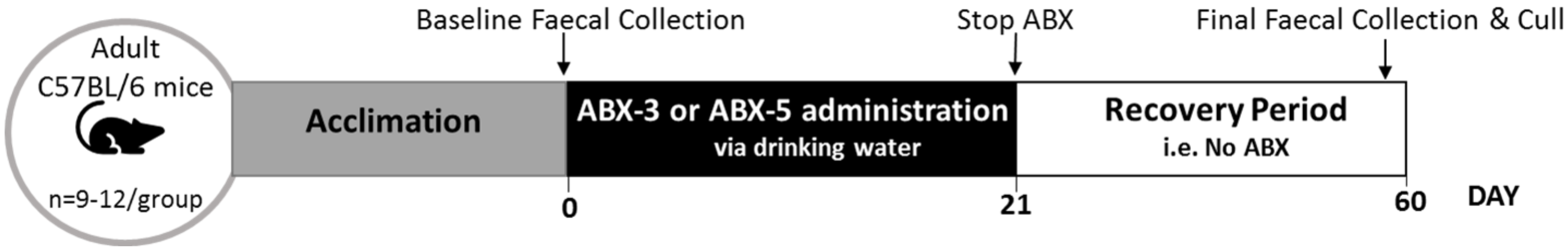

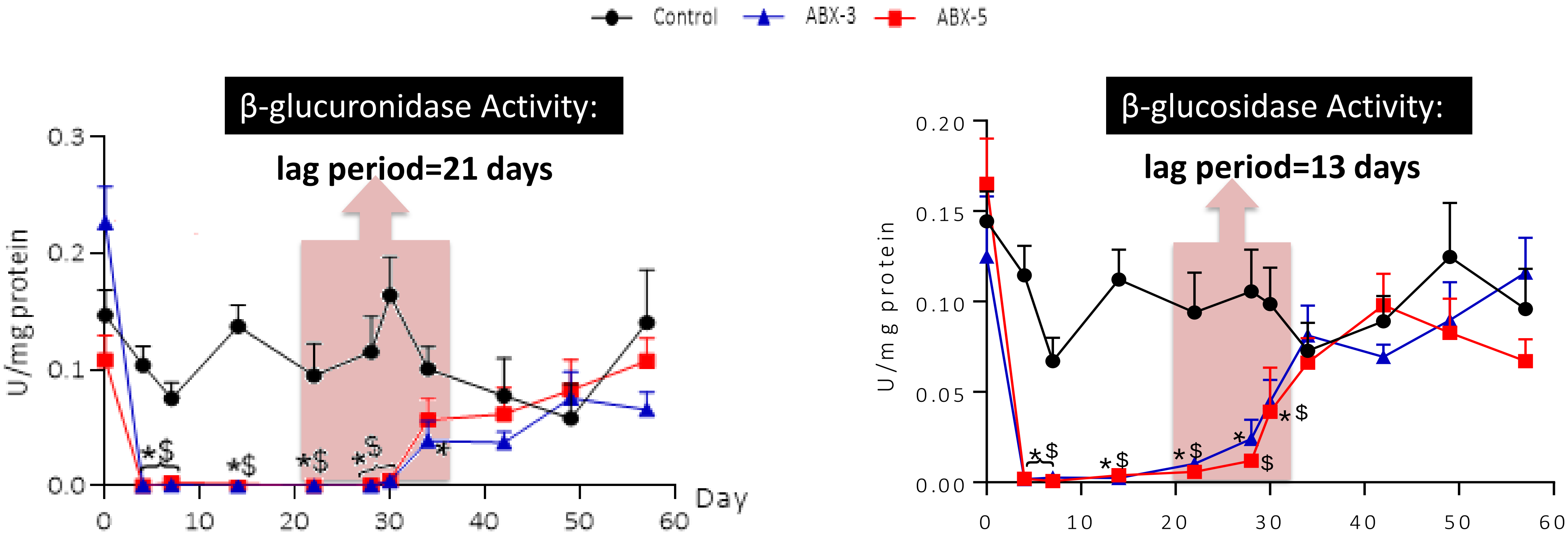

Walsh et al, Gastro. Liver. Physiol. 2020 https://doi.org/10.1152/ajpgi.00026.2020

***ABX-3 Cocktail:** Ampicillin & Vancomycin & Neomycin
****ABX-5 Cocktail:** Ampicillin & Vancomycin & Ciprofloxacin & Imipenem & Metronidazole

**p<0.05; RM-ANOVA with Fishers LSD*
n=9-12/group

Implications for Phase II metabolism

Microbiota-Derived Enzyme:	Hypothesised reaction mechanisms:	Drug (or Metabolite) Substrate:	Ref:
β-glucuronidase	Remove glucuronic acid moiety from hepatic phase 2 metabolites	Irinotecan (SN-38 glucuronide) NSAIDS, e.g. Indomethacin and Diclofenac	(Yamamoto et al., 2008, Saitta et al., 2014)
β-glucosidase	Hydrolyse the glycosidic bond of a carbohydrate moiety to release non-reducing terminal glycosyl residues	Prodrugs Herbal substances e.g. anthrocyanins, genistin and naringin	(You et al., 2015)
Azoreductase	Reduction of azo or quinone bonds	Azo-containing drugs, e.g. Olsalazine (5ASA prodrug) Nitrofuran antibiotics Ester containing prodrugs	(Ryan, 2017)
Carboxylesterase	Hydrolyse ester, thioester, amide, or carbamate containing drugs to respective free acids Hydrolyse esters to carboxylic acids	Aspirin, Ester containing prodrugs	(Kim et al., 2016, Laizure et al., 2013, Imai and Ohura, 2010)
Nitroreductase	Reduction of the nitro group	Metronidazole Benzodiazepines	(Koch et al., 1979, Elmer and Remmel, 1984, Takeno et al., 1990)
N-acetyltransferase	Transfer of acetyl group to nitrogen or oxygen atom of primary arylamines, hydrazines and N-hydroxylated metabolites	5-aminosalicylic acid	(Deloménie et al., 2001, van Hogezand et al., 1992)
Sulfatases	Hydrolysis of sulfate esters utilising formylglycine	Sulfate ester hepatic metabolites	(Koppel et al., 2017, Ulmer et al., 2014)

Implications of Antibiotic treatment on Phase II metabolism

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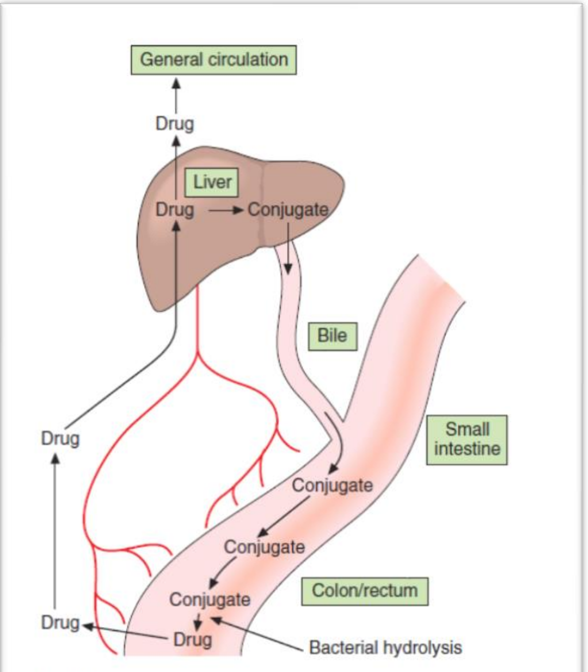
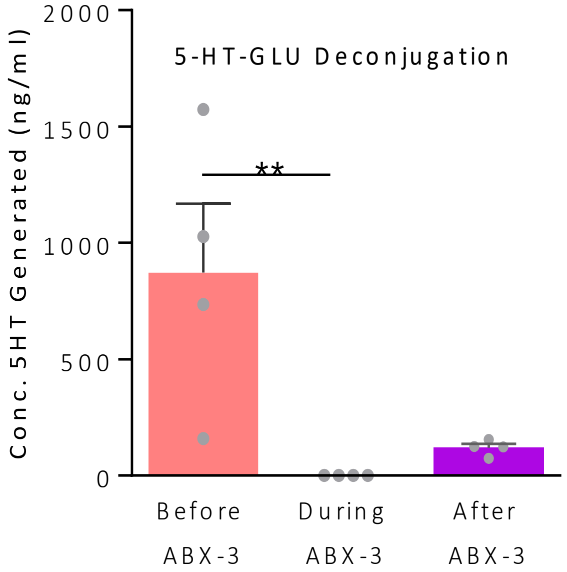


Fig. 2.13
Enterohepatic circulation of drugs.



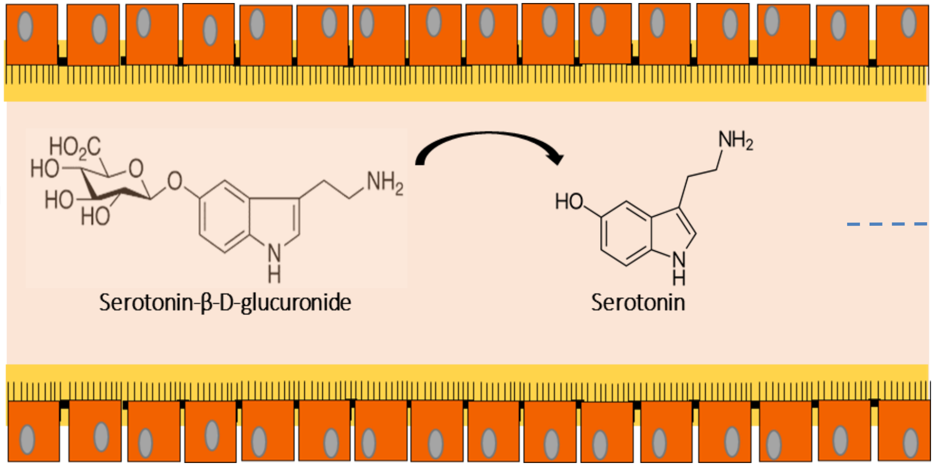
$**p<0.01$;
ANOVA (RM or one-way)
n=9-12/group (enzyme)
n=4 (5-HT)

Walsh et al, Gastro. Liver. Physiol. 2020 https://doi.org/10.1152/ajpgi.00026.2020

intestinal lumen

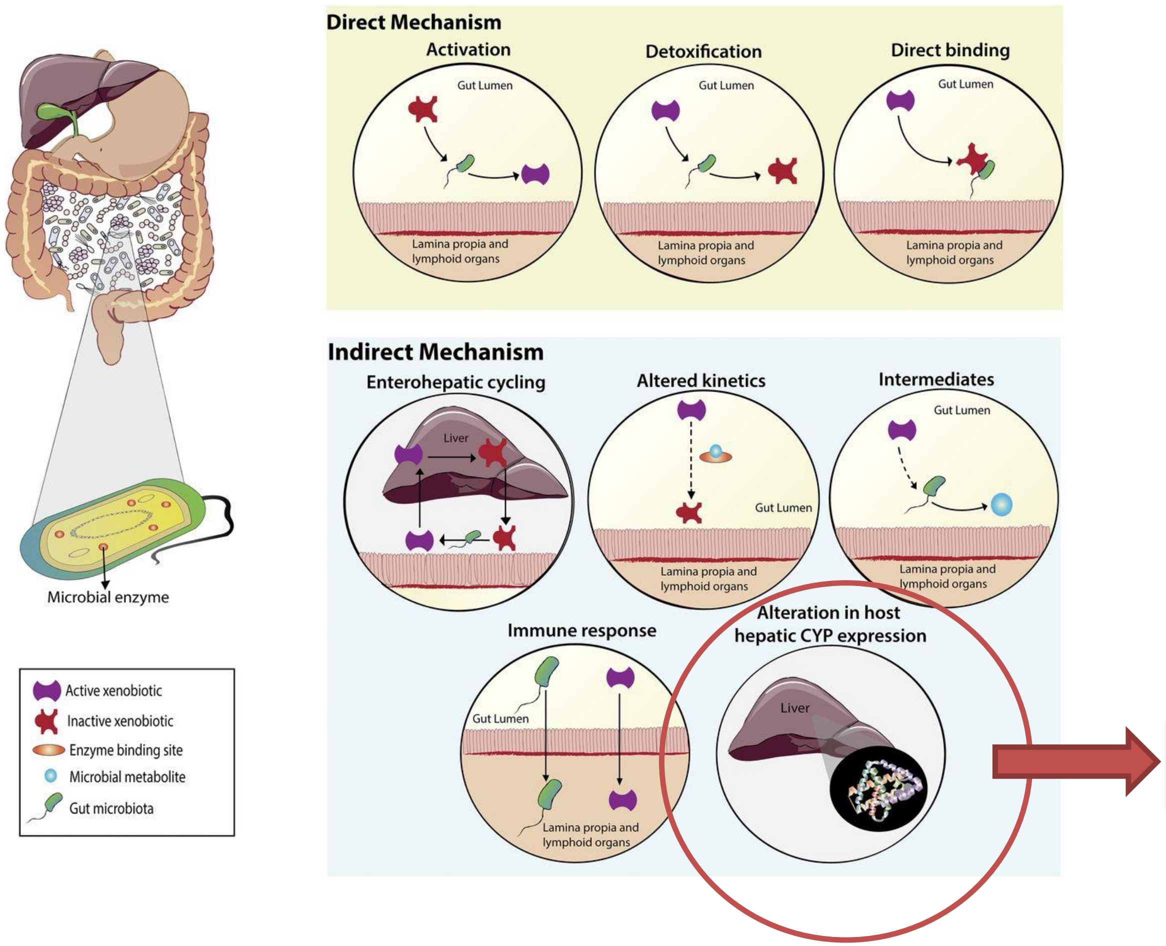
mucus layer

enterocytes



Implications for Gut Function?

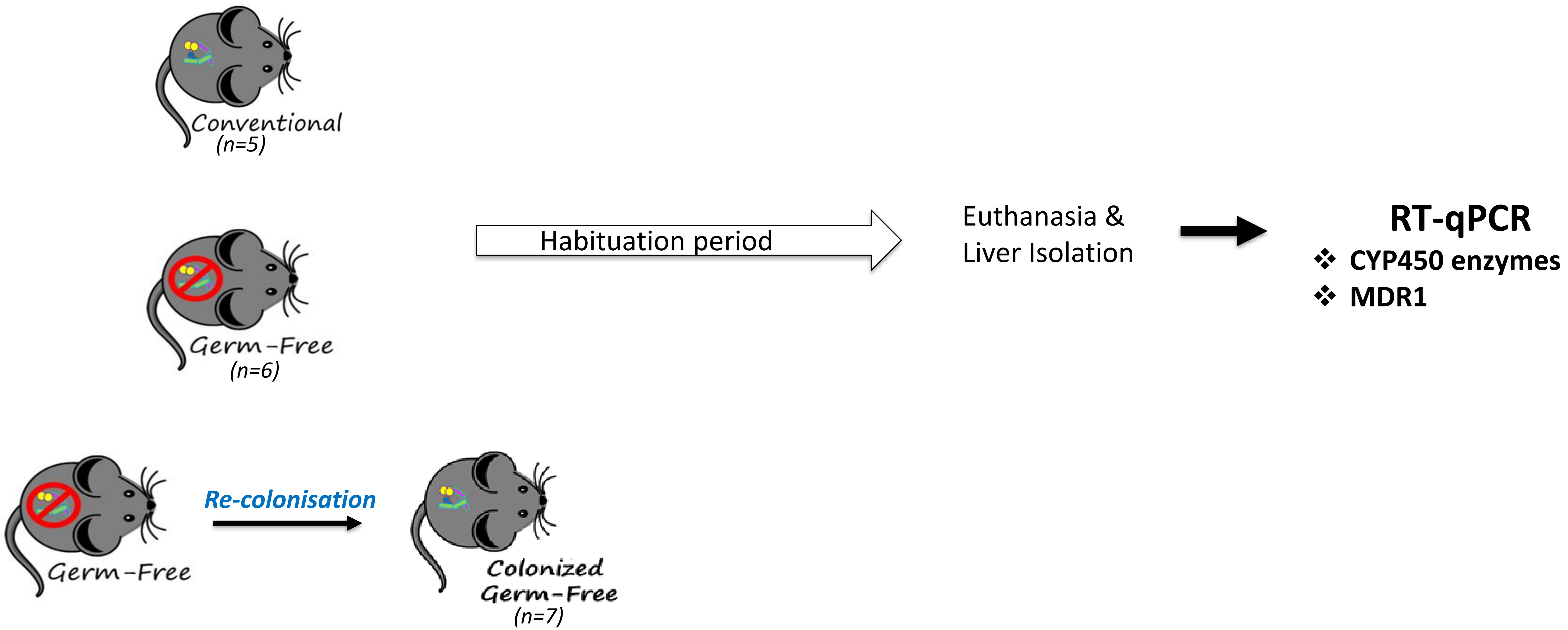
Microbiome – Host metabolism interplay



2. Alter Microbiome → Alter Hepatic Genes?

Clarke, Sandhu, Griffin, Dinan, Cryan & Hyland. Pharmacol Rev 2019;71:198-224

Microbial Regulation of Hepatic Drug Metabolism and Transport?



Walsh et al, J. Pharm. Pharmacol. 2020 https://doi.org/10.1111/jphp.13276

CYP/MDR Enzymes Subject to Microbial Regulation

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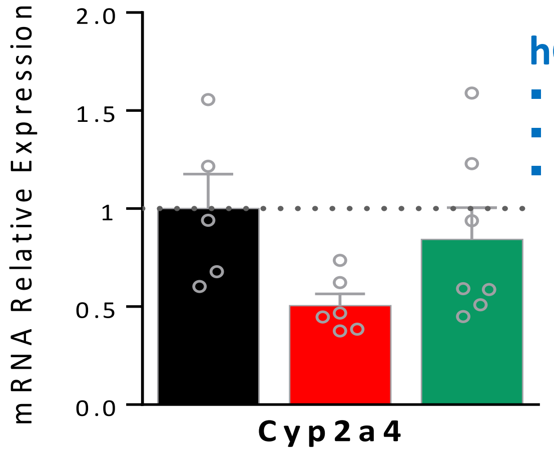
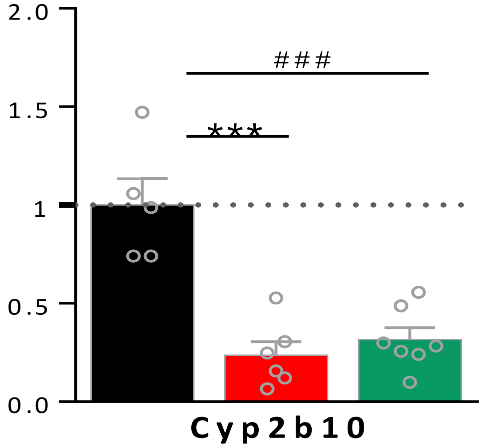
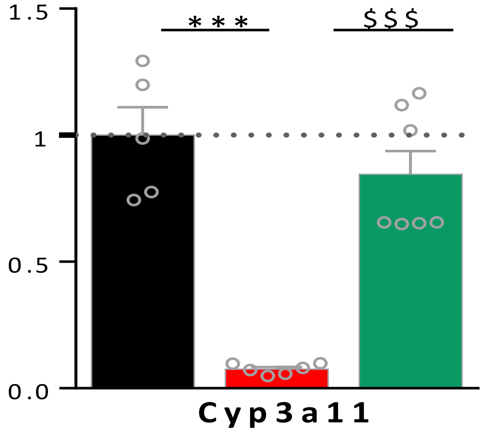


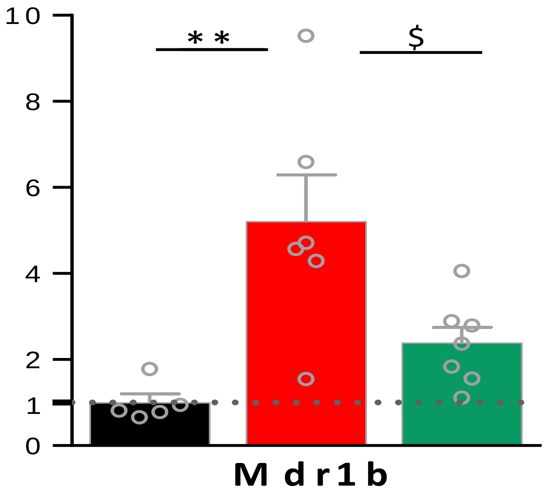
hCYP2A6
- Letrozole
- Nicotine
- Nifedipine



hCYP2B6
- Ketamine
- Methadone
- Tramadol



hCYP3A4
- Macrolides
- Domperidone
- Citalopram



hMDR1
- Verapamil
- Digoxin
- Ranitidine

p>0.05;p<0.01; ***p<0.001*
One-way ANOVA
n=5-6/group
Conv=conventional
GF=germ-free

Walsh et al, J. Pharm. Pharmacol. 2020 https://doi.org/10.1111/jphp.13276

Prebiotics → Modulate CYP/MDR expression?

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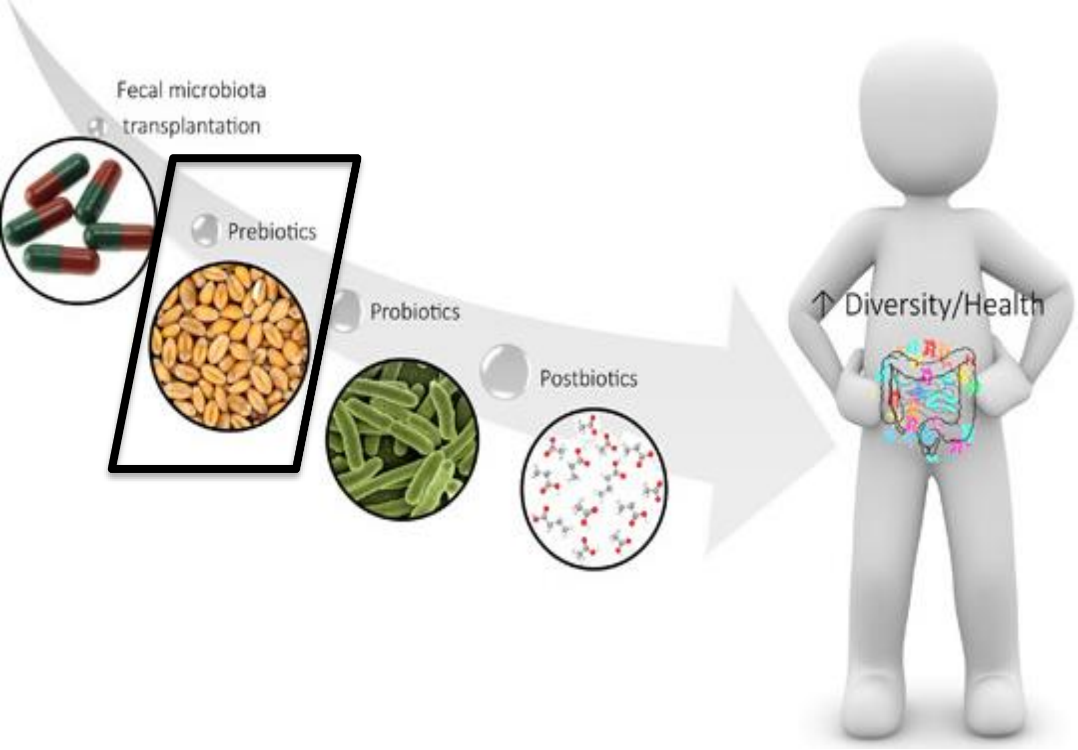
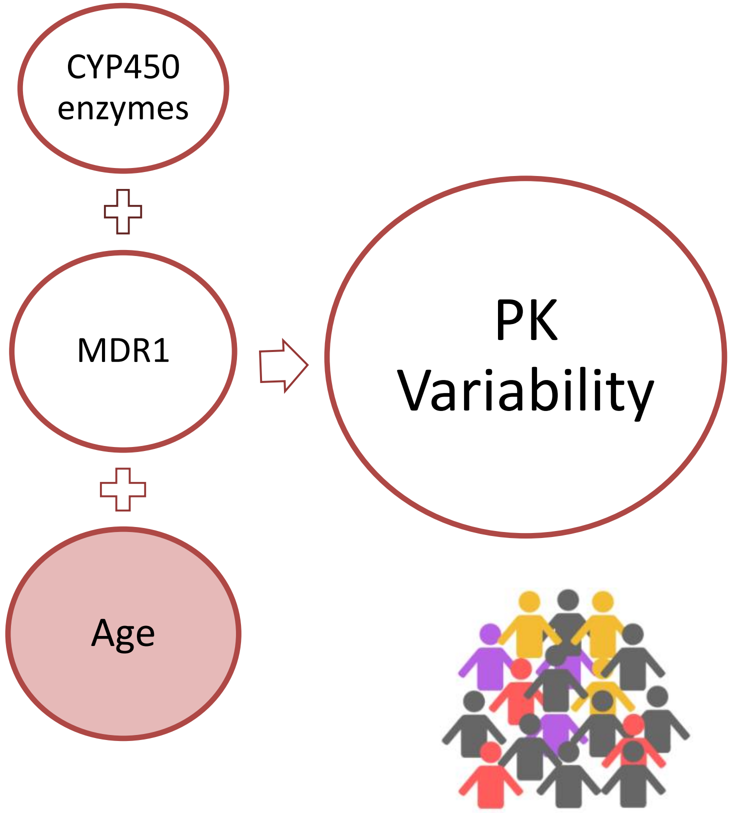
1. Impact of Microbiota-Targeted Intervention on Host Metabolism?



2. If so, could prebiotics influence hepatic expression?



Walsh et al, J. Pharm. Pharmacol. 2020 https://doi.org/10.1111/jphp.13276

Impact of Microbiota-Targeted Intervention on Hepatic Genes?

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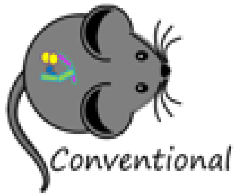
Young Mice
(2months*)



Control

Prebiotic-Treated

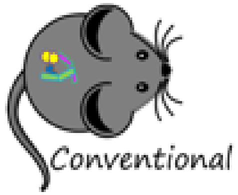
Standard Chow or

14 week treatment

Chow Supplemented with 10% FOS-Inulin

Euthanasia & Liver isolation

RT-qPCR



Control

Middle-Aged Mice
(10months*)

e.g. dietary sources of inulin

Male C57BL/6 (n=9-10/group)
*approx. age @ study start-date
FOS; fructooligosaccharide

Walsh et al, J. Pharm. Pharmacol. 2020 **https://doi.org/10.1111/jphp.13276**

Prebiotic Mix alters Specific CYPs and MDR1 in Liver

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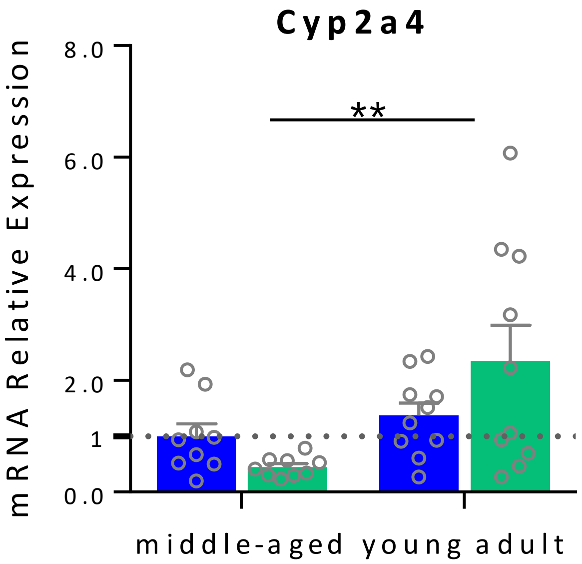
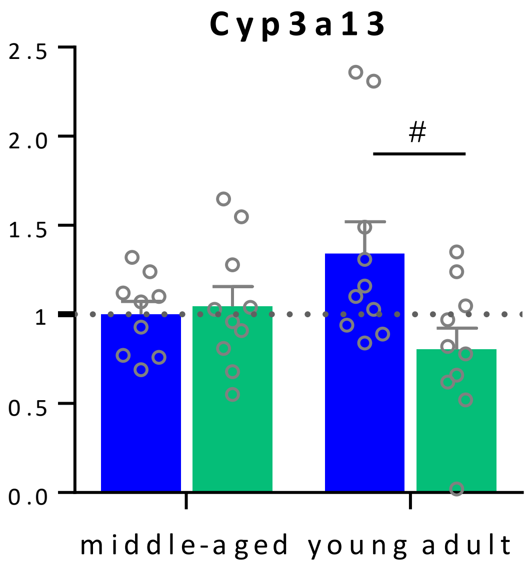
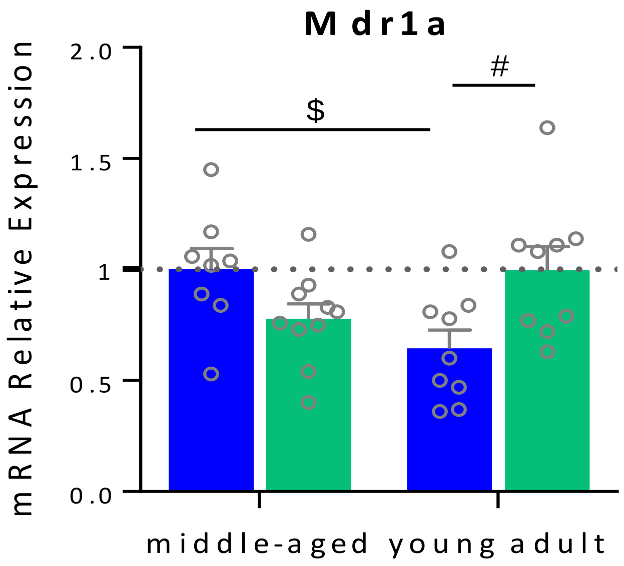
Walsh et al, J. Pharm. Pharmacol. 2020 https://doi.org/10.1111/jphp.13276



control prebiotic-treated





*; p<0.05; **; p<0.01
n=9-10/group
Two-way ANOVA

Microbiome – Host metabolism interplay

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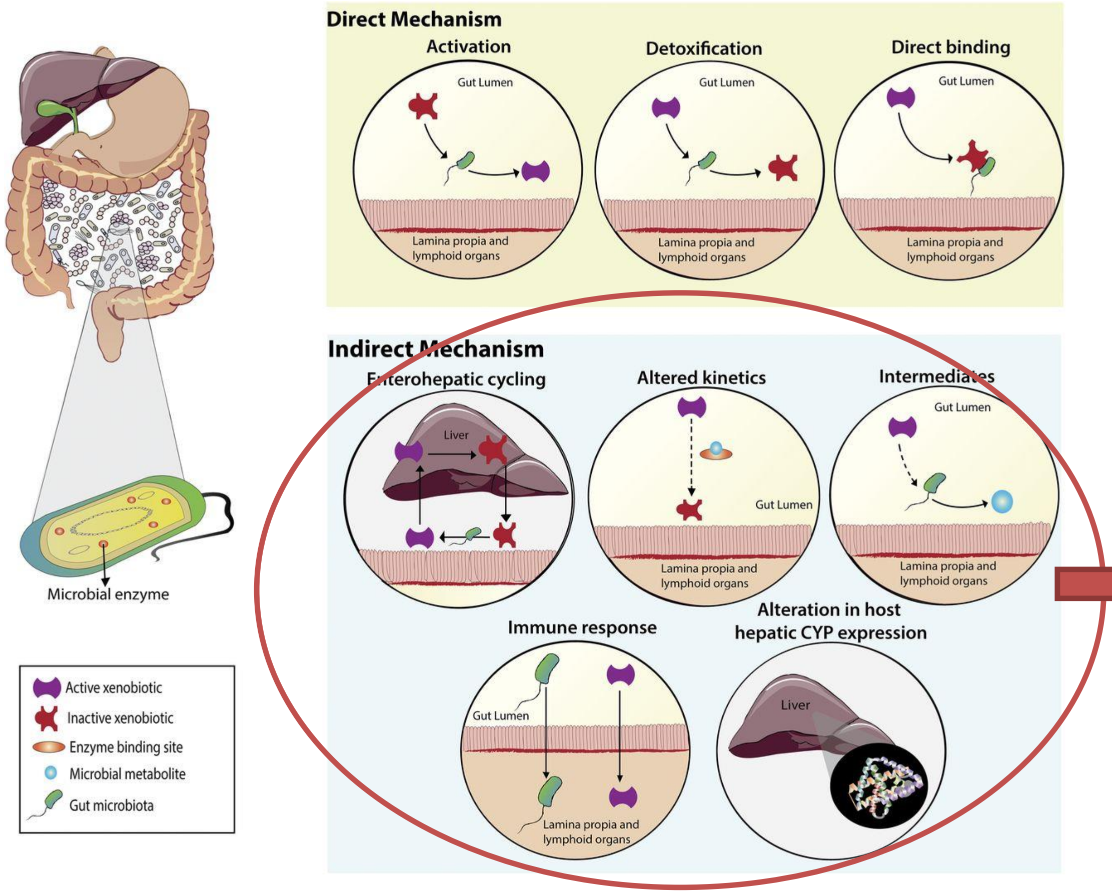

Alter Microbiome → Alter Drug Pharmacokinetics?

Clarke, Sandhu, Griffin, Dinan, Cryan & Hyland. Pharmacol Rev 2019;71:198-224

Alter Gut Microbiome → alter Drug PK in vivo?

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Probiotic-treated

Antibiotic-treated

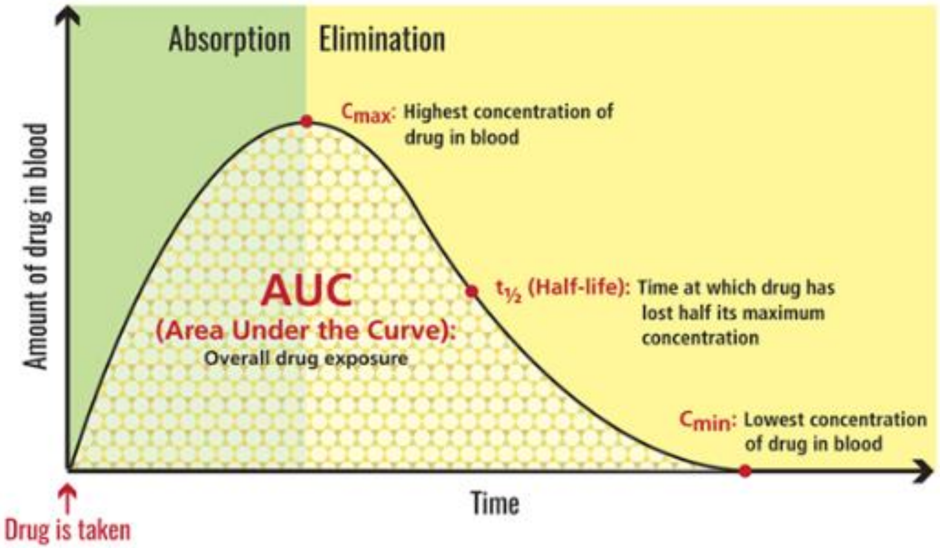
Vehicle

+

Single Oral Drug Dose

→

Altered Drug Pharmacokinetics?????



Sprague Dawley Rats; n=7/group
Antibiotic cocktail → ampicillin 1g/L; vancomycin 500mg/L; imipenem 250mg/L
Probiotic cocktail → VSL3 ($5 \cdot 10^{10}$ bacteria/kg/day)

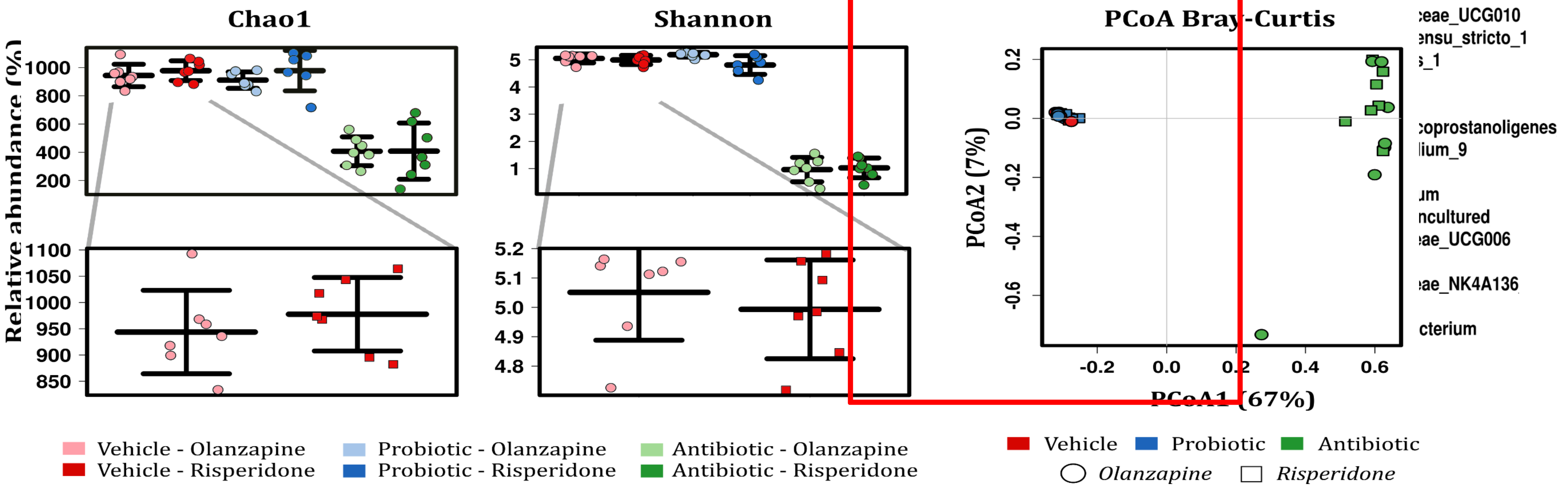
Walsh et al, under révision

Impact of Interventions on Microbial Signature

Changes in Composition (genus level)

Alpha Diversity

Beta Diversity



Walsh et al, under révision

Microbiota-depletion Increases Systemic OLZ Absorption

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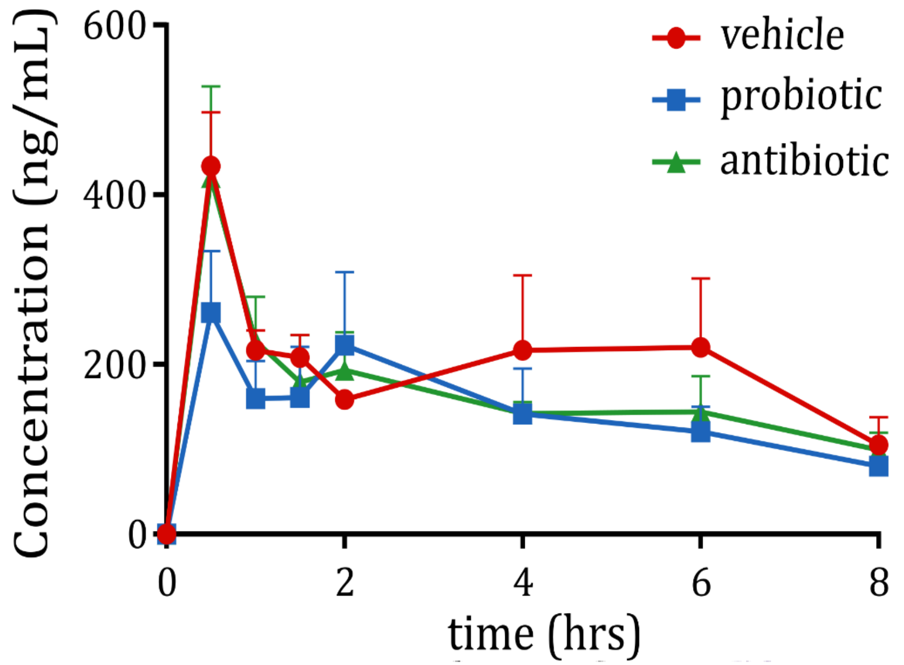
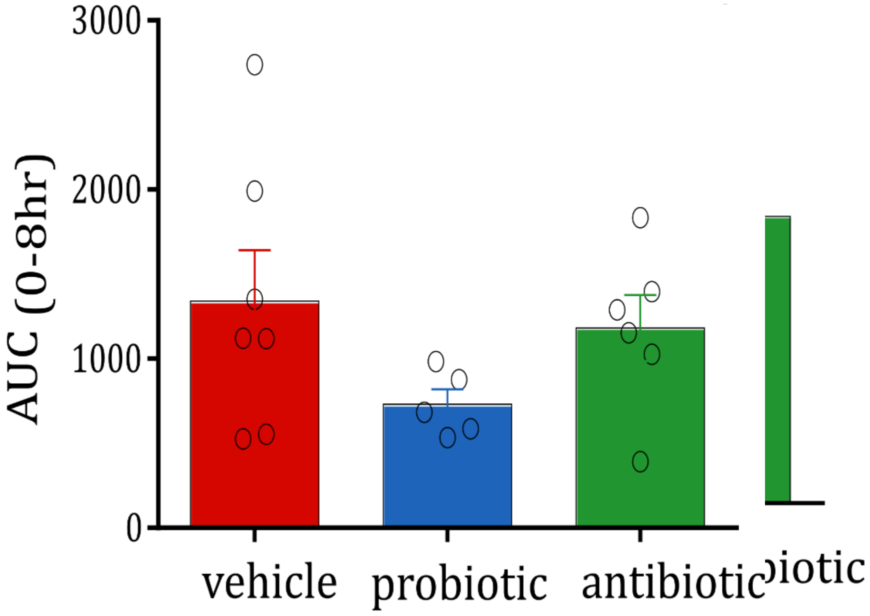
Risperidone PK Profile



Risperidone AUC

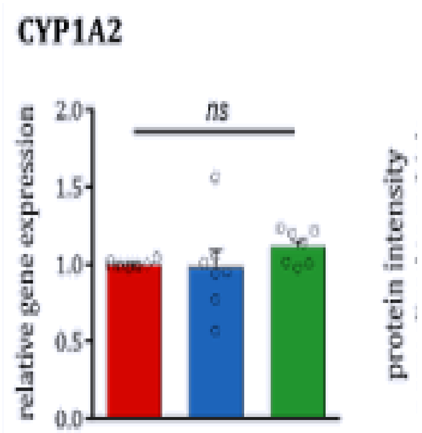


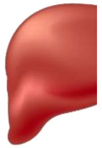
- ❑ ABX=1.8x ⇧ in Olanzapine Availability
- ❑ Microbiota-depletion alters PK after Single Olanzapine Dose

Walsh et al, under révision

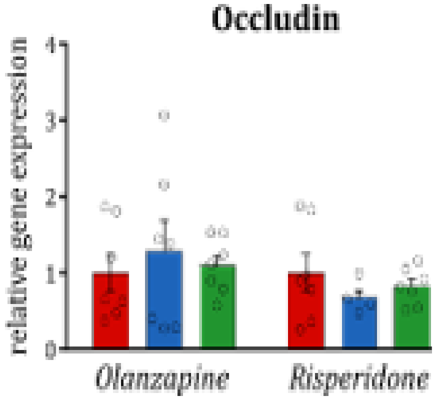
The Quest for Identifying Underlying Mechanism

1) ABX impact on hepatic gene expression?





2) Altered efflux/loc

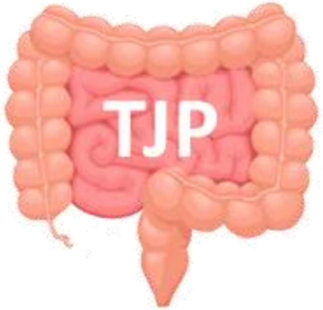


3) ABX impact on fecalase-mediated metabolism?

3. Microbiota Depletion Effects on OLZ → Mechanism

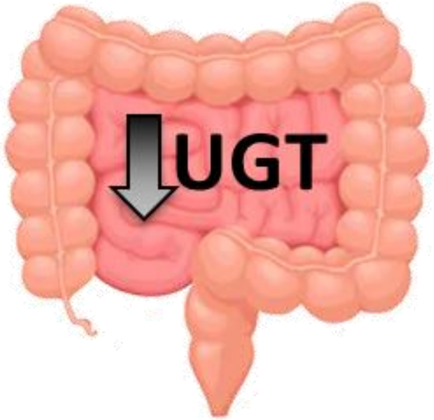
= no change

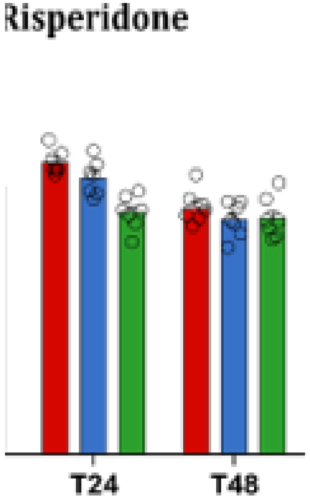
= no change



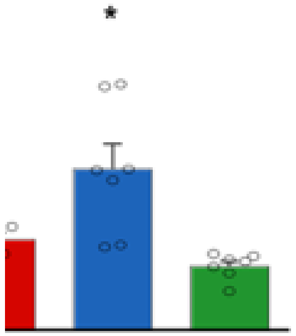
= no change

FIRST PASS METABOLISM





in duodenum?



Can Microbiota influence drug solubility?

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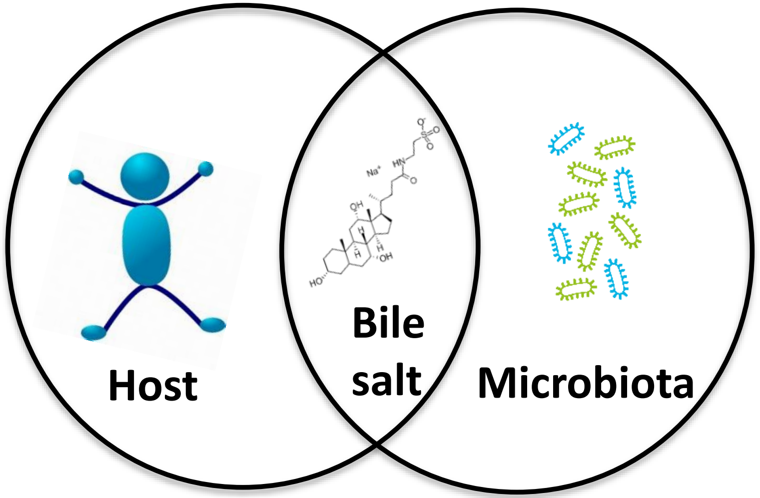

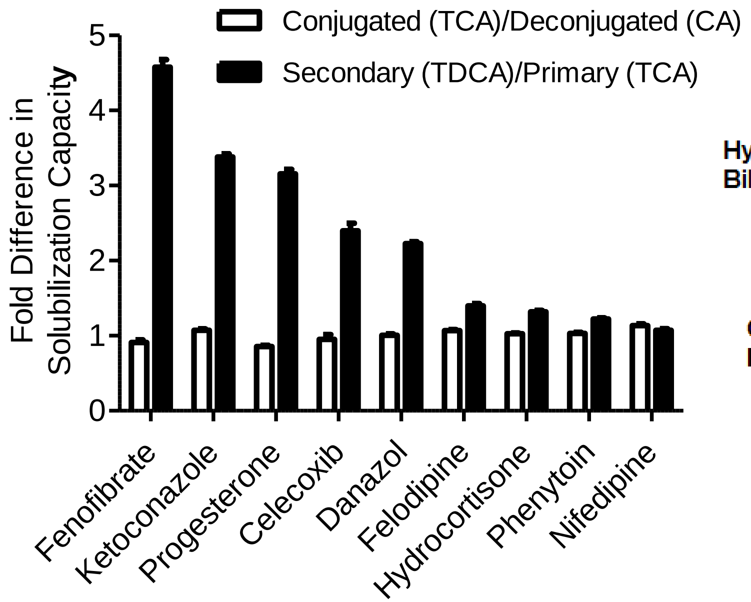

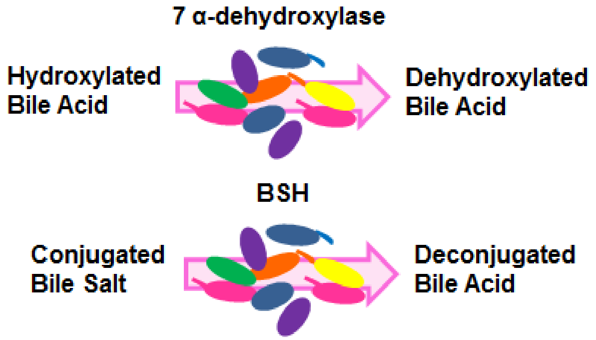

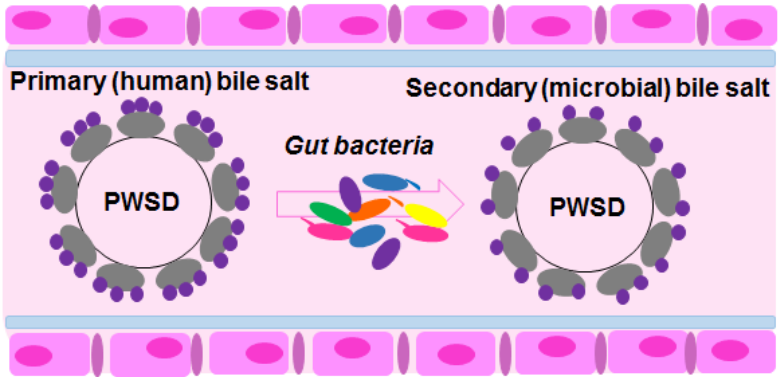

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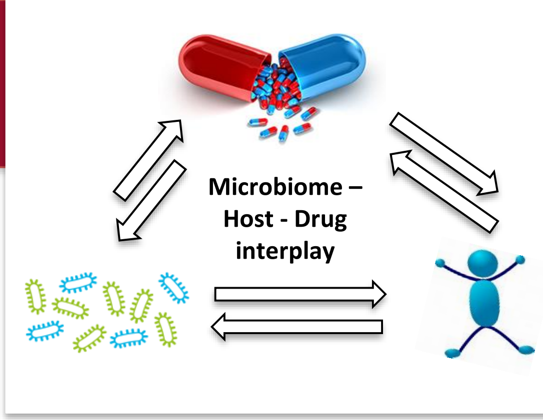
Impact of Gut Microbiota-Mediated Bile Acid Metabolism on the Solubilization Capacity of Bile Salt Micelles and Drug Solubility

Elaine F. Enright,[†,‡] Susan A. Joyce,[‡,§] Cormac G. M. Gahan,[‡,†,∥] and Brendan T. Griffin*[,†,‡]

[†]School of Pharmacy, [‡]APC Microbiome Institute, [§]School of Biochemistry & Cell Biology, and [∥]School of Microbiology, University College Cork, Cork, Ireland

Concluding comments



Influence of Microbiome on Drug Pharmacokinetics

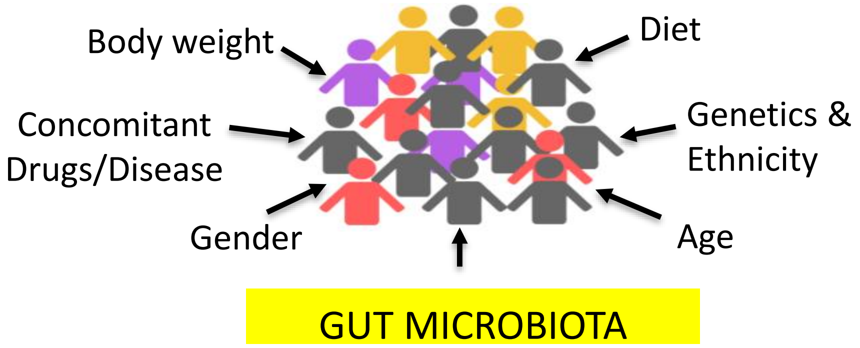
- Pro-drug activation
- Drug metabolism
- Drug conjugate metabolism
- Drug-Microbiome-drug interaction
- Host-microbiome-drug interaction

Direct drug PK effects

↑ Bioavailability ↑ Clearance ↓ Clearance

Indirect drug Pharmacokinetic effects

Inter-individual Variation in Drug Response



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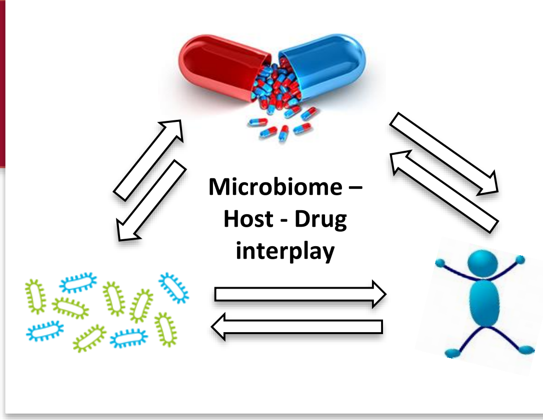

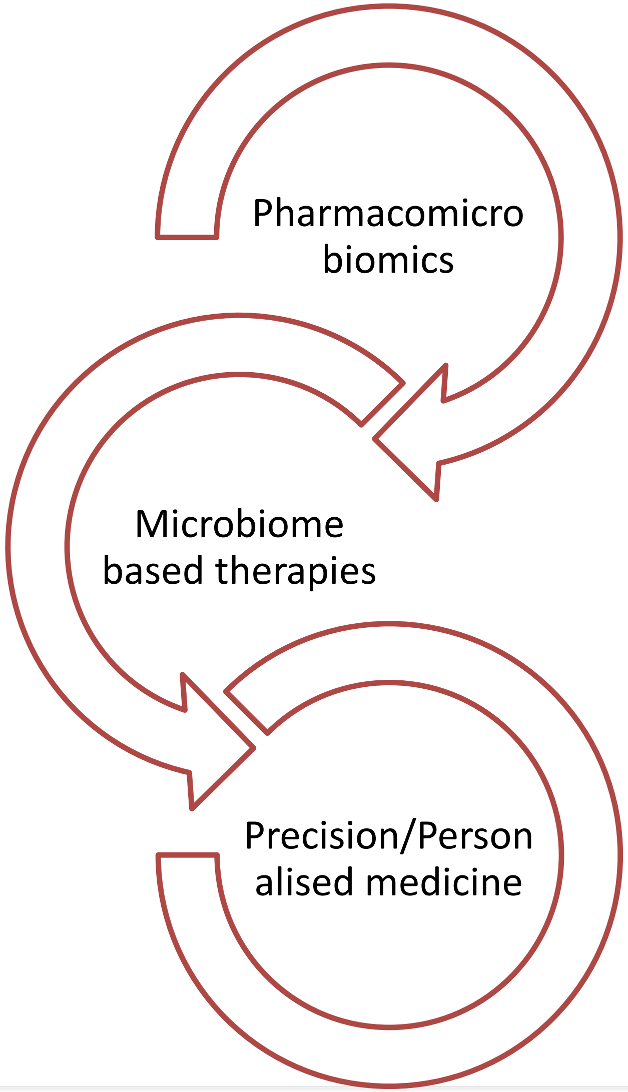

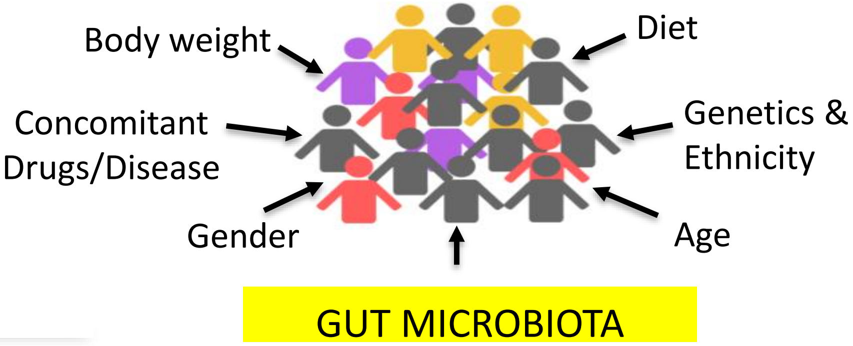

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For what's next

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