

Impact of Non-antibiotics on the Gut Microbiome

Georg Zeller

EMBL



Drug - Microbiota Interactions @ EMBL Heidelberg

Bridging between omics-centric microbiome analysis and microbiology / chemogenomics

Maier, L.^{*}, Pruteanu, M.^{*}, Kuhn, M.^{*}, *et al.*, Nature 2018



L. Maier



M. Pruteanu



M. Kuhn



EMBL Interdisciplinary
Postdoc Fellow



A. Typas



P. Bork

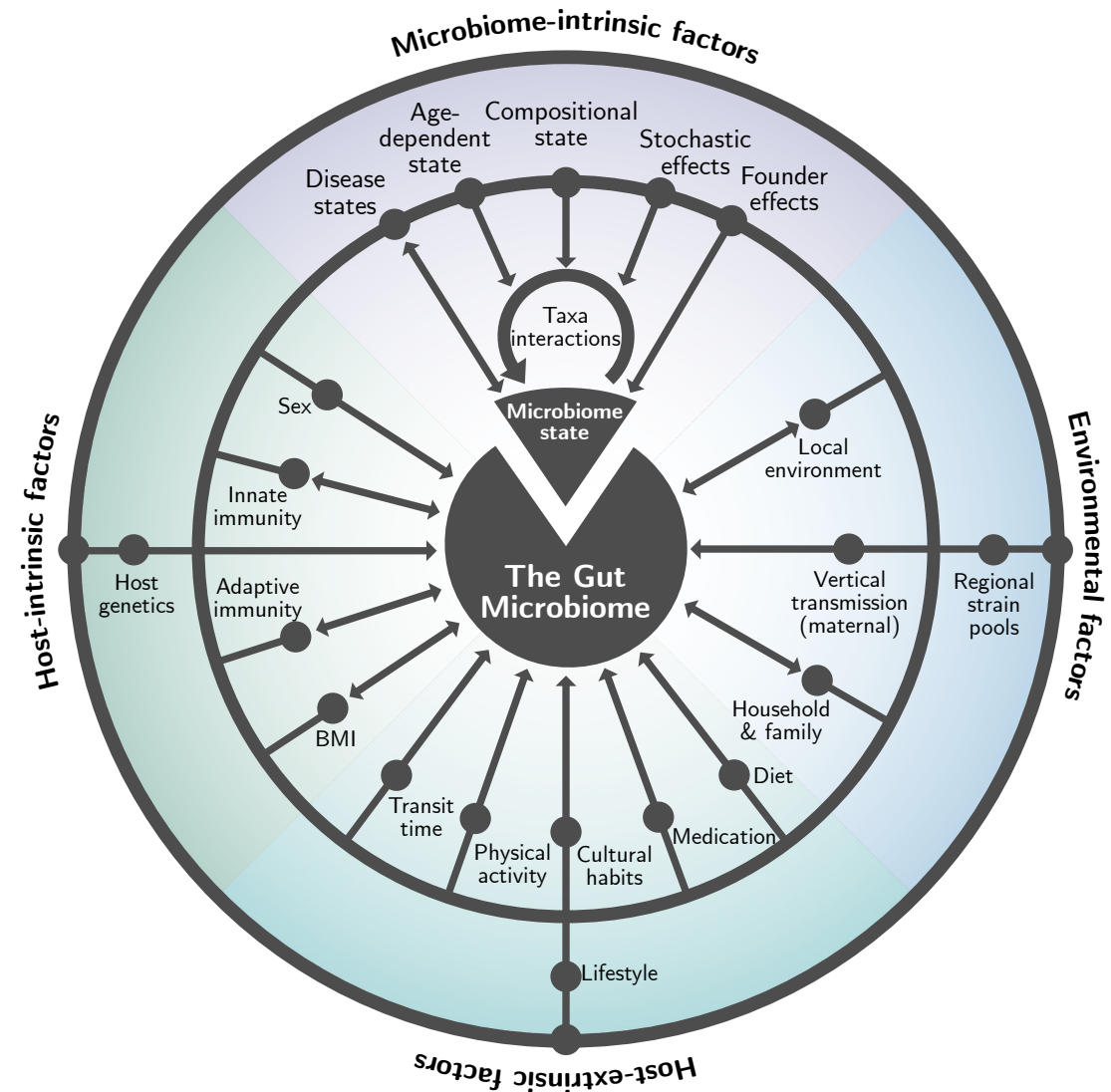


K. Patil



G. Zeller

What shapes the gut microbiome?

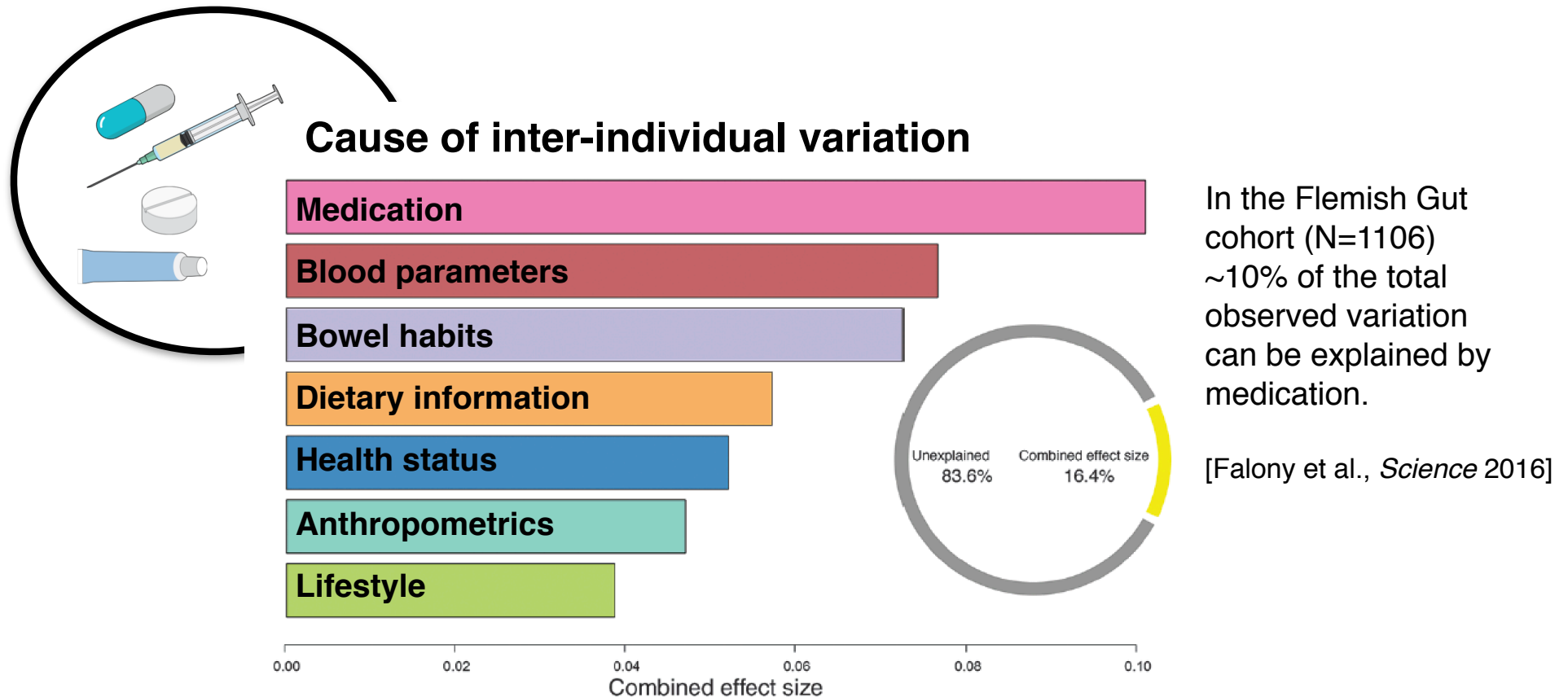


Which factors underly highly individualised composition?

[Schmidt et al., *Cell* 2018]

Impact of medication on gut microbiome noted in cohort studies

Xenobiotics



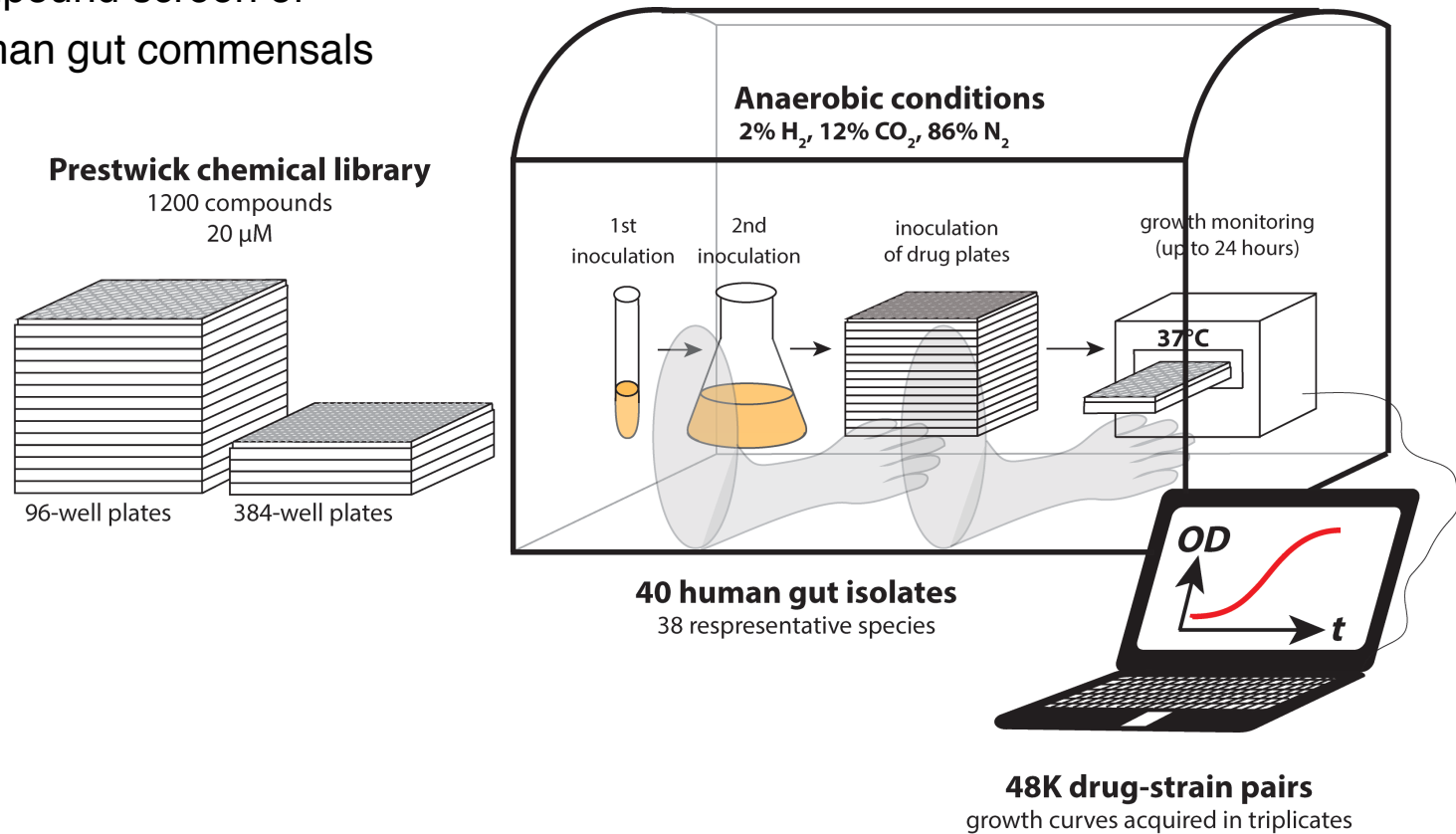
Metagenomic association studies cannot answer some pivotal questions:

- Are effects direct? If so, what is the target?
- Is the drug effect on microbiota part of the mode of action or an undesired side effect?

A high-throughput drug screen for human gut bacteria

Our approach: Systematic study of drug-microbiome interface

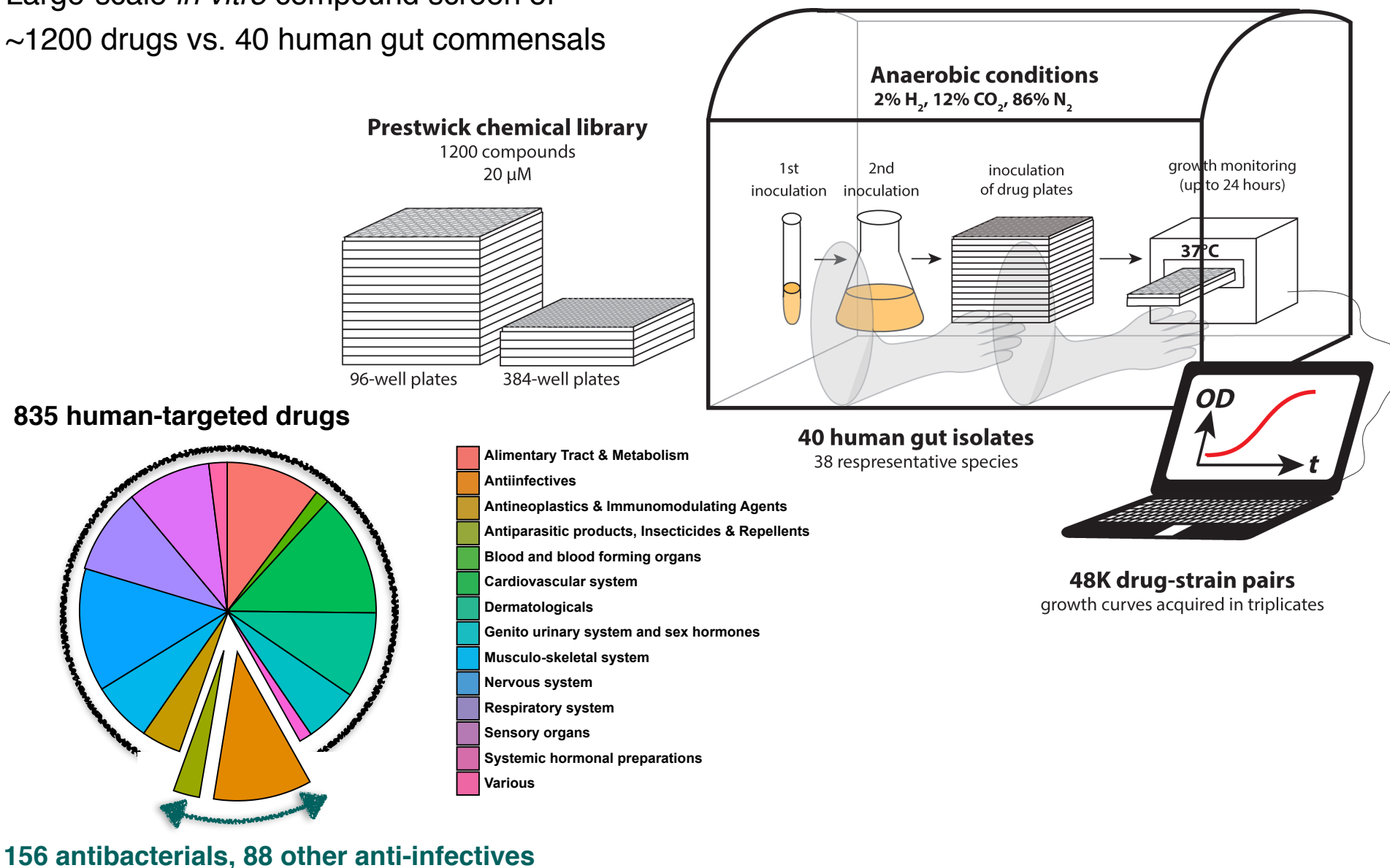
Large-scale *in vitro* compound screen of
~1200 drugs vs. 40 human gut commensals



A high-throughput drug screen for human gut bacteria

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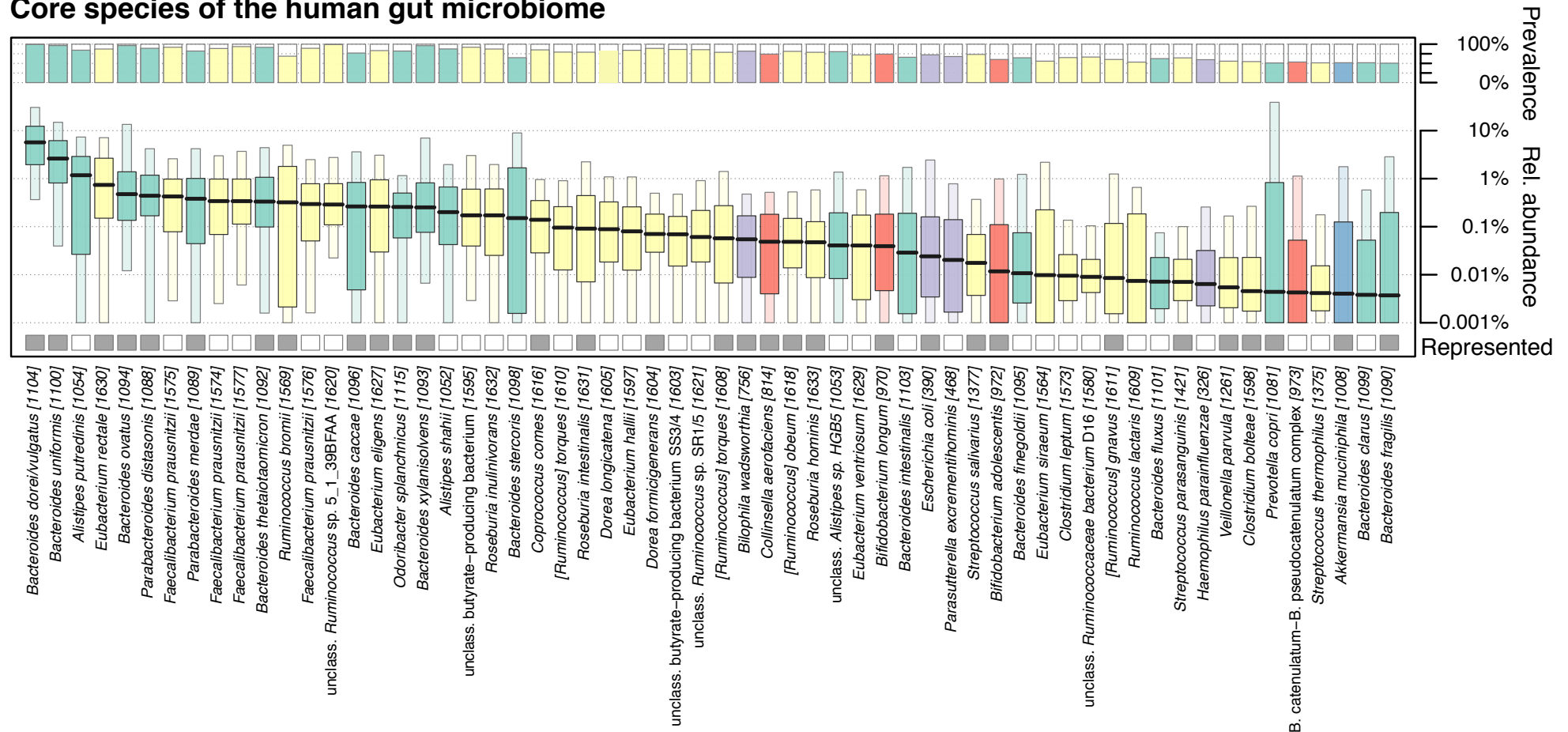
Large-scale *in vitro* compound screen of
~1200 drugs vs. 40 human gut commensals



Intestinal species representation in the drug screen

Species Selection

Core species of the human gut microbiome



40 strains (from 38 species, 21 genera)

largely cover the healthy human microbiome:

~ 80% of the assignable average abundance at genus level

~ 60% at species level

Major insights

Impact of drugs on human gut microbes is extensive

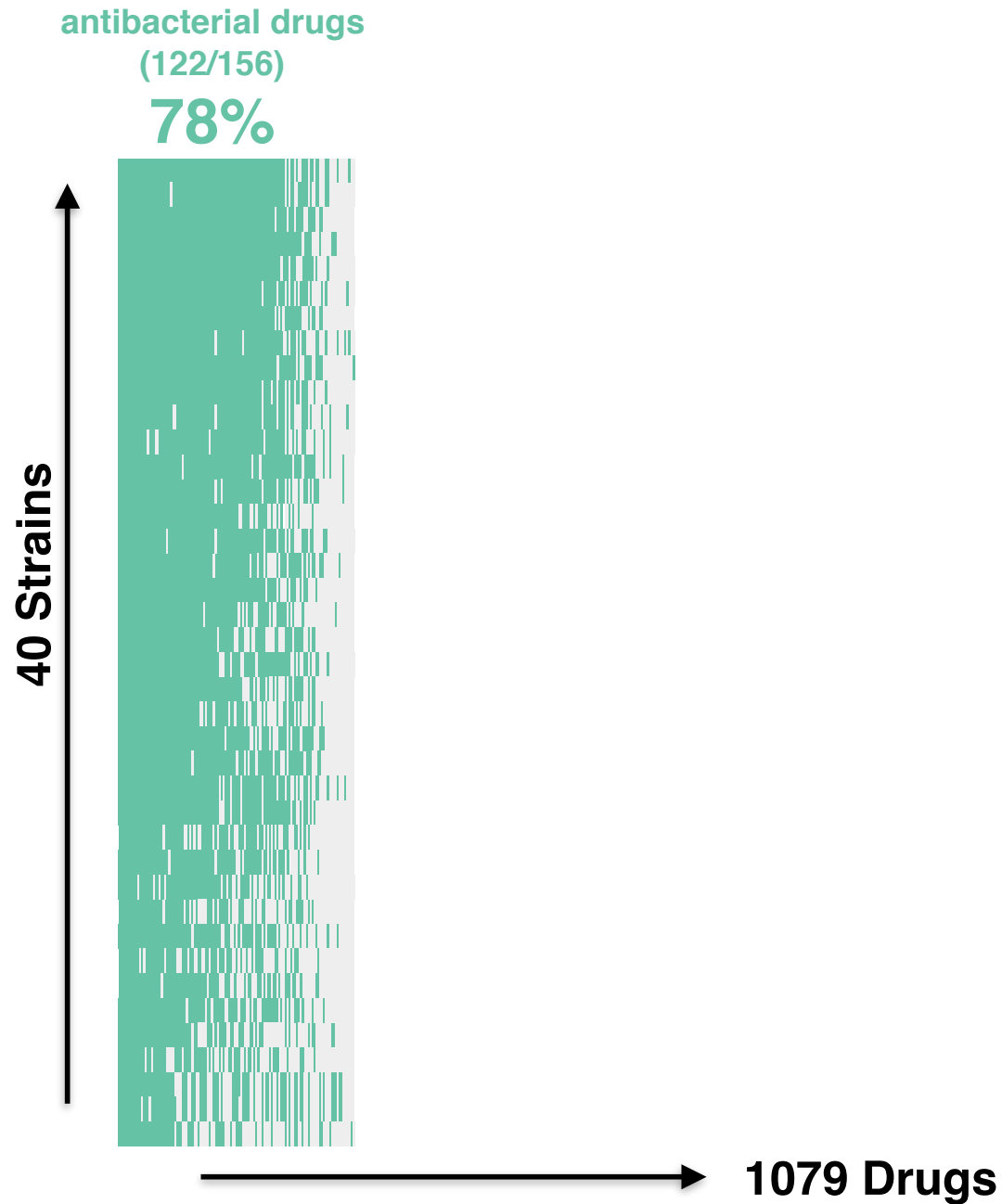
In vivo relevance

- ➔ Drug concentrations tested are physiologically relevant
- ➔ Effects are reflected in side effects pattern
- ➔ Concordance with clinical observations

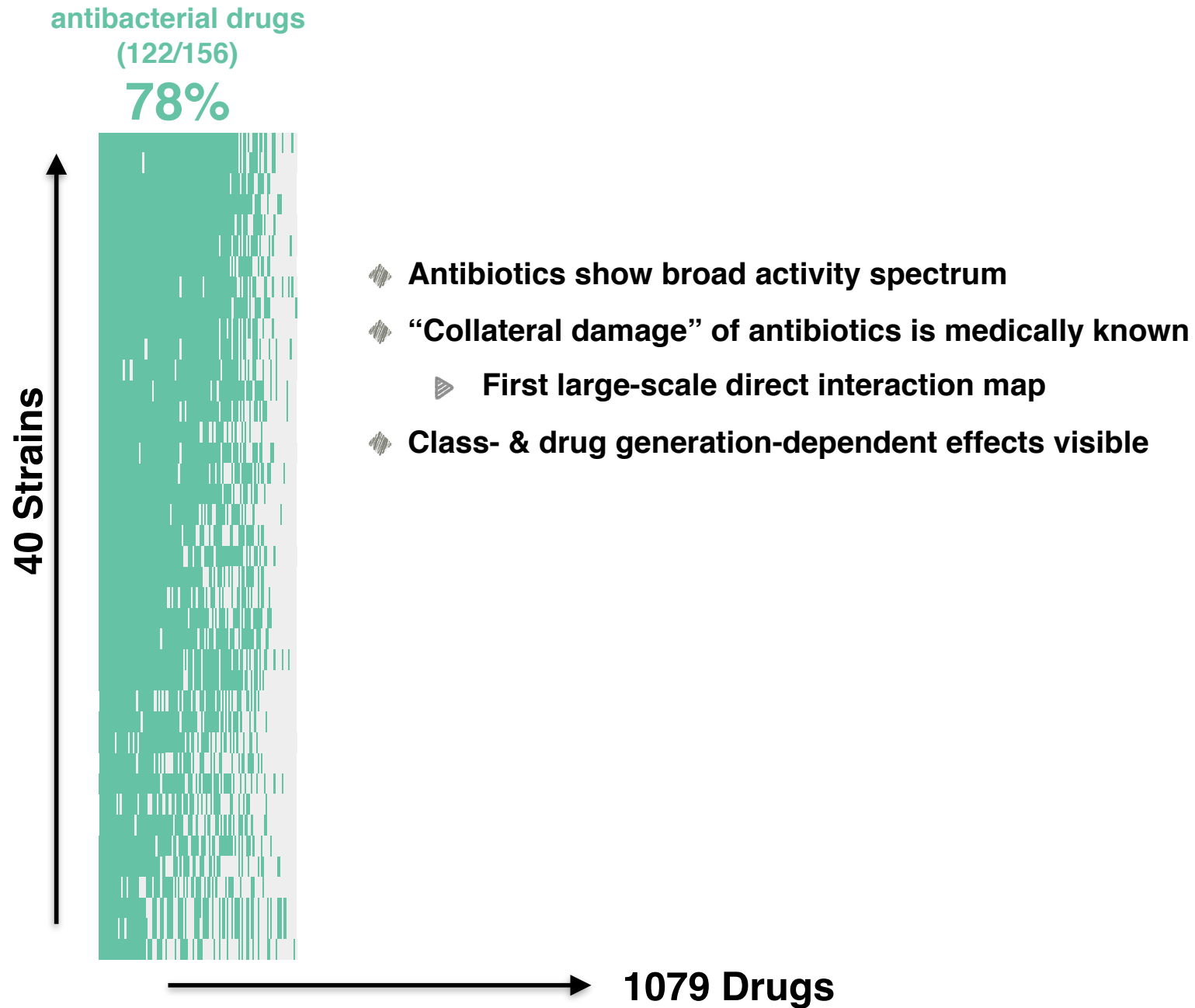
Specific therapeutic classes consistently affect gut microbes

Antibiotic resistance mechanisms protect against human-targeted drugs

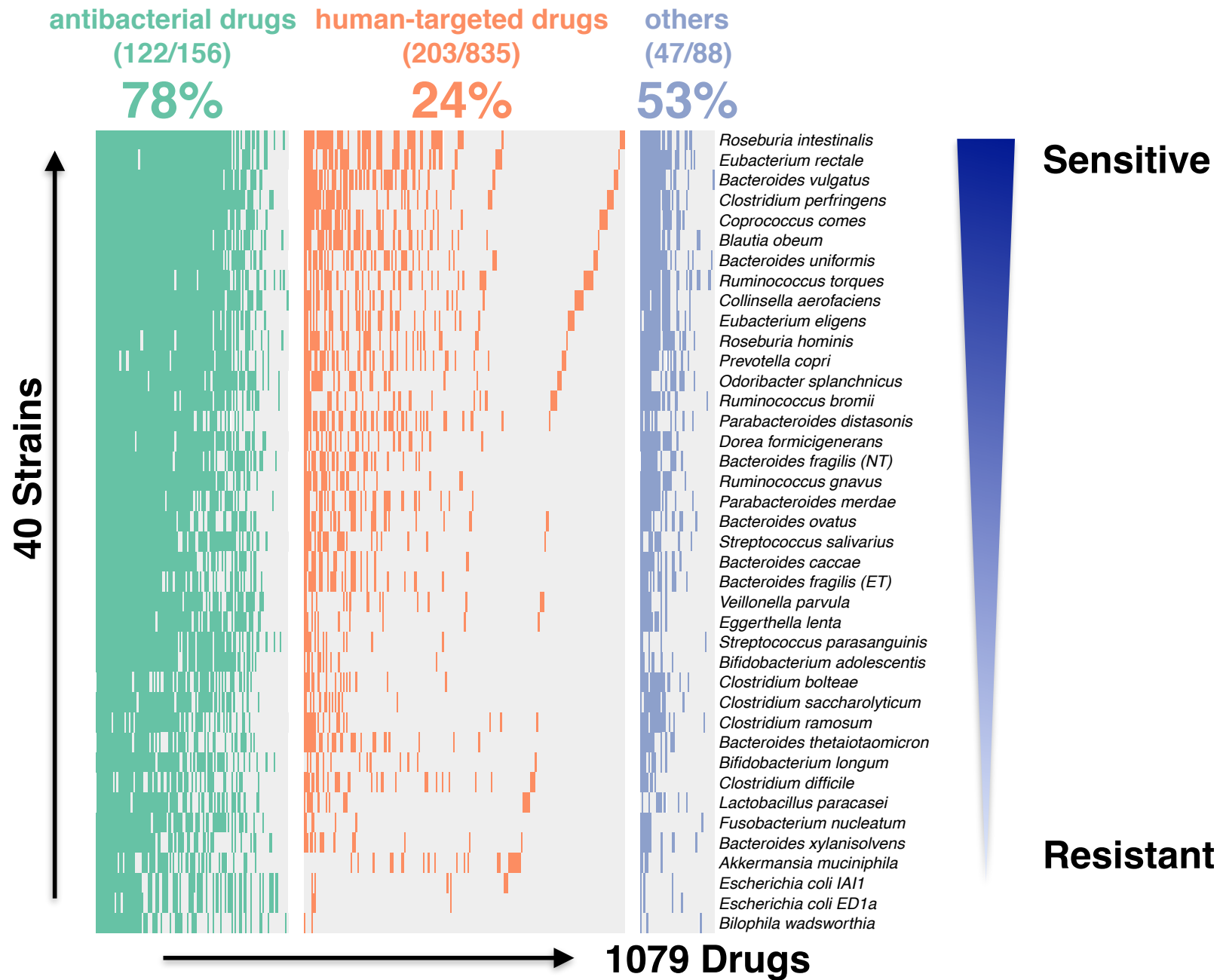
Human-targeted drugs have a broad impact on gut microbes



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***In vivo* relevance**

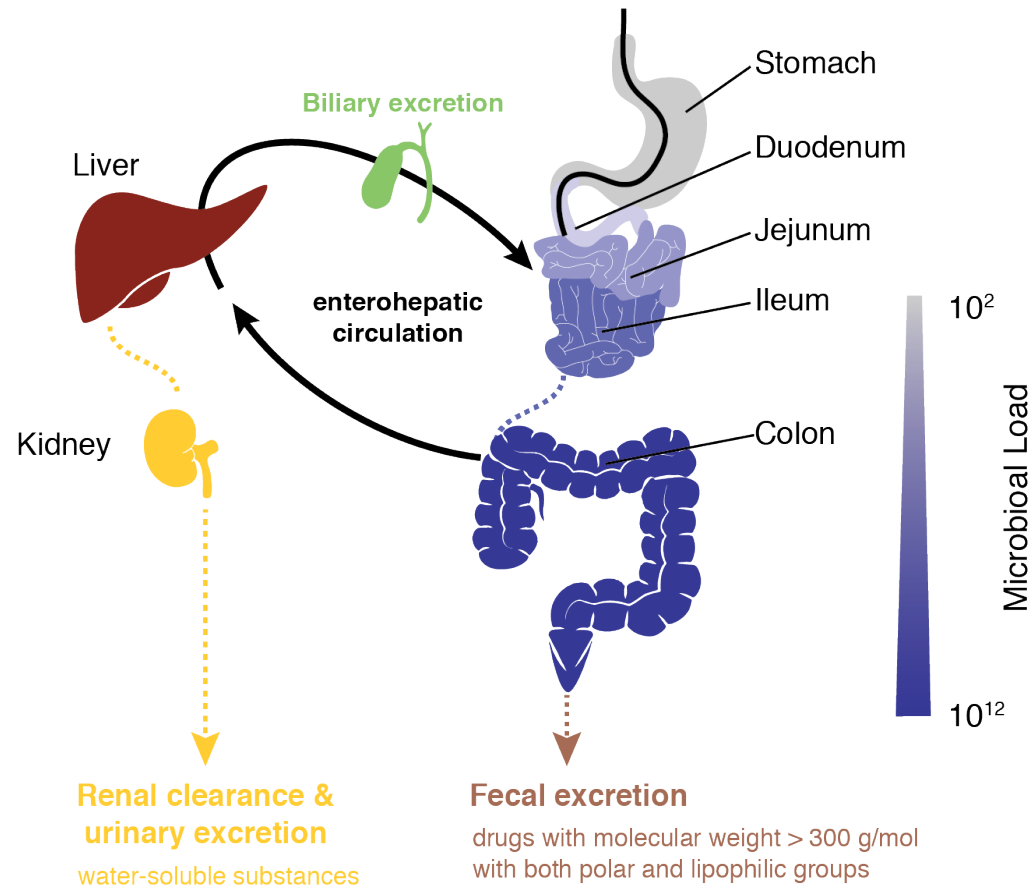
- ➔ **Drug concentrations tested are physiologically relevant**
- ➔ **Effects are reflected in side effects pattern**
- ➔ **Concordance with clinical observations**

Specific therapeutic classes consistently affect gut microbes

Antibiotic resistance mechanisms protect against human-targeted drugs

Estimating intestinal drug concentrations

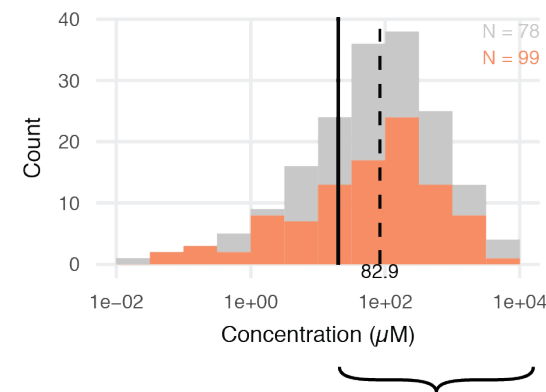
Concentration estimation based on available daily dose and pharmacokinetics data



Estimated colon concentration

Human-targeted drugs

- with anticomensal activity
- inactive



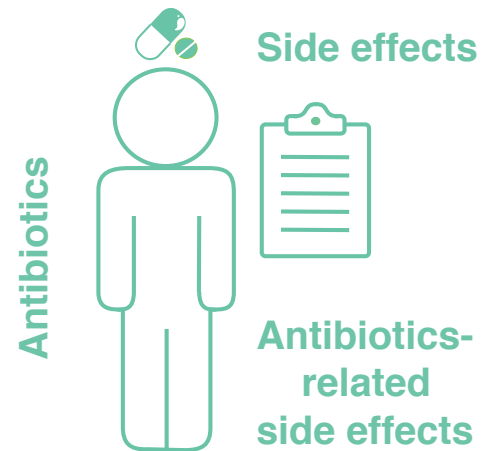
71% of human-targeted drugs with anticomensal activity are estimated to reach colon concentrations > 20 μM

Validation: IC₂₅ determination: 25 drugs x 27 strains

precision: 94%

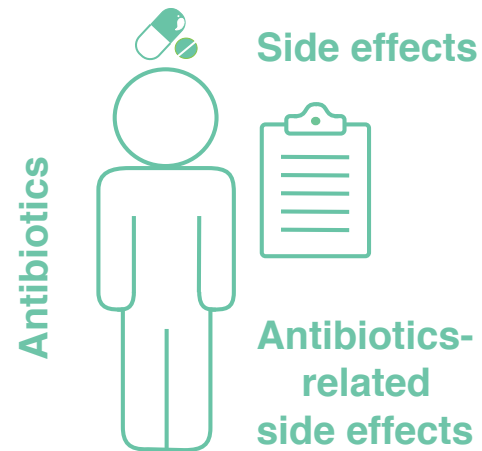
recall: 85%

In vivo relevance reflected in side effects and clinical studies

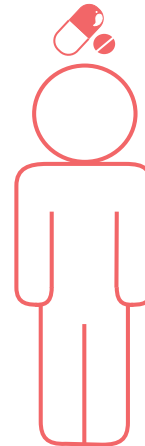


[Side effect data from Kuhn et al.,
Nucl. Acids Res. 2015]

In vivo relevance reflected in side effects and clinical studies



Human-targeted drugs
with activity against gut
microbes



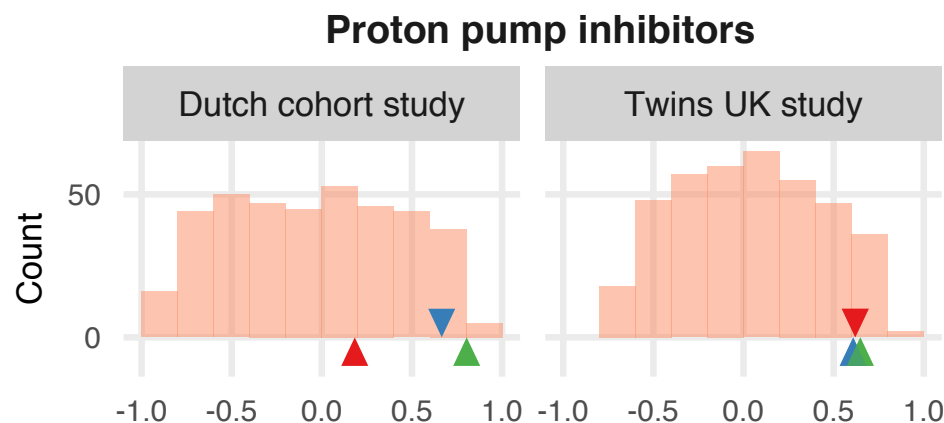
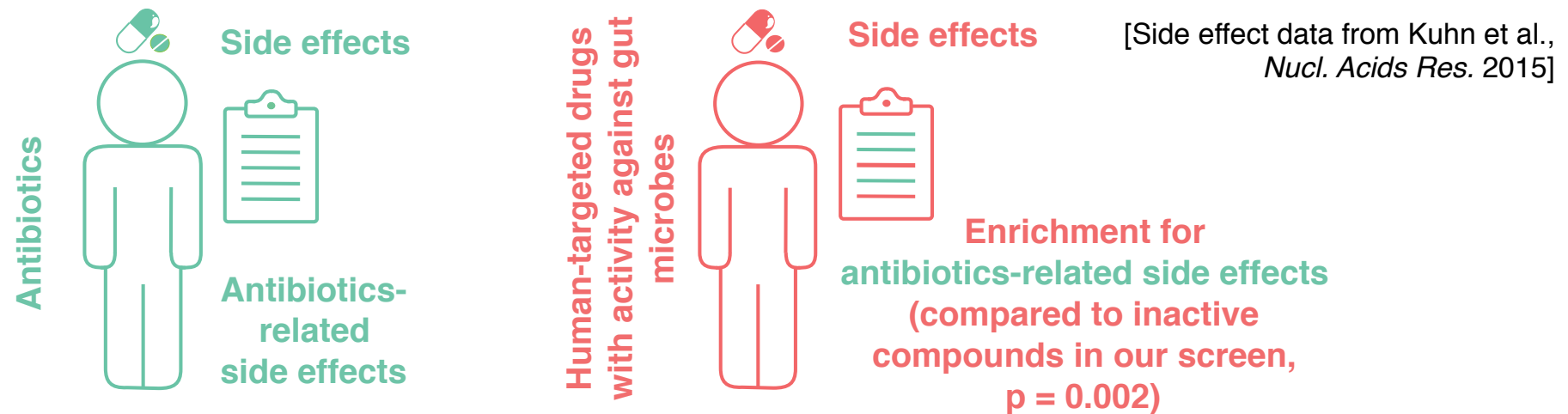
Side effects



Enrichment for
antibiotics-related side effects
(compared to inactive
compounds in our screen,
 $p = 0.002$)

[Side effect data from Kuhn et al.,
Nucl. Acids Res. 2015]

In vivo relevance reflected in side effects and clinical studies



Spearman correlation between association coefficient and screen p-value

Drug: ▲ Rabeprazole ▲ Lansoprazole ▲ Omeprazole

[Dutch cohort study: Imhann et al., *Gut* 2016]

[Twins UK study: Jackson et al., *Gut* 2016]

Major insights

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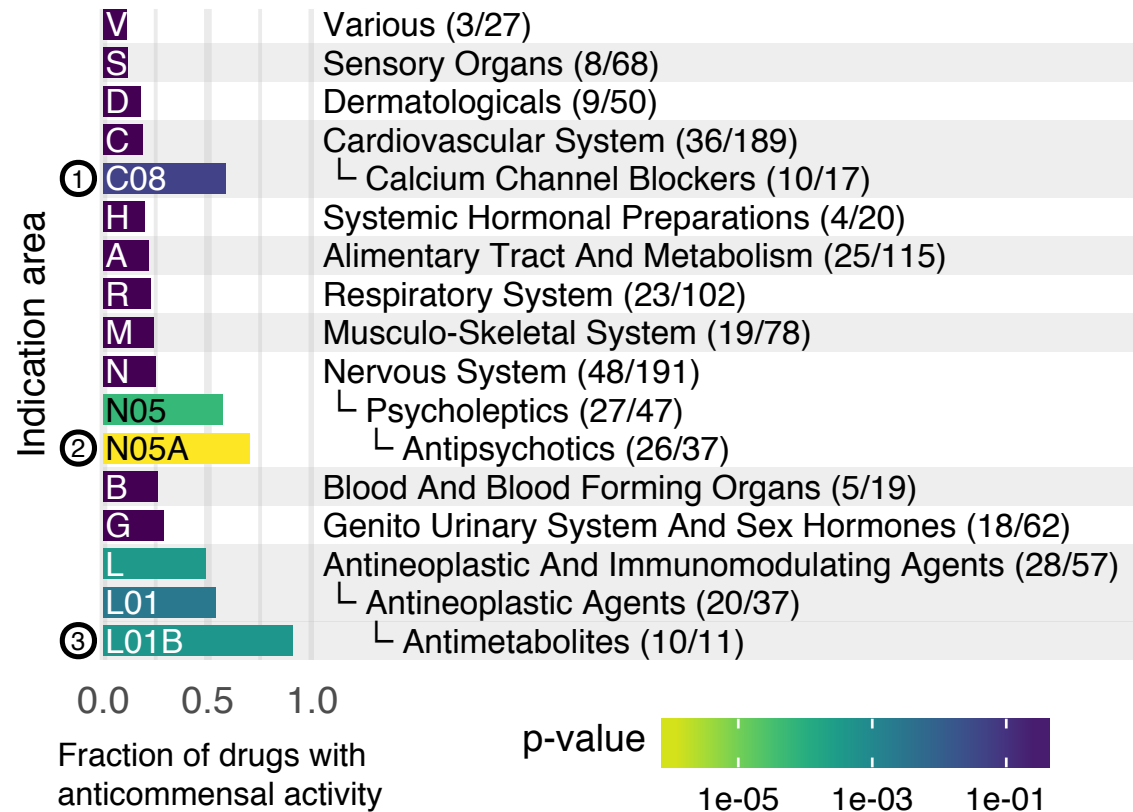
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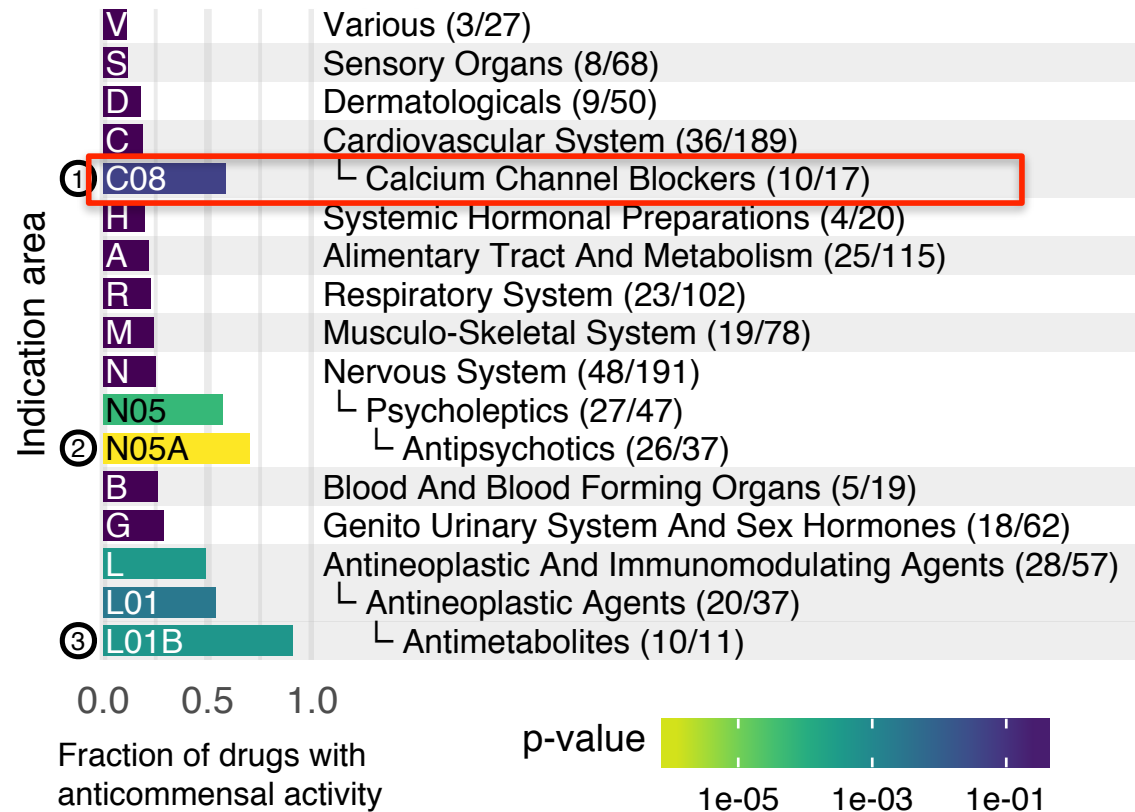
Specific therapeutic classes consistently affect gut microbes

Antibiotic resistance mechanisms protect against human-targeted drugs

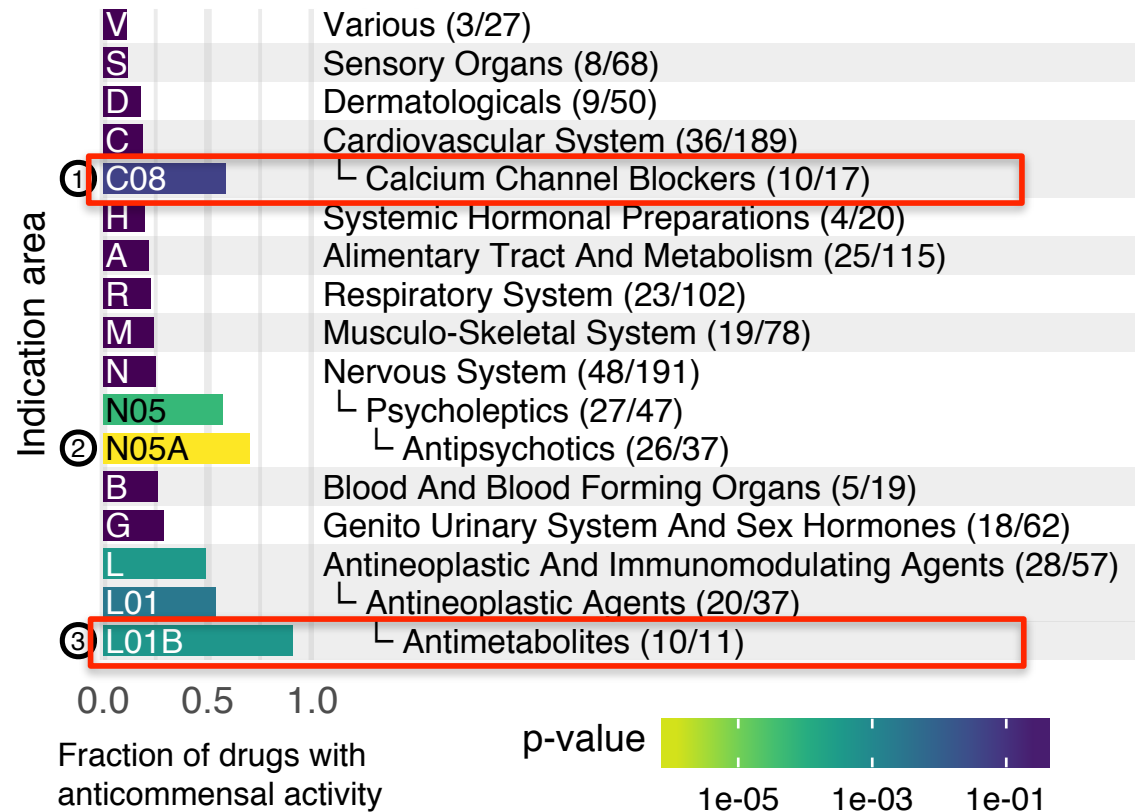
Specific therapeutic classes strongly affect gut commensals



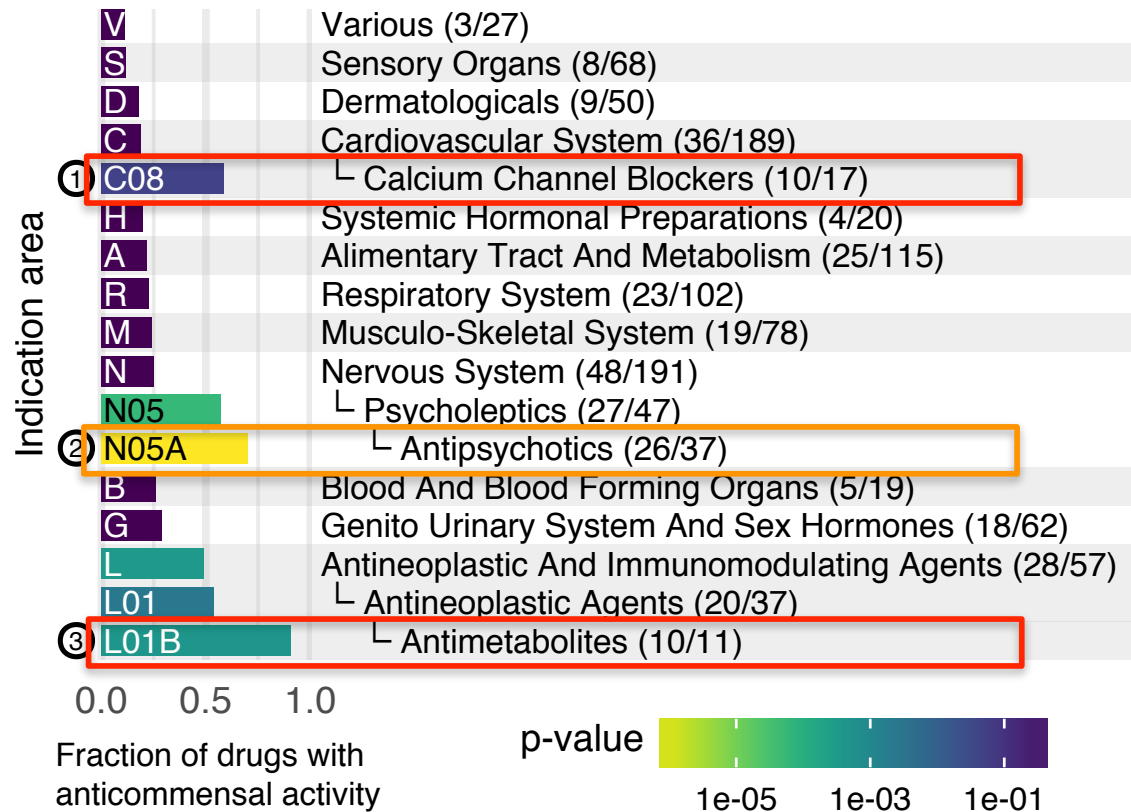
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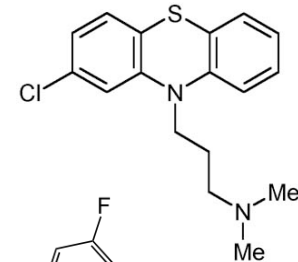


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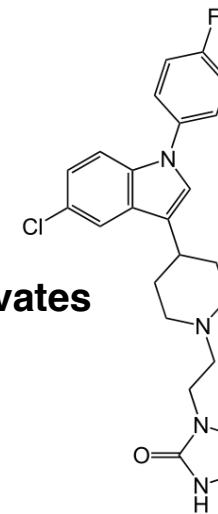


Phenothiazines

Chlorpromazine



Indole derivatives



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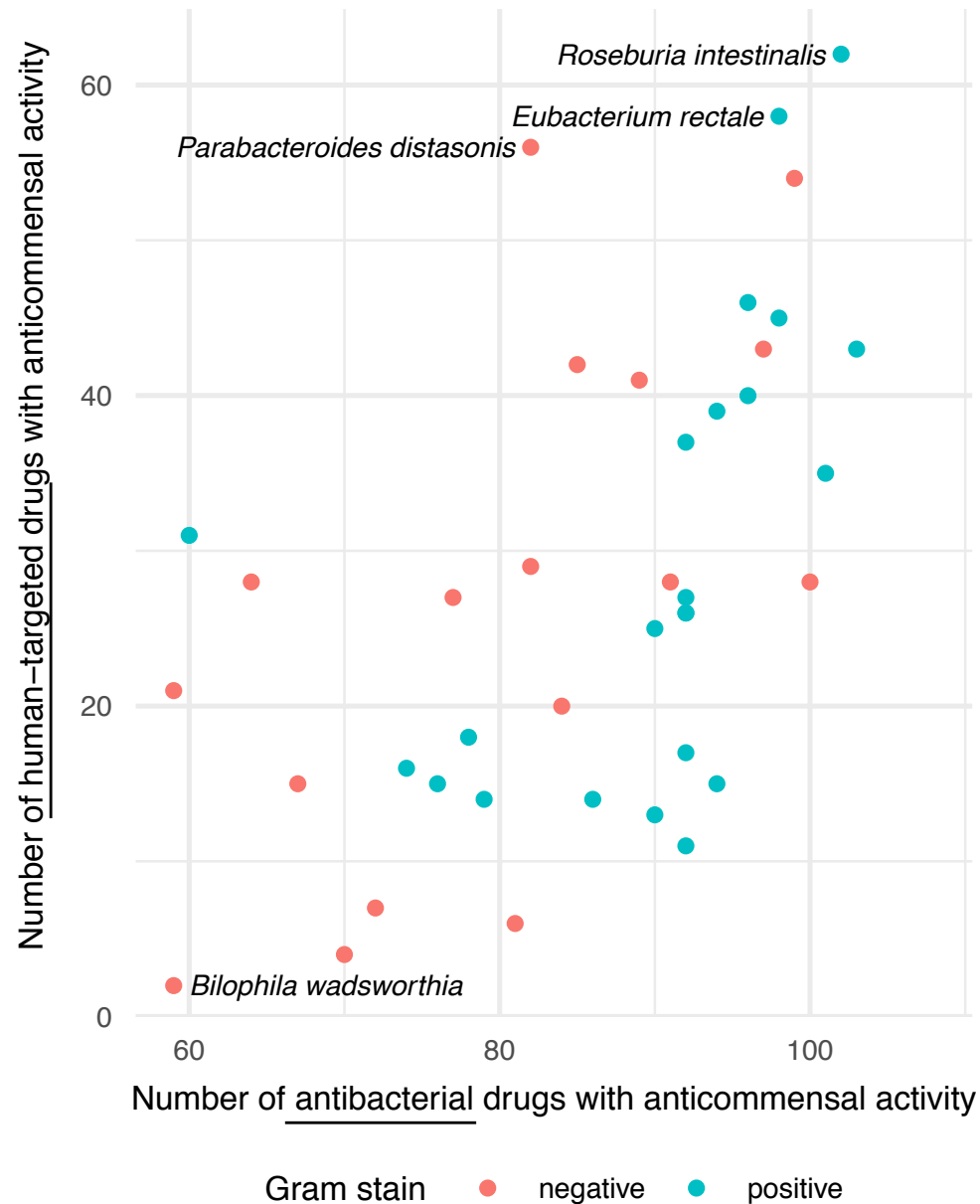
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Cross-resistance mechanisms

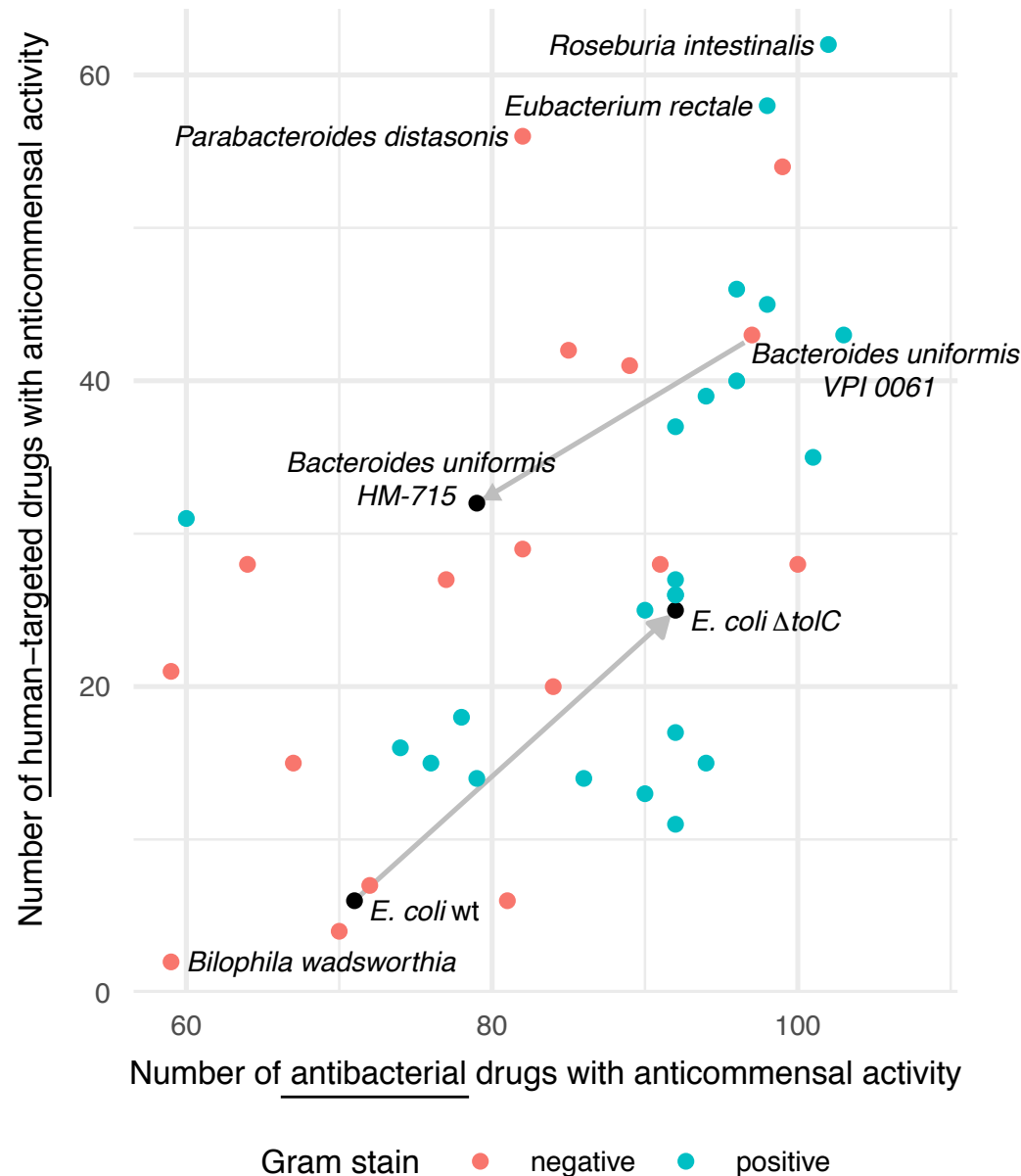


**Cross-resistance
between antibiotic and
human-targeted drugs:**

**Correlated sensitivity
profiles**

$$r_s = 0.6$$

Cross-resistance mechanisms



- ◆ Small genetic changes sensitise similarly against both types of drugs
- ◆ Efflux pumps (TolC) are an important mechanism of cross-resistance
- Risk of acquiring antibiotic resistance by consuming non-antibiotic drugs

Summary and implications

Medication



- ◆ Extensive impact of non-antibiotics drugs on human gut commensals (higher precision than sensitivity)
- ◆ Screen hits are reflected in side effect patterns and metagenomic cohort studies
- ◆ Cross-resistances between antibiotics and human-targeted drugs

Summary and implications

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- ◆ Extensive impact of non-antibiotics drugs on human gut commensals (higher precision than sensitivity)
- ◆ Screen hits are reflected in side effect patterns and metagenomic cohort studies
- ◆ Cross-resistances between antibiotics and human-targeted drugs
- ▶ Can human-targeted drugs be repurposed as antibiotics?
- ▶ Can drug therapy be improved (side effects / efficacy)?
- ▶ Is there a risk of drug therapy driving antibiotic resistances?

Summary and implications

Medication



Thank you!

- ◆ **Extensive impact of non-antibiotics drugs on human gut commensals (higher precision than sensitivity)**
- ◆ **Screen hits are reflected in side effect patterns and metagenomic cohort studies**
- ◆ **Cross-resistances between antibiotics and human-targeted drugs**
- ▶ **Can human-targeted drugs be repurposed as antibiotics?**
- ▶ **Can drug therapy be improved (side effects / efficacy)?**
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