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Systematically investigating the impact of medication on the gut microbiome

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In the recent years, there is accumulating evidence for a strong impact of medication on the gut microbiota composition. This evidence comes from metagenomics-based associations and extends beyond classical antibacterials to a handful of human-targeted drugs. To answer whether such effects are direct and explore their consequences in human health, we need to develop experimental platforms that will allow for systematic profiling of drug–microbiota interactions. Here, we discuss approaches, considerations, experimental setups and strategies that can be used to tackle this need, but can be also readily transmitted to related questions in the microbiome field. A comprehensive understanding of how therapeutics interact with gut microbes will open up the path for further mechanistic dissection of such interactions, and ultimately improve not only our understanding of the gut microbiome, but also drug safety and efficacy.

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Our understanding of the human microbiome has increased dramatically in the past decade. We now have a good understanding of the microbiota composition across different body locations, how it changes with time within or across individuals [1]. This vast improvement in chartographing the human microbiome has been fueled by advances in metagenomics and associated data analysis pipelines, allowing us to go from phylum/genus-level to strain-level views of the microbiome of thousands of individuals world-wide. At the same time, associations between microbiome shifts and lifestyle, diet and disease markers are increasingly being reported. As the field advances, studies are being more controlled for statistical coherence, technical biases and confounding factors [2,3]. Medication, presumably confounding many earlier studies, has recently emerged as one of the most influential contributors in the gut microbiota composition [4•,5]. This link goes beyond bona fide antibacterials, raising a number of interesting questions that need to be addressed in the future. Here, we give a short overview on the medication–microbiome relationship, and discuss approaches and concerns for investigating this matter systematically in the future.

Evidence that non-antibiotic drugs influence the gastrointestinal microbiome

The collateral damage that antibacterials exert on our natural flora has been long known, though more appreciated in the recent past [6]. Despite the increased interest, even for antibiotics, we often have limited resolution of their effects on gut commensals, with for example, MIC breakpoints being reported for Gram-negative or Gram-positive anaerobes as collective groups in EUCAST [7]. For non-antibiotics, our knowledge is even scarcer. Generally, polypharmacy increases the rates of gastrointestinal disorders, and can mimic conditions such as inflammatory bowel disease (IBD) [8]. More specifically, a handful of drug classes have been probed in the past couple of years and associated with microbiome shifts (Table 1): proton pump inhibitors [9–11,12•,13•], non-steroidal anti-inflammatory drugs (NSAIDs) [14,15], atypical antipsychotics [16,17], antidiabetics [18,19••,20••] and chemotherapeutics [21,22]. With the increased attention in the role of medication on microbiota shifts [4•,5], more drugs are bound to be tested in the future, likely in more controlled studies (more individuals, individual drugs). Although such data-driven associations have high clinical relevance, they fail to provide answers in two fundamental questions:

(i) Are these effects direct and if so, what is the precise bacterial target of the drug?
(ii) Is the drug effect on microbes (part of) its primary pharmacological mode of action (MoA) or an undesired side effect?

Direct effects on gut microbes are conceivable for many non-antibiotic drugs. For example, various antipsychotics and antidepressants are known for their antibacterial activities. The first marketed antidepressant, the monoamine oxidase inhibitor iproniazid, actually is a repurposed tuberculostatic [23]. The largest class of antipsychotics (and with several derivatives as antihistamines), the phenothiazines were first identified for

Table 1

Evidence that non-antibiotics impact gut microbiome composition.

Therapeutic class	Drugs tested	Study reference	
		Human	Rodent
Medication in general	Diverse drugs	[4•,5]	–
	Polypharmacy	[58]	–
Antiulcer/antireflux	Diverse proton pump inhibitors	[9,11,12•,13•]	[59] [b]
	Omeprazole	[10]	–
Antidiabetic	Metformin	[19••,20••]	[60] [a]
	Acarbose	[18]	–
Antipsychotic	Atypical antipsychotics	[17]	–
	Risperidone	[16]	[61] [a]
	Olanzapine	–	[62] [a]
Nonsteroidal anti-inflammatory drugs	Diverse NSAIDs	[14,15]	–
	Indomethacin	–	[63] [a]
Chemotherapeutics	Diverse drugs	[21,22]	[64] [b]
Statins	Ezetimibe, simvastatin	–	[65] [a]
Corticosteroids	Diverse drugs	–	[66] [a]
Environmental chemicals	General effect	–	[67] [b]
	Carbendazim (fungicide)	–	[68] [a]
	Trichloroacetamide (disinfectant)	–	[69] [a]

[a] Mouse model
[b] Rat model.

their anti-infective properties [24]. Perhaps not-surprisingly, phenothiazines such as thioridazine, are now being considered for repurposing as anti-tuberculosis agents [25]. Newer antidepressant classes, such as selective serotonin reuptake inhibitors (SSRI), have also been reported to inhibit bacterial efflux pumps [23,26]. Many more human-targeting drugs or non-antibacterial anti-infectives are known to inhibit growth of particular microbes, but their mechanistic basis or what is the full extent of such effects, whether they are relevant for gut microbes and whether they can occur *in vivo* in the gut (drug concentration, microbial communities) are all elusive matters that need to be systematically addressed in the future.

More challenging to experimentally address is whether reported microbiome effects are part of the drug's primary MoA or just a side effect. For example, many psychotropic drugs induce weight changes [27] and a possible contribution to this adverse effect by the gut microbiome has been recently proposed [28]. More generally, gastrointestinal side effects are common for many drugs and could be partially due to the drug impact on the gut microbiome. By contrast, microbiome shifts being part of the MoA of the drug is less expected and has never been a consideration in drug discovery until very recently. Evidence for this comes from metformin, an antidiabetic drug inducing strong microbiome shifts in type II diabetes (T2D) patients [19••]. Following this observation, it was shown that fecal transfer from metformin-exposed individuals into germ-free mice improved glucose tolerance [20••], and that late-release metformin in the colon (thus not active in the liver) increased drug efficacy [29••,30••]. Together these findings underline a gut microbiome-mediated mechanism behind metformin's antihyperglymic MoA.

Overall, the role of medication on our gut microbiome composition is likely to be much larger than previously anticipated. This has considerable ramifications both for human health and for drug development, especially when taking into account the increasing consumption of pharmaceuticals worldwide. It also constitutes a tremendous challenge in the coming years to comprehensively characterize this drug–microbiome interface.

Considerations when systematically probing the drug–microbiome–host interface

Although statistical associations from metagenomics studies in clinical cohorts indicate physiological relevance of findings, they need to be further validated as they can be indirect or biased by confounders. Metformin provides a perfect example of the latter. Although earlier studies reported specific gut microbiome signatures for T2D patients [31,32], the signal turned out later to be due to metformin, the leading drug against T2D, and not the disease itself [19••]. Indeed, in a subsequent interventional study, metformin treatment of naïve T2D patients significantly altered the relative abundance of >80 bacterial strains [20••]. Therefore, to systematically study the drug–microbiome interface in controlled manner, single drugs have to be first monitored and other contributing factors (other medication, health status, geographic/age/gender biases, microbiome diversity of cohort) need to be taken into account. This is hard to be done for all drugs on the market (>1400 obtained FDA-approved by the end of 2013 [33] and several drug candidates in the pipeline), let