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Thwarting Antibiotic Resistance by Concealing the Host

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Abstract
All currently available antibiotics target bacterial proteins and, as a result, are subject to resistance through the sampling of genetic space and progressive accumulation of mutations in pre-existing proteins by these rapidly reproducing pathogens. In this prospective, I present the potential benefits that may be derived from designing drugs that bind host proteins concealing them from bacterial virulence factors. In addition to circumventing the inevitable resistance that will ensue from any antibiotic that targets bacterial proteins, these drugs are much less likely to disrupt the host microbiome and thus may avoid the repercussions of broad spectrum antibiotics like *C. difficile* colitis.

Keywords: antibiotic resistance, antibiotic, bacteria, demographic stochasticity, host

The human microbiome[1] has evolved to thrive in the human body. The rationale for the microbiata's biased evolution is almost certainly the stable environment and constant source of nutrients provided. The trillion commensals that live on and within each of our bodies are not benign occupants but instead are active contributors to both our physiology and immune system. For example, development of the gastrointestinal immune system appears to be dependent on a species-specific microbiome.[2] This interspecies variation in microbiome composition suggests a strong selective host influence. Because of this interdependent physiology, co-development, and co-evolution, it might be more accurate in collectively referring to each human and its trillion commensals as a superorganism.[3]

Demographic stochasticity proposes that relative to a dominant native community, the smaller an immigrating population, the less likely it will establish colonization. This principle at least partially explains the protective nature of the trillion commensals against the great variety of potential pathogens that we continuously sample or that might be present at low, subclinical levels.[4] This concept is exemplified by *Clostridium difficile*, whose population can explode across a relatively barren gastrointestinal tract that has been scorched by broad-spectrum antibiotics.[5] Both pathogenic and commensal organisms are able to overcome demographic stochasticity through virulence and colonization factors, respectively. These virulence factors come in a variety of different forms:[5] a few examples include pili/fimbriae that allow bacteria to adhere to the host, secreted proteins that interact with the host to elicit physiological responses such as the secretion of fluid, even bacterial secretion systems that can introduce bacterial proteins directly inside host cells. What all these virulence factors have in common is that they target specific host structures (proteins, carbohydrates, and lipids) to allow the organism to take up residence in a specific niche.

Since 1928, when Alexander Fleming had his fortuitous accident that resulted in the discovery of penicillin, we have tried controlling populations of pathogenic bacteria by adding antibiotics to culture media both *in vitro* and similarly *in vivo* within the human body. Antibiotics are extremely important, as evidenced by the correlation between survival and the time to initiation of appropriate antibiotics in sepsis.[6] Essentially all currently available antibiotics can be grouped by their mechanism of action: inhibition of (1) bacterial

cell wall synthesis, (2) bacterial protein synthesis, (3) bacterial nucleic acid synthesis, and (4) bacterial metabolic pathways. What all of these have in common is that they are bacteriocentric.

Analogous to the Born-Oppenheimer approximation in Quantum Mechanics (from the point of view of an electron, the nucleus is motionless), bacteria and humans operate on different time scales. Within the human incubator, some bacteria can divide on the order of 30 minutes (under ideal conditions).[7] This is in stark contrast to humans, who can reproduce ~annually after 12 years (under less than ideal conditions) –or– the similar timeline required for a new antibiotic to reach market. This difference in time scale has resulted in the emergence of methicillin-resistant *Staphylococcus*, cephalosporin-resistant *Neisseria*, vancomycin-resistant *Enterococcus*, fluoroquinolone-resistant *Escherichia*, carbapenem-resistant *Klebsiella*, and more concerning multi-drug resistant organisms like extensively drug-resistant *Mycobacterium tuberculosis* in far less than the lifetime of a single human being. These resistances have evolved by either mutating pre-existing proteins within the bacterium (by either spontaneous mutation or hypermutation) or transferring genetic material for resistance proteins between organisms. It does not matter what *bacterial* protein is targeted, whether it be the ribosome, metabolic proteins, drug efflux transporter, or even virulence factors. Bacteria operate on different time scales, which allows them to sample genetic space and progressively acquire advantageous mutations. Any mutation that will allow the bacterium to spend more time in the host, will be evolutionarily advantageous.

Many virulence factors expressed by pathogenic bacteria target specific host proteins on and within our cells. If we design drugs that target these same host proteins, concealing them such that the virulence factors no longer recognize them, these bacteria will no longer have a selective advantage over our commensals. It should be mentioned, that the concept I am presenting: creating drugs to conceal the host from pathogens is not novel, but the benefits derived by using such drugs has not been fully expounded upon. For example, Maravinoc is a small molecule that is FDA-approved for the treatment HIV-1 infection. It binds C-C chemokine receptor 5 (CCR5) present on human CD4 cells, concealing this receptor from HIV, which inhibits perpetuation of the infection.[8] Further, this concept has also been discussed with respect to fungal infections in a recent review.[9]

A subtle but significant difference between drugs that target host proteins and all currently available antibiotics that target bacterial proteins is that bacteria are unable to evolve resistance to the former by the accumulation of mutations in pre-existing proteins, because their target has been essentially eliminated. If, for instance, the virulence factor was altered in such a way that it acquired affinity for the binary complex of host:drug, it would lose affinity for the host once the drug was removed (Fig. 1). It is not possible to *linearly* evolve affinity for a different region of the same host protein because this is a new protein surface, requiring a new interface. This later point is also in disaccord with the observation that proteins tend to interact with one another via very restricted regions called hot spots.[10] Thus, by designing a drug that binds the same surface as a virulence factor, it is possible to render the virulence factor(s) impotent and without any means of recovering functionality through mutation. In order for the bacterium to live within this now inhospitable host, and escape demographic stochasticity, it would have to either acquire the genetic information for –or– develop a novel virulence factor and/or host target *de novo*. Creation of a new virulence factor is a stochastic process occurring extremely infrequently, equivalent to a pathogen jumping species or developing a predilection for a different niche. This places bacteria back onto our much slower time scale.

Another advantage of using drugs that target specific human proteins is that these chemicals are much less likely to alter the population of healthy commensals because these organisms likely lack similar mechanisms of colonization to the virulence factors expressed by the pathogens we are trying to eliminate. Thus, the use of these

antibiotics might avoid both the serious repercussions of broad-spectrum antibiotics like infection by *C. difficile* or other opportunistic infections and even relatively benign side-effects like erratic anticoagulation with warfarin.[11]

There will always be a need for broad spectrum antibiotics especially in the critically ill[6] because the antibiotic strategy discussed here will be highly specific, likely requiring testing for specific virulence factors, analagous to the sensitivities that are routinely checked of cultured pathogens or genetic mutations in cancer. Further, the pathogen may produce multiple virulence factors that target different host structures,[12] requiring multiple drugs. I have exclusively discussed protein targets of virulence factors as these are the most 'drugable'; however, several virulence factors target host carbohydrate and even lipid moieties.[13] These host structures will likely be more difficult to conceal due to the lack of tertiary structure as well as the shear quantity of these structures. Lastly, drugs that target host proteins may potentially elicit detrimental physiological responses. These effects may be similar to those elicited by the bacterium engaging the same host protein; however, the nature and magnitude of the effect will depend on the specific host target and whether the drug acts as an agonist, partial agonist, inverse agonist, or silent antagonist.

By targeting and concealing host proteins from bacteria, it should be possible to circumvent both the inevitable resistance that bacteria will obtain to any conceivable antimicrobial agent that targets bacterial proteins as well as avoid the repercussions from upsetting the equilibrium of the human superorganism.

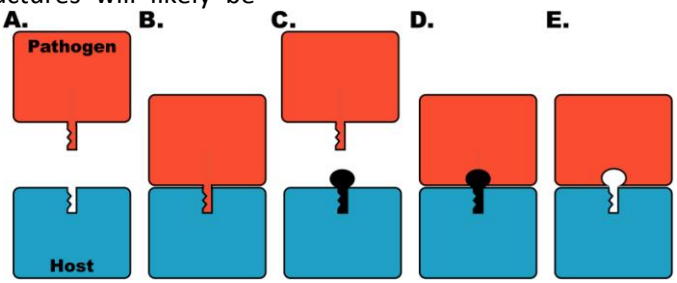

Figure 1. Visual Demonstration that Concealing the Host Receptor Precludes Acquired Resistance. A. Cartoon representation of a pathogen (red) with a complimentary binding surface for a host (blue). **B.** Association between the pathogen and the host. **C.** As an antibiotic (black key) is introduced that binds to the same site as the pathogen, the pathogen is no longer able to bind to the host. If the pathogen was able to mutate such that it would develop affinity for the binary complex of host and drug (**D)** it would lose affinity for the native host once the drug was removed (**E**). Thus, there is no mechanism for a pathogen to *linearly* evolve resistance to a drug that binds to and conceals a host receptor.

Conflict of Interest Statement

The author declares that he has no conflict of interest.

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