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INTERPRETIVE ESSAY

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The evolution of bacterial social life

From the ivory tower to the front lines of public health

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ABSTRACT

Drug-resistant bacteria are a huge and growing threat to public health. A solution exists in theory, but had not yet been put to a practical test. The accompanying paper by Ross-Gillespie *et al*., the theory is put to a test and performs successfully. As predicted, using a drug that targets bacteria's shared secreted 'public goods' molecules instead of cell components did not drive the bacterial evolution of drug resistance, and therefore retained its effectiveness. This result holds great promise for better drugs and vaccines against many infectious diseases, and also for better cancer therapies.

KEYWORDS: drug resistance; microbial public goods; microbial cooperation; disease evolution; cancer therapy

RESISTANCE TO ANTIBACTERIAL DRUGS IS A HUGE AND GROWING MEDICAL PROBLEM

The evolution of drug-resistant bacteria is one of the most important problems in medicine and public health. Warnings of the danger it poses have been sounded for years and continue to grow direr. Last year, antibiotic-resistant bacteria of just one family, the Enterobacteriaceae, were described by the director of the US Centers for Disease Control and Prevention, and by the UK's chief medical officer, as a coming health 'nightmare', and as a 'catastrophic threat' [1].

The paper in this issue by Ross-Gillespie *et al.* is an encouraging ray of hope for avoiding this nightmare and averting this threat for the longer term. Starting with penicillin, a long list of antibiotics has failed one after the other, as bacteria evolve resistance to them. Up till now, the response has been to try to move on quickly to the next new antibiotic, which we hope will forestall the perennial crisis for a few months or years before joining the list of obsolete drugs. Unfortunately, it is becoming clear that the pipeline of new drug-resistant bacteria runs faster than the pipeline of new drugs, so that we are playing a game of catch-up that becomes increasingly urgent. If

achievable, the goal of developing drugs that remain effective would be a life-saving breakthrough, and the work by Ross-Gillespie *et al*. [2] brings us closer to realizing that hope.

As often happens with basic research, the ideas that are emerging as central to solving this very practical problem began as purely academic exercises—in this case, as academic inquiries into how species change over time, and into the social lives of bacteria.

We now understand why antibiotics predictably lose effectiveness.

When disease-causing bacteria become resistant to antibiotics or other drugs, this is a heritable change in an entire population of organisms that allows them to meet a new environmental challenge. To any biologist, this smacks of Darwinian evolution, and indeed that is exactly what it is. Bacterial species evolve quickly both because their huge populations offer many opportunities for mutations, and because they readily exchange genetic information, even between species. Some of this genetic heterogeneity influences drug sensitivity or resistance, and thereby provides fodder for Darwinian selection. No drug has perfect effectiveness, killing every bacterial cell. Instead, the most drug-sensitive cells are killed, leaving the most resistant to survive, reproduce and pass on their drug resistance to their progeny. Over many rapid generations of bacterial cells, this selection process drives the population's evolution toward increasing drug resistance.

BIOLOGISTS HAVE DISCOVERED THAT BACTERIA ARE QUITE SOCIAL

In contrast to the highly cooperative cells that make up a multicellular organism like us, bacteria were once viewed as fundamentally solitary. Closer observation has showed this to be untrue [3, 4], and biologists have scrambled to keep up with these discoveries by extending evolutionary theory for the origins of cooperation to explain not only social animals such as ants and humans, but also cooperation among bacteria, which can even include individual self-sacrifice for the good of the group [5]. Consequently, 'the microbe as a generic loner has been increasingly challenged in recent years, which have seen an explosion of research on the topics of bacterial individuality and social behaviour' [6]. The key biomedical implication of this research is that the social lives of pathogens may be an Achilles' heel for attack by 'anti-social' therapeutic strategies that disrupt this cooperation.

Much like a colony of termites or a family of beavers, a colony of bacteria can thrive where a single individual could not, and for similar reasons: by coordinating their efforts and sharing their resources, a group can build a home in which they are sheltered and fed. Understanding these social strengths also suggests new ways to turn them into weaknesses by disrupting cooperation. Because disease-causing bacteria rely on coordination and cooperation to succeed in attacking their human host, it has been proposed that 'anti-social' strategies for disrupting this cooperation could lead to new antibacterial drugs that do not quickly lose effectiveness. For bacteria, the most limiting nutrient is often iron, which is essential and difficult to extract from the environment. To solve this problem, bacterial cells produce and secrete molecules called siderophores that acts as molecular sponges for scarce iron. The bacterial cell then collects the siderophore molecules it released and extracts the iron they soaked up. This too turns out to be a social endeavor. A bacterial cell can collect and use the siderophores its neighbors released, as well as its own. Thus when a group of bacterial cells all release siderophore molecules, they collectively create a shared environment of high iron availability that they all thrive in. Diffusible and shared molecules such as siderophores that benefit a larger collective rather than just the cell producing them are termed by microbiologists as 'public goods', and they have been proposed as particularly promising targets for drugs that could keep their effectiveness despite microbial evolution.

THEORY PREDICTS THAT ANTI-SOCIAL THERAPIES WILL KEEP THEIR EFFECTIVENESS

Evolutionary theory predicts that drugs targeting cooperation among bacterial cells will not cause strong selection among cells, and therefore will be less vulnerable to the problem of evolved drug resistance. Standard drugs that target individual cells select among their variants, leaving the most drug-resistant ones alive to reproduce and pass on their drug resistance to the next generation. In contrast, removing the hospitable microenvironment that cells collectively build affects them all equally, without selecting among them. If some cells are better able to benefit their neighbors, even in the presence

of an interfering drug, they will not live to pass on that ability, because it will allow the survival of their neighbors instead of themselves.

This prediction is solidly grounded in classical evolutionary theory [7] and has been supported by detailed computer simulations [8], but until now it had not been tested in a controlled experiment. Ross-Gillespie *et al.* set out to carefully test the theoretical promise of this strategy, and their results are good news indeed. Not only did targeting public goods molecules (in this case, siderophores) prevent sickness and death in their experimental animals, but it also retained this effectiveness in the same conditions under which a standard antibiotic quickly lost effectiveness as the bacteria evolved resistance.

IT IS NOT JUST ABOUT ANTIBIOTICS

The 'anti-social' strategy that worked so well in this study may have very broad medical application. The problem of evolved drug resistance is not limited to antibiotics, or to bacteria. It is also acute for non-bacterial infectious diseases such as influenza, malaria and many others [9].

Moreover, evolution can drive resistance to antibodies as well as to drugs, leading to the phenomenon of 'vaccine escape' by bacterial, viral and protozoan diseases [10–13]. In this arena, the same idea that was intentionally tested for drugs by Ross-Gillespie *et al.* was unintentionally tested long ago by deploying both vaccines that target microbial cells and vaccines that target the public goods molecules they secrete. Vaccine escape has often arisen against vaccines that target the cell-intrinsic molecules of bacteria such as *Salmonella* [14] and *Neisseria* [15]. In contrast, vaccines against tetanus and diphtheria target the external 'public goods' toxins that these bacteria secrete, instead of cell-intrinsic molecules. In contrast to the cell-targeting vaccines, these 'anti-social' vaccines have been used widely, yet have retained their effectiveness for many decades, in the USA [16], as well as in Asia [17] and the former Soviet Union [18]. This suggests that such anti-social vaccines are also robust against pathogen evolution, and better retain long-term effectiveness.

In addition to infectious disease, the problem of evolved drug resistance also causes much cancer mortality. During cancer treatment, therapeutic drugs often lose effectiveness before the patient is cured, leading to drug-resistant relapse and death. This form of drug resistance also results from the 'natural selection' imposed on heterogeneous cancer kills by drugs that kill the most drug-sensitive variants, leaving the most drug-resistant cells to survive and pass on their drug resistance to their progeny. This, again, is Darwinian evolution, playing out on a small-scale inside a single patient. Much like the unending quest for new antibiotics, the unending quest for new cancer therapies is also too slow and expensive, and here too, we need better strategies. Because cancer cells also rely on their own kinds of shared 'public goods', the same principles that allow 'anti-social' drugs like siderophore quenchers to retain effectiveness against evolving bacteria may also allow new cancer drugs that quench cancer public goods to retain effectiveness against evolving cancer cells that evade traditional drugs [19].

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