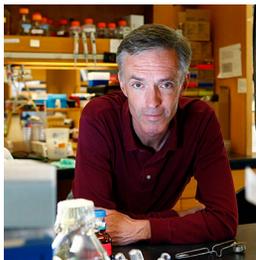


Overcoming Antibiotic Resistance

We invited eleven experts in their fields to share their insights on the growing threats of antibiotic resistance, and how we, as a community, can address them.

Complex Host-Microbe-Antibiotic Interactions



James J. Collins
MIT

To strengthen our antibiotic arsenal, we need to expand our understanding of how antibiotics act and how resistance arises. Efforts in network biology have revealed that the actions of antibiotics are more complex than previously thought. Antibiotics downstream of their target-specific interactions have been shown to induce metabolic responses and redox alterations that contribute to the resulting lethality, stasis, or tolerance. These studies have largely been limited to *in vitro* settings, but recent efforts have indicated that the behaviors of a drug and a bug in a dish can be quite different from those in a host. Synthetic biology studies with engineered bacteria demonstrated that the presence of non-replicating bacteria *in vivo* does not necessarily lead to a tolerant infection, as would be expected from dozens of related *in vitro* experiments. We clearly need to better query infection environments to better understand *in vivo* interactions of pathogens and antibiotics, and to study how their respective interactions with the host and microbiota can lead to drug tolerance and resistance. The latter is particularly important given the growing evidence that antibiotics, immune cells, and microbes (bacteria and viruses) attack pathogens, in part, through similar antibacterial mechanisms. Deciphering the dynamic ecosystem of infection sites and learning how to embrace its complexity could improve our chances in our battles with bacterial pathogens.

Novel Antibiotic Discovery: Difficult but Necessary



Eric Brown
Genentech

Multidrug resistance in bacterial pathogens poses a major threat to medical progress. Because the number of distinct scaffolds for clinically useful antibiotics is limited, a single resistance mechanism can render an entire class of antibiotics useless. Although the most straightforward way to combat resistance is to identify more chemically distinct antibacterials, this has proven to be exceedingly difficult. Only a few essential bacterial gene products are conserved, amenable to inhibition, and sufficiently diverged from eukaryotic orthologs. Furthermore, the bacterial envelope is a formidable barrier against antimicrobials, and efflux systems rapidly remove toxic molecules. It is no wonder that natural products with intrinsic antimicrobial activity have been the best starting points for most antibiotics! Even so, only a few have become drugs due to intolerable eukaryotic toxicities or unacceptable distribution, metabolism, or excretion. Intense, focused medicinal chemistry efforts are required to extend the spectrum and improve the drug-like properties of natural antimicrobials. Even after optimization, clinical development can be cumbersome, and antibiotic stewardship, needed to slow the emergence of resistance, limits commercial potential. Thus, drug companies are faced with a quandary: how to overcome a difficult scientific problem, slow clinical development, and minimal commercial return for an unquestionable medical need. Together, we must look for innovative ways to support the discovery and development of treatments for multidrug resistant bacterial infections.

Sustainable Stewardship Needs Evolution



Michael Baym
Harvard Medical School

Recently, the *New York Times* ran a headline “Revenge of the Bacteria: Why We’re Losing the War,” while a review in this journal discussed an “Approach to Combat Antibiotic-Resistant Bacteria.” While these martial metaphors underscore the life-and-death nature of antibiotic resistance, they are misleading. In war, the involved parties know they’re fighting. That’s not what’s going on here: we try to kill bacteria, but bacteria aren’t trying to do anything. They simply survive and adapt to whatever specific environment they happen into. Bacteria have no plan, and evolution is not infinite. Thus, we can potentially predict what will evolve as a result of our interventions. We aren’t outmaneuvering an opponent; we’re learning the rules of a complex but finite system. The last 80 years have taught us that whenever we introduce an antibiotic, resistance rapidly emerges. The same drugs that save lives spur evolution, rendering them ineffective. We still need new antibiotics, but equally a detailed understanding of the evolution of resistance. Learning what types of resistance disappear more rapidly in the absence of use, and what, if any, sensitivities can be forced by specific treatment combinations would allow us to treat the system in addition to the patient. Discovery and stewardship efforts are critical, but only by understanding the evolution will we find a sustainable solution to antibiotic resistance.

Antibiotics Au Naturel



Gerard D. Wright
McMaster University

Fleming's discovery of penicillin's activity and its subsequent isolation and use in the treatment of infection are landmarks in modern medicine. This story reveals two foundational axioms of antibiotic discovery. First, microbial natural products are privileged sources of antibiotics. Second, antibiotics are distinct drugs under constant threat of ineffectiveness due to the evolution of resistance.

Despite the initial success of natural products, no new approved antibiotic drug classes have been found since the mid-1980s. The pivot away from this source of drug leads has been paralleled by the worst drought in antibiotic discovery since Fleming's era. As a result, new antibiotic supply is being outstripped by increasing numbers of highly resistant bacteria.

How did we get here? Following Fleming's discovery, the discovery platform was industrialized, resulting in the rapid delivery of most of the chemical classes of antibiotics in current use. This provided a false sense of security. The research community outside these industries was encouraged to move toward other areas such as cancer. There are few antibiotic discovery centers now.

Paradoxically, natural product research has never been more exciting. Our understanding of the genetic programs that encode this rich chemical diversity, our ability to rapidly identify them from genomic sequences, and the growing capacity to expand them using synthetic biology augurs for a new hopeful Golden Age in antibiotics.

An Enriching Gut Resistome: A Double-Edged Sword



Gautam Dantas
Washington University in St. Louis School of Medicine

The gut microbiome is constantly challenged by biotic and abiotic perturbations. Antibiotics represent the most acute of these challenges, as they inhibit or kill microbes by targeting conserved cellular processes. Periodic antibiotic exposure, through therapy or contamination, is nearly universal in the human population, resulting in both acute and persistent microbiome reconfigurations. This means changes in the relative and absolute abundance of microbial species and their encoded functions, including potential permanent loss and gain. The suite of genetic determinants that enable microbiome resistance to antibiotic insults are collectively termed the resistome. An enriched gut resistome is a double-edged sword. On one hand, resistance genes in the microbiome can be horizontally acquired by pathogens, compromising infection treatment. On the other hand, the resistome can enable resilience in commensal microbes during antibiotic exposure, enabling more rapid recovery and maintenance of colonization resistance against invading microbes. A historical overreliance on cultured pathogens has resulted in severe underestimation of the gut resistome. Recent advances in culturomics, next-generation sequencing, functional metagenomics, and *in silico* remote-homolog resistance gene prediction are helping address a more accurate gut resistome characterization. A key challenge toward translating these discoveries in the era of microbiome-targeted diagnostics and therapeutics is understanding the balance between the risks of resistome enrichment for pathogen resistance acquisition and the potential benefits for maintaining microbiome resilience.

Challenges of *Pseudomonas aeruginosa* Treatment



Lori Burrows
McMaster University

Gram-negative opportunist *Pseudomonas aeruginosa* is among the most challenging bacterial pathogens to treat. Although it causes fewer infections than some other species, the consequences of those infections can be severe. Its metabolic versatility, virulence, ability to form recalcitrant biofilms on medical devices and hospital surfaces, and intrinsic resistance to many common antibiotics, coupled with expression of multiple efflux systems, make it a tough bug to battle once established. Pan-resistant strains are beginning to emerge, and few antibiotics in the pipeline have activity against *P. aeruginosa*. There are no licensed vaccines, and the few that have advanced into clinical trials have failed to demonstrate the efficacy that developers had hoped. Even if such a vaccine should work well, economic questions about who would most benefit remain. Particularly susceptible populations such as people with cystic fibrosis are an obvious choice, but universal vaccination against an opportunistic pathogen for which infections can be difficult to predict is otherwise hard to justify. Researchers continue to tackle *P. aeruginosa* using a variety of approaches, including development of biofilm inhibitors, antibiotic adjuvants (molecules that enhance penetration of conventional antibiotics), biologics (antimicrobial peptides or monoclonal antibodies), and bacteriophages. To stay ahead of this adaptable adversary, we'll need to treat *P. aeruginosa* infections as we now do those of *Mycobacterium tuberculosis*, using combination therapies coupled with rapid diagnostics.

Drug Resistance in MRSA—the Next Big Challenge

George Y. Liu
University of California, San Diego

It is easy to feel optimistic that we are gaining on MRSA. After all, the incidence of MRSA infections is declining, we have developed new classes of antibiotics that appear less susceptible to resistance development, and research into staphylococcal metabolic pathways and nutritional immunity has yielded promising targets. Yet given sufficient time, *S. aureus* will undoubtedly develop resistance to all antimicrobial agents if infection incidence remains high and antibiotic use uncontrolled. An effective staphylococcal vaccine has been elusive for decades, underlined recently by yet another failed vaccine trial. The latest trial, STRIVE, tested a vaccine consisting of four staphylococcal antigens and an adjuvant aimed at boosting a different type of immune response. In essence, the vaccine appeared to have addressed what experts perceived to be major weaknesses of previous trials, but the outcome was no different. Hence, we are back at the drawing board and left to contemplate our fundamentally flawed animal model that has yet to show any predictive value and that has not been amenable to quick fixes. The staphylococcal field needs to reflect on the urgent challenge ahead and perhaps make a concerted effort to develop a “dedicated” animal model of staphylococcal infection that more closely mimics human infection. Without a working translational model, we will be left to wonder about the value of staphylococcal research.

Genetics and Tuberculosis: A Case of New Meets Old

Philip W. Fowler
University of Oxford

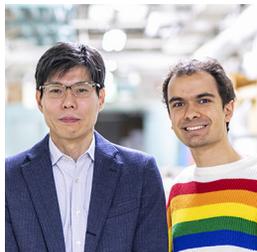
Tuberculosis (TB) has afflicted humans for thousands of years. It kills more people than any other infectious disease and, unsurprisingly, has evolved antibiotic resistance. Only a few antibiotics are effective against it and one must also take multiple antibiotics for months. Rapid and accurate detection of antibiotic resistance is vital, yet only a quarter of the 558,000 people estimated by the WHO to have developed multi-drug-resistant TB in 2016 were started on appropriate therapies. The reduction in the cost of genetic sequencing has enabled genetics-based clinical microbiology; the genome of the pathogen is sequenced and, by examining the genes known to confer resistance, we can predict which antibiotics will be effective. TB is the test case par excellence for this approach since its genetics are straightforward and the clinical benefits are high. This is no pipe dream: Public Health England transitioned to using genetics for TB in March 2017. Research efforts are concentrating on mapping all the remaining genetic variants that confer resistance. For example, the CRyPTIC project will have collected, tested, and sequenced 25,000 TB samples by the end of 2020. Members of the public can help via our citizen science project, bashthebug.net. So will we overcome antibiotic resistance? No, but I hope through genetics, and other approaches discussed in this Voice piece, we will learn to live with it.

Targeting Biofilms to Reduce Antibiotic Use

Cynthia B. Whitchurch
University of Technology Sydney

Chronic infections and infections of medical devices are associated with microorganisms living in biofilm communities. Biofilms are a challenging problem because, compared with free-living bacteria, they are extremely tolerant to the effects of antibiotics, often rendering them recalcitrant to antibiotic therapy. Catheter-associated urinary tract infections are the most common type of infection acquired in healthcare facilities and considered to be the largest reservoir of multi-drug-resistant “super-bugs” due to the inappropriate use of antibiotics against them. A few non-antibiotic approaches to treat biofilm infections, either in isolation or in combination with traditional antibiotics, are being explored. These include bacteriophages, quorum-sensing inhibitors, matrix-degrading enzymes, inducers of biofilm dispersal, negative pressure, and alternative treatments such as honey and curcumin. However, in this case, the adage “prevention is better than cure” applies. Understanding the factors that promote initial attachment of pathogens to surfaces may lead to improvements in medical device design or choices of materials to prevent subsequent biofilm formation, or which limit the spread of biofilms along the device. The sources of biofilm pathogens, the factors that initiate biofilm formation and lead to manifestations of infection, are currently poorly understood. There is an urgent need for a greater understanding of biofilms so that appropriate prevention and treatment approaches that avoid or reduce the use of antibiotics can be developed.

Harnessing Gut Commensal Consortia



Ashwin N. Skelly and Kenya Honda
Keio University School of Medicine

While antimicrobial-resistant (AMR) bacteria are recalcitrant to conventional treatment, an emerging body of evidence suggests that manipulation of the microbiota may be an effective alternate approach. Indeed, several clinical trials have found fecal microbiota transplantation (FMT) to be more efficacious than standard vancomycin treatment against *Clostridium difficile*. Nevertheless, the variable composition of FMT therapeutics has led to heterogeneous results and concerns regarding safety and production feasibility. Thus, identifying specific species or consortia that can decolonize invading AMR pathogens and elucidating the underlying mechanisms will be paramount going forward. For example, one could envision treating *C. difficile*, carbapenem-resistant Enterobacteriaceae, vancomycin-resistant enterococci, and extended-spectrum β -lactamase-producing Enterobacteriaceae, all of which are major sources of rampant nosocomial disease, with a live bacterial cocktail to clear the pathogen and resolve intestinal inflammation. A similar strategy could be employed to alleviate symptoms of inflammatory bowel disease by decolonizing pro-inflammatory microbes like *Klebsiella* species and adherent-invasive *Escherichia coli* (AIEC). Recent studies have shown that members of the indigenous microbiota inhibit pathogen colonization via multiple mechanisms including nutrient competition, secretion of antimicrobial products, and activation of the host immune system. Harnessing these microbial activities in the form of live bacterial therapeutics represents a promising approach to combatting the growing threat of AMR pathogen infection as well as treating other gut bacteria-associated diseases.

Time to Turn the Phage on Antibiotics



Steffanie A. Strathdee and Thomas L. Patterson
University of California, San Diego

Tom didn't plan on being a poster child for the global superbug crisis any more than Steff planned on being an advocate for phage therapy. But when their professional and personal lives collided and Tom acquired a pan-resistant *Acinetobacter baumannii* infection that nearly killed him, Steff enlisted help from a global network of phage researchers who managed to deliver phage cocktails just in time to save his life. Reports on this case went viral, and in a good way. Tom's case has re-vitalized interest in phage therapy, where it had been relatively abandoned outside of the former Soviet Union and parts of Eastern Europe. Dozens of new patients have been treated as a result, the majority of which have been successful. In 2018, UC San Diego launched the Center for Innovative Phage Applications and Therapeutics (IPATH), the first dedicated phage therapy center in North America. IPATH's goal is to conduct rigorous clinical trials of phage therapy so that its efficacy can be established beyond single case reports. It's unlikely that the development of new antibiotics alone can reverse the growing problem of antimicrobial resistance. Phage therapy appears to be the most promising alternative to antibiotics and deserves to be rigorously studied. The couple recently published their memoir, *The Perfect Predator: A Scientist's Race to Save Her Husband from a Deadly Superbug*.