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Current Opinion in Microbiology

Expanding and enhancing our antibacterial arsenal

Editorial overview

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Current Opinion in Microbiology 2011, **14**:511–512

Available online 22nd September 2011

1369-5274/$ – see front matter

DOI 10.1016/j.mib.2011.09.005

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Our knowledge of the microbial world is expanding at an unprecedented pace: we are just starting to appreciate the diversity, complexity, evolvability and metabolic potential of bacteria, which represent the most abundant biomass in the world. Can some of this knowledge be harnessed to preserve our ability to cure bacterial infections in spite of the increasing frequency of drug-resistant pathogens? Skeptics may say that the way bacterial infections are diagnosed and treated has changed little over the past two generations, while the number of new drugs has not kept up with increased resistance. Yet, there appears to be some light at the end of the tunnel and the topics covered in this issue provide valuable insights into emerging aspects related to antibacterials, while providing also an update of what is cooking in the developmental pipeline.

Amini and Tavazoie discuss in their article how advances in genomics are characterizing all steps connected with the discovery and characterization of new antibacterial agents, from the discovery and validation of new targets to the optimization and manipulation of antibiotic biosynthesis in producer strains, from understanding their mode of action to the emergence of antibiotic resistance, from understanding pathogenesis to metagenomics, up to *theragnostics* and personalized treatment. However, possibly because of the effectiveness of empirical antibacterial therapy, genomics technologies are only being incorporated into clinical practice at a relatively slow pace.

Do alternatives exist to current antibacterial therapy? Two reviews in this issue cover different aspects. Fischbach argues about the advantages of combination therapy in fighting bacterial infections. While combination therapy is standard care in some therapeutic areas, it has been the exception rather than the rule in antibacterial therapy, except for treating tuberculosis (see also review by Riccardi and Cole in this issue). Interestingly, in an important lesson from Nature, 'combination therapy' seems to be the rule rather than the exception in the microbial world, where many strains produce several classes of bioactive compounds, often targeting the same pathway.

A different strategy for antibacterial intervention is represented by the use of bacteriophages, which in principle can provide the specificity and selectivity required to target the pathogen(s) of interest. Interestingly, combination therapy is typically considered as the most promising approach when using phages. These concepts, along with a historical overview of phage therapy, are discussed by Lu and Koeris, who also provide a poignant account of the technological and regulatory hurdles that phage therapy must overcome to reach the market.

Two reviews cover selected antibacterial targets. Srivastava *et al.* provide detailed information on the mechanism of action of compounds that interfere

with the 'switch region' of RNA polymerase. Remarkably, this region alone is inhibited by three distinct classes of unrelated natural products, while other classes of natural products target different regions of this enzyme. We are thus witnessing one more example of Nature's capacity for designing bioactive compounds. As further discussed in this issue, one of the switch region inhibitors – lipiarmycin aka Dificid^{TM} – has been approved this year by the FDA for treating *Clostridium difficile*-associated diarrhea. This drug represents one example of the critically needed new chemical classes of antibacterial agents to reach the patient.

Parsons and Rock discuss the state of the art on fatty acid biosynthesis as an antibacterial target, providing a well-balanced opinion piece that helps solve a recent controversy on the topic. However, Parsons and Rock also emphasize our lack of understanding of basic essential cellular pathways in relevant human pathogens and how the *Escherichia coli* paradigm for many of these processes should not be taken for granted in unrelated bacteria.

Coleman provides an overview of the diazabicyclooctanes, a new class of potent β-lactamase inhibitors unrelated to β-lactams. As he documents, appropriate combinations of these inhibitors with existing β-lactam drugs are effective against pathogens expressing many classes of β-lactamases. In addition to representing examples of combination therapy under clinical development, the diazabicyclooctanes illustrate how non-essential, highly flexible enzymes can be inhibited by unrelated classes of compounds.

Sommer and Dantas provide an illuminating overview of the changes that can occur in the human microbiome upon antibiotic treatment and how these changes can contribute to resistance in a clinical setting. Remarkably, changes in the human microbiota occur rapidly upon antibiotic treatment but are slow to revert upon antibiotic removal. Thus, there appears to a price to pay when exposing the human microbiota to broad-spectrum antibacterials, although we still do not know how high this price is. As Sommer and Dantas point out, antibiotic treatments cause transient increases in the normally low-abundance *Proteobacteria*, which include drug-resistant strains of *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and the *Enterobacteriaceae*. Thus, future antibacterial therapies should take into consideration major alterations of the human microbiota, which, as pointed out also by Amini and Tavazoie, can only be effectively evaluated by metagenomic studies.

The last two reviews provide updates on the developmental pipeline: Jabes reports on antibacterial compounds under clinical development, including some promising drug candidates at the preclinical stage, while a separate review by Riccardi and Cole is dedicated to anti-tuberculosis agents. In both cases, the authors observe that the developmental pipeline has not looked this rich in many years. This is particularly significant in the case of tuberculosis (TB), long-considered a neglected disease. As Riccardi and Cole show, the deployment of resources from public and private sources and the dedicated work of several teams have brought forward several promising drug candidates. Nonetheless, this is no time to rest on laurels, as the inevitable attrition rate of clinical development will result in just a few approved drugs for a disease that requires combination therapy. Two important observations can be made by comparing the two pipelines. The first is that, with few exceptions, biotech companies are taking charge of the development pipeline for antibacterial agents. Interestingly, this is not the case for the anti-TB drugs, where large pharmaceutical companies are significantly involved. The second observation is that, while anti-TB drugs under development are mostly of synthetic origin, natural products and their semi-synthetic derivatives significantly contribute to the developmental pipeline, despite a general disinterest in such compounds by most companies. Jabes also highlights the paucity of developmental drugs targeting Gram-negative pathogens, which may further exacerbate the impact on the human microbiota pointed out by Sommer and Dantas.

How many of the antibacterials currently under development will eventually become marketed drugs? Only time will tell. While the overall attrition rate of antibacterials during clinical development is lower than for other therapeutic areas, this favorable situation may be affected by development being carried out by small companies (for which marketing a compound can be a life-or-death scenario) or by politically motivated programs.

In the battle of ''our wits against their genes'' (to quote Joshua Lederberg), all is not lost. On the contrary, as this special issue highlights, we are well poised to expand and enhance our antibacterial arsenal, taking advantage of new approaches, platforms and discoveries arising from a range of fields, including genomics, synthetic biology, chemical biology and high-throughput screening.