Expert Opinion on Drug Discovery

ISSN: 1746-0441 (Print) 1746-045X (Online) Journal homepage: http://www.tandfonline.com/loi/iedc20

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To cite this article: Anthony Travis, Olga Chernova, Vladislav Chernov & Rustam Aminov (2018): Antimicrobial drug discovery: lessons of history and future strategies, Expert Opinion on Drug Discovery, DOI: 10.1080/17460441.2018.1515910

To link to this article: https://doi.org/10.1080/17460441.2018.1515910

Accepted author version posted online: 23 Aug 2018.
Published online: 29 Aug 2018.

EXPERT OPINION ON DRUG DISCOVERY
https://doi.org/10.1080/17460441.2018.1515910

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EDITORIAL

Antimicrobial drug discovery: lessons of history and future strategies

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ARTICLE HISTORY Received 11 July 2018; Accepted 21 August 2018

KEYWORDS Antimicrobials; antimicrobial resistance; novel antimicrobials

1. Introduction

The discovery and development of the main classes of antimicrobials used in therapy of humans and animals has been recently overviewed [1]. The introduction of antimicrobials into clinical practice fundamentally changed the way that microbial infections are controlled and managed and has contributed to a significant decrease in morbidity and mortality rates caused by microbial infections on mankind. Despite the overall success of antimicrobials, their efficacy and reliability has been severely compromised in recent years, due to the emergence and spread of antimicrobial resistance (AMR) among pathogens [2].

2. Natural history of antimicrobials and AMR

A common perception of antimicrobials as clinical 'weapons' used to kill pathogens is based on the relatively recent history of discovery and use of antimicrobials in medical and veterinary practice. They are indeed very efficient at killing pathogenic microbes when administered at high concentrations. However, research with sub-clinical concentrations of antimicrobials during the last decade have demonstrated different effects. It is evident that physiological responses of bacteria to antimicrobials are concentration-dependent and that there is a continuum of responses regulated by specific sets of bacterial genes depending on exposure to different concentrations of antimicrobials. When the concentration of an antimicrobial reaches a therapeutic level, it results in a bactericidal or bacteriostatic action, which is what is expected for any given antimicrobial. The concentration-dependent effects of antimicrobials have been described as the 'hormesis' concept [3]. In natural ecosystems, antimicrobial substances may play a signaling role and regulate some aspects of bacterial interactions in microbial communities because the biomass of antimicrobial producers and the corresponding output of their antimicrobials is apparently very low. Therefore, antimicrobial-AMR combinations are probably widespread in natural ecosystems playing an important role in regulatory circuits.

Once isolated, purified, characterized, and approved, antimicrobial compounds are used at high concentrations in the treatment of microbial infections as well as at lower concentrations in agriculture and for purposes other than the treatment of disease. Some AMR genes, including some from distant ecosystems, inevitably come into the contact with a corresponding antimicrobial because of extensive horizontal gene exchange driven by mobile genetic elements in bacteria [4]. If a bacterial host with a corresponding AMR gene passes the selection on to another generation, then there is opportunity for the gene to be disseminated both horizontally and vertically.

3. Antimicrobial era and AMR

The main factors that have contributed to, and accelerated, AMR are the over-use of antimicrobials in human and veterinary medicine as well as prophylactic, metaphylactic, and growth-promoting uses in agriculture [5]. Whilst the clinical use of antimicrobials has its own negative consequences, that could be improved by imposing stricter regulations and education, the scale of clinical use of antimicrobials is much lower than in agriculture. Most antimicrobials produced globally are used in agriculture, and usually used at low concentrations that may drive bacterial evolution toward high-level AMR [6]. In addition, many antimicrobials used for clinical treatment of humans and animals are excreted unchanged, contributing to low-dose antimicrobial exposure of bacteria in the environment.

Another aspect of AMR that needs careful consideration is the strategy used in the design of semisynthetic antimicrobials: in addition to improvement of the PK/PD parameters of naturally occurring antimicrobial compounds, broadening the spectrum of target microorganisms is usually one of the design objectives allowing targeting a wider range of infectious agents [1]. The negative aspect of this approach is that more pathogenic and commensal microbiota are exposed to the selective pressure of antimicrobials, which increases the selection for and probability of AMR emergence.

4. Expert opinion

The major classes of the antimicrobials in use today were discovered during the 'golden age' of antimicrobial research [2]. Since then, the main objective of antimicrobial drug development has been concentrated on improving PK/PD properties,

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overcoming pathogen resistance, and extending the spectrum of microorganisms targeted. Although most pathogens can still be controlled, the number of failures in clinical therapy is growing at the alarming rate because of the rapid expansion of AMR pathogens. The demand for new antimicrobials is high, but it is clear that the strategies of antimicrobial development that have been used until now should be reconsidered carefully and other paths of antimicrobial drug discovery explored.

4.1. Exploration of further ecological niches and sources

Most antimicrobials were discovered in a limited number of ecosystems including soil and a narrow range of taxonomic entities consisting mainly of the actinomycetes. There are many ecosystems other than soil that have still to be explored for novel antimicrobials, for example, the marine environment, especially marine sediments. Other sources that could be exploited include antimicrobial peptides and compounds of animal or plant origin.

The vast genetic diversity of uncultivated microbiota in many different ecosystems is not accessible using classical microbiological techniques, but its potential for antimicrobial production can be accessed indirectly through metagenomics. Complete chemical synthesis of antimicrobials, which was pioneered by Paul Ehrlich more than a century ago [2], was modified in the late 1990s as the technique of fragment-based lead discovery. Identification of small ligands using this approach relies on the availability of pathogen genomes, development of bioinformatic tools for identification of potential targets and drug-target interactions, as well as improvements in X-ray crystallography, NMR spectroscopy, and large-scale screening systems. Small ligands identified this way may then be used to discover larger and more potent ligands. Antimicrobials could also be engineered to possess dual target activities by combining the known antimicrobials into the hybrid molecules.

4.2. Spectrum of antimicrobial activities

The design of 'next generation' semisynthetic antimicrobials has almost inevitably included the requirement for a broad-spectrum activity. As mentioned earlier, although this provides a short-term advantage for antimicrobial use in clinical prescription and treatment, in the long-run the result is a more rapid development of AMR due to a broader base of genetic diversity for selection. In which case, development of narrow spectrum antimicrobials would be a better option. The ideal strategy, however, would be to target a specific pathogen given the capability of 'express' diagnostics. In that regard, antimicrobials could be designed to target 'virulome' components that would not require the killing of a pathogen. Mitigation of virulence factors in the virulome of a pathogen leaves it 'unarmed' and therefore less capable of inflicting damage in the host. It is important that commensal bacteria, without virulence factors, should not be affected thus preventing a common side effect of antimicrobial therapy, dysbiosis. The base of genetic diversity for selection of resistance among virulence genes is very limited because the virulome represents only a small part of the microbiome that is confined to specific pathogens. At the same time, there are discernible needs for broad-spectrum antimicrobials, especially for infections with unclear etiology, which require immediate intervention. Besides, the economic aspect of drug development may favor the broad-range coverage, thus ensuring better investment returns.

4.3. Bacteriophages and their products

Targeting bacteria by phage is precise and highly specific. The idea of using phages in clinical therapy of infections was proposed by Félix d`Hérelle [7]. This approach, however, was overshadowed by the successful use of antimicrobials in the treatment of infectious disease. A renewed interest in phage therapy is being driven by the alarming rate of AMR, which could be mitigated by phage therapy [8]. Phage therapy is specific, has no reported side effects such as adverse immune responses [8] and does not affect commensal microbiota, so avoiding dysbiosis. Unlike conventional drugs phages multiply in the presence of their target microbes and amplify their local antimicrobial effects. Phages also limit the evolution and spread of AMR. Unlike antimicrobials, phages are effective against biofilm-forming pathogens [8]. And finally, phage-resistant bacteria remain sensitive to other phages. Introduction of new phages is a much faster and inexpensive process than the development of new antimicrobials.

However, there are regulatory issues associated with the re-introduction of phage therapy [9]. Phage proteins, for example lysins, could represent a more feasible approach to meet the existing regulatory criteria for drug approval. Another potential downside of phage therapy is associated with phage genetics: as mobile genetic elements, they can participate in transfer of undesirable genes such as encoding AMR or virulence [10].

4.4. Treatment of diseases other than infection

Antimicrobials may also play a regulatory role in eukaryotic cells, including humans and animals [11]. Antimicrobials may exert anti-inflammatory, anticancer, immunomodulatory, immunosuppressive, and other activities. Antimicrobials could, therefore, be used in the treatment of different types of cancer, cardiovascular diseases, a range of autoimmune disorders, neurodegenerative conditions, chronic respiratory diseases, and other diseases with a strong inflammatory component. They are potentially useful in the treatment of psychiatric illness and substance abuse conditions.

The treatment of non-infectious diseases by antimicrobials is clearly gaining momentum, and it is important to avoid any additional contribution to AMR. It has been established, at least for some antimicrobials including macrolides, that ligands responsible for antimicrobial and anti-inflammatory activities are independent and can be modified separately [12]. This allows to retain therapeutic properties of antimicrobials for none-infectious disease treatment while eliminating antimicrobial activity to prevent the spread of AMR.

4.5. Strategies to retain the lifespan of antimicrobials

The nemesis of antimicrobial therapy is AMR, which, almost inevitably, penetrates into pathogens. To slow down this

process and extend the useful lifespan of antimicrobials, a combination of measures involving a variety of professions and agencies is required. Critical to this is research on the development of alternatives to antibiotics and improved diagnostic tools. New global regulatory frameworks are needed to define standards for antimicrobial use, legislative measures, and their enforcement. Clinical research to optimize PK/PD-based antimicrobial use would also help to decrease the concentration and time of exposure to antimicrobials in clinical use. Clinicians and researchers should interact more with the public to provide antimicrobial stewardship, education, and training. Public health professionals should make efforts to improve hygiene, sanitation, and infection control all of which are vital to reduce our reliance on antimicrobials. Less dependence on antimicrobials in livestock production could be a major contribution to reducing AMR. It is especially important to prevent overlap between classes of antimicrobial used in animals and humans. A better knowledge of the dynamics of AMR in different ecosystems is critical for evidence-based decision-making. In particular, for the development of waste treatment technology to reduce discharge of antimicrobials and AMR genes/bacteria into the environment from their use in agriculture, community, hospitals, pharmaceutical industry, and other sources.

Funding

This manuscript was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

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