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Review

Using bacterial genomes and essential genes for the development of new antibiotics

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ABSTRACT

The shrinking antibiotic development pipeline together with the global increase in antibiotic resistant infections requires that new molecules with antimicrobial activity are developed. Traditional empirical screening approaches of natural and non-natural compounds have identified the majority of antibiotics that are currently available, however this approach has produced relatively few new antibiotics over the last few decades. The vast amount of bacterial genome sequence information that has become available since the sequencing of the first bacterial genome more than 20 years ago holds potential for contributing to the discovery of novel antimicrobial compounds. Comparative genomic approaches can identify genes that are highly conserved within and between bacterial species, and thus may represent genes that participate in key bacterial processes. Whole genome mutagenesis studies can also identify genes necessary for bacterial growth and survival under different environmental conditions, making them attractive targets for the development of novel inhibitory compounds. In addition, transcriptomic and proteomic approaches can be used to characterize RNA and protein levels on a cellular scale, providing information on bacterial physiology that can be applied to antibiotic target identification. Finally, bacterial genomes can be mined to identify biosynthetic pathways that produce many intrinsic antimicrobial compounds and peptides. In this review, we provide an overview of past and current efforts aimed at using bacterial genomic data in the discovery and development of novel antibiotics.

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1. Introduction

Widespread antibiotic resistance poses an important threat to modern medicine. Infections caused by antibiotic resistant strains from multiple bacterial species continue to increase in incidence, and in some cases there are only a few antibiotics with appropriate antimicrobial activity that continue to be effective. Recent reports describing the identification and spread of antibiotic resistance genes that reduce susceptibility to "last resort" antibiotics such as carbapenems and colistin add to concerns that infections that are untreatable with currently available antibiotics may become a reality [1,2]. The United States Centers for Disease Control and Prevention published a "Threat Report" in which it was estimated that more than 2 million individuals acquire antibiotic resistant infections every year in the U.S. alone, resulting in approximately 23,000 deaths [3]. The future global impact of antimicrobial resistance has potential to be devastating, as a government commissioned study in the United Kingdom estimated that by the year 2050, 10 million deaths per year could result from antimicrobial resistance in certain bacterial, viral and parasitic infections if current trends continue [4]. The economic implications of antimicrobial resistance also warrant concern given estimates from the same study indicating that by 2050 the unabated increase in the incidence of resistant infectious and their associated mortality could result in a reduction in the global gross domestic product of between 2% and 3.5% (approximately $100 trillion between 2014 and 2050).

In light of these estimates, it may seem obvious that efforts to develop new antibiotics with novel mechanisms of action should be a priority. However, in spite of the fact that the need for new antibiotics has been outlined by a number of experts [5–7], there has been a dearth of novel molecules approved for clinical use over the last three decades [8,9]. A major factor contributing to the dwindling antibiotic pipeline is the decreasing number of companies within the pharmaceutical sector that continue to pursue the development of novel antimicrobials [10]. While decreased profitability compared to other clinical indications that require longer term therapy is commonly cited as a major contributing factor to a reduction in active antibiotic development programs, there are other factors that likely also play a role in this decline. The antibiotics that have been developed to date using traditional discovery methods that employ high throughput screening of natural compounds may be those molecules that are most readily identified using these methodologies [11]. For example, the screening of natural products synthesized by actinomycetes and different fungal species has been successful in identifying novel antimicrobial compounds. However, the molecules that were previously identified may represent the antimicrobial compounds that are most commonly produced by these microorganisms, and were thus more easily detected using these traditional approaches. Although natural product screening can continue to be optimized to identify less abundant molecules, the yield of these techniques in terms of the number of new compounds that are identified may not return to levels seen during the decades between the 1930s and 1970s, which saw the introduction of multiple new antibiotics with novel mechanisms of action. For these reasons, the chemical modification of previously identified molecules with known targets is increasingly being employed for antibiotic development [12,13]. An obvious limitation of this approach is that only a finite number of modifications can be made to existing compounds. Perhaps more worrisome, however, is the fact that this approach may not result in the development of new compounds with novel mechanisms of action, an issue of critical importance given that resistance to one compound within an antibiotic class often produces cross resistance to other antibiotics within the same class.

The increasing number of bacterial genome sequences, together with techniques that permit global transcriptional and proteomic profiling of bacterial cells under different conditions, may provide information that can be applied to the development of novel antimicrobials. In this review, we provide an overview of how bacterial genomes have been employed in the search for new antibiotics since the first complete bacterial genome sequence was available in 1995 [14], and provide examples from the recent literature that demonstrate current efforts related to antimicrobial development that are being undertaken in order to exploit the massive amount of information that the genomic era has provided.

In this context, a number of recent initiatives aim to facilitate the development of novel antimicrobials and their introduction into the clinic. In 2014 an Executive Order signed by President Obama entitled Combating Antibiotic-Resistant Bacteria aimed to take a comprehensive approach toward preventing the emergence of antimicrobial resistance and developing next generation antibiotics (www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria). This initiative provides 1.2 billion USD to fund a coordinated effort involving multiple government agencies in the fight against antibiotic resistance. Additionally, the Innovative Medicines Initiative's New Drugs for Bad Bugs initiative, which is funded by the European Commission, aims to facilitate the development and evaluation of novel antimicrobials by creating public private partnerships that take advantage of capacities within the public sector to advance products in the pharmaceutical industry's antimicrobial pipeline [15]. In 2016, the CARB-X initiative was launched in order to accelerate development of new antimicrobials in the preclinical stages of development with the goal of advancing them into clinical testing. Over the first five years, the CARB-X initiative aims to promote the advancement of at least 20 new compounds into human trials [16].

2. Target based antibiotic discovery

Traditionally, the identification and development of compounds with antibacterial activity has relied upon the empiric testing of both natural and non-natural compounds with exponentially growing bacterial cells. This approach, together with the development of analogues of compounds showing antibiotic activity through chemical modification, has been the mainstay of the pharmaceutical industry and has produced the majority of antibiotics approved for clinical use. It is worth noting that the screening of compound libraries and the modification of existing antimicrobials continue to be used extensively within the pharmaceutical and biotechnology sectors for the identification of compounds with antibacterial activity [11,13]. Over the last two decades, the availability of genome sequencing techniques and transcriptomic and proteomic approaches that permit the global characterization of bacterial components has raised the possibility that antibiotic discovery can be performed by first identifying high value bacterial targets, and then developing compounds that inhibit these targets. Once bacterial targets with the desired characteristics are identified (discussed below), these targets can be incorporated into *in vitro* biochemical assays that permit high throughput screening of chemical libraries for the identification of inhibitory compounds (Fig. 1). The antibacterial activity of hits identified during high throughput screening can then be characterized using standard assays with bacterial cells. Leads that demonstrate adequate antimicrobial activity can then be further developed in preclinical and clinical studies similarly to molecules identified using traditional discovery methods.

The major advantage of target based antibiotic discovery is that, at least in theory, it facilitates the identification of compounds that