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Novel target sites in bacteria for overcoming antibiotic resistance

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Abstract

Resistance to marketed antibiotics continues to increase. During the last 10 years some 200 bacterial genome sequences have become available, giving rise to expectations that genomics would provide a plethora of novel targets and hence a flood of new therapeutic agents. Contrary to some predictions the genomic effort has yet to yield a substantial number of novel class agents in clinical development. What are the reasons for the differences between expectations and reality? This article reviews what has been achieved in the exploitation of bacterial genomes for the discovery of novel antibacterials.

Keywords: Bacterial genomics; Target validation; Compound libraries; Lead identification; New class antibacterials

Contents

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1. Introduction

Antibacterial discovery and development was unquestionably a success story of the 20th century with a succession of new products coming on stream to meet medical needs. With this success eventually came complacency derived from the belief that the scourge of infectious disease had been overcome: pharmaceutical companies assigned effort to meet medical needs in other therapeutic areas, being particularly attracted to developing therapies for the treatment of chronic conditions. The need for a 'commercially attractive' return on investment has continued the trend towards increasing research and development on chronic conditions as R&D costs spiral upwards due to regulatory requirements in safety, efficacy and manufacturing. As pharmaceutical companies have headed for the exit [1,2], resistance to marketed antibiotics has inexorably risen, giving rise to concerns that the industry would no longer be able to meet future needs for new and effective antibacterial therapies. This concern is supported both by the steady decrease in the number of approved new antibacterial agents since the mid-1980s and also the failure to bring new class agents, with the exceptions of Zyvox™ (linezolid) and Cubicin™ (daptomycin), to the marketplace. Current alarm is such that discourse concerning the breadth and scale of the antibiotic resistance problem is no longer confined to the scientific and medical press. The progressive increase in the frequency of appearance of hospital infections caused by drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), and the increasing diversity of bacteria that display drug-resistance phenotypes, are now problems of such apparent magnitude that they form the subject of diverse non-specialist magazine articles, government pamphlets and television and radio documentaries.

The view that the development of new antibiotics that do not suffer from the current "resistance problem" will depend on the exploitation of novel targets has been espoused over many years, but early efforts were hampered by a lack of targets, exacerbated with what would now be considered to be 'low throughput' screening capabilities, and no knowledge of the 3D structures of protein targets. The availability of bacterial genome sequences in the mid-1990s was heralded as an unprecedented opportunity to provide hundreds, if not thousands, of potential new targets that would lead to new class antibacterials. We describe here the status of the efforts to identify and exploit novel targets for antibacterials, and offer some thoughts on the future potential for productive utilisation of the mass of bacterial pathogen genome data.

2. Selection of novel targets

Attempts at target-directed discovery of new antibacterial agents pre-date the "genomic era" of course [3,4]. Many laboratories interested in the discovery of new antibacterials have instigated programs intended to discover and develop drugs acting via novel mechanisms or against novel targets. Although the large number and the great diversity of such efforts preclude a discussion of pre-clinical phase programs here, we can nonetheless draw attention to three areas of research which could be considered notable due to their comparatively widespread prominence within the pharmaceutical research community. The three areas are inhibitors of fatty acid biosynthesis [5,6], aminoacyl–tRNA synthetases [7] and two-component signal transduction (2CST) systems [8]. Research in all three areas pre-dates the genomics era and inhibitors of enzymes from all three groups have been known for over a decade.

Partial proof of concept exists for two of these groups. Thus, the topical antibiotic Bactroban™ (mupirocin; pseudomonic acid) is a potent inhibitor of isoleucyl–tRNA synthetase and Isoniazid is an inhibitor of the fatty-acid synthase in *Mycobacterium tuberculosis*, thereby finding utility as an anti-tuberculosis drug. Although no inhibitors of any of the remaining aminoacyl–tRNA synthetases (18 in Gram-positive bacteria and 19 in Gram-negative bacteria) have reached the clinic, potent antibacterial inhibitors of methionyl–tRNA synthetase [9] and phenylalanyl–tRNA synthetase [10] have been discovered.

There are no known examples of inhibitors of 2CST systems or of fatty acid biosynthesis in late pre-clinical phase. The evolution of 2CST inhibitors might be considered unlikely, as of the 17 2CST systems in *S. aureus* only the YycF/YycG pair is essential to survival under laboratory conditions [11] and the histidine kinase component of the pair (YycG)