

Nature's clarion call of antibacterial resistance: Are we listening? Ursula Theuretzbacher^{1*} & Jeffrey H Toney²

Addresses

¹Center for Anti-Infective Agents
Eckpergasse 13
1180 Vienna
Austria
Email: utheuretzbacher@cefaia.com

²Montclair State University
Department of Chemistry and Biochemistry
Richardson Hall Room 352
1 Normal Avenue
Montclair
NJ 07043
USA

*To whom correspondence should be addressed

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Antibiotic resistance is recognized as a major problem worldwide in the management of infectious disease, both in hospital settings and in the community. Therefore, there is an urgent need for new antibiotics, particularly those effective against multidrug-resistant bacteria such as *Acinetobacter*, *Pseudomonas*, many *Enterobacteriaceae*, as well as enterococci and staphylococci. There is also a growing need for new agents with activity against resistant community-acquired pathogens. Major pharmaceutical companies have either abandoned or reduced antibiotic research and development in favor of areas such as chronic illness. In general, the anti-infectives pipelines of pharmaceutical companies are more focused on the antiviral market; however, some large pharmaceutical companies have entered into collaborative discovery projects with smaller companies. Although these smaller companies face many additional challenges, several are still pursuing a wide variety of approaches.

Keywords Antibiotics, antibiotic resistance, drug development, efflux, virulence

Introduction

The continuing increase in antimicrobial resistance in hospitals in the US and in other countries remains a

concern (Table 1) [1••]. Although resistance rates may be lower in some European countries (varying by ~ 100-fold), the resistance problem in Europe is most notable in intensive care units [2••]. It is not known whether programs aimed at the prudent use of antibiotics will enable countries with very high endemic levels of resistance to decrease the level in future years. Established resistance is proving difficult to displace; moreover, new resistant isolates continue to emerge and proliferate at new sites. Even with more appropriate antibiotic prescribing, it seems likely that antibacterial resistance will continue to accumulate in many pathogens.

The production of analogs based on fewer than ten antibacterial chemical scaffolds over the past 50 years has resulted in the development and marketing of over 100 antibacterial agents. However, with the exception of the oxazolidinone pharmacophore, no new scaffolds have emerged in the past 30 years to address emerging resistance problems. In 2002, none of the 89 new drugs that appeared on the market were antibacterials. In 2003 and 2004, only two new antibacterial agents were launched [3•].

Current research and development activities

Despite the clear need for new antibiotics, few companies are developing novel antibacterial agents, and those that do face significant barriers to market entry [3•,4•,5]. Complications involved with this process include: (i) the proportion of infections that cannot be treated with present agents is limited, (ii) infections with resistant organisms are widely scattered, such that the design of clinical trials is complicated, (iii) serious infections involving resistant pathogens offer a limited number of patients for clinical trials, and (iv) regulatory agencies require complex clinical trials before they grant marketing approval.

Nevertheless, a number of smaller companies are pursuing novel antibiotic development, mostly relying on in-licensing or acquiring late-stage experimental compounds from large

Table 1. Antibiotic resistance rates in nosocomial infections in intensive care unit patients.

Antimicrobial-resistant pathogen	Resistance rates in 2003 (%)	Percentage increase in resistance rates (2003 versus 1998 to 2002)
Enterococci resistant to vancomycin	28.5	12
Methicillin-resistant <i>Staphylococcus aureus</i>	59.5	11
Methicillin-resistant <i>Staphylococcus epidermidis</i>	89.1	1
<i>Escherichia coli</i> resistant to third-generation cephalosporins or aztreonam	5.8	0
<i>Klebsiella pneumoniae</i> resistant to third-generation cephalosporins or aztreonam	20.6	47
<i>Pseudomonas aeruginosa</i> resistant to imipenem	21.1	15
<i>Pseudomonas aeruginosa</i> resistant to quinolones	29.5	9
<i>Pseudomonas aeruginosa</i> resistant to ceftazidime	31.9	20
<i>Enterobacter</i> spp resistant to third-generation cephalosporins	31.1	6

The figures in this table are pooled mean resistance rates for antimicrobial-resistant pathogens associated with nosocomial infections in hospitals in the US. (Adapted from the National Nosocomial Infections Surveillance System Report, issued October 2004.) [1••].

pharmaceutical companies reluctant to devote the resources necessary for regulatory approval. A diverse choice of targets has been pursued by these small companies, producing several novel classes of agents. Although critical for certain resistance needs, these agents are unlikely to provide a widely usable novel class of antibacterials as many of these small companies lack sufficient funds to support development into early clinical phase. Development efforts are mainly focused on anti-staphylococcal drugs that target a sufficiently large market (Tables 2 and 3) or on anti-pseudomonal drugs that are especially needed in cystic fibrosis (CF) and ventilator-associated pneumonia (VAP).

There are currently more than 400 companies worldwide involved in R&D programs in the anti-infectives field [U Theuretzbacher, unpublished data]. However, many of the

antibiotics in development are analogs of an existing chemical class. Future antibiotic development needs to employ several strategies to be successful, including the modification of existing antibiotic structures [6], the targeting of resistance mechanisms and virulence factors, and the identification of new targets.

Modification of existing antibiotic structures

Modifying existing, empirically used, broad-spectrum antibacterials may establish a temporary way of circumventing resistance. Analogs in almost all of the existing antibiotic classes are under examination, and several are in late-stage clinical development (Table 4). Most of the modified cephalosporins and carbapenems are under development by Asian companies. These include Meiji Seika Kaisha, Astellas Pharma (formerly Yamanouchi Pharmaceutical and Fujisawa Pharmaceuticals), Shionogi &

Table 2. Select new antibiotics and vaccines targeted against multiresistant *Staphylococcus aureus*.

Therapeutic	Company	Description	Stage of development	Reference
Veronate	Inhibitex Inc	Polyclonal immune globulin for prophylactic use	Phase III	[83]
Aurograb	NeuTec Pharma plc	Recombinant antibody fragment that binds to the cell wall through the recognition of the ATP binding cassette transporter GrfA	Phase III	[84]
Tefibazumab	Inhibitex Inc	Humanized monoclonal antibody against protein clumping factor A. Prophylactic and therapeutic uses.	Phase II	[85]
BSYX-A110	MedImmune Inc	Chimeric anti-lipoteichoic acid monoclonal antibody.	Phase II	[86]
<i>Staphylococcus epidermidis</i> vaccine	Nabi Biopharmaceuticals	Non-capsular polysaccharide conjugate vaccine.	Phase I	[87]
StaphA HP (ETI-211)	EluSys Therapeutics Inc	Heteropolymer conjugate of a murine monoclonal antibody recognizing human complement receptor 1 cross-linked to a murine monoclonal antibody against <i>S aureus</i> protein A, that binds and removes <i>S aureus</i> from the bloodstream	Preclinical	[88]
Cy401 CY-403	CytoGenix Inc	Oligodeoxynucleotide (antisense oligonucleotide sequence), bacterial DNA-dependent RNA polymerase.	Preclinical	[89-91]
JuvaVax	Juvaris BioTherapeutics Inc	Vaccine utilizing cationic lipid-antigen-DNA complexes.	Preclinical	[92]

Table 3. Select new and modified compounds targeted against multidrug-resistant Gram-positive cocci.

Compound	Company	Description	Stage of development	Reference
Dalbavancin	Pfizer Inc	Semisynthetic derivative of the natural glycopeptide A-40926	Pre-registration	[93]
Telavancin	Theravance Inc/ Astellas Pharma Inc	Semisynthetic glycopeptide and peptidoglycan inhibitor	Phase III	[94]
Oritavancin	Targanta Therapeutics Inc	Glycopeptide	Phase III	[95]
Ramoplanin	Oscient Pharmaceuticals Corp	Glycolipodepsipeptide antibiotic	Phase II	[96]
RX-01	Rib-X Pharmaceuticals Inc	Ribosomal 50S subunit inhibitor	Phase I	[97]
Friulimicin	Combinature Biopharm AG	Lipopeptide	Preclinical	[98]
ECO-0501	Ecopia BioSciences Inc	Glycosylated polyketide that acts on cell membranes	Preclinical	[99]
Bacterial and fatty acid biosynthesis inhibitors	Affinium Pharmaceuticals Inc	Bacterial enoyl-ACP reductase inhibitors	Preclinical	[100]
Various compounds	SIGA Technologies Inc	Sortase inhibitors, inhibiting anchoring surface protein virulence factors in the peptidoglycan layer	Lead optimization	[101]
ACL-16773	Alchemia Ltd	Transglycosylase inhibitor	Preclinical	[102]
Various compounds	Targanta Therapeutics Inc	RNA polymerase inhibitors	Lead optimization	[103]