Growing threat of Gram-positive resistance – a challenge to the industry

Major efforts are being made in the pharmaceutical industry to develop compounds with activity against the increasing number of Gram-positive aerobic cocci that are resistant to current antimicrobial agents. In the late 1970s and 1980s most antibacterial compounds being progressed were broad-spectrum agents with particularly good activity against Gram-negative bacteria. However, some had only modest activity, relative to earlier compounds, against Gram-positive organisms. The market for agents with specific and high activity against staphylococci, streptococci and enterococci was, at that time, believed to be well supplied and financially less attractive.

Rise in resistance

The past decade has seen an extraordinary change in the situation, with multiresistant cocci becoming increasingly common, and the number of drugs available to treat some of the infections declining rapidly.

Methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. epidermidis* have become commonplace in both large and small hospitals, and institutions can act as a reservoir. These staphylococci frequently are not just resistant to penicillins, but to the majority of β-lactams, macrolides, tetracyclines, fluoroquinolones, aminoglycosides and many other agents. MRSA outbreaks can be extremely difficult and costly to control, requiring stringent infection control measures, isolation of patients and even the closure of wards.

The pneumococcus, like many streptococci, classically was exquisitely sensitive to penicillin. Penicillin tolerance was observed in some strains of *Streptococcus pneumoniae* some decades ago, but the strains usually responded to higher doses of penicillin, were rare and not considered a major problem. The incidence of such strains has now increased worldwide, as has the degree of tolerance to penicillin, with some strains now being fully resistant. This decrease in susceptibility to penicillins has been accompanied by a marked increase in resistance to erythromycin, widely used as a second-line therapy in pneumonia, to fluoroquinolones and to many other antibacterials commonly used in the community. Unlike the staphylococci, these resistant pneumococci are commonest in the community, but are now spreading to the hospital environment.

The third group of cocci that have developed resistance are the enterococci, mostly *E. faecalis* and *E. faecium*. These organisms are unusual in that they are inherently moderately resistant to penicillins as well as to many other agents, but as they are not highly virulent, they were rarely a problem. However, these organisms are opportunists, and as the numbers of severely debilitated and immunocompromised patients has risen, so has the incidence of enterococcal infections. Enterococci have a remarkable ability to develop resistance. One of the few agents to have good activity against them was the glycopeptide vancomycin, but strains have now emerged with resistance even against this antibiotic, the commonest type (Van A) being plasmid-mediated and producing a very high level of resistance.

This report focuses on some agents being progressed with activity against resistant Gram-positive cocci (Table 1), including vancomycin-resistant enterococci (VRE) and reflects information presented at the 36th Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC) in New Orleans in September 1996.

Modified tetracyclines, known as glycylglycines (CL331002, Lederle), have good activity against most Gram-positive cocci, including tetracycline-resistant strains and VRE, possibly showing the best activity of all compounds available at present. However, little new information was available, just two *in vitro* studies, and there have been suggestions that there may be toxicity problems.

Everninomycin is an oligosaccharide natural product being developed by Schering-Plough. It apparently has good

Table 1. Compounds of interest under development

Compound	Class	Company	Development phase
RP59500 Synercid®	streptogramin	Rhône-Poulenc Rorer (RPR)	awaiting registration
U100592 U100766	oxazolidinone	Pharmacia & Upjohn	II
LY333328	glycopeptide	Lilly	preclinical
Everninomycin	oligosaccharide	Schering-Plough	preclinical
CL331002	glycylglycine	Lederle	preclinical
RU64004 RU66647	ketolide	Hoechst Marion Roussel	I/II
Sparfloxacin	fluoroquinolone	Dainippon/RPR	awaiting registration
Trovafloxacin	fluoroquinolone	Pfizer	III/IV
BAY12-803	fluoroquinolone	Bayer	preclinical

activity against VRE, but the compound has been at the preclinical stage for some time and no new information has been released. There have been problems with nephrotoxicity, which are claimed to be resolved.

Oxazolidinones were first disclosed by DuPont some years ago. However, the compounds showed bone marrow toxicity, and since little interest was then shown in narrow-spectrum compounds, they were not progressed. The current compounds (U100592 and U100766; Figure 1) are under development by Pharmacia & Upjohn, and were first announced at ICAAC in 1995. They are just entering Phase II. Their precise mode of action is unclear, although it is known that they inhibit protein synthesis at an early stage. They show no cross reaction with any other antibiotics, and are active against all Gram-positive cocci tested, including macrolide- and vancomycin-resistant strains. However, their minimal inhibitory concentration (MIC) values are only modest. A paper by the company (Dr R.D. Schaadt and coworkers) reported that high doses had been administered to man, but the levels achieved in the plasma were not bactericidal.

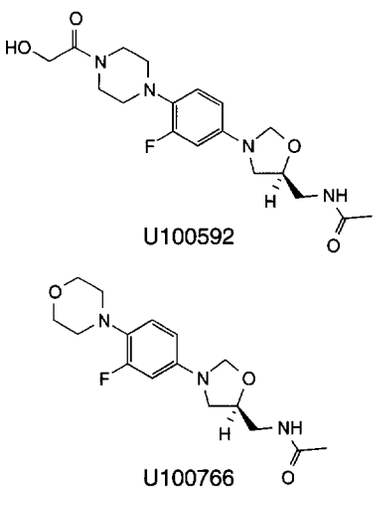

Figure 1. *Oxazalidinone compounds under development by Pharmacia & Upjohn (entering Phase II).*

Ketolides. Hoechst Marion Roussel are progressing 14-membered-ring macrolides termed ketolides that are claimed to be superior to erythromycin against various Gram-positive organisms, including enterococci and penicillin- and erythromycin-resistant pneumococci. Information was presented on two such compounds, RU64004 and RU66647. The compounds have a long serum half-life, and like most macrolides, penetrate lung tissues well. Although they are more active than erythromycin against a number of resistant strains, as they are closely related to other macrolides, some degree of cross-resistance is to be expected, and indeed the MIC values quoted were in some cases rather high (8–16 mg/l).

Glycopeptides. A modified semisynthetic glycopeptide, LY333328, is under development by Eli Lilly, and it appears to have good activity against a number of VRE. The compound is bactericidal against some strains, but not against all. There is, however, a major problem in interpreting some of the data, because the compound is markedly affected by the composition of the medium, whereas vancomycin is not. Undoubtedly the compound has promising activity, but not surprisingly, there is some cross-resistance with vancomycin. Some studies showed that Van A-resistant strains were less sensitive to LY333328 than vancomycin-sensitive strains. Much will depend on the safety profile and bioavailability of this promising agent.

Streptogramins. A synergistic combination of two semisynthetic streptogramins, quinuprisitin and dalfopristin in a 30/70 ratio (RP59500, Synercid®, Rhône-Poulenc Rorer) is awaiting approval. This is an injectable preparation; an oral preparation, RP106972, a synergistic mixture of two other streptogramins, is at an earlier stage. The compounds are inhibitors of protein synthesis, binding to the 50S subunit of the ribosome, and are rapidly bactericidal against most strains of cocci. The major asset of these streptogramins is their good activity against vancomycin-resistant *E. faecium*, perhaps the most difficult species to inhibit. Good activity is also seen against pneumococci and staphylococci, including many multi-resistant strains. Activity against *S. faecalis* is poorer. Synercid® is licensed for emergency use in severe infections unresponsive to other agents, and although, as with all drugs, some severely ill neutropenic patients may respond poorly, clinical studies have shown that Synercid® can give success rates of about 70% in many difficult cases.

Fluoroquinolones, although not targeted specifically at Gram-positive organisms have, with the latest compounds, found a new role, because their activity against these organisms is greatly improved relative to the earlier compounds such as ciprofloxacin. Several of these new compounds are being promoted for use in respiratory tract infections. Sparfloxacin is the first of the fluoroquinolones with good activity against most Gram-positives and includes in its spectrum many ciprofloxacin- and multi-resistant staphylococci and pneumococci. Activity against enterococci is moderately good with MIC values of approximately 0.5–1.0 mg/l. The compound is already marketed in Japan by Dainippon and is also licensed to Rhône-Poulenc Rorer who, in spite of some problems over the phototoxic potential of the compound, anticipate approval in the USA and Europe soon. Clinical studies indicate its value for respiratory tract infections, but as it is only available as an oral product, its use in hospital infections will be limited.

Trovafloxacin. There has been considerable interest in the new Pfizer fluoroquinolone trovafloxacin, which is seen as a rival to sparfloxacin in this lucrative market. The compound is slightly more active than sparfloxacin against staphylococci and pneumococci, has similar activity against enterococci, and is claimed to have a low potential for phototoxicity. However, although there were many presentations about this compound at ICAAC, and it is believed to be in late Phase III, only one clinical study was presented.

New fluoroquinolone. The first presentations were made at this meeting of a new fluoroquinolone from Bayer, BAY12-803, with activity very close to that of trovafloxacin. Pharmacokinetic data in human subjects for doses up to 400 mg were presented, and animal studies suggested a negligible potential for phototoxicity. This compound is still at an early stage, but could be a strong rival for trovafloxacin. The keen interest in this field was illustrated by the other presentations describing fluoroquinolones still at preclinical stages from Toyama, Wakanaya, Hokuriki Seiyaki and Cheil Jedang.

Intractable problem

A common theme at the conference was the ability, sooner or later, of the microbe to develop resistance to any agent, even those that are structurally unrelated to existing antibiotics. This is particularly marked with the enterococcus, one of the most difficult groups to inhibit. A number of speakers believed that the way forward was not a total reliance on the pharmaceutical industry, but the careful and more controlled use of both existing and new agents, perhaps in rotation and in combination, together with stringent infection-control methods. Undoubtedbly, the problem of resistance to antimicrobials in Gram-positives is not going to be solved easily or permanently.

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Book review

Ethical Issues in Drug Research: Through a Glass Darkly by M. J. Parnham, IOS Press, 1996. £48.00 (x + 155 pages)
ISBN 90 5199 279 3

The past decade or so has seen a dramatic increase in the number of books on applied ethics. Writing in this field is not easy. A moral philosopher may know little of the specific topic in hand; a specialist in the particular field may know little ethics; a multi-author volume may be turgid and dull. Nevertheless, the genre is by now well enough established for there to be an increasing number of excellent books on such subjects as environmental ethics, medical ethics, our use of animals and genetic engineering.

The time is therefore ripe for a first-rate book on ethical issues in drug research. I am afraid, though, that this is not it. In fairness, this is, in many ways, a well written book. It covers a tremendous amount and parts of it I enjoyed reading considerably. I think I would enjoy sitting next to Parnham at a dinner party.

The chief problem is simply that the author is not expert in ethics. The days have gone when anyone, however well meaning, can write a book on ethics without a serious academic grounding in the subject. For example, Parnham's attempt to summarize Singer's views on animal experiments and his critique of Singer are wholly inadequate.

A second problem is Parnham's avowal of Christianity. As a Church of England minister I am more likely, it might be supposed, than many to be convinced of the acceptability of such a position. However, in a multicultural society a book on ethics that presupposes a particular religious viewpoint needs, at the very least, some sort of substantive analysis of how its own assumptions relate to those held by humanists and adherents of other religions; unfortunately, we do not get this. Also, there are places where the writing could be considered offensive or even construed as racist.

Parnham's book certainly stimulates thought and I would be happy to recommend it as a retirement present for someone who had worked all his or her life in drug discovery.

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In short...

In December **Aurora Biosciences** and **Bristol-Myers Squibb** (BMS) announced a research and licensing agreement that could be worth over $40 million. The deal gives BMS rights to use Aurora's fluorescent screening technology and also sets the terms for a collaboration on the development of Aurora's ultra-high-throughput screening (ultra-HTS) system. This miniaturized, automated system is targeted to screen 100,000 samples per day using proprietary fluorescence-based screens. Aurora is hoping to find two or three additional collaborators, who will get co-exclusive access to the ultra-HTS system.