parameters is essential for the prediction of *in vivo* parameters. Although the effect of CYP allosterism on the IVIVC and pharmacokinetic DDI is not fully understood, CYP allosterism has been frequently observed in the screening of new chemical entities for inhibitory activity against CYPs. Substrate- and effector-dependent CYP inhibition have been found to exhibit the kinetic discrepancies that have hampered the understanding and interpretation of the data and the decision-making process at later stages in the drug development process [7]. Because multiple binding sites that have allosteric characteristics exist, the K_m and V_{max} values for a particular substrate can be changed by the presence of another substrate (or effector). The magnitude of the change is dependent on the concentration of the substrate that serves as an allosteric ligand. Thus, multiple, variable kinetic parameters could considerably complicate the prediction of the IVIVC.

As a result, a quantitative relationship between the substrate concentration (i.e. substrate and/or effector) and the kinetic parameters (K_m and V_{max}) should be characterized. Such knowledge could enable the accurate prediction of pharmacokinetics and DDI from the targeted drug concentration. Most importantly, to avoid severe clinical DDI, the influence of CYP allosterism on pharmacokinetics must be considered with reference to those factors that are known to alter CYP pharmacokinetics, including compounds that induce CYP expression and inhibit CYP activity.

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Fighting superbugs with superdrugs

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The annual *Superbugs and Superdrugs: A Focus on Antibacterials* conference, held on 1–2 March 2004, London, UK, gave an insight into what is happening in the global fight against drug-resistant bacteria. Various topics from the antibacterial drug discovery and development field were covered by leading specialists, including the strategies employed to identify novel targets and the regulatory incentives offered to spur the development of antibacterial agents.

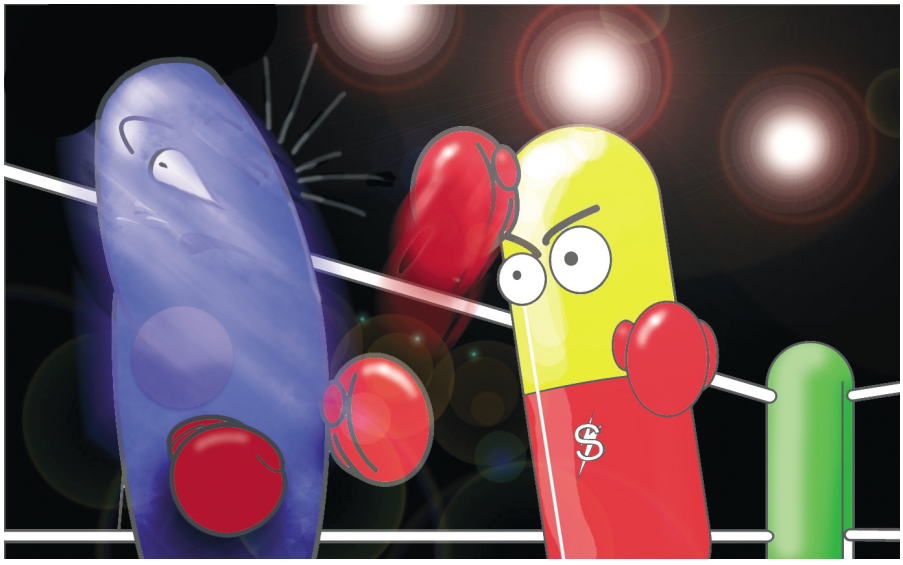
It initially appears to be all doom and gloom in the fight against superbugs. The prevalence of superbugs, such as vancomycin-resistant *Staphylococcus aureus* (VRSA) and methicillin-resistant *Staphylococcus aureus* (MRSA), is increasing at a rapid rate both in the hospital sector and in the community. Recent surveys revealed that resistance rates were higher in bacterial isolates derived from in-patients when compared with those from out-patients or from general practice [1]. Furthermore, the increase in multiple antibiotic resistance appears to be linked to hospital cross-infection. In England and Wales, MRSA is now responsible for the majority of cases of adult bacteraemia. In 1990, only 0.9% of adult bacteraemia cases were recorded with MRSA as the causative agent, but this percentage had risen to 13.0% by 2000 [2]. Despite the media interest in these superbugs, the pharmaceutical industry appears to show little interest in including antibacterials in their research portfolio. So, what can be done to curb the growth of these deadly superbugs?

Promoting antibacterial development and education

The US FDA (http://www.fda.gov) has recognized the importance of

producing novel antibiotics and has endeavoured to provide new regulatory incentives to encourage antibacterial development within the pharmaceutical industry. Janice Soreth, from the FDA, explained in detail the key regulatory steps that are involved in the approval of new molecular entities (NMEs). The number of NMEs approved each year peaked in the mid-1990s but, since then, the numbers approved have dramatically decreased (for figures, see: http://www.fda.gov/cder/rdmt/default.htm). To improve this record, the FDA has introduced a fast-track designation programme, which aims to approve specific NMEs for fast-track development within a period of 60 days. To be considered for fast-track development, Soreth explained, the NME itself must be 'intended to treat serious or life-threatening conditions and demonstrate the potential to address unmet medical needs (fast-track products), so that the fast-track product can reach the market as soon as possible'. Soreth also stressed the importance of providing high-quality data when submitting applications to the FDA and the use of relevant pre-clinical information, all of which can help to streamline the approval process and accelerate the assessment of safety and efficacy data of new antibacterial agents. At the conclusion of the presentation, Soreth revealed that the FDA has recently set up a series of workshops and advisory committee meetings to examine the best approaches to clinical trial design in infectious diseases. As an example, if a much-needed new antibiotic was being tested, the FDA might consider a reduced number of participants undergoing a clinical trial programme.

From a different perspective, John Barrett (Merck, USA; http://www.merck.com) explained the process of drug resistance, as well as why the past decades have not seen much progress in the discovery of new antibacterial agents. Bacteria can develop resistance to a particular drug by two different methods: (i) the exogenous pathway; and (ii) the endogenous pathway. The exogenous resistance pathway involves the incorporation of exogenous genetic material by bacteria exposed to antibiotic-producing organisms, for example, or commensal organisms that are carrying a resistance element; this type of resistance is transferred horizontally. In the endogenous route, mutations in a target bacterium result in the development of drug-resistance; this type of resistance is inherited vertically. For example, a mutation could result in the overproduction of the antibiotic target to levels that are greater than the concentration of the antibiotic, thus enabling the bacterium to 'soak up' the antibiotic and maintain the function of the antibiotic target. Barrett indicated that it is important to consider these resistance mechanisms when looking for antibacterial targets. Barrett went on to suggest that the only way to stay ahead of the emergence of resistant bacteria is to produce different drugs with a novel mechanism of action or to use antiresistance approaches.



Laura Harris (DataMonitor; http://www.datamonitor.co.uk) gave an overview of the anti-infective field from a business perspective and discussed the different companies that are involved in the anti-infective market. Harris described the latest strategy to be adopted by some of the pharmaceutical companies – public–private partnerships (PPP) [3]. There have been several partnerships formed between academic institutes and pharmaceutical companies, for example, GSK and Action TB (http://www.gsk.com/community/tbprogrammes.htm), which is an international research programme with the aim of discovering new antituberculosis targets and potential vaccine candidates. In addition, a collaboration between Tokama Chemical Company (http://www.toyama-chemical.co.jp/eng) and BMS (http://www.bms.com) has resulted in the development of T3811, a quinolone synthetic antibacterial agent. The main advantage of these partnerships is that they provide opportunities for smaller companies and enable larger companies to maintain anti-infective research in their portfolios.

Harris also suggested that education could help to slow down the development of drug-resistance and stated that it is important to educate

physicians in a consistent manner, worldwide. The attitude towards prescribing antibacterial drugs varies between physicians from the USA and those from Europe – US physicians are more likely to prescribe a more-expensive drug to treat a multidrug-resistant pathogen compared with European physicians. Hospital physicians are apparently reluctant to prescribe new drugs, even in the face of increasing drug resistance, and community physicians tend to stay loyal to two or three products that they are familiar with. Together, these factors and behaviours make it difficult for new drugs to break onto the market, particularly when there are so many generic drugs available.

Novel targets and strategies

Many antibiotics that are currently in use, such as tetracycline and chloromycetin, inhibit the ribosome. For example, tetracycline inhibits the binding of transfer RNA to the ribosome, thus preventing protein synthesis. Chloromycetin, a synthetic antibiotic, has a similar mode of action to tetracycline – chloromycetin inhibits protein synthesis by binding to the ribosome and interfering with the formation of peptide bonds between amino acids. Joyce Sutcliffe (Rib-X Pharmaceuticals; http://www.rib-x.com) posed the question – why not study the structure of bacterial ribosome further in the search for a novel antibacterial? Rib-X has been using the 50S subunit of the *Haloarcula marismortui* ribosome as the starting point for a structure-based drug design approach to antibacterials. Analysis of this ribosome has highlighted structural details that are specific to pathogenic bacteria and the sequence of the 16S rRNA subunit indicated that the ribosome of *H. marismortui* is derived from a eubacterial species. The hybrid nature of the *H. marismortui* ribosome will be valuable in understanding antibiotic selectivity, commented Sutcliffe.

Richard Bott (Genencor International; http://www.genencor.com) embraced a different approach in the fight against bacteria: to stop bacterial infection before it starts. Bott's approach is based on the exploitation of bacterial adhesins as therapeutic targets. Adhesins, which are small-molecule ligands that are found on the surface of bacteria, bind to specific receptors on the host cell surface during host cell attachment. The binding interactions between specific adhesins and host cell receptors are crucial for the initiation of infection. Some of these adhesins have been characterized, for example, the Le-binding adhesin in *Helicobacter pylori* (associated with gastric ulcers and stomach cancer) binds to fucosylated Lewis blood group antigens. Bott explained that adhesins also have a role in the aggregation of one or more bacterial species to produce a biofilm and cited dental plaque as an example. *Actinomyces naeslundii*, which is one of the bacterial species found in biofilms of dental plaque, binds to *Streptomyces oralis* via Type II pilus adhesin-binding galactose. Genencor has been generating ligand-targeted proteases (LTPs) against bacterial adhesins that can inhibit the host cell attachment process. In the case of dental plaque, the LTP S1562b prevented aggregation between *A. naeslundii* and *S. oralis in vitro*. LTPs have the advantage of specificity that is conferred by the ligand itself and therefore resistance is less likely to develop.

There is a desperate need for therapeutics against the increasing prevalence of Gram-positive bacterial infections argued Barry Eisenstein (Cubist; http://www.cubist.com). Eisenstein was proud to announce that daptomycin [Cubicin™ (Cubist Pharmaceuticals; http://www.cubist.com)], the first antibacterial of its class with a novel mechanism of action, is undergoing Phase III clinical trials for endocarditis and bacteraemia, and Phase IV clinical trials for various indications including post-operative surgical wounds and osteomyelitis. Daptomycin, which is a lipopeptide, binds specifically to the cell membranes of bacteria (but not those of mammalian cells) and acts by disrupting the ion-concentration gradient. The distinct bactericidal property of daptomycin lies in its ability to induce cell death without cell lysis occurring, hence there are no inflammatory reactions associated with the administration of this drug. Daptomycin has a promising safety profile and repeated-dose toxicity experiments in animals demonstrated that the adverse side-effect (degeneration of muscles) was reversible and was related to dosing frequency. In clinical trials, the efficacy of daptomycin was comparable to that of vancomycin (among others). In addition, daptomycin has the benefit of targeting a wide range of Gram-positive bacteria: it is effective against *S. aureus* and MRSA.

The case for dual-targeting drugs

Gyrase B-directed drugs were the topic of two presentations. Jeffrey Stein (Quorex; http://ww.quorex.com) commented that there are several novel and validated targets available that provide numerous opportunities for new 'drug franchises'. One of these is to inhibit components of bacterial DNA replication and repair – DNA gyrase and topoisomerases – in a manner such that fluoroquinolone-resistant bacteria can also be targeted. Type II topoisomerase is well conserved across different species of bacteria and, importantly, there are key sequence differences between bacterial and human topoisomerases. By targeting two distinct components of the bacterial DNA replication pathway, there should be less potential for resistance to occur. Quorex's initial development lead QX52525 was found to be effective

against bacterial sepsis by oral dosing in mouse models of *Staphylococcus* and did not show any toxicity complications following a five-day dose tolerance study in rats. The second gyrase B presentation, given by Paul Charifson (Vertex; http://www.vertex.com), looked at using an enzyme-based HTS method to isolate gyrase B from various bacterial species. Rapid optimization of enzyme inhibition was then translated into potent antibacterial activity. Interestingly, Vertex's studies showed that gyrase inhibitors have different primary and secondary target preferences. Charifson explained that when VRT676327, which is effective against various bacterial species, was used to treat *S. aureus* infections, the compound first targeted gyrase B and then Par E, but this preference was reversed in *Streptococci pneumoniae* and only a single target, gyrase B, was observed in *Haemophilus influenza*.

Superbug versus superdrug

In conclusion, there is a flicker of hope that the goal of controlling the development of and spread of superbugs can be reached. It is clear that there are numerous issues that must be addressed to successfully tackle the superbug problem, including searching for novel therapeutic agents that have a different mechanism of action to the antibacterials currently available or, better still, producing a superdrug that has more than one target. The significance of educating physicians and patients on the appropriate prescription of drugs and drug compliance, respectively, was also highlighted and, in the case of hospital-acquired infections, general hygiene management. Maybe then, with a collective effort, it will not be too long before the superdrug can defeat the superbug.

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