(NCEs) at $350 million (total costs, including attrition of leads) per drug by 2005, but this will provide a TSR of less than 10%. Using R&D costs of $500 million per drug, only 26 NCEs could be launched and the TSR approaches zero. According to Arlington these estimates may be 'soft', as some experts now put R&D costs for drug development as high as $660 million. He concludes that the industry must transform itself in less time than it currently takes to develop a single new product by:

- Focusing – companies must understand very clearly what their business is and where it needs to be in 2005.
- Technology – innovations in technology must be used to reduce the costs in drug development and improve the quality of new products.
- Information technology – companies must use advances in informatics and knowledge management to harness the vastly expanding quantity of information generated in R&D and emerging in the public domain.
- Organization and team structure – companies must reinvent themselves as a new type of organization that facilitates the development and retention of new skills and enables people to work seamlessly and effectively across organizational and geographical boundaries.

Clearly, many new challenges face the industry and there is now realization that changes are coming very fast. The way forward lies in simpler, cheaper, streamlined drug development relying on the best use of informatics and knowledge management. As time passes, several of the traditional drug development steps can be expected to be performed *in silico*, with greater than ever reliance on research partners and the contract sector. Drugs will be more focused and patient groups smaller. Patient power will grow and the industry will have to respond through an increased focus on value with appropriate pricing, and middlemen (pharmacists and doctors) will feel the pressure. Competitive advantage will go to the smartest and fastest adapters.

The writing is on the wall for those companies that fail to adapt quickly enough to the pressures of cost containment, competition and technology.

The next Pharma Directions conference is to be held on 5–7 June 2000 in Cannes, France. For more information, contact Tracy Moring, ECPI conferences, tel: +44 171 242 1548, fax: +44 171 242 1508, e-mail: tracym@aic-uk.com

REFERENCE

1 Fenwick, S. (1999) *Drug Discovery Today* 4, 3

David Hughes

Researchers reveal ways to defeat 'superbugs'

For many years, the focus of antimicrobial development has shifted away from bacterial to viral pathogens. In addition, new antibiotics released onto the market were usually seen as 'me too' variations of existing therapies. With the advent of numerous resistant 'superbugs', such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP), an alarm has started to resound. Physicians have been faced with an ever-growing list of resistant bacteria threatening the lives of their critically ill patients as many time-honored drugs are not working against new, constantly mutating bacterial strains.

Fortunately, the pharmaceutical and biotechnology industries have risen to the challenge. With an array of new antimicrobial drugs, as well as new methods of preventing the development of bacterial infection with superpathogens, these superbugs are not now quite the 'doomsday' threat they were in the early 1990s.

With these issues in the forefront, a distinguished group of industry researchers gathered in London on 13–14 April 1999, for the conference, *Superbugs and superdrugs: innovations in anti-infectives*. The purpose of the meeting was to examine the latest advances in the treatment of life-threatening bacterial infections, as well as to present new methods of identifying and developing new antimicrobials. Chief among the presentations were those focusing on new therapies for pathogens resistant to multiple antibiotics, with an emphasis on resistant gram-positive organisms (Table 1).

George Miller (Microcide, Mountain View, CA, USA) outlined the company's strategic approach to targeting antibiotics and genomics. Microcide's targeted antibiotic program includes MC02479/RWJ54428, a cephalosporin antibiotic that is active against VRE and MRSA but not against ampicillin-resistant *Enterococcus faecium*. This product has been produced in partnership with Johnson & Johnson (Raritan, NJ, USA) and is in late-stage pre-clinical development, with clinical studies planned for later in the year.

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Table 1. New antimicrobials in the pipeline

Company	Product	Class	Major antibacterial activity
Parenteral antibiotics			
Cubist	Daptomycin	Lipopeptide	VRE, MRSA, PRSP, GISA
GlaxoWellcome	Sanfetrinem	Trinem	*S. aureus, M. catarhalis, H. influenzae*
GlaxoWellcome	GV143253	Trinem	MRSA, PRSP
GlaxoWellcome	Grepafloxacin	Quinolone	*S. pneumoniae*, *S. aureus*, other respiratory bacteria
Hoechst Marion Roussel	HMR3647	Ketolide	PRSP, erythromycin-resistant streptococci
Microcide	MC02479	Cephalosporin	VRE, MRSA, GISA
Pharmacia & Upjohn	Linezolid	Oxazolidinone	VRE, MRSA, PRSP
Rhône-Poulenc Rorer	Synercid	Streptogramin	MRSA, PRSP, vancomycin-resistant *E. faecium*
Topical polypeptides			
AMBI	NISIN	Peptide	*C. difficile*
BioSearch Italia	Ramoplanin	Depsipeptide	*S. aureus*, VRE
IntraBiotics	Protegrin IB367	Protegrin	Gram-positive and gram-negative bacteria, yeasts
Peptide Therapeutics	PT15096	Protease inhibitor	*P. gingivalis*
Peptide Therapeutics	PT15103	Non-peptidic inhibitor	*P. gingivalis*
Parenteral polypeptides			
AMBI	Lysostaphin	Bacterial protein	Specific for *S. aureus*
XOMA	Neuprex	Protein fragment derived from human neutrophils	Gram-negative bacilli, adjunctive therapy for gram-positive species

Abbreviations: *C. difficile, Clostridium difficile*; *E. faecium, Enterococcus faecium*; GISA, glycopeptide immediately-resistant *Staphylococcus aureus*; *H. influenzae, Haemophilus influenzae*; MRSA, methicillin-resistant *Staphylococcus aureus*; *M. catarhalis, Moraxella catarhalis*, PRSP, Penicillin-resistant *Streptococcus pneumoniae*; *P. gingivalis, Porphyromonas gingivalis*; *S. aureas, Staphylococcus aureus*; *S. pneumoniae, Streptococcus pneumoniae*; VRE, vancomycin-resistant entercoccus.

Microcide is also pursuing a targeted genomics program that includes finding methods of attacking bacterial and fungal essential genes, the bacterial gene program being carried out in partnership with Pfizer Inc. (Groton, CT, USA). Earlier in the session, Jeffrey Edwards (AstraZeneca Pharmaceuticals, Macclesfield, UK) gave an overview of beta-lactam antibiotics and details of meropenem, a carbapenem drug developed by AstraZeneca. Edwards reviewed modern antimicrobial drug development, specifically the utilization of *Escherichia coli* and *Saccharomyces cerevisiae* genomes, which has allowed the identification of numerous genes as potential drug targets. He also discussed the role of microbial proteomics in qualifying protein targets and reviewed methods for studying post-translational protein modifications, identifying disease-associated proteins, elucidation of protein function and protein cellular location and protein–protein interactions.

Michael Marriott (GlaxoWellcome, Middlesex, UK), presented the company's new line of antibiotics, including the trinems and a new quinolone, grepafloxacin. Clinical trials of the trinem antibiotic, sanfetrinem, have been conducted for acute exacerbations of chronic bronchitis and acute otitis media, with results superior to those reported for the comparator agent, augmentin (amoxicillin with clavulanate potassium). Other trinems are also being developed by GlaxoWellcome that have activity against MRSA. Marriott also discussed the company's broad-spectrum quinolone antibiotic, grepafloxacin, which has been clinically evaluated in more than 10,000 patients with upper and lower respiratory tract infections, with efficacy comparable to that of clarithromycin and amoxicillin.

New antibiotics that target VRE and MRSA

Information on the daptomycin development program at Cubist Pharmaceuticals (Cambridge, MA, USA) was presented by Frank Tally. Daptomycin is a natural-product antibiotic of the lipopeptide class with rapid bactericidal activity against most clinically relevant gram-positive pathogens, including MRSA, VRE, PRSP and glycopeptide intermediately susceptible *S. aureus* (GISA), and obtained a worldwide licence to develop, manufacture and sell the drug in November 1997. Previous phase II studies conducted by Eli Lilly and Company (Indianapolis, IN, USA) exhibited comparable efficacy of daptomycin to conventional therapies, such as vancomycin and oxacillin, for skin and soft-tissue infections and bacteremia (bloodstream infections) and a favorable safety profile for daptomycin. At doses higher than those planned for Cubist's phase III trials, two subjects experienced mild, reversible adverse effects on skeletal muscle, with no reports of cardiac or smooth muscle abnormalities. Results of Cubist's non-clinical investigations suggest that once-a-day administration of daptomycin might be more effective than a 12-hour dosing regimen and might decrease the potential for skeletal muscle abnormalities.

Cubist's daptomycin US Food and Drug Administration (FDA) investigational

new drug application was accepted in January 1999 and the FDA stated it qualified for fast-track review. Phase III clinical trials for the treatment of complicated skin and soft tissue infections and an open-labeled phase II dose evaluation for the treatment of bacteremia began patient enrolment in March 1999, and data from the bacteremia trial should be available at the end of the year. A new drug application is planned for around the year 2001.

Ivan Brumpt (Rhône-Poulenc Rorer, Collegeville, PA, USA) presented data on the antibacterial activity of Synercid®. This agent is a combination of two streptogramin antibiotics, quinopristan and dalfopristin. Although each component is bacteriostatic, the combination of the two compounds is bactericidal. Synercid is active against MRSA, PRSP and vancomycin-resistant *E. faecium* but not against *E. faecalis*. The compound has been extensively evaluated for the treatment of community-acquired pneumonia, complicated skin and skin-structure infections, nosocomial pneumonia and in an emergency-use program for critically ill hospital patients. Clinical efficacy was equal to the comparator agents in community-acquired pneumonia and complicated skin and skin-structure infections, but Synercid was effective against 82% of infections caused by MRSA and 65.5% of those caused by vancomycin-resistant *E. faecium* in compassionate (patients enrolled at hospitals outside the specific protocol because no other therapies are available) uncontrolled studies. However, the incidence of peripheral venous irritability was high and led to discontinuation of the drug in approximately 11% of the patients. Synercid is now awaiting marketing approval in the USA and Europe.

Linezolid (Pharmacia & Upjohn, Bridgewater, NJ, USA), a new potent oxazolidinone antibiotic, is the first agent in its class to be developed for the treatment of gram-positive bacterial infections. This compound inhibits protein synthesis by a novel mechanism: it attacks the functional initiation complex at the A site of the 50S ribosomal subunit, is bacteriostatic, and can be administered orally or intravenously. Dean Shinabarger (Pharmacia & Upjohn) presented uncontrolled phase II clinical trial data for Linezolid for community-acquired pneumonia and skin and soft-tissue infections, with favorable results. Phase III controlled comparative trials are also currently being conducted for this compound against community-acquired pneumonia, nosocomial pneumonia, skin and soft-tissue infections and bacteremia and a new drug application submission is planned for this year.

Francesco Parenti from BioSearch Italia (Gerenzano, Italy) outlined his company's procedures for identifying potentially valuable antibiotics present in natural substances. The company's lead compound, ramoplanin, is a cyclic depsipeptide for topical administration. The product has been licensed to the US company IntraBiotics Pharmaceuticals Inc. (Mountain View, CA, USA), who are developing a nasal ointment formulation to eliminate nasal carriage of *S. aureus* and an oral formulation for the elimination of VRE carriage in the gastrointestinal tract. An intravenous formulation of ramoplanin is in pre-clinical development. BioSearch has also licensed a glycopeptide analogue of teicoplanin, BI397, to Versicor Inc. (Fremont, CA, USA) for clinical development for the treatment of gram-positive infections.

The history of macrolides and ketolides was discussed by Andre Bryskier from Hoechst Marion Roussel (Paris, France), who then focused on one of their development candidates, HMR3647. This compound has demonstrated excellent activity against PRSP and erythromycin-resistant streptococci but only poor activity against MRSA and VRE. The drug is being developed as a once-a-day therapy for respiratory tract infections and is currently in Phase III clinical trials.

A vaccine is currently under development at MedImmune (Gaithersburg, MD, USA) to prevent uropathic *E. coli* infections, which account for 80–85% of urinary tract infections. The pathogenesis of these infections is mediated via type 1 pili that facilitate attachment of *E. coli* to mucosal cells in the urinary bladder. Scott Koenig (MedImmune) presented data on the development of a specific anti-adhesion vaccine that prevents binding of *E. coli* to human bladder cells and has been shown to protect against cystitis in animals. Pre-clinical development of the vaccine is expected to be completed later this year, with Phase I trials planned for the end of the year.

David Sahm (MRL Diagnostics, Cypress, CA, USA) presented information on an extensive microbial database, 'The Surveillance Network' (TSN), which contains antimicrobial susceptibility data on clinical bacterial isolates from 191 hospitals in the US and 21 million test results from 1.5 million microbial isolates. TSN is being expanded to include Canada, Australia, Europe and Asia.

Protease inhibitor-antimicrobial peptides

The second day of the conference featured more new products under development (Table 2), as well as a discussion of regulatory changes in the European community.

Paul Wallace of Peptide Therapeutics plc (Cambridge, UK) presented data on bacterial protease inhibitors. The company has targeted gingiplanin, a protease from *Porphyromonas gingivalis*, which has been implicated in periodontal disease. Peptide Therapeutics is employing a peptide library to map this protease as well as 21 others. So far, two inhibitors of gingiplanin have been identified: PT15096, a peptidic inhibitor, and PT15103, a non-peptidic inhibitor.

Protegrins are naturally occurring antimicrobial peptides isolated from porcine neutrophils. John Fiddes from IntraBiotics Pharmaceuticals (Mountain

Table 2. Platform technologies for discovering anti-infectives

Company	Technology
GPC	Pathogen DNA database
GTC	Pathogen DNA database, proteomics and gene chips
MedImmune	Vaccine for uropathic *Escherichia coli*
Microcide	Targeted genomics
Peptide Therapeutics	Bacterial protease inhibitors
RiboGene	Translation factors

View, CA, USA) discussed his company's development of protegrin IB367, a synthetic protegrin analogue containing 17 amino acids with a broad spectrum of activity against gram-positive and gram-negative bacteria and yeasts. The protegrins are limited to topical use because of systemic toxicity and are not absorbed by topical or oral application. Protegrin IB367 is being developed both as a topical treatment for oral mucositis in cancer patients and as an aerosol formulation for the treatment of respiratory infections in cystic fibrosis patients. Phase I oral mucositis trials have shown the drug to be safe and to decrease counts of oral bacteria. This drug, however, requires six times-a-day dosing. A double-blind, placebo-controlled Phase II trial is currently in progress and results should be available sometime this year. Meanwhile, an aerosol formulation has already been shown to be safe in Phase I studies in cystic fibrosis patients.

Jon de la Harpe (AMBI Inc., Tarrytown, NY, USA) spoke on peptide antimicrobials for multidrug-resistant bacteria. NISIN, a 35 amino acid-bacterial peptide used as a food preservative, has now been formulated for the treatment of colitis caused by *Clostridium difficile*. Another bacterial protein, lysostaphin, has been shown to be effective in a rabbit model of *S. aureus* endocarditis. However, the emergence of resistant strains, could limit the use of lysostaphin to adjunctive therapy.

One approach to the problem of bacterial resistance was outlined by Patrick Scannon (XOMA, Berkeley, CA, USA). The company's lead product, Neuprex™ (BPI_{21}), is a 193 amino acid-protein fragment derived from a bactericidal glycoprotein from human neutrophils. This drug is active against gram-negative bacilli and augments the antibacterial activity of several antibiotics, including vancomycin, against gram-positive species. Clinical studies are under way to evaluate Neuprex for adjunctive therapy in gram-positive infections with a Phase III study examining its effects against the gram-negative bacteria, pediatric meningococcemia.

In closing the conference, Mair Powell of the Medicines Control Agency (London, UK) reviewed regulatory changes in Europe as they relate to the development of antibiotics for emerging resistant pathogens. New regulations include the listing of resistance rates in drug labeling, with the requirement that companies update their resistance data every five years.

The consensus at the conference was that the industry understands the challenge posed by emerging superpathogens and has developed some promising drugs. Although this is certainly no time for complacency, it is clear that intensive research and development, combined with the latest technologies, can succeed in finding ways to defeat a host of highly resourceful and constantly evolving microbial adversaries.

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Combinatorial chemistry and HTS – feeding a voracious process

Referring to the spectacular speed with which combinatorial chemistry has become accepted as routine, Richard Houghten, President of the Torrey Pines Institute for Molecular Studies (La Jolla, CA, USA) and one of the pioneers in the field, is reported as saying, 'Whereas ten years ago a good medicinal chemist might make 50 to 100 compounds a year, that same chemist is probably expected to make in the thousands or tens of thousands today.' (*Chemical & Engineering News*, 6 April 1998). This serves to demonstrate the power of combinatorial chemistry and associated high-throughput screening (HTS) techniques. These technologies offer the potential to significantly accelerate the drug discovery process and have been embraced by the pharmaceutical industry and the biotechnology companies alike, where there is constant pressure to reduce the time and costs involved in getting a new drug onto the market.

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