



Symposium 7.1

New Beta-Lactam Antibiotics

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Beta-lactam antibiotics are considered to be some of the safest and most reliably efficacious antimicrobial agents that are in clinical practice. Although the introduction of penicillin as a therapeutic option occurred over sixty years ago, new beta-lactams with expanded properties are still being investigated in early and late stage clinical development.

New beta-lactam-containing agents include those antibiotics with in vitro antibiotic activity against methicillin-resistant *Staphylococcus aureus*. These agents were frequently selected from Drug Discovery programs based on their tight binding to the *mecA* gene product in *S. aureus*, penicillin-binding protein (PBP)2a, or PBP 2'. MICs against MRSA strains tend to be in the range of 1-4 µg/ml for most of these agents. Compounds in this class include: 1) ceftobiprole, a broad spectrum anti-MRSA cephalosporin that has completed two Phase III complicated skin and skin structure (cSSSI) clinical trials; 2) ceftaroline, an anti-MRSA cephalosporin with activity against many Enterobacteriaceae that has completed a Phase II cSSSI trial; 3) CS-023/RO-4908463, a carbapenem in Phase II clinical trials with microbiological activity against MRSA and cephalosporin-resistant Enterobacteriaceae; 4) ME1036, a broad spectrum carbapenem in Phase 1 studies, with activity against MRSA as well as against most Enterobacteriaceae; and 5) SMP-601/PZ-601, a preclinical carbapenem with in vitro activity against many multidrug-resistant Gram-positive and Gram-negative bacteria.

Other beta-lactam agents in development include doripenem, a carbapenem with enhanced activity against *Pseudomonas aeruginosa*; doripenem has recently completed clinical trials in the United States for complicated urinary tract infections and intra-abdominal infections. FR264205 is an unusual preclinical cephalosporin with promising in vitro activity against *Helicobacter pylori* and AmpC-hyperproducing *P. aeruginosa*.

Although these agents combined are active against many serious pathogenic bacteria, there are still gaps in the antimicrobial spectrum that could be filled by additional beta-lactam-containing molecules. Inhibitors of metallo-beta-lactamases, or serine carbapenemase inhibitors, or beta-lactamase inhibitors that serve to inhibit multiple enzymes in a Gram-negative strain could provide even broader therapy when combined with one of the compounds above. Some investigational beta-lactamase inhibitors include NXL104, a novel lactam-containing molecule currently in Phase 1 studies, and several preclinical monobactams or penicillanic acid sulfones. Future studies will be necessary to determine whether these agents will be robust enough, with appropriate pharmacokinetic properties, to proceed into therapeutic trials as a combination product with a suitable beta-lactam-containing partner.