A number of pharmaceutical research approaches can be taken to combat the problems of emerging antibiotic resistance. One of the most important strategies has been synthetic improvement of known antibiotic classes in order to produce analogues that circumvent existing resistant mechanisms. This approach has been successfully applied to producing additional quinolone, beta-lactam, tetracycline, glycopeptide, macrolide and rifamycin antibiotics. In this presentation several new drugs for the treatment of bacterial infections that have been developed along this line will be discussed.

The development of new fluoroquinolones with expanded antimicrobial activity is currently an area of interest. While the predecessor fluoroquinolone agents ciprofloxacin and levofloxacin demonstrate excellent Gram-negative activity and borderline Gram-positive activity, newer agents offer broader spectrums of activity with greater in vitro potency against Gram-positive organisms, particularly *S. pneumoniae* and even *S. aureus*. Levofloxacin was the first quinolone to be approved for the treatment of penicillin-resistant Streptococcus pneumoniae (PRSP) in community-acquired pneumonia. In late 1999, the respiratory quinolones namely moxifloxacin and gatifloxacin were approved by the US FDA for clinical use. Each of these drugs contains a C-8-methoxy group which is thought to confer better bactericidal activity against staphylococci compared with the analogous C-8-H or C-8-ethoxy compounds. The glycylcyclines or the 9-glycinyltetracyclines have been developed to overcome bacterial resistance mechanisms that emerged to earlier members of the tetracycline class. Peptidic antibiotics have generated much interest as novel antibacterial agents. Among the peptide antibiotics in clinical evaluation is the protegrin IB-367, which has entered Phase III clinical trials, particular treating oral mucositis.

The oxazolidinones represent a new structural class of antibiotics. They have a unique mechanism of action involving inhibition of the initiation step of protein synthesis and are not cross-resistant to other classes of antibiotics. Linezolid is the first of a new class of antibacterial agents, known as the oxazolidinones. In early 2000, the oral and parenteral dosage forms of linezolid were approved for treatment of community- and hospital-acquired pneumonia and methicillin-resistant Staphylococcus aureus (MRSA). It may represent a significant advance in the treatment of MRSA, PRSP and vancomycin-resistant enterococci (VRE). Ketolides are semi-synthetic macrolide antibiotics with improved activity against several erythromycin-resistant pathogens. Telithromycin is the first ketolide having activity against staphylococci expressing inducible macrolide-lincosamide-streptogramin B resistance and many enterococcal strains. The synthetic streptogramin combination of quinupristin/dalfopristin was approved for limited use for the treatment of infections caused by VRE.
Combinations of beta-lactams and beta-lactamase inhibitors have become one of the most successful antibacterial strategies in the treatment of bacterial infections. The clinical situation now indicates that second-generation beta-lactamase inhibitors capable of encompassing both class A and class C enzymes would combat emerging resistance and provide a vital addition to the lists of hospital antibiotics. However, there are the complications of developing a combination product; such as selecting appropriate beta-lactam partner and achieving compatible pharmacodynamics and pharmacokinetics.

Genetics has provided a major preoccupation for researchers in infectious disease susceptibility for almost a century. A range of clinical phenotypes associated with infectious diseases, racial differences in susceptibility, and twin studies all contributed to the view that the host genotype contributes to disease severity. Population studies also contributed to the view that infectious diseases can act as a strong selective influence in molding human evolution and population genetic structure. Novel bacterial targets that have been examined on the basis of their essentiality or their contributions to susceptibility, in vitro, include lipid A, sortase, deformylae, efflux pumps, and two-component regulatory systems. Recently described inhibitors of these targets include carbohydroxamido-oxazolidines that inhibited the second step of lipid A biosynthesis with an IC$_{50}$ value as low as 30nM, and minimum inhibitory concentrations of 1 to 3ug/ml against Escherichia coli. Cell-wall-active inhibitors such as vancomycin and moenomycin were shown to be effective inhibitors of the staphylococcal sortase. Efforts are also being made to identify genes that are essential during the infection process, with the hope of finding novel targets expressed in vivo, but possibly not in vitro.

The current epidemic of bacterial resistance is attributed, in part, to the overuse of antibiotics leading to development of the new compounds circumventing the problems of bacterial resistance. Antibiotics can decrease patient morbidity due to infections and can be life saving drugs as well. However, their high efficacy and relative lack of adverse effects has resulted in overuse in many situations, and increasing resistance to available drugs has become a worldwide problem. A reduction in antibiotic use is a critical component to reduce rates of resistance. International efforts to improve antimicrobial prescribing should be encouraged. Novel agents that have been recently approved should only be reserved for treatment of infections caused by resistant pathogens.