



Development of Novel Antibiotics : Hopes and Despair

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The majority of currently available antimicrobials were discovered more than 25 years ago. Indeed, since 1980, only one new class of antimicrobial agents (the oxazolidinones) has been discovered and developed for clinical use. There are a number of reasons for this including the fact that most of the easy targets allowing selective toxicity have been discovered and the fact that it is increasingly costly to bring new antimicrobials to the market. For these reasons, a number of large pharmaceutical companies have dropped out of the antibiotics "business." Although it was hoped that biotechnology companies would make up for the slack, there has been a very high mortality rate in these companies in the United States and elsewhere. Although microbial genomics initially showed a good deal of promise for the discovery of new antimicrobials, it has not been as easy as hoped to use genomics in the development of new antimicrobials. A number of approaches utilizing structure-based rational drug design are currently underway, including *in silico* (virtual) screening and the search for new antimicrobials based on crystal structure of the ribosome and various other ligands. The search for novel "classic" antimicrobial agents goes on and a number of companies are screening such diverse substances as hemolymph from insects and seaweed in the hope of discovering new agents. The use of combinatorial libraries, while promising, in a number of instances has resulted in more leads than can be reasonably followed. Agents such as quinupristin/dalfopristin, the oxazolidinones and daptomycin are examples of newly developed "classic" antimicrobials. The chemical modification of known agents to overcome resistance has also been useful and has resulted in a variety of new agents including dalbavancin, a teicoplanin analog, telavancin, a lipoglycopeptide analog, the ketolides, the glycylicyclines, the aminomethylcyclines, and a variety of oxazolidinone, fluoroquinolone, carbapenem and cephalosporin analogs. The successful implementation of the beta-lactamase inhibitors as antimicrobial potentiators has led to a search for other such agents. Inhibitors of efflux pumps represent a particularly attractive approach, but thus far it has been impossible to design agents which inactivate all of the pertinent efflux mechanisms in target bacteria. A number of biotechnology and pharmaceutical companies are continuing to look for new bacterial targets for antimicrobial agents. Among the more promising targets are DNA ligase, glycogen synthesis, signal peptidase proteins, secretory pathways, lipid biosynthesis, biofilm formation and peptide deformylases. The development of inhibitors of genes relating to pathogenesis sounds attractive, but despite a good deal of work in this area, no candidate drugs have been successfully marketed. The same may be said of antisense nucleotides - a very promising, but up to now disappointing avenue of approach for the discovery of new antimicrobial agents due to nonspecific binding, nonspecific effects, clinical and metabolic instability and lack of binding specificity as well as problems in delivering intact oligonucleotides to intracellular targets.