Dual targeting antimicrobials and the circumvention of resistance

Since the 1990s, a group of researchers based at St George's has made a number of seminal contributions in the development of dual targeting antibiotics and the circumvention of antibiotic resistance, which could benefit the development of new drugs in a wide range of bacterial pathogens.

Background and research

Streptococcus pneumoniae, the gram-positive bacterium responsible for pneumococcal pneumonia and numerous other infections, including some cases of meningitis, is typically sensitive to penicillins, but serious concern exists over the emergence of penicillin-resistant strains.

Consequently, efforts have been made to develop other antibiotics effective against this pathogen.

Quinolones are a class of synthetic antibiotics that can prevent bacterial DNA from replicating by interfering with the action of bacterial enzymes that unwind DNA prior to replication.

Professor Mark Fisher and colleagues successfully demonstrated that antibacterial quinolones selectively target these bacterial enzymes, which led to the concept that 'dual targeting' drugs minimise the emergence of drug resistance.

During the course of their studies, Fisher and colleagues were approached by SmithKline-Beecham to define the mode of action of gemifloxacin (Factive), a fluoroquinolone licensed from LG Pharmaceuticals.

Their studies showed that gemifloxacin fulfils the criteria of a dual targeting antibacterial agent and these studies were instrumental in the approval of the drug by the FDA for the treatment of community-acquired pneumonia arising from S. pneumoniae, from penicillin-resistant S. pneumoniae and from multidrug-resistant S. pneumoniae.

In 2008, Fisher and colleagues also established the mode of action of besifloxacin, a novel fluoroquinolone developed by Bausch and Lomb.

Their work contributed significantly to the FDA approval for the drug in May 2009, which was extended in Sept 2012 to other indications, including virulent sight-threatening pathogens such as Pseudomonas aeruginosa.

Impact

Fisher and colleagues' work is being exploited by pharmaceutical companies to design a new generation of drugs that target resistant bacteria. Without the knowledge of the molecular structure discovered by the Fisher Group, these approaches would be severely limited and largely dependent on relatively inefficient trial-and-error screening.

Fisher and colleagues' discoveries are providing key leads for compound development and could benefit the creation of new drugs in a wide range of bacterial pathogens.

Besifloxacin has been shown to resolve bacterial conjunctivitis more rapidly and efficiently than other treatments on the market, providing significant patient benefit.

The drug has become a highly effective treatment with correspondingly increased usage and sales in the USA. InSite Vision recorded $1.2 million besifloxacin royalty revenues in 2011, and $2.1 million for 2012. 400,000 prescriptions for besifloxacin were filled in the US from November 2010 through March 2012.

Gemifloxacin is now marketed worldwide, with pharmaceutical companies emphasising its potency and dual action properties through reference on their websites to Fisher's work. Gemifloxacin continues to be used in the treatment of refractory pneumococcal infections and achieved sales of $5.1m and $6.3m the US in 2010 and 2011.