



## Symposium 7.2

### New Fluoroquinolones

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Fluoroquinolones have had multiple cycles of development and been used increasingly broadly over time. After some post-marketing removals for toxicities, there are now seven marketed fluoroquinolones in the United States, the most recent being gemifloxacin, which is notable for its exceptional potency against *Streptococcus pneumoniae*. A number of other quinolones are under development and in many cases provide further enhancements in activity against some or many gram-positive bacteria. Examples include DX-619, garenoxacin, GF-001001-00, and WCK-771 with particularly enhanced potency against staphylococci, including quinolone-resistant strains of MRSA, and DW224a, DC159a, WCK1153, and WQ-3335 with notable increased potency against *S. pneumoniae* (including quinolone-resistant strains) and other respiratory pathogens. Only a few, such as sitafloxacin and DK-507k, have had enhanced activity over those of ciprofloxacin and levofloxacin against enteric gram-negative bacteria and/or *Pseudomonas aeruginosa*. Clinical development has however been slow in many cases.

Because the topoisomerase targets of fluoroquinolones are essential, large, and complex enzymes, it is known that there are other chemical structures that could inhibit topoisomerase function and possibly be developed as new antimicrobial agents without compromise from existing quinolone resistance mechanisms. The coumarins are known prior examples of such non-quinolone structures that interact with topoisomerases in a manner distinct from that of the quinolones. More recently aminobenzimidazoles, heteroaryl isothiazolones, and NXL101 have also been shown to have topoisomerase-targeted activity against gram-positive bacteria. Hybrid molecules such as oxazolidinone-quinolone hybrids have also been revisited.

The identification of new structures of the quinolone and non-quinolone classes with potent activity particularly against gram-positive bacteria provides some optimism that topoisomerases can continue to be exploited as targets of antimicrobial therapy in the context of increasing resistance to earlier quinolones. The need for new quinolones with additional potency against resistant gram-negative bacteria, however, remains a challenge.