



DIPARTIMENTO DI FARMACIA E BIOTECNOLOGIE

## Life & Chemical Sciences Seminars

# A Mechanistic Approach to Overcoming Quinolone Resistance

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**Venerdì 4 maggio ore 14:30** – presso Aula 1 via Belmeloro 6  
(ospite Prof.ssa A. Minarini)

### **Abstract**

Quinolones are among the most commonly prescribed antibacterials worldwide and are used to treat a broad variety of bacterial infections in humans. However, because of the wide use (and overuse) of these drugs, the prevalence of quinolone-resistant bacterial strains has been growing steadily since the 1990s. This rise in quinolone resistance threatens the clinical utility of this important drug class. Quinolones target the bacterial type II topoisomerases, gyrase and topoisomerase IV. These enzymes regulate DNA under- and over-winding and remove knots and tangles from the genetic material. Gyrase and topoisomerase IV create transient double-stranded breaks in DNA in order to carry out their essential cellular functions. Quinolones take advantage of this DNA scission activity and stabilize the covalent enzyme-cleaved DNA intermediate. Thus, they kill cells by converting gyrase and topoisomerase IV into toxic “nucleases” that fragment the bacterial chromosome. Dr. Osheroff’s talk will provide background on type II topoisomerases and how they interact with quinolones. He will then describe how this knowledge has been used to design novel quinolones that overcome resistance. Finally, he will discuss recent experiments with novel naphthyridone/aminopiperidine-based drugs that alter enzyme-mediated DNA cleavage by a unique mechanism and retain their activity against quinolone-resistant mutant enzymes.

### **Biosketch**

Neil Osheroff received his B.A. in Chemistry from Hobart College in 1974 and his Ph.D. in Biochemistry and Molecular Biology from Northwestern University in 1979. He was a Helen Hay Whitney Foundation postdoctoral fellow in Biochemistry at the Stanford University School of Medicine from 1980-1983 and joined the faculty of the Vanderbilt University School of Medicine in 1983. Dr. Osheroff is a Professor of Biochemistry and Medicine and holds the John G. Coniglio Chair in Biochemistry. He has authored over 250 papers and has graduated twenty-eight Ph.D. students. Dr. Osheroff’s research focuses on topoisomerases, enzymes that remove knots and tangles from the genetic material and modulate torsional stress in DNA. Beyond their critical physiological roles, human topoisomerases are the targets for several important anticancer drugs, and bacterial type II topoisomerases are the targets for quinolone antibacterials. The Osheroff laboratory has made seminal contributions to our understanding of how topoisomerases function and how anticancer and antibacterial agents interact with these enzymes and alter their catalytic functions. Dr. Osheroff has received awards for mentoring, teaching, curricular design, educational service, and affirmative action/diversity. Over the past five years, he has presented more than eighty talks at fifty institutions/meetings in eighteen different countries.

*Commissione Ricerca e Attività Correlate*