

The NIH Chemistry Seminar Series Presents:

Professor Scott Singleton

University of North Carolina

Eshelman School of Pharmacy

“Rec-ing the DNA Repair Shop:

A Strategy for Confronting Antibiotic Resistance”

Time: 10:00 am

May 1, 2009

Place: Building 8,

1st floor conf. room (123)

Abstract: Antibiotic resistance is an ever-increasing problem for modern chemotherapy of bacterial infectious diseases. In this post-genomic era, target-based drug discovery against proteins considered essential for in vitro bacterial viability has yielded few new therapeutic classes of antibiotics. In light of the limited pipeline of new antibacterials, drug-resistant pathogens are a clear and urgent danger to public health and national biodefense. Novel strategies will be required to overcome this problem, and one potential solution involves screening targets considered non-essential for in vitro viability. Indeed, two-thirds of *Escherichia coli* genes have been characterized as non-essential, and exploring this previously ignored segment of the bacterial genome may offer possibilities for the discovery of non-traditional pharmaceutical targets and agents that attenuate pathogenicity or potentiate the pharmacologic effects of known antibacterial agents. In this context, we have focused on the bacterial RecA protein as a prospective target. RecA plays crucial roles in the repair of DNA damage and stalled replication, but also participates in processes that promote stress-induced mutation and horizontal gene transfer. We hypothesized that small molecule inhibitors of RecA would sensitize bacteria to established antibacterial agents and prevent the development and acquisition of genes conferring drug resistance. We have identified nucleotide analogs, structured peptides, transition metal complexes, and polysulfated naphthyl compounds as inhibitors of the in vitro activities of RecA. More recently, we have discovered cell-permeable small molecules that inhibit RecA activities in live bacterial cultures and we have developed conjugates of peptide nucleic acids (PNA) that abrogate recA gene expression in live bacterial cultures.

Host: Dan Appella (appellad@mail.nih.gov)

Co-sponsored by: The Chemistry Interest Group

