Combating Antibiotic Resistance: The Computational Design of Erm Inhibitors.

Jason P. Rife and Glen E. Kellogg
Department of Medicinal Chemistry

The contributions made by antibiotics to public health in the last 100 years have been astonishing. In the United States the three leading causes of death were all bacteria infections: tuberculosis, pneumonia, and gastrointestinal tract infection. Today, only lower respiratory tract infection cracks the top-ten leading causes of death in the United States. However, in the last 15 years the developed countries have actually been losing ground in the fight against bacterial infectious disease. Recent losses are mainly due to the emergence and spread of antibiotic resistance throughout all classes of bacterial pathogens. One of the most common forms of resistance, MLS-resistance, is brought about via the bacterial acquisition of a methyltransferase gene termed *erm*. *Erm* encodes for an enzyme that chemically modifies a single nucleotide within the ribosome. A ribosome so modified is no longer sensitive to a host of common antibiotics, like erythromycin, at clinically relevant doses. Many companies and academic laboratories are interested in designing an adjuvant to restore the usefulness of erythromycin (and other antibiotics) against MLS resistant bacteria.

Close structural homology between the Erm protein and two human methyltransferases raises the concern that an inhibitor of the Erm protein might also inhibit one of the two human homologues. Inhibition of either human protein might be a source of toxicity. Therefore, the design of Erm protein inhibitors should address from the start the differences that exist (as small as they may be) in the binding pockets of the Erm protein and the human homologues to maximize selectivity. A host of computation tools will be utilized to map-out the binding pockets of the Erm protein and its human homologues, Dim1 and mtTFB. From those predicted interaction maps we will computationally design inhibitors that we expect to be maximally selective for the Erm protein.