The Development of Small-Molecule Disruptors of the MazEF Protein Complex to Kill Antibiotic-Resistant Bacteria

Nora Wang and Paul J. Hergenrother

Antibiotic resistant bacteria such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterrococci (VRE) are increasingly the cause of hospital-acquired infections. The genes that encode antibiotic resistance are often borne on extrachromosomal DNA called plasmids. One way that plasmids are maintained in bacteria is through the utilization of toxin-antitoxin (TA) systems. TA systems are comprised of a plasmid-borne gene cassette that encodes a stable toxic protein and a labile antitoxin protein. The antitoxin and toxin form a protein complex, neutralizing the activity of the toxin. This complex remains intact in plasmid-containing cells, as both proteins are translated. However, in plasmid-free cells, the labile antitoxin is no longer translated and is rapidly degraded, exposing the toxin to find its target within the cell. In this way, plasmid-free cells are killed and only antibiotic-resistant cells remain.

Recently, our group has found that one such TA system, the MazEF system, is ubiquitous in VRE infections. Thus, it is our goal to develop small molecules that disrupt the MazEF protein-protein interaction. In this way, the MazEF toxin will be exposed to kill the antibiotic-resistant bacteria in which it is contained.