Antibacterials were discovered in the 1930’s, -40’s and 50’s and represent one of the most important eras of drug discovery to reduce human mortality in its history. Most, but not all, were identified from bacterial or fungal cultures, and used for obtaining a selective growth and survival advantage. Within years of the introduction of each successive class of antibacterials into clinical use, resistance to that antibiotic class was observed. For over thirty years, the Blanchard lab has studied the mechanisms of resistance to various classes of antibacterials, and focused on those that are enzymatically mediated. We have defined structures and mechanisms of several of enzymes that generate aminoglycoside resistance and β-lactam resistance. We also discovered a novel mechanism for generating fluoroquinolone resistance. While we hoped the pharmaceutical industry would try to develop inhibitors to the expression or activity of these systems, or be immune to their action – “resisting resistance” – in fact the opposite has occurred, with almost no pharmaceutical company investing in this research, but rather dropping antibacterial discovery efforts completely. As a result the rise in life-threatening infections due to drug-resistant bacteria is on the rise, as is the cost of treatment, and mortality. Three different systems will be explored in this presentation.