Dynamics and evolution of specificity of TA complexes

Toxin-antitoxin (TA) systems are ubiquitous genetic modules promoting bacterial survival by regulation and arrest of cell growth in response to stresses such as phage infection, antibiotic exposure, or macrophage uptake. While toxins target essential biological processes affecting growth of a cell, antitoxins specifically neutralize their cognate toxins and allow for cell growth. In the most prevalent type II TAs, the antitoxin is a protein that directly binds its cognate toxin with a neutralization domain (ND), resulting in formation of a tight toxin-antitoxin complex. Besides the ND, the antitoxin also contains a DNA binding domain enabling it to transcriptionally control the toxin-antitoxin operon. Another key feature of TAs is the common presence of several paralogues of the same system within the same organism. The frequent complete insulation of numerous paralogous TAs, where there is high specificity with no cross-pairing, suggests that a neutralizing cross-interaction is detrimental to the cell.

I am interested in studying the evolution of specificity of paralogous TA systems through toxin size variation by addition of structural add-on elements then allowing the antitoxin to evolve a specific neutralizing sequence. I found that such size alteration occurs at either N- or C-terminal toxin ends in various TA systems. Building on the experience gained while studying three paralogous *Salmonella* TacAT1-3 TA systems, I will continue to explore the significance of add-ons in contribution to development of neutralization specificity reducing paralogue cross-talk conflict. I will also investigate the activation of an important family of TAs involved in persistence of pathogenic *Salmonella*. Overall, these studies will provide new insights into the dynamics of evolution of paralogous protein-protein complexes and protein-DNA complexes, thereby opening avenues of interfering with these important stress response elements in bacteria.