Antibacterial Drug Development

Gram-positive bacteria are formidable human pathogens. Staphylococci are responsible for more than a million hospital-acquired bacterial infections every year. *Streptococcus pneumoniae* is responsible for a major portion of 3 million deaths worldwide of children from pneumonia and meningitis and for a large number of deaths from pneumonia that occurs in elderly individuals. In addition, individuals infected with HIV and other immunosuppressive conditions are at high risk of invasive diseases caused by *S. pneumoniae* and *S. aureus*. Compounding their importance is the recent steep increase in multi-drug resistance found in bacteria. New approaches for the prevention and treatment of bacterial infections require greater understanding of the molecular structures of the chosen intervention targets and of the pathogenic role played by the target in the infectious process.

Bacterial infections are very complex and involve the action of a large sophisticated arsenal of virulence factors, many of which are surface-bound or secreted. Surface proteins often fall into one of four functional categories: microbial adhesion to host tissues, protection from host defense mechanisms, acquisition of nutrients for bacterial growth, and secretion of toxins and invasions. These virulence factors carry out important roles in the infectious process. The possibility of human interventions interrupting this process through interference with virulence, as opposed to bacterial growth, is a possibility, but not yet a reality. The enzyme sortase, found in all gram+ bacteria, catalyzes transpeptidation between sorting signals present in proteins destined to the bacterial surface and cross-bridge peptides in a cell wall precursor known as lipid II. Sortase-deficient strains, failing to anchor surface proteins, are often found to be attenuated in their virulence. Hence, sortase seems to be an attractive potential target for antibacterial therapy. We recently determined the crystal structures of *Staphylococcus aureus* SrtA and its substrate LPETG complex, and SrtB and its inhibitor complexes.

A novel small-molecule inhibitor for *S. aureus* SrtA with low µM *in vitro* IC₅₀ has recently been reported. Molecular modeling and ‘DOCKing’ efforts, using the crystal structure of SrtA, helped us position this lead compound in the enzyme active site. We have identified several small molecules with similar structural features in the commercial databases and are able to ‘DOCK’ them in the enzyme active site and have generated a ‘lead structure template’ for further synthesis. Our early synthetic efforts have resulted in the identification of better binding ligands. The goal is to make structural modifications to this lead compound to improve its binding affinity and optimize drug like properties. We plan to achieve this through an integrated approach of using X-ray crystallography, SAR (Structure activity relationship) studies, enzyme kinetic measurements and molecular modeling.