Staphylococcus aureus and Staphylococcus epidermidis are leading causes of severe bacterial infections worldwide. We in the Blackwell laboratory have taken several approaches to target virulence in the Staphylococci. Production of many virulence factors in Staphylococci is controlled by the accessory gene regulator (agr) quorum sensing (QS) system, which can be targeted to reduce bacterial invasion. We have recently developed an interesting new class of peptidomimetics that inhibit agr in S. aureus at sub- to low-nanomolar concentrations. NMR structural studies revealed hydrophobic and hydrophilic regions that appear important for QS antagonism, in agreement with prior studies of peptide-derived antagonists. In S. epidermidis, agonism of agr reduces biofilm formation, which is a major virulence factor associated with S. epidermidis infections. We performed NMR structural studies to elucidate the important peptide conformations required for agonism in S. epidermidis. Our lab is currently focused on developing new QS modulators based on these studies.