UNC

SCHOOL OF MEDICINE

Microbiology and Immunology

DISSERTATION SEMINAR

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“Harnessing interspecies antagonism to enhance antibiotic efficacy.”

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ABSTRACT

Lauren Radlinski: Harnessing interspecies antagonism to enhance antibiotic efficacy
(Under the direction of Brian Conlon)

Beyond genetically encoded mechanisms of resistance, the factors that contribute to antibiotic treatment failure within the host are poorly understood. Traditional susceptibility assays fail to account for extrinsic determinants of antibiotic susceptibility present during infection and are therefore poor predictors of treatment outcome. To maximize the reach of current therapeutics, we must develop a more sophisticated understanding of antibiotic efficacy in the infection environment. Here we demonstrate that interspecies interactions between two important opportunistic pathogens, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, alters *S. aureus* response to antibiotics. We show that the *P. aeruginosa*-produced endopeptidase LasA potentiates lysis of *S. aureus* by vancomycin, rhamnolipids facilitate proton-motive force-independent aminoglycoside uptake, and that small molecule 4-hydroxy-2-heptylquinoline-N-oxide (HQNO) induces multidrug tolerance in *S. aureus* through respiratory inhibition and reduction of cellular ATP. We further demonstrate rhamnolipid-mediated potentiation of aminoglycoside uptake and killing of *S. aureus* restores susceptibility to otherwise tolerant persister, biofilm, small colony variant, anaerobic, and resistant *S. aureus* populations.

Furthermore, bacterial pathogens that replicate within the intracellular niche are protected from antibiotics that cannot penetrate the eukaryotic membrane. Identifying and disrupting the pathways used by these pathogens to modify the intracellular niche in order to survive is an alternative strategy for limiting bacterial proliferation. Here, we use *Francisella tularensis* as a model intracellular bacterial pathogen to identify and describe the bacterial metabolic pathways and host-derived nutrients necessary for intracellular and *in vivo* growth. These findings reveal potential new therapeutic strategies for disrupting bacterial nutrient acquisition that may be broadly applicable for treating other important intracellular pathogens.

Overall, the findings presented here suggest that antibiotic susceptibility is contingent on a multitude of factors including interspecies interaction and the physiological replicative niche. Further elucidation of key antibiotic susceptibility determinants *in vivo,* as well as of strategies to overcome barriers to antibiotic efficacy may lead to a more holistic and personalized approach to therapy that will aid in the resolution of persistent infection.