**ACRONYM:** **COLLATERALDAMAGE**

**Title:** **Using collateral sensitivity to reverse the selection and transmission of antibiotic resistance**

**Keywords:** **Collateral sensitivity, resistance-reversal, antibiotic resistance, in vivo models, theoretical biology**

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## Abstract:

Urgent action is required to stem the "apocalyptic" spread of antimicrobial resistance (AMR). However, because the pace of novel drug development lags behind the evolution of novel AMR determinants, new strategies of containment are required. In this multi-disciplinary proposal we develop a resistancereversal strategy based on the concept of collateral sensitivity (CS). CS between a pair of antibiotics occurs when a mutation causing resistance to one antibiotic potentiates susceptibility to another.

By exploiting CS relationships through sequential drug application, resistant strains can be specifically targeted which will reduce their frequencies in the community and slow their transmission. Our broad aim in this proposal is to realize the unique promise of CS-informed therapies. To do so, our work packages integrate theoretical biology, evolutionary and molecular microbiology, and in vivo modeling with a specific focus on arresting the transmission of resistant Escherichia coli and Streptococcus pneumoniae.

Combining theory and experiments, we will: 1) test the generality of CS across hundreds of clinical strains of E. coli, and S. pneumoniae; 2) quantify how horizontal transmission of antimicrobial resistance determinants modify CS-networks; 3) identify the underlying molecular mechanisms of CS; and 4) determine the conditions under which CS mediated reversals of resistance occur in vivo.

The expected outcomes of the proposal are to provide pre-clinical recommendations for therapy to reduce the emergence and transmission of these two globally important bacterial pathogens and to provide a framework to develop CS-based strategies for other bacterial threats.