Effect of Novel Shock Inhibition on Efflux Pump Inhibitor NMP

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As a natural mechanism of extruding harmful substrates, bacterial efflux pumps have become increasingly relevant in the antibiotic resistance crisis. Spanning the outer membrane of all bacteria, efflux pumps are in charge of extruding bile salts, cationic dyes, disinfectants, and antibiotics. Mechanisms of inhibiting resistance pathways, especially the efflux of antimicrobials, promises new methods for infection treatment. This project focuses on AcrAB-TolC, a tripartite pump prevalent in almost all gram-negative bacteria. Transcriptional studies of resistant E. Coli have shown upwards of a 7-fold increase in the expression of this efflux pump. Recent advances in sequencing and protein modeling have allowed for the identification of putative efflux inhibitors, which block transport and thus prevent the degradation of antibiotic concentrations within the cell itself. One such chemical, 1-(1-naphthylmethyl)-piperazine (NMP), has been shown to have moderate inhibitory effects on AcrAB-TolC. This project identifies a novel application method: “shocking” the bacteria into efflux dimerization, and subsequently administering NMP. This method of shock inhibition yielded a decrease in the minimum inhibitory concentration of ciprofloxacin in E. Coli. The continued stressor of subinhibitory ciprofloxacin or SDS, combined with shock treatment of efflux pump inhibitor NMP, triggered a significant decrease in the transcription levels of bacterial xenobiotic genes, suggesting the ability of shock inhibition to mitigate the issue of efflux pump overexpression.