Targeting the GraRS Two-Component System in Staphylococcus epidermidis: Computational Identification and in vitro Validation of a Novel Adjunctive Cocktail Therapy for Antibiotic-Resistant Infections

Srikanth, Aditi (School: Carroll Senior High School)

Antibiotic resistance is a rising global health threat, causing over 5 million deaths worldwide annually. This is a particular concern in hospital settings where bacterial infections can spread rapidly amongst patients and give rise to highly drug-resistant strains. Staphylococcus epidermidis exemplifies this threat; this pathogen has a 24.4% mortality rate, and 70% of isolates are multidrug resistant (MDR), making it one of the most difficult hospital-acquired infections to treat. These challenges highlight the need for alternative therapeutic strategies beyond conventional antibiotics. Here, this project targets the GraRS two-component system, a central regulator of virulence and drug resistance in this pathogen that is not targeted by current antibiotics, and evaluates the efficacy of GraRS allosteric inhibitors in inhibiting S. epidermidis growth. From ~40 natural compounds with known antibacterial properties, Absorption, Distribution, Metabolism, and Excretion (ADME) filtering selected 10 orally viable candidates for GraRS docking, yielding four top hits: sesamin, sesamolin, guggulsterone, and beta-ecdysterone, which were verified using protein-ligand interaction profiling (PLIP). These natural products were tested in vitro by spectrophotometric growth assays, both individually and in tandem. Furthermore, Caenorhabditis elegans cytotoxicity screening was used to confirm antibacterial activity with minimal host toxicity. Strikingly, combination therapy using low doses of these four compounds drastically reduced bacterial growth without impacting host survival. Together, these findings demonstrate how natural products can be leveraged to develop orally bioavailable therapeutics to combat multidrug-resistant bacterial pathogens.

Awards Won: