Novel Inhibitors for Conserved Regions of RecA To Slow Bacterial Antibiotic Resistance

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Drug-resistant infections are expected to cause 10 million deaths annually by 2050. The increased prevalence of resistant bacteria has resulted in a scarcity of therapeutic alternatives, making it critical to develop novel drugs. RecA is present in all free-living bacteria and is the slowest evolving gene in DNA metabolism, with a ~60–70% average sequence conservation across all bacteria. It is involved in two highly mutagenic pathways: horizontal gene transfer and the SOS response, making it an ideal target to block bacterial evolutionary processes, which can help slow the acquisition and spread of antibiotic resistance. The limitation of current inhibitors like zinc acetate and suramin is specificity, as there is a danger of toxic off-target effects due to inhibitors acting on homologous human proteins like RAD51. This is addressed by generating novel broad-spectrum inhibitors which target the RecA's most conserved regions with greater specificity. Druggable pockets were selected which correspond to RecA's most conserved regions, inhibitors were generated based on an input dataset of compounds, and the strength of the inhibitor-protein interaction was assessed by GROMACS MD simulations. Top compounds had docking affinities with a 100-fold selectivity to RecA over RAD51, and a Kd for RecA less than that of currently known experimental inhibitors by a factor of 10, suggesting that these compounds inhibit RecA with greater specificity. With further optimization and drug development, this could potentially lead to a new adjuvant therapy or antibiotic. Additionally, this approach can be extended to other pathogenic proteins to generate similar highly potent therapeutics, increasing our antipathogenic arsenal to combat a wide variety of diseases.

Awards Won:
Third Award of $1,000