Screening for AmpR-Specific Inhibitors to Combat P. aeruginosa Infections

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Abstract Details

Pseudomonas aeruginosa, a Gram-negative bacterium, an opportunistic pathogen that infects individuals suffering from reduced immunity or damaged tissue. The treatment of these infections has become a major problem due to its increasing antibiotic resistance. Many multi-drug resistant isolates of *P. aeruginosa* can thwart most antibiotic classes including ?-lactams, fluoroquinolones, and aminoglycosides. Its ability to combat ?-lactams is in part due to expression of AmpC, a major chromosomally encoded ?-lactamase. The expression of *ampC* is positively regulated by AmpR. Besides antibiotic resistance, AmpR is an important regulator of various factors that are required for establishing acute and chronic infections. Loss of *ampR* makes *P. aeruginosa* susceptible to ?-lactams and less virulent than the wild type. We hypothesize that AmpR is a potential therapeutic target. In the absence of new drugs in the pipeline, the aim of this study is to find an AmpR-specific inhibitor to assist and improve the use of currently available ?-lactam treatment. A small-molecule library from Torrey Pines Institute will be used in this study. Two reporter systems, *lux* and *lacZ,* fused to a P_{ampC} promotor will be used to assess AmpR activity. Positive hits will be those that inhibit 50% P_{ampC} activity in the presence of sub inhibitory concentration of imipenem, a ?-lactam. The top positive hits will be screened for their ability to cause human cell-cytotoxicity. The non-cytotoxic hits will be assessed for their ability to affect *P. aeruginosa* virulence and antibiotic resistance using various *in vitro* assays. Determination of potential AmpR inhibitors will prove to be useful in fighting off infections and may save countless patients suffering from these infections.

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