Screening for AmpR-Specific Inhibitors to Combat P. aeruginosa Infections by Kevin Morales | Hansi Kumari | Supurna Dhar | Kalai Mathee

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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