THE HARTWELL FOUNDATION

2015 Individual Biomedical Research Award

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Detecting Antibiotic Resistance with RNA Sensors

Antibiotics are a foundation of pediatric healthcare. The emergence of antimicrobial resistance is thus one of the most serious threats not only to children but to our entire population. Infections from resistant bacteria are now so common that some pathogens have become resistant to multiple antibiotic classes. The Centers for Disease Control and Prevention recently estimated that drug resistant bacteria account for more than 2 million illnesses and over 23,000 deaths every year in the U.S. Unfortunately, children are among the highest risk populations for diseases caused by pathogens that include prominently, Staphylococcus aureus (MRSA), Streptococcus pneumoniae (1.5 million ear infections per year) and Pseudomonas aeruginosa (particularly in cystic fibrosis). The current "gold standard" method for performing antibiotic susceptibility testing (AST) is effective, but extremely slow (minimum 48-72 hours). Unfortunately, delays in administration of appropriate therapy can generate latent antibiotic resistance due to inappropriate choice of antibiotic, prolong illness and increase the risk of death. To complicate matters, to avoid delays many treatment decisions are being made without susceptibility data and only refined later, as necessary. In short, there is a major unmet need to improve AST for the diagnosis and treatment of bacterial infections. When susceptible microbes encounter exposure to antibiotics, they trigger a stereotypical transcriptional response (activation or repression of gene transcription that controls making RNA from DNA) as rapidly as within a few minutes. The expression of a transcriptional response is a molecular signature that represents one of the earliest detectable cellular changes distinguishing susceptible from resistant bacterial strains. Ahmad proposes to develop innovative RNA sensor technology that can exploit these molecular signatures, which will enable development of a new, clinically relevant, low-cost and easy-to-use diagnostic system for AST. To achieve this, he will engineer highly-sensitive molecular sensors that couple RNA recognition to rapid amplification of colorimetric outputs in a cell-free expression system that can be freeze dried and arrayed onto low-cost substrates like paper. The RNA sensor technology will be developed and validated with high priority bacterial organisms that represent an urgent threat to U.S. children. If Ahmad is successful in translating his diagnostic approach into a low-cost, solid state platform, it will usher in a revolutionary advance for quick identification of bacterial infections. The ability to quickly distinguish susceptible from resistant bacterial strains will provide substantial benefit to the current standard of care and enable early identification of the most effective antibiotic. The result will be to reduce morbidity and mortality caused by bacterial infections and associated antibiotic toxicities in affected children.