THE HARTWELL FOUNDATION

2016 Individual Biomedical Research Award

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Targeting Antibiotic Resistance and Biofilm Formation in Bacterial Infections

Chronic bacterial infections pose dangerous health risks and are particularly challenging in children. Most antibiotics target processes that are important for bacterial viability, but bacteria can rapidly adapt and develop resistance. For example, in 80% of persistent infections the principle survival strategy bacteria deploy is organizing as a biofilm, which blocks efficiently the action of most antibiotics. To further protect themselves from any unfavorable changes in the environment bacteria may also undergo adaptation by changing their metabolic processes to favorably alter local conditions. These bacterial defense mechanisms make it possible for bacteria to protect their niche and continue to colonize during antibiotic therapy, and represent a challenging impediment to the development of new and effective drugs. Based upon the current paradigm for biofilm formation, bacteria adhere to the surface of cells and each other in a process determined by the strength of the interaction between extendable filamentous appendages (pili) located at the surface of a bacterium and certain receptor molecules located on the host cell membrane. It is inferred that the process begins with bacterial pili-mediated adhesion at a distance, followed by retraction of the pili and ultimately, intimate adhesion of the bacterium to the surface of host cells or other bacteria, but the mechanistic details important for overcoming antibiotic resistance remain obscure. Nikhil hypothesizes that electrostatic interactions play an important role in this regard and has developed a novel multimodal imaging method based upon atomic force microscopy and fluorescence microscopy to discover the mechanism that drives this process. Using a single cystic fibrosis lung surface epithelial cell and a single Pseudomonas aeruginosa bacterium (a ubiquitous multidrug resistant pathogen recognized for its association with serious illnesses) in his model system, he intends to simultaneously measure charge and adhesion forces under various conditions, in vitro. If Nikhil is successful and can demonstrate how bacterial pili deploy for cell-cell adhesion, targeting such a mechanism will lead to a new class of drugs designed to suppress biofilm growth and limit antibiotic resistance. Such target drugs might be transformative, because to overcome this unique aspect of bacterial survival may exceed the ability of bacteria to adapt. For those children with chronic pediatric bacterial infections, new drugs to inhibit biofilm formation will have a significant positive impact on reducing morbidity and mortality.