THE HARTWELL FOUNDATION

2014 Individual Biomedical Research Award

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Controlling Microbial Ecology to Combat Antibiotic Resistance

The emergence of antibiotic resistance is a rapidly growing problem and perhaps the greatest threat to public health of our time. Resistant infections are increasingly prevalent in children who face an elevated risk of adverse outcomes. This is particularly true for very young children with underdeveloped immune systems or those children who are immune compromised as a result of aggressive interventions to treat other life-threatening diseases. Today, over 30% of pediatric cancer patients will develop infections and sadly, 4% of patients in pediatric intensive care will develop hospital acquired bloodstream infections (sepsis). To avoid infections that negatively affect heart valves, or as the result of implanted medical devices such as catheters, effective antibiotics are crucial. Indeed, antibiotics represent one of the great triumphs of 20th century science and have saved countless lives. Unfortunately, the efficacy of such “wonder drugs” is rapidly declining due to the emergence of drug resistant pathogens. From a technical perspective, bacteria have a remarkable ability to adapt to pharmaceutical stress. There are an estimated 20,000 potential genes across bacterial species that may confer resistance to antibiotics. For instance, such genes may code for bacterial enzymes that will destroy the antibiotic, the bacterial cell surface proteins which prevent the antibiotic from entering the bacteria, or a mutant form of the bacteria that will prevent it from being a target of the antibiotic. Bacteria have proven to be stubbornly agile and efforts to develop new antibiotics are substantially lagging behind the pace of emerging antibiotic resistance. To address the urgent need for an entirely new strategy, Kevin offers a paradigm to control the growth and the composition of bacterial populations that will exploit native interactions between drug-sensitive and drug-resistant bacteria. In short, he hypothesizes that the response of an infection to treatment is not simply the result of a collection of molecular and cellular components but also how those components interact with each other. His approach relies on precise temporal administration of antibiotics to manipulate the delicate microbial ecosystem (variety and numbers of different bacteria) that comprises an infection, thereby prolonging the efficacy of existing drug treatments. Kevin proposes to deploy a model system using clinically important pathogens, gram negative *E. coli* and gram positive *E. faecalis.* He will examine the “social” dynamics of bacterial populations and determine how those dynamics affect treatment strategies. His approach will be to use a combination of custom-built, computer-automated culture devices of his design; assays for population growth based on high-throughput DNA sequencing technology; and confocal microscopy to measure and quantify population growth dynamics under different conditions. If successful, Kevin will demonstrate that bacterial community-level interactions offer an additional means to overcome antibiotic resistance, reducing the elevated risk of adverse outcomes in childhood bacterial infections in susceptible children.