THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Resensitizing Antibiotic Resistant Bacteria with Novel Kinase Inhibitors

Penicillin, methicillin and related antibiotics (collectively called β-lactams) were once the "miracle" drugs that enabled much of modern medicine. Many medical interventions require antibiotics for success. Unfortunately, antibiotic resistance, particularly to β-lactam antibiotics is rampant, even in childhood infections. One particularly problematic bacterial infection is methicillin resistant Staphylococcus aureus (MRSA), which causes hospital and community-acquired diseases, including most notably infections to skin and soft tissue. Antibiotic resistance to MRSA has reached epidemic proportions, as it now exceeds HIV/AIDS as a cause of death in the United States. MRSA can be contracted in daycare settings and school locker rooms and when severe, may require amputation of a limb to control the spread of the infection. Fortunately, in many cases non-antibiotic drugs called kinase inhibitors can be used in combination with β-lactam antibiotics to effectively make bacteria sensitive to therapy. Unfortunately, excessive use of antibiotics is accelerating the resistance of many bacterial infections to these kinase inhibitors, as well. Thus, there is an urgent need for new and more effective drugs that will extend the spectrum of activity of beta-lactam antibiotics. In proof of principle experiments, Rob has shown that Streptococcus pneumoniae (bacteria that are known to cause pneumonia, middle ear infections, meningitis, and blood infections) and Listeria monocytogenes (associated with food borne infections) can both be sensitized to β-lactams following treatment with kinase inhibitors. Based upon bacterial genetic data that indicate deletion of the kinase enzyme in MRSA will reverse the antibiotic-resistant phenotype, he believes that molecular modifications of existing kinase inhibitors will enhance their effectiveness to resensitize MRSA to β-lactam antibiotics. Specificity is important, but the molecular mechanisms of inhibitor-bacterial kinase interaction must be understood in order to predict or design improved inhibitors for bacterial kinases. To achieve this, he will examine computer-driven 3D molecular structures of known kinase inhibitors and determine what attributes are needed to inhibit the antibiotic resistant MRSA kinase, which will then be followed by a detailed search for other molecules in a database of 21 million commercially available compounds that might provide a new MRSA kinase inhibitor. The structure activity relationship for the best candidate compounds will be confirmed in assays against several known kinases, against MRSA in broth and ultimately, in a mouse model system. Computer-generated refinements will support the rational design of a more potent and selective inhibitor, which will be synthesized for evaluation. If Rob is successful, antibiotic resistant infections that are otherwise untreatable will be cured by common, inexpensive oral antibiotics.