THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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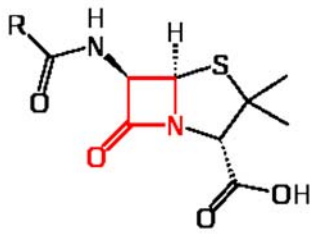
Improving the Treatment of Infections in Children with Cancer: Computational Modeling to Rapidly Identify and Overcome Antibiotic Resistance in Bacteria

Over 10,000 children develop cancer each year in the U.S. and >80% can now be cured, but only if they survive immunocompromised treatment-associated infections. While effective use of antibiotics has enabled therapies such as chemotherapy and bone marrow transplantation, 30%-90% of children still develop infections. Despite best efforts, it is remarkable that up to half of childhood cancer deaths occur from infection. Figuratively, the bacteria are catching up with the antibiotics — several recent isolates of bacteria have proven resistant to all FDA-approved drugs and have caused fatal infections in children. Given that gram negative bacteria account for much of the associated mortality in immunocompromised infections, beta-lactam antibiotics (e.g., penicillin derivatives, cephalosporins, etc.) with a broad spectrum of antibacterial activity are typically selected; most work by inhibiting bacterial cell wall biosynthesis. Unfortunately, this current standard of care is a "one size fits all" approach that often requires treating infections with a cocktail of antibiotics, using an escalation protocol that anticipates some combination will eventually work. The challenge is to use the right antibiotic from the start. Unfortunately, to select the correct approach from the outset requires understanding what accounts for antibiotic resistance. What is known today is that beta lactamase, an enzyme produced by many bacteria, breaks down the beta-lactam ring in the penicillin molecule and related drugs to destroy the antibiotic, conveying resistance to the bacteria. To overcome resistance, beta-lactam antibiotics are often given to the patient with beta-lactamase inhibitors; but the emergence of resistance to such inhibitors has increasingly reduced their practical effectiveness. To address this problem, Peter hypothesizes that differences in the molecular structure formed between beta-lactamase enzyme-drug complexes will yield an understanding of which bacterial mutations lead to drug resistance and how to design better antibiotics to overcome the resistance. To rapidly determine drug resistance from a clinical sample and thus enable targeted antibiotic therapy, he proposes an entirely new approach — leveraging real-time advanced sequencing technology and cloud computing. To predict the best drug to use against an infection he will use DNA sequencing technology in combination with computational analysis to identify key bacterial mutations present in a clinical sample. If he is successful, the result will be the most effective antibiotics being used for each child's particular infection, overcoming the high mortality associated with infection during immunosuppression.



Core Molecular Structure of Penicillins
beta-Lactam Ring in Red