The path to new antibiotics: Researchers find vulnerable enzyme in pathogens

August 27 2009

Researchers at Burnham Institute for Medical Research (Burnham), University of Texas Southwestern Medical Center and University of Maryland have demonstrated that an enzyme that is essential to many bacteria can be targeted to kill dangerous pathogens. In addition, investigators discovered chemical compounds that can inhibit this enzyme and suppress the growth of pathogenic bacteria. These findings are essential to develop new broad-spectrum antibacterial agents to overcome multidrug resistance. The research was published in the Cell journal *Chemistry & Biology* on August 27.

Andrei Osterman, Ph.D., an associate professor in Burnham's Bioinformatics and Systems Biology program, and colleagues, targeted the bacterial nicotinate mononucleotide adenylyltransferase (NadD), an essential enzyme for nicotinamide adenine dinculeotide (NAD) biosynthesis. NAD has many crucial functions in nearly all important pathogens and the bacterial NadD differs significantly from the human enzyme.

"It's clear that because of bacterial resistance, we need new, wide-spectrum antibiotics," said Dr. Osterman. "This enzyme is indispensable in many pathogens, so finding ways to inhibit it could give us new options against infection."

According to the National Institutes of Health, drug resistance is making many diseases increasingly difficult—and sometimes impossible—to treat. They point to tuberculosis and methicillin-resistant *Staphylococcus*

aureus (MRSA) as two pathogens that pose a serious threat to human health.

Using a structure-based approach, the team searched for low-molecular-weight compounds that would selectively inhibit bacterial NadD, but not the human equivalent, by screening, in silico, more than a million compounds. Experimental testing of the best predicted compounds against *Escherichia coli* and *Bacillus anthracis* (anthrax) led them to a handful of versatile inhibitory chemotypes, which they explored in detail. Using protein crystallography, a 3D structure of the enzyme in complex with one of the inhibitors was solved providing guidelines for further drug improvement.

"This is proof-of-concept that NadD is a good target to create antibacterial agents," said Dr Osterman. "This knowledge will be useful for both biodefense and public health. The next step is to find better inhibitors. We do not have a silver bullet yet, but we are certainly hitting a golden target."

Source: Burnham Institute (news : web)