Scientists discover mechanism to make existing antibiotics more effective at lower doses

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A new study published in the September 11, 2009 issue of *Science* by researchers at the NYU School of Medicine reveals a conceptually novel mechanism that plays an important role in making human pathogens like *Staphylococcus aureus* and *Bacillus anthracis* resistant to numerous antibiotics.

The study led by Evgeny A. Nudler, PhD, The Julie Wilson Anderson Professor of Biochemistry at NYU Langone Medical Center, provides evidence that Nitric Oxide, or NO, is able to alleviate the oxidative stress in bacteria caused by many antibiotics and also helps to neutralize many antibacterial compounds. Eliminating this NO-mediated bacterial defense renders existing antibiotics more potent at lower, less toxic, doses. With infectious diseases the major cause of death worldwide, the study paves the way for new ways of combating bacteria that have become antibiotic resistant.

NO is a small molecule composed of one atom of oxygen and one of nitrogen. It was known as a toxic gas and air pollutant until 1987, when it was first shown to play a physiological role in mammals, for which a Nobel Prize was later awarded. NO has since been found to take part in an extraordinary range of activities including learning and memory, blood pressure regulation, penile erection, digestion and the fighting of infection and cancer. A few years ago, the Nudler's group from NYU demonstrated that bacteria mobilize NO to defend against the oxidative

stress. The new study from the same group supports the radical idea that many antibiotics cause the oxidative stress in bacteria, often resulting in their death, whereas NO counters this effect. This work suggests scientists could use commercially available inhibitors of NO-synthase, an enzyme producing NO in bacteria and humans, to make antibiotic resistant bacteria like MRSA and ANTHRAX more sensitive to available drugs during acute infection.

"Developing new medications to fight antibiotic resistant bacteria like MRSA is a huge hurdle, associated with great cost and countless safety issues," says Nudler. "Here, we have a short cut, where we don't have to invent new antibiotics. Instead, we can enhance the activity of well established ones, making them more effective at lower doses."

"We are very excited about the potential impact of this research in terms of continuing to push the boundaries of research in the area of infectious diseases," said Vivian S. Lee, MD, PhD, MBA, vice dean for science, senior vice president and chief scientific officer of NYU Langone Medical Center. "With the emergence of drug resistant bacteria, it's imperative that researchers strive to find conceptually new approaches to fight these pathogens."

Source: NYU Langone Medical Center