Slight change to antibacterial drug may improve tuberculosis treatments

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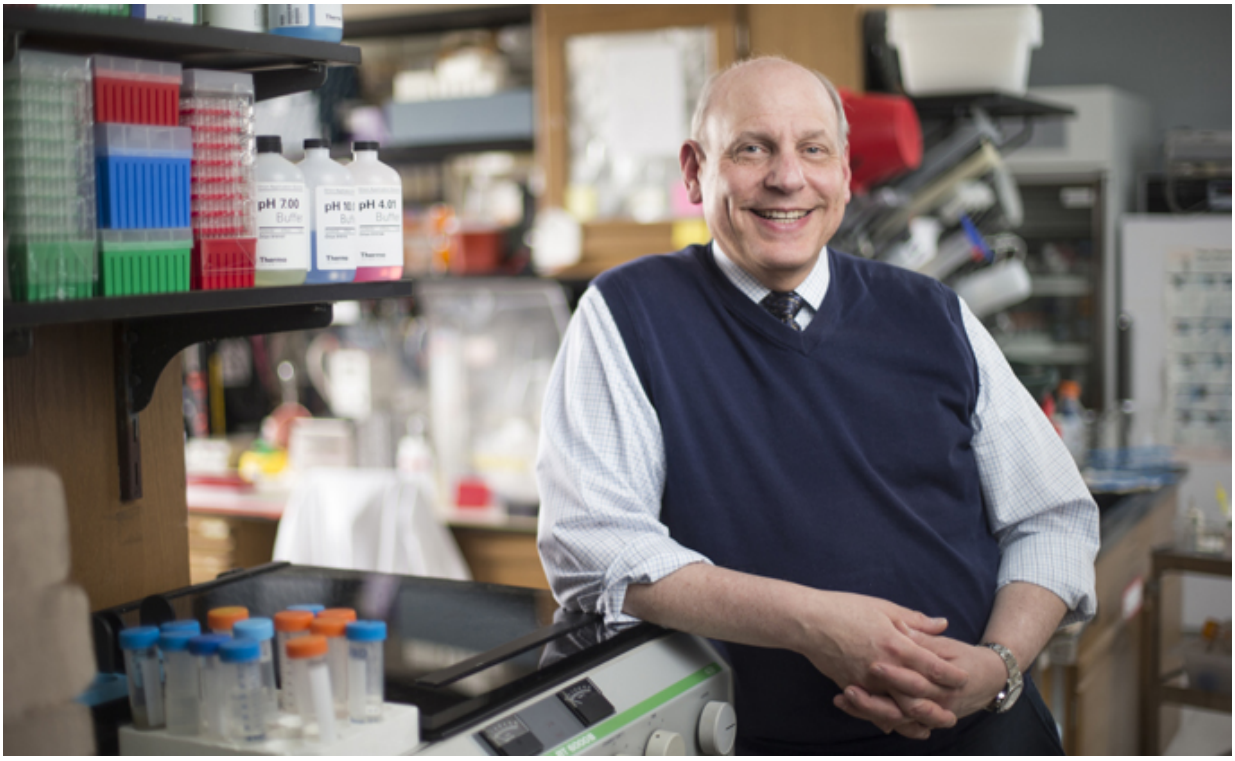

Neil Osheroff, Ph.D., and colleagues are working to create an antibacterial drug that could be more effective against its target enzyme in tuberculosis. Credit: Photo by John Russell

Researchers with Vanderbilt University have discovered that one small chemical change to an existing antibacterial drug results in a compound that is more effective against its target enzyme in tuberculosis.

Not only does the new compound—a derivative of the fluoroquinolone moxifloxacin—work better against the wild-type tuberculosis enzyme, it maintains activity against resistant forms of the enzyme, said Neil Osheroff, Ph.D., John Coniglio Professor of Biochemistry.

The findings, reported in the *Proceedings of the National Academy of Sciences*, could lead to a more effective treatment for tuberculosis.

"We're really excited about the translational potential of this work," Osheroff said.

Tuberculosis (TB) is one of the world's deadliest diseases. One third of the world's population is infected with TB, and in 2014, 1.5 million people died from the disease, according to the World Health Organization.

Although TB is considered curable, the six-month multi-drug regimen is difficult to complete—particularly in low-income parts of the world—and resistance to drugs in the first-line regimen is growing.

Broad-spectrum fluoroquinolone antibacterials, such as levofloxacin and moxifloxacin, are used in second-line tuberculosis treatment regimens, and they are being tested as part of a newer first-line regimen. But resistance to fluoroquinolones, which are commonly prescribed for a wide variety of infections, is also on the rise.

To understand how bacteria become resistant to fluoroquinolones, Osheroff and his team have studied the interaction between the drugs and their target enzyme, a bacterial type II topoisomerase.

"By understanding how the drugs interact with the enzyme, we can learn how resistance occurs and then hopefully develop strategies for overcoming that resistance," he said.

Topoisomerase type II enzymes cut DNA and stitch it back together to manage knots and tangles and facilitate DNA replication. The fluoroquinolones bind the enzymes and stabilize the cut DNA-enzyme complex, resulting in a chopped up genome.

Graduate student Katie Aldred, Ph.D., now a faculty member at the University of Evansville, characterized the interaction of fluoroquinolones with the tuberculosis topoisomerase II enzyme, called gyrase.

She confirmed the importance of certain gyrase amino acids to the interaction, and demonstrated how mutations that change those amino acids weaken or eliminate the interaction and result in resistance to the drug.

The researchers discovered that a certain position in the fluoroquinolone molecule was particularly important to the drug-gyrase interaction and that chemical changes at the critical position impacted the interaction.

Changing moxifloxacin at the critical position resulted in a compound (8-methyl moxifloxacin) that was more potent against the wild-type gyrase. The new compound was also effective against gyrase containing clinically relevant resistance mutations—even more effective than moxifloxacin itself was against the wild-type gyrase.

"By making one small change in moxifloxacin, we've come up with a much better drug against the wild-type gyrase enzyme; it maintains activity against resistant enzymes; and in all cases, it forms more stable DNA strand breaks," Osheroff said.

The hope, he added, is that the modified moxifloxacin will be an effective drug that results in a better treatment for tuberculosis.

"This project has been a lot of fun; we get to do highly mechanistic biochemistry that has really important ramifications," Osheroff said.

More information: Fluoroquinolone interactions with Mycobacterium tuberculosis gyrase: Enhancing drug activity against wild-type and resistant gyrase, Katie J. Aldred, DOI: 10.1073/pnas.1525055113 , www.pnas.org/content/early/201 … /1525055113.abstract

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