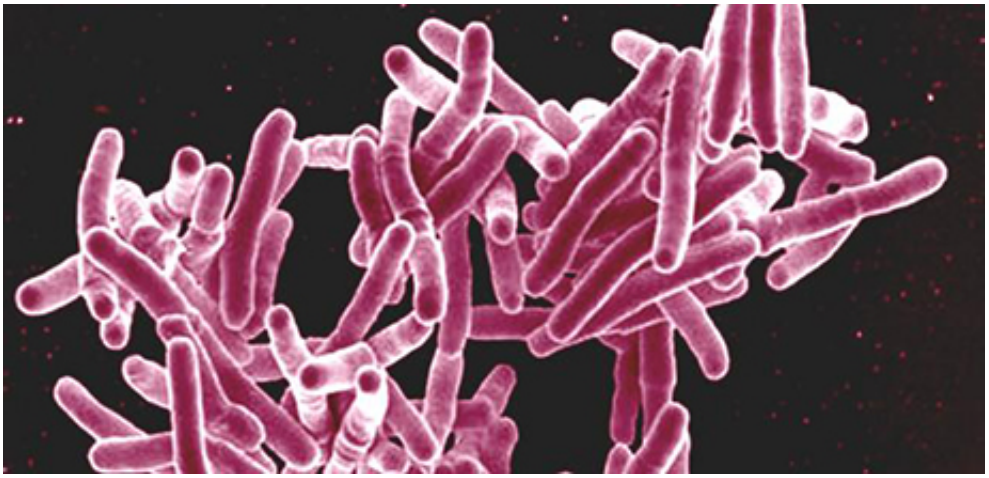
A new target in the fight against TB

July 8 2013, by Danny Freedman



(Medical Xpress)—Researchers have identified a potential new route for attacking tuberculosis that may hold promise against drug-resistant strains of the disease and even dormant TB infections.

In a new study, led Cynthia Dowd, assistant professor of chemistry, researchers designed and tested molecules that work like a chemical Trojan Horse, sneaking past the defenses of TB-causing bacterial cells and, once inside, blocking functions essential for survival.

The study appears in the July 1 edition of the medicinal chemistry journal *MedChemComm*.

"TB remains a huge threat to global public health," Dr. Dowd said. "… New therapeutics are essential for combating drug-resistance and staying one step ahead of the bug, so to speak. Our work seeks to validate a drug target that is not used by current drugs."

The effects of tuberculosis—a chronic bacterial infection, usually of the lungs—hang over thousands in the United States and millions worldwide. Though rates are improving, there were an estimated 8.7 million new cases of TB in 2011 and 1.4 million deaths, according to the World Health Organization. About one-third of the world population is thought to have latent TB, an inactive infection that carries no TB symptoms and cannot be spread unless it becomes activated.

In the new study, the chemicals targeted an enzyme known by the abbreviation Dxr. Enzymes drive life-sustaining chemical reactions inside cells and are common targets for drug treatments. Operating like a lock-and-key mechanism, enzymes like Dxr have openings that fit complementary-shaped molecules. Once they attach to the enzyme, molecules are broken down or combined to forge yet other molecules for use inside the cell.

Enzyme inhibitors, like those created by the research team, act as false keys and block that process. "The key doesn't open the lock, the key gums up the lock," Dr. Dowd said. "It occupies the lock so the right key can't fit in there."

The team set out to hamper two of those locks, or binding sites, on the Dxr enzyme: one for fosmidomycin, a proven disruptor of Dxr that is repelled by the cell wall of the bacteria that causes TB; and the binding site for a molecule called NADPH.

Building on their previous work showing that a molecule can be chemically disguised to gain entry into the TB cell, the researchers

mimicked both fosmidomycin and NADPH in a masked, two-pronged key that stretched from one binding site to the other. The two-pronged approach, rather than two separated chemicals, can offer a tighter fit into the binding sites, Dr. Dowd said.

The work was a success, and a surprising one at that—the false key for NADPH actually missed its mark and landed in another, unrecognized binding site on the enzyme.

The discovery marks the first time the Dxr enzyme has been used to kill TB, Dr. Dowd said, lending hope that the findings could be used to sidestep resistance TB has built up along other drug pathways. And since Dxr is involved in basic, root-level functions of cells, she said, it may also prove useful against dormant TB infections.

The team is now trying to determine exactly how the chemical works and how to sharpen its potency.

Already the team has "newer compounds that have better [results] than this," she said.

And whatever anxiety may have been caused by scientific serendipity now has been replaced with the excitement of seeing a new angle on an old problem. "It helps us move into an area where nobody else is," Dr. Dowd said. "… It forces you to think outside the box and think about things in a new way."

Provided by George Washington University