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New drug targets may fight tuberculosis and other bacterial infections in novel way

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Over the course of the 20th Century, doctors waged war against infectious bacterial illness with the best new weapon they had: antibiotics. But the emergence of dangerous, multi-drug resistant strains of tuberculosis and other killer infections means that in the 21st century antibiotics are losing ground against bacterial disease.

Now, researchers from Weill Cornell Medical College in New York City say exciting new molecular targets -- so-called "virulence factors" that bacteria use to thrive once they are in the host -- present an alternative, potent means of stopping TB, leprosy and other bacterial illness.

"We have developed the first inhibitor of a key small molecule from Mycobacterium tuberculosis and Mycobacterium leprae (which causes leprosy) utilized to subvert human host's defenses and damage and invade human host's cells during infection," explains study senior author Dr. Luis Quadri, Associate Professor of Microbiology and Immunology at Weill Cornell.

"With this work, we now have proof of principle for the inhibition of this virulence factor in bacteria cultured in the lab. Our next step is to explore whether this inhibitor can stop these pathogens from multiplying in a mouse host, curtailing infection," Dr. Quadri says.

The findings -- published online today in *Chemistry and Biology* and appearing in the journal's Jan. 26 print edition -- highlight what Dr. Quadri has called a "paradigm shift" in infectious disease research.

"We are moving beyond antimicrobials such as antibiotics, which kill the bacterium directly, to anti-infectives, that may have no effect against the pathogen in the test tube but which do compromise its ability to infect and spread in the host," he explains. "We believe that the expansion of the drug armamentarium to include such anti-infective drugs could help the fight against multi-drug resistant infection that has become such a challenge today."

According to World Health Organization data, TB remains one of the world's top-ten leading causes of death, killing nearly two million people each year. Multi-drug resistant strains of M. tuberculosis -- as well as even more dangerous, extensive-drug-resistant (XDR) strains of the bug -- are emerging each year.

"Obviously, we are going to require more than the traditional antimicrobial approach to turn this situation around," Dr. Quadri says.

In this study, Dr. Quadri, along with co-lead researchers Drs. Julian Ferraras and Karen Stirrett, focused on particular small-molecule virulence factors called phenolic glycolipids (PGLs).

Various strains of M. tuberculosis use PGLs to weaken our body defenses whereas M. leprae uses PGLs to damage and invade our nerve cells during infection.

"Therefore, we hypothesize that drugs blocking PGL synthesis would reduce the adaptive fitness of PGL-producing M. tuberculosis strains in the human host by eliminating PGL-dependent immunomodulatory effects. These drugs may also diminish the ability of M. leprae to invade nerve cells and produce nerve function impairment," Dr. Quadri explains.

In complex work in the laboratory, the researchers investigated and then

elucidated a crucial, early step in PGL biosynthesis. They also pinpointed a key enzyme, called FadD22, that is essential to that stage of the process.

"Based on that, we collaborated with Dr. Derek Tan's lab at Memorial Sloan-Kettering Cancer Center to synthesize a molecule that targets FadD22 and successfully inhibits that early step in PGL production," Dr. Quadri said.

Follow-up work using both enzyme assays and M. tuberculosis assays confirmed that the new inhibitor does block the production of PGLs. Although it was technically not possible to test the inhibitor in M. leprae, that pathogen is very closely related to M. tuberculosis, so the researchers believe their agent would inhibit production of PGLs there, as well.

Work is already underway to come up with other, even more potent PGL biosynthesis inhibitors, Dr. Quadri says, with an eye to testing the best candidates in an animal model.

"We are not saying that anti-infectives will ever replace antibiotics, but with pathogens as deadly as M. tuberculosis or as debilitating as M. leprae, you'd ideally like to have as many pharmaceutical weapons in your armamentarium as you can, to use either alone or in combination," Dr. Quadri says.

The new discoveries are highly encouraging, he adds.

"I believe that drugs targeting virulence factors are just one component of the paradigm shift in the antimicrobial drug discovery for the 21st century -- one that will offer patients more options in the fight against truly global killers," he says.

Source: New York- Presbyterian Hospital