Iowa State University researcher uncovers potential key to curing tuberculosis

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Reuben Peters is leading the team of scientists from Iowa State; the University of Illinois; and Cornell University, that is attempting to find ways to minimize tuberculosis. The group had their research published in the Aug. 28 issue of the *Journal of Biological Chemistry*, and their research is also scheduled to be the cover article in an upcoming issue of the *Journal of the American Chemical Society*. Credit: ISU photo by Bob Elbert

Researchers at Iowa State University have identified an enzyme that helps make tuberculosis resistant to a human's natural defense system. Researchers have also found a method to possibly neutralize that enzyme, which may someday lead to a cure for tuberculosis.

Tuberculosis is caused by *Mycobacterium tuberculosis* and is a contagious disease that is on the rise, killing 1.5 to 2 million people worldwide annually.

Reuben Peters, associate professor in the department of biochemistry, biophysics and molecular biology, is leading the team of scientists from Iowa State; the University of Illinois, Urbana-Champaign; and Cornell University, Ithaca, New York, that is attempting to find ways to minimize the disease. The group had their research published in the Aug. 28 issue of the Journal of Biological Chemistry, and their research is also scheduled to be the cover article in an upcoming issue of the Journal of the American Chemical Society.

When most infections are introduced into humans, the body defends itself with certain cells -- called macrophage cells -- that kill the invading micro-organisms. The macrophage cells engulf and destroy these microbes, such as the *Mycobacterium tuberculosis*.

Peters found that the mycobacterium tuberculosis produces a defensive molecule that prevents the macrophage cells from destroying them. Peters and his team named the defensive molecule edaxadiene.

Peters' next step was to try to find molecules that bind with the edaxadiene-producing enzymes from tuberculosis and neutralize them. This makes the tuberculosis cells unable to produce edaxadiene. Without edaxadiene, tuberculosis cells would have a reduced ability to resist being killed by the macrophage cells.

Peters thinks he may have already found one.

"We have inhibitors that bind tightly to one of the enzymes that make edaxadiene in a test tube," said Peters.

Finding an inhibitor that works outside of the test tube, and in humans, and is stable, and can be ingested safely by humans, and can help kill tuberculosis is a process that may take a decade.

But Peters sees a huge reward at the end of the process.

"This is the project where I tell my students, 'If we can make even just a 1 percent impact, we can save 15,000 - 20,000 lives a year.' That is really a significant contribution towards alleviating human suffering," said Peters.

Peters' group found the molecule by comparing the genetic makeup of tuberculosis - which kills humans - to the type that kills cattle but doesn't seem to have any effect on humans - *Mycobacterium bovis*.

"Their genetic sequences are more than 99.9 percent identical," said Peters. "However, whereas, tuberculosis causes disease in humans, the bovis variety is much less infectious in humans, although it does cause disease in cattle."

One of the small differences in the genetic information between the two mycobacteria may hold the key to why one infects humans while the other does not.

"The bovis mycobacterium is missing only one nucleotide in the gene for one of the edaxadiene-producing enzymes, but that turns out to be very important as it prevents that enzyme from functioning," he said.

"The critical piece for this idea is that *Mycobacterium bovis* doesn't make edaxadiene, and doesn't affect humans much, whereas Mycobacterium tuberculosis does make edaxadiene and is infectious in humans," Peters said.

"We think this is the big difference between the two mycobacterium, mainly because this is the only difference I know of that seems to affect their infection process," he added.

"This work presents tantalizing evidence that edaxadiene helps the tuberculosis bacterium evade the body's defenses," said Warren Jones, who oversees enzymology grants at the National Institutes of Health's National Institute of General Medical Sciences, which funded the research. "By exploring ways to block the production of this molecule, Dr. Peters is pioneering a new approach for combating this deadly pathogen."

One of the hurdles that will confront Peters in finding human cures is that the effect of edaxadiene may be specific to humans, so the normal testing process may be difficult.

The normal testing sequence involves testing in the laboratory, then on smaller animals, then larger animals, and then to humans.

Since edaxadiene may be important for the ability of tuberculosis to infect humans, rather than animals, preventing production of edaxadiene by tuberculosis may not have much effect in animals, which will be challenging for the process of bringing a cure to drugstore shelves, according to Peters.

Peters added that he is eager to take on the next challenge in the fight against tuberculosis.

Source: Iowa State University (news : web)