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New avenues for overcoming tuberculosis drug resistance

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Tuberculosis (TB) continues to be a global health problem, in part due to the exceptional drug resistance displayed by the TB-causing agent, *Mycobacterium tuberculosis*. Beyond even acquired drug resistance, these bacteria are also inherently resistant to many other common antibiotics, which limits the available options in finding alternative treatments to resistant TB strains.

However, in a presentation at the American Society for Biochemistry and Molecular Biology's annual meeting, titled "Drug resistance in tuberculosis," John Blanchard of the Albert Einstein College of Medicine will discuss his group's work at eliminating this inherent drug resistance, which may help in the battle against the emerging extensively-drug resistant TB strains. The talk will take place on Tuesday, April 27 at 9:55 am PST in Anaheim Convention Center Room 304C.

"These XDR strains are even more resilient than multi-drug resistant (MDR) strains," notes Blanchard. They are resistant to almost everything we currently have in the kitchen."

Blanchard, a professor at Albert Einstein's department of biochemistry, and his team have specifically targeted an enzyme called beta-lactamase, which can break down and disable beta-lactams, a large family of antibiotics that includes penicillin and its relatives.

"When the *M. tuberculosis* genome was sequenced a few years ago, the presence of this beta-lactamase enzyme was discovered," Blanchard says,

"which was surprising since beta-lactams have never been systematically used to treat TB."

Perhaps just as surprising was that most scientists didn't pay much attention to the *M. tuberculosis* beta-lactamase discovery, but Blanchard thought it would be an attractive therapeutic target, considering several beta-lactamase inhibitors had been developed for other bacteria.

"If we could inactivate this inactivator enzyme, it would expose TB bacteria to a whole new range of antibiotics," he says.

While *M. tuberculosis* was resistant to most beta-lactamase inhibitors, Blanchard's group found that the drug clavulanate was effective in shutting down the TB enzyme. The combination of clavulanate with the beta-lactam meropenem could effectively sterilize laboratory cultures of TB within two weeks, including several XDR-strains.

Blanchard notes this finding was exciting since, despite such high rates of drug resistance, research into new TB drugs is not a high priority in industrialized countries (for socio-economic reasons), and thus the best short-term approach might be identifying other already FDA approved antibiotics that are effective against TB -like meropenem and clavulanate.

Blanchard is currently progressing with the next steps of the therapeutic process, which includes both detailed animal studies and setting up some small-scale trials with XDR-TB patients in developing nations.

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