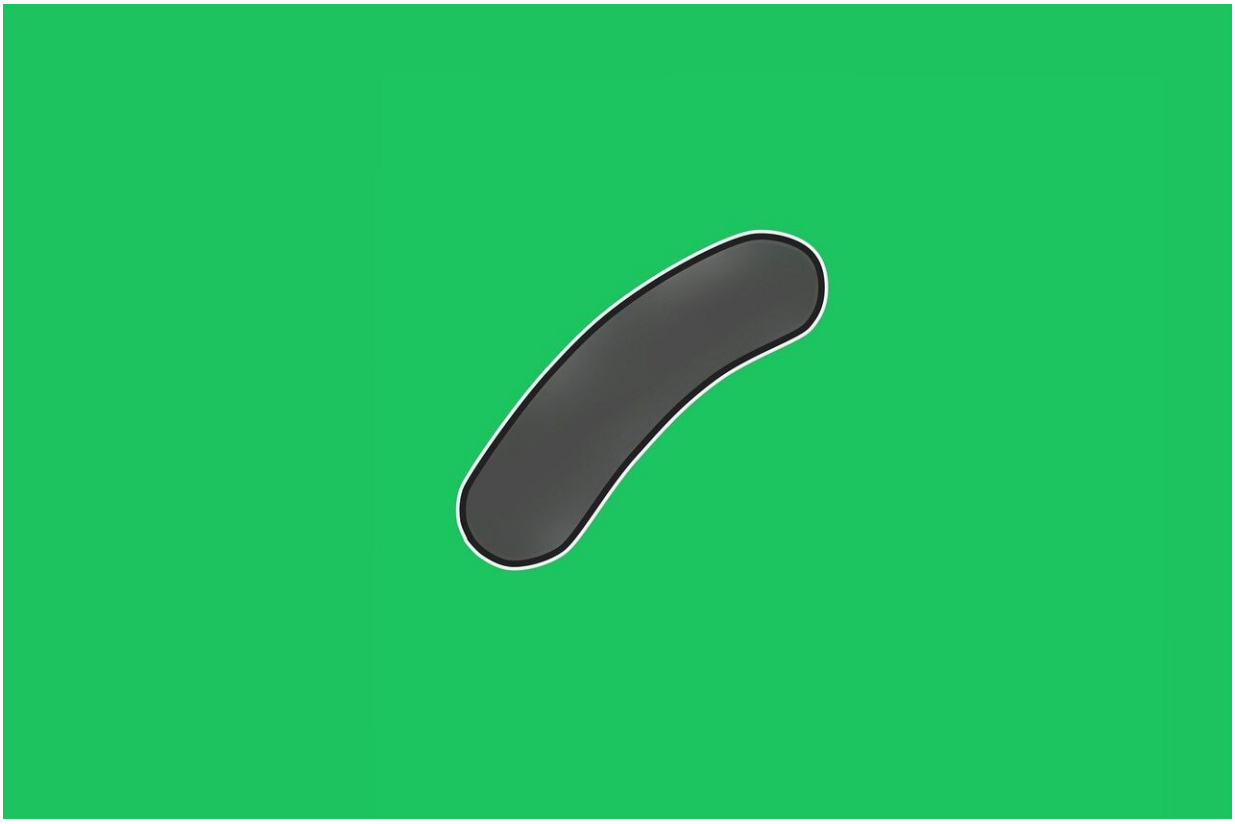
New tuberculosis drug may shorten treatment time for patients

February 11 2019



Credit: CC0 Public Domain

A new experimental antibiotic for tuberculosis has been shown to be more effective against TB than isoniazid, a decades-old drug which is currently one of the standard treatments. In mouse studies, the new drug

showed a much lower tendency to develop resistance, and it remains in the tissues where the Mycobacterium tuberculosis bacteria reside for longer, killing them more effectively. The research is published February 11 in *Antimicrobial Agents and Chemotherapy*, a journal of the American Society for Microbiology.

The goal of TB drug development programs is to develop universal treatment regimens that will shorten and simplify TB treatment in patients, which typically takes at least six months, and sometimes more than a year, said lead author Gregory T. Robertson, Ph.D., Assistant Professor, Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins.

The new drug, called AN12855, has several advantages over isoniazid. Isoniazid, requires conversion to its active form by a Mycobacterial enzyme, KatG, in order to kill the pathogen, which creates a couple of problems. First, in some M. tuberculosis, KatG is nonfunctional. That doesn't make M. tuberculosis any less pathogenic, but it prevents the drug from working.

That creates an easy avenue for the development of drug resistance. Under selection pressure from isoniazid, the tuberculosis bacteria with nonfunctional KatG—those that don't activate the drug—are the ones that reproduce. Under these circumstances, drug resistance may develop.

A hallmark of human tuberculosis is the presence of "heterogeneous pulmonary disease." This includes a host defense involving confinement of invading bacteria within small cyst-like bodies called granulomas, that lack vasculature and often prevent the drug from reaching the pathogen. Most mouse TB models used for clinical evaluation of new drugs fail to produce this advanced lung pathology. Thus, they give little insight into how drugs might behave in the presence of advanced lung disease that is typical of human tuberculosis.

In the study, the investigators used a new TB mouse model that develops these M. tuberculosis-containing granulomas to compare isoniazid and AN12855. "We discovered that the drugs differed dramatically with respect to their abilities to kill the pathogen in highly diseased tissues," said Dr. Robertson. AN12855 proved more effective, "without selecting for appreciable drug resistance," said Dr. Robertson

The superior efficacy is not surprising: AN12855 was superior in gaining entry and being retained in the granulomas, "where M. tuberculosis is found in highest numbers," said Dr. Robertson. "Whether this translates into improvements in treatment of human disease will be the subject of future studies."

"Our studies also further validate the use of a new TB mouse efficacy model (dubbed C3HeB/FeJ) as a research tool to study the impact of heightened human-like disease states on the activity and distribution of TB antibiotics that are in various stages of development," said Dr. Robertson. That could accelerate development of better TB treatments.

"Despite significant progress in combatting tuberculosis, TB remains the leading infectious cause of death worldwide," said Dr. Robertson. According to WHO, 10 million people fell ill with TB in 2017 and 1.6 million died from the disease." Multidrug resistance is a further challenge to the mission to control TB globally, he said. "Collectively, our group has pioneered the use of new TB mouse efficacy models to help advance innovative new therapies designed to shorten the length of TB treatment."

Provided by American Society for Microbiology