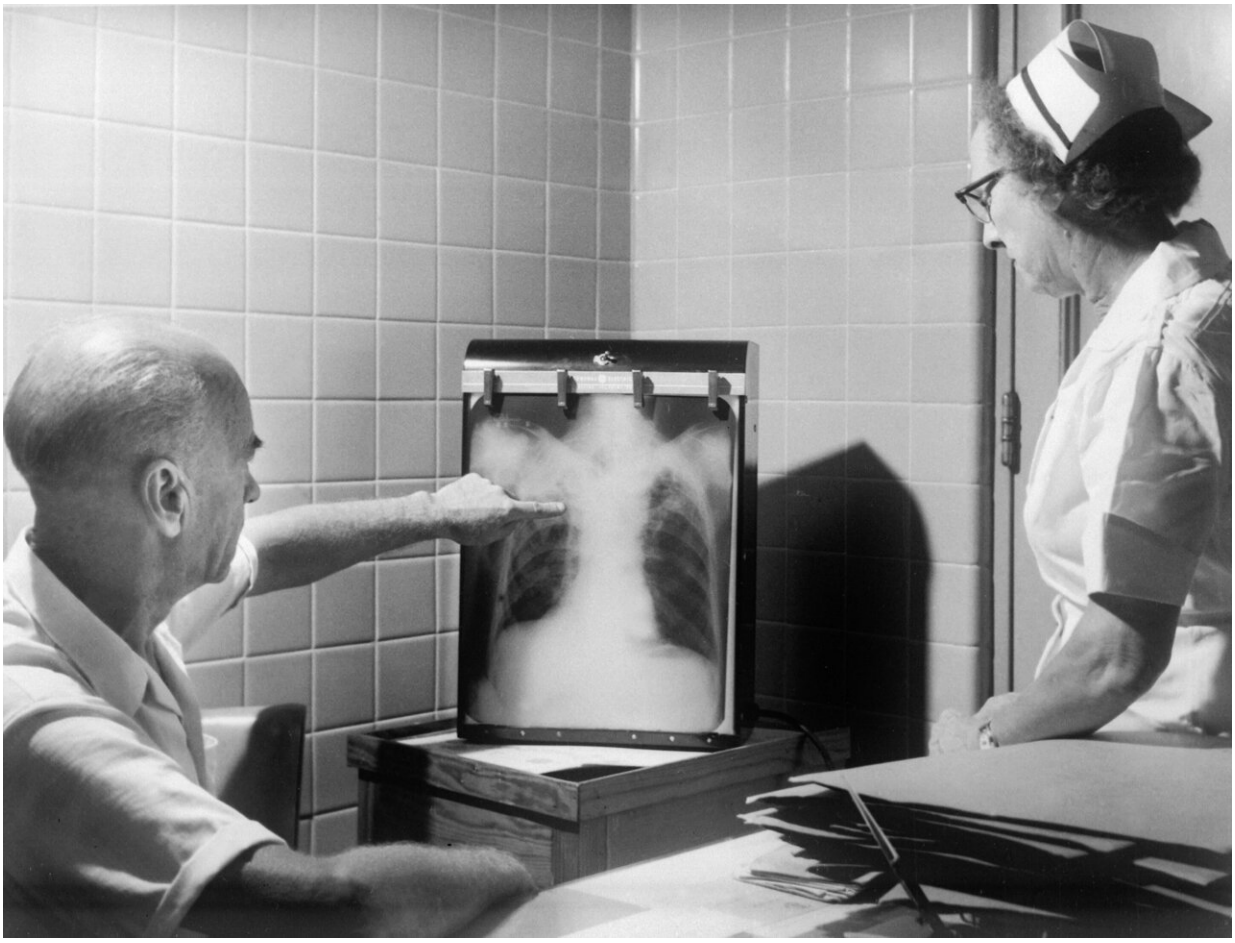
Can drug resistant TB be reversed with a novel small molecule? Scientists turn to an animal model to find out

May 24 2022, by Delthia Ricks



Credit: Unsplash/CC0 Public Domain

Tuberculosis is a major public health concern, an ancient bacterial disease that has claimed the lives of kings, presidents, poets and at least one star of Hollywood's silver screen-era. Yet even now in the 21st century, it's still impossible to shake the scourge. TB kills someone around the globe every 22 seconds, the World Health Organization estimates.

As staggering as that death toll may seem, tuberculosis remains a persistent reminder that it is the killer that has stalked humankind for at least 3,000 years. It was so prevalent in the 19th century that by the 1880s it was a leading cause of death, claiming the lives of 1 in every 7 people in the United States and Europe. History is littered with the names of famous people who've succumbed to the disease: Composer Frederic Chopin died of tuberculosis as did U.S. presidents James Monroe and Andrew Jackson; King Henry VII of England; poet John Keats; author Jane Austen and 20th century actress Vivien Leigh, who starred in *Gone with the Wind*.

One reason that tuberculosis is still a worldwide menace can be explained by the infectious agent's capacity to repel antibiotics, thwarting many of the potent antibiotics developed to kill it. The disease is especially worrisome in resource poor regions of the globe where mitigation efforts are expensive and the pandemic dealt a blow to TB control efforts. With public health departments stretched to the breaking point coping with SARS-CoV-2, tuberculosis control programs have suffered a setback during the pandemic, according to WHO.

Solving the resistance problem is critical because isolates of the causative bacteria, Mycobacterium tuberculosis, are increasingly resistant worldwide. The bacteria can rebuff an array of antibiotics, including frontline treatments, isoniazid and rifampin. Worse, the bacteria are showing signs of resistance to backup drugs, such as ethionamide, which means fewer and fewer options eventually may be

left on pharmacy shelves.

An international team of scientists analyzing drug resistance in TB bacteria has trained a spotlight on growing levels of resistance to ethionamide, a second-line antibiotic usually reserved for multidrug-resistant tuberculosis. The team is led by Marion Flipo, and collaborators at Université de Lille, Inserm, and Institut Pasteur de Lille in France.

The researchers are synthesizing small molecules to determine which ones can enhance the activity of ethionamide, a type of medication that is known as a prodrug. This means that ethionamide—and others in this class—are converted to their active form once inside the bacteria.

Intriguingly, M. tuberculosis possesses an enzyme—MmyA—which is capable of converting ethionamide into its active form. Once converted, ethionamide is transformed into a bactericide—a TB annihilating compound that destroys the bacteria. In essence, the conversion causes M. tuberculosis to participate in killing itself.

But in the knock-down-drag out world of survival of the fittest, the bacteria have undergone an evolutionary change, and numerous isolates have acquired genes allowing them to repel ethionamide. As a result, the drug doesn't kill these resistant strains, which means that TB thrives in these patients who, without treatment options, could die of the disease.

Flipo and team members in France, elsewhere in Europe and in the United Kingdom, found that one of the molecules under development—SMARt751—reverses the bacteria's resistance to ethionamide. In the presence of SMARt751, the bacteria can no long bypass ethonamide and survive. Based on their extensive laboratory research, scientists are so far paving the way with to outfox the resistance strategies of M. tuberculosis.

Writing in *Science Translational Medicine*, Flipo and colleagues report that SMARt751 restores ethionamide's role as a prodrug because M. tuberculosis, in the presence of SMARt751, undergoes a quick series of molecular events, and then dies, the scientists said.

"The lead compound, SMARt751, interacted with the transcriptional regulator VirS of *M. tuberculosis*, which regulates the MymA operon encoding a monooxygenase that activates ethionamide," Flipo asserted, referring to the molecular switch that SMARt751 flips to render M. tuberculosis vulnerable to the prodrug ethionamide again.

"SMARt751 boosted the efficacy of ethionamide in vitro and in mouse models of acute and chronic TB. SMARt751 also restored full efficacy of ethionamide in mice infected with M. tuberculosis strains carrying mutations in the ethA gene, which cause ethionamide resistance.

"SMARt751 was shown to be safe in tests conducted in vitro and in vivo," Flipo continued. "The sensitivity of Mycobacterium tuberculosis to antibiotic prodrugs is dependent on the efficacy of the activation process that transforms the prodrugs into their active antibacterial forms."

In 2020, the most recent year for complete statistics, there were more than 10 million new cases of tuberculosis and 1.5 million deaths worldwide. It's estimated by the U.S. Centers for Disease Control and Prevention that approximately 1 in 30 new TB cases, or 3.5% are multidrug resistant. The agency additionally estimates that 1 in 5 previously treated cases of tuberculosis, or 20.5%, are multidrug resistant.

In the face of those statistics and in the midst of an ongoing coronavirus pandemic, tuberculosis remains a top priority for the World Health Organization, and combatng antibiotic resistance is part of that fight,

WHO experts say.

Although drug resistance may seem on one level to be an academic puzzle studied by scientists such as Flipo, it has become a major global health problem. The WHO has predicted drug resistant microbial infections could become a leading cause of death by 2050 unless steps that are being pursued now successfully address the problem. Multidrug resistance is associated with multiple microbial species—bacteria, fungi and viruses. All have evolved a host of strategies allowing them to repel the chemical warfare that humans deploy to kill them.

Flipo and colleagues, meanwhile, are continuing their research on novel approaches to reversing drug resistance involving M. tuberculosis. Of note is SMARt751's capacity to reverse drug resistance in animal models infected with M. tuberculosis strains harboring a mutation that predisposes the bacteria to resistance.

Resistance genes are often located on plasmids or transposons and can be transferred from one bacterial cell to another. A plasmid is an extra-chromosomal, self-replicating DNA molecule. Plasmids occur naturally in bacteria. A transposon, on the other hand, is a DNA sequence that moves around to different positions within the bacterial genome.

Because the small molecule SMARt751 reverses resistance to ethionamide in M. tuberculosis, Flipo and colleagues were able to make a few predictions about what they expect will happen once it reaches the clinic and humans receive doses of the compound—and ethionamide—which must be taken simultaneously.

Flipo and colleagues predict that a mere 25 mg dose of SMARt751 daily could cut effective doses of ethionamide by fourfold in humans. This lower dose would likely decrease the risk of resistance and side effects that are common with current doses of ethionamide alone, they say.

More information: Marion Flipo et al, The small-molecule SMARt751 reverses Mycobacterium tuberculosis resistance to ethionamide in acute and chronic mouse models of tuberculosis, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.aaz6280