MedicalXpress

Research revealing 'persistent bacteria' could be key to future tuberculosis trials

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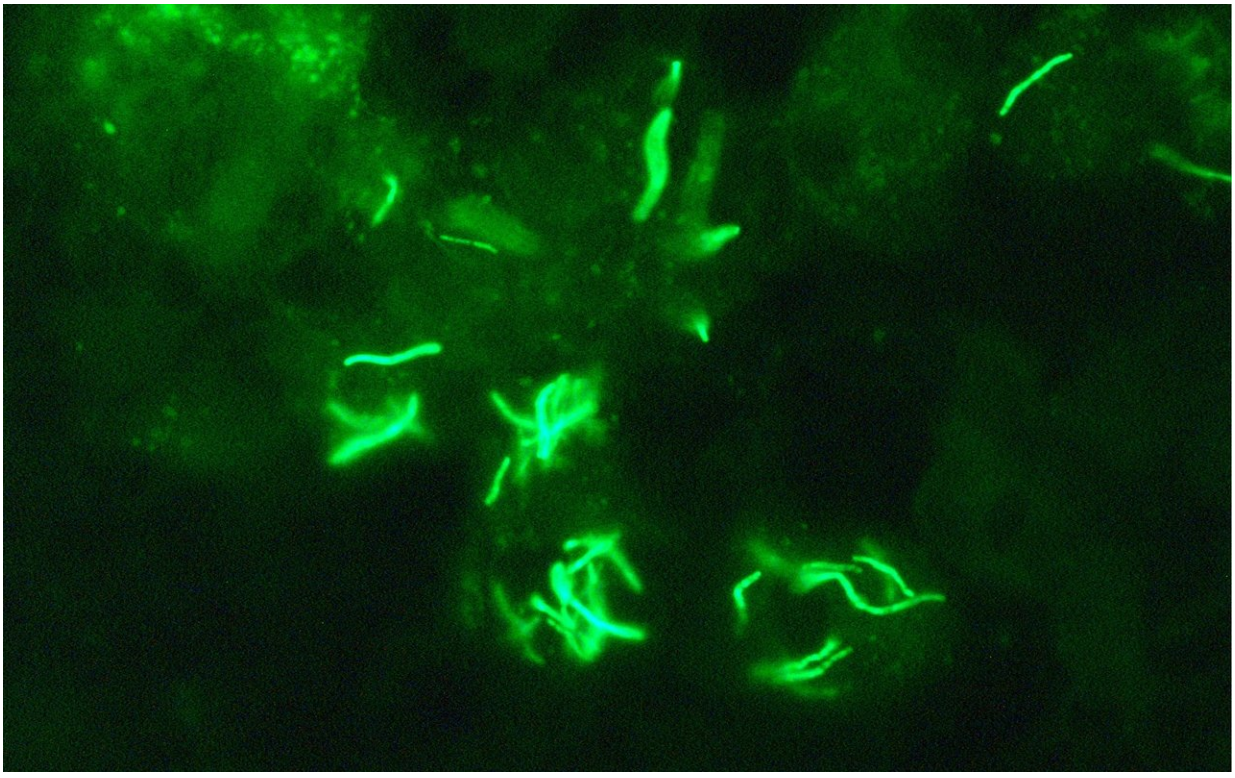
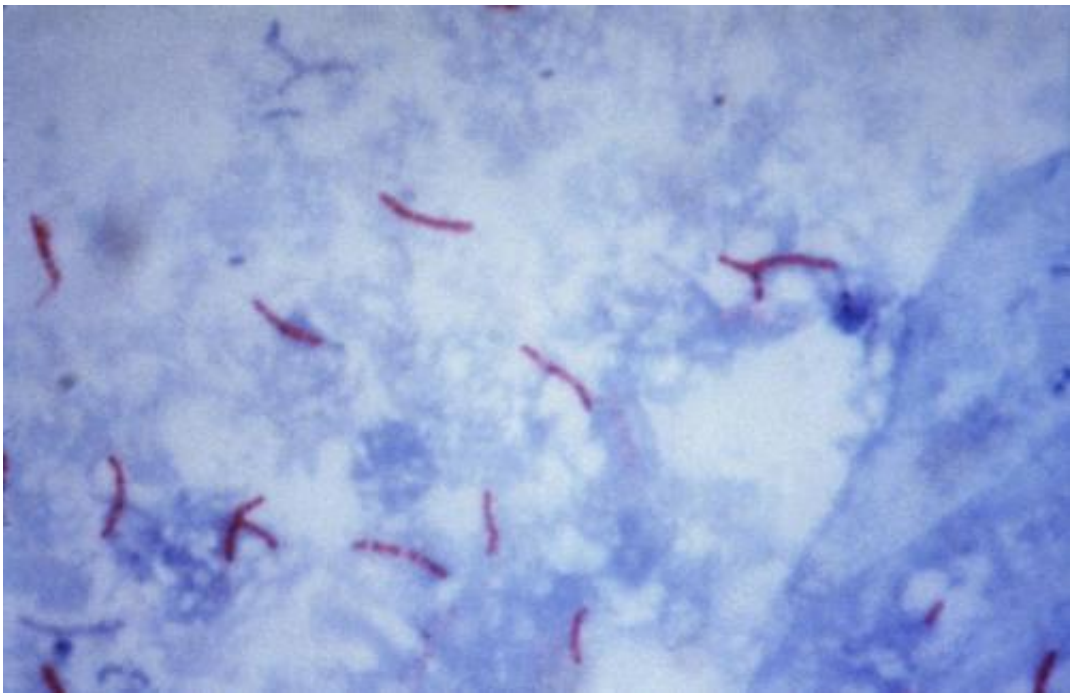


Credit: St. George's University of London

Research carried out by St George's, University of London into tuberculosis treatments has clearly shown the 'persistent bacteria' that make treating the disease so difficult for the first time, using a new combination therapy.

Tuberculosis (TB) is a life-threatening infection that kills millions of people worldwide each year. TB is hard to treat, with patients often needing to take multiple antibiotic drugs for as long as 6 months. Even then, this long treatment does not necessarily clear the infection completely, because TB bugs "go to sleep" and cannot be detected using hospital tests. These invisible TB bugs, known as "persisters", can remain despite antibiotic treatments and then reactivate to cause full-blown TB infections. These persister bugs present a major difficulty for scientists developing new drugs to combat TB. Researchers have been trying to shorten the TB treatment duration for many decades but in order to do so they need to have an accurate way of 'seeing' the invisible persistent bacteria.

Dr. Yanmin Hu, Senior Research Fellow at St George's University of London, used resuscitation promoting factor (RPF) - a number of small protein molecules which 'wake up' sleeping tuberculosis bacteria—in research that looked at switching two components of the current TB treatment regime, isoniazid or ethambutol—with the drug moxifloxacin. Moxifloxacin replacement drug regimens have been studied in recent human trials with unsuccessful results in term of shortening TB treatment duration.



This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

Mice with TB infection were treated with regimens in which either isoniazid or ethambutol was replaced by moxifloxacin. The effectiveness of the regimens was compared to the standard regimen for bacterial colony count elimination. Disease relapse rates were also measured. While the moxifloxacin-replacing isoniazid regimen killed the TB bacteria more quickly than the standard and moxifloxacin-replacing ethambutol regimens, after the treatment, persistent bacteria in the mice organs were still present when examined using RPF. Because of the presence of sleeping invisible persisters at the end of treatment, TB relapses were seen in mice with both moxifloxacin replacement drug regimens. This explains why these drug regimens were not been able to

shorten the TB treatment duration in humans before since they were unable to kill persisters.

Dr. Hu led the study, which involved researchers from St George's, the University of Liverpool, and the University of St Andrews. She explained: "In 40 years of modern TB treatment these persistent bacteria have never been so clearly identified. The only way to see their presence was to look at patient relapses. Our study showed that neither of these new hopes containing moxifloxacin for shortening the treatment duration killed the persistent bacteria. Our research demonstrates that in future clinical studies we must measure the persistent bacteria in this way if future research into shortening TB treatment regimes is ever to be successful."

"Moxifloxacin Replacement in Contemporary Tuberculosis Drug Regimens Is Ineffective against Persistent Mycobacterium tuberculosis in the Cornell Mouse Model" will be published online on June 26 in *Antimicrobial Agents and Chemotherapy*.

More information: Yingjun Liu et al. Moxifloxacin replacement in contemporary tuberculosis drug regimens is ineffective against persistent Mycobacterium tuberculosis: Novel insights from the Cornell mouse model, *Antimicrobial Agents and Chemotherapy* (2018). DOI: 10.1128/AAC.00190-18

Provided by St. George's University of London