Scientists make significant discovery in the fight against drug-resistant tuberculosis

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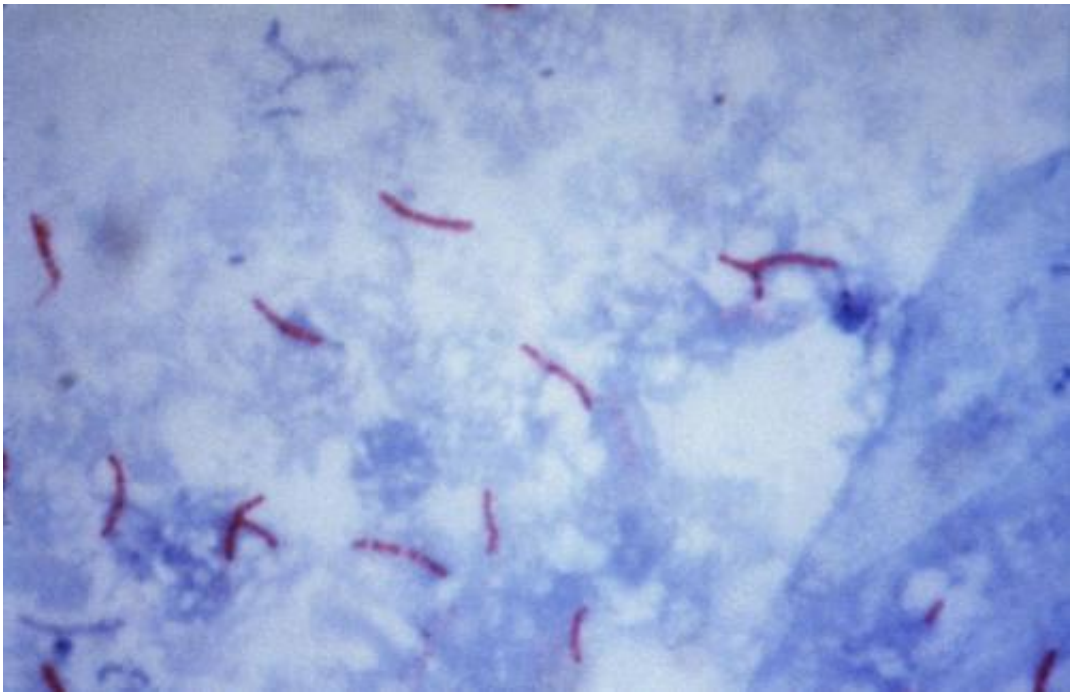


This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains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

A team of scientists have identified a naturally occurring antibiotic that may help in the fight against drug-resistant Tuberculosis.

Each year, approximately 10 million people fall ill with Tuberculosis (TB) and around 1.7 million die from the devastating disease worldwide.

One of the main antibiotics for TB is rifampicin, however, many strains of the Tuberculosis-causing bacteria - *Mycobacterium tuberculosis* - have developed resistance to it. Approximately 600,000 people every year are diagnosed with rifampicin-resistant tuberculosis.

Now researchers from Newcastle University and Demuris Ltd have identified that a naturally occurring antibiotic, called kanglemycin A—related to the antibiotic rifampicin—is active against rifampicin-resistant *Mycobacterium tuberculosis*.

The findings of their study have been published today in the journal, *Molecular Cell*, and it is hoped that this compound and the enhanced understanding gained from these studies may lead to effective new drug treatments in the future.

Exciting findings

The team used chemical, biophysical, molecular biology and microbiological methods, as well as X-ray crystallography, to show how kanglemycin A binds to its target RNA polymerase and how it manages to overcome resistance.

It was known that rifampicin binds to a groove in the RNA polymerase molecule and that mutations that change the amino-acid sequence of the RNA polymerase can prevent this binding, while maintaining the ability to produce RNA.

Kanglemycin A binds to the same groove, but its structure revealed extensions that also bind just outside the groove allowing it to maintain its affinity to the rifampicin-resistant RNA polymerase and antibiotic

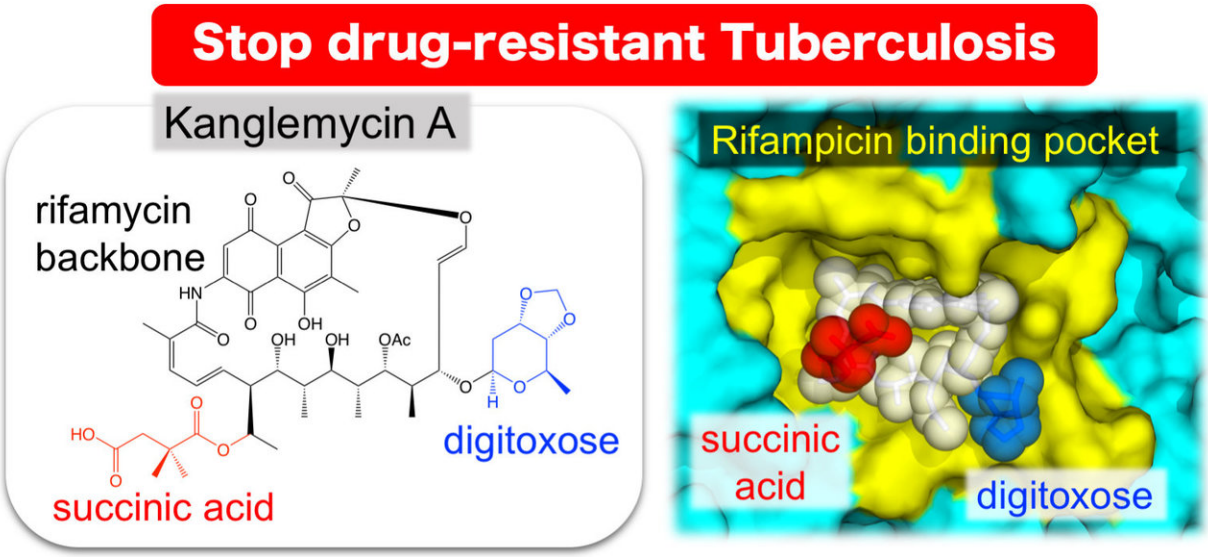
activity in rifampicin-resistant bacteria.

Professor Nikolay Zenkin, from Newcastle University's Institute for Cell and Molecular Biosciences, led the international study.

He said: "Treatment of TB involves a cocktail of antibiotics administered over many months, and resistance to several key antibiotics is becoming a major public health problem around the world.

"Our findings are very exciting and the first step towards developing a new, effective drug treatment for patients with rifampicin resistant TB to prevent fatalities in the future."

Dr. Michael Hall, from Newcastle University, who led chemical characterization of kanglemycin A, added: "This is an exciting development for the future treatment of rifampicin resistant TB and shows what can be achieved when local businesses and universities work together."



The natural antibiotic kanglemycin A binds bacterial RNA polymerase at the rifampicin binding-pocket, but maintains potency against rifampicin-resistant mutants due to two unique chemical groups (digitoxose and succinic acid) that increase its affinity to rifampicin-resistant RNA polymerase by binding just outside the rifampicin-binding pocket. Credit: Murakami Laboratory, Penn State

Searching for new antibiotics

Researchers screened more than 2,000 extracts from filamentous soil bacteria using a collection from Newcastle University spin-out company, Demuris Ltd, to assess their ability to inhibit cell growth or prevent the production of RNA— an essential process in all living organisms—in bacteria.

Professor Zenkin said: "The main finding of our study is that kanglemycin A is effective against rifampicin resistant RNA polymerases and can also kill rifampicin resistant *Mycobacterium tuberculosis*.

"We describe the details of the inhibition mechanism and how kanglemycin A manages to stay active against the drug-resistant bacteria.

"The results will help to accelerate approval of kanglemycin A for use in patients with Tuberculosis, and provide a rationale for the further development of new drug treatments."

Katsuhiko Murakami, professor of biochemistry and molecular biology department at Pennsylvania State University, who led crystallographic characterization of interactions of kanglemycin A with RNA polymerase, believes the discovery is essential for public safety.

He said: "Recent development of drug-resistant *Mycobacterium tuberculosis* has made treatment of this disease even more challenging.

"Identifying new compounds that are effective against the rifampicin-resistant RNA polymerase is incredibly important for public health."

Antibiotics needed

The research project involved a large multidisciplinary team involving Newcastle and Penn State university scientists, Public Health England, Newcastle upon Tyne Hospitals NHS Foundation Trust and Demuris Ltd.

Dr. Nick Allenby, Principal Scientist at Demuris Ltd, which own and will be taking on the commercialization of the compound, said: "There is an urgent need for new antibiotics to combat drug resistant *Mycobacterium tuberculosis*.

"We have shown that our compound discovered through a collaboration between Newcastle University and Demuris is effective against these drug resistant strains.

"However, before we can start to think about using the compound much more work and development is needed. The next step for our compound is to prove that it is safe and effective for use in the clinic."

More information: Mode of action of kanglemycin A, an ansamycin natural product that is active against rifampicin-resistant Mycobacterium tuberculosis. Nikolay Zenkin et al. *Molecular Cell*. DOI: 10.1016/j.molcel.2018.08.028