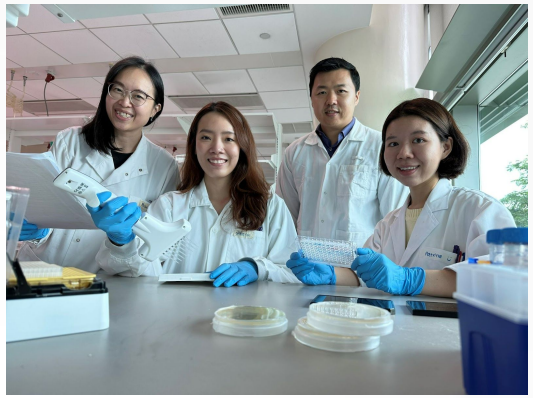
NOVEL COMBINATION THERAPY TO COUNTER ANTIBIOTIC-RESISTANT MYCOBACTERIUM ABSCESSUS INFECTIONS

Mycobacterium abscessus is a non-tuberculous mycobacterium (NTM) that causes lung-related infections and is becoming increasingly resistant to clarithromycin, a key antibiotic for NTM treatments. SMART researchers from the Antimicrobial Resistance (AMR) Interdisciplinary Research Group (IRG) have discovered rifaximin as a clarithromycin potentiator that can increase clarithromycin sensitivity and improve bacterial killing against *Mycobacterium abscessus*.

This combination of rifaximin and clarithromycin showed efficacy both *in vitro* and in a zebrafish embryo infection model, and is promising to effectively treat lung-related infections caused by NTMs.

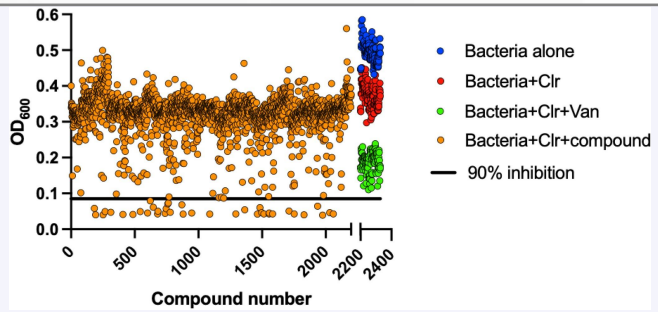


SMART AMR researchers Peiying Ho, Sharon Ling, Boon Chong Goh, and Patrina Chua (from left to right) performed compound screening to identify novel antibiotic combinations.

BACKGROUND

NTM infections, of which *M. abscessus* is one of the most prevalent, cause pulmonary infections in humans with immune deficiencies or underlying lung conditions. These infections are difficult to treat due to the bacterium's extensive innate resistance to many commonly used antibiotics. There is an urgent medical need for the identification of compounds that are clarithromycin potentiators in order to effectively restore clarithromycin efficacy against *M. abscessus*.

METHODOLOGY



Researchers performed cell-based phenotypic screening of a compound library (see figure above) against clarithromycin-resistant *M. abscessus*, and evaluated the toxicity and efficacy of the top compound in a zebrafish embryo infection model.

RESULTS

The study showed that rifaximin synergises with clarithromycin to reduce the load of *M. abscessus* in infected zebrafish. This builds on the strong synergy already observed *in vitro* between the two drugs, with clarithromycin's minimum inhibitory concentration (MIC) significantly lowered in the presence of rifaximin - meaning that rifaximin significantly reduces the amount of clarithromycin needed to inhibit and kill *M. abscessus*.

CONCLUSION & NEXT STEPS

As clarithromycin is the only highly effective oral antibiotic for treating *M. abscessus* infections, the identification of compounds that are clarithromycin potentiators, such as rifaximin, can help address existing challenges faced in treating NTM infections.

The researchers are now preparing for preclinical studies to evaluate this drug combination against *M. abscessus*, and are also collaborating with a commercial manufacturing partner to create inhalation formulations suitable for delivering the drug combination directly to the lungs for use in human clinical trials.

In collaboration with: Nanyang Technological University Singapore; National University Hospital; Massachusetts Institute of Technology