Singapore-MIT Alliance for Research and Technology

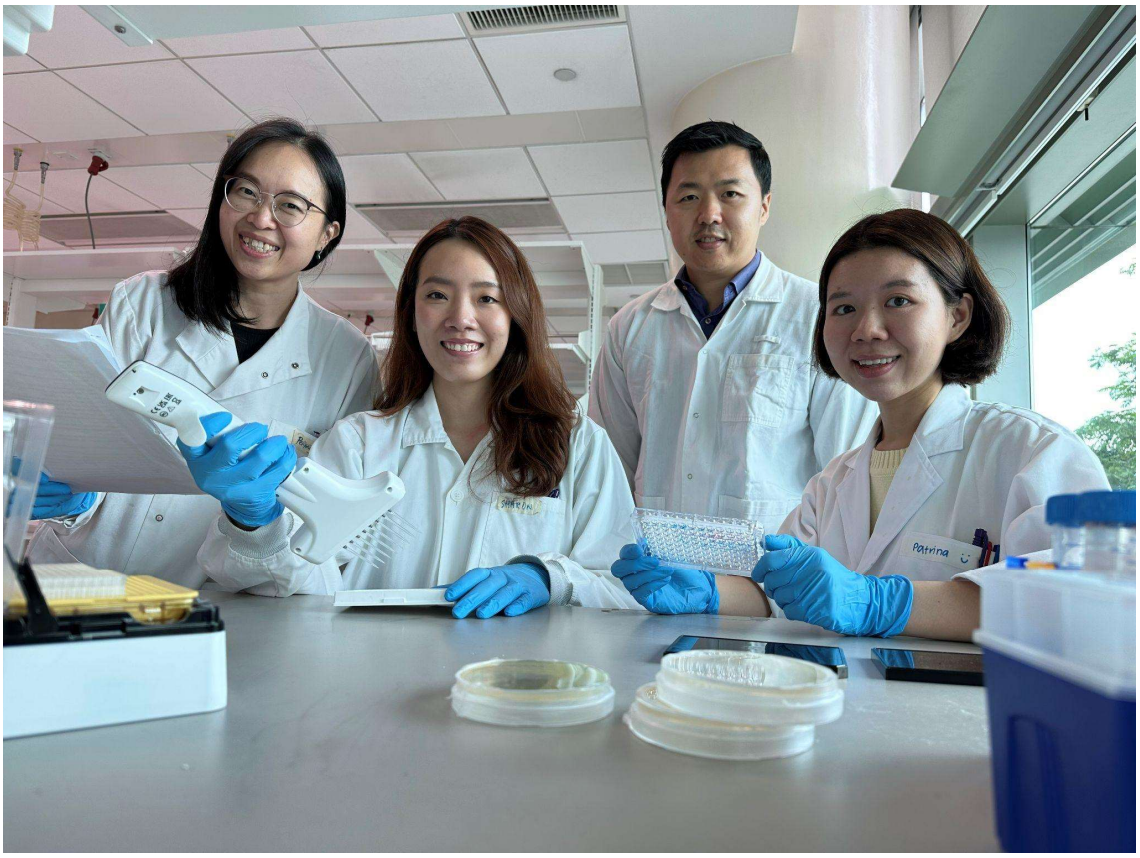
SMART researchers discover novel combination therapy to counter antibiotic-resistant *Mycobacterium abscessus* infections

- *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*
- *The study discovered rifaximin as a clarithromycin potentiator that can increase clarithromycin sensitivity and improve bacterial killing against Mycobacterium abscessus*
- *The combination of rifaximin and clarithromycin is promising to effectively treat lung-related infections caused by NTMs*

Singapore, 6 June 2023 - Researchers from the Antimicrobial Resistance (AMR) Interdisciplinary Research Group (IRG) at Singapore-MIT Alliance for Research and Technology (SMART), MIT's research enterprise in Singapore, in collaboration with Nanyang Technological University Singapore (NTU Singapore) and National University Hospital (NUH), have discovered a novel therapy by combining two antibiotics, rifaximin and clarithromycin, to treat *Mycobacterium abscessus (M. abscessus)*, a non-tuberculous mycobacterium (NTM) that causes chronic lung-related infections.

Infections caused by NTM are a fast-growing health concern worldwide, particularly in the context of lung-related infections. Among NTMs, *M. abscessus* is one of the most prevalent, causing pulmonary infections in humans with immune deficiencies or underlying lung conditions. *M. abscessus* has also been linked to severe infections in various other parts of the body, including the skin, joints, soft tissues, and surgical sites. These infections are difficult to treat due to the bacterium's extensive innate resistance to many commonly used antibiotics.

Currently, *M. abscessus* infections are treated by a multidrug regimen that includes clarithromycin, but some *M. abscessus* subspecies acquire resistance upon repeated exposure to the drug. As a result, available treatment options are limited, leading to prolonged and recurrent infections and even fatalities in some cases. With clarithromycin being the mainstay of NTM treatments and currently the only highly effective oral antibiotic for treating *M. abscessus* infections, 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*.



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.
Photo Credit: SMART AMR

A recent study by SMART researchers, *"Rifaximin potentiates clarithromycin against Mycobacterium abscessus in vitro and in zebrafish"*, published in the scientific journal, *JAC-Antimicrobial Resistance*, revealed promising findings on the use of rifaximin (an antibiotic commonly used to treat gastrointestinal bacterial infections) as a clarithromycin potentiator with the ability to increase clarithromycin sensitivity and improve its ability to kill *M. abscessus*. During the discovery stage of the study, the researchers conducted drug screening campaigns and successfully identified several drug candidates as clarithromycin potentiators. Further preclinical testing of these drug candidates confirmed rifaximin as the most effective clarithromycin potentiator, with the combination of rifaximin and clarithromycin showing efficacy both *in vitro* and in a zebrafish embryo infection model.

"We recognise the urgent need to address the growing problem of clarithromycin resistance in *M. abscessus* and are pleased to have discovered rifaximin as a potent clarithromycin potentiator. Despite being primarily used for gastrointestinal infections and having limited activity against drug-resistant *M. abscessus*, our study demonstrated the synergistic effect of rifaximin with clarithromycin in effectively eliminating the bacteria," said Dr Boon Chong Goh, first author of the paper and Principal Research Scientist at SMART AMR.

“With limited treatments available due to *M. abscessus* innate resistance to most antibiotics, including clarithromycin, the novel discovery of the strong combination between rifaximin and clarithromycin is a significant step towards addressing the challenge of treating NTM infections. As FDA-approved drugs, we will be able to quicken the process and translate the findings into improved treatment outcomes for patients suffering from *M. abscessus* infections,” added Professor Peter C Dedon, corresponding author of the paper, Co-Lead Principal Investigator at SMART AMR and Professor at MIT.

The researchers are furthering their research with animal preclinical studies to prepare for human clinical trials. As both rifaximin and clarithromycin are approved by the U.S. Food and Drug Administration, the preclinical studies evaluating their combination against *M. abscessus* can be accelerated. The team is 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.

The research is carried out by SMART and supported by the A*STAR Singapore Therapeutics Development Review (STDR), the SMART Innovation Centre, and the National Research Foundation (NRF) Singapore under its Campus for Research Excellence And Technological Enterprise (CREATE) programme. The NTU Singapore researchers played an important role in performing the zebrafish embryo infection model, and NUH provided the clinical isolates of *M. abscessus*.

About Antimicrobial Resistance Interdisciplinary Research Group (AMR IRG)

The AMR IRG is a translational research and entrepreneurship program that tackles the growing threat of antimicrobial resistance. By leveraging talent and convergent technologies across Singapore and MIT, we aim to tackle AMR head-on by developing multiple innovative and disruptive approaches to identify, respond to, and treat drug-resistant microbial infections. Through strong scientific and clinical collaborations, our goal is to provide transformative, holistic solutions for Singapore and the world.

For more information, please log on to: http://amr.smart.mit.edu/#home

About Singapore-MIT Alliance for Research and Technology (SMART) [新加坡-麻省理工学院科研中心]

Singapore-MIT Alliance for Research and Technology (SMART) is MIT's Research Enterprise in Singapore, established by the Massachusetts Institute of Technology (MIT) in partnership with the National Research Foundation of Singapore (NRF) since 2007. SMART is the first entity in the Campus for Research Excellence and Technological Enterprise (CREATE) developed by NRF. SMART serves as an intellectual and innovation hub for research interactions between MIT and Singapore. Cutting-edge research projects in areas of interest to both Singapore and MIT are undertaken at SMART. SMART currently comprises an Innovation Centre and three Interdisciplinary Research Groups (IRGs): Antimicrobial Resistance (AMR), Critical Analytics for Manufacturing Personalized-Medicine (CAMP), Disruptive & Sustainable Technologies for Agricultural Precision (DiSTAP).

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