

SMART researchers develop novel combination bacterium- and host-targeted therapy for treating vancomycin-resistant bacterial infections

- *Antimicrobials with the potential to act as immune stimulators and overcome bacterial resistance are emerging as important alternative approaches to fighting antimicrobial resistance*
- *The novel combination therapy pairs Mitoxantrone (MTX) and vancomycin to target both antibiotic-resistant pathogens and the host immune system to combat vancomycin resistance*
- *MTX is a promising compound to enhance the host immune system, enabling it to clear bacterial infections more effectively and improve infected wound healing*

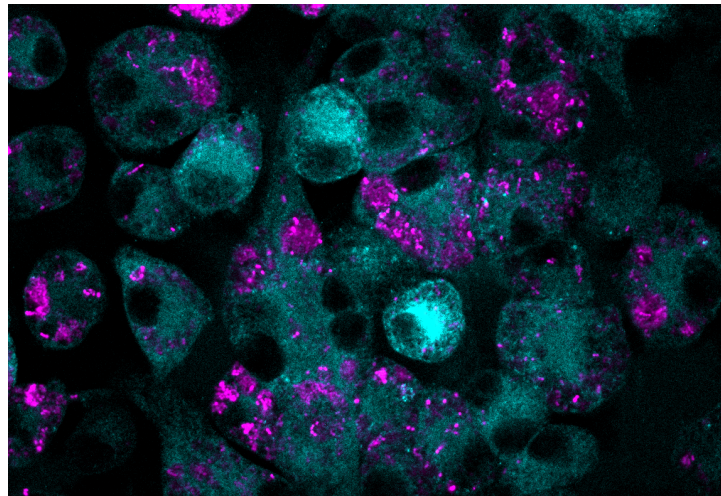
Singapore, 7 March – Researchers from the [Antimicrobial Resistance](#) (AMR) Interdisciplinary Research Group (IRG) at [Singapore-MIT Alliance for Research and Technology](#) (SMART), MIT's research enterprise in Singapore, in collaboration with Singapore Centre for Environmental Life Sciences Engineering (SCElse), Nanyang Technological University (NTU), Massachusetts Institute of Technology (MIT), and University of Geneva, have developed a novel combination therapy using an anticancer agent, mitoxantrone (MTX), together with an antibiotic, vancomycin, for treating bacteria that are resistant to the vancomycin, which is also known as vancomycin-resistant *Enterococcus faecalis* (VRE). The therapy uniquely targets both VRE and the host, stimulating the host immune system to more effectively clear bacterial infections and accelerate infected wound healing.

Antimicrobial resistance is a significant global health concern, causing [4.95 million deaths from infections associated with or attributed to antimicrobial resistance](#) in 2019 alone. By 2050, the [Asia-Pacific region is forecasted to account for 47% of AMR-related deaths worldwide](#) if immediate and coordinated actions are not taken to avert a potential drug-resistance crisis. In response to this aggravating health threat, new and innovative approaches to treating bacterial infections are being developed, including the use of antimicrobials that can overcome resistance mechanisms and host-directed therapies that enhance the innate human immune system to combat bacterial infections.

VRE is a 'hard-to-kill' bacteria due to its increasing antibiotic resistance and can cause serious infections, including urinary tract, bloodstream, and wound infections associated with catheters or surgical procedures. The treatment of VRE infections has posed a significant challenge as the bacteria exhibit resistance to vancomycin – an antibiotic commonly used to treat endocarditis, skin, stomach and intestine infections caused by Gram-positive bacteria – and other commonly used antibiotics.

In this research, the team tested MTX's effectiveness and antibiotic activity against VRE, both *in vitro* and *in vivo*. Despite VRE's resistance to vancomycin, MTX was found to inhibit the growth of VRE more effectively when used in the presence of vancomycin. This outcome is due to the synergistic relationship between MTX and vancomycin, which makes VRE more sensitive to vancomycin by lowering the vancomycin concentration required to kill VRE. The research also demonstrated that MTX improved wound healing by enhancing the ability of macrophages - a type of white blood cell that kills microorganisms, removes dead cells, and

stimulates the action of other immune cells - to fight off VRE infections and by recruiting more immune cells to the site of infection.



A confocal microscopy image of macrophages treated with MTX (cyan) that have eaten bacteria (magenta)

Photo Credit: Singapore-MIT Alliance for Research and Technology (SMART)

In a paper titled [“Mitoxantrone Targets Both Host and Bacteria to Overcome Vancomycin Resistance in *Enterococcus faecalis*”](#), published in the scientific journal *Science Advances*, the research demonstrated that MTX, typically used to treat acute leukaemia, prostate, and breast cancer, as well as multiple sclerosis, is a powerful antibiotic against VRE. It works synergistically with vancomycin, boosts macrophage recruitment and bactericidal activity, and holds great potential as a dual bacterium- and host-targeted therapy for overcoming VRE.

“Facing the global health threat of antimicrobial resistance, innovative and effective solutions to combat bacterial infections are necessary. Through our research, we discovered the potent combination between MTX and vancomycin, which is highly effective in inhibiting the growth of VRE. Furthermore, it also possesses the ability to enhance the host immune system and improve wound healing by bringing more immune cells to the site of infection and by making the immune cells better at killing bacteria,” shared Dr Jianzhu Chen, co-corresponding author of the paper, Principal Investigator at SMART AMR, and Professor of Biology at the Koch Institute for Integrative Cancer Research at MIT.

“The treatment options for VRE infections are severely limited due to its intrinsic and acquired resistance to many conventional antibiotics, including vancomycin. Our team’s breakthrough in the discovery of mitoxantrone as a highly effective dual bacterium- and host-targeted therapy against VRE, represents a major step forward in the fight against VRE infections,” said Dr Ronni da Silva, first author of the paper and Postdoctoral Researcher at SMART AMR.

The researchers are continuing their research with further preclinical studies to prepare for a clinical trial, specifically targeting the development of topical treatments for chronic diabetic wound infections. Dr Kimberly Kline, co-corresponding author of the paper, Principal Investigator at SMART AMR, and Professor at the University of Geneva, added, “Our research sets an important foundation to explore the potential impact of utilising

mitoxantrone for the treatment of bacterial infections. As we continue to explore the full range of applications with further research, we aim to bring about a transformative change with new and innovative therapies to overcome vancomycin resistance in the future.”

The research is carried out by SMART and supported by the National Research Foundation (NRF) Singapore under its Campus for Research Excellence And Technological Enterprise (CREATE) programme. The researchers at MIT, SCELSE, NTU, and the University of Geneva, contributed vital scientific input, assisted in project development, performed data analysis and conducted experiments.

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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 five Interdisciplinary Research Groups (IRGs): Antimicrobial Resistance (AMR), Critical Analytics for Manufacturing Personalized-Medicine (CAMP), Disruptive & Sustainable Technologies for Agricultural Precision (DiSTAP), Future Urban Mobility (FM) and Low Energy Electronic Systems (LEES).

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For more information, please visit: <http://smart.mit.edu>

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>

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