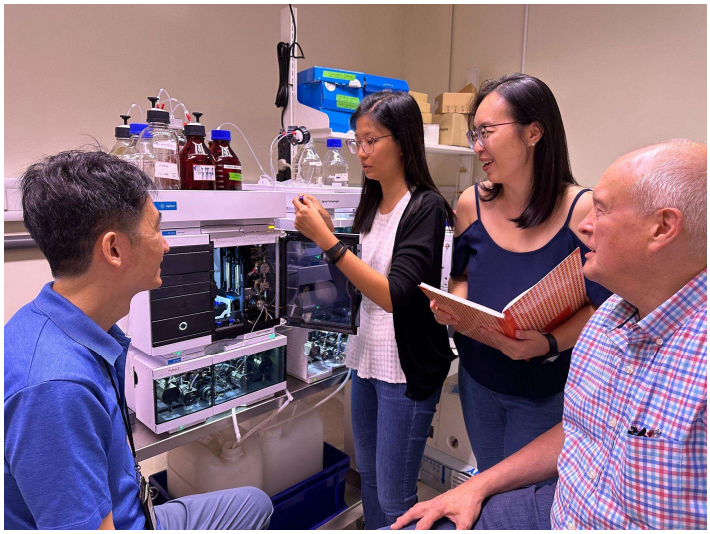
SMART researchers uncover novel bacterial communication system to combat antimicrobial resistance

- *Using a sophisticated mass spectrometry technology developed at SMART and MIT, researchers discovered that RlmN is a stress sensor for reactive oxygen species (ROS) – highly reactive molecules which can cause damage to bacteria*
- *They found that RlmN is capable of directly and rapidly activating the production of proteins that allow bacteria cells to adapt and survive*
- *This breakthrough could help researchers design drugs that prevent this adaptation and survival response*

Singapore, 19 July 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 Singapore Centre for Environmental Life Sciences Engineering (SCELSE), Nanyang Technological University Singapore (NTU Singapore) and Massachusetts Institute of Technology (MIT), have discovered a new stress signalling system that enables bacteria cells to adapt and protect themselves against the immune system and certain antibiotics. An enzyme, RlmN, was observed to directly sense chemical and environmental stresses, and rapidly signal for the production of other proteins that allow the bacteria cell to adapt and survive. This breakthrough discovery of RlmN as a stress sensor has revealed a new mechanism of antimicrobial resistance that can be targeted for drug development.



(L to R) SMART researchers Dr Cui Liang, Dr Lee Wei Lin, Dr Ho Peiying, and Principal Investigator Prof Peter Dedon used a sophisticated mass spectrometry technology developed at SMART and MIT to understand how bacteria cells adapt and survive antibiotics (Photo: SMART AMR)

All living cells have sensors that detect environmental changes – such as reactive oxygen species (ROS) or free radicals – caused by cell stress or metabolism. According to the well-known central

dogma of molecular biology, this is achieved using a two-step system comprising transcription and translation. This means that genes are transcribed into messenger RNAs (mRNA), which are subsequently translated on ribosomes by transfer RNAs (tRNAs) to produce proteins – the functional building blocks of cells.

SMART AMR's discovery of the RlmN system illustrates that cells possess a much quicker mechanism for cell responses. This shortcut is the first example of a direct connection between a sensor system and translation machinery to generate proteins to combat ROS.

In a paper titled "An RNA modification enzyme directly senses reactive oxygen species for translational regulation in Enterococcus faecalis", published in the scientific journal *Nature Communications*. The researchers document their discovery of RlmN as a stress sensor for ROS in *Enterococcus faecalis* (*E. faecalis*) – a common bacteria found in the human gut that can cause a variety of infections, with catheter-associated urinary tract infections being the most prevalent. They found that when RlmN is suppressed upon contact with ROS, it leads to the selective production of resistance proteins and other pathways associated with antimicrobial resistance known to occur during bacterial responses to stress. RlmN inhibition thus represents a signalling mechanism for bacterial drug resistance and immune evasion, since ROS is induced by certain antibiotics and human immune cells.

The discovery was made using a sophisticated mass spectrometry technology developed at SMART and MIT to simultaneously identify all 50 different Ribonucleic acids (RNA) modifications in bacteria. This approach allowed them to observe changes in cell behaviour or pattern mutations that cannot be detected when studied individually.

Using this tool, the researchers exposed *E. faecalis* cells to low, non-toxic doses of various antibiotics and toxic chemicals made by the immune system. They found that only one of the 50 modifications changed – a chemical called 2-methyladenosine (m2A) decreased. As this modification was known to be made by RlmN in other better-studied bacteria, SMART AMR researchers proved that this too, was the case in *E. faecalis* and went on to show how it is inactivated by ROS.

"This is the first time a direct connection has been found between ROS and RlmN, and it may be a step forward in developing new treatments for bacterial infections. By understanding how RlmN works and the different ways in which bacteria respond to stress, we could uncover other stress sensors that rely on similar mechanisms," said **Professor Peter Dedon, Co-Lead Principal Investigator at SMART AMR, MIT Professor** and co-corresponding author of the paper.

"Bacteria are incredibly adaptable and can evolve to resist drugs designed to kill them. This growing resistance is a silent pandemic that poses a global threat to public health as it reduces the efficacy of existing antibiotics and increases mortality rates from infections. Thus, understanding the mechanisms bacteria utilise to adapt against stressors helps researchers develop new and novel therapies to combat AMR. Moving forward, SMART AMR will work on gaining a comprehensive

understanding of this new mechanism of stress response and possible drug resistance," said **Dr Lee Wei Lin, Principal Research Scientist at SMART AMR** and first author of the paper.

As novel, high-impact solutions to combating AMR are a top priority to improve public health, understanding bacterial stress survival mechanisms is an important step forward for the scientific community. By understanding these cell adaptation and survival mechanisms, researchers can design drugs that prevent the adaptation response and ensure that the pathogens retain their sensitivity to antibiotics.

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.

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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 four Interdisciplinary Research Groups (IRGs): Antimicrobial Resistance (AMR), Critical Analytics for Manufacturing Personalized-Medicine (CAMP), Disruptive & Sustainable Technologies for Agricultural Precision (DiSTAP), and Mens, Manus and Machina (M3S).

SMART research is funded by the National Research Foundation Singapore under the CREATE programme.

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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