NUS National University of Singapore | Infectious Diseases Translational Research Programme, Yong Loo Lin School of Medicine

Research Seminar

27 January 2026 **3-4pm**

MD6-03-05, CeTM Learning Room 03-05

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Development of "resistance proof" antimicrobial peptides to fight pathogenic bacteria

Abstract

Antibiotic resistance in bacteria has become a serious threat to public health. Therefore, there is an urgent need to develop new classes of antimicrobial agents. Nowadays, natural antimicrobial peptides (AMPs) and their synthetic derivatives are considered as promising alternatives to traditional antibiotics. The broad molecular diversity of AMPs, in terms of sequences and structures, suggests that their activity does not depend on specific features of amino acid sequence or peptide conformation. We therefore selected two common properties of AMPs, (high percentage of hydrophobic and cationic amino acids), to develop a novel approach to synthesize random antimicrobial peptide mixtures (RPMs). We have discovered that RPMs of hydrophobic and cationic α-amino acids, such as phenylalanine and lysine, display strong and broad antimicrobial activity towards Gram-negative, Gram-positive, clinically isolated antibiotic resistant "superbugs", and several plant pathogenic bacteria. In my talk, I will share with you our efforts to explore the mode of action of RPMs and their potential as bioactive agents for multiple applications. RPMs rapidly killed both Pseudomonas aeruginosa and Staphylococcus aureus efficiently, and disrupted preformed biofilms by both pathogens. Importantly, RPMs were efficacious against both pathogens in mouse models of bacteremia and acute pneumonia. Interestingly, we demodtrated that S. aureus was not able to develop resistance towards RPMs comapred to individual sequnce antimicrobial peptides demonstrating the vadility of combination therapy also in the area of antimicrobial peptides. Our results demonstrate illustrate the effectiveness of RPMs and their great potential as novel antimicrobial agents. .

Recommended Readings

1. Goldberg et al, Cell-autonomous innate immunity by proteasome-derived defence peptides, *Nature*, 2025 Mar;639(8056):1032-1041. doi: 10.1038/s41586-025-08615-w.
2. Lau et al, Antibacterial efficacy of an ultra-short palmitoylated random peptide mixture in mouse models of infection by carbapenem-resistant Klebsiella pneumoniae, *Antimicrob Agents Chemother*, 2023 Nov 15;67(11):e0057423. doi: 10.1128/aac.00574-23.
3. Maron et al, Uncovering the genetic basis of Staphylococcus aureus resistance to single antimicrobial peptides and their combinations, *iScience*, 2025 May 14;28(6):112671. doi: 10.1016/j.isci.2025.112671.
4. Yehuda et al, The quorum-sensing peptidic inhibitor rescues host immune system eradication: A novel infectivity mechanism, *Proc Natl Acad Sci U S A*, 2023 Aug 29;120(35):e2301045120. doi: 10.1073/pnas.2301045120.