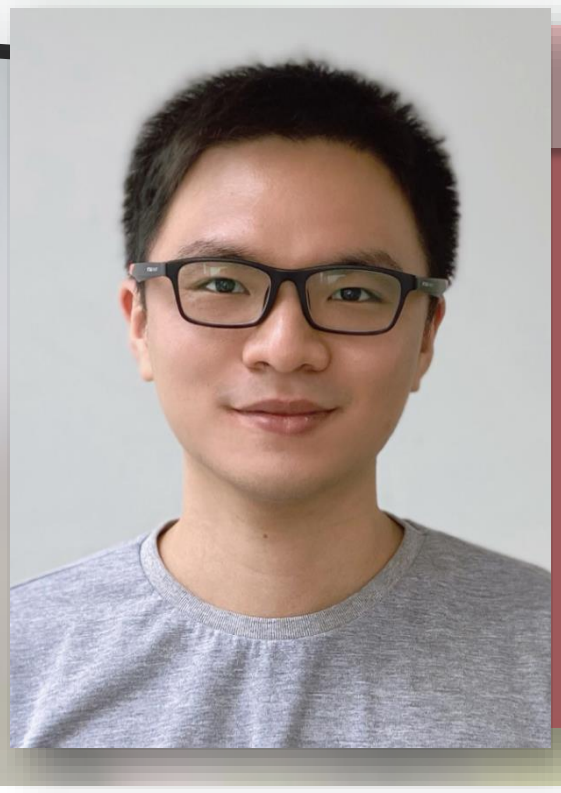
Department of Biochemistry
Yong Loo Lin School of Medicine

**PhD Qualifying Examination (Virtual)**

# Understanding multidrug resistance transmission and the action of polyimidazolium derivatives in combating MDR infection


Antimicrobial resistance (AMR) is on the rise and a global concern as existing antibiotics, including the last resort antibiotics for Gram-negative bacterial infections such as carbapenems, are rapidly losing their potency. Drug resistance can be acquired through horizontal gene transfer but features contributing to rapid transmission remain to be characterized. Therefore, understanding the spread of resistance determinants and developing novel antimicrobials effective against multidrug resistant (MDR) bacteria are critical for treating drug resistant infections. Here, we aim to tackle the problem of AMR by examining two aspects — (1) the transmission of carbapenem resistance plasmid (CR-plasmid) and, (2) defining the mechanism of action (MOA) of a novel antimicrobial drug effective against MDR bacteria. In the first project, we examined the transmission potential of a CR-plasmid called pKPC2. It was found to be the most predominant Enterobacteriaceae-associated CR-plasmid in Singapore through genomic analysis of CaPES isolates, which is a collection of clinical carbapenem-resistant Enterobacteriaceae isolates from six local hospitals. Our results suggest that pKPC2 belongs to the IncP plasmid group with broad host range and it incurs minimal fitness cost to its bacterial hosts. It also exhibited remarkable stability in absence of selection pressure. A comparative study with the second most dominant Enterobacteriaceae-associated CR plasmid in Singapore, pNDM1 (an IncN2 plasmid) showed that pKPC2 is more transmissible with higher conjugation frequency amongst various Enterobacteriaceae spp. posing a risk for rapid dissemination. Further investigations on the factors accountable for such alarmingly high transmissibility and stability will help to gain better insights for future infection controls. In the second project, we aimed to elucidate the MOA of PIM1 — a potent compound against MDR bacteria. We used PIM1 oligomer (OIM1-6) and showed that drug uptake correlates with its potency, and uptake is correlated with a functional proton motive force. Once taken up into the cytoplasm, it could bind to intracellular macromolecules such as DNA. Another inactive derivative called OIM1-6-C2 retains DNA binding properties, but lacks ability to be taken up by the cells. The potency of this inactive derivative can be restored to a similar level as its active counterpart in presence of membrane permeabilizing antibiotics (colistin). Overall, the findings from these projects will improve and contribute to strategies to combat against AMR.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**Time:** **4.30pm**

**Seminar Platform:** **Zoom**
Link: Click here
Meeting ID: 848 5482 2788
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