NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme: Antimicrobials and Drug Resistant

Research Project Title: Design and mode of action of antimicrobials (peptides and mimetics) and mechanisms of bacterial resistance

Principal Investigator/Supervisor: A/P Surajit Bhattacharyya

Co-supervisor/ Collaborator(s) (if any):

Project Description

a) Background:

Drug resistant bacterial pathogens are of significant threat to the public health around the globe. There is an urgent need to develop new antibiotics; however, the pipeline for producing new drugs has been highly reduced over past 30 years. The US Food and Drug Administration (FDA) had approved 20 new antibiotics between 1980 and 1984, but only three new antibiotics were approved in recent years. The lack of new antibiotics is a reflection of reduced productivity of drugs in the pharmaceutical industry. As existing drugs are becoming old, finding new drugs turns out to be difficult. Most importantly, the growing number of resistant bacterial strains indicates that new antibiotics should function with a different mode of action. It is now well documented methicillin resistant Gram-positive *Staphylococcus aureus* (MRSA) infections are difficult to treat. Infectious diseases caused by Gram-negative bacteria are even more major threat in human health. Notably, the spread of multidrug-resistant so called 'ESKAPE' pathognes i.e. *Enterococcus*, *Staphylococcus aureus*, *Klebsiella*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*, is an enormous challenge. Many drugs against Gram negative bacteria show limited efficacy due to the outer membrane barrier. In order to treat bacterial infections, development of novel antibiotics with different mode of action is highly critical. Cationic Antimicrobial Peptides (AMPs) are vital components of innate immunity of host defence system. AMPs are multifunctional molecules demonstrating direct killing of broad range of bacteria including multiple drug resistance strains. AMPs are found to demonstrate anti-viral, anti-fungal and anti-parasitic activity. Some AMPs have been known to kill cancer cells. Reports have also suggested signalling functions of AMPs that would modulate functions of innate immune cells. As a mode of action, most AMPs cause lysis of bacterial cells by destabilizing integrity of membranes. AMPs remain bactericidal over the course of evolution plausibly indicating difficulty of bacteria to change the membrane compositions and structures. Now, it has been well conceived that the broad spectrum antibacterial activity in conjunction with shorter size and cell selectivity of AMPs could be employed to develop novel antibiotics. Pronounced interests have been noted for structure-activity (SAR) correlations of AMPs, designing novel AMPs and various antimicrobial applications of AMPs containing organic scaffolds.

b) Proposed work:

Mechanism of action of AMPs in bacterial cell killing remains unclear, due to the fact that 3-D structures of AMPs have not been obtained in appropriate cellular environments. Interactions with outer-membrane components would like to influence mode of action and mechanisms of AMPs. Bacterial cells are protected from antibacterial substances employing additional membrane components exposed to

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the external environment. Gram-positive bacteria contain a thick peptidoglycan layer whereas Gram-negative bacteria are surrounded by an asymmetric outer-membrane. The outer leaflet of the outer-membrane is predominantly consisted of a specialized lipid called lipopolysaccharide (LPS). By contrast to peptidoglycan, LPS establishes a permeability barrier limiting access to antibiotics, antibacterial drugs and other molecules. As LPS in the outer-membrane protects live bacteria, LPS from dead bacteria is highly toxic to humans and other animals. LPS, as known as endotoxin, is a leading agent of septic shock or sepsis. In the absence of any therapeutic modality, annually 120,000 people are estimated to be deceased due to the septic shock syndromes. There have been constant searches for effective drugs to prevent sepsis related fatality. Molecules that would bind and neutralize endotoxin are highly sort after. LPS of the outer membrane of Gram negative bacteria is critically involved in interactions with cationic AMPs. In this on-going research, we will determine 3-D structures of host defence peptides and proteins and designed peptides in LPS and correlate their activity. A broad range of methods e.g. peptide design, expression, NMR, ITC, optical spectroscopy, dynamic light scattering, biological assays are used to gain insights into structure and functions of AMPs.

Over past and current years, my research group has determined atomic-resolution structures and mapped interactions of a number of potent AMPs with LPS by use of NMR spectroscopy. We have solved LPS-bound 3-D structures and interactions of a number of AMPs including pharmaceutically important MSI-594 (Chemistry, 2009, JACS, 2010), pardaxin (JBC, 2010), temporins (JBC, 2011, PLOS-One, 2013), beta-hairpin peptides, protegrins (BBA, 2012, BBA 2014), de-novo designed beta-boomerang AMPs (Biochemistry, 2007, JBC, 2009, Antimicrobial Agents & Chemo. 2014, Bioconjugate Chem. 2012, Chem. Comm, 2014). Our research have discovered novel structural folds of AMPs and demonstrated critical structural features of AMPs required for bacterial cell killing.

Supervisor contact:

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Please apply at the following:

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