00401 Combination Therapy of Antimicrobial Peptides and Antibiotics on Multidrug Resistance Pseudomonas Aeruginosa 4877

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Aims: Currently, designing antibiotics to treat diseases that are caused by multidrug resistant (MDR) bacteria is a great challenge due to high mortality rate caused by those pathogens. In particular, the rapid emergence of MDR pseudomonas aeuroginosa (PAE); a nosocomial pathogen highlights the need for the discovery of effective antibiotics to meet global healthcare threats. Antimicrobial peptides (AMPs) are potential next generation antibiotics for combating bacterial resistance because these molecules act on the bacterial membrane, an evolutionarily conservative component of bacterial cell. The aim of this study is to examine the synergy effect of FDA approved antibiotics [such as fluoroquinolones and Polymyxin B (PMB)] with the combination of 4 different AMPs developed in our group against clinically isolated MDR PAE strains.

Methodology: Key parameters of synergy for the design of combinational therapy were identified by measuring the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and time-kill kinetics.

Result: Both Gatifloxacin and Besifloxacin display MIC of 12.5µg/mL and MBC of 100µg/mL. Three synthetic AMPs (B20xx,C8-B20xx,C8C3R) showed lower an MIC of 6.25µg/mL and Nonapeptide has an MIC of 12.5µg/mL. All the tested AMPs achieved MBC of 50µg/mL. Gatifloxacin were selected to further proceed to the checkerboard and time-kill studies. The combination of Gatifloxacin+B20xx and Gatifloxacin+C8-B20xx showed the fractional inhibitory concentration index (FICI) value of 0.5, denoting weak synergism; however the combination of Gatifloxacin+Nonapeptide displayed the FICI of 0.375, suggesting strong synergism. At 1 MIC, the combination of Gatifloxacin+B20xx or Gatifloxacin+Nonapeptide was found to be extremely potent with 3-log reduction after 24 hours.

Conclusion: This study suggested that direct effects of AMPs on bacterial outer membrane are responsible for the synergy between AMPs and antibiotics thereby lowering the level of drug resistance.