29th ECCMID
Amsterdam, Netherlands
13 – 16 April 2019
The congress of ESCMID

O0200 Lysin GN123 resensitizes carbapenem-resistant *Pseudomonas aeruginosa* to imipenem

Aubrey Watson[1], Jun Oh[1], Karen Sauve[1], Cara Cassino[1], Raymond Schuch*[1]

[1] ContraFect, ContraFect Corporation, Yonkers, United States

Background: Antibiotic-resistant Gram-negative (GN) pathogens pose a public health threat which necessitates the development of new antimicrobials with novel mechanisms of action. Bacteriophage-derived lysins (cell wall hydrolases) represent one such novel approach, currently in Phase 2 for the treatment of *S. aureus* bacteremia including endocarditis. Whereas the therapeutic use of lysins against GN pathogens has previously precluded by the inability to efficiently penetrate the outer membrane (OM), we recently described a series of lysins designed to penetrate the OM and exert antimicrobial activity against *P. aeruginosa*. Here, we demonstrate the capacity of 9 GN lysins to synergize with imipenem and resensitize carbapenem-resistant *P. aeruginosa* in vitro.

Materials/methods: Synergy between GN lysins and imipenem was examined in checkerboard assays using Casamino Acid Media (supplemented with 150 mM NaCl). We examined imipenem-resistant (N=4; MIC = 16 µg/mL), -intermediate (N=1; MIC = 4 µg/mL), and -susceptible (N=2; MIC = 2 µg/mL) clinical isolates of *P. aeruginosa*. Fractional inhibitory concentration index (FICI) values were determined for all combinations; values of ≤0.5 indicate synergy

Results: Synergy was observed for each of 9 GN lysins tested in addition to imipenem in a screen against a single imipenem-resistant isolate (FICI = 0.156-0.5). In an expanded analysis of one lysin, GN123, synergy was also observed against 7 *P. aeruginosa* isolates (FICI = 0.188-0.375). The imipenem MICs of the resistant and intermediate isolates (16 and 4 µg/mL, respectively) were reduced to at least 0.25 µg/mL in each synergistic combination, which is below the imipenem breakpoint of ≤2 µg/mL. For the 2 imipenem-susceptible (MIC = 2 µg/mL) isolates, the imipenem MIC was reduced to 0.25 and 0.007 µg/mL.

Conclusions: These findings indicate that GN lysins can resensitize *P. aeruginosa* to imipenem, driving MICs below breakpoint values in vitro. This novel ability of lysins to resensitize antibiotic resistant strains to conventional antibiotics may have important therapeutic implications and is a promising mechanism to combat and "reverse" antimicrobial resistance.