O0200 Lysin GN123 resensitizes carbapenem-resistant Pseudomonas aeruginosa to imipenem

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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.