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In-vivo Efficacy of combinations of novel antimicrobial peptide SPR741 and rifampicin in neutropenic murine thigh infection models of Gram-negative bacterial infection

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Background: The lack of antimicrobial drugs in the clinical pipeline, plus the continuing increase in antimicrobial resistance has led of a crisis where infections are occurring that are essentially unresponsive to antimicrobial therapy. One approach to addressing the lack of treatment options is potentiation of antimicrobial agents to increase the spectrum of activity and/or enhance activity. In these studies we assessed the efficacy of combinations of a novel antimicrobial cationic peptide (SPR741) with rifampicin in murine models of thigh muscle infection.

Material/methods: Male ICR mice were rendered neutropenic using doses of 200 and 150 mg/kg cyclophosphamide on days -4 & -1, respectively. Mice were infected by IM injection into the lateral thigh muscle on day 0 with either *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 43816) or *Enterobacter cloacae* (KPC114, [bla_{KPC-2}]). Treatment with SPR741 and rifampicin were co-administered intravenously at 1, 9 and 17 h post infection. SPR741 was administered at 40 and 60 mg/kg/dose, the doses of rifampicin were based on preliminary dose-response experiments (range 2.75-20 mg/kg/dose). Control treatments of polymyxin B or tigecycline were included. Mice were euthanized 25 h post infection and the thigh muscle quantitatively cultured.

Results: SPR741 and rifampicin were well tolerated when co-administered and all animals continued to the study end. All isolates demonstrated robust *in vivo* growth of 3.3-5.3 log10 CFU/g thigh tissue between pre-treatment and vehicle-treated mice. Monotherapy with SPR741 and rifampicin at the

highest doses administered had little effect on burden. By contrast, in all models, combinations of 60 mg/kg/dose SPR741 with rifampicin led to containment or reductions in burden compared to pre-treatment (+0.3, 0.8, and 1.5 log10 CFU/g for ATCC 25922, ATCC 43816 and KPC114, respectively). When treated with combinations using 40 mg/kg/dose SPR741, the resulting burdens (+1.8, +0.7, and 0.7 log10 CFU/g for ATCC 25922, ATCC 43816 and KPC114, respectively) ranged from pre-treatment levels. For *K. pneumoniae* and *E. cloacae* combinations with 60 mg/kg/dose SPR741, reduced burdens to below pre-treatment levels, indicating bactericidal activity.

Conclusions: The combination of SPR741 with rifampicin was effective at reducing the thigh burden of mice infected with *E. coli, K. pneumoniae* and *E. cloacae,* including strains expressing bla_{KPC} compared to untreated or monotherapy. The combination of SPR741 with rifampicin against *K. pneumoniae* and *E. cloacae* produced a bactericidal result. These studies support continued development of novel antimicrobial cationic peptides for the treatment of multi-drug-resistant Gram-negative infections.