**ABSTRACT**

Due to increasing levels of antimicrobial resistance of bacteria recovered from patients with VAP and VILI, antimicrobial treatment options are often limited to a very narrow range of drugs or drug combinations. A novel and broad-spectrum antimicrobial agent with superior activity against a wide spectrum of bacteria is SPR741, a novel antimicrobial cationic peptide. The current study evaluated SPR741 in a murine pneumonia model and combinatorial therapy with SPR741 and rifampicin.

**METHODS**

Male ICR mice were rendered neutropenic using 2 doses of cyclophosphamide on days -4 & -1. Mice were rendered unconscious using ketamine and xylazine (857) 242-1600. Control treatments of polymyxin B or tigecycline were included. Mice were euthanized and the lungs harvested at 26h post infection and quantitatively plated. Lungs were treated with SPR741 (40 or 60mg/kg/dose) and polymyxin B 20mg/kg (2, 6, 10, 14, 18, and 22h post infection). The studies were conducted at Evotec (UK) Ltd, Manchester, UK and Spero Therapeutics, Cambridge, MA, USA.

**RESULTS**

The combination of SPR741 with rifampicin was highly effective at reducing the lung burden of mice infected with *K. pneumoniae*, or *A. baumannii*. The studies support continued development of the novel antimicrobial cationic peptide for the treatment of MDR Gram-negative infections.

**CONCLUSION**

- The combination of SPR741 with Rifampicin was highly effective at reducing the lung burden of mice infected with *K. pneumoniae*, or *A. baumannii*.
- Efficacy of the combination was achieved using clinically relevant rifampicin treatment regimens.
- These studies support continued development of the novel antimicrobial cationic peptide for the treatment of MDR Gram-negative infections.

**INTRODUCTION**

The spread of multi-drug resistant Gram negative bacteria appears unstoppable. In some localities bacteria resistant to all available antibiotics are causing infections, effectively taking us back to the pre-antibiotic era.

The Gram negative bacterial cell membrane acts as a barrier to the entry of many antimicrobial agents rendering the bacteria resistant or at best only weakly susceptible to a potentially useful antimicrobial agent. An attractive approach to addressing the lack of treatment options is potentiation of existing antimicrobials to either increase the spectrum of activity or enhance activity. The Gram negative bacterial cell membrane acts as a barrier to the entry of many antimicrobial agents rendering the bacteria resistant or at best only weakly susceptible to a potentially useful antimicrobial agent. An attractive approach to addressing the lack of treatment options is potentiation of existing antimicrobials to either increase the spectrum of activity or enhance activity.

**METHODS**

**Immunosuppression:**

Cyclophosphamide was administered at 150mg/kg IP (D-4) 100mg/kg IP (D-1) to induce neutropenia throughout the infection.

**Mouse Strain:**

ICR male (6-8 mice per group) were used in the studies.

**Infection:**

Mice were rendered unconscious using ketamine and xylazine then infected with 0.04mL of a bacterial suspension were administered IP (20µL per nostril) and mice held upright for 30 minutes. Strains used were *K. pneumoniae* ATCC 43816 and Achromobacter baumannii ATCC BAA 747. Lungs were harvested at 26h post infection and quantitatively plated.

**Treatment:**

Treatment (mg/kg/dose) Rifampicin, 0.375 SPR741, 40 SPR741, 80 Rifampicin, 0.375 + SPR741, 40 Rifampicin, 0.375 + SPR741, 80

**Conclusions:**

The studies support continued development of novel antimicrobial cationic peptide for the treatment of multi-drug-resistant Gram-negative infections.