### ADVANCED PYRROLOCYTOSINE LEADS ARE POTENT IN VITRO AGAINST ENTEROBACTERIACEAE EXPRESSING THE PLASMID-MEDIATED COLISTIN-RESISTANCE GENE, MCR-1

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**REVISED ABSTRACT**

**RESULTS**

**INTRODUCTION**

Antimicrobial resistance is a serious global health threat, with the ESKAPE group of pathogens considered urgent priority. Since the first report of plasmid-mediated colistin resistance gene (MCR-1) in Enterobacteriaceae in 2015, global surveillance has identified the alarming dissemination of this gene and related alleles throughout human, agricultural and environmental isolates. The spread of plasmid-mediated colistin resistance is a serious threat to the clinical utility of an important antibiotic of last resort, raising some critically ill patients with no treatment options for serious infections caused by MDR Enterobacteriaceae. New antibiotics that retain potency in the presence of resistance to current antimicrobial therapies are urgently needed.

Pyrrolocytosines are a promising new broad-spectrum antibiotic class that has been rationally designed to bind to an under-exploited region of the ribosome, and therefore are not susceptible to plasmid-mediated resistance mechanisms which limit the utilities of other translation inhibition antibiotics. Pyrrolocytosines have been uniquely optimized to circumvent cell-envelope barriers that prevent the penetration and accumulation of antibiotics in bacteria, especially in Gram-negative species. Advanced leads of the RX-04 program have demonstrated preclinical safety and potency efficacy in animal models of peritonitis and respiratory, deep tissue, and urinary tract infections caused by difficult-to-treat multidrug-resistant ESKAPE pathogens, including colistin-resistant Enterobacteriaceae. In the present study, we report the potency of four advanced leads: RX-P873, RX-P2111, RX-P2382 and RX-P2418 against a set of mcr-1 positive Enterobacteriaceae. Our findings confirm that pyrrolocytosines retain activity against bacteria expressing an emerging resistance mechanism that undermines the use mechanism of Gram-negative bacteria.

**METHODS**

**CONCLUSIONS**

- RX-P873, RX-P2111, RX-P2382 and RX-P2418 are advanced pyrrolocytosine leads with potent antibacterial activity against multidrug-resistant Enterobacteriaceae expressing plasmid-mediated colistin resistance.

- Through rational design, these advanced leads have been optimized for target-based potency, bacterial uptake, efflux avoidance, antibacterial spectrum, preclinical safety and efficacy, supporting their continued advancement towards clinical development for the treatment of serious infections caused by multidrug-resistant ESKAPE pathogens, including those resistant to antibiotics of last resort such as colistin.