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Peptide-modified β-lactam antibiotics with an extended efficacy spectrum

Multidrug-resistant bacteria represent one of the biggest challenges facing modern medicine. Recentyl, we developed a method to reestablish the activity of vancomycin by conjugation of polycationic peptides [1]. Based on these previous findings, in this study, we demonstrate the transferability of this modification strategy to β-lactam antibiotics. Most β-lactam antibiotics are not applicable for enterococcal infections due to intrinsic resistance. To ocervome this limitation, polycationic peptides were conjugated to representatives from each of the four classes of β-lactam antibiotics to extend their antimicrobial spectrum. By use of this modification strategy, the β-lactam–peptide conjugates gained an up to 1000-fold increase in antimicrobial activity against vancomycin-susceptible and vancomycin-resistant enterococci [2]. Besides the extended efficacy spectrum, the conjugates showed an altered biodistribution profile and target binding as well as low toxicity *in vitro* and *in vivo*. Furthermore, in a rodent systemic infection mouse model (vancomycin-resistant enterococci), treatment with the ceftazidim–peptide conjugate reduced bacterial burden in the liver compared to its originator. These findings highlight the potential of this modification strategy as a promising platform strategy to overcome bacterial resistance.

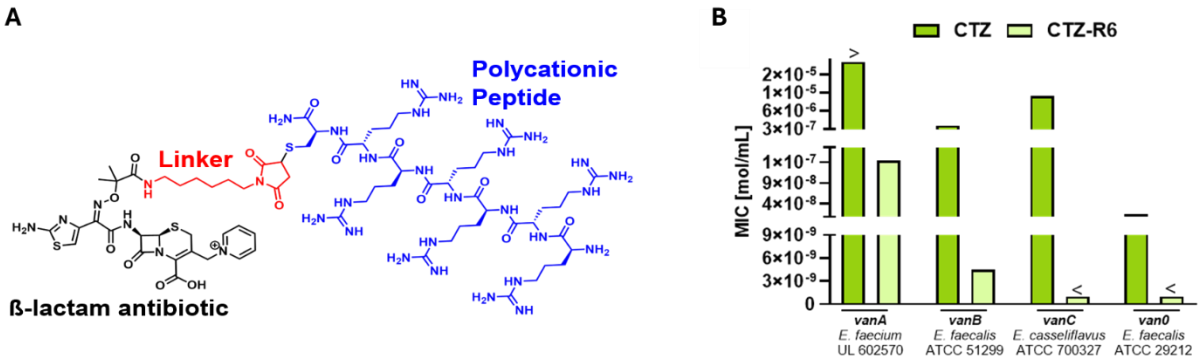

Figure 1. The number of antibiotic-resistant bacteria is steadily increasing. To overcome this problem, we conjugated polycationic peptides to β-lactam antibiotics, which extended their efficacy spectrum against enterococci [2]. (A) Representative for this study, the ceftazidime-hexa-arginine conjugate (CTZ-R6) is shown. (B) The minimum inhibitory concentration of CTZ-R6 against a range of enterococci is depicted [2].

[1] F. Umstätter et al., Angewandte Chemie International Edition 59 (2020) 8823-8827.
[2] J. Werner et al., Advanced Science (2024) e2411406.