Targeting Enterococci – How to Overcome β-Lactam Resistance

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Introduction

Enterococci are third to second most common pathogen in nosocomial infections. With their intrinsic resistance against cephalosporines and most other β-lactam antibiotics, the treatment of enterococcal infections remains challenging. With the rising resistance against last resort antibiotics and the emergence of vancomycin-resistant enterococci (VRE), current therapy options are critically limited [1]. A promising way to overcome this burden is to re-sensitize resistant strains to modified approved antibiotics [2].

Methods

Therefore, we conjugated polycationic peptides to selected β-lactam antibiotics using a bifunctional linker moiety. These conjugates were screened for their antimicrobial efficacy, pharmacokinetics and affinity to penicillin-binding proteins (PBPs).

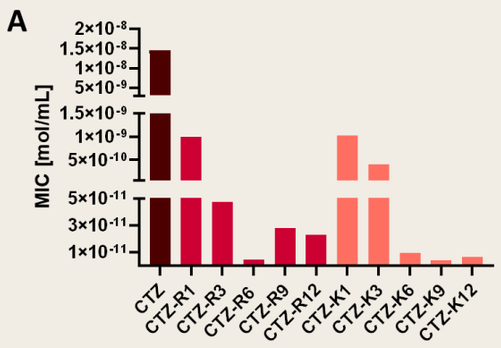

Figure 1. Antimicrobial activity of ceftazidime-peptide conjugates. Increasing the positive peptide charge resulted in higher antimicrobial activity with the highest activity observed for CTZ-R6 and CTZ-K9 on both tested strains, namely *Bacillus subtilis* DSM 10 (A) and *Acinetobacter bohemicus* DSM 100419 (B). Further increasing of peptide charge did not result in a more potent compound. Data is shown as median ($n = 3$).

Results

For the most promising ceftazidime-R6 conjugate, a broadened spectrum and up to 1000-fold higher efficacy could be demonstrated against vancomycin-susceptible enterococci and VRE without increasing cytotoxicity. In vivo studies in rodents showed an altered way of excretion and demonstrated therapeutic efficacy against VRE.

Discussion

The altered PBP-binding profile as well as the faster killing mechanism of the conjugates compared to their originator β-lactam suggest an altered mode of action. [3] These findings go along with our previously reported findings on FU002, a vancomycin derivative, and represent a possible platform technology for cell-wall addressing antibiotics and particular against enterococci. [4]

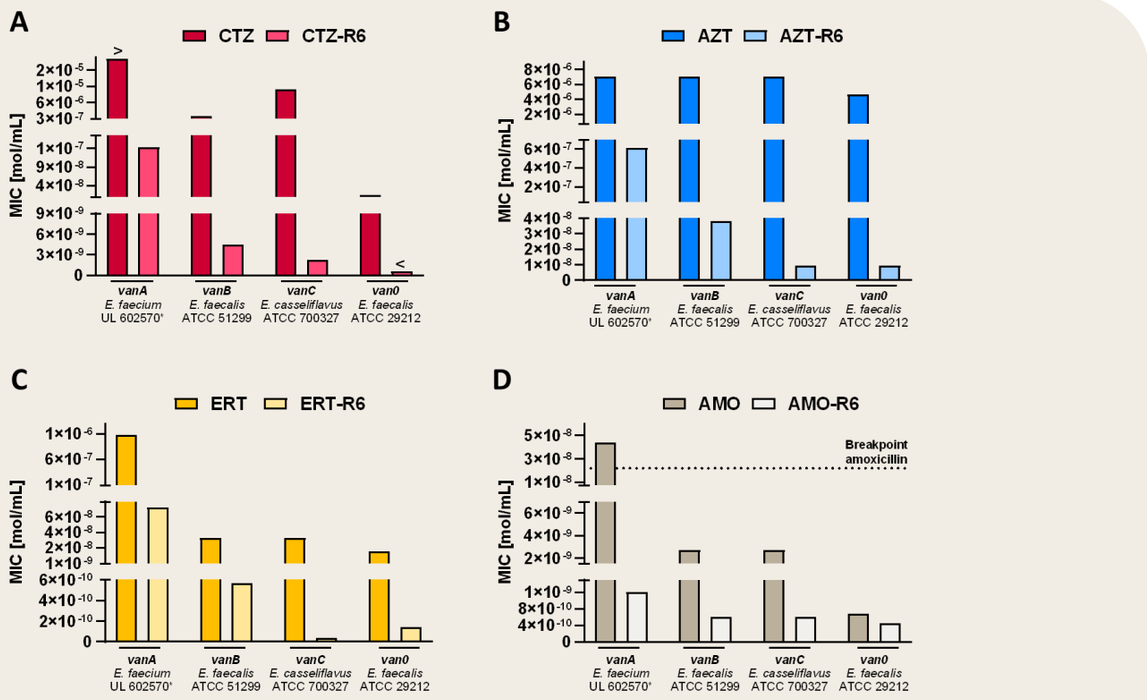

Figure 2. Antimicrobial activity of β-lactam-peptide conjugates and their originator on enterococci. All studied conjugates, namely ceftazidime-R6 (A), aztreonam-R6 (B), ertapenem-R6 (C) and amoxicillin-R6 (D), showed a superior activity on the tested enterococci strains including a clinical isolate (*). Even though surpassing the originator with increasing level of vancomycin resistance, the potency decreased accordingly. The indicated resistance breakpoint for amoxicillin is defined by EUCAST. Data is shown as median ($n = 3$).

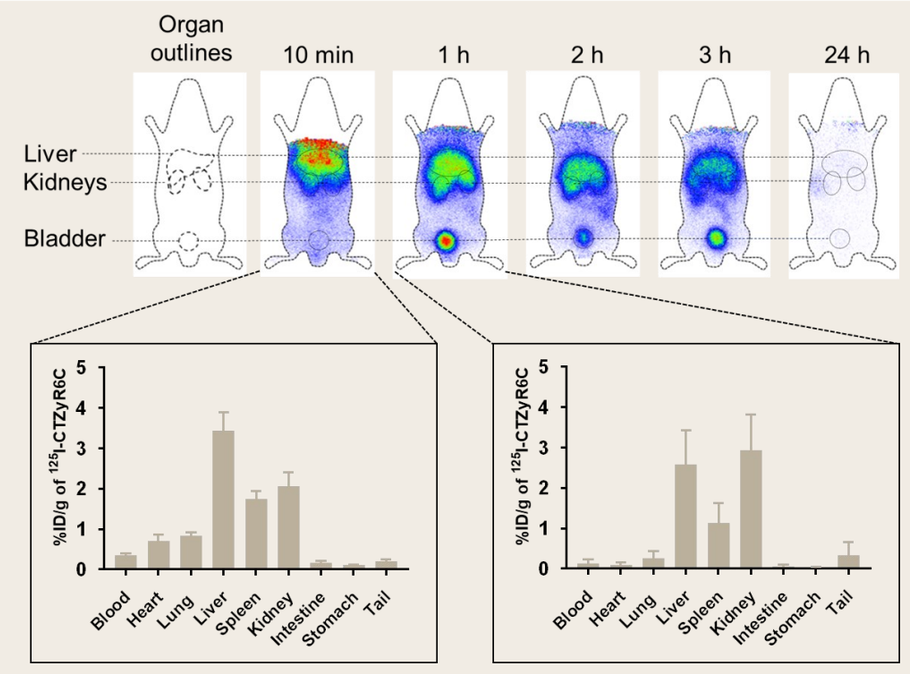

Figure 3. Biodistribution of ceftazidim-yR6 in female Wistar rats. As shown by scintigraphy, the intravenous application of ^{125}I-labeled CTZ-yR6 through a lateral tail vein resulted in a high accumulation of the compound in the liver and kidneys up to 3 h post injection. This could be confirmed by biodistribution studies for 10 min and 1 h post injection. 24 h post injection, no more signal of ^{125}I-CTZ-yR6 could be detected. Data is shown as mean + SD ($n = 3$).

References

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3. Werner J. *et al.* (2024), Conjugation of Polycationic Peptides Extends the Efficacy Spectrum of β-Lactam Antibiotics. Adv Sci. (Weinh), e2411406.
4. Umstätter F. *et al.* (2020), Vancomycin Resistance Is Overcome by Conjugation of Polycationic Peptides. Angew Chem Int Ed Engl., 59(23).

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