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Poster abstract submission

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Poster title

Preclinical development of vancomycin polycationic peptide conjugate (VN-R6C) with high antimicrobial activity in vitro and in vivo

Poster abstract

Multidrug-resistant bacteria are considered as one of the most imminent threats to modern medicine worldwide. While there are numerous drugs available for standard therapy, there are only a few compounds capable of serving as a last resort treatment for severe infections. Especially, infections caused by the ESKAPE pathogens are associated with numerous types of resistances. Therefore, approaches to treat infections with multidrug-resistant bacteria must be implemented.

Here, a strategy of reactivating the established glycopeptide antibiotic vancomycin by structural modification with a hexa-arginine polycationic peptide was investigated (Figure 1). The conjugate synthesis provided yields of over 65% in each of the two reaction steps required. The lead conjugate VN R6C showed high antimicrobial potential on over 50 clinical isolates of linezolid- and/or vancomycin-resistant enterococci (VRE, LVRE; Figure 2). The higher antimicrobial activity was also demonstrated by improved killing kinetics against selected strains. Radiolabeling with 125I enabled the in vivo determination of the pharmacokinetics in SWISS mice by molecular imaging and biodistribution studies. In comparison to unmodified vancomycin, an altered biodistribution profile was observed. While vancomycin is rapidly excreted by the kidneys, the polycationic-conjugate shows a hepatobiliary excretion profile. In vitro biocompatibility studies on liver (Hep-G2 and primary human heptocytes), kidney (HEK-293) and human red blood cells as well as a murine toxicity study showed no relevant toxicity. Further ADME screening, including serum, plasma and S9 liver microsome stability and metabolite profiling, CYP-inhibition and hERG-channel blocking emphasized drug-like properties. The in vivo efficacy of the conjugate was confirmed by VRE infection models in G. mellonella. Additionally, a systemic vancomycin-susceptible S. aureus murine infection model resulted in a significant reduction of CFU in the liver. The transfer to murine VRE infection models is still ongoing. In conclusion, these results highlight the drug-like properties of the lead conjugate VN-R6C. The combination of low toxicity and high in vivo efficacy of the hexa-arginine vancomycin conjugate makes it well suitable for further preclinical and potential clinical development as new antibiotic against multidrug-resistant bacteria.

Research topic PK/PD

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