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ROVANCE – Resistance Overcoming Antibiotics New Chemical Entities:
A Platform Technology to Overcome Bacterial Resistance

Multidrug-resistant bacteria represent one of the greatest challenges for modern medicine. The increasing resistance against glycopeptide antibiotics compromises the efficacy of vancomycin, for a long time considered as the last resort for the treatment of resistant Gram-positive bacteria.[1,2] To reestablish its activity, polycationic peptides were conjugated to vancomycin. Several derivatives that bear the poly arginine peptide moiety at four different sites of vancomycin were synthesized through site-specific conjugation.[3-5]

The lead conjugate V_N-R6C showed high antimicrobial activity (up to 1000-fold increased) on 15 clinical isolates of linezolid- and vancomycin-resistant enterococci (LVRE, E. faecium) as well as on 25 clinical isolates of vancomycin resistant *E. faecium* and *E. faecalis*. The higher antimicrobial activity was also demonstrated by improved killing kinetics against selected strains of enterococci and staphylococci. Furthermore, the antimicrobial potential of the lead candidate V_N-R6C could be demonstrated in a murine *in vivo* systemic infection model. Blocking experiments using d-Ala-d-Ala revealed a mode of action beyond the inhibition of cell-wall formation. Further, the peptide modification enables modulation of the pharmacokinetics allowing specific organ targeting.

Encapsulation of V_N-R6C in PEGylated liposomal nanocarrier systems prolonged the half-life of the drug after intravenous administration: studies in Wistar rats revealed a significantly prolonged circulation of the liposomal antibiotic. Microdilution testing proved that the liposomal encapsulation of V_N-R6C does not diminish the antimicrobial activity against staphylococci and enterococci. Highlighting its great potency, liposomal V_N-R6C exhibited a superior therapeutic efficacy when compared to the free drug in a *Galleria mellonella* larvae infection model.

Beyond vancomycin, the strategy could be proven effective for other glycopeptide and cell wall targeting antibiotics, indicating its potential applicability as a platform technology (referred to as ROVANCE technology).

References:

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