Peptidomimetic antibiotics targeting essential outer membrane proteins as a new weapon in the fight against resistance in Gram-negative bacteria

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Infectious diseases and the emergence of new multi-drug resistant (MDR) bacteria are one of the major contributors to human morbidity, and it has become a pressing issue to find new antibiotic classes, which can kill bacteria via novel mechanisms of action. Although synthetic med-chem approaches have allowed the discovery of some antibiotics (sulphonamides, quinolones and oxazolidinone), most of them have been isolated from natural sources. The cationic antimicrobial peptides (CAMPs) are naturally occurring molecules acting in the innate immune systems of many organisms. We have shown that CAMPs provide an important source of inspiration for the discovery of new antibiotics with novel mechanisms of action.

The β-hairpin is a recurring structural motive found in naturally occurring CAMPs, which also often mediates protein-protein and protein-nucleic acid interactions. The design of protein epitope mimetics (PEMs) based on this structural motive is now recognized as a successful approach for antimicrobial discovery [1]. A new family of ß-hairpin antibiotics based on the antimicrobial peptide protegrin-I was synthesized, and several rounds of optimization gave L27-11 as a novel pseudomonas-specific antibiotic. A clinical lead compound called murepavadin (POL7080) active in the nanomolar range against Gram-negative *Pseudomonas* spp. is now in clinical development, but is largely inactive against other Gram-negative and Gram-positive bacteria. Studies on the mode of action of L27-11 showed that the peptidomimetic targets the essential β-barrel protein LptD, which functions in outer-membrane biogenesis [2]. Based on the same approach, another interesting peptidomimetic antibiotic was discovered, called JB-95, with potent antimicrobial activity against *Escherichia coli*. Studies on its mode of action showed that JB-95 could selectively destabilize the OM but not the inner membrane of *E. coli,* likely through interaction with selected β-barrel OM proteins, including BamA and LptD [3].

These discoveries have proven the importance of essential OM proteins in Gram-negative bacteria as targets to kill Gram-negative bacteria, and opened a door for the discovery of new clinical candidates. The vast possibilities in PEM design to find new specific antibacterial agents are still underexploited. The ability to target essential bacterial proteins, including for example the lipopolysaccharide transport (Lpt) machinery, can provide new weapons to fight antimicrobial resistance.

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[3] Urfer, M., et al., *J. Biol. Chem.* 2016, 291(4), 1921-1932.