BamA inhibitors to kill Gram-negative pathogens

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Abstract

The WHO's top-priority or "critical" Gram-negative pathogens like *Acinetobacter baumannii* and P*seudomonas aeruginosa* are especially difficult to treat due to their double-membrane barrier and efflux pumps. To develop innovative treatment options against the AMR strains of these genera, novel targets are needed. The target should be specific, essential and easily accessible for the drug.

The natural product darobactin A targets the outer membrane protein BamA and thereby arrests the function of the beta-barrel assembly machinery, a protein complex that is required for viability and pathogenesis of specifically Gram-negative bacteria. Darobactin A is a ribosomally synthesized and post-translationally modified peptide (RiPP) that consists of seven amino acids with two intramolecular rings.

Here, we report how BamA inhibitors with improved antibiotic activity are mutasynthetically produced and profiled against clinical isolates of concern. High-throughput approaches to screen derivative libraries to further expand the class of bicyclic BamA inhibitors will be discussed. For selected frontrunners, first updates concerning PK/PD values and planned *in vivo* animal infection studies should be presented.