Potential first-in-class treatment of Gram-negative infections

Enhanced antimicrobial peptides (AMPs) with low risk of resistance, high potency and low toxicity
Background

The continuous emergence and worldwide rapid spreading of multidrug-resistant (MDR) Gram-negative bacteria represent a serious threat to human health. Gram-negative infections constitute a large fraction of hospital-acquired infections. Even pan-resistant pathogenic bacterial strains have now developed, which obviously is a critical problem that calls for new treatment options to meet the urgent unmet need.

In particular, antibacterial agents based on antimicrobial peptides (AMPs) appear to be promising, since this compound class is suggested to be less prone to rapid development of antimicrobial resistance. AMPs have been explored for the last two decades, but due to high toxicity, only a few (e.g. colistin/polymyxins and daptomycin) have been marketed. Most AMPs (including those marketed) act via membrane-disruptive mechanisms, which may give rise to undesired toxic side effects.

In contrast, modification of intracellularly acting AMPs with our transport-enhancing constructs provides a unique class of antimicrobials with a favourable ratio between efficacy and general cytotoxic side effects.

The invention

Our transport-enhancing constructs increase the bacterial uptake of the conjugated AMP substantially (up to 32-fold). We achieve an increased potency and a significantly reduced cellular toxicity in mammalian cells, increasing the likelihood of successful translation of AMPs into new therapeutics. By acting on targets (some potentially new) that are different from the targets of current AMP-derived antibiotics, our modified AMPs overcome pre-existing resistance to e.g. colistin, which is one the most important last-resort antibiotics for Gram-negative MDR infections.

Key features

- Potent activity against:
  - Gram-negative pathogens (e.g. E. coli, K. pneumoniae, P. aeruginosa and A. baumannii)
  - Multidrug-resistant strains
- Low frequency of resistance
- Low toxicity to mammalian cells
- In vivo proof of concept in an animal model
- Scalable synthesis

Development status

We have proof of concept in vivo (TRL 3). Early data on compound properties, antimicrobial activity and early toxicological assessment are available for lead compounds. Further determination of antimicrobial spectrum, safety profile and structure-activity optimisation is ongoing.

Intellectual property rights

PCT application filed, claiming priority from our European patent application filed on 16 Sep 2020.