Discovering novel lipopeptides: Targeting polymyxin-resistant Gram-negative ‘superbugs’

Tony Velkov
Monash University, Australia

The world is facing an enormous and growing threat from the emergence of bacteria that are resistant to almost all available antibiotics. Multidrug resistance is a significant public health issue in regard to both Gram-positive and Gram-negative bacteria, but the problem is arguably most grave for the latter class of bacteria. In recent years, virtually no novel drugs targeting multidrug-resistant (MDR) Gram-negative bacteria, in particular Pseudomonas aeruginosa, have been developed. As described in the “Bad Bugs, No Drugs” paper published by the Infectious Diseases Society of America (IDSA), “as antibiotic discovery stagnates, a public health crisis brews”. Therefore, there is an urgent need for new antibiotics, particularly those active against Gram-negative “superbugs”, such as P. aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae. It is precisely this mismatch between increasing multidrug resistance and the dry antimicrobial-drug development pipeline, as highlighted in the “Bad Bugs Need Drugs” campaign, that led the IDSA to place P. aeruginosa, A. baumannii and K. pneumoniae on a “hit list” of the six top-priority dangerous MDR microorganisms. These pathogens have been identified as requiring the most urgent attention for discovery of novel antibiotics. Meanwhile, the polymyxins are increasingly being used as last-line therapy to treat infections caused by Gram negative bacteria that are resistant to essentially all other currently available antibiotics. Polymyxins were discovered more than 50 years ago. We have employed the core polymyxin structure to develop a series of lipopeptide antibiotics with demonstrated potent in vitro and in vivo activity against most MDR and polymyxin resistant strains.

Biography

Tony Velkov, holder of a Ph.D. degree, is an National Health and Medical Research Council of Australia CDA1 Industry fellow at the Monash University Institute of Pharmaceutical Sciences. His areas of expertise include drug development against multi-drug resistant nosocomial bacterial infections, intracellular drug transport, and host-pathogen receptor interactions. Additionally, his research expertise encompasses the areas of drug-design, crystallography, NMR, protein biochemistry, structural biology and small molecule-protein interactions (Surface plasmon resonance, isothermal titration calorimetry, fluorescence), that are the backbone of the drug-discovery projects he is involved in or leads.