Overcoming Bacterial Resistance to Antibiotics: Synthesis, Mode of Action and Structure-Activity Relationship Studies of depsipeptide Antibiotics Katanosin B, Plusbacin A\textsubscript{3} and Fusaricidin A

Due to the widespread use of broad spectrum antibiotics, bacterial resistance has been increasing rapidly in recent years and now presents a serious threat to public health. For the last thirty years the antibiotic vancomycin has been the last line of defence against bacterial strains that are resistant to most of other antibiotics. This glycopeptide acts by binding to the terminal D-Ala-D-Ala dipeptide of peptidoglycan precursor lipid II, preventing maturation of bacterial cell wall. Lipid II is a membrane-anchored $\beta(1,4)$-linked GlcNAc-MurNac disaccharide that is polymerized by the transglycolylases located on the outer surface of the bacterial membrane. The most common form of resistance to vancomycin occurs in enterococci when the bacteria acquire genes encoding enzymes that remodel the dipeptide terminus of peptidoglycan precursors from D-Ala-D-Ala to D-Ala-D-lactate so that vancomycin cannot bind to them. Prevalence of vancomycin-resistant enterococci (VRE) has already become an important problem, and even the emergence of S. aureus clinical isolates with reduced vancomycin susceptibility has been reported recently. Thus, novel antibiotics to replace vancomycin are urgently required. Drugs with different modes of action from vancomycin could be promising candidates against vancomycin-resistant strains.

Promising candidates for reverting multi-drug resistant bacteria are naturally occurring cyclic depsipeptide antibiotics katanosin B, plusbacin A\textsubscript{3} and fusaricidin A. All these natural products exhibit strong activity against methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci (VRE). According to recent published data katanosin B and plusbacin A\textsubscript{3} inhibit transglycosylation and transpeptidation steps of bacterial cell wall biosynthesis by an unidentified mechanism that differ from D-Ala-D-Ala binding. However, their exact mode of action is not yet precisely understood. Mode of action of antibiotic fusaricidin A still needs to be determined.
Our goal is to develop total solid-phase synthesis of these three cyclic depsipeptide antibiotics and to characterize their antibacterial mode of action. Since all these natural products are structurally less complex than the glycopeptide antibiotic vancomycin, we believed that peptide chemotherapeutics derived from these three antibiotics may find future use for development of new, more potent antibiotics against methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium*.

Structures of katanosin B, plusbacin A<sub>3</sub> and fusaricidin A. Unusual amino acids are marked in blue.