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Development of novel antimicrobial lipopeptides against MDR Gram-negative 'superbugs'

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The octapeptins are a family of naturally occurring cyclic lipopeptide antibiotics with a broad antimicrobial spectrum against multidrug-resistant (MDR) Gram-negative and Gram-positive 'superbugs'. Octapeptins were discovered over 30 years ago, consequently there is limited information on their chemical biology and structure-activity-relationships (SAR). Accordingly, the broad aim of our study is to explore the chemical biology of the octapeptins through a SAR approach. Synthetic chemistry will be employed to generate a large series of novel analogs that will be evaluated against the biological systems the octapeptins are known to modulate. The best approach to achieve this is through the substitution of existing amino acids with novel derivatives rather than chemical modification of the side-chain functionalities. This can only be achieved through a 'total synthesis' approach which is a particularly challenging task considering the complex chemical structure of the octapeptins. To the best of our knowledge, we are the first group to have developed an efficient routine 'total synthesis' of octapeptins on a scale that would allow for mechanistic investigations of antibacterial activity and resistance. For the first time our novel approach will interface the chemistry and biology of these important antibiotic compounds to investigate the underlying SAR with the purpose of creating new functions. More specifically the ultimate aim is to med-chem out liabilities such as nephrotoxicity whilst concomitantly improving the antimicrobial activity and spectrum, thereby creating the foundations for a new generation of safer and more efficacious antibiotics.

Biography

Tony Velkov completed PhD in 2000 from Monash University. His anti-infective discovery research is at the leading edge globally. He was awarded a NHMRC Research Fellowships in 2006, 2011 and 2014. The quality and impact of his independent research was recognized by the NHMRC with an Excellence Award in 2011. He has published over 50 papers in high-caliber journals, 3 book chapters and 15 conference presentations. The dynamic team he leads consists of 3 postdocs, 3 RAs and 9 PhD students. Over the last 6 years, he has obtained >$9M funding from the NIH, NHMRC and foundations.

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