THE SYNTHESIS AND OPTIMISATION OF NEW ANTIBIOTICS

Andrew Abell

Department of Chemistry, University of Adelaide
Centre for Nanoscale BioPhotonics (CNBP), University, 5005 Adelaide, Australia

The rise of antibiotic-resistant micro-organisms is a major threat for healthcare providers across the world and new classes of antibiotic are desperately required. One emerging target for the development of such antibiotics is the essential metabolic enzyme, biotin protein ligase (BPL). BPL catalyses protein biotinylation through the formation of the adenylated reaction intermediate, biotinyl-5'AMP, from its substrates biotin and ATP. Here we report the rational design, synthesis and evaluation of chemical analogues of biotinyl-5'AMP that function as inhibitors of the BPLs from pathogenic bacteria such as *Escherichia coli*, *Staphylococcus aureus* and *Mycobacterium tuberculosis*.

Detailed studies are presented on *in situ* synthesis optimization of inhibitors using the target enzyme as a template; the importance of halogenation in optimising antimicrobial activity; protein crystallography, computation and simulation to optimize inhibitor design, synthesis, and biological profile; and the synthesis and development of fluorescent probes for super-imaging fluorescence microscopy. The fluorescent probes provide new insights into the mechanism of uptake, efflux and metabolism of BPL inhibitors in *S. aureus*. Studies on developing a photoswitchable antibiotic to minimise toxicity and resistance will also be presented.