“C” is for central: exploring the roles of condensation domains in non-ribosomal peptide synthesis

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The glycopeptide antibiotics (GPAs) are a structurally complex and medically important class of peptide natural products that include the clinical antibiotics vancomycin and teicoplanin. They contain a large number of non-proteinogenic amino acids and are produced by a linear non-ribosomal peptide synthetase (NRPS) machinery comprising seven modules. Furthermore, GPAs are extensively crosslinked late in their biosynthesis on the NRPS assembly line by the actions of a cascade of Cytochrome P450 enzymes, a process which contributes to the rigidity and structural complexity of these compounds. Due to the challenge of synthesising GPAs, biosynthesis remains the only means of accessing GPAs for clinical use, which makes understanding the biosynthesis of GPAs of great importance.

In this presentation, I will detail results from our recent studies into the NRPS machinery, the P450-catalysed cyclisation cascade and the interplay of these two important biosynthetic processes during GPA biosynthesis. Our work in understanding the non-ribosomal synthesis of GPA peptides demonstrates the vital roles that condensation (C)-type domains play beyond peptide bond formation, and shows that selectivity during GPA biosynthesis is mediated through the careful orchestration of critical modification steps and interactions between the peptide-producing NRPS machinery and *trans*-modifying enzymes. I will also discuss related results concerning C-domains from other NRPS-systems, which supports the importance of these biosynthetic domains in contributing to the fascinating structural diversity observed in non-ribosomal peptides.