Forward for ICCP2015 issue of Biopolymers Peptide Science

David J Craik and Conan K Wang

Institute for Molecular Bioscience, The University of Queensland,

Brisbane, 4072, Qld, Australia

We welcome readers to this special edition of Biopolymers Peptide Science which includes a selection of papers presented at the 3rd International Conference on Circular Proteins. The conference was held at the Tangalooma Resort on Moreton Island, Queensland, Australia from 1st to 4th November 2015. The conference was attended by approximately 70 delegates from 9 countries, including Japan, Canada, USA, Germany, Brazil, Sweden, Austria, and the Philippines. It included talks from more than 44 speakers, along with 28 poster presentations. This special issue comprises 18 articles covering a range of areas of cyclic peptides from discovery to biosynthesis and characterization, to drug design, bioavailability and nomenclature (Figure 1).

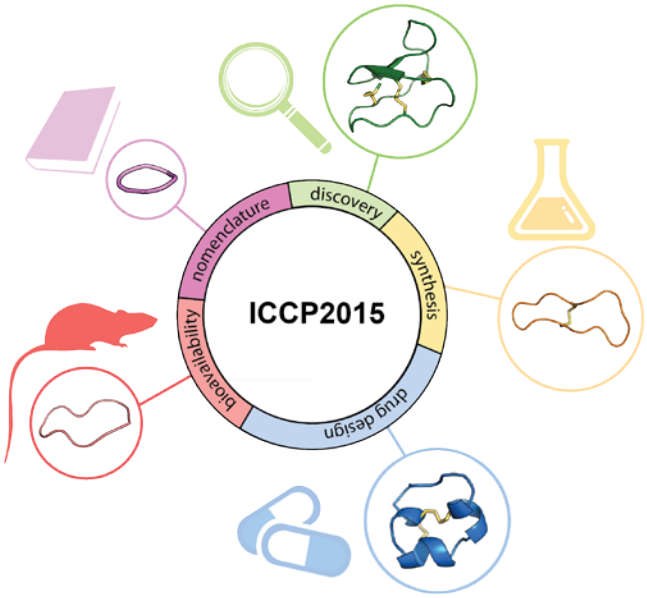

Figure 1. *This issue is divided into five sections, starting with articles on the discovery of cyclic peptides, and then moving to studies on the their synthesis and applications and delivery, returning finally to discussions on their nomenclature.*

In the discovery section are four articles from Johannes Koehbach, Nicolau Cunha, Ploypat Niyomploy and Bastian Franke, covering the discovery of cyclic peptides from across the world. This section opens with a review of peptidomic and transcriptomic methods for the discovery of cyclic peptides, highlighting some of the techniques that have worked so far as well as the challenges that lie ahead. The review provides an excellent introduction to the next three articles, which are more focused studies that exemplify specific discovery techniques, reporting the discovery of novel Brazilian cyclotides and their genes, the discovery of cyclotides in Southeast Asian plants and the discovery of seed cyclic peptides from Mexican plants. These studies support the general anticipation that many more cyclic peptides including ones with novel topologies (and from organisms other than plants) await discovery.

The synthesis section includes four articles from Sweden, USA and Australia. In the first of these articles Ulf Göransson and colleagues (Uppsala University, Sweden) describe a single step affinity purification method for cyclotides that promises to dramatically accelerate the production of highly purified cyclotides. Julio Camarero and colleagues (University of Southern California, USA) describe the successful application of intein-mediated protein splicing for the bacterial expression of SFTI-1. The intein-based approach has so far demonstrated broad versatility for cyclic peptide recombinant expression and thus promises to allow recombinant libraries of cyclic disulfide-rich peptides to be produced and screened. In the next article, Norelle Daly and colleagues (James Cook University, Australia) describe the role of an N-terminal precursor fragment of cyclotides in defining folding. In the final article of this section, Wilfred Van der Donk and colleagues (University of Illinois, USA) describe the lanthionine family of cyclic peptides and investigate their biosynthesis, describing an interesting relationship between the sequence of lanthionine precursors and the stereochemical composition of the mature peptide.

The next six articles describe applications of cyclic peptides in drug design. The starting article from Aline Dantas de Araujo reviews recent methods for stapling peptides by cross-linking cysteine side chains. Stapling strategies have attracted increasing attention as approaches for restricting conformation and enhancing biopharmaceutical properties. An application of the lactam-bridge stapling approach is described in the article that follows by Sónia Troeira Henriques and

colleagues, in which the authors report lactam-stapled peptides that target the MDM2 and MDMX proteins involved in cancer pathogenesis. The third article in this section is by Richard Clark and colleagues and describes the use of various linker sequences to connect the N- and C-termini of Vc1.1, a cone snail toxin that has great potential as an analgesic agent. The authors have previously shown that addition of a linker sequence can enhance the stability and activity of Vc1.1, and here show that the linker sequence is also a useful site for expanding functionality. The next two articles from Minying Cai and Victor Hruby provide a summary of cyclization strategies that can be used to modify bioactive peptides, focusing on melanocortin peptides, which are involved in a range of cellular functions, as examples. The final article in this section from Christopher Hipolito reviews the state-of-the-art in terms of combinatorial library based screening approaches, which promise to accelerate the discovery of high affinity cyclic peptide leads.

One of the major challenges in the field of peptide drugs is their generally poor bioavailability. In the bioavailability section, two articles investigate the bioavailability of cyclic peptides. The first article is a review on the structural and physicochemical properties of cyclic peptides that are important for passive permeability, a pre-requisite for high oral bioavailability. In general, cyclic peptides have demonstrated higher permeability than linear peptides, with chemical/structural/computational strategies for further improving their permeability being recently proposed, but there are still many challenges in the translation of high-affinity peptide leads to orally administered drugs. The second article by Ulf Göransson and colleagues examines methods for the detection of cyclic peptides in brain homogenate and plasma, establishing accurate quantification methods that will be useful for studying the bio-distribution of cyclic peptide drugs.

The final paper in this issue is from Martin Reaney and colleagues and addresses the issue of cyclic peptide nomenclature. As the conventional nomenclature scheme was designed with linear peptides in mind, this paper takes a exploratory look into challenges of naming cyclic peptide and raises some potential solutions.