

David J. Craik

David Craik is an Australian Research Council Professorial Fellow in the Institute for Molecular Bioscience, University of Queensland. He is the author of 285 refereed publications and is lead inventor on three patents. He moved to University of Queensland in 1995 to establish a new biomolecular structure NMR laboratory in the Centre for Drug Design and Development, following his award of an ARC Professorial Fellowship. Prior to this he was Dean of the School of Pharmaceutical Chemistry and Professor of Medicinal Chemistry at the Victorian College of Pharmacy, Monash University. He is the past Chairman and Chief Executive Officer of the Australian and New Zealand Society for Magnetic Resonance, past co-editor and now editorial board member of *Current Medicinal Chemistry*, and on the editorial boards of the *Encyclopedia of Spectroscopy and Spectrometry*, *The Handbook of Magnetic Resonance*, and *Biopolymers: Peptide Science*. He is editor of the book *NMR in Drug Design*. His contributions to medicinal chemistry and NMR have been recognized by the award of the Adrien Albert medal of the Royal Australian Chemical Institute (1993) and the ANZMAG medal of the Australian and New Zealand Society of Magnetic Resonance in 2004. His research interests focus on the application of NMR in drug design and development, and on toxins, including conotoxins. His group has a particular focus on structural studies of disulfide-rich proteins, and on the discovery and applications of circular proteins and novel protein topologies.

S-7 DISCOVERY AND APPLICATIONS OF THE CYCLOTIDES

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The cyclotides are a recently discovered family of plant-derived peptides that have a range of exciting applications in drug design and agriculture. They have a diverse range of biological activities, including uteronic, anti-HIV, antimicrobial, and insecticidal activities, the latter suggesting that their natural function is in plant defense. The cyclotides are typically about 30 amino acid in size, contain a head-to-tail cyclized backbone and incorporate three disulfide bonds arranged in a cystine knot topology. In this motif an embedded ring in the structure formed by two disulfide bonds and their connecting backbone segment is penetrated by the third disulfide bond. The combination of this knotted and strongly braced structure with a circular backbone renders the cyclotides completely impervious to enzymatic breakdown and makes them exceptionally stable. The cyclotides are the largest of several groups of naturally occurring circular proteins that have been discovered over recent years.

This presentation will describe the discovery of the cyclotides in plants, their structural characterization by NMR and studies on their folding mechanism. Their cyclic cystine knot motif makes the cyclotides exceptionally stable: they retain bioactivity after boiling and are resistant to enzymatic breakdown. Their stability and compact structure makes them an attractive framework for peptide-based drug design applications. Folding studies on the cyclotides and synthetic acyclic permutants have provided an insight into the mechanism of formation of the cyclic cystine knot motif.

