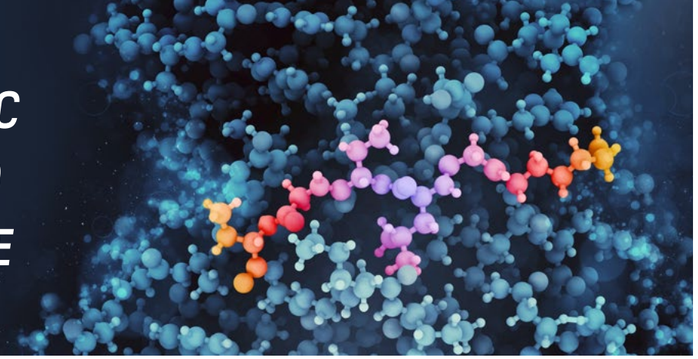
FOLDAMERS : SYNTHETIC PEPTIDES WITH DEFINED SECONDARY STRUCTURE



Presented by ANDRE COBB, Senior Lecturer in Organic Chemistry, **King's College London**

Andre studied Chemistry at King's College London before moving to UCL to conduct his PhD with Professor Charles Marson. From there he moved to the University of Cambridge for his postdoctoral research, first with Professor Florian Hollfelder in Biochemistry developing synthetic enzymes, and then Professor Steven V. Ley CBE FRS in the Department of Chemistry where he developed organocatalytic methodology, as well as some medicinal chemistry. In 2005 he moved to the University of Reading to begin his independent research career and in 2012 he was promoted to Senior Lecturer in Organic Chemistry. Then in October 2016 the research group returned to Andre's alma mater at King's College London. Andre is also the Associate Editor of the RSC's New Journal of Chemistry.

Nature has selected folded linear polymers to carry out its most elaborate functions. For example, proteins and peptides are ostensibly linear systems, but fold into more complex structures, leading to a specific arrangement of the associated side chains and thus dictating the ultimate function. This complex relationship between the structure of the biopolymer and its activity has inspired chemists to develop their own unnatural oligomers with strong and predictable folding properties, known as "foldamers" with the long term goal of creating artificial folded architectures that will not only equal the abilities of biopolymers, but surpass them. The distinctive advantages that a foldamer can bring over biological molecules include novel functionality, smaller size and greater biostability. Foldamer research has mainly been curiosity driven, yet the applications that have emerged from it have been far-reaching and range from molecular recognition, information storage and transfer, through to use as drug-delivery vehicles, catalysts, self-assembling systems for biomaterials, and as peptidomimetics and antimicrobials. Although foldamers can themselves be made from a variety of different constructs, the most intriguing are the peptidic ones inspired by nature. A very nice example comes from the Gellman group based at the University of Wisconsin-Madison who have constructed a range of helices based on homologated amino-acids. These monomers have one or two extra carbons between the C- and N-termini and as a consequence can form helical structures not encountered in nature.

Q&A WITH ANDRE COBB

1. ***Based on your research and work on foldamers, what are the current challenges that you are facing?***

Other than funding, the main problems lie in translating all the structural knowledge we have into application. We're getting there, but I think we are still some way off having a therapeutic foldamer or one that has some kind of commercial utility. Although the field has been going for two decades, this is still early days in terms of realising all the possibilities of these systems.

2. ***Where do you see the peptide industry heading within the next few years?***

It's hard to say. It is obvious that posttranslational modifications are a cornerstone of peptide science and it would be nice to see more techniques being developed for that which go beyond the usual cysteine/lysine derivatisation. The Gaunt group at Cambridge for instance has developed a really fascinating methionine modification procedure. The peptide industry should also look towards a greater range of unnatural homologated amino acids as constructs for foldamers. As their utility becomes increasingly apparent, so will their uptake in fields such as peptidomimetics and chemical biology.

3. ***Why is peptide synthesis such a promising field and how do you see it developing in the future?***

The way one sells peptide science to undergraduates is to highlight the fact that in spite of there only being 22 proteinogenic amino acids, nature manages to construct entire organisms (more or less) from them. The higher order structural diversity of proteins is remarkable given this fact. Now, imagine what you could do if you had even more secondary structural diversity. Different sized helices, different sheets, three dimensional constructs that have never even been thought of. It is an exciting time to be involved in the field.

4. ***As a speaker at the 2020 Peptides & Oligonucleotides Congress, what are you most looking forward to seeing at the event? What is your main goal when attending conferences such as this one?***

I am really looking forward to hearing about the work of other synthetic organic chemists in both the peptide and nucleic acid streams, and I hope that I can make some useful connections.

To find out more about Andre's involvement in the upcoming Peptides & Oligonucleotides Congress – Click Here

In a landmark report, and an astonishing demonstration of peptidomimetics, Gellman and his group produced foldameric homologues of the Bim BH3 domain and assessed their ability to bind to the BH3 recognition site on the Bcl-xL protein – itself a member of the anti-apoptotic Bcl-2 family.

To summarise, these intriguing and highly designable systems – resistant to proteases and with the potential to far outstrip small molecules with regards to specificity – could have tremendous impact – not just in the area of peptidomimetics – but also on many of the applications mentioned above.