BIOMOL STRUCT

GUEST LECTURE SERIES

RATIONAL AND COMPUTATIONAL *DE NOVO* DESIGN OF DYNAMIC PEPTIDE AND PROTEIN ASSEMBLIES

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Thursday, 02.12.2021, 15:00

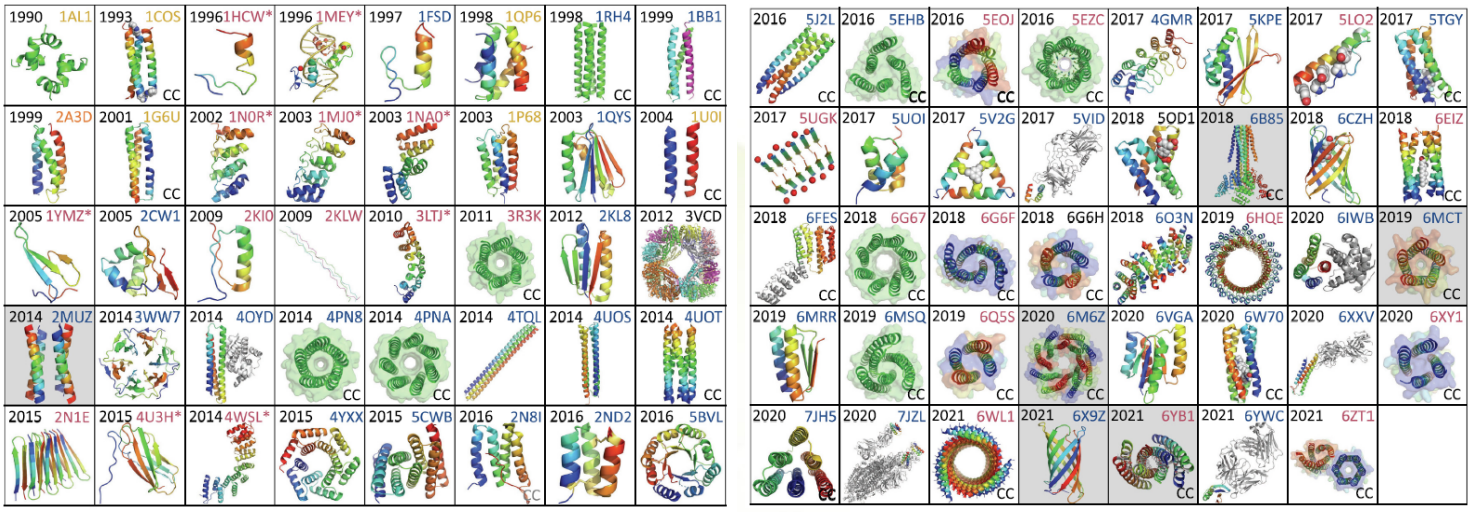
via Zoom: https://bristol-ac-uk.zoom.us/j/8279635732?pwd=M0NRdDMzTEwveWlZeTdOWlYxK2dkUT09

Abstract

Protein design - i.e., the construction of entirely new protein sequences that fold into prescribed structures - has come of age: it is now possible to generate a wide variety stable protein folds from scratch using rational and/or computational approaches. A new challenge for the field is to move past protein structures offered up by nature and to target the so-called 'dark matter of protein space'; that is, protein structures that should be possible in terms of chemistry and physics, but which biology seems to have overlooked or not used prolifically. This talk will illustrate what is currently possible in this nascent field using de novo α-helical coiled-coil peptides as building blocks.[1]

Coiled coils are bundles of 2 or more α helices that wrap around each other to form rope-like structures. They are one of the dominant structures that direct natural protein-protein interactions. Our understanding of coiled coils provides a strong basis for building new proteins from first principles. The first part of my talk will survey this understanding,[1] our design methods,[2,3] and our current "toolkit" of de novo coiled coils.[4-5]

Next, I will describe how the toolkit can be expanded used to generate some dark-matter protein structures. I'll focus on the rational and computational design of α-helical barrel proteins, which have 5 or more helices surrounding accessible central channels.[6] Finally, I'll discuss how these synthetic barrel proteins can be put to use to make new nanotube materials,[7] rudimentary catalysts,[8] membrane-spanning pores,[9] components of a new types of sensing devices,[10] and proteins that switch conformational state.[11]



A gallery of high-resolution de novo designed peptide and protein structures.
DN Woolfson, Journal of Molecular Biology 433; 167160 (2021)

Biographical sketch

Dek Woolfson is Professor of Chemistry and Biochemistry; Principal Investigator of BrisSynBio, a UKRI-funded Synthetic Biology Research Centre; Director of the Bristol BioDesign Institute at the University of Bristol; founding member of the Max Planck-Bristol Centre for Minimal Biology; and Founder of Rosa Biotech.

Dek took his first degree in Chemistry at the University of Oxford, UK in 1987. In 1991, he gained a PhD in Chemistry and Biochemistry at the University of Cambridge. He then did post-doctoral research at University College London (1991 – 92) and the University of California, Berkeley (1992 – 94). He returned to the UK to take up a Lectureship in Biochemistry at the University of Bristol (1994 – 95). From 1996 – 2005 he was Lecturer through to Professor of Biochemistry at the University of Sussex. He moved back Bristol in 2005 to a joint chair in Chemistry and Biochemistry.

Dek's research has always been at the interface between chemistry and biology, applying chemical methods and principles to understand biological phenomena such as protein folding and stability. He has a long-standing interest in the challenge of rational protein design, and how this can be applied in synthetic biology and biotechnology. His particular emphasis is on making completely new protein structures not known to natural biology using a combination of rational and computational design. The current focuses of his group are in the parametric design of protein structures, assemblies and materials, and porting these into living cells to intervene in and to augment natural biological functions.

In 2011, Dek became the first recipient of the Medimmune Protein and Peptide Science Award of the Royal Society of Chemistry; in 2014, he received a Royal Society Wolfson Research Merit Award, and he gained an ERC Advanced Grant; in 2016 he won the Interdisciplinary Prize of the Royal Society of Chemistry; and in 2020 he received a Humboldt Research Award (also known as the Humboldt Prize).

References

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2. CCBuilder: an interactive web-based tool for building, designing and assessing coiled-coil-protein assemblies. CW Wood et al. Bioinformatics 30, 3029-3035 (2014)
3. ISAMBARD: an open-source computational environment for biomolecular analysis, modelling and design. CW Wood et al. Bioinformatics 33, 3043–3050 (2017)
4. A basis set of de novo coiled-coil peptide oligomers for rational protein design and synthetic biology. JM Fletcher et al. ACS Synth Biol 1, 240-250 (2012).
5. A set of de novo designed parallel heterodimeric coiled coils with quantified dissociation constants in the micromolar to sub-nanomolar regime. F Thomas et al. J Am Chem Soc 135, 5161-5166 (2013).
6. Computational design of water-soluble α–helical barrels. AR Thomson et al., Science 346, 485-488 (2014)
7. Modular design of self-assembling peptide-based nanotubes. NC Burgess et al., J Am Chem Soc 137, 10554-10562 (2015)
8. Installing hydrolytic activity into a completely de novo protein framework. AJ Burton et al., Nature Chemistry 8, 837-844 (2016)
9. A monodisperse transmembrane a-helical peptide barrel. AJ Scott et al., Nature Chemistry 13, 643-50 (2021)
10. De novo-designed alpha-helical barrels as receptors for small molecules. F Thomas et al., ACS Synth Biol 7, 1808-16 (2018)
11. Structural resolution of switchable states of a de novo peptide assembly. WM Dawson et al. Nature Communications 12, ARTN:1530 (2021)