iNEXT workshop on Integrated methodologies and approaches for structural biology

Name of Speaker: **Neil Ranson**
University / Research Institute / Department: **Astbury Centre for Structural Molecular Biology, School of Molecular & Cellular Biology, Faculty of Biological Sciences, University of Leeds**

Title of Lecture: **Structural studies on protein aggregation in human disease**

Abstract:

All amyloid fibrils contain a cross-β fold. How this cross-β structure differs in fibrils formed from proteins associated with different diseases remains unclear. I will describe how we have combined cryo-EM and solid-state NMR to determine the structure of an amyloid fibril formed *in vitro* from β_2-microglobulin (β_2m), the culprit protein behind dialysis-related amyloidosis. The fibril is composed of two identical protofilaments assembled from subunits that do not share β_2m's native tertiary fold, but are formed from similar β-strands. The fibrils share motifs with other amyloid fibrils, but also contain unique features including π-stacking interactions perpendicular to the fibril axis and an intramolecular disulfide that stabilises the subunit fold. I will also describe models for additional fibril morphologies (at lower resolution) and show that they are built from the same subunit fold, and a suggest a model for how larger heterogeneous aggregation could be driven. The results provide insights into the mechanisms of fibril formation and the commonalities and differences within the amyloid fold in different protein sequences.

Research Profile:

I am a Structural Biologist, and my lab is focused on determining 3D structures using cryo-EM, and understanding how structure and conformational change drives biological function. I did my degree (1993) and PhD (1997) in Biochemistry in Bristol, then cross-trained into structural biology at Birkbeck College with Helen Saibil. I began my independent lab in 2002 as a Fellow at the University of Leeds, where I am now Professor of Structural Molecular Biology. My research is focused in three broad areas of structural biology: (i) virology - especially conformational change, receptor binding, assembly and uncoating, (ii) protein aggregation and amyloid formation and (iii bacterial outer membrane proteins, and the biogenesis of the outer membrane. All projects aim to discover fundamental insights into biological mechanisms and how to exploit these for new therapy.

Three selected publications:

1. Iadanza, M.G., Silvers, R., Boardman, J., Smith, H., Karamanos, T., Griffin, R.G.‡, Ranson, N.A.‡ and Radford, S.E.‡. (2018). The cryo-EM structure of a β-2-microglobulin fibril shows the molecular basis of a common amyloid architecture. *Nature Communications*, DOI:10.1038/s41467-018-06761-6

2. Hesketh, E.L, Saunders, K., Fisher, C., Potze, J., Stanley, J., Lomonossoff, G.P.‡ & Ranson, N.A.‡ (2018). The 3.3 Å structure of a plant geminivirus using cryo-EM *Nature Communications*, 9, 2369. DOI:10.1038/s41467-018-04793-6
3. Iadanza, M.G*., Higgins, A.J.*, Schiffrin, R., Calabrese, A., Brockwell, D.J., Ashcroft, A.E., Radford, S.E. ‡ & Ranson, N.A.‡ (2016). Lateral opening of the intact β-barrel assembly machinery captured by cryo-EM *Nature Communications.* DOI:10.1038/ncomms12865

CEITEC Masaryk University
Kamenice 735/5
625 00 Brno, Czech Republic
+420 549 495 511, info@ceitec.cz
www.ceitec.eu