B·DEBATE International Center for Scientific Debate BARCELONA

KAREN MCLUSKEY CV

SPEAKER AT:

THE DEATH OF PLANT CELLS.
FROM PROTEASES TO FIELD APPLICATIONS

October, 2nd and 3rd , 2013, Barcelona

Karen McLuskey, Research Fellow at the Wellcome Trust Center for Parasitology, University of Glasgow, UK

Karen McLuskey studied Chemistry with Computer Applications at the University of Glasgow, where she was first introduced to X-ray crystallography. For her PhD she investigated the primary events bacterial photosynthesis, using membrane-protein crystallography, under the supervision of Profs. Neil Isaacs (crystallography) and Richard Cogdell (plant biochemistry). She completed two post-doctoral positions: the first with Prof. Wim Hol, University of Washington, Seattle and the second with Prof. Bill Hunter, University of Dundee, Scotland. Both of these posts involved using multi-disciplinary approaches involving X-ray crystallography, to investigate the structure/function relationships of proteins involved in the pathogenesis of disease caused by parasites. During this time she became interested in structure-based drug design and while in Dundee she was involved in the discovery of inhibitors for both Leishmania and Trypanosomes. Continuing with this type of work, she subsequently moved back to Glasgow University where she is currently working at the Wellcome Trust Centre for Parasitology with Prof. Jeremy Mottram, as a Research Fellow in structural biology.

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Structural Insights into Why Metacaspases Are Not Caspases

The mammalian caspases (cysteine-dependent aspartate-specific protease)s are major regulators of apoptotic cell death pathways, proliferation and inflammation. Over a decade ago, metacapsases (and paracaspases) were discovered during a search for caspase orthologues in non-metazoan organisms. Notably absent in mammals, metacaspase sequences were identified in plants, yeast and parasitic protozoa and classified as part of the caspase structural family (Clan CD, Family C14 (MEROPS)). However, their substrate specificity and requirements for activation set them aside from the caspases: Caspases are Asp-specific functional dimers that are activated by dimerisation or by intra-chain cleavage, whereas metacaspases have Arg/Lys specificity, function as monomers, do not require processing for activity and are activated by calcium. Determining the X-ray crystal structure of a metacaspase from the protozoan parasite Trypanosoma brucei (TbMCA2) allowed the structural basis for these functional differences to be elucidated. It also allowed an in-depth analysis of the topological differences and similarities between, not only the caspases and metacaspases, but also the paracaspases and other available Clan CD family members, providing clear evidence that the metacaspases are structurally distinct from the caspases. In addition, biochemical and functional studies support the opinion that parasitic protozoa do not exhibit regulated cell death, demonstrating that trypanosome metacaspases are not caspases, after all.

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