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Editorial overview: Membranes: Recent methods in the study of membrane protein structure

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Tamir Gonen is a Group Leader at the Janelia Research Campus of the Howard Hughes Medical Institute. Prior to his current position, he was an Associate Professor of Biochemistry and the Director of the Molecular Electron Microscopy Laboratory at the University of Washington in Seattle where he was also a Howard Hughes Medical Institute Early Career Scientist. His research aims are to understand the structure and function of membrane proteins involved in nutrient uptake, cellular communication, water uptake and homeostasis. His group is currently focusing on method development for cryo-EM in particular MicroED where nano-crystals of biological material are studied by electron diffraction.

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Gabriel Waksman is the Director of the Institute of Structural and Molecular Biology at UCL and Birkbeck, Head of Department of Structural and Molecular Biology at UCL and Head of Department of Biological Sciences at Birkbeck. Over the past 20 years, he has developed a research programme into the structural and molecular biology of bacterial secretion. His current research aims to elucidate secretion mechanisms by large membrane-embedded macromolecular systems involved in pilus biogenesis and in DNA secretion.

Membrane proteins and complexes have remained the 'parent pauvre (poor relation)' of structural biology. The complexity of handling these proteins has been a solid barrier to progress. Yet, it suffices to point to the fact that 50% of drugs are targeted to membrane proteins and receptors to realise how important these proteins are.

But these are exciting times in structural biology of membrane proteins. X-ray crystallography has dominated the field until recently and has been used by structural biologists to make seminal contributions. In this issue, we have invited a number of crystallographers to present and discuss their work. But crystallography is unlikely to maintain its supremacy in future years. Indeed, we welcome here a few new kids on the block. First and foremost, this issue brings to the fore the formidable progress made by electron cryo-microscopy (cryo-EM) in deriving structures at high resolution. The relatively recent availability of direct electron detectors is revolutionising the field and we have invited contributions of some of the actors driving the field of membrane protein structural determination by cryo-EM. Another technique, MicroED, exploits the soft energy of electrons and their strong interaction with matter to carry out diffraction experiments on vanishingly small crystals using TEM to atomic resolution, making this technique potentially applicable to membrane proteins where the crystals are often indeed very small. Finally, advances in solid state NMR paves the way towards imaging membrane proteins directly in membranes and potentially with atomic resolution.

Contributions from X-ray crystallographers include that of Tsai et al. on proton/sodium pumping membrane-bound pyrophosphatases (M-PPases) and Berks et al. on the structure of the Tat complex in bacteria. Tat protein transport system is found in the cytoplasmic membrane of prokaryotes and the thylakoid membrane of plant chloroplasts. It transports folded proteins. Recent advances have provided views of two of the three proteins that make up this complex and have shed light into the export mechanism. M-PPases are predominant in plants and bacteria, and protect cells from abiotic stress such as cold, drought, salt stress and low light illumination. M-PPases couple pyrophosphate (PPi) metabolism to membrane-potentials. How they do so was recently illuminated by the laboratories of Shu and Goldman and their findings are reviewed here.

Zhou and colleagues describe recent progress on the structure and function of the TrkH/KtrB ion channel while Buchanan and colleagues highlight

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insights into the transport of small molecules across membranes. Frank and co-workers describe X-ray free electron lasers, their development and recent progress at studying membrane proteins arranged as two-dimensional arrays. Finally, Venkatakrishnan et al. analyse the most recent crystallographic set of GPCR structures with emphasis on the conservation of the trans-membrane scaffold, and variability of the intracellular loops and C-terminal tail where most of the intracellular action resides.

Contributions from electron microscopists include that of Trokter et al. on type IV secretion systems (T4SS) in bacteria. T4SS are secretion systems are one of 6 secretion systems in Gram-negative bacteria but the only one to transport DNA. Trokter et al. review the field of T4SS research, notably expanding on the most recent advance, the structure of an almost complete system, which was solved by electron microscopy, revealing a unique architecture. Cheng and colleagues determined the high-resolution structure of TRPV1, a channel that eluded crystallographers for years, by using single particle cryo-EM. Here the particles were meticulously prepared and imaged using the latest technological advances in cryo-EM including new detectors and algorithms to correct for motion. Yeager and colleagues highlight a few examples where cryo-EM was used to help solve crystal structures of important protein complexes.

Finally, Gonen and colleagues describe the development of a new method for structural biology called MicroED where structural information of biological material is obtained by electron diffraction from very small crystals to atomic resolution. Baldus and colleagues discuss recent progress and potential applications of solid state NMR to investigate membrane protein dynamics and function in synthetic bilayer preparations. But this technique has potential to provide direct, site-specific information at high resolution for membrane proteins *in situ* in cellular contexts.

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