In this issue

Membrane proteins: Gatekeepers, sentries, morpherers and oil magnets

'Serpent!' screamed the Pigeon.
*'I'm **not** a serpent!' said Alice indignantly. 'Let me alone!'*
'Serpent, I say again!' repeated the Pigeon.
*'But I'm **not** a serpent, I tell you!' said Alice. 'I'm a __I'm a __'*
*'Well! **What** are you?' said the Pigeon. 'I can see you're trying to invent something!'*
'I__I'm a little girl', said Alice, rather doubtfully, as she remembered the number of changes she had gone through, that day.

— Lewis Carroll
in *Alice's Adventures in Wonderland*

Membrane proteins (MPs) are, of course, important. They are responsible for cells to live and carry out their daily ablutions. These MPs arise from watery depths and live in the oily environs changing their views as the need suits them. It is difficult to pin them down to only certain functions. They seem to have amongst them – channels, gates, receptors, proteases, endonucleases, transporters, respiratory proteins, oxidases, etc. – and are ready to associate themselves with a variety of other molecules. There are interfacial membrane proteins, peripheral membrane proteins, integral membrane proteins and those with transmembrane portions. These are less stuffy than their globular counterparts but likely to be more important as drug targets and in biomedicine. But probe a little deeper as to what we know of protein inhabitants of the walls and their associates and you realize how much more needs to be done Articles in this issue focus on palmityolation that contributes to membrane association, interaction of proteins with model plasma membrane components and the effect of lipopolysaccharides on protein stability.

In 1980, Garavito and Rosenbusch obtained the first membrane protein crystals of bacterial porin that diffracted. Electron microscopy and circular dichroism established the exclusive beta sheet composition of this pore protein and a beta barrel structure was proposed. In 1985 Diesenhofer, Huber and Michel obtained the first X-ray high-resolution structure of a membrane protein which was the bacterial reaction centre made from alpha helices. It was only in 1990 that the first high-resolution structure of a bacterial porin was obtained which established them to be a beta barrel. The world of integral membrane proteins seems to be made of alpha helices and beta barrels. From then on if you take the 20,000 plus structures in the protein databank (www.rcsb.org) there are about 80 unique membrane protein structures (http: //blanco.biomol.uci.edu/Membrane_ Proteins_xtal.html) covering about 36 different folds. This includes also proteins of the same type from different species. But each of the structures has thrown up a wealth of detail. What we need are clearly more structures – for which we need to overcome the problems of protein production and crystallization.

The deluge of genome sequences shows that membrane proteins comprise nearly 25–30% of the proteins in the proteome. In all three kingdoms of life the proportion of membrane proteins remains similar (Stevens and Arkin, *Proteins: Structure, Function, and Genetics*, 2000, **39**, 417–420). However these estimates are for mostly alpha helical membrane proteins. There are many methods for prediction of alpha helical membrane proteins but few that predict beta stranded ones (Chen and Rost, *Applied Bioinformatics*, 2002, **1**, 21–35). Our understanding of tertiary and quaternary structure prediction for membrane proteins is also poor. The energetics of folding of membrane proteins needs to be understood further.

The review article by Varshney and Mathew (**page 166**) walks one through the architecture and functioning of the potassium channel, an integral membrane protein made of alpha helices. Way back in the fifties, Hodgkin and Huxley postulated the existence of these potassium channels. The rest, as they say, is history culminating in the Nobel Prize-winning work on the structural foundations of the potassium channel by Roderick MacKinnon. The structural and architectural features of potassium channels are shown to be perfectly adapted to fit their function. They solve the electrostatic problem of stabilizing ions – without making them as stable as they are in water – by using plenty of water and helix dipoles to counteract the unfavourable dielectric environment within the membrane. Furthermore, the problem of stabilizing potassium in preference to sodium is handled by precisely matching the geometry of oxygen atoms around a partially desolvated potassium ion. In this review, the focus is on the basic channel properties: activation, inactivation and ionic selectivity. The physiological parameters are discussed in the light of recent X-ray crystal structures of bacterial Kv channels, and a body of work combining mutagenesis with electrophysiology and spectroscopy. The structural information, more so considering the difficulties involved in X-ray and NMR work involving membrane proteins, can be complemented by biophysical techniques, such as AFM, FTIR and fluorescence spectroscopy. Chattopadhyay and Raghuraman (**page 175**) review the application of various approaches based on fluorescence spectroscopy to explore the organization and dynamics of membrane proteins and peptides. They point out that information obtained using fluorescence spectroscopy of membrane proteins could prove vital for a better understanding of cellular structure and function in health and disease, the importance and use of the analysis of depth of penetration of membrane proteins and peptides utilizing fluorescence quenching, site-directed fluorescence labelling and the wavelength-selective fluorescence approach. Such experimental approaches need to be supplemented by theoretical models. The article by Mathur *et al.* (**page 181**) goes into the energetics of insertion of helical pairs into membranes, which is an important event in the folding of membrane proteins as well as in the way molecules like diptheria toxin attach to the membrane. A variety of biological processes, for example, viral infection and signal transduction, involve interaction between proteins and protein fragments in lipid bilayers. The theoretical development presented in the work provides a platform for a detailed study of the molecular events that underlie these processes.

In a simplified view of the world of membrane proteins, beta barrels seem to

populate so far the outer membrane, and alpha helicals appear to prefer the inner membrane. The twain do meet as in the case of the Type I transport system such as that involving TolC. Federici *et al.* describe (**page 190**) the structure and function of TolC. The porin-like beta barrel head formed by the trimeric TolC has an almost 100 Å long alpha helical bundle tail. This interacts with an inner membrane antiporter protein such as AcrB, mediated by a membrane fusion protein such as AcrA. The structure of AcrA is not known, but solution scattering studies indicate that it could span the periplasm. The structure of the trimeric AcrB is like a jellyfish made from the monomers which have twelve transmembrane alpha helices. A tantalizing hypothetical structure of the complex is seen in the article. The next article touches on the highly immunogenic trimeric OmpC, made of beta barrel monomers, from *Salmonella typhi*. Arockiasamy *et al.* (**page 197**) mention the problems they face in trying to get a high-resolution crystal structure. In that process they find the importance of lipopolysaccharide association for the stability and folding of OmpC. The interaction of membrane components with proteins is important in the stability or mechanism of the protein. This is described by Musti Swamy (**page 203**) using the bovine seminal plasma protein PDC-109 (which as you might guess is 109 aa in size) that binds to the plasma membrane of the spermatozoa upon ejaculation and plays a critical role in priming the sperm cells for fertilization to take place. Electron spin resonance and surface plasmon resonance studies are used to discuss the interaction of PDC-109 with model membranes and with the plasma membrane of the spermatozoa. Apart from non-covalent interactions as described above, proteins also get covalently modified and thus increase their capacity to associate with the membrane. The covalent attachment of lipid moieties to proteins takes place in many forms best studied in eukaryotic and viral systems. S-palmitoylation is the reversible addition of palmitate to proteins on cysteine residues via a thioester linkage. Palmitoylation increases the hydrophobicity of proteins and contributes to their membrane association. Basu (**page 212**) reviews the understanding of protein S-palmitoylation as one of a repertoire of dynamic post-translational protein modifications that can control protein trafficking, localization, partitioning into domains, protein–protein interactions and functions.

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