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Editorial

Membrane proteins — do we catch up with the breathless pace of soluble protein structural biology?

It seems in the human nature to strive for whatever is just slightly beyond reach. Henderson and Unwin described the first membrane protein structure in 1975, a bacteriorhodopsin, through pioneering electron microscopy studies of the bacterial purple membrane [1], and later in the early 1980s Michel and coworkers presented the first crystal structure of a membrane protein, the photosynthetic reaction center from *Rhodopseudomonas viridis* [2]. However, besides few other breakthroughs progress was slow, and commenting in 2000 on future perspectives of membrane protein research, James Bowie stated the eminent question we have paraphrased in the title: "Will we ever catch up with the breathless pace of soluble protein structural biology?" [3]. At the time only 26 unique membrane protein structures had been published, most of them beta-barrels, and each representing years of effort by dedicated teams.

Since then it has become clear that the answer will be a resounding yes, although with some moderation. First we witnessed the pioneering breakthroughs on samples obtained from abundant, native sources as mentioned above, and which continue to offer favorable opportunities that should not be overseen, but since the late 1990s we have seen numerous examples of bacterial membrane proteins expressed in *Escherichia coli* that represent homologues of mammalian proteins, spearheaded not least by the potassium channels [4]. Over the last 10 years also heterologously expressed eukaryotic membrane proteins have produced crystals [5–8] with spectacular recent achievements on receptors of key interest in pharmacology such as the GABAA receptor [9] and of course a plethora of G-protein coupled receptors [10,11]. New frontiers will expectedly include larger membrane protein complexes and higher level structure and function of biomembrane systems as they have now become amenable also for cryo-electron microscopy studies (e.g. [12,13]).

However as predicted by Bowie and others, there has been no panacea to the challenges of producing and characterizing membrane proteins. The tool-box has definitely expanded and it has been repeatedly shown that the job can be done. Ion channels, G-protein coupled receptors, flexible transporters — the list is growing. Although the determination of a membrane protein structure or the characterization of its intimate mechanism of function is still highly time-consuming and challenging endeavors, even the toughest membrane proteins are within reach of a dedicated effort. The importance of such prior knowledge cannot be overstated.

So is it getting any easier or are we just seeing the proportional outcome of huge investments? Yes and no. Methods have developed and matured, certainly also tapping from general expertise in life sciences, but at the same time we are now working towards much more challenging targets, and such targets typically represent specific physiological or biotechnological problems — we deliver now "on demand" and not so much for a proof of concept anymore.

Here we present eleven reviews from prominent laboratories in the membrane protein field. As membrane protein crystallography has matured over the last 15 years, the merger with biochemistry is also clearly consolidating — biochemistry and crystallography are interdependent challenges and gains and no one is in a better position to crystallize a membrane protein than he or she who knows how it responds. We are now way past the point where a membrane protein structure will raise any eyebrows if not qualified by functional studies.

In this special issue of BBA General Subjects on structural biochemistry and biophysics of membrane proteins we have decided to focus on a number of membrane protein families for which new information has recently seen the light and spawned new ideas or a revised look on old concepts.

Neutze and coworkers take a revised look on bacteriorhodopsin – the very first membrane protein we came to see – leading to new conclusions on which structural intermediates are in fact to be considered and how. The peptide transporters seem to conform to a new scheme for transport in the major facilitator superfamily as presented by Simon Newstead. Following different transporter rationales, peptide accumulating ABC transporters in adaptive immunity are reviewed by Seyffer and Tampé. Going into how lipids are flipped in the membrane, Palmgren et al. looks at phospholipid flipping mechanisms by P-type pumps and ABC transporters, while membrane protein–lipid interactions are reviewed by Koshy and Ziegler from a structural perspective with functional implications. Turning to pharmacological sites in membrane proteins Delarue and coworkers review the pentameric ligand-gated ion channels that in human include many neurotransmitter receptors, while binding sites for substrate and inhibitors are reviewed by Claus Løland focusing on LeuT as a member of the neurotransmitter:sodium symporter family. Palmgren and coworkers have also provided a review on the elusive family of P5-ATPases, a membrane protein family that surprisingly, and despite years of scrutiny still are of unknown function even though they are found in every eukaryotic species (and not in any single prokaryote investigated so far). The Waksman group presents structural aspects of pili-based adhesion and secretion systems in bacteria, while Jaehme and Slotboom provide a timely overview of another ABC transporter family, namely the modular vitamin uptake systems in bacteria, which are also among prime modalities of microbiomes. Finally, we have the first insights into the mechanism of the exciting glucose superfamily of the Phosphotransferase system, reviewed by Zhou et al.

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Transport and signaling inside cells, among cells, and in interaction with the surrounding environment – be that hot volcanic springs, biofilms or brain tissue – are essential processes in life and will continue to provide us remarkable new examples of what nature holds in store for us to see and understand. Similarly, membrane proteins are fundamental to our understanding of healthy living, nutrition, and mechanisms of disease and medicine. We have also repeatedly seen that the insight into membrane proteins can have the most surprising later applications, such as optogenetics, which derived from investigations of channel-rhodopsin receptors in algae that are gated by light [14]. It is certainly not a time to close the book on the enormous and highly sophisticated biology of micro-organisms to focus on pharmacological targets in human — that would be a historical mistake of lost opportunities.

We hope this issue will be an inspiring collection of contributions to those interested in some of the most fascinating molecules and great mysteries of life.

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Bjørn Panyella Pedersen received his PhD in 2008 after working with proton and sodium/potassium P-type ATPases under the mentorship of Poul Nissen. Later he did his postdoctoral research at University of California-San Francisco together with Prof. Robert M Stroud, where they focused on understanding calcium/proton exchange and phosphate uptake across membranes. Currently he is Assistant Professor and group leader of a small laboratory at Aarhus University. He is a structural biologist and his research focuses on elucidating the molecular mechanisms of various transport processes across the cellular membrane at the atomic level, presently focusing on sugar and cholesterol uptake.

Poul Nissen is a professor of protein biochemistry at Aarhus University. After a PhD in 1997 he was a postdoc at Yale where he worked on the first structures of the ribosome with Peter Moore and later Nobel laureate Tom A. Steitz. Poul Nissen initiated own research on membrane transport proteins in 2000. Since 2007 he has been the director of the PUMPkin center of the Danish National Research Foundation, and since 2013 of DANDRITE, the Danish node of neuroscience of the Nordic-EMBL Partnership for Molecular Medicine. Poul Nissen is an elected member of the Royal Danish Academy of Science and Letters, the Academy of Technical Sciences in Denmark, and the European Molecular Biology Organisation (EMBO).