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Stanley Opella – The conqueror of membrane protein structure

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Proteins that span biological membranes perform some of the most important biochemical processes that are vital for life. Understanding their structural organisation is a prerequisite for developing drugs for treatment of diseases including various forms of cancer, cardiovascular disease, disorders of the immune and nervous systems etc. However, unravelling the detailed structural organisation of these proteins in their native membrane bound state has been virtually impossible. Amongst membrane proteins that are particularly important for drug development are G-protein-coupled receptors (GPCRs) which are a large family of membrane proteins. Approximately 50% of the currently available medications target this class of proteins. Detailed structural characterisation of these proteins is vital for developing drugs that can interact with specific binding sites and control their activities. Unfortunately, the most powerful technique for determining the three-dimensional structure of proteins, namely X-ray crystallography, cannot be readily used since membrane proteins are difficult to crystallise. To aid crystallisation of membrane proteins, it is necessary to remove the lipids that surround the protein, by adding detergents. Additional procedures used to obtain crystals include forming complexes with other proteins or even through insertions or deletions of entire protein domains within the GPCR protein. However, these manipulations could alter the structure of the GPCR which can hinder or slow down the process of designing drugs that require precise knowledge of the binding site within the intact protein molecule in its native lipid membrane environment. Consequently, one of the greatest challenge facing structural biologists is to be able to conquer the structure of membrane proteins without resorting to such manipulations which are often referred to as "*divide and conquer*". The man who has been successful in meeting this challenge is Stanley Opella (Fig. 1) and his group at the University of California at San Diego [1]. They used solid state NMR spectroscopy to determine the complete three-dimensional structure of a GPCR protein, called CXCR1, intact in its membrane environment (Fig. 2). This is the first time the high-resolution structure of such a large protein has been elucidated in its biologically relevant state. For this reason, Stanley Opella can be rightly described as the conqueror of membrane protein structure. This landmark achievement paves the way for determining the structure of not only other GPCRs but of other membrane proteins in their native membrane environment. Previously X-ray crystallography has been used to gain information on the structure of GPCR's which helped to provide better insights into the mechanism of action of this class of proteins. The importance of this work was recognised through the award of a Nobel Prize in Chemistry to Robert Lefkowitz and Brian Kobilka [2,3]. The breakthrough made by Stanley Opella and his group will further advance our understanding of GPCRs and accelerate the development of life saving drugs.

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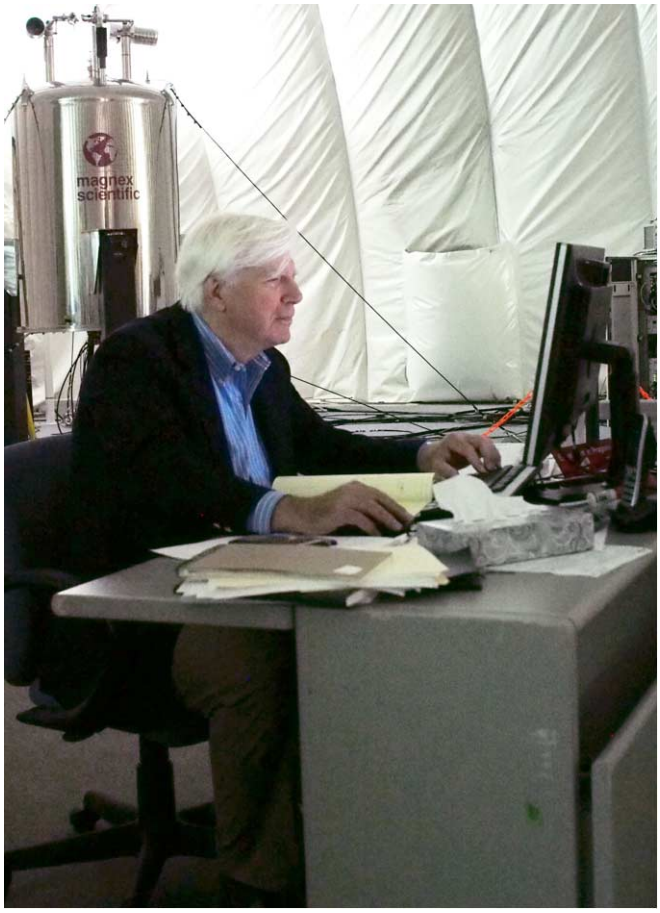

Fig. 1. A recent photograph of Stanley Opella operating the NMR spectrometer inside "*The Bubble*" (see Fig. 3). (Colors are visible in the online version of the article; http://dx.doi.org/10.3233/BSI-140087.)

Stanley Opella completed his PhD in 1974 at Stanford University under the supervision of O. Jardetzky and H.M. McConnell. He was a postdoctoral fellow at MIT (1975–1976) working in the laboratory of J.S. Waugh. In 1976 he became a faculty member in the Department of Chemistry at the University of Pennsylvania. Stanley Opella moved to the University of California, San Diego in 2000, where he is Distinguished Professor of Chemistry and Biochemistry. Figure 3 shows the "*The Bubble*" at the University of California, San Diego. This air-supported structure houses the NMR spectrometers that are used by Stanley Opella's group for determining protein structure at high resolution. I personally came to know Stanley Opella in the 1990s when I was myself engaged in research characterising membrane protein structure in their native membrane environments using Fourier transform infrared spectroscopy [4]. Impressed by his work on the structure determination of a membrane-bound protein using solid state NMR spectroscopy, I visited him in his laboratory at the University of Pennsylvania. He is a kind, co-operative and hospitable person. Stanley Opella is a remarkable man who has been painstakingly and patiently working on developing solid state NMR spectroscopy for analysis of membrane proteins for four decades. His early work focused on structure analysis of small proteins such as the Pf1 coat protein [5]. The ultimate goal was to extend the technique to characterising large membrane proteins. His patience and perseverance paid off with the structural elucidation of the GPCR protein which was

Fig. 2. A painting of the three-dimensional structure of CXCR1 protein by Judith McCabe-Jarvis. (Colors are visible in the online version of the article; http://dx.doi.org/10.3233/BSI-140087.)

published in *Nature* in 2012 [1]. This achievement must have caught the attention of the Nobel committee. In due course, I anticipate Stanley Opella to be awarded a Nobel prize for being the first to conquer the structure of a large membrane protein, intact in its native environment, and in the process take membrane protein structure determination to a new frontier. It has been over a quarter of a century since the last Nobel prize was awarded for work on the three-dimensional structure determination of a large membrane protein structure [6]. Johann Deisenofer, Robert Huber and Hartmut Michel had to remove the protein from its native biomembrane environment and add detergents in order to obtain crystals that are suitable for X-ray diffraction [6]. However, the painfully slow progress in this field has led a sense of resignation that it will be virtually impossible to characterise membrane protein structure, intact in their native membrane environment, and "*divide and conquer*" approach is the only way forward. In this context, the breakthrough by Stanley Opella and his team brings a refreshing new impetus and vigour in this important field of research and the "*divide and conquer*" approach to solving membrane protein structure may be a thing of the past.

Acknowledgements

I would like to thank Judith McCabe-Jarvis who painted the high resolution structure of the GPCR (Fig. 2). I would also like to thank Christopher Grant for his photograph of the 'bubble' (Fig. 3).

Fig. 3. The NMR spectrometers which Stanley Opella's group operate are housed in this air-supported structure that is called "*The Bubble*". Picture taken by Christopher Grant. (Colors are visible in the online version of the article; http://dx.doi.org/10.3233/BSI-140087.)

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