Preface

The 2006 Biochemical Society Annual Symposium 'The cell biology of inositol lipids and phosphates' was held at Birmingham University on 29–31 March. There were two reasons for this choice of topic and venue. First, the inositides field has progressed in an unforeseeable manner in the last 25 years with many of the key advances being made by Biochemical Society members and secondly, 2006 marked the retirement of one of the major U.K. figures in the field, Bob Michell. The meeting brought together international leaders in the field, many of whom were previous Michell laboratory members, to discuss recent progress as well as to highlight areas that remain poorly understood. This volume contains contributions from the speakers at the Symposium.

Bob Michell's original hypothesis presented in the mid 1970s focused upon PtdIns hydrolysis regulating an increase in intracellular free Ca^{2+} concentration; the first four chapters of this volume address recent work in this area. Michael Berridge, who played a central role in demonstrating that Ins(1,4,5)P_3 was responsible for the release of stored Ca^{2+}, considers its role in generating Ca^{2+} oscillations, while Katsuhiko Mikoshiba provides a complete update on the IP_3 receptor. The phospholipase C family has recently grown and Tony Lai describes his identification of PLCζ and its novel roles in fertilization. The original Michell hypothesis suggested that phospholipase C activity activated ion channels. Jim Putney confirms this prediction describing the TRP superfamily of ion channels, three members of which (TRP3, 6 and 7) are activated by diacylglycerol, while two others can also be activated downstream of phospholipase C activation.

In addition to being a substrate for phospholipase C, PtdIns(4,5)P_2 can be phosphorylated by PtdIns 3-kinases. Roger Williams considers the importance of PtdIns3*P*, the product of the Class III PtdIns 3-kinase, in membrane trafficking, his contribution highlights the benefits of a structural biology approach in understanding mechanism. Phill Hawkins and Len Stephens present their studies into the roles of PtdIns 3-kinase pathways in regulating the neutrophil NADPH oxidase, demonstrating roles for three distinct 3-phosphorylated inositides. The importance of lipid messenger removal is demonstrated by Pete Downes's studies into PTEN, while Mark Lemmon describes the structural basis of PH domain-phosphoinositide binding.

The role of phosphoinositides in membrane trafficking has been clearly demonstrated. Silvia Corvera discusses PtdIns3*P*, particularly in relation to FYVE domain binding, while Antonella De Matteis considers the importance of phosphoinositides in the Golgi complex emphasizing the functions of PtdIns4*P*. Bernard Payrastre considers the emerging importance of PtdIns5*P* in cell regulation highlighting the emergence of selective binding domains for this lipid. In contrast, Steve Dove reviews our understanding of PtdIns(3,5)P_2 as a

lipid messenger in regulating membrane trafficking, primarily in *Saccharomyces cerevisiae*, although noting that this lipid has signalling roles in other organisms. Vojo Deretic describes the roles of phosphoinositides in both phagocytosis and autophagy, in particular he describes how *Mycobacterium tuberculosis* arrest phagosomal maturation by preventing PtdIns3*P* production.

The type II PtdIns*P* kinases are primarily PtdIns5*P* 4-kinases. Robin Irvine considers the distinct tissue and intracellular localizations of the members of this enzyme family pointing out the poorly understood nature roles of these kinases. Christina Mitchell reviews the 5-phosphatases which act upon phosphoinositides and inositol phosphates; her detailed review describes phenotypic changes associated with loss of expression of these enzymes and highlights those studies that point to an association between these enzymes and human disease. One of the intracellular localizations of the type II PtdIns*P* kinases described by Robin Irvine is the nucleus and Bernard Payrastre highlights the importance of PtdIns5*P* in the nucleus. John York describes the emerging roles for the nuclear inositol polyphosphates and kinases in both yeasts and metazoans. Another key role for inositol lipids in cells is as GPI anchors. Andreas Conzelmann describes the biosynthesis and remodelling of these lipids in a number of model organisms, including yeasts, protozoa and mammalian organisms. Steve Shears continues the theme of addressing the less understood areas by considering the potential physiological roles of the inositol polyphosphates.

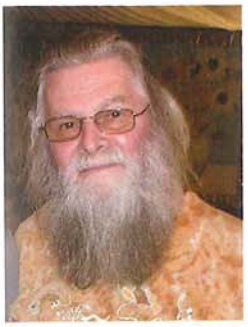
Andrew Morris describes the regulation of phospholipase D. This is an example of a protein whose activity and localization are both regulated by PtdIns(4,5)P_2 which binds to two sites, one a defined PH domain, but the other a less well understood 'polybasic' region pointing to the existence of further phosphoinositide-binding structures. Shamshad Cockcroft concludes the volume by considering the importance of the PtdIns transfer proteins. These do not simply transfer PtdIns from one membrane to another, but play an intimate role in the regulation of a number of physiological events, such as cell division.

Finally, Bob Michell addresses the evolution of the multiple roles of the inositol-containing compounds and considers their importance in biology. This extensive, thought-provoking analysis of the literature also considers concepts from a number of the other chapters thereby integrating many of the topics of the symposium.

The symposium allowed us to bring together many of those working upon the cell biology of inositol lipids and phosphates; this generated much interesting and stimulating discussion as well as honouring Bob Michell and his contributions to the field. I hope this volume will have a similar stimulatory effect. Thus I am extremely grateful to the authors for their scholarly contributions and Mike Cunningham and all at Portland Press for their assistance in editing and producing this volume.

Michael Wakelam

A tribute to Bob Michell



Bob Michell has been a major figure in lipid biochemistry for more than 30 years. His interest in the inositol phospholipids dates back to his Ph.D. studies in Tim Hawthorne's laboratory at the University of Birmingham when he demonstrated that PtdIns kinase is a plasma membrane enzyme in liver. This work was to prove particularly significant in the 1980s when the importance of the location of polyphosphoinositides at the plasma membrane was appreciated.

After a period of postdoctoral work at Harvard Medical School, Bob returned to Birmingham and was appointed to a lectureship in 1970. He established an active and influential group that added to and extended the published work demonstrating that a range of external stimuli activates the turnover of inositol lipids. This work convinced Bob that the selective activation of phospholipase C-catalysed hydrolysis of PtdIns played a key role in a general mechanism of cellular activation. As a result of this he developed the concept that receptor-stimulated inositol lipid hydrolysis was critical to the mechanism whereby intracellular calcium concentration is elevated. He presented this hypothesis in a seminal review article published in Biochimica et Biophysica Acta in 1975. This highly cited article (over 2200 citations) had a significant effect upon those members of the scientific community investigating the regulation of cellular function by intracellular signals. In addition to fostering significant debate, Bob's theory increased interest in the regulation and function of inositol lipid hydrolysis, stimulating many investigators to enter the field. Much of his research after the publication of his review was aimed at testing and developing the hypotheses he had presented. His laboratory generated increasingly strong evidence for a link between inositol lipid hydrolysis and calcium mobilization during the late 1970s, while in the early 1980s, he was responsible for two key findings. First, his group demonstrated that the actual inositol lipid hydrolysed as a result of receptor occupation was PtdIns(4,5)P_2. This plasma membrane lipid is produced by the phosphorylation of PtdIns by two specific kinases, one of which he had been studying in the 1960s. Secondly, they demonstrated that the Ins(1,4,5)P_3 product of the hydrolytic reaction was rapidly degraded by a specific 5-phosphatase. These studies pointed to Ins(1,4,5)P_3 being an important second messenger molecule, a proposition subsequently proven by other groups.

Not surprisingly, much of the credit for solving the role of PtdIns(4,5)P_2 hydrolysis has gone to those who demonstrated the specific functions of the two messenger hydrolytic products; however, without Bob's input, the progress

would have undoubtedly been slower. This is not only because of his own theoretical and practical work, but also because of his ability to train, stimulate and inspire an impressive group of graduate students (e.g. Motassim Billah, Shamshad Cockroft, Peter Downes, Phill Hawkins and Andrew Morris), postdoctoral fellows (e.g. Eduardo Lapetina, Chris Kirk, Steve Shears and Steve Dove) and others (such as Len Stephens) who came in contact with him.

For some, the work described above would have been enough, but not Bob; he continues to make significant contributions to lipid signalling. He has now published more than 250 research papers, and indeed he was a major driving force behind the identification of PtdIns(3,5)P_2, yet another inositol lipid with signalling properties. Much of the current work in his laboratory, together with Steve Dove, involves determining the regulation and function of this novel lipid signalling pathway.

Bob has made a huge contribution to science, and lipid biochemistry in particular, by virtue of his astonishing intellect. A scientific conversation with him can be stimulating, illuminating and critical all at once. His enthusiasm and breadth of knowledge is truly amazing, and he is the perfect person to try out an idea on provided you are prepared to have a bus driven through the holes he invariably finds! His support for other scientists and his particular promotion for those who are up and coming is a reflection of his view of the world and his attitude to science.

Bob has received many awards in recognition of his immense contribution to biochemistry, notably being made a Fellow of the Royal Society in 1986. The Biochemical Society honoured his achievements with the Ciba Medal in 1988 and the Morton Lectureship in 2002, and recognized his extensive contributions to the field with this Annual Symposium. Although Bob 'retired' from his position at the University of Birmingham on Friday 29 September 2006, he was back at work on the following Monday!

Michael Wakelam
15 November 2006