In memory of Michael J. O. Wakelam (1955–2020): a pioneer in lipid signalling and lipidomics

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Prof Michael Wakelam at Metabomeeting in Cambridge, 2015. Picture provided by Dr. Andrew Nicholls, GlaxoSmithKline

Anyone with an interest in phosphatidylinositols, and in particular phosphatidylinositides (phosphorylated forms of phosphatidylinositols) (Fig. 1), has to show meticulous attention to detail as these unforgiving compounds are notoriously difficult to separate by chromatography, consist of an array of isomers and structurally similar compounds and yet have vital signalling roles across the life course of the cell.

The phosphatidylinositides exist at low concentration, often for fleeting moments during the signalling cascade, and to add to their complexity interact with a variety of other signalling pathways to regulate metabolism as well as having other fundamental regulatory roles in the cell. These lipids are not for the faint hearted and require a special class of character in terms of dedication, determination and perhaps a sense of optimism if one is to unravel their roles in cellular signalling. Professor Michael Wakelam was one such character who possessed all these qualities as a scientist and pioneered the understanding of the role of lipids in cell signalling.

Michael was educated at the University of Birmingham, undertaking both his undergraduate degree in Medical Biochemistry (1977) and PhD in Biochemistry (1980) at the university. He had a huge affinity for the city and was a great source of information about where to go for the best restaurants I am told by my Birmingham colleagues. He did his first post-doc at the University of Konstanz, Germany and it was here that he studied the fusion of cell membranes in myocytes (Wakelam, 1983). This is a calcium stimulated process and Michael set out to study the role that lipids, and in particular phosphatidylinositols, play within this. Using a combination of radiolabels, thin layer chromatography and Dowex columns, he demonstrated that there was a rapid conversion of phosphatidylinositides to phosphatidic acid and 1,2-diacylglycerol during myoblast fusion. This was an early demonstration of how three lipid signalling pathways can interact to regulate fundamental cellular processes. He then moved to Imperial College London as a Beit Memorial Fellow before joining the University of Glasgow in 1985 as a Lecturer, where he was subsequently promoted to Senior Lecturer and then Reader. While at Glasgow and working with Miles Houslay and colleagues, he examined the role of desensitization of signalling pathways. While every signalling pathway needs to have a mechanism to turn the signal off, glucagon-stimulated adenylate cyclase activity in hepatocytes was known to dip shortly after the initial burst

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A phosphatidylinositol

A phosphatidic acid

A phosphoinositol-3,4,5-trisphosphate

Fig. 1 Structures of some of the lipids studied by Prof. Wakelam in his career. Notice these lipids have been drawn with arachidonic acid in the sn-2 position which can be cleaved to form eicosanoids and the bridging phosphate can be hydrolysed to produce diacylglycer-

ols, both important classes of signalling molecules in their own right demonstrating the complexity of lipid signalling pathways. Inositol 1,4,5-trisphosphate can also be formed from phosphoinositol-3,4,5-trisphosphate

of activity of the glucagon pathway (Murphy et al. 1987). In a series of papers Wakelam and Houslay examined this process demonstrating that this was not down to product inhibition through cAMP and instead other signalling pathways interacted to dampen the initial burst of activity. While most studies of the time relied on the incorporation of radioactive labelled substrates such approaches could not discriminate within a class of lipids and address basic questions about whether particular fatty acids made a difference. To address this Michael and Trevor Pettitt developed a 3,5-dinitrobenzoyl derivatisation and HPLC method for the analysis of diacylglycerols, and in particular diacylglycerides (DAGs) (Pettitt and Wakelam, 1993). This allowed them to investigate individual DAGs, identifying pools of polyunsaturated fatty acid containing DAGs that were derived from the phosphatidylinositol pool and a separate group of DAGs derived from phosphatidylcholines. This method still performs very favourably even when compared with the reverse phase approaches most of us use in lipidomics today.

In 1993 he returned to Birmingham as Professor of Molecular Pharmacology. Here he joined the Cancer Research UK (CRUK) Institute for Cancer Studies and conducted many of his ground breaking studies into the role lipid signalling plays in cancer cell biology. He was also more actively involved in mass spectrometry. In conjunction with the chromatography methods he had co-developed, mass spectrometry began to give a unique

insight into how specific lipids contribute to pathways, demonstrating that there is more than just the lipid head group in determining the role of a given lipid. With Robin Irvine of the University of Cambridge and colleagues, the Wakelam group investigated the processes that regulate cell adhesion. For those of us with long memories this was still largely a mystery to the scientific community (and is still not fully understood). Using a combination of GFP-tagged proteins, mass spectrometry of lipids, RNAi knockdown of enzymes and some inventive enzymology they demonstrated that phospholipase D2-derived phosphatidic acid regulates integrin-mediated adhesion through the generation of phosphatidylinositol 4,5-bisphosphate (Powner et al. 2005).

In 2007, he became director of the Babraham Institute, Cambridge as well as being made Professor of Lipid Signalling by the University of Cambridge. Michael oversaw a huge expansion in biotechnology on the Babraham campus and once said that he was the only person to have the Biotechnology and Biological Sciences Research Council (BBSRC) pay for a roundabout when they expanded the campus—he told me the price but I have been sworn to secrecy! He continued work on understanding lipid signalling in cancer, taking part in the CRUK grand challenge, but also worked on metabolic diseases, ageing (Hahn et al. 2019) and understanding how rhinoviruses alter the host cell metabolism during viral replication (Nguyen et al.

2018). I would also recommend his recent review with Valerie O'Donnell (Cardiff University) and Jamie Rossjohn (Cardiff University) describing lipid signalling in innate immunity (O'Donnell et al. 2018)—an excellent introduction to the field and lipid signalling in general.

Michael was also a champion of lipid classification and tools for lipid identification, becoming a principle investigator on the LipidMaps consortium when the Wellcome Trust took over funding the tools and resources produced by the consortium. As part of this work he took part in updating the LipidMaps classification of lipids when these were expanded from a predominantly mammalian focused description to include lipids from plants and microbes, classifying a rich array of polyketides, sterols and isoprene compounds found across life (Fahy et al. 2008). In 2018 he was awarded the Moreton Lecture for his outstanding contributions to lipid biochemistry by the Biochemical Society.

Prof Michael Wakelam talking at Metabomeeting in Cambridge, 2015. Picture provided by Dr. Andrew Nicholls, GlaxoSmithKline

Michael Wakelam died on the 31st March, 2020 from respiratory complications believed to arise from a COVID-19 infection. He is survived by his wife Jane and sons Alex and Patrick. My personal memories of Michael can be encapsulated as him being a thoroughly “nice bloke” to use a colloquialism that is common around Birmingham. I originally met him at a symposium when I was still feeling my way into the lipidomics world and remember his warm words of encouragement and the offer of chatting over a beer about where my work was going. He was a great internal PhD examiner for two of my best PhD students who I think had enjoyable vivas despite appearing at the end intellectually exhausted and quite drained—but in a good way! I hugely enjoyed his company at conferences but I think I will leave the final words to my two former PhD students:

- Dr. Lee Roberts, now Associate Professor of Molecular Physiology and Metabolism, University of Leeds who commented “He was very approachable, a complete gentleman and incredibly insightful when it came to discussing science and my PhD work. As my internal PhD examiner he arranged a tea and biscuit break during the viva. Very civilised!”
- Dr. Ben McNally, now at The Crick Institute “I found him a really friendly and approachable man, and excellent scientist. His enthusiasm for science definitely translated to the dance floor as well!”

I will miss him hugely both scientifically and personally, as I am sure many members of the metabolomics and lipidomics community will.

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