Michael John Owen Wakelam 1955–2020

We have lost a distinguished biochemist who dedicated his career to the study of phosphatidylinositol signalling in metabolic regulation and to the advancement of lipidomics.

Michael John Owen Wakelam passed away on 31 March, 2020 at the age of 64, much too early. He became known to colleagues and friends as a scientist highly regarded for his research. He was honoured in 2018 with the Morton Lectureship of the Biochemical Society and was elected a fellow of the Royal Society of Biology. In 2019, he was elected a member of the Academia Europaea.

Credit: Babraham Institute

Academic career

It was not by chance that Michael turned his focus to phosphatidylinositols (PIs) and lipid signalling. He was a student and later a professor at the University of Birmingham at a time when Britain was the world's hub of pioneering phospholipid research, such as that by J. N. Hawthorne and Bob Michell on PI in Birmingham. Bob Michell inspired Michael extraordinarily, and they even published a joint review. Subsequently, Michael moved to Cambridge to serve as the director of the Babraham Institute, where Rex Dawson and Robin Irvine studied phospholipids, particularly PI metabolism and signalling. A joint publication by Michael and Irvine appeared as well. Certainly, Michael's scientific engagement can be seen in the tradition of these eminent phospholipid scientists.

Michael's career path is impressive. He received his BS degree in medical biochemistry in 1977 and his PhD in biochemistry in 1980 from the University of Birmingham. From 1981 to 1983, he was a postdoctoral fellow at the University of Konstanz in Germany, and he then spent a further 2 years as a Beit Memorial Research Fellow at Imperial College London. In 1985, he was offered a position as a lecturer in biochemistry at Glasgow University, where was promoted to reader and stayed until 1993. The University of Birmingham asked him to come 'back home' to take up a professorship in molecular pharmacology at the Institute for Cancer Studies, where he remained until 2006. During that time, he was the associate dean of the School of Medicine from 2003 to 2006, and between 2004 and 2007, he was the chair of the Medical Research Council Molecular and Cellular Medicine Board, as well as a member of the Medical Research Council. On the basis of all these accomplishments, in 2007, Michael was chosen as the director of the Babraham Institute, and he received an honorary professorship in lipid signalling at the University of Cambridge Clinical School. In addition, he was an honorary professor at Birmingham University and a visiting professor at King's College London.

Michael's research spanned more than four decades, and one of its core aims was to advance understanding of the roles and regulation of lipid signalling pathways in inflammation and cancer, with an emphasis on PI molecules. A major focus of his lab at the Babraham Institute was the use and development of lipidomics methodologies for determining the functions of individual lipid molecular species and their application in identifying novel targets for therapeutic intervention. Michael's scientific work was published in more than 230 original articles and reviews, and he was a much-sought-after speaker at international meetings. In addition, he undertook editorial duties for several top lipid journals (*BBA Molecular and Cell Biology of Lipids*, the *Journal of Lipid Research* and *Current Opinion in Pharmacology*) and served on the steering committee for the International Conferences for the Bioscience of Lipids and on the scientific advisory board for the Keystone Symposia on Molecular and Cellular Biology.

Lipid signalling and metabolism

Notably, Michael's research did not begin with lipids; the subject of his PhD thesis, under the supervision of Deryck Walker at the University of Birmingham, was the inducible expression of hepatic glucokinase. As a postdoctoral associate at the Faculty of Biology at the University of Konstanz, he worked with Dirk Pette, who was a specialist in glycolytic enzymes, in the tradition of Theodor Bücher from Munich, but who focused on muscle biology at the University of Konstanz. Michael's first articles at the University of Konstanz were on the control of glucose 1,6-bisphosphate by various effectors in cultured muscle cells, and he arrived, obviously inspired by Michell's thinking, at PI breakdown in the course of myoblast fusion. This research culminated in an article showing that cation channels in cultured embryonic skeletal cells are sensitive to a neurotransmitter-like action of ATP (H. A. Kolb and M. J. O Wakelam, *Nature* **303**, 621–623; 1983). The article not only represents Michael's entry into the PI field but also is his first investigation of signalling.

After he joined Imperial College London, he collaborated with Chris Marshall and Alan Hall at the Institute of Cancer Research, and his interest in signal transduction was strengthened when he turned his focus to PI metabolism in relation to *ras* oncogenes. This work, as well as the research conducted afterwards in the Molecular Pharmacology Group at the Department of Biochemistry at Glasgow University, was pivotal to his contributions to the fields of lipid signalling and lipid second messengers. Two publications in 1986 are especially noteworthy, given their tremendous impact on the scientific community. One article, a collaborative effort with colleagues from London and Glasgow, demonstrates that p21 N-Ras is one of the signalling hubs responsible for the formation of a phosphatidylinositol trisphosphate signal. The second article examines signalling via the glucagon receptor and shows that glucagon, at low physiological concentrations, causes PI breakdown with production of inositol phosphates and independently stimulates adenylate cyclase activity, putatively through two glucagon receptors. Interestingly, more than 30 years later, the concept of the dual mode of glucagon-receptor signalling resurfaced when the structure of the glucagon receptor was analysed in greater depth.

Towards the end of his time in the biochemistry lab at Glasgow University, Michael began to appreciate the importance of mass spectrometry (MS) for understanding the different molecular structures of a lipid in terms of its function. As a result, Michael's subsequent work expanded on the roles of lipid second messengers, by using newly developed MS-based techniques to characterize the build-up and breakdown of lipid molecular species serving as intracellular second messengers. In the 1990s, his group published a series of important articles on observations that diacylglycerols acting as second messengers not only are derived from inositol lipid hydrolysis but also are highly dependent on phospholipase D–mediated cleavage of phosphatidylcholine, a textbook pathway taught to all biochemistry students today.

In 1993, Michael was appointed as a professor of molecular pharmacology at the Institute for Cancer Studies at the University of Birmingham, where he intensified the use of MS. He reported his many impressive results at conferences, notably that the direction of PI action depends heavily on the chemical structure of the constituent fatty acids in the PI molecule. In this respect, for Michael, a key species was phosphatidylinositol-4',5' bisphosphate. He found that hydrolysis by phospholipase C produces polyunsaturated diacylglycerol species, whereas hydrolysis by phospholipase D generates saturated/monounsaturated phosphatidic acid species. The former activate protein kinase C, and the latter, among other functions, activate the formation of actin stress fibres. His group demonstrated that, with the help of two enzymes, saturated/monounsaturated diacylglycerols and polyunsaturated phosphatidic acid species are produced yet are metabolically inactive. This work was published 1997 and provided ample evidence of the messenger concept put forward by Michael. From this and other publications, it is clear that Michael's experimental approach increasingly transitioned from thin layer chromatography, elaborate liquid chromatography and radioactive-tracer methods to high-end MS. His pertinent publication (T. R. Pettitt, S. K. Dove, A. Lubben, S. D. J. Calaminus and M. J. O. Wakelam, *J. Lipid Res*. **47**, 1588–1596; 2006) is a seminal article on how to analyse the entire cascade of PI-phosphate species with simpler liquid chromatography in combination with MS.

Engagement for lipidomics

In 2007, Michael started as the director of the Babraham Institute, which was well suited for his broad interests and his penchant for accompanying technologies. The flourishing of lipidomics in Europe owes much to Michael's foresight and activities. Editorials in lipidomics journals appeared in Europe in 2003, but when news came from the United States that, under the leadership of Ed Dennis at the University of California San Diego, the large project Lipid Metabolites and Pathways Strategy (LIPID MAPS) had been funded, a new undertaking began, which evolved into an internationally accepted classification system and structure database (LMSD). In response to this event, with crucial help from Michael, the Directorate General 12 of the European Union was convinced to solicit applications for a large collaborative project in the area of high-throughput analysis of lipids and lipid–protein interactions in mammalian cells. Michael's group and 20 more from academia and industry joined the then-successful application for the LipidomicNet project. The project, centred on lipid droplets and lipidomics technology including bioinformatics, began in 2008. Michael and others within the project were dubbed 'the Viennese Coffee Club' by the coordinator because of their sometimes diverging opinions, which led to spirited yet always fruitful discussions. For example, Viennese Coffee Club members at one point became irritated by literature reporting incorrect MS data; that is, the levels of structural elucidation that were claimed for lipid species were inconsistent with the instrument resolving power. Consequently, a shorthand annotation for the correct presentation of lipid MS data was developed, and an article was published in 2013, with Michael as senior author. This annotation was subsequently adopted by the International Lipid Classification and Nomenclature Committee (ILCNC).

The LipidomicNet project clearly strengthened relations across the Atlantic. European colleagues, including Michael, were asked to join the ILCNC and were co-authors of the two fundamental classification articles published in 2005 and 2009. However, by 2013, the LipidomicNet grant from the European Union had ended, and the long-running LIPID MAPS grant in the United States was also coming to an end. Luckily, Michael from the Babraham Institute and Valerie O'Donnell from Cardiff University teamed up with Ed Dennis and Shankar Subramaniam from the University of California San Diego and secured a follow-up LIPID MAPS grant from the Wellcome trust in 2017. This funding was a major relief, and it has safeguarded and enabled further development of an informative website, webinars and valuable databases.

Michael's scientific horizons and sensibilities were profoundly shaped by his time as a young professor of molecular pharmacology in the oncology research environment at the University of Birmingham; the effects remained visible throughout his time at the Babraham Institute. He participated in two clinical trials in the Cancer Studies Unit at Birmingham. His publications clearly show that he felt that knowledge from basic biology and biochemistry with cultured cells and other models are prerequisites for understanding metabolism in health and disease. In addition, the vast professional network that he established over the years and the instrumental facilities that he had available enabled him to address a variety of aspects in cancer research and viral infectious diseases.

Michael, usually together with colleagues from his lab, was also a prolific writer of reviews reflecting his main competences, such as PI-related metabolism and aspects of cancer as well as lipidomics. Moreover, his lipidomics activities ranged from bioinformatics concerns to cutting-edge MS methods (J. Clark et al. *Nat. Methods* **8**, 267–272; 2001) for the quantification of

phosphatidylinositol (3,4,5)-trisphosphate molecular species in cells and tissues. Finally, Michael, together with Valerie O'Donnell and colleagues, steadily promoted the maintenance and advancement of the LIPID MAPS project.

Babraham initiatives

When Michael became the director of the Babraham Institute on the Babraham Research Campus in Cambridge in 2007, the institute's focus since the new millennium had been on basic biomedical molecular and cell biology, specifically signalling (where Michael's research fit in), immunology and epigenetics. Beyond his scientific achievements, Michael had a major impact as director, making invaluable contributions to the well-being and growth of the institute. First, and most importantly, he built an inclusive and diverse culture in the institute (as evidenced, for example, by two Athena Swan silver awards), where everyone, including PhD students, was able to share in the fun of science and science culture. Second, he built superb core facilities that continually sought to acquire cutting-edge technologies and the machinery needed. Third, he worked with the government and Biotechnology and Biological Sciences Research Council in a major expansion of the Babraham Research Campus; the science minister at the time inaugurated the investment, and the campus is now one of Europe's largest of its kind and uniquely has a thriving research institute at its centre. Fourth, because every institute funded with taxpayer money must have a reason to exist, Michael developed the current mission, which encompasses research on healthful aging through the human lifecycle. This aim brings together many of the scientific strengths of the institute in a holistic view of how cellular and molecular processes change over the life course. Fifth, Michael was critically involved in setting up the EU-LIFE multinational European initiative, an alliance of 14 leading biomedical institutes involved in discussions on science, funding, best practices, staff exchanges and collaboration. This effort has brought much-needed European and international exchange among biomedical communities, and has yielded new tangible outcomes, such as the EU LifeTime initiative.

Colleague and mentor

In all his dealings, Michael was the same Michael to everyone and in that sense was a man of the people. He would talk to everyone, preferably in person rather than by phone or e-mail, and in doing so got part of his daily exercise by shooting across the Babraham campus in his unique half-walking/half-running style. On Friday evenings at 5:30, he could often be found at the campus bar, having a pint with people from stores, health and safety, and security. He was always interested in hearing others' thoughts, be they about family, politics, articles accepted or research grants awarded, in which case he was always very pleased for people. He loved his family—his wife, Jane, and his two sons, Alex and Patrick—and he proudly talked about their achievements and progress in life.

His enthusiasm and positive energy were there for everyone to benefit from. In his decision-making, he was a consensus seeker who used his emotional intelligence to great effect and scarcely ever overruled others. Michael was very much looking forward to retiring from his position as director, not only to spend more time with his beloved family but also to return to the students and postdocs in his lab and to share his love of science and lipidomics with them. This aspect is where the loss of Michael feels particularly cruel; we greatly empathized with Michael's looking forward to having fun in the lab again after years of hard work in looking after so many people at Babraham and internationally. We will miss him as a friend and a colleague; already, we are thinking: what would Michael have said, or what would Michael have done? These thoughts will be with us for a very long time. ❐

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