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Phosphatidylinositol metabolism, phospholipases, lipidomics, and cancer: In Memoriam: Michael J. O. Wakelam (1955–2020)

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Michael J. O. Wakelam, Director of the Babraham Institute in Cambridge, UK (**Fig. 1**), tragically died on March 31, 2020, at the age of 64, apparently of complications from a suspected SARS-CoV-2 virus infection. Michael also served as Honorary Professor of Lipid Signaling at the University of Cambridge Clinical School, Honorary Professor at the University of Birmingham, and Visiting Professor at King's College London. He served as an Associate Editor for ASBMB's *Journal of Lipid Research* since 2013, where he provided special expertise on phosphatidylinositol (PI) metabolism, phospholipases, lipidomics, and cancer detection. He was awarded the Morton Award Lectureship by the Biochemical Society in 2018 for outstanding contributions to research in lipid biochemistry and was elected a member of the Academia Europaea in 2019.

IMPORTANT CONTRIBUTIONS TO LIPID RESEARCH

Michael made seminal contributions to lipid biochemistry and was among the most distinguished lipid biochemists who have contributed immensely to the growing field of lipidomics, in which he focused particularly on phosphatidylinositol phosphates (PIPs) and their signaling in cancer. He is especially noteworthy for his enormous contributions to the field of lipid signaling through his primary research and his participation in the international lipid community where he demonstrated significant leadership. At the time of his death, Michael was arguably the preeminent 'lipid signaler' in the UK.

Following his early work on hepatic glucokinase expression during his Ph.D. studies in Birmingham (1980), Michael first became interested in lipids through his work on inositol, the head group of all PIs, during a postdoctoral fellowship



Fig. 1. Michael J. O. Wakelam (courtesy of the Babraham Institute).

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in Konstanz, Germany. At that point, he was investigating the role of inositol lipid turnover and calcium in regulating muscle biology. Back then, inositol lipids were extremely difficult to measure, requiring labor intensive ^{32}P -based methods, and there was no possibility of being able to delineate the molecular species involved (in terms of fatty acyl chains). Most research in that area focused on the proteins/enzymes rather than the actual lipids, with the actual demonstration of formation of these rather transient lipid mediators themselves being extremely challenging. This was an area that Michael creatively addressed later using mass spectrometry (described below).

Following his move to Glasgow in 1985, Michael's longstanding research efforts led him to identify a key role for Ras in the regulation of phospholipase C. Specifically in 1986, while working as Lecturer, he published a seminal paper showing that Ras activates phospholipase C to generate inositol (1,4,5) triphosphate (IP_3) (1). Also, while still in Glasgow, he discovered that DAG could be generated from PC, and not only from inositol lipid hydrolysis, as was the dogma at that time (2). It was around that time that Michael became interested in the application of MS to lipid research, utilizing what was then a method that required the user to work closely with physicists and engineers. His early MS work included characterization of the acyl chains on DAGs derived from PCs. He also creatively employed MS to the characterization of PA generated by phospholipase D in signaling and lipid synthesis (3, 4).

In 1993, Michael returned to Birmingham (Fig. 2). Here, one of his seminal contributions was to uncover the significance of acyl chain composition in PI signaling using newer

generation benchtop lipidomics approaches. This required novel method development, by Michael working initially with Trevor Pettitt, to establish cutting edge mass spectrometric techniques to observe these extremely transient and hard-to-analyze lipids. The difficulty with detecting inositol lipids using MS results from their instability, where they effectively lose their phosphate groups upon ionization. Michael, working with Jonathan Clark, Phil Hawkins, and Len Stephens at Babraham, pioneered a new approach to derivatize these molecules, using TMS diazomethane. This solved the issue for $\text{PI}(3,4,5)\text{P}_3$ s, enabling him to define, for the first time, their fatty acyl chains in human neutrophils and tissues. Michael also demonstrated a key role for the wider structural motifs reflecting acyl chain composition in their mechanisms of action. Two key papers stand out, the first with Pettitt in the *Journal of Lipid Research* (5) and the second, following his move to Babraham in *Nature Methods* (6). Furthermore, in line with his ongoing long-term interest not only in the lipids but also the enzymes that generate them, Michael uncovered key elements in the regulation and selective functions of phospholipase D isoforms (PLD1 and PLD2). These discoveries, in particular the key role of the PH domain in PIP_2 -dependent regulation, are fundamental to our understanding of the role of these enigmatic enzymes in signaling and lipid biosynthesis (7).

While at Babraham (2007–2020), Michael continued to direct a very active research laboratory, no mean feat given the huge amount of work he was doing as Director of the Institute. During that time, with his laboratory, he worked on phospholipase D, autotaxin, and lysophosphatidic acid



Fig. 2. Michael Wakelam working at the bench at Birmingham University around 2006 (courtesy Simon Rudge).

in cancer, among other areas, also supporting a generation of novel technologies, including new software to analyze and understand the complexity of lipid mediators in health and disease. In the last several years, he had researched a large number of different areas of applied health and disease, supporting extensive collaborations with local, national, and international colleagues. These include major programs on aging, insulin resistance, and viral infection as well as cancer, his long-term interest throughout his career.

TRAINING, CAREER, AND PERSONAL LIFE

Michael earned his undergraduate and doctoral degrees at Birmingham University in 1977 and 1980, respectively, in the lab of Deryck Walker. During that time he met Jane Fensome, whom he later married. He carried out

postdoctoral studies in Germany at the laboratory of Dirk Pette in Konstanz, Germany, and then moved to London on a Beit Memorial Fellowship in 1983. There he worked with Chris Marshall and Alan Hall at the Institute of Cancer Research. Michael started his independent scientific career in 1985 as a Lecturer, Senior Lecturer, and Reader in Biochemistry at the University of Glasgow, as part of the Molecular Pharmacology group led by Miles Houslay, before being appointed Professor of Molecular Pharmacology at the University of Birmingham from 1993 to 2006.

While at Birmingham, Michael and Jane welcomed Alex and Patrick into the world, their two sons to whom Michael was devoted. In Birmingham, he demonstrated leadership in the cancer area and carried out critical studies on phospholipid metabolism, astutely realizing the importance of effective clinical collaboration in obtaining high quality biopsies for lipid analysis. He curated an important set of colorectal tumor samples to further research in this area.



Fig. 3. First meeting of the LIPID MAPS International Lipid Classification and Nomenclature Committee (ILCNC) held in La Jolla, CA, July 7, 2006 (left to right: Christian Raetz, Masahiro Nishijima, Takao Shimizu, Eoin Fahy, Edward Dennis, Manish Sud, Michael Wakelam, Fritz Spener, Robert Murphy, Yousuke Seyama, Gerrit van Meer, and Shankar Subramaniam).

During that time, he also developed cutting-edge methods for mass spectrometry that were to become a mainstay of his lab from then on. Throughout his career, Michael trained numerous graduate students and postdoctoral fellows, many going on to contribute to the field of lipid signaling and assume faculty positions at a large number of universities in the UK.

In 2007, Michael Wakelam was recruited and appointed as the Institute Director and Group Leader at The Babraham Institute in Cambridge. While leading the Institute, he maintained his main residence with his wife Jane in Birmingham to which he regularly commuted every weekend, heading off early on Friday afternoons. When at Babraham, Michael was initially housed in a Babraham accommodation, but later on, he and Jane purchased a house in a small village outside of town. Thereafter, they took turns residing during weekends between Cambridge and Birmingham. At various times, Alex and/or Patrick stayed with Michael in Cambridge, while either finishing their degrees or starting work and commuting into London. Michael often talked

about meeting one or other of his sons in the pub when they lived nearby.

BABRAHAM INSTITUTE DIRECTORSHIP

Michael successfully led the Babraham institute for 13 years through challenging times with respect to government research funding including from the BBSRC. Importantly, he expanded and supported signaling research through capital investment and recruitment, creating and inspiring the UK's leading groups of scientists in this area, including Phil Hawkins, Len Stephens, Martin Turner, Klaus Okkenhaug, Simon Cook, Heidi Welch, and Nick Ktistakis, all of whom run laboratories with a significant lipid research component.

Michael was instrumental in building a world-class lipid mass spectrometric facility ('lipidomics') at Babraham that has made seminal contributions to our understanding of the role of lipid metabolism in cancer and the role of



Fig. 4. First meeting of the LIPID MAPS Wellcome Trust Principal Investigators (front row) and the International Committee for Lipid Classification and Nomenclature (ICLCN) held in Cardiff, UK, in March 2017 (right to left: Michael Wakelam, Edward Dennis, Valerie O'Donnell, Shankar Subramaniam; back row: Takao Shimizu, Fritz Spener, Marcus Wenk, Al Merrill, Robert Murphy, and Eoin Fahy).

phosphatidylinositol-3-kinase (PI3K) signaling in disease. During his tenure, he expanded dramatically the scope of activities at the Institute, including further development of an industrial park so that discoveries by Institute scientists could be translated into commercial enterprises, expanding the biotech community in Cambridge and surrounding areas.

In late 2019, after more than a decade of outstanding leadership of the Institute, Michael started planning and making arrangements to step down from the Director role, looking forward in late 2020 to getting back into the laboratory and more fully embed himself in lipidomics research again.

CONTRIBUTIONS TO THE INTERNATIONAL RESEARCH COMMUNITY

Michael tirelessly contributed to the international lipid community. He was an organizer of several international lipid research meetings, including a planned 2021 Keystone Symposia on “Lipidomics of Health and Disease” and a recent Federation of American Societies of Experimental Biology (FASEB) Summer Conference. Michael served on the Steering Committee of the International Conferences

on the Bioscience of Lipids (ICBL) and the Scientific Advisory Board for Keystone Symposia. He served as an Associate Editor of the *Journal of Lipid Research* and held editorial positions with key lipid journals, including *Biochimica Biophysica Acta Section on Cellular and Molecular Biology of Lipids* and *Current Opinion in Pharmacology*.

Throughout his career, Michael contributed critical ‘lipid expertise’ to high-profile collaborative efforts that have identified key roles for lipid metabolism and signaling. Of special note, Michael was a key contributor to the LIPID MAPS Consortium’s effort in developing lipidomics from the beginning and served as a founding member of the LIPID MAPS International Lipid Classification and Nomenclature Committee (ILCNC), which first met in 2006 (Fig. 3). He was a founding member of a Europe-based initiative, LipidomicNet, an EU FP7 project that ran from 2008 to 2012, led by Gerd Schmitz from Regensburg, Germany, that sought to integrate lipidomics data for the analysis of lipid droplets in health and disease.

Following his involvement with the international lipidomics initiatives, Michael’s key contribution to the LIPID MAPS initiative was highlighted when he provided the global resource with a new home in the UK. Indeed, the databases were relocated to Babraham coinciding with the award of a Wellcome Trust Biomedical Resources grant




Fig. 5. Michael Wakelam relaxing at dinner with international colleagues during the most recent (April 2019) LIPID MAPS Wellcome Trust meeting, which he hosted at the Babraham Institute in Cambridge [left to right: Michael Wakelam (Cambridge, UK), Al Merrill (Atlanta, GA), Edward Dennis (La Jolla, CA), Takao Shimizu (Tokyo, Japan), and Fritz Spener (Graz, Austria)].

in 2016 (Fig. 4). Most importantly, Michael was a key player in obtaining the LIPID MAPS Wellcome Trust Grant to continue and expand the LIPID MAPS Website and Databases. This effort included establishing key LIPID MAPS sites at the Babraham Institute in Cambridge, UK, led by himself, and at Cardiff University, Wales, led by Valerie O'Donnell, and continuing at the UC San Diego site led by Shankar Subramaniam and the ILCNC Advisory Committee led by Edward Dennis. Michael was intimately involved in planning the next renewal cycle for the LIPID MAPS grant to Wellcome Trust, and his input into this will now be hugely missed by all of us involved in the continuing LIPID MAPS initiative (Fig. 5).

In the UK, Michael made major contributions to the biochemistry infrastructure by serving as a member of the MRC Cell Board A Grants Committee, the MRC Advisory Board, and the Studentship Panel. He also served as Chair of the Career Establishment Grants and New Investigator Awards Panels and as a member of the Monitoring and Evaluation Steering Group.

CONCLUDING REMARKS

In summary, Michael Wakelam made fundamental scientific contributions to our understanding of lipid signaling and metabolism, including its role in cancer, and he was a major contributor and developer of the now established lipidomics field. He was clearly among the world authorities in lipid studies. His community activities and scientific leadership at Babraham as well as with the LIPID MAPS initiative, the top lipid journals, and lipid conferences made

him an indispensable member of the international lipid community of scientists. Michael Wakelam will be greatly missed. 

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