From cell signalling to human health

Co-ordination of cell activities through inositol lipid signalling systems

Fundamental cell biology research at the Babraham Institute is laying the groundwork for new treatments for cancers, chronic inflammation and other diseases all caused by defects in the mechanism that transmits signals within cells. By working with companies on the Babraham Research Campus, in the local Cambridge area and beyond, the Institute is ensuring a rapid development pathway from discovery research to biotechnology, drug development and clinical application.

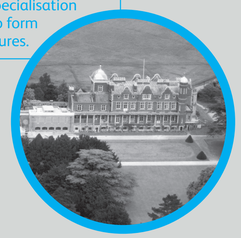
Living cells are complex systems of molecules that work together to maintain life and respond to ever-changing conditions. Cell signalling systems exist to detect these changes and initiate appropriate responses within the cell. They do this by controlling the activity of a small number of key 'signal transduction' proteins, which in turn regulate a cascade of further events. These include affecting the activity of other proteins, metabolic changes and altered gene expression. Together these co-ordinate complex cell behaviour, such as growth and development.

Signalling research at the Babraham Institute has focused on systems that involve regulating the abundance of a group of molecules called 'inositol lipids' inside cells.

Inositol lipids are found in the membranes that enclose cells, in addition to forming structures changes in their abundance act as signals to alter gene activity, metabolism and other behaviours within a cell. Amongst other things, the balance of these lipids acts as a key control mechanism for cell growth, division and survival. Disruption of inositol lipid signalling can lead to a range of illnesses including immunodeficiencies and cancers.

1948

Babraham Hall & estate purchased by the Agricultural Research Council (ARC) at the suggestion of founding Director Professor Ivan De Burgh Daly to establish the newly-funded Institute of Animal Physiology (IAP). The Institute has a mission to improve agricultural animal health and productivity following World War II[1]. The initial study of lipids at the Institute contributed to our fundamental understanding of cells, their specialisation and capacity to form different structures.



1960

Rex Dawson's pioneering work at the Institute on purifying and studying the metabolism of membrane lipids leads to the identification of 'tri-phosphoinositide'[2]. This inositol lipid has become known as 'PIP2'.

1964

Having joined the Institute in 1952 to study the membranes that surround living cells, Alec Bangham provides the first evidence that cell membranes are made of double layers of lipid molecules. His work shows that lipids in water can organise themselves into membranes like those around a cell; he calls these structures 'Banghasomes'.

1964

Rex Dawson discovers that cells can split lipid PIP2 molecules in the membrane into a water-soluble chemical called inositol trisphosphate (IP3) and membrane-bound diacylglycerol (DG). The enzyme responsible for this is now called Phospholipase C (PLC)[3].

Liposomes

Liposomes are microscopic spheres made up of a double layer of lipids surrounding a water-based centre. This is a simplified version of living cells, which are mostly water surrounded by a lipid membrane. Lipids are a group of molecules that include fats and oils, there are many different lipids in biology with a wide range of roles. Lipids form membrane structures, are effective energy stores and play a part in cell signalling.

The structural similarities between liposomes and cells mean they can be used to deliver drugs or genes into cells. Liposomes are able to fuse with the surface of cells, releasing their contents inside the cell. They can even be targeted to specific parts of the body to more effectively deliver drugs where they are needed.

1965

Gerald Weissman is a visiting researcher at the Institute. He suggests the alternative name 'liposomes' for Alec Bangham's 'Banghasomes'. Bangham's work with Institute colleagues Jeff Watkins and Malcolm Standish would lay the foundations of liposome research worldwide (Over 55,000 publications up to end 2017)[4].

1979

Michael Berridge, working in the ARC-affiliated unit in the Department of Zoology (Cambridge), provides evidence that hormone-stimulated metabolism of inositol lipids regulate the levels of calcium inside cells[5]. This is one of the first examples of inositol lipid metabolism controlling other cell behaviours.

1983

The Agricultural Research Council becomes the Agricultural and Food Research Council

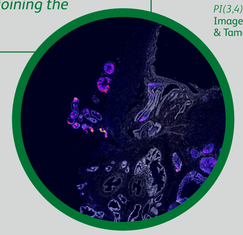
1983

Robin Irvine, working initially with Rex Dawson and then leading his own laboratory at the Institute, joins forces with Michael Berridge to bring together previous research. They demonstrate that IP3, which is produced from PIP2 by PLC (shown in 1964), can travel into cells and cause calcium release (seen in 1979) from internal stores[6]. This defines the 'PLC' signalling pathway as a critical link that allows many different signals received on the surface of cells to control internal activities[7].

1991/92

Len Stephens and Phill Hawkins join Robin Irvine's group and go on to show that enzymes called PI3-kinases (PI3Ks) chemically modify PIP2 to form a new signalling molecule called PIP3. (PI3Ks feature in over 31,000 publications between 1991 and end 2017)[8].

"At the time, researchers knew very little about the PI3-kinase enzymes, except that they were associated with several proteins implicated in cancer. We knew that PI3-kinase enzymes modified a family of inositol lipids, which had been studied at the Babraham Institute since the 1960s, but we didn't know what these lipids were or what role they played in the cell." Dr Phill Hawkins, Group Leader, Babraham Institute, talking about joining the Institute in the late 80s.



PI(3,4)P2 in mouse tissue
Image: Anna Kielkowska & Tamara Chessa

1993

The Institute of Animal Physiology is renamed to the Babraham Institute to reflect a new approach and scientific vision. The Babraham Institute would become focused on fundamental biology with a focus on lifelong health and the biology of ageing. This would include a shift away from agricultural research and the use of larger animals.

1994

BBSRC forms from the merger of the AFRC with bioscience aspects of the Science and Engineering Research Council.

1994

Len Stephens and Phill Hawkins find PI3K activity in white blood cells and identify an enzyme called PI3Kgamma. This attracts the attention of pharmaceutical companies, including GSK. They hope to draw on the Institute's discoveries to develop new drug therapies. Over 25 years later, GSK still support work by Stephens and Hawkins.

Research overview: lipid signalling

All cells receive a constant stream of information from their surroundings in the form of chemical messages. These messages are mainly received at the surface of the cell and trigger specific signal responses inside the cell.

One of these responses is to activate an enzyme called phospholipase C (PLC), which converts an inositol lipid called PIP2 into IP3 and diacylglycerol (DG). The rise in IP3 stimulates the release of calcium inside the cell and this then carries the signal to other systems.

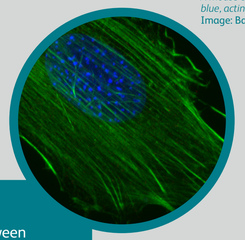
Another response to signals from outside the cell is to activate PI3 kinase (PI3K) enzymes. PI3K attaches an extra phosphate group to PIP2 to make a new inositol lipid in the membrane called PIP3. The increase in PIP3 activates another protein called PKB, initiating a series of events that help co-ordinate cell growth.

Mistakes in PI3Ks can have a wide range of effects. These changes can contribute to various cancers as well as other diseases including immunodeficiencies – where the body is less able to fight infections.

1996

Collaborations between Institute scientists and Onyx Pharmaceuticals leads to the discovery of how PIP3 regulates protein kinase B (PKB, also called AKT) . This turns out to be a key signalling pathway that allows growth factors outside cells to regulate cell growth and survival.
The pathway has since been shown to play a role in many human cancers. The collaboration with Onyx generates several patents around the genetics, composition and function of PI3K enzymes.

"In many cancers, there is a random mutation in PI3-kinase, which switches it permanently on. PIP3 is constantly being made, and the signalling pathway cannot be switched off as it normally would.
In the presence of too much activating signal, things go wrong. One of those things, because PI3-kinase controls cell growth, is that the cells grow too much, and this is one of the hallmarks of the early stages of cancer." Dr Len Stephens, Head of the Signalling Programme and Associate Director, Babraham Institute.



A mouse cell – nucleus in blue, actin filaments in green
Image: Barzan Sadiq

1998
The Institute ceases research with direct agricultural relevance.

1999
Researchers at the MRC-LMB and the Institute together uncover the structure of PI3Kgamma molecules. This work, supported by the BBSRC, offers exciting new ways to develop drugs to regulate PI3K signalling[11].

"PI3-kinase is probably the single most important signalling pathway in cell biology that's currently understood. That's because it's almost uniquely able to control lots of different things." Dr Len Stephens, Head of the Signalling Programme and Associate Director, Babraham Institute.

2002
A collaboration between Martin Turner, A BBSRC-funded Group Leader at the Institute, and US-based Icos Corporation results in a PI3K delta knock-out mouse model. These mice lack the PI3K delta protein, so can be used to study what this protein does and the effects of its loss. They show that the PI3K delta mouse model has a weakened immune system. The model enables researchers to study this effect and investigate possible treatments. Research on the immune system is another key research theme at the Babraham Institute[12].

2006
Michael Wakelam joins as the Institute's new Director. He brings specialist expertise in the analysis of lipid molecules inside cells, enabling new research to examine how lipids produced by PI3Ks affect cells.

2008
Autophagosomes are a kind of cellular 'dustbin' used to recycle cell components and their malfunction is thought to be at the heart of several age-related diseases, such as neurodegeneration. In this year, Nicholas Ktistakis discovers how autophagosomes are formed from structures regulated by PI3Ks[13].

2008
Institute scientists advise company PIramed on the development of PI3K inhibitors. This type of drug could become a treatment for cancer as well as for a range of diseases of the immune system. PIramed was subsequently bought by Roche for £108M who took on the development of their two PI3K drug candidates.

2011
The Institute develops an innovative new approach to measure the levels of PIP3 in cells and biopsies leading to a collaboration with GSK on clinical trials[14].

2011
Gilead Sciences begin developing a PI3K delta inhibitor drug based on research from the Institute. This would lead to the drug Idelalisib (Zydelig).

2012
The Institute launches a collaboration with Karus Therapeutics to investigate the use of PI3K inhibitors in treating inflammatory diseases such as rheumatoid arthritis. Our research helped Karus to secure further investment to pursue this work.

2013
Klaus Okkenhaug at the Institute, in collaboration with researchers at the University of Cambridge, discovers a new human genetic disease responsible for increased susceptibility to lung infections. The disease is named activated PI3K delta syndrome or APDS[15].

"We have established a very effective long-term working relationship with the PI3K team at Babraham Institute. Several GSK projects have benefited from their world leading expertise and technical advice, which has given us a competitive edge." Dr. Augustin Amour, a researcher in the Respiratory Therapy Area at GSK.

2013
A report on the Institute's economic impact by Alacrita LLP identifies more than 20 potential drugs in clinical trials based on PI3K research at the Institute. In total, the report reveals over £350M investment in PI3K by pharmaceutical companies up to January 2013.

2014
Idelalisib (Zydelig) is licensed for use in treating chronic lymphoid leukaemia (CLL). Around 3,700 cases of CLL are diagnosed in the UK each year.

2014
Institute becomes a founding signatory of the Concordat on Openness on Animal Research.

2015
The Institute becomes part of the Therapeutics Consortium, a part of the Milner Therapeutics Institute. The organisation specifically aims to unite research, drug development and treatment to create a faster transition from discovery to treatment throughout biomedicine in Cambridge.

2017
The Wakelam group and the Institute's Bioinformatics facility become part of the international LIPID MAPS consortium as part of a new round of four years of funding from the Wellcome Trust. LIPID MAPS provides a vital online resource for lipid researchers worldwide to share their data and insights into the role of lipid molecules in all aspects of biology. The Babraham Institute is now responsible for managing and maintaining this crucial research tool.

References

1. I. de Burgh Daly, (1957) A. R. C. Institute of Animal Physiology, Babraham, Cambridge. Proceedings of the Royal Society B. DOI: 10.1098/rspb.1957.0004.
2. Dittmer, J. C., and R. M. Dawson. (1960). The isolation of a new complex lipid: triphosphoinositide from ox brain. Biochim. Biophys. Acta. 40: 379–380
3. Thompson, W., and R. M. C. Dawson. (1964). The triphosphoinositide phosphodiesterase of brain tissue. Biochem. J. 91: 237–243
4. Bangham, A.D., Standish, M., & Weissmann, G. (1965) The action of steroids and streptolysin S on the permeability of phospholipid structures to cations. J Mol Biol 13 (1), 238-252.
5. Berridge, M. J., and J. N. Fain. (1979). Inhibition of phosphatidylinositol synthesis and the inactivation of calcium entry after prolonged exposure of the blowfly salivary gland to 5-hydroxytryptamine. Biochem. J. 178: 59–69
6. H. Streb, R. F. Irvine, M. J. Berridge & I. Schulz (1983)Release of Ca2+ from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. Nature, 306, 67–69.
7. MJ. Berridge & RF. Irvine (1984). Inositol trisphosphate, a novel second messenger in cellular signal transduction. Nature. 312, 315–321
8. L. R. Stephens, K.T. Hughes & R. F. Irvine (1991) Pathway of phosphatidylinositol(3,4,5)-trisphosphate synthesis in activated neutrophils. Nature. 351, pp 33–39 and Hawkins PT, Jackson TR, Stephens LR. (1992), Platelet-derived growth factor stimulates synthesis of PtdIns (3,4,5)P3 by activating a PtdIns(4,5)P2 3-OH kinase. Nature. 358(6382):157-9.
9. Stephens L, Smrcka A, Cooke FT, Jackson TR, Sternweis PC, Hawkins PT. (1994) A novel phosphoinositide 3 kinase activity in myeloid-derived cells is activated by G protein beta gamma subunits. Cell. Apr 8;77(1):83-93
10. Stokoe D, Stephens LR, Copeland T, Gaffney PR, Reese CB, Painter GF, Holmes AB, McCormick F, Hawkins PT. (1997) Dual role of phosphatid ylinositol-3,4,5-trisphosphate in the activation of protein kinase B. Science. Jul 25;277(5325):567-70
11. EH. Walker, O Perisic, C Ried, L Stephens & RL. Williams (1999). Structural insights into phosphoinositide 3-kinase catalysis and signaling. Nature. 402, pp 313–320.
12. Clayton E1, Bardi G, Bell SE, Chantry D, Downes CP, Gray A, Humphries LA, Rawlings D, Reynolds H, Vigorito E, Turner M.J (2002) A crucial role for the p110delta subunit of phosphatidylinositol 3-kinase in B cell development and activation. J. Exp Med. 196(6):753-63
13. EL Axe, SA Walker, M Manifava, P Chandra, HL Roderick, A Habermann (2008) Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum, The Journal of cell biology 182 (4), 685-701
14. J Clark, KE Anderson, V Juvin, TS Smith, F Karpe, MJO Wakelam, LR Stephens & PT Hawkins (2011). Quantification of PtdInsP3 molecular species in cells and tissues by mass spectrometry. Nature Methods. 8, pp 267–272
15. Angulo I et al. (2013), Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage. Science. 342(6160):866-71. doi: 10.1126/science.1243292. Epub 2013 Oct 17.