PI3-kinase: from basic cell biology to new cancer therapies

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asic cell biology research at the Babraham Institute is leading to new treatments for cancers, chronic inflammation and other diseases all caused by defects in an important molecular mechanism that transmits signals within a cell and which is controlled by the ‘PI3-kinase’ enzymes.

Since the late 1980s, Babraham scientists have made significant contributions to our knowledge of a class of enzymes called the ‘PI3-kinases’, and to the analytical methods required to study them. Researchers from Babraham now collaborate with, and provide informal consultancy services to, pharmaceutical companies and clinicians interested in developing drugs to treat cancers and other diseases caused by mutations in the PI3-kinase pathway.

This was only possible thanks to long-term support for research into the fundamental biology of the PI3-kinase enzymes at the Babraham Institute, which receives strategic funding from BBSRC.

Leading global research efforts

Today, the Babraham Institute is at the forefront of global efforts to understand PI3-kinase, building on a history of research into the PI3-kinase pathway that began at the Institute in 1988. Since then, Babraham researchers have built collaborations with both the pharmaceutical industry and clinicians, enabling fundamental knowledge of PI3-kinase to be used to develop new therapies and benefit patients.

For example, Babraham scientists worked with Professor Edwin Chilvers and Dr Alison Condliffe at the University of Cambridge to identify the role of PI3-kinase enzymes in a genetic disease that causes severe immune deficiency. The

THE BABRAHAM INSTITUTE

The Babraham Institute, based on the Babraham Research Campus near Cambridge, UK, receives strategic funding from BBSRC for research into the biology of lifelong health and wellbeing.

In 2013/14 the Babraham Institute received £28.8M from BBSRC, consisting of Institute Strategic Programme Grants (ISPGs) and Campus Capability Grants (CCGs), capital and other funding. The ISPGs and CCGs from BBSRC provide strategic funding to help deliver the Council’s priorities. They enable the Institute to leverage funding from other sources, including industry. Support from BBSRC is complemented by funding from other Research Councils, especially the MRC, and medical charities such as Cancer Research UK.

The Institute plays an important role in the broader life science research community around Cambridge. Babraham researchers have established close links with local biotechnology companies, including those on the Babraham Research Campus. They also work with colleagues at the University of Cambridge, Addenbrooke’s Hospital and the Wellcome Trust Genome Campus, amongst others.

These case studies illustrate the impact of major scientific breakthroughs at the Institute, and the development of the Institute’s infrastructure and capability. Professor Michael Wakelam, Director of the Babraham Institute, says, “Long-term support from BBSRC has and continues to enable world-class bioscience at Babraham, which is leading to a wide range of current and future impacts from the Institute’s research such as those outlined in these case studies.”

**IMPACT SUMMARY**

BBSRC and its predecessor AFRC have supported PI3-kinase research at Babraham since the late 1980s. This is leading to new therapies for various cancers, immune-deficiency and inflammation.

Babraham scientists:

- are advising GSK on sample collection and analysis for a clinical trial, using novel mass spectrometry methods developed at Babraham.
- are working with clinicians to understand and develop treatments for various diseases caused by PI3-kinase mutations.
- received funding from US biotechnology company Icos Corporation for mouse genetics research. A drug to treat chronic lymphocytic leukaemia, discovered by Icos Corp., has recently completed phase III clinical trials.
- worked with US company Onyx Pharmaceuticals, resulting in several patents.
- advised biotechnology company PIramed shortly before the company was acquired by pharmaceutical company Roche for £108M in 2008. Roche now has one of PIramed’s PI3-kinase inhibitors in phase II clinical trials.
- began a formal collaboration with Karus Therapeutics Ltd in 2012, which is helping Karus secure further investment for PI3-kinase research.
- initiated collaborations with and provided advice to various companies including AstraZeneca, Novartis, UCB and Infinity.
Lipids are a group of molecules that include fats and waxes. Many play important biological roles and one type of lipid, the phospholipids, form the cell membranes of all biological cells.

The Babraham Institute has supported lipid research since the 1960s, when Alec Bangham invented liposomes – small bubble-like structures with a lipid membrane that have since had a significant impact on society, from helping premature babies’ lungs function via delivery of drugs to specific sites in the body to the formulation of many cosmetics.

Lipid research continued at Babraham through the 1960s and 1970s with Rex Dawson and Robin Irvine concentrating on a small group of lipids called phosphoinositides. In 1988 Stephens joined Irvine’s laboratory to investigate the fundamental biology of the PI3-kinases and how they were involved in phosphoinositide metabolism.

The enzyme activity of PI3-kinase was first reported by Dr Lewis Cantley and colleagues in Boston in 1988. In the same year, PI3-kinase research began at Babraham when Stephens joined the institute. Shortly afterwards, Dr Phil Hawkins moved his fellowship to Babraham to continue an earlier collaboration with Stephens. “The Institute, and Robin [Irvine, whose lab Stephens and Hawkins joined], provided the flexibility and the environment for Len and I to continue to work here in the early days… the Institute had a long-term view that this general field of science was one they wanted to invest in,” explains Hawkins.

At the time, researchers knew very little about the PI3-kinase enzymes, except that they were associated with several proteins implicated in cancer. They also knew that PI3-kinase enzymes modified a family of lipid molecules called ‘phosphoinositides’, which had been studied at the Babraham Institute since the 1960s (see box ‘What are lipids?’).

In 1991 Stephens defined how PI3-kinase produced a compound called PIP₃ and suggested that PIP₃ was an ‘intracellular messenger’ which enabled PI3-kinase to control many other cellular functions.

As the functions of PI3-kinase were revealed, the pharmaceutical industry began to take an interest. In 1993 Stephens and Hawkins were invited to present their work on PI3-kinase to pharmaceutical company GSK. They also worked with US company Onyx Pharmaceuticals in 1995, resulting in several patents related to the PI3-kinase pathway.

In 1999, Babraham scientists worked with Roger Williams and colleagues at the MRC Laboratory of Molecular Biology in Cambridge to decipher the molecular structure of the PI3-kinase enzymes, raising the possibility of designing drugs targeted to specific sites within the enzymes.

Investing in capability
The PI3-kinase expertise at Babraham was further strengthened when group leaders Martin Turner and
Klaus Okkenhaug joined the institute in 1997 and 2003, respectively. Their work focused on the role of PI3-kinase in the immune system, and both made use of mouse genetics as their main approach.

By using genetically modified mice, alongside better molecular tools called selective inhibitors, Babraham researchers found that the four PI3-kinase isoforms each played a specific role in the body. They all convert a molecule called PIP2 into another called PIP3, when certain hormones such as insulin bind to receptors on the outside of the cell membrane.

This changes the concentration of PIP3 in the cell, which acts as a 'master signal', activating many other proteins and enabling a single hormone to influence a range of different cellular processes.

The mouse genetics research led directly to industry funding for Babraham. In 1999, US biotechnology company Icos Corporation funded Turner's group to develop a line of genetically modified mice in which the gene or PI3-kinase delta had been deactivated.

Research using this mouse model showed that a compound that inhibited PI3-kinase delta could potentially be used to treat a number of diseases. This led to the creation of inhibitors that targeted PI3-kinase delta, including the forerunners of a compound called CAL-101. In 2011, CAL-101 was acquired by Gilead Sciences Ltd. The drug has recently been approved for clinical use by the US FDA to treat chronic lymphocytic leukaemia. Cancer Research UK estimates that around 2,800 people are diagnosed with this currently incurable form of leukaemia in the UK each year.

Investments from BBSRC also enabled Babraham to continue to develop the mass spectrometry and mouse genetics research facilities required to study all four isoforms. Professor Michael Wakelam's appointment as Director of the Institute in 2006 brought lipidomics (which enables researchers to identify all of the lipids in a sample, relying on techniques such as mass spectrometry) to complement the existing lipid and PI3-kinase research. "There was investment in analytical techniques at Babraham going back to the late 1980s and early 1990s, which allowed the definition of what the key molecules were. We've carried on updating those analytical methodologies in a way that few others have been able to do," says Wakelam.

According to Okkenhaug, “There are not many centres around the world where you could ask questions about each of the isoforms and which have the tools to get answers.”

**From basic biology to the clinic**

The fact that PI3-kinase plays a signalling role in many cellular functions means that mutations in the PI3-kinase genes often cause serious illness. For instance, mutations in a gene called PIK3CA, which codes for one of the proteins that makes up the PI3-kinase enzyme, have been found in 32% of colorectal cancers, 27% of brain cancers and 25% of gastric cancers. PI3-kinase also plays an important role in other diseases, such as chronic inflammatory or immune deficiency.

"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,” explains Stephens. “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.”

In 1997 researchers at Columbia University in the US discovered a gene called PTEN, which is a ‘tumour suppressor’. This means that, should this gene be disabled by a mutation, the cell is much more likely to turn cancerous. Further study of PTEN revealed that the protein it codes for works in opposition to PI3-kinase, converting the PIP3 made by PI3-kinase enzymes back into PIP2. A mutation which deactivated PTEN would allow PIP3 to build up in the cell, with consequences similar to a mutation which led to the production of too much PIP3. PTEN has since been found to be one of the most widely-mutated tumour suppressor genes in all human cancers.

“Now more and more patients are found that have a mutation in the PI3-kinase pathway,” says Okkenhaug. “Sometimes the effect of that mutation is quite predictable; they activate PI3-kinase and cause cancer. Other diseases are less obvious. So the mutations can cause also massive overgrowth or immune deficiency. How activating mutations cause immune deficiency is less obvious, almost counter-intuitive.”

“We get that information from the clinic and we have to go back and say we need to understand the basic biology a bit better. So we go back to mouse models because we realise there are bits of the biology we don’t understand.”

Pharmaceutical industry interest
Recognising the potential to develop new treatments for cancer, chronic inflammation and other illnesses, major pharmaceutical companies now have PI3-kinase research programmes. There are more than twenty potential drugs based on PI3-kinase research in clinical trials and the pharmaceutical industry has invested more than £350M in PI3-kinase research up to January 2013.

For instance, Babraham researchers are now working with GSK to develop a ‘bespoke’ test to identify PIP3 in clinical samples for a GSK clinical trial. The test takes advantage of novel mass spectrometry methods for measuring PIP and PIP2, which were developed by Dr Jonathan Clark and others at Babraham, and adapted for use in the clinical trials. The Babraham researchers also advised on the choice of sample and how the sample should be processed.

Babraham researchers also worked with biotechnology company Piramed, which had two research programmes to develop drugs that inhibit PI3-kinase, shortly before the company was acquired by pharmaceutical company Roche for £108M in 2008. Roche has since taken one of the compounds being developed by Piramed through to phase II clinical trials.

In 2012, Stephens and Hawkins began a formal collaboration with Karus Therapeutics Ltd to investigate the role of PI3-kinase in immune responses, contributing to the development of PI3-kinase inhibitors to treat rheumatoid arthritis and other inflammatory disease. The collaboration has helped Karus secure further investment for their PI3-kinase programme. “The insights of researchers at the Babraham Institute and the subsequent collaborative research programme was key to us convincing new investors that our PI3K programme was both scientifically innovative and commercially valuable,” says Shuttleworth.

“The current clinical and commercial excitement in the therapeutic value of PI3K inhibitors has flowed directly from basic research, much of which has been carried out in the...
UK and is now translating into the commercial sector,” he adds. “Our work with the Babraham Institute has helped us to harness our competitive edge, helping us to confirm our position in key market segments and providing a foundation for our R&D plans”.

Other industry interactions have included BBSRC-funded

Industry Partnering Awards (IPA) and CASE studentships, as well as projects funded by industry partners and other funders.

Further discoveries

Alongside their collaborations with industry, the Babraham researchers have continued to explore the basic biology of PI3-kinase. Recently the researchers have shown how PI3-kinase is regulated and, identified the different roles of PI3-kinases alpha, delta and gamma in lymphocytes, which play an important role in our immune system.

According to Wakelam, “It’s clear this work on PI3-kinase isn’t finished.”

REFERENCES


2. Figures from BBSRC Annual Report 2013/14. £28.8M consisting of £12.5M strategic funding, including the ESPGs and CCGs, £10.5M capital funding and £5.8M other funding, including competitive grants. See: http://www.bbsrc.ac.uk/publications/accounts/bbsrc-annual-13-14.aspx


5. Activated PI3K Delta Syndrome


7. At the time the Babraham Institute formed part of The Institute of Animal Physiology and Genetics Research (IAPGR) and was supported by BBSRC’s predecessor, the Agriculture and Food Research Council (AFRC).


12. Icos Corporation was acquired by Elly Lilly in 2007, see: http://en.wikipedia.org/wiki/Icos


22. Capturing the Economic Impact of the Babraham Institute, January 2013 by Aboria LLP


24. See press release [Reference/webpage no longer available – Feb 2016]

