

The Babraham Institute undertakes innovative, world-leading life sciences research to generate new knowledge of biological mechanisms underpinning ageing, development and the maintenance of health. Research focuses on signalling and genome regulation, particularly the interplay between the two; by determining how the body reacts to dietary and environmental stimuli and manages microbial and viral interactions, we aim to improve wellbeing and healthier ageing.

Researchers are studying intracellular signalling pathways to elucidate the mechanism of action of PI3-Kinases, MAP kinases, small GTPases and calcium-mediated signalling in the immune, cardiovascular and nervous systems or in processes like angiogenesis. The key proteins often represent targets for therapeutic intervention. Babraham is developing expertise in Mass Spec lipidomics analysis and Next Generation Sequencing, integrating basic and translational research.

Babraham Bioscience Technologies Ltd. (BBT) delivers the Institute's knowledge exchange remit and facilitates academic-commercial links. An example is the translation of the Institute's pioneering work in epigenetics, resulting in several patent applications.

Commercialisation is achieved mainly through licensing to companies, including an ongoing relationship with CellCentric Ltd. BBT also manages the campus Bioincubator, home to 28 early-stage bioventures, including a biopharmaceutical spin-out based on the Institute's antibody expertise.

The Institute supports the Biotechnology and Biological Sciences Research Council's (BBSRC) mission to drive advances in fundamental bioscience to underpin pharmaceuticals, health and wellbeing during ageing, contributing to wealth creation for the UK.



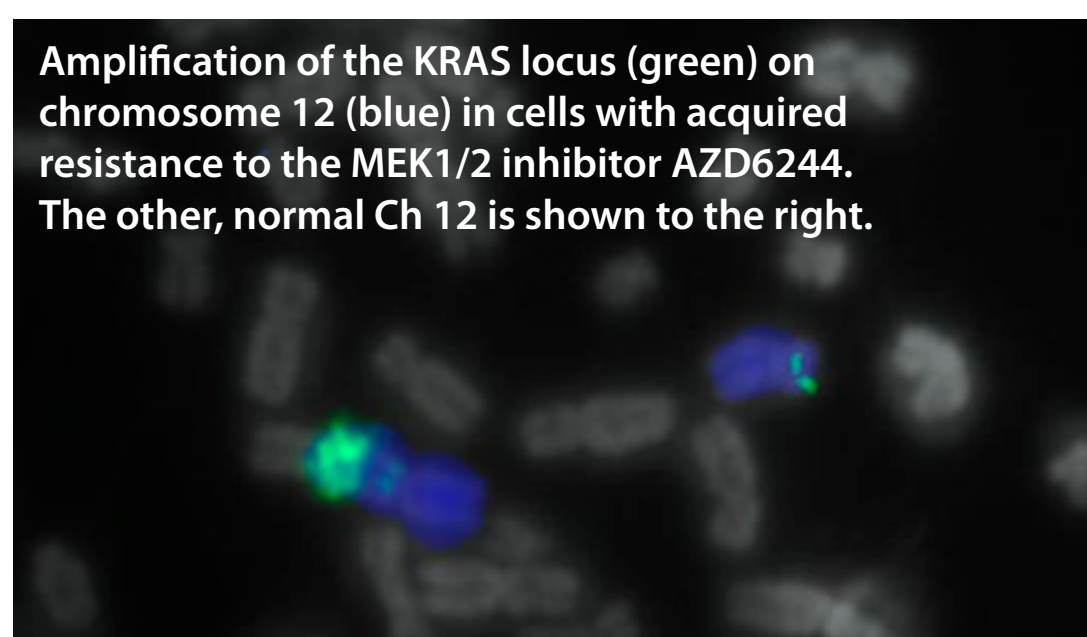
## Case Studies and Knowledge Exchange at the Babraham Institute

### Acquired resistance to MEK1/2 Inhibitors

*Simon Cook - Laboratory of Signalling and Cell Fate*

A growing problem in treating tumours is their ability to develop resistance to new chemotherapeutic drugs, causing disease relapse. A recent breakthrough at Babraham has been the discovery of how tumour cells can acquire resistance to an anti-cancer drug (AZD6244). The research, a collaboration with scientists at AstraZeneca and the MRC Cancer Cell Unit in Cambridge, provides new insight into a protein pathway that normally controls cell division (the BRAF-MEK-ERK pathway), and greater understanding of tumour cells' versatility to overcome therapies targeting this pathway.

- The RAF-MEK1/2-ERK1/2 signalling pathway controls cell proliferation and is frequently defective in cancer.
- Inhibitors of the MEK1/2 enzymes are currently in clinical trials.
- We have identified a common mechanism by which tumour cells with BRAF or KRAS mutations develop resistance to MEK1/2 inhibitors.
- New clinical trials in which MEK1/2 and BRAF inhibitors are used in combination are now underway.
- The research suggests that treatment with AZD6244 in combination with other inhibitors of the pathway may be more successful and has implications for more efficient use of the new generation of drugs in development or undergoing clinical evaluation.



Little *et al* (2011) *Science Signalling*: Amplification of the driving oncogene, KRAS or BRAF, underpins acquired resistance to MEK1/2 inhibitors in colorectal cancer cells.

### Phosphoinositide 3-kinase (PI3K) signalling in angiogenesis

*Sonja Vermeren - Inositide Laboratory*

- ARAP3, discovered at Babraham, is an important signalling protein that regulates angiogenesis and is controlled by another signalling protein, PI3K.
- ARAP3 in turn regulates the small GTPases RhoA and Arf6, signalling proteins important for cell motility, a crucial aspect of angiogenesis.
- Mice lacking ARAP3 die before birth because of the failure to 'sprout' new blood vessels during embryonic development.
- The identification of a novel player in these pathways and greater understanding of angiogenesis may lead to innovative drug targets for anti- and pro-angiogenic therapies.

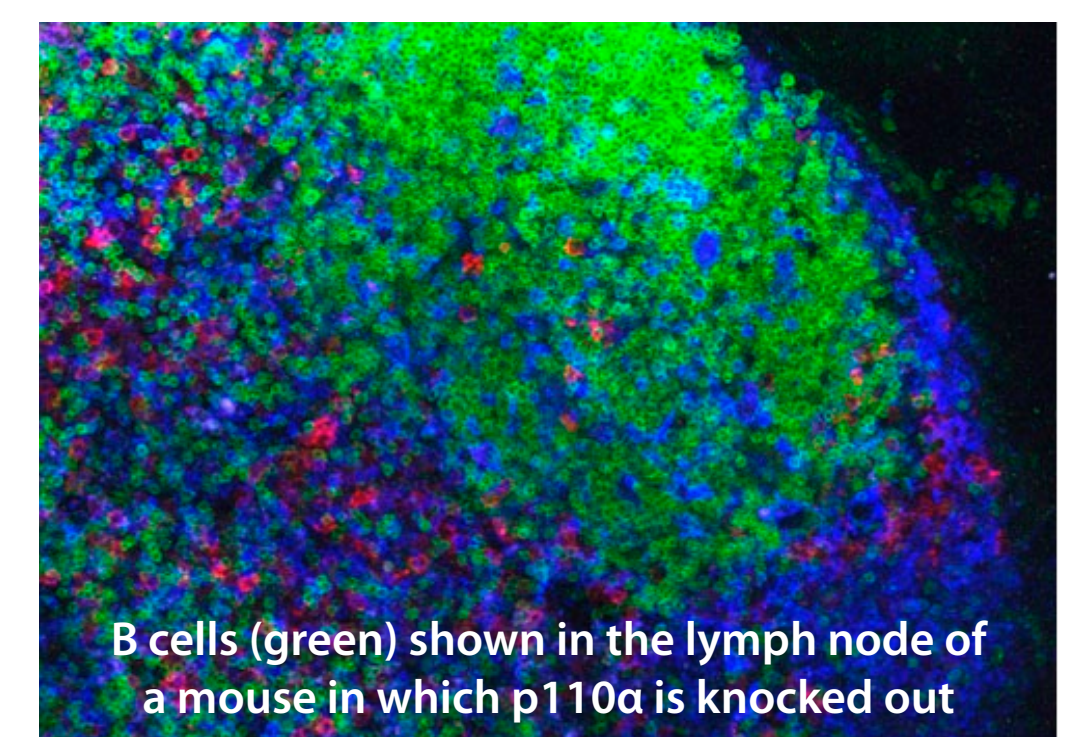
Gambardella *et al* (2010) *Science Signalling*: PI3K signaling through the dual GTPase-activating protein ARAP3 is essential for developmental angiogenesis.

**Recent News:** In collaboration with the Beatson Institute in Glasgow, Heidi Welch's group (Inositide Laboratory) has recently found that P-Rex1, a guanine-nucleotide exchange factor for the small G protein Rac, is overexpressed in melanoma cells, controls their migratory behaviour, and is required for melanoma metastasis in mouse models (unpublished data).

### Selective Phosphoinositide 3-kinases (PI3K) Inhibitors

*Klaus Okkenhaug - Laboratory of Lymphocyte Signalling & Development*

- PI3Ks are involved in many cellular processes e.g. cell growth, proliferation, motility, intracellular trafficking and the immune response.
- With a strong history of discovery in PI3K research, Babraham scientists have recently shown that the p110 $\alpha$  subunit of PI3K, known to play an important role in malignancy, is not essential for B cell development.
- Selective inhibitors are being studied as potential non-immunosuppressive therapies.



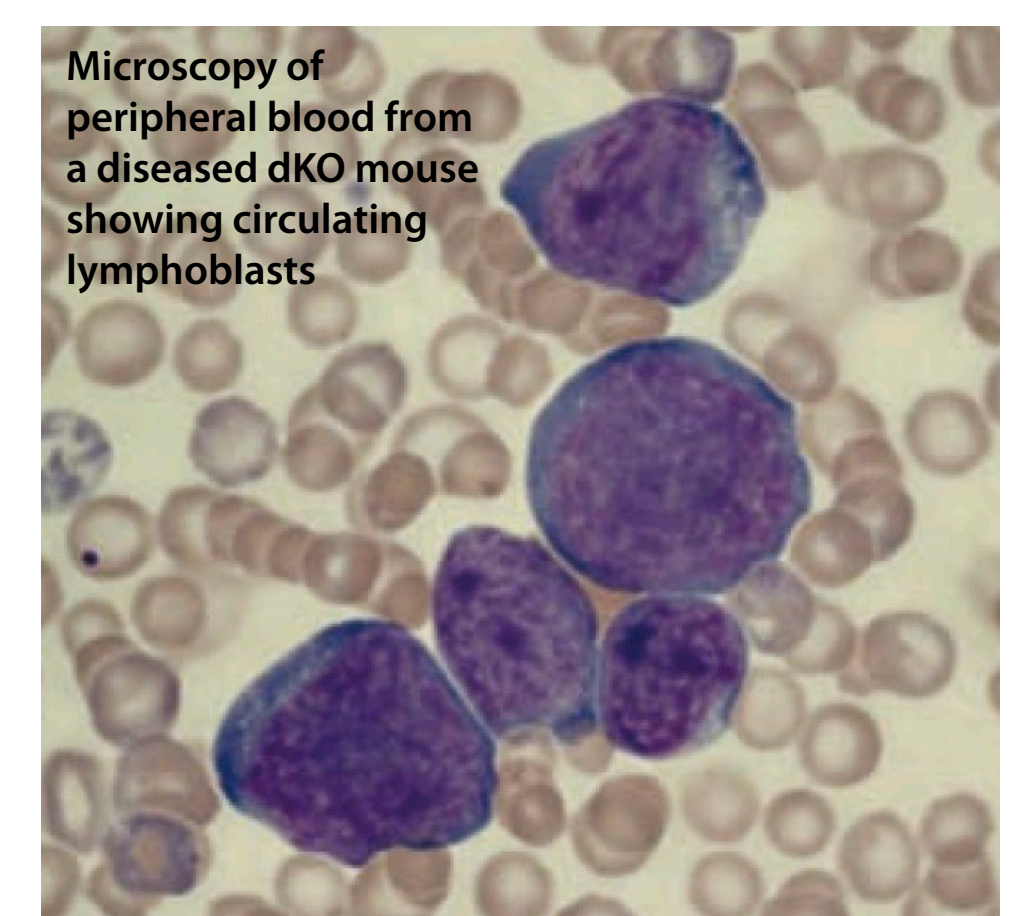
Ramadani *et al* (2010) *Science Signalling*: The PI3K isoforms p110 $\alpha$  and p110 $\delta$  are essential for pre-B cell receptor signalling and B cell development.

### RNA binding proteins in the development of leukaemia

*Martin Turner - Laboratory of Lymphocyte Signalling & Development*

- Babraham scientists have discovered a completely new mechanism behind the development of a type of leukaemia.
- Mice missing two key genes (encoding RNA-binding proteins ZFP36L1 and ZFP36L2) developed an aggressive form of leukaemia similar to Acute Lymphoblastic Leukaemia, the most common form of leukaemia in children.
- These mice cannot produce 'silencer' proteins, which normally regulate the activity of other genes (e.g. through mRNA degradation and translational repression) to ensure the development of a healthy individual.
- Higher levels of Notch1, a protein with a key role in T cell development, are produced in the absence of the 'silencers'; consequently the cells multiply out of control leading to leukaemia.
- Manipulating the stability and destruction of mRNA may be useful for developing anti-cancer agents and treating human leukaemia.

Hodson *et al* (2010) *Nature Immunology*: Deletion of the RNA-binding proteins ZFP36L1 and ZFP36L2 leads to perturbed thymic development and T-lymphoblastic leukaemia.



### Chromosomal translocations during leukaemia

*Cameron Osborne - Laboratory of Nuclear Dynamics*

- The impact of genome organisation on susceptibility to leukaemia is also being studied. Cancers are frequently associated with chromosomal translocation; the 'transcription factory model' helps explain how this occurs, despite the distances between the genes involved.
- Genes frequently found fused together in Burkitt lymphoma commute to the same transcription factory to be activated. Chromosomal translocations may occur while multiple genes are docked simultaneously at a factory.

Osborne *et al* (2007) *PLoS Biol*: Myc dynamically and preferentially relocates to a transcription factory occupied by Igh.