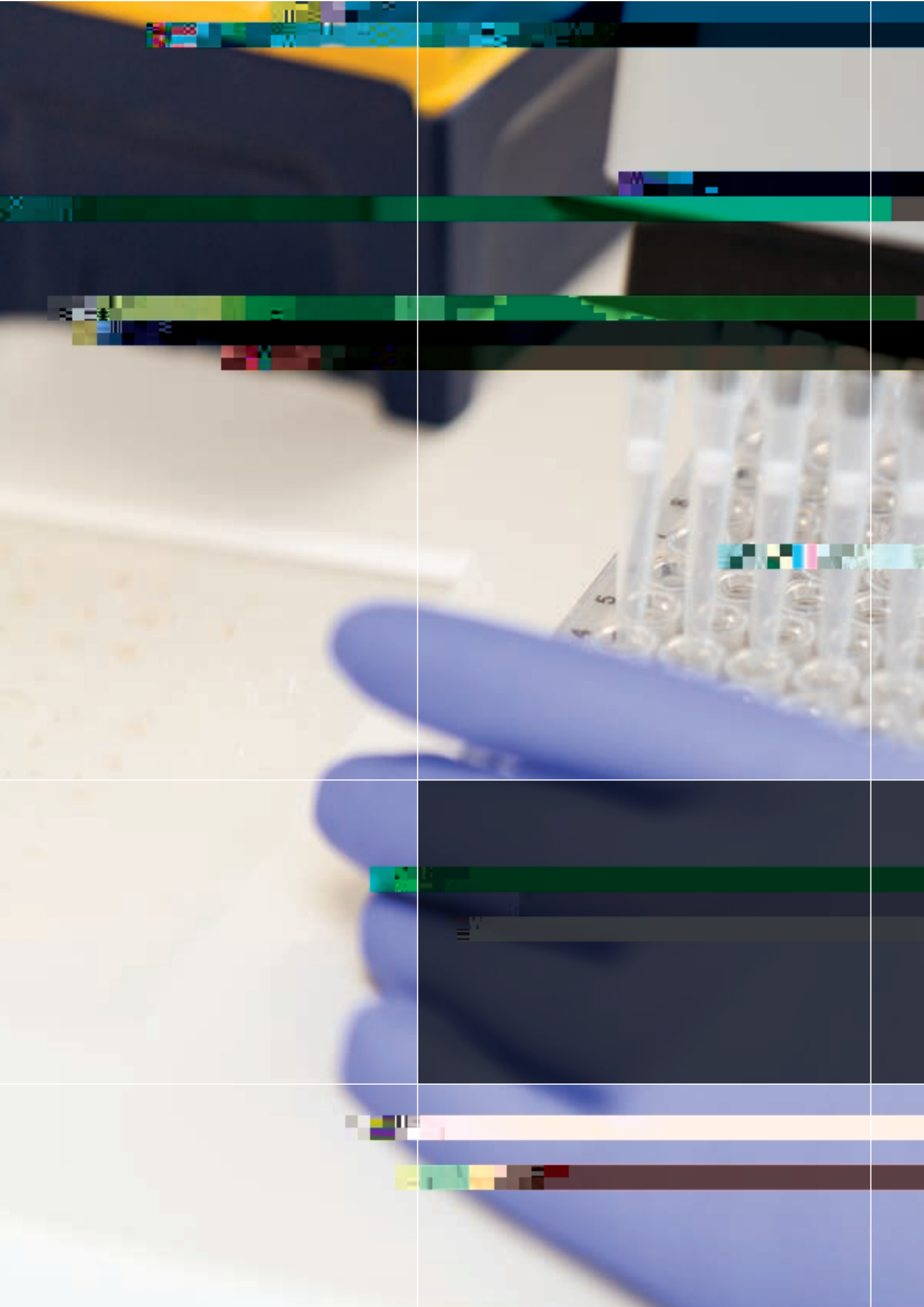
Babraham Institute



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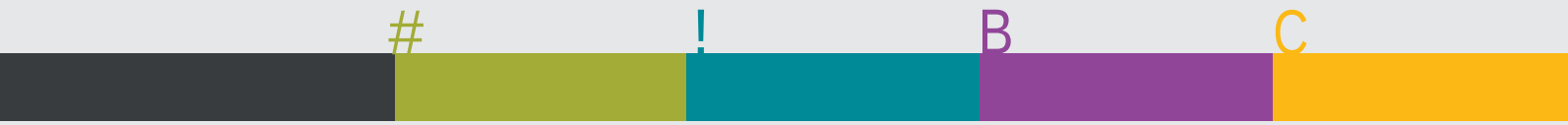
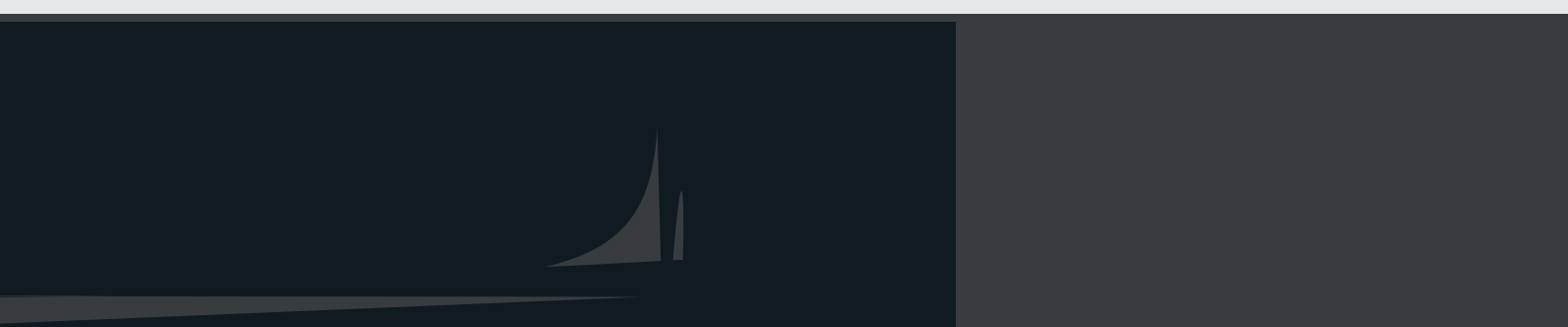
Welcome to the Babraham Institute Annual Research Report, which provides a summary of the InstituteÕs key research foci, progress and activities in 2016. The Babraham InstituteÕs vision is to build upon our pre-eminence as a bioscience research institute, making seminal contributions to understanding that enhance lifelong health and wellbeing whilst addressing strategic imperatives within the BBSRC Strategic Plan.

This collection of 2016 research reports demonstrates how our researchers are tackling challenging problems facing an ageing global population by developing and applying new technologies and pioneering approaches. The four research features included in this report highlight discoveries made in 2016 Ð all with importance for uncovering the basis of health and disease.



Collaboration and cooperation is central to BabrahamÕs approach. This is illustrated by a glance at our interactions throughout 2016: hosting over 90 visiting researchers within the InstituteÕs labs to share knowledge and expertise, 23 international academic



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RESEARCHERS

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T cells coordinate immune function by di" erentiating into highly specialised cellular lineages. Whereas e"ector CD4+ and CD8+ T cells promote immune activation and drive clearance of infections and cancer, CD4+ regulatory T cells (Treg), which are dependent upon the transcription factor Foxp3, suppress their function, preventing excessive autoimmune and allergic reactions. The mechanisms by which these powerful cells make such decisions, or Ôlineage choicesÕ, are not completely clear.

We are interested in understanding the general principles and speci!c mechanisms driving appropriate lineage choices during T cell dë erentiation, and the implications of this for immune function in health and disease. We are particularly interested in the following questions:

1. E"ector cells and regulatory T cells arise from common precursors yet establish dichotomous functional programmes. What are the transcriptional control circuits that enable these dichotomous functional programmes to be established?

2. Regulatory T cell populations remain stable throughout the adult lifespan and into old age. This remarkable stability is required to prevent otherwise lethal in#ammation. What are the mechanisms that enable durable maintenance of the regulatory T cell programme throughout life?

3. The suppressive function of regulatory T cells can prevent appropriate function of the immune system during chronic infections and cancer. What are the external signals driving inappropriate lineage choices in these contexts? Can these processes be modulated?

We have made substantial progress in understanding the mechanisms and external signals underlying lineage choice in T cell dë erentiation. Highlights from this yearÕs research include establishing a critical role for the transcription factor BACH2 in immunological memory (1), identifying extracellular ionic potassium as a key regulator of T cell activation (2), and identifying post-translational regulatory processes that act upon the transcription factor Hif1a to drive immunosuppressive regulatory T cell dë erentiation (3).

Our immune system does a remarkable job of defending us against germs, repelling invaders and keeping us healthy. A key part of this system are our B cells Ð highly specialised cells capable of responding to myriad disease-causing pathogens. Not only are they hugely diverse in the pathogens they recognise, they can remember the pathogens we have been exposed to in the past, providing us with immunity against future attacks.

The vast repertoire of responses that these cells possess is due to their unique ability to cut up and rearrange their own DNA. ÒThis variable-diversity-joining recombination only happens in these cells‚Ó says Dr Martin Turner of the Immunology research programme, who wants to get to the bottom of when this takes place, and how the mechanism works.

B cells develop in a sequence. During the process, there are several discrete stages where DNA is broken and re-joined, allowing the cells to produce the many di" erent antibodies we need to protect ourselves from many di" erent infections. Rearranging DNA, however, is a risky process.

Breaking DNA at the wrong point in the sequence can cause cells to die, and making mistakes when re-joining DNA can lead to even more sinister consequences. When this happens, the mutated genes can create cancer-causing immune cells, resulting in diseases such as lymphoma and leukaemia. ÒImmune cell cancers, such as lymphomas and leukaemias, are the payback we get for a functioning immune system‚Ó he explains. ÒThe good news is that knowing more about this DNA re-shu%ing mechanism, including what happens when it goes wrong, means that in the future weÕll be able to treat these types of cancers better.Ó

During their development, B cells switch very rapidly between periods of quiescence (or rest) and proliferation. When they are resting, they cut up and rearrange their DNA, but as soon as this happens there is a rapid burst of cell proliferation. The problem4sn0p469Do10.1(e is a r)5(l0.1(eting)15(* [ong 6)Tj

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The more we learn about autophagy, the more fascinating, important and complex it becomes. Literally the process of Ôself-eatingÕ, autophagy is the cellÕs way of recycling itself to survive short-term starvation, as well as cleaning itself of unwanted and potentially harmful material. Although most of us know little about it, autophagy is vital from the moment we are born until we die.

ÒItÕs a quiet pathway, but itÕs super important,Ó says Dr Nicholas Ktistakis, group leader in the Signalling research programme. ÒIt is an ancient pathway Đ all cells have it Đ but normally it works in the background.Ó

Despite its usually unsung role, the better we understand autophagy, the more we discover about its links with health and disease. As newborns, it is what tides us over the period immediately after birth when our cells are our only fuel. Boosting autophagy seems strongly linked with longevity. There is evidence that by cleaning our cells of potentially damaging material, autophagy could be involved in protecting against neurodegenerative diseases such as AlzheimerÕs and ParkinsonÕs. We now know that cancer cells use autophagy to fuel their uncontrolled growth. And it is even linked to the health bene!ts of fasting, including the 5:2 diet.

First described in 1963, Ktistakis has found references to autophagy dating back to 1860. During the past 50 years we have learned that many steps, and more than 30 genes, are involved in autophagy, and that two protein complexes Đ mTOR and ULK Đ are pivotal to the process. We have also discovered that it can be turned on and o" with remarkable rapidity, and that switching on autophagy by inactivating mTOR can increase lifespan in model organisms by an astonishing 30%.

Autophagy works by forming small membrane-bound sacs or autophagosomes to bag up material for clean up or for fuel. ItÕs likely that these two types of autophagy Đ the selective clean-up variety and the general nutrient-generating type Đ share the same machinery but rely on di" erent signals.

Understanding these early signals is a key focus for KtistakisÕ group and other researchers at the Institute. ÒA lot of our work is trying to !gure out the signal the cell uses to start the process. It happens very quickly Đ within 15 minutes of detecting a drop in nutrients Đ and must stop very fast when conditions improve, because you donÕt want to be digesting yourself for any longer than necessary,Ó Ktistakis explains.

ÒWe want to understand it at the molecular level Đ what happens when the signal arrives, how quickly mTOR is switched o" and on, and what happens when ULK is activated and leads to formation of the autophagosome. IÕm interested in this early part of the pathway Đ in identifying how dynamic it is and which are the important players controlling how it happens.Ó

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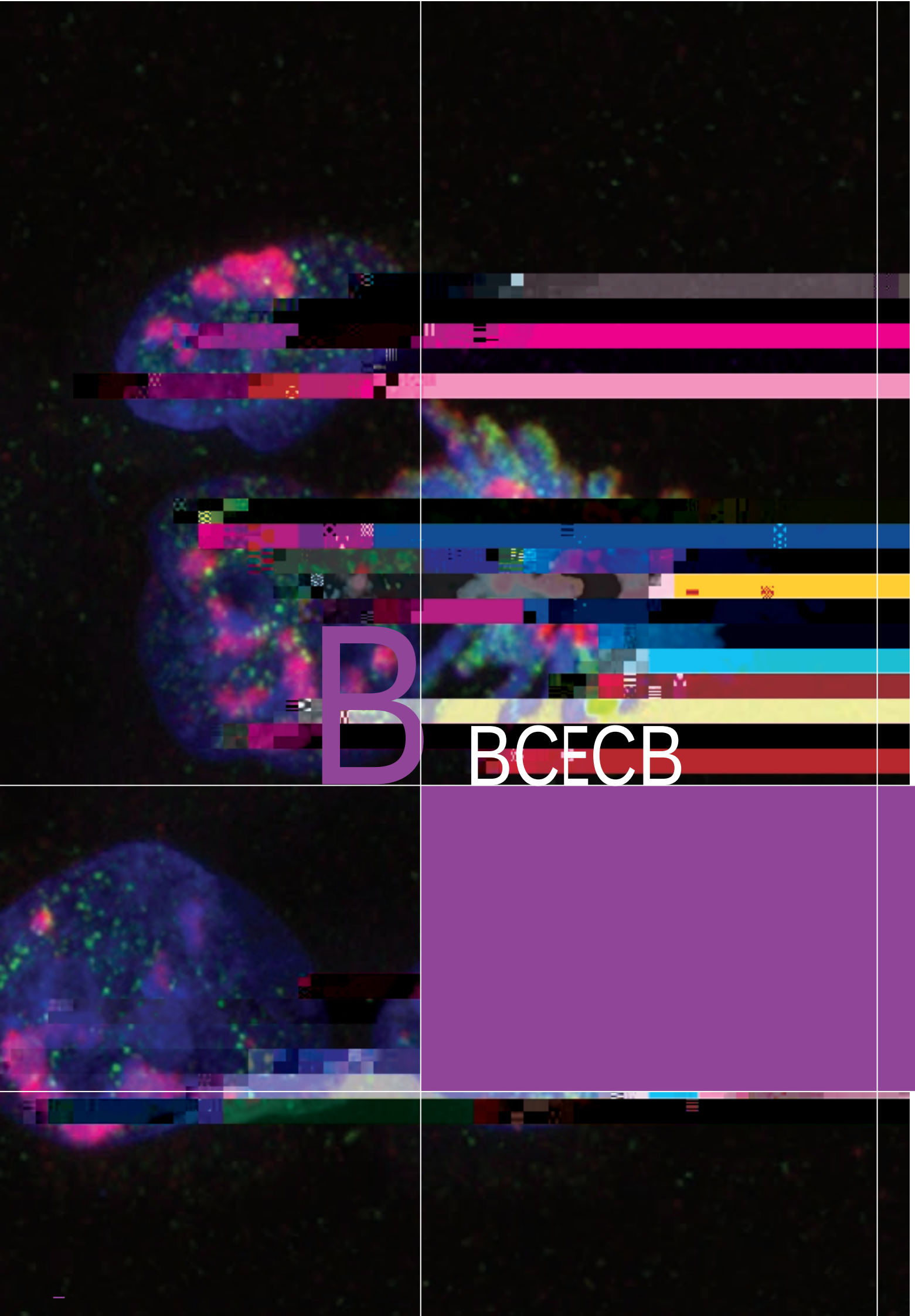
But studying such a complex, !nely-tuned and rapidly reactive system is a huge technical challenge Ð one recently solved by the expertise in biological chemistry and imaging technologies in the InstituteÕs core facilities and collaborating teams. With so many proteins involved, many of which are protein complexes rather than single proteins, developing ways to tag them with #uorescent markers in order to observe autophagy as it happens is a tall order.

And itÕs not the only challenge. Studying events so early in the pathway, before the autophagosome is visible, means Ktistakis had to develop new ways of seeing. By teaming up with scientists at the Francis Crick Institute in London and the Zeiss Microscopy Labs in Munich, the Babraham group has successfully combined live imaging with other forms of microscopy. These new techniques reveal how the !rst autophagy structure forms and the protein and membrane associations that lead to it developing into a fully-#edged autophagosome.

According to Ktistakis: ÒWe now know more about where the autophagosomes form, and how the autophagy machinery uses the cellÕs membranes to generate these tiny sacs. We still donÕt know how these regions are selected, but we are keen to !nd out, because it will give us the !nal level of understanding.Ó

Understanding is important, but itÕs the impact this knowledge could have on our lives that matters. Once we understand the process fully, it could enable us to !nd ways of harnessing autophagy to tackle neurodegenerative diseases and cancers, helping us age more healthily.

ÒWhen autophagy is more active, it is likely to make cells healthier, so knowing more about the process increases our ability to !nd ways to manipulate or boost it for future therapeutic bene!t. The idea ultimately is that if we understand autophagy enough we can change it in a way that bene!ts the cell and the organism,Ó Ktistakis concludes. ÒWe think this is probably a very good idea.Ó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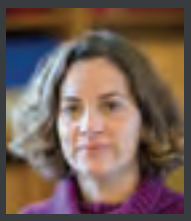

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From neurones and hepatocytes to lymphocytes and erythrocytes, our bodies contain more than 200 di"erent types of cell. Thanks to them, we can perform the myriad functions necessary to survive, thrive and reproduce. But how does this extraordinary diversity develop from one cell type Đ the zygote Đ when most of our cells contain the same genetic information?

ItÕs a puzzle Professor Wolf Reik, head of the Epigenetics research programme, has been working on for the past 30 years. ÒEvery cell in the body contains the same DNA, so there must be something else that interprets it in a dierent way,Ó he explains. ÒThis Ôsomething elseÕ is actually several things Đ transcription factors, proteins on the DNA that switch genes on and o" Đ and itÕs also epigenetics.Ó

Literally meaning Ôon top of our genesÕ, epigenetics refers to an extra layer of control achieved by annotating our DNA with a series of tags, such as the simple methyl group of one carbon and three hydrogen atoms. ItÕs thought that each cell type has a dierent set of tags Đ a dierent epigenome. Akin to highlighting recipes in a cookbook that together form a speci!c menu you want to create, each epigenome enables a speci!c cell type to develop by ensuring that only genes relevant to that cell type are switched on.

As well as enabling cell di" erentiation, the system must also be heritable, so that as we grow and repair ourselves, our cells and organs retain their individual identities. ÒThere is a memory in the system, and thatÕs important,Ó says Reik. ÒAs a liver cell divides, it needs to remember that itÕs a liver cell, and epigenetics helps with that.Ó

Equally importantly, the system must be able to forget, so that when we produce eggs and sperm, the newly developing embryo can start the development process afresh. ÒThis is vital because after fertilisation, new embryos must undergo this process of diversi!cation again, building new cell types and new organs. Without erasing the cellsÕ memory, the whole thing might become confused and lead to developmental problems and abnormalities,Ó he says.

ReikÕs group is particularly interested in the epigenomes of stem cells, extraordinary cells with the capacity to develop into any type of cell in the body, and which are present in early embryos. By studying these cells, they are discovering how epigenetic information a"ects the way that important organs Đ such as the placenta, heart and brain Đ function throughout our lives. ÒItÕs a hugely exciting area for us now,Ó he says. ÒIn early development, once you get away from all the

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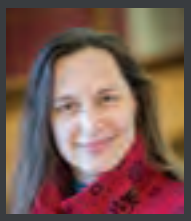

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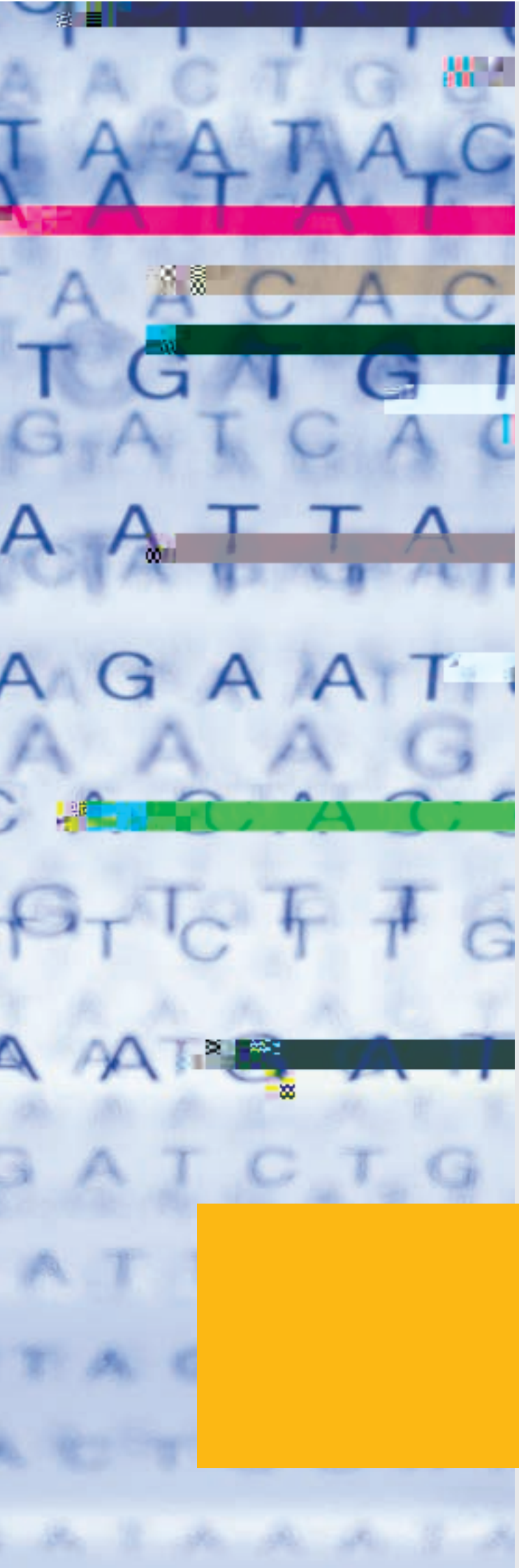

According to Fraser: ÒWhat weÕve found is that these SNPs are in regulatory elements, so by being able to map these onto speci!c

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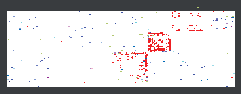

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The BabrahamInstituteÕs basic science bene!ts in a very real sense from its proximity to a number of industry-leading biotechnology companies on the Babraham Research Campus. One of many examples of such interactions is a new collaboration forged between the researchers in the Immunology programme and the campus company Cancer Research Technology (CRT). CRT is the commercialisation arm of Cancer Research UK and has an in-house drug discovery unit, CRT Discovery Laboratories, which translates cutting-edge science into innovative new therapies for cancer patients.

Following on from an earlier campus collaboration grant from the InstituteÕs Knowledge Exchange and Commercialisation programme, group leaders Rahul Roychoudhuri and Klaus Okkenhaug were awarded a Cancer Research UK Small Molecule Drug Discovery Project for three years to perform high-throughput screening of new small molecule immune-stimulatory drugs for immune-based therapy of cancer. This project is a collaboration with Stuart Farrow and Laura Rosenberg at CRT.

By designing new cell-based functional reporter assays for the function of immunosuppressive molecular pathways in T cells, Institute scientists hope to leverage the expertise and resources of CRT to identify new small molecules that can suppress such pathways. This approach will utilise high-throughput small molecule screens using compound libraries held by CRT and the Institute for Cancer Research (ICR). The research will be led by new Institute scientist Teresa will join the Roychoudhuri group as a postdoctoral research scientist in 2017.

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Kymab Ltd, a company based on the Babraham Research Campus, have been using the InstituteÕs Flow Cytometry facility for the past four years and this relationship has developed into a strong collaboration. Having identi!ed "ow cytometry and cell sorting techniques as central to their work into drug and vaccine discovery, Kymab purchased a BD FACSAria Fusion sorter in July 2015. Having had experience of the expertise with the Flow Cytometry facility, they chose to place this high-end instrument into the facility to be run by Institute specialists. With priority bookings given to Kymab, any spare capacity is available for use to support the InstituteÕs science.

This collaboration has ensured that the Kymab-owned instrument is a well maintained, well used piece of core equipment. The bene!ts of this arrangement are seen by both parties as Institute researchers have access to a high-end cell sorter and Kymab have access to the expertise in the facility as well as access to the facilityÕs other sorters in case of any required maintenance on KymabÕs Fusion sorter. Not only does the collaboration cover cell sorting, but wider advice on experimental design, data analysis and other aspects of "ow cytometry is also provided.

This close collaboration highlights the value of academicÐcommercial partnerships made possible by the co-location of a world-class Institute with leading biotechnology and life science companies.

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The InstituteÕs Signalling programme studies the signalling pathways that regulate how cells develop and respond to their environment to maintain lifelong health. Many of these pathways are also de-regulated in diseases making them attractive drug targets. For example, the KRAS-regulated RAF-MEK-ERK signalling pathway is very important in cancer; 20% of all cancers harbour mutations in KRAS but no anti-KRAS drugs exist. Whilst RAF and MEK inhibitors have been approved for clinical use, tumours quickly adapt and acquire resistance. New approaches are required to develop new distinct RAF, MEK or ERK inhibitors and to target mutant KRAS, a protein that some consider undruggable.

Simon Cook, a group leader in the Signalling programme, has studied the ERK pathway for 20 years. He uses inhibitors that target the pathway as research tools but recognised that they might also be relevant as future anti-cancer drugs. This led him to contact PhoreMost Ltd, a company co-situated on the Babraham Research Campus. PhoreMost is a new-model drug discovery company that seeks to inhibit the most intractable drug targets using its novel SiteSeeker¨ technology, a live-cell phenotypic assay system that can rapidly identify unexpected or ÔcrypticÕ druggable sites in speci!c disease-driving targets and pathways that cannot be readily seen using conventional non-cell based analytical methods.

Using a campus collaboration grant from the InstituteÕs Knowledge Exchange and Commercialisation programme, Rebecca Gilley in SimonÕs group and Grahame McKenzie at PhoreMost have established cell-based assays for the KRAS-RAF-MEK-ERK pathway that are compatible with PhoreMostÕs screening technology. This has prompted a successful joint application to Innovate UK and interest in a three-way collaboration with a drug discovery company based in the USA.


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