Babraham Institute

2017

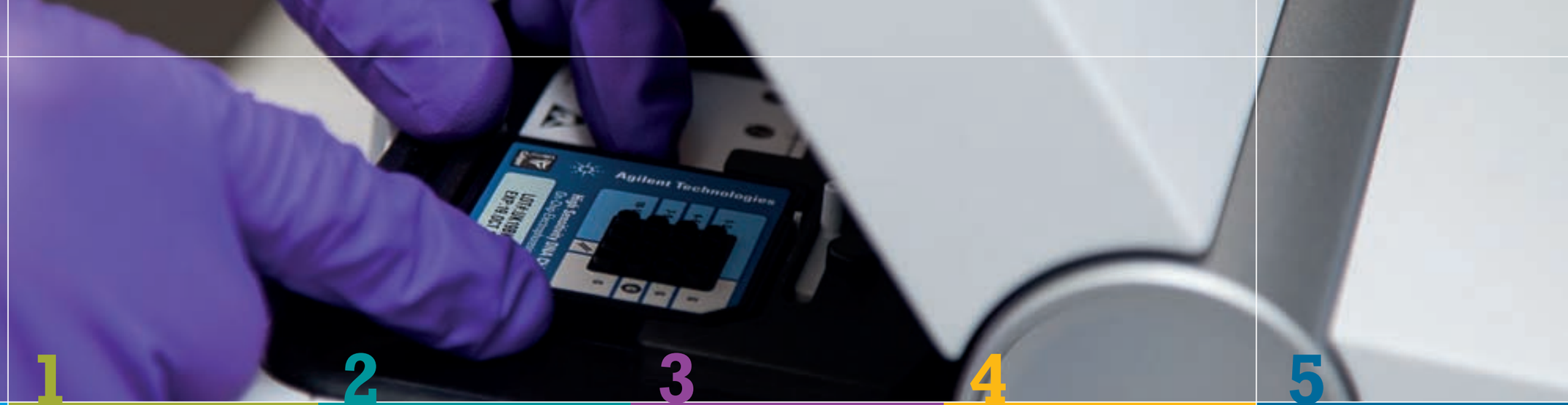
Babraham Institute
Annual Research Report

Life sciences research for lifelong health

The world's ageing population is a Global Grand Challenge facing us all and affecting governments, healthcare and research worldwide. In the UK, nearly 1 in 5 people are now over 65 and this is expected to rise to 1 in 4 by 2050. We're living much longer than ever before, but we're not living healthier. Our bodies still decline into old age at around the same point that they always have, a concept called healthspan. If our society is to keep functioning, we must find ways to extend our healthspan soon.

The Babraham Institute unites wide-ranging expertise in fundamental biology to address these challenges. We aim to gain a detailed understanding of ageing and lifelong health by studying epigenetic changes to gene regulation, investigating how cells respond to diet and their environment and examining the role of the immune system in health throughout our lives.

Contents



Director's welcome

Each year, the Babraham Institute's cutting-edge research pushes the boundaries of what we know about fundamental human biology. In line with the BBSRC Strategic Priority: Science for Health, our mission is to tackle the challenges of an ageing population by making discoveries that enhance lifelong health and wellbeing.

This Annual Research Report is a collection of the ground-breaking progress the Institute has made in 2017 and our plans for the future. Through the Feature articles included, we explore how the Institute maximises its impact by working with industry, academia, politicians and the public to share our findings and use our research to drive meaningful changes and greater scientific awareness.

Research features:

Professor Michael Wakelam
Institute Director

Our Science

2017 has been a time of change for the Institute, but this has not diminished our position as a world-leading centre of excellence and this year has produced some outstanding highlights. We have developed a means to study the epigenetic clock in mice providing a new way to understand and measure ageing (1), devised a system for tracking stem cell development (2), made discoveries about the dynamics of DNA (3) and uncovered a new mode of cell cannibalism (4). As we move into 2018, I look forward to welcoming new research groups who we will be recruiting to join the Institute and lead our research in exciting new directions.

Our Facilities

We are privileged to have nine outstanding scientific facilities which have provided peerless support to researchers at the Institute and beyond throughout 2017. Together with our research groups they have developed techniques and tools to address specific research challenges and many of these are being used by researchers worldwide. The specialised training sessions offered by the facilities attract delegates from from far afield and continue to be in high demand from both academia and industry.

Our Impacts

The Institute's impact activities through knowledge exchange, commercialisation, public engagement and communications have had many successes through the year. In particular, 2017 saw the Institute host the Ageing Cell conference attracting renowned specialists in ageing research from across the world. Events like this emphasise the Institute's focus on collaboration and on working at a global scale to drive scientific progress and wider impacts. Towards the end of the year we were also thrilled to win an award for Openness in Animal Research from Understanding Animal Research in recognition of our school outreach work.

119
VISITING RESEARCHERS

96
PUBLICATIONS

130
COMMERCIAL PROJECTS

Key Awards

- Institute Director, Professor Michael Wakelam was awarded the prestigious Morton Lectureship by the Biochemical Society
- Dr Rahul Roychoudhuri was awarded a Lister Prize by the Lister Institute for Preventive Medicine
- Dr Peter Rugg-Gunn successfully secured his tenured position in the Institute's Epigenetics Programme

I hope you enjoy discovering more about the Institute and our research as you read this report.

Professor Michael Wakelam
Institute Director

Publications

More Institute press releases at www.babraham.ac.uk/news

1. Tick Tock, stay ahead of the ageing clock! https://www.babraham.ac.uk/news/2017/04/tick-tock-stay-ahead-of-the-ageing-clock
2. A Tale of Two States https://www.babraham.ac.uk/news/2017/03/a-tale-of-two-states
3. Genetic DJ: Growing cells remix their genes https://www.babraham.ac.uk/news/2017/07/genetic-dj-growing-cells-remix-their-genes
4. Cannibal cells may limit cancer growth https://www.babraham.ac.uk/news/2017/07/cannibal-cells-may-limit-cancer-growth

Performance in 2017

OUR COLLABORATIVE ACADEMIC PROJECTS
UK AND WORLDWIDE

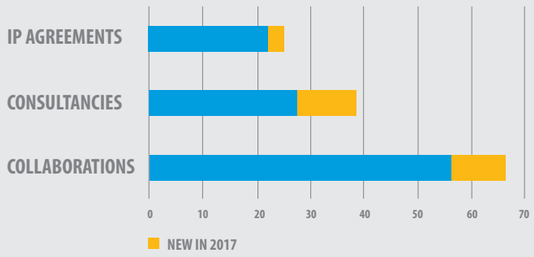
Working with others in 2017

44 ACTIVE PROJECTS

31 COUNTRIES

111 ORGANISATIONS

Working with commercial partners



People we've trained in our scientific facilities this year

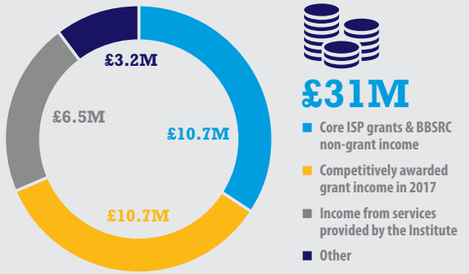
1167

BIOINFORMATICS **927**

FLOW CYTOMETRY **140**

IMAGING **100**

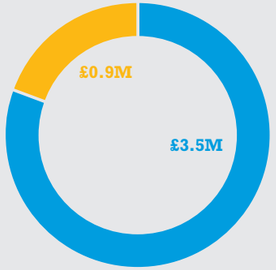
2017 income



£31M

- Core ISP grants & BBSRC non-grant income
- Competitively awarded grant income in 2017
- Income from services provided by the Institute
- Other

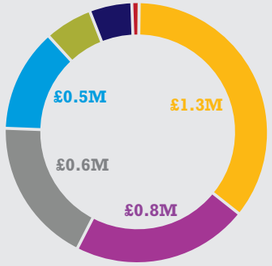
Value of all grants awarded in 2017



£4.4M

- UK funders
- International grants*

Value of UK grants awarded in 2017



£3.6M

- BBSRC
- MRC
- Cancer Research UK
- Wellcome Trust
- Lister Institute of Preventive Medicine
- Innovative UK
- Rosetrees Trust

*International grant sources:
European Commission (EC), European Molecular Biology Organisation (EMBO), SENS Research Foundation

2017 successes

50
PUBLIC ENGAGEMENT EVENTS

INVOLVING

130
RESEARCHERS

9,000
PEOPLE ENGAGED

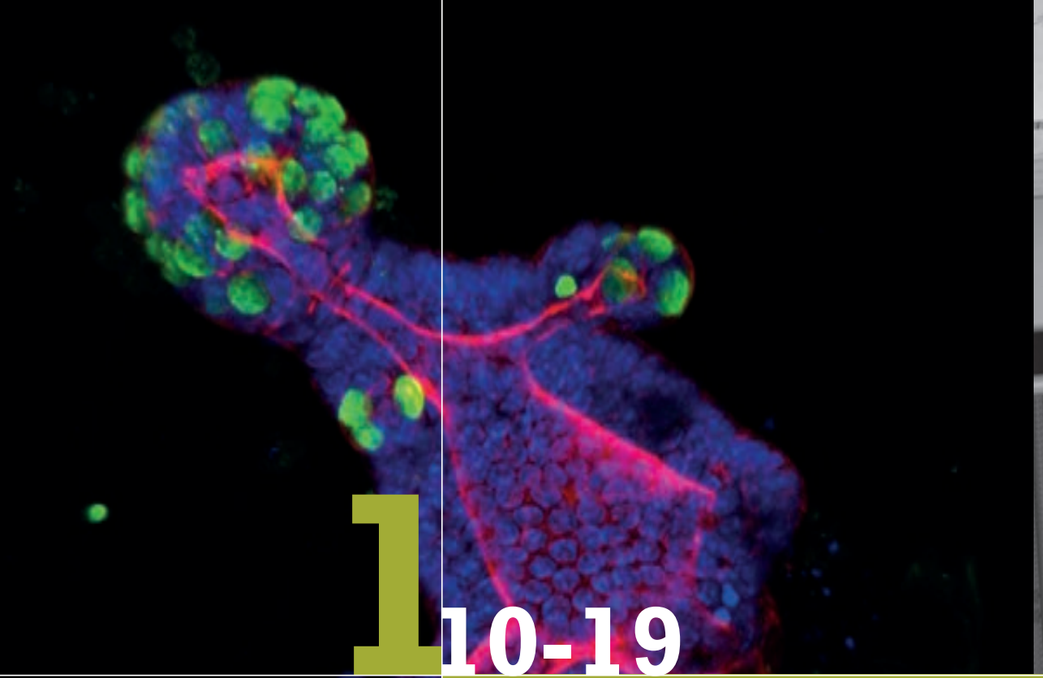
96
PUBLICATIONS

79
RESEARCH PUBLICATIONS

17
REVIEWS

Openness on Animal Research Awards 2017 Winner

11
PhDs COMPLETED



1 10-19

Immunology

The immune system includes cells called lymphocytes, a type of white blood cell, that defend the body from infections including bacteria, viruses and fungi as well as cancer. As we age, the immune system tends to weaken and this contributes to the increased risk of illness during old age. A weakened immune system also means that older people don't always respond fully to vaccinations.

By studying a combination of human samples and mouse models we aim to enhance our understanding of the role of lymphocytes in the immune system. We do this by examining:

- The mechanisms linking ageing to reduced response to vaccinations
- How lymphocytes interact with cells in the lungs to prevent infections
- How different molecular signals influence gene activity and ultimately the growth and behaviour of lymphocytes

Group leaders

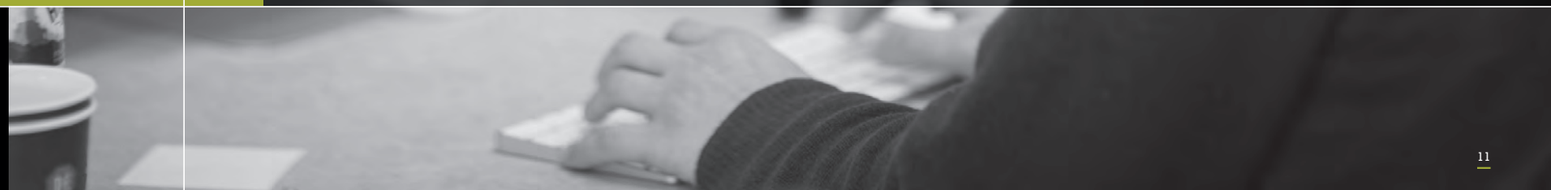
Martin Turner

Geoff Butcher

Michelle Linterman

Klaus Okkenhaug

Rahul Roychoudhuri



Martin Turner

Group members

Senior research associates:
Sarah Bell
Manuel Diaz-Munoz
(Left in 2017)

Postdoctoral researchers:
Elisa Monzon-Casanova
Cesare Sala
(Left in 2017)
Alexander Saveliev
Michael Screen
Ram Venigalla

PhD students:
Fengyuan Hu
Twm Mitchell
(Started in 2017)
David Turner

Visiting students:
Irene Salvia
Eugenie Werbenko

Research assistants:
Kirsty Bates
Vanessa D'Angeli
(Started in 2017)

The persistence and activation of lymphocytes

We study molecular mechanisms that regulate changes in gene expression needed to produce, maintain and activate cells, called lymphocytes, in the immune system. Our work focuses on the role of proteins that bind to messenger RNA – molecules that provide the essential intermediate step in information transfer from DNA to proteins. These proteins regulate how lymphocytes behave by exerting quantitative and qualitative control on messenger RNA.

Current Aims

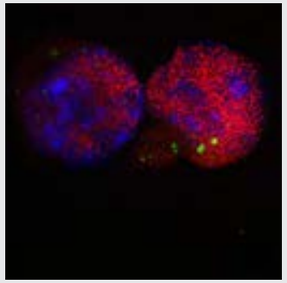
We study RNA binding proteins (RBPs) because they control gene expression firstly by regulating the abundance of the mRNA produced by a gene and secondly by controlling the types of mRNA produced through processes such as alternative splicing and polyadenylation. The activities of RBPs are regulated by systems that sense changes in the cellular environment. Moreover, these systems integrate signal transduction with epigenetic and transcriptional control (the rate at which mRNAs are produced) to enable dynamic changes in gene expression and the maintenance of stable cellular states. These are fundamental processes for all cells and our focus is on how RBPs regulate immunity.

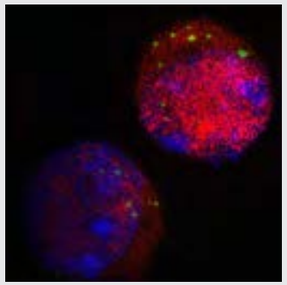
Progress in 2017

We showed that, in B cells, the RBP encoded by the Zfp36l1 gene was essential for the survival of a subset of B lymphocytes called Marginal Zone B cells. It suppressed genes normally expressed by other types of B cells and so contributed to the maintenance of cellular identity. We identified that another RBP, TIA1, binds to and suppresses mRNA encoding the tumour suppressor p53. DNA damage released p53 mRNA from control by TIA1. This led to an increase in p53 proteins as part of the DNA damage response. We also showed that the polypyrimidine tract binding protein was critical for the selection of B cells in the germinal centre. It regulated alternative splicing of genes needed for rapid B cell proliferation.

Selected Impact Activities

- Part of the EU H2020 COSMIC Consortium aiming to develop ways to combat diseases of the immune system
- Hosted projects for the Institute Schools' Day
- Developing a partnership with CRT and Celgene





Structured Illumination Microscopy (SIM) images for the RNA binding proteins ELAVI1 (red) and DCP1 (green) with DNA stained in blue in activated B lymphocyte cells

Publications

- Newman, R. *et al.* (2017) Maintenance of the marginal zone B cell compartment specifically requires the RNA binding protein ZFP36l1, ***Nat. Immunol.*** 18(6):683-693
- Díaz-Muñoz, M.D. *et al.* (2017) Regulation of mRNA translation and subcellular location controls protein synthesis of key modulators of the DNA damage response during B cell activation, ***Nat. Commun.*** 8(1):530. PMID: 28904350
- Monzón-Casanova, E. *et al.* (2018) The RNA binding protein PTBP1 is necessary for B cell selection in germinal centers, ***Nat. Immunol.*** 19, 267–278

www.babraham.ac.uk/our-research/lymphocyte/martin-turner

Geoff Butcher

Group members

Postdoctoral researcher:
John Pascall

Research assistant:
Silvia Innocentin

Maintaining a healthy immune system

Defending the body from disease requires an effective immune system with stable populations of mature T and B lymphocytes – types of white blood cells. A group of proteins called GIMAPs, play an important but ill-understood role in ensuring there are always enough of these cells. By studying GIMAPs we can improve our understanding of lymphocyte survival and discover new opportunities to treat certain diseases.

Scientific History

Dr Butcher is in the process of concluding his work on GIMAPs in preparation for retirement in 2019. Having joined the Institute in the late 1970s, he has led a group here since 1987 and served as Head of Immunology during the late 1990s.

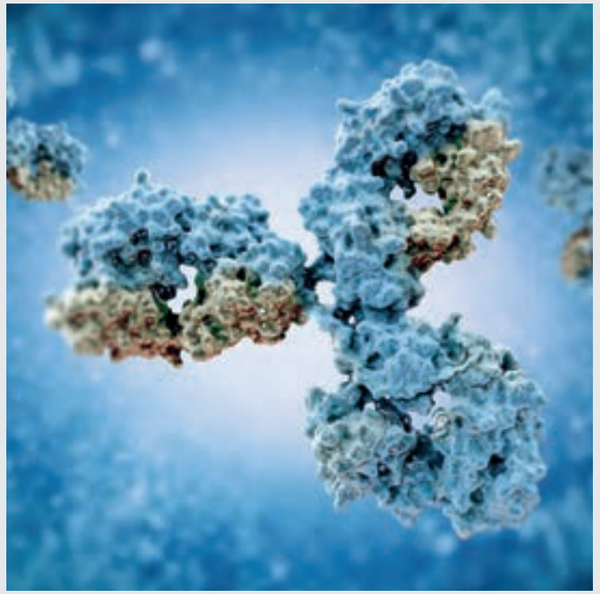
His group has made significant and long-lasting contributions to understanding the immune system and its role in human health. Amongst these, work with Jonathan Howard and Nobel Prize-winner César Milstein led to what became known as the first 'useful' monoclonal antibodies. For the first time homogeneous antibody reagents could be produced to specifically target any chosen molecule and were a key step towards revolutionary antibody therapies.

A second major contribution, again with Jonathan Howard, was the discovery of the TAP peptide transporter, which is involved in how cells alert CD8+ T lymphocytes to potential illnesses.

Progress in 2017

Recent work has concentrated on two of the GIMAPs. Work on GIMAP1 has shown that essentially all mature T and B lymphocytes are dependent on GIMAP1 for their survival. The investigation showed that losing GIMAP1 from lymphocytes leads to fatal damage, which appeared to be initiated inside mitochondria – the power plants of the cell. How GIMAP1 normally supports mitochondrial health is currently unknown.

Meanwhile, work on GIMAP6 demonstrated that it has a role in autophagy – a process of destruction often used to recycle old or damaged parts of a cell – inside lymphocytes. Its absence leads to an intermediate T lymphocyte deficiency. Like GIMAP1, it may also influence mitochondrial health by preventing autophagy from removing damaged or unnecessary mitochondria.



An artistic representation of an antibody

Publications

- Datta *et al.* (2017) Survival of mature T cells in the periphery is intrinsically dependent on GIMAP1 in mice. ***Eur J Immunol.*** 47:84-93
- Pascall *et al.* (2018) GIMAP6 is required for T cell maintenance and efficient autophagy in mice. ***PLoS ONE*** (accepted for publication).

www.babraham.ac.uk/our-research/lymphocyte/geoffrey-butcher

Michelle Linterman

Group members

Research fellow:
Alice Denton

Postdoctoral researchers:
Alexandre Bignon
(Left in 2017)
Edward Carr
Danika Hill
Wim Pierson
(Left in 2017)
Louise Webb

PhD students:
Marisa Stebegg
Alyssa Silva-Cayetano
Ine Vanderleyden

Visiting students:
Nathan Benac
(Left in 2017)
Clotilde Hennequin
(Left in 2017)

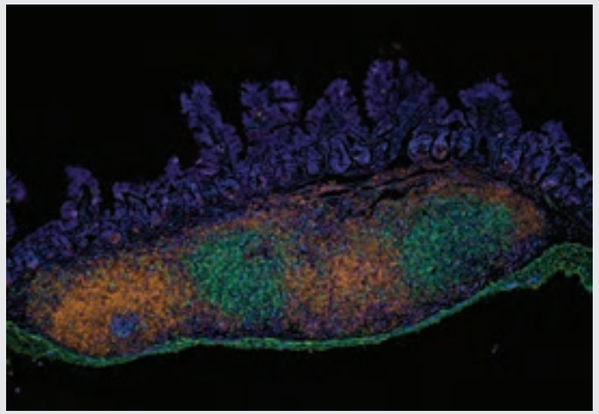
Research assistants:
Sigrid Fra-Bido
(Started in 2017)
Silvia Innocentin

How white blood cells respond to vaccination

Our ageing population creates a new challenge for medical science; to facilitate healthy ageing. With age, the function of the immune system declines, rendering older people more susceptible to infections and less able to benefit from vaccination. Our research aims to understand how the immune system changes with age, to determine if we can improve vaccination efficacy in older people.

Current Aims

At the heart of the immune response to vaccination is the germinal centre (GC) – a dynamic structure that forms in secondary lymphoid tissues (lymph nodes) after immunisation, and produces long-lived plasma cells and memory B cells. Plasma cells secrete antibodies that block pathogens from establishing an infection and memory B cells ensure long-term immunity. A defining property of the GC is the collaboration of multiple cell types: proliferating B cells, T follicular helper cells (Tfh), T follicular regulatory cells (Tfr) and follicular dendritic cells. Our research aims to understand the function of these cell types in a normal response to vaccination, and to determine how this changes with advancing age.



This image shows the localisation of different immune cells in a mouse Peyer's patch. Peyer's patches are lymphoid organs in the lining of the intestine. Here, B and T cells participate in the so-called germinal centre response to produce antibodies in response to the gut microbiota. Naïve B cells are shown in orange (anti-IgD), while proliferating cells – including germinal centre B cells – are blue (anti-Ki67). All T cells are stained green (anti-CD3) and regulatory Foxp3+ T cells can be recognised by their purple centre (anti-Foxp3).

Progress in 2017

In the past year our team has extensively characterised the cellular changes that occur in the GC response with advancing age in mice. We have been able to confirm our findings from animal models by running human influenza vaccination studies, and assessing the behaviour of human cells in culture. We have found that not all cell types are weakened in older individuals and we have shown that dendritic cells and CD4+ helper T cells have impaired activation with age. In the next year, we aim to understand the molecular basis that underpins reduced cellular function.

Selected Impact Activities

- Television interview with BBC Look East (West)
- Presentation of our human vaccination work to the public at the Cambridge BioResource Open evening
- Multiple presentations of our work at the 19th Germinal Centre Conference, Venice, Italy

Publications

www.babraham.ac.uk/our-research/lymphocyte/michelle-linterman

- Fonseca, V.R. *et al.* (2017) Human blood Tfr cells are indicators of ongoing humoral activity not fully licensed with suppressive function, ***Sci. Immunol.*** 2(14)
- Bignon, A. *et al.* (2017) Escherichia coli Heat-Labile Enterotoxin B Limits T Cells Activation by Promoting Immature Dendritic Cells and Enhancing Regulatory T Cell Function. ***Front. Immunol.,*** 8:560
- Vanderleyden, I. and Linterman, M.A. (2017) Identifying Follicular Regulatory T Cells by Confocal Microscopy. ***Methods Mol. Biol.*** 1623:87-93

Klaus Okkenhaug

Group members

Research fellows:
Anita Chandra
Andrew Conway Morris

Postdoctoral researchers:
Krishnendu Chakraborty
Fabien Garcon
(Left in 2017)
Birthe Jessen
(Left in 2017)
Amy MacQueen
(Left in 2017)
Priya Schoenfelder
Anne-Katrien Stark

PhD students:
Rafeah Alam
Christina Courreges
Fiorella Cugliandolo
Saad Idris
(Left in 2017)
Ai Hui Doreen Lau
Daisy Luff

Research assistant:
Bahram Firouzi
(Left in 2017)

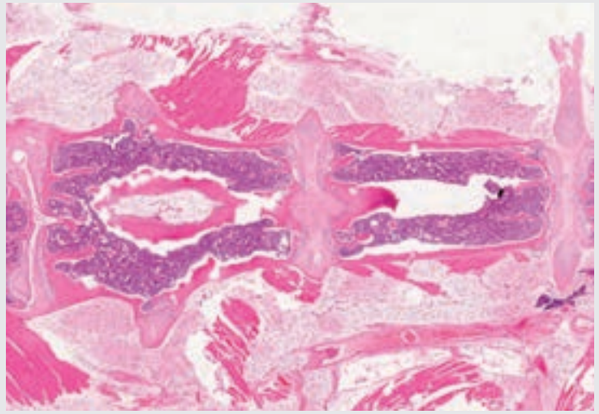
Klaus Okkenhaug has now left the Institute to take up the Chair of Immunology at the Department of Pathology, University of Cambridge. He is pleased to have spent 15 wonderful years at the Babraham Institute.

PI3K proteins in immunity, infection and cancer

The PI3K family of enzyme proteins control many aspects of immune function. PI3Ks are required for the normal development and survival of lymphocyte immune cells. They also allow the immune system to respond to and protect against infections and cancer. We aim to better understand how drugs that target specific PI3Ks can best be exploited for clinical benefit.

Current Aims

We aim to understand how the PI3Ks control the development and function of the immune system. Much of our work has focused on the role of the PI3Kδ isoform which is found in many cells of the immune system. PI3Kδ is the target for the drug Idelalisib which is now approved for the treatment of certain immune cell cancers affecting B cells. However, many questions remain about the impact of PI3Kδ inhibition on different types of cell in the immune system, both in health and diseases. Moreover, the recent discovery of patients with a primary immunodeficiency syndrome (called APDS) caused by over activation of PI3Kδ raises further questions about the physiological role of this enzyme.



Mouse bone marrow stained for hematoxylin and eosin. The image contains mutated B lymphocytes that cause lymphomas.

Progress in 2017

We have developed a mouse model of APDS and shown that it reproduces many aspects of the human disorder.

This has allowed us to identify cellular and biochemical mechanisms that contribute to immunodeficiencies in APDS. In parallel, our colleagues at GSK have initiated a clinical trial using their PI3Kδ inhibitor nemiralisib. This demonstrates the relevance of our work using genetic models to inform the development and use of novel therapeutics.

Selected Impact Activities

- Wellcome Trust Clinical Fellowships for Anita Chandra and Andrew Conway Morris
- Klaus Okkenhaug appointed as Professor of Immunology at the University of Cambridge
- Organised Keystone Meeting: PI3K Pathways in Immunology, Growth Disorders and Cancer

Publications

https://www.path.cam.ac.uk/directory/klaus-okkenhaug/

- Coulter, T.I. *et al.* (2017). Clinical spectrum and features of activated phosphoinositide 3-kinase delta syndrome: A large patient cohort study. J ***Allergy Clin. Immunol.*** 139, 597-606 e594
- Kishore, M. *et al.* (2017). Regulatory T Cell Migration Is Dependent on Glucokinase-Mediated Glycolysis. ***Immunity*** 47, 875-889 e810
- Mauro, C. *et al.* (2017). Obesity-Induced Metabolic Stress Leads to Biased Effector Memory CD4(+) T Cell Differentiation via PI3K p110delta-Akt-Mediated Signals. ***Cell Metab.*** 25, 593-609

Rahul Roychoudhuri

Group members

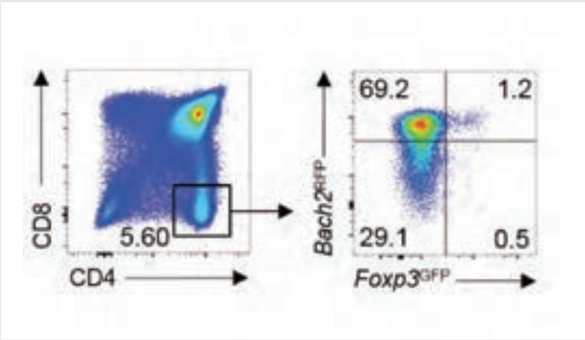
Postdoctoral researchers:
Teresa Lozano
(Started in 2017)
Rabab Nasrallah

PhD students:
Francis Grant
Charlotte Imianowski
(Started in 2017)
Firas Sadiyah

Visiting researchers:
Shaun Png
(Left in 2017)
Michaela Pucci
(Left in 2017)
Panagiota Vardaka
(Started in 2017)

Volunteer:
Melanie Stammers
(Left in 2017)

Moderating the reactions of the immune system



Flow cytometry results showing different amounts of proteins inside individual cells. Bach2 and Foxp3 are both proteins that control gene expression in cells called CD4+ thymocytes when they begin specialising to become Treg cells. Both proteins play essential roles in the development of Treg cells. Appropriate development and maintenance of Treg cells populations is required throughout the lifecourse to prevent otherwise lethal inflammation.

Effector T cells (Teff) of the immune system can prevent infections and cancer but they can also cause autoimmune and allergic inflammation. These harmful responses are restrained by tolerance mechanisms, which prevent harmful and potentially lethal inflammatory responses. While tolerance mechanisms are beneficial, a similar process – called immunosuppression – restricts the immune system's ability to tackle chronic infections and cancer. We study molecular mechanisms of tolerance and immunosuppression, their effects as we age and their roles in disease.

Current Aims

1. To determine the control processes that influence gene expression and guide the production of the cells involved in tolerance and immunosuppression, called regulatory T (Treg) cells
2. To establish the role of enhancers in cell type-specific gene expression and regulation of the production and function of Treg and effector T (Teff)
3. To understand how Teff cells are regulated and constrained by their surroundings, particularly in immunosuppressed tissues such as within tumours

Progress in 2017

An international collaboration with scientists in the US and UK has led us to discover a human disease called BACH2-related immunodeficiency and autoimmunity (BRIDA). This disease results from changes to the BACH2 gene, which we found is required for the differentiation of Treg cells and long-lived memory cells.

We have developed tools to monitor key factors involved in early and late Treg cell specification at a single-cell level (see figure) and examined epigenetic factors involved in this process. We have gained insights into how dysfunction of T cells and myeloid cells contributes to immunosuppression. We are developing powerful CRISPR-Cas9 based approaches to systematically examine the control of T cell functions.

Selected Impact Activities

- We were awarded a Lister Institute Research Prize recognising the medical significance of our work on tolerance
- We received funding from Cancer Research UK (CRUK) to support collaboration between the Institute and CRUK-Therapeutic Discovery Laboratories to develop new therapies
- We hosted students as part of Schools' Day, using flow cytometry to spot the differences between groups of cells

Publications

www.babraham.ac.uk/our-research/lymphocyte/rahul-roychoudhuri

- Afzali, B. *et al.* (2017) BACH2 immunodeficiency illustrates an association between super-enhancers and haploinsufficiency. ***Nat Immunol*** 18:813-823
- Igarashi, K. *et al.* (2017) BACH transcription factors in innate and adaptive immunity. ***Nat Rev Immunol*** 17:437-450

Vaccinations: a Global Challenge

The Institute's research is having a major impact on global public health. Although the first vaccines were developed more than two centuries ago, infectious diseases such as malaria and influenza still affect millions of people each year. By improving our understanding of the immune system and its response to modern vaccines, the Institute is paving the way for better vaccines that will protect more people from life-threatening diseases.

When it comes to human health, our immune system is our most important defence against illness and disease. Producing antibodies is one of the ways that the immune system counteracts pathogens – the causes of illness. Yet, this system is not perfect. Sometimes the body produces antibodies against the wrong things – resulting in allergies, autoimmune diseases and organ rejection – while at other times it fails to produce enough antibodies to fight infections including malaria and influenza. And as we age, our immune system becomes less adept at combatting infection and responding to vaccination.

As well as being extraordinarily powerful, our immune system is amazingly complex and continues to pose significant scientific challenges. Key among these is how to design 'flu vaccines that are more effective in an ageing population, and how to boost the efficacy of vaccines to prevent malaria. Dr Michelle Linterman, a Group Leader in the Institute's Immunology research programme, is making important advances in both.

"One of our major goals is to improve vaccine efficacy as we age. The seasonal 'flu vaccine provides 80% protection against infection if you're aged between 18 and 60. Over the age of 60 vaccine efficacy decreases – and for people over 70 it's only 25% effective," she explains. "This does not mean that older people shouldn't get vaccinated, because complications associated with 'flu can be very serious. But it does mean there's an opportunity to improve the way these vaccines work for older persons."

Part of the problem arises from how clinical trials have traditionally been run. Almost all immunology research – including vaccine trials – is done in young animals and people; what's lacking is research in the populations that vaccines most need to protect. This is true not only of 'flu but in malaria too.

Most malaria vaccine trials are run in European populations, and success here often fails to translate to those in most need – the people who live in malaria-endemic areas.

Most vaccines provide protection against infection via production of antibodies, the proteins our immune cells secrete. In 'flu, for example, these antibodies bind to the virus and prevent it from infecting our cells. At the same time, antibodies signal to other immune cells to destroy the virus. Our immune systems are very diverse, which helps to protect us from pandemics, but complicates vaccination programmes as individual responses to vaccines are very variable.

What's needed is more cleverly-designed trials, which is exactly what Michelle and her team are doing in both Cambridge and East Africa. To design better 'flu studies, she's using the Cambridge Bioresource, a unique panel of 17,000 volunteers willing to take part in research and who have already donated DNA.

'Our immune system is amazingly complex and continues to pose significant scientific challenges'

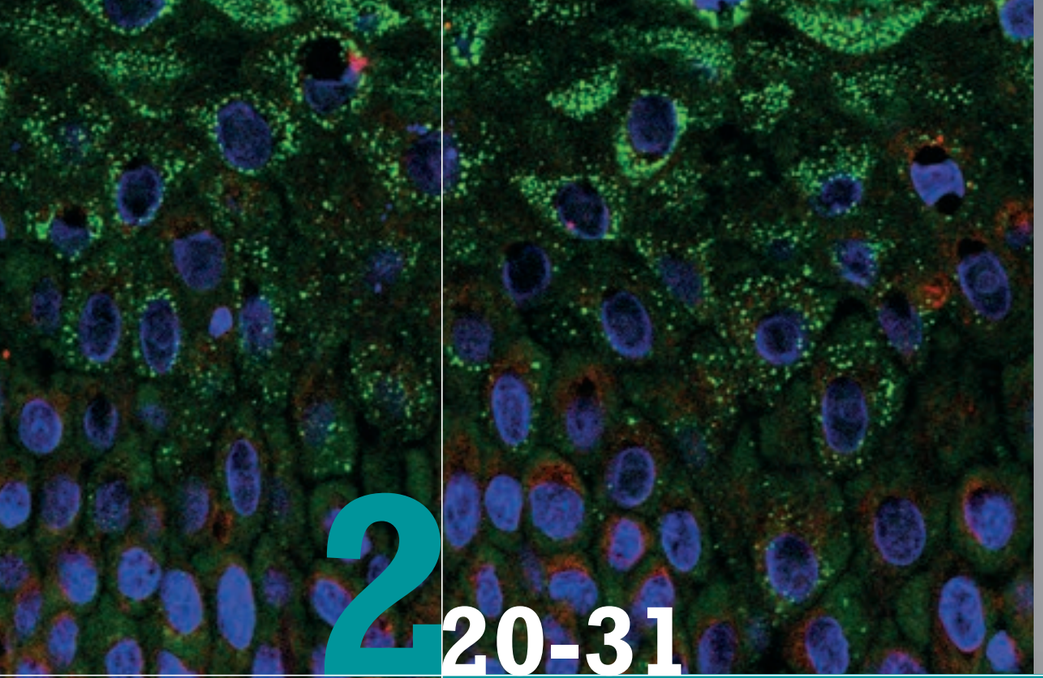
"The Cambridge Bioresource is a phenomenal research resource; it allows us to design much smarter studies because we can select people with particular genotypes and recruit people to studies much more quickly than before."

These studies are revealing why older people produce fewer antibodies after 'flu vaccination, opening up new ways of making vaccines more effective. "We've run two studies showing that the T cell response is impaired," she says. "And now we know where the cellular defect lies, it should be possible to change the adjuvants – the ingredients in vaccines that stimulate the immune system – to boost these T cells."

Thanks to support from the Global Challenges Research Fund, Michelle is working on large-scale collaborative vaccine trials in malaria-endemic Tanzania and Mozambique. Her aim is to understand – in immunological terms – why people respond so differently to existing malaria vaccines, and discover whether new adjuvants could make malaria vaccines more effective. After analysing samples from children vaccinated with RTS,S (which is the best malaria vaccine on the market but one with plenty of room for improvement), the team uncovered important differences in the immune cells of children who respond well to the vaccine compared with those who do not. They also made new discoveries in the adjuvant trials.

"We've just finished a study in young Africans that clearly shows that a new adjuvant does a good job of boosting T cells," she concludes. "Being involved in trials of new adjuvants is very exciting. Our research shows that these adjuvants could help boost the T cell response after vaccination in older people, and it illustrates that our fundamental science is crucial to delivering better vaccines across the world."

'Our fundamental science is crucial to delivering better vaccines across the world'



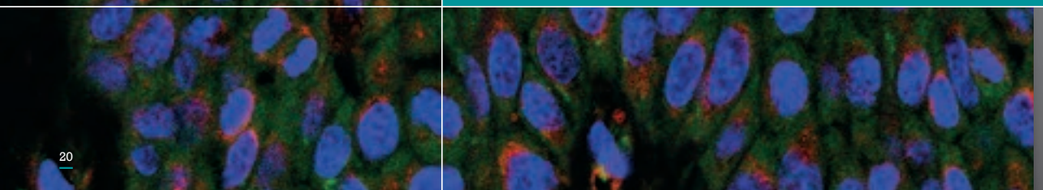
2 20-31

Signalling

The process of cell signalling consists of several interconnected mechanisms that allow cells to communicate, co-ordinate and respond rapidly to change. By examining these signalling mechanisms and their interactions we seek to understand the effects of signalling on cell growth, survival and behaviour.

Our current focus is to discover the role that signalling has in helping cells to respond and adapt to damage, illness, dietary changes and ageing by investigating:

- How cells called neutrophils detect and respond to infections
- How changes in diet affect metabolism and growth
- The effect of signalling mechanisms on the rate of ageing
- The role of autophagy in recycling cell components following damage or starvation



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Nicholas Ktistakis

Nicolas Le Novère

Michael Wakelam

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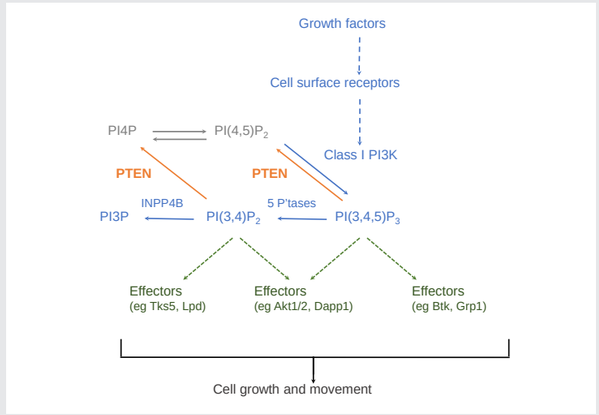
PI3K enzyme signalling within cells

Signalling pathways are biological systems that allow cells to communicate and respond to changes in their surroundings. This can include changes in the levels of hormones, growth factors or nutrients. One such signalling pathway involves the production of chemical signals called PI(3,4,5)P3 and PI(3,4)P2 by proteins called phosphoinositide 3-kinases (PI3Ks). This pathway plays a major role in the regulation of growth, metabolism, and immunity, and changes to this pathway are seen during ageing and in various human cancers.

Current Aims

Our work covers three aspects of PI3K signalling.

1. Understanding how phosphatase enzymes regulate signal strength and duration by reducing levels of PI(3,4,5)P3 and PI(3,4)P2.
2. Examining the differences between PI3K isoforms to inform pharmaceutical organisations (GSK, AstraZeneca & Karus Therapeutics) hoping to develop anti-inflammatory/anti-cancer drugs that target PI3Ks.
3. Investigating the chemical details of why PI(3,4,5)P3 and PI(3,4)P2 have such significant effects inside cells. In addition, we are developing mass spectrometry approaches to better measure PI(3,4,5)P3 and PI(3,4)P2 for research and clinical purposes.



An outline of the PI3K signalling pathway. Stimulation of PI3K by receptor proteins leads to the conversion of PI(4,5)P2 to PI(3,4,5)P3. Phosphatase enzymes convert PI(3,4,5)P3 back to PI(3,4)P2 or to PI(4,5)P2. The balance of these molecules affects how a cell behaves. The PTEN protein primarily acts as a 3-phosphatase, limiting PI(3,4,5)P3 levels. Loss of PTEN increases PI(3,4,5)P3 leading to excessive growth signalling and cancer. We have now shown that PTEN also acts as a PI(3,4)P2 phosphatase and we plan to look at the role of PI(3,4)P2 in tumours.

Progress in 2017

We have identified a role for the tumour suppressor PTEN as a major regulator of PI(3,4)P2 levels (See figure). By investigating different PI3K isoforms, we have uncovered some key properties that allow growth factors to selectively activate PI3Kα and β in fibroblast cells, and revealed how inflammatory stimuli activate PI3Kγ in neutrophil immune cells. We are also beginning to understand the roles of several proteins in the creation of new, and the recycling of existing, PI lipid molecules involved in PI3K signalling. Finally, we have worked with other researchers and companies to measure PI(3,4,5)P3 levels in different contexts both for research and clinical trials.

Selected Impact Activities

- Presented our work at four international conferences and several UK and EU universities
- We collaborated with pharmaceutical organisations (GSK, AstraZeneca, Karus) and academic groups in four different countries
- Took part in the Institute Schools' Day giving student groups the chance to get hands-on with research in the lab

Publications

www.babraham.ac.uk/our-research/signalling/len-stephens /phillip-hawkins

- Malek, M. *et al*. (2017) PTEN Regulates PI(3,4)P2 Signaling Downstream of Class I PI3K. ***Mol. Cell.*** 68: 566-580
- Durrant, T.N., Hutchinson, J.L. *et al*. (2017) In-depth PtdIns(3,4,5)P3 signalosome analysis identifies DAPP1 as a negative regulator of GPVI-driven platelet function. ***Blood Adv***. 1:918-932
- Cerny, O. *et al*. (2017) cAMP Signaling of Adenylate Cyclase Toxin Blocks the Oxidative Burst of Neutrophils through Epac-Mediated Inhibition of Phospholipase C Activity. ***J Immunol***. 198:1285-1296

Simon Cook

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Signals controlling cell fate decisions

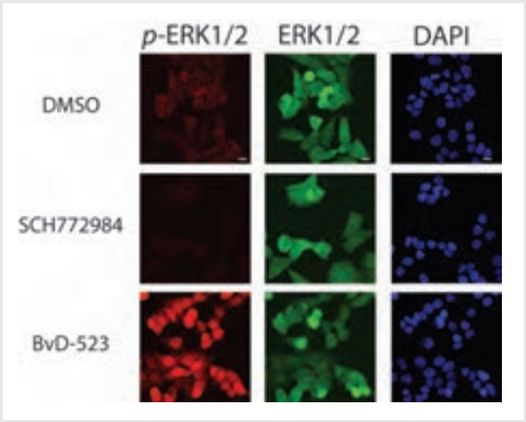
Information from a cell's surroundings contribute to how it behaves and how it will change in the future – called cell fate decisions. Proteins called protein kinases influence cell fate decisions – whether to divide, change cell type or die – by transmitting information from the outside into the cell. We are interested in how protein kinase pathways function, how they are controlled and how they determine cell fates.

Current Aims

Our current work is focused on studying two particular protein kinase families: the extracellular signal-regulated kinases (ERKs, such as ERK1/2) and the related dual-specificity tyrosine phosphorylation-regulated kinases (DYRKs, such as DYRK1B and DYRK2). These protein kinases affect the cell by regulating other specific proteins (substrates), changing their properties (activity, location, binding partners). We want to understand how the ERKs and the DYRKs control cell fate decisions by defining how their activity is controlled, where in the cell they function and by identifying the substrates (proteomics) and the gene expression programmes (genomics) that they control.

Progress in 2017

It is increasingly important to understand where in the cell protein kinases function. To do this we have used a novel chemical biology approach in which a very selective ERK1/2 inhibitor that becomes fluorescent inside cells allows us to directly visualise ERK1/2 in cells. ERK1/2 signalling seems to be key in determining whether, and how, cells die. For example, the accumulation of damaged or misfolded proteins can drive cells to undergo programmed cell death by apoptosis. We have found that ERK1/2 signalling protects cells against apoptosis by supporting the production of pro-survival proteins. In new work, we have identified a range of DYRK substrates and are investigating their role in the clearance of damaged and misfolded proteins. Damaged proteins accumulate in our cells as we grow old and in some diseases so we are working with pharmaceutical companies to help guide their drug discovery efforts.



Representative high-content microscopy (HCM) images showing the rapid nuclear accumulation of p-ERK1/2 (red) following 2h treatment of HCT116 cells with the catalytic ERK1/2 inhibitor (ERKi) BvD-523. In contrast, the dual-mechanism ERKi SCH772984 effectively inhibits ERK1/2 phosphorylation. The nucleus is stained with DAPI (blue) and a total ERK1/2 (green) control is shown. Image: Dr Andrew Kidger, Cook lab.

Selected Impact Activities

- RAS pathway drug discovery collaboration with PhoreMost funded by Innovate UK. Accompanying KEC blog by Rebecca Gilley
- Industrial collaborations on ERK inhibitors (Astex Pharmaceuticals), MEK inhibitors (AstraZeneca) and ubiquitylation (MISSION Therapeutics)
- Hosted two teachers (Helen Penketh and Sarah Hyland) on a STEM Insight placement

Publications

www.babraham.ac.uk/our-research/signalling/simon-cook

- Sipthorp, J. *et al*. (2017) Visualisation of Endogenous ERK1/2 in Cells with a Bioorthogonal Covalent Probe. ***Bioconjug. Chem.*** 28:1677-1683
- Cook S. *et al*. (2017) Control of cell death and mitochondrial fission by ERK1/2 MAP Kinase signalling. State-of-the-art review. ***FEBS Journal*** 284:4177-4195
- Darling, N.J. *et al*. (2017) ERK1/2 signalling protects against apoptosis following endoplasmic reticulum stress but cannot provide long-term protection against BAX/BAK-independent cell death. ***PLoS One*** 12(9): e0184907

Oliver Florey

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Autophagy pathways: cell eating from inside and out

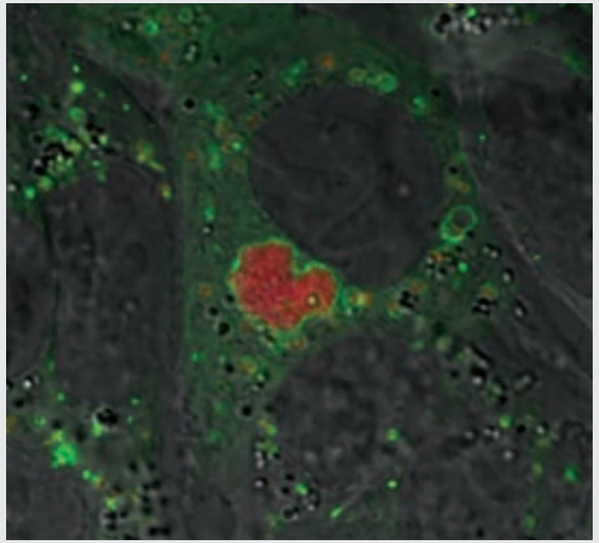

Image shows a MEF cell – a type of cell that is easy to grow and study in the lab – targeting an autophagy protein called LC3 (green) to a phagosome housing a dead cell (red). Phagosomes, approximately meaning 'eaten body', are structures in cells that contain things that have been brought in from outside the cell.

Cells need to be able to break down and recycle parts of themselves, a process called autophagy, so they can stay healthy. Disruption of this process is associated with many age-related effects, including cancer and neurodegeneration. Our research explores the molecular mechanisms underlying autophagy and several similar pathways to understand their roles in health and disease.

Current Aims

We are continuing our key goal of understanding the upstream regulation and downstream consequences of a 'non-canonical' autophagy pathway, which utilises some of the molecular machinery used in autophagy to target external material eaten by cells, such as pathogens and dead cells. This impacts many important processes within the cell. Using innovative reagents and strategies developed in our lab, we are now exploring the role of this pathway in the immune system and extending our knowledge of its regulation. The future hope is that we can manipulate the pathway for therapeutic benefit.

Progress in 2017

The lab has had a great year, publishing papers that extend our understanding of how cancer cells cannibalise each other and the unconventional autophagy pathway that regulates many important processes in the cell, including how the immune system responds to pathogens – the causes of illness.

Selected Impact Activities

- Publication in *eLife* on cell cannibalism in cancer featured in a number of science blogs and magazines
- Dr Joanne Durgan attended a Climate Reality Leadership Corps training seminar in Pittsburgh USA. She is now initiating a Green Labs initiative at the Babraham Institute
- Katherine Fletcher, a PhD student in the lab, took part in a range of public engagement activities including poster presentation sessions for Cambridge Academy for Science & Technology

Publications

- Durgan, J. *et al*. (2017) Mitosis can drive cell cannibalism through entosis. ***eLife***, 6:e27134
- Jacquin, E. *et al*. (2017) Pharmacological modulators of autophagy activate a parallel noncanonical pathway driving unconventional LC3 lipidation. ***Autophagy***, 13:854-867
- Fletcher, K. *et al*. (2017) The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes. ***EMBO J.***

www.babraham.ac.uk/our-research/signalling/oliver-florey

Nicholas Ktistakis

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Dynamics of autophagy in animal cells

Through a process called autophagy, cells are able to digest parts of themselves as a way to repair damage or to provide a source of nutrients to help survive starvation. My group aims to understand how this pathway is triggered and what the molecular details of the autophagic response are.

Current Aims

By screening many different chemicals, we have identified one with a role in autophagy. We are in the process of establishing how this chemical alters the dynamics of mitochondrial autophagy (mitophagy) in mammalian cells. We are also examining how autophagy is modulated during the differentiation of stem cell-like iPS cells into neuronal lineages – nerve and brain cells. As part of this work we have generated iPS cells with changes to their genes which affect the autophagy process.

Progress in 2017

We have made use of a combination of genetic experiments, live imaging and super resolution microscopy to study mitophagy. Our work has established a clear order for the activation of key cell components involved in the early stages of autophagy and mitophagy. In collaboration with the group of Eeva Liisa Eskelinen in Finland, we have reconstructed electron microscopy data to reveal the rearrangements of cell membranes that happen during mitophagy. Drawing on images from living cells we're also working in collaboration with the group of Nicolas Le Novère here at the Institute. We are generating computer models of autophagy and using these to compare between non-selective and selective autophagy processes.

Selected Impact Activities

- Gave invited talks in Germany, Canada, Finland, Japan, Croatia, Argentina and the UK on autophagy regulation
- Hosted the Economics Minister of Greece at the Babraham Institute to discuss the success of the Babraham Research Campus in fostering academic and commercial innovation
- Dr Ktistakis is the President of the Cambridge Hellenic Learned Society (consisting of academics and professionals of Geek/Cypriot origin) that organises seminars and other activities throughout the year

Similarities and differences between non–selective and selective autophagy. In both cases, a new compartment forms in the cell surrounding other existing cell components. This is akin to the soap bubble on the left or the tarpaulin cover on the right. Non-selective autophagy generates a randomly sized 'bubble', called an autophagosome that engulfs material indiscriminately. By contrast, selective autophagy has a specific target in the cell, and generates an autophagosome that precisely fits around that target so that it can be isolated from the rest of the cell and efficiently broken down for recycling. Credits: pixabay and yes2tech on Instructables.com

Publications

- Karanasios, E. *et al*. (2016) Autophagy initiation by ULK complex assembly on ER tubulovesicular regions marked by ATG9 vesicles. ***Nat. Commun.*** 7:12420
- Manifava, M. *et al*. (2016) Dynamics of mTORC1 activation in response to amino acids. ***eLife***. 5. pii: e19960
- Walker, S.A. *et al*. (2017) Correlative Live Cell and Super Resolution Imaging of Autophagosome Formation. ***Methods Enzymol***. 587:1-20
- Florey, O. & Ktistakis, N.T. (2017) editors Autophagy Protocols (46 authors). ***Methods Mol. Biol.*** in press

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Nicolas Le Novère

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Modelling biological systems

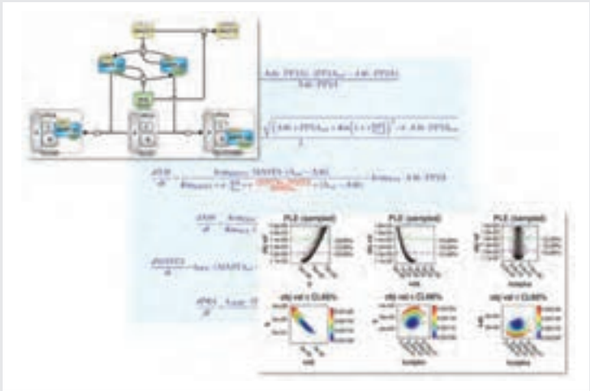
Complex behaviours of biological systems arise from the ever-changing interactions of their many parts. To understand this behaviour and the effect of various changes including ageing and disease, we need to consider these systems as a whole. This is only possible using computers to analyse large amounts of data, and simulate mathematical models reproducing the systems. Our particular interest lies in examining links between cell signalling, metabolism and epigenetics.

Current Aims

Our work focuses on two main topics. First, the regulation of intracellular signalling, in particular examining how cells decode calcium, cAMP and phosphoinositides signals and how they decide on the correct response to these signals. And second, the interplay between metabolism and epigenetic regulation of genes i.e. how changes to the availability of metabolites and energy in the cell regulate the expression of genes, during development, tissue repair and ageing. We study these processes in a range of biological models, including embryonic stem cells, heart cells and neurons. In addition, we develop software tools to improve the building and sharing of mathematical models and numerical simulations.

Progress in 2017

In collaboration with Yale University, we uncovered a signalling switch that responds to cAMP signals in neurons from the part of a brain involved in reward and locomotion. Combining biochemical approaches and mathematical modelling, we identified a switch-like mechanism for inhibiting or activating a key regulatory protein, called Protein Phosphatase A (see figure). We also launched a community effort to reconstruct the entire metabolism of the nematode worm *C. elegans*. Together with gene expression, protein and metabolite measurements, the resulting model is expected to be a key resource to investigate the impact of metabolism on epigenetics and ageing.



Mathematical model of a bi-stable switch regulated by cAMP chemical signals and regulating protein phosphatase 2A function. Upper-left, a schematic view of the biological components of the switch showing how cAMP molecules work with ARPP-16, MAST and PKA proteins to regulate Protein Phosphatase A. Background, equations describing the relationships between MAST, PKA and two states of ARPP-16. Lower-right, experimental measurements used to estimate some of the values needed for the equations, calculated using our software Sbpipe.

Selected Impact Activities

- Coordinated the Systems Modeling Community of Special Interest of the International Society for Computational Biology
- Participated in an eLife Community Webinar aimed at early career researchers
- Released of over 6,000 patient specific computational models of tumour metabolism, free through the BioModels database

Publications

http://lenoverelab.org

- Malek, M. *et al*. (2017) PTEN regulates PI(3,4)P2 signalling downstream of class I PI3K. ***Mol. Cell***. 68(3): 566-580
- Diaz-Muñoz, M.D. *et al*. (2017) Tia1 dependent regulation of mRNA subcellular location and translation controls p53 expression in B cells. ***Nat. Commun.*** 8:530
- Musante, V. *et al*. (2017) Reciprocal regulation of ARPP-16 by protein kinase A and MAST-3 kinase provides a cAMP-regulated switch in protein phosphatase 2A inhibition. ***eLife*** 6: e24998

Michael Wakelam

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Understanding how fats keep us healthy

Fat molecules, also called lipids, play many roles inside and outside of cells. For example, they act as barriers, carry signals and are energy sources. Amongst other things, lipids are signals that help cells to respond to changing diet, infections and ageing. By using a range of methods to examine different lipids inside and outside of cells we aim to enhance our understanding of the varied roles they perform.

Current Aims

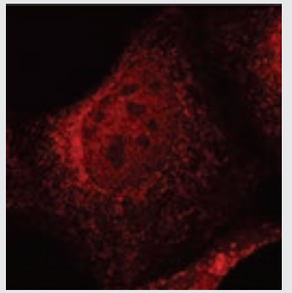
We research how lipids inside and outside of cells drive signalling and metabolic pathways that are necessary for cells to survive in response to changes such as the loss of nutrients, the loss of oxygen, and viral infection. We're also studying how cells maintain the correct levels of lipid needed for healthy ageing.

Progress in 2017

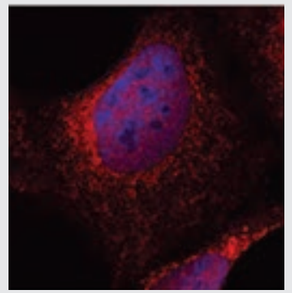
Dietary restriction (DR) involves limiting the food intake of an animal. We have shown that DR – an extensively documented condition that extends lifespan in a variety of organisms – alters the lipid profile of the mouse liver. DR causes a decrease in lipid content in cells. In addition, the lipids that are synthesised contain smaller fatty acid molecules – ones with shorter chains of carbon atoms. This helps to explain why DR protects ageing animals from the ill effects of fat accumulation.

In collaboration with Professor Jane McKeating in Oxford, we have also discovered that a lipid called lysophosphatidic acid, which is made outside cells, supports the replication of hepatitis C virus in liver cells particularly when they are deprived of atmospheric oxygen.

ACSS2



ACSS2 + DAPI



Microscopy imaging of the ACSS2 protein (red) in HEK-293 cells, a type of human cells often studied in the lab. ACSS2 is a key enzyme that acts at an early step in the synthesis of lipids and is found throughout cells. Images were taken using the Nikon A1R confocal microscope at 60x magnification. DAPI was used to show DNA in the cell nucleus (blue). Scale bar 0.05 mm. Image credit: Dr Arsalan Azad.

Selected Impact Activities

- Represented the Babraham Institute partnership with the Cambridge Academy for Science and Technology, through the design and provision of an employer-led three-month learning Challenge Project
- Hosted four summer students (Nuffield, sixth-form and University undergraduates)
- Industrial collaboration on autotaxin inhibitors with Cancer Research Technology

Publications

www.babraham.ac.uk/our-research/signalling/michael-wakelam

- Hartler, J. *et al*. (2017) Deciphering lipid structures based on platform-independent decision rules. ***Nat. Methods***. 12:1171-1174
- Hahn, O. *et al*. (2017) Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. ***Genome Biol***. 18, 56
- Farquhar, M.J. *et al*. (2017) Autotaxin-lysophosphatidic acid receptor signalling regulates hepatitis C virus replication. ***J Hepatol***. 66, 919-929

Heidi Welch

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Cell signalling through Rho-GTPase and GEF proteins

Proteins known as Rho-GTPases are molecular switches that enable cells to move through their surroundings. We study how these Rho-GTPases are controlled, particularly by other proteins called GEFs that switch them on. Our recent research has identified new roles of GEFs in the immune system and in cancer. In addition, we have made progress in understanding how GEFs are controlled and we developed tools for monitoring Rho-GTPase activity inside cells.

Current Aims

We previously discovered a family of GEF proteins that we called P-Rex. We have described how one of these proteins, P-Rex1, controls how white blood cells are drawn to the site of an infection and help to fight the disease once they arrive.

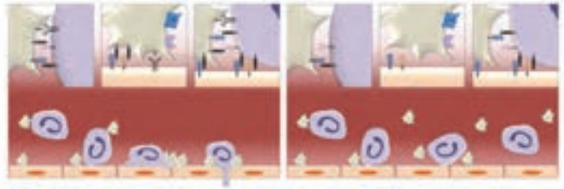
P-Rex1 and other GEFs inside blood platelet cells play surprisingly large roles in these processes (see figure). Our current aim is to evaluate the importance of a protein called Norbin – a regulator of P-Rex1 which we recently identified – in controlling defence against infections. We are also investigating the functions of other GEFs in the immune system, studying the roles of P-Rex GEFs in metabolism, and developing new methods for monitoring GEF activity.

Progress in 2017

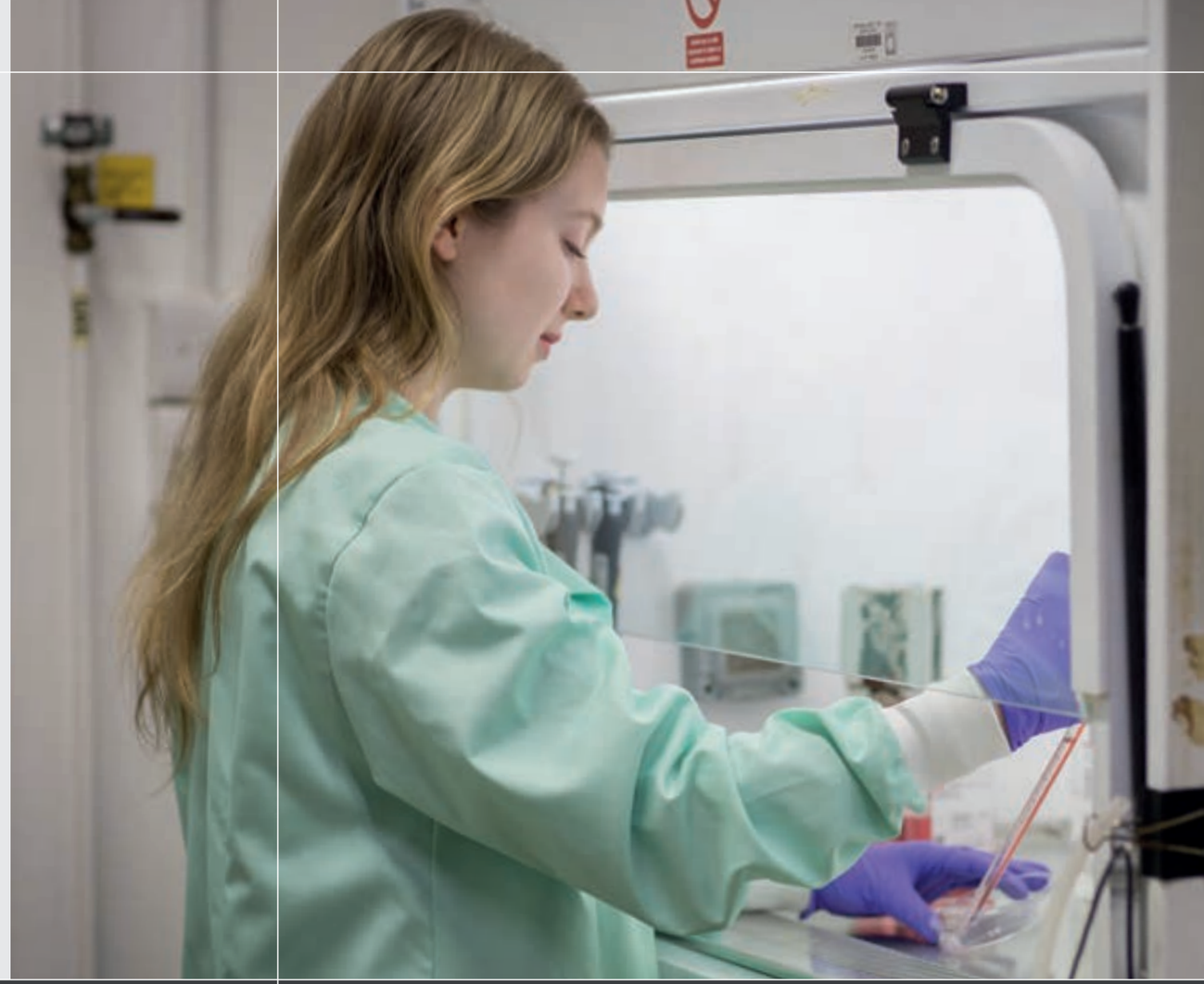
We recently generated a mouse model that allows us to monitor the activity of Rac – a type of Rho-GTPase protein – in real time within living cells and tissues. One of our projects involved helping our collaborators to establish a similar mouse model for monitoring the activity of the related Rho-GTPase called RhoA. This work showed that RhoA is mostly active at the rear of migrating white blood cells, its activity increases as the cells approach sites of infection, and the activity oscillates throughout the cell during migration in a similar way to Rac activity.

Selected Impact Activities

- Awarded a BBSRC iCASE PhD studentship in collaboration with Vernalis Research Ltd, Cambridge
- Presented to the PhD Training Programme, Biomedical Center, Ludwig Maximilian University Munich, Germany, Nov 2017
- Ran a 'prep you own DNA and test your ancestry by PCR' lab on Schools' Day 2017



Platelet GEFs control the tissue recruitment of white blood cells. GEF proteins P-Rex1 and Vav activate platelets and make them become sticky during inflammation and infections. The sticky platelets glue themselves to white blood cells and to the blood vessel wall. These sticky platelet bridges enable the white blood cells to move into infected tissues to fight germs. Platelets without P-Rex1 and Vav cannot do this, so white blood cells cannot reach infected tissues, which can cause immunodeficiency. However, the lack of platelet glue also reduces overall inflammation which can help by improving inflammatory conditions such as allergic reactions.



Publications

www.babraham.ac.uk/our-research/signalling/heidi-welch

- Hornigold, K. *et al*. P-Rex1. Encyclopedia of Signaling Molecules, 2nd Edition, Ed. ***S Choi***. in press
- Pitchford, S. *et al*. (2017) Platelets in neutrophil recruitment to sites of inflammation. ***Curr. Opin. Hematol***. 24:23-3
- Nobis, M. *et al*. (2017) A RhoA-FRET biosensor mouse for intravital imaging in normal tissue homeostasis and disease contexts. ***Cell Rep***. 21:274-288

Making the Most of Signalling Research

Bringing together the Institute's researchers with scientists in the 60 companies on the Babraham Research Campus is helping turn innovative ideas into new benefits for human health – fast. Over the past two years, members of the Signalling research programme have transformed a conversation over coffee into a collaboration that could deliver new ways of treating some of the most intractable human cancers.

As Dr Simon Cook has discovered, caffeine can be a powerful catalyst. In the past 18 months, what began as a conversation over coffee with scientists from PhoreMost – one of the 60 biotech companies that share the Babraham Research Campus – has developed into a collaboration that could yield new ways of treating some of the most intractable human cancers.

Simon, a group leader in the Institute's Signalling research programme, works on protein kinases. By attaching phosphate groups to cellular proteins, these enzymes help to form our cells' communication system, switching on and off their most basic functions – from surviving or dying to dividing and differentiating.

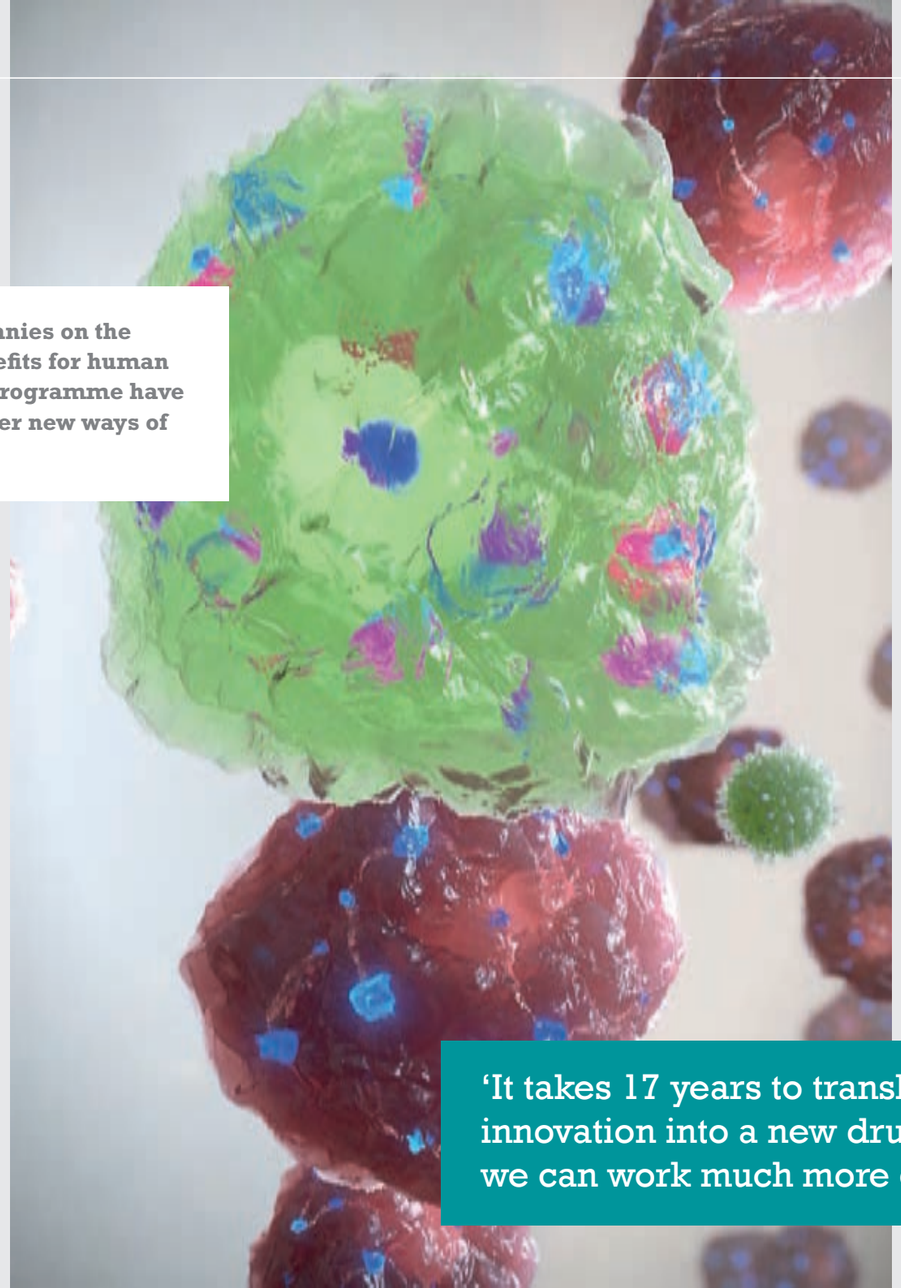
"We've been interested in one of these pathways, called ERK, for many years," he says, "partly because we want to understand its basic biology – how it controls cell division, survival and differentiation – but also because the gene that controls this pathway, KRAS, is one of the most common oncogenes in human cancer."

In fact, KRAS mutations are responsible for almost 30% of all human cancers, including 25% of non-small cell lung cancer, 40% of colorectal cancer and up to 90% of pancreatic cancer, which remains one of the hardest of all cancers to treat. But although scientists have known for more than 30 years that mutations in KRAS cause cancer, they have struggled to develop drugs that inhibit KRAS.

The biggest barrier is KRAS's biochemistry. "It's properties are unique. It binds to a co-factor called GTP, which in an ideal world would make a good drug target," Simon explains. "But the affinity with which it binds is so tight – and it's such a small protein – that it's always been viewed as un-druggable."

All that could be set to change thanks to the unique environment of the Babraham Research Campus. Just metres away from Simon's lab – which has over 25 years experience in KRAS biology – is the innovative drug discovery company PhoreMost. Spun out of the University of Cambridge in 2014, PhoreMost has developed a completely new way of screening diseased cells to find hidden targets that can then be turned into drugs for previously untreatable diseases.

It's hard to imagine a more promising pairing. "PhoreMost are literally next door to my lab – we often bump into them over coffee – so I knew about their technology. They can interrogate novel druggable spaces in proteins that conventional drug discovery hasn't been able to find – and we had the targets they needed," Simon recalls. "Using their SITESEEKER platform to find a new druggable space for the KRAS pathway we're studying seemed like a perfect partnership."



'It takes 17 years to translate basic innovation into a new drug or company… we can work much more cleverly'

'The fact we work alongside scientists from so many varied companies enables us to turn new ideas into new collaborations'

So after coffee and conversation, Simon took advantage of the Babraham Research Campus Collaboration Fund (BRCCF) – a scheme that encourages collaboration between Institute researchers and their neighbouring biotech companies – to set up a collaboration. And after successfully showing that they could build Simon's knowledge of KRAS into PhoreMost's screening technology, they were awarded £600,000 funding from Innovate UK in 2017 to get a new procedure up and running.

Nine months on and Simon's team are close to perfecting a system with PhoreMost. The new cell line will be able to indicate whether or not a molecule has inhibited the KRAS pathway by living or dying. When KRAS is switched on, the cells die; conversely, anything that inhibits KRAS means the cells survive. These cells can then be studied to find out exactly what protected them.

"The first step is using PhoreMost's technology to find these cryptic spaces on KRAS that have defied conventional drug discovery," he explains.

"Our dream is that if we find things binding to KRAS, we can work with crystallographers to discover where it's binding. And once we know the structure, we can design a drug-like molecule that does the same thing."

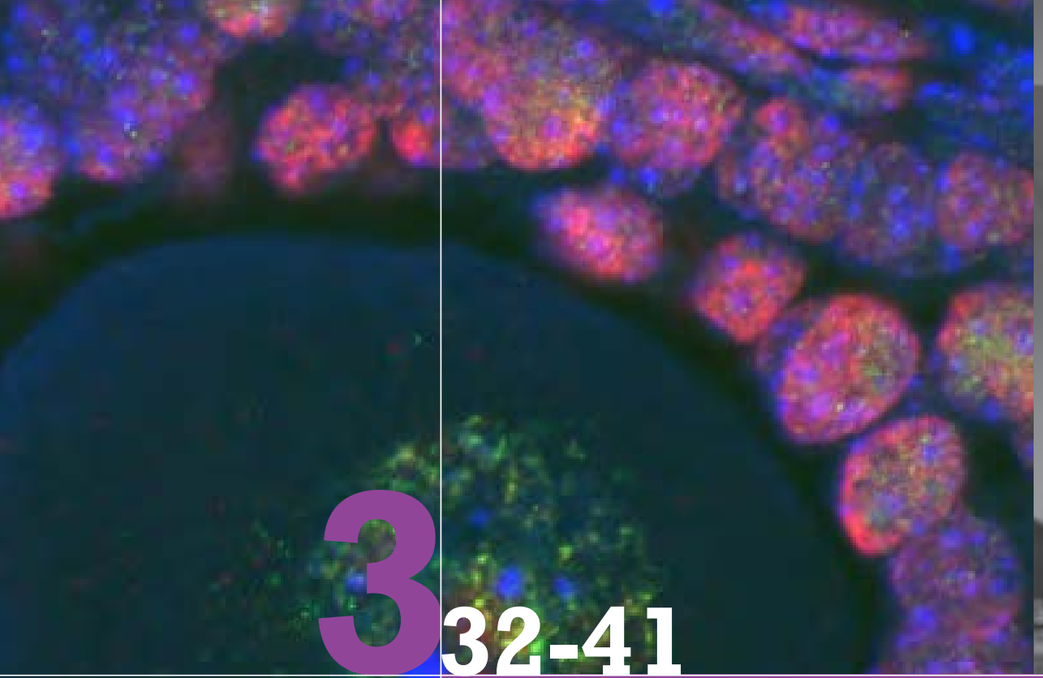
If the collaboration ultimately leads to new drugs for diseases like pancreatic cancer, it will mark an extraordinary advance. But it's the huge potential that this way of working represents that's the real game changer, Simon believes.

"I'm a great believer in publicly-funded research – the Institute does world-class research on a budget and because our funding comes from taxation we have a duty to squeeze every possible impact out of it. The fact we work alongside scientists from so many varied companies enables us to turn new ideas into new collaborations."

Working this smartly radically speeds up the time it takes to turn new knowledge into impact. "On average it takes 17 years to translate basic innovation into a new drug or company. That's too long and too random," Simon concludes. "The Babraham Research Campus shows that we can work much more cleverly. Here, we can facilitate and accelerate – funding basic bioscience and bringing people together who might otherwise never have talked."

PHORE MOST DRUGGING THE UNDRUGGABLE

We work with Innovate UK



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Epigenetics

Inside cells, genetic information stored in DNA is packaged by proteins into a structure called chromatin. Epigenetics is the study of chemical modifications to DNA and to chromatin and the effects that these modifications have on genome function. Epigenetic marks are involved in the creation of different types of cells from stem cells and epigenetic changes over time are associated with ageing. Epigenetic marks also provide a form of cellular memory, recording certain information about past events and potentially carrying it between parent and child.

Our work in this area aims to enhance our understanding of how epigenetics shapes human development and affects healthy ageing by examining:

- How stem cells develop into different types of cells
- How subtle epigenetic differences influence cell diversity
- The impacts of diet on epigenetics, health and ageing
- The inheritance of epigenetic memory between generations
- How life events affect biological ageing through the epigenetic clock
- New approaches and technologies to drive further progress

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Peter Rugg-Gunn

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Epigenetic reprogramming in development and ageing

We are interested in epigenetic mechanisms in mammalian development and ageing. Epigenetic mechanisms are able to regulate gene expression and can behave as a form of memory that records the history of a cell. These mechanisms include chemical changes to DNA or DNA-associated proteins. We are particularly interested in how epigenetic memory is established when cells become different from each other in early embryonic development, and how such epigenetic memory decays during ageing.

Current Aims

We are examining the link between epigenetic marks in a cell, the epigenome, and the activity of different genes. We have developed technologies to record the epigenome in parallel with transcription – the first step in the process of gene expression – inside single cells. We are using this to understand why stem cells develop into different cell types – for example specialising to become blood or muscle rather than gut cells. We are also trying to find out how the epigenome changes with age, including at the single cell level, and how this may affect cell and organ function as we age.

Progress in 2017

We have established the first systematic molecular map, based on single cell transcriptome sequencing, of cell fate decisions in early mouse development. Interestingly, we found that slight variations in gene expression, called 'noise', increases before cells become committed to becoming different cell types. We have established the first non-human ageing clock based on epigenetic DNA methylation. The clock is accurate enough to record the chronological age of mice with an error of 3.3 weeks. Interestingly, biological interventions that shorten lifespan (ovariectomy, high fat diet) accelerate the clock.

Selected Impact Activities

- POSTnote parliamentary briefing on 'The ageing process and health'
- Speaker at 'The many faces of epigenetics' interdisciplinary workshop Oxford with natural and social scientists
- Contributed to a social science (ethnography) research project at the University of York about our researchers titled 'Modelling Ageing @ BI'

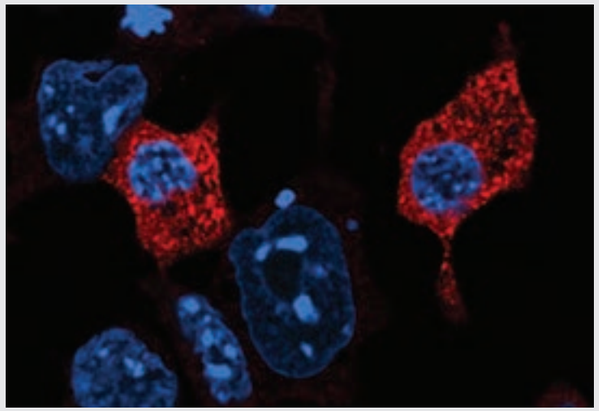

Image of fluorescently labelled embryonic stem cells. These cells have been modified to mimic the effects of epigenetic reprogramming changes that happen in developing embryos. DNA in the cells is marked in blue. Red indicates cells that contain active transposons – mobile pieces of DNA that can become active during reprogramming.

Publications

www.babraham.ac.uk/our-research/epigenetics/wolf-reik

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- Kelsey, G., Stegle, O., Reik, W. (2017) Single-cell epigenomics: Recording the past and predicting the future. ***Science*** 358(6359):69-75
- Mohammed, H *et al*. (2017) Single-Cell Landscape of Transcriptional Heterogeneity and Cell Fate Decisions during Mouse Early Gastrulation. ***Cell Rep***. 20(5):1215-1228
- Stubbs, T.M., *et al*. (2017) Multi-tissue DNA methylation age predictor in mouse. ***Genome Biol***. 18(1):68

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Stress, metabolism and effects on healthy ageing

We are now able to view ageing as a genetically controlled system that we can potentially learn to regulate. Of the thousands of genes that have been linked to ageing, many affect how living things deal with external challenges linked to stress and nutrition. Such findings underscore the balance between genes and environment that govern our lifespans. Our lab aims to understand the non-genetic influences on lifespan and responses to stress by using the nematode worm *C.elegans* as a model organism.

Current Aims

Our overarching aim is to understand the molecular details of ageing and to discover new ways to slow or even reverse the ageing process. With that goal in mind, we use *C. elegans* to understand:

1. The significance of non-genetically encoded variation in the expression of genes that respond to external cues such as temperature and nutrients. We are interested in finding how early molecular differences in the way worms respond to stress can influence and be predictive of lifespan.
2. The early global metabolic remodelling events that occur at the beginning of ageing, in both normal and long-lived worms. Our aim is to identify potential nutritional interventions that can delay the process of ageing.

Progress in 2017

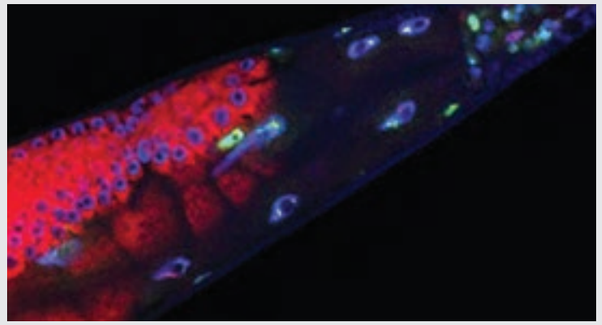
We have developed and optimised techniques and statistical methods to assess variability in gene expression. Using these techniques, we have examined the expression of stress and nutrient responsive genes and found that variation between worms can have an effect on fitness and overall survival. In particular, non-genetic variation in tissues from the brain and gut can have long-term consequences for healthspan.

By examining the first molecular events that occur during early ageing in both normal and long-lived animals we have identified key gene expression switches. These switches regulate genes involved in metabolism and contribute to early global metabolic remodelling events. We have also improved the *C. elegans* Metabolic Reconstruction network and are developing several modelling approaches to characterise gene expression switches and metabolic fluxes during early ageing.

Selected Impact Activities

- We have successfully launched WormJam, a community driven effort geared towards improving the *C. elegans* metabolic reconstruction network. Including organising two GENIE/COST workshops
- Our collaboration with the Sophianum School and the Technasium Scheme won an Openness in Animal Research award
- Presentation at Pint of science festival "epigenetics: Nature vs nurture" and sharing *C.elegans* research with primary and secondary school students

Young adult worms after heat shock (a sudden increase in temperature; 34°C for 30 mins). DNA inside cells is stained in blue. Messenger RNA (mRNA) from the hsp-90 gene are in red and mRNA from the hsp-70 gene are in green.



Publications

www.babraham.ac.uk/our-research/epigenetics/olivia-casanueva

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Research associate:
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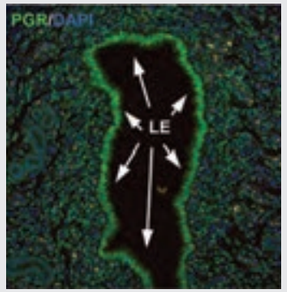
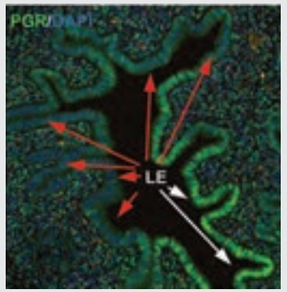
(Left in 2017)

The effect of age on womb function and pregnancy

*E3.5 uterus **Young** female*



*E3.5 uterus **Aged** female*



Uteri from young and aged female mice 3.5 days into pregnancy. The progesterone receptor protein (PGR) is shown in green and DNA labelled in blue using a stain called DAPI. White arrows point to the luminal epithelium (LE) – cells that line the uterus – with strong PGR expression. In young females the PGR signal is evenly distributed throughout the entire LE. Red arrows in aged uteri point to regions of the LE with reduced PGR levels.

A functional placenta is critical for normal embryonic development and lifelong health. The placenta develops from cells derived both from the embryo and from the mother. Trophoblast stem cells originate from the fertilised embryo and come together with cells from the mother's uterus to form a highly unique integrated unit. We focus on how genes are regulated during placenta formation and the effects of maternal age on this process.

Current Aims

It is well known that maternal age has a profound impact on fertility and reproductive success, an association commonly attributed to the decrease in egg cell fitness. The potential impact of ageing on the uterus has not been investigated to the same extent. During 2017, we focused on finalising our ongoing studies in which we were specifically investigating the effect of maternal age on uterine cells. This work was based on our observation that, in mice, the physiological environment of older mothers has a greater impact on placental and fetal development than the age of the egg cells themselves.

Progress in 2017

During 2017, we established that age impedes the capacity of uterine cells to respond to the pregnancy hormones oestrogen and progesterone. This hormonal signal normally triggers a reaction called decidualisation, in which cells lining the uterus transform to support embryo implantation and early placenta formation. In aged mice, the decidualisation response is slower. Moreover, some cells in aged uteri lack the progesterone receptor protein. These aged cells also show slower proliferation rates and reduced levels of the signalling molecule pSTAT3. Together, these molecular changes underpin the decidualisation and placentation defects we observe in older female mice that lead to a dramatic increase in developmental abnormalities.

Selected Impact Activities

- Talk at Cambridge Therapeutics Forum
- Radio interviews for DeutschlandFunk and the Naked Genetics podcast with Kat Arney
- Institute Public Engagement Prize & presentation at Royal Society Partnership Conference for Claire Senner and 6th form pupils from Hitchin Girls' School

Publications

www.babraham.ac.uk/our-research/epigenetics/myriam-hemberger

- Brighton, P.J *et al.* (2017) Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium. ***eLife*** 6
- Turco, M.Y. *et al.* (2017) Long-term, hormone-responsive organoid cultures of human endometrium in a chemically defined medium. ***Nat. Cell Biol.*** 19, 568-577
- Woods, L. *et al.* (2017) Decidualisation and placentation defects are a major cause of age-related reproductive decline. ***Nat. Commun.*** 8, 352

Jon Houseley

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Michelle King
(Started in 2017)
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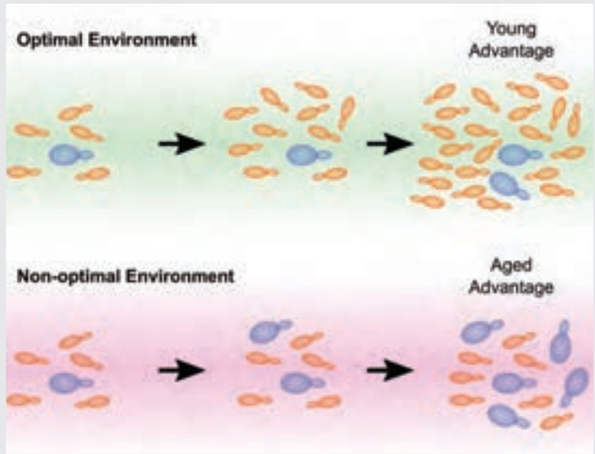
(Left in 2017)

How cells interact with their environment

We study how cells adapt to their environment at the genetic and epigenetic level, particularly how they adjust to challenging and toxic environments. This contributes to our understanding of how our cells change in response to environmental pressures and as a consequence of ageing. Our work aims to discover ways of improving health throughout life and to find better approaches to chemotherapy.

Current Aims

- Determine how new genetic changes occur and whether these can be stimulated by the environment
- Establish when and how drug resistance occurs in cancer cells
- Understand the mechanistic link between nutrients in the environment and the ageing process



In yeast, older cells (blue) are at a disadvantage during growth in their normal environment yet they are actually fitter in non-optimal environments compared to younger cells (orange).

Progress in 2017

We have published the first clear demonstration that certain complex cells can stimulate genetic changes at particular sites in their genome. We've also shown that they do this to accelerate the acquisition of new traits. This suggests that changes such as drug resistance are not always random and may be preventable. Using yeast as a model of cell biology, we have also shown that the effects of ageing depend on the environment. The decline of ageing cells is not absolute and aged cells are fitter than young cells in some circumstances. This is helping us to understand the impact of nutrition on the ageing process.

Selected Impact Activities

- Article featuring our research on stimulated mutation in Quanta and WIRED magazines
- Article on our ageing research in Cambridge Independent
- Research Presentation at the "2nd DNA Replication as a Source of DNA Damage Conference" in Rome, July 2017

Publications

www.babraham.ac.uk/our-research/epigenetics/jon-houseley

- Hull, R.M. *et al.* (2017) Environmental change drives accelerated adaptation through stimulated copy number variation. ***PLoS Biol.*** 15: e2001333
- Frenk, S. *et al.* (2017) Aging yeast gain a competitive advantage on non-optimal carbon sources. ***Aging Cell*** 16: 602-604
- Sayou, C. *et al.* (2017) RNA Binding by Histone Methyltransferases Set1 and Set2. ***Mol. Cell Biol.*** 37: e00165-17

Gavin Kelsey

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Epigenetic legacies from eggs

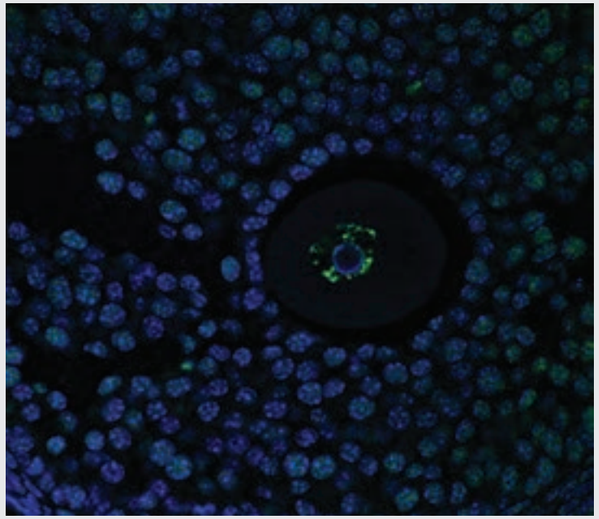
As well as genetic information, the egg and sperm also contribute epigenetic annotations that may influence gene activity both during and after fertilisation. We examine epigenetics during egg development and the effects of epigenetic marks on gene activity in the embryo. Our goal is to understand whether, through epigenetics, factors such as a mother's age or diet have consequences on the health of a child.

Current Aims

We investigate how epigenetic states are set up in oocytes – which develop into egg cells – and influence gene expression in the embryo. For example, repressive chromatin marks in oocytes lead to long-term silencing of genes inherited from the mother, particularly in cells that will form the placenta. We are also interested in how variations in DNA methylation, another type of epigenetic mark, come about in oocytes and whether we can use this variation as a marker for oocyte quality and embryo potential. To investigate these questions, we develop methods to profile epigenetic information in small numbers of single cells.

Progress in 2017

A major advance has been our ability to map chromatin states – how the chromosomes themselves are modified – in very small numbers of cells. This has revealed some unexpected properties of the epigenetic landscape in oocytes, such as widespread accumulation of H3K4me3, a modification normally tightly associated with active gene promoters. Using genetic mutants we investigated interactions between H3K4me3 and other layers of epigenetic information. For example, we find that methylation on DNA can prevent H3K4me3 modification on chromosomes. This indicates a link between genetic information in DNA and the positioning of H3K4me3 in the genome.



A mouse egg cell inside an ovary. DNA in each cell is shown in blue, epigenetic methylation marks are shown in green. Image: Dr Courtney Hanna

Selected Impact Activities

- Teacher training session on how to measure epigenetic marks in the genome using current sequencing technologies
- Lecture "Animal Models to Study Human Disease" for the Institute of Continuing Education, University of Cambridge by Courtney Hanna
- Visit to the University of Jordan, Amman as part of Global Challenge Research Fund (GCRF) Impact Accelerator Award (IAA) to promote infrastructure for bioinformatics analysis and training

Publications

www.babraham.ac.uk/our-research/epigenetics/gavin-kelsey

- Gahurova, L. *et al.* (2017) Transcription and chromatin determinants of de novo DNA methylation timing in oocytes. ***Epigenetics & Chromatin*** 10:25
- Kelsey, G., Stegle, O. and Reik, W. (2017) Single-cell epigenomics: recording the past and predicting the future. ***Science*** 358:69-75
- Hanna, C.W. *et al.* (2018) MLL2 conveys transcription-independent H3K4me3 in the oocyte. ***Nat. Struct. Mol. Biol***

Peter Rugg-Gunn

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(Left in 2017)

Epigenetic regulation of human development

How DNA is packaged in cells and the use of biochemical switches in the genome are key aspects of the epigenetic control of gene activity. We are interested in understanding how epigenetic processes are established during human development and during the differentiation of stem cells to form various cell types. This is important for understanding health and for finding ways to use stem cells in regenerative medicine.

Current Aims

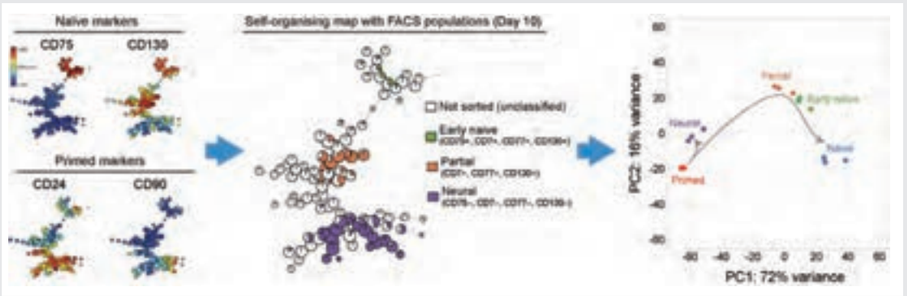
Our aim is to understand how epigenetic processes help to control human development and stem cell differentiation, in particular as cells enter and exit an unspecialised state called pluripotency. Over the next year, we would like to find out what mechanisms drive the changes in gene regulation and chromatin organisation as cells become pluripotent and how this happens against a backdrop of widespread epigenetic reprogramming. We will also investigate how human pluripotent cells undergo specialisation towards mature tissues such as pancreatic beta cells, and whether we can make this more efficient by toggling epigenetic switches at key stages in the process.

Progress in 2017

One highlight this year was charting the first molecular roadmap of the transition between naïve and primed human pluripotent states. By identifying new ways to isolate early-stage naïve cells, we have revealed exciting insights into the dynamics and the interplay of epigenetic and transcriptional events that occur during cell reprogramming. We defined genes that are activated at either the early or late stages of naïve cell formation, and we have used genetic approaches to ask which of these genes are required for reprogramming. Mapping DNA interactions has also revealed how rewiring of gene regulation occurs between different cell states.

Selected Impact Activities

- Clara Novo co-organised the first EU-LIFE International Postdoc Retreat, held in Lisbon in October
- Clara Novo spoke about her research at the Cambridge 'Pint of Science' Festival
- Peter Rugg-Gunn helped to draft new guidelines for assessing the safety of human pluripotent stem cells in clinical applications



We recently identified a set of cell-surface proteins that can distinguish between naïve and primed human pluripotent stem cells (left). By using specific antibodies to visualise these proteins, we can now track and isolate specific cell types during the transition between naïve and primed states (centre). Gene expression analysis reveals the similarities and differences between each of the isolated cell populations (right) and tells us about the pathways that contribute to cell state changes.

Publications

www.babraham.ac.uk/our-research/epigenetics/peter-rugg-gunn

- Collier, A *et al.* (2017) Comprehensive Cell Surface Protein Profiling Identifies Specific Markers of Human Naive and Primed Pluripotent States. ***Cell Stem Cell*** 20: 874-890
- Rugg-Gunn, P (2017) Naive pluripotent stem cells as a model for studying human developmental epigenomics: opportunities and limitations. ***Epigenomics*** 9: 1485-1488
- Freire-Pritchett, P *et al.* (2017) Global reorganisation of cis-regulatory units upon lineage commitment of human embryonic stem cells. ***eLife*** 6. pii: e21926

Informing Policy on Ageing

Ensuring that the Institute's world-leading research has a direct impact on people's health means translating – and contextualising – our science for many audiences. For parliamentarians and policy makers, healthy ageing is among the 21st century's most pressing problems. So as well as pioneering research on healthy ageing, we're ensuring science is accessible to decision makers through our knowledge exchange programme.

Across a handful of generations, average life expectancy in the UK has doubled. A baby girl born in 1841 could expect to live just beyond her 42nd birthday; one born in 2016 can expect to live until the age of 83. This extraordinary change is a triumph of public health; but it also presents major health and social challenges. Today, longer life expectancy is associated with increasing incidence of chronic diseases, from dementia and diabetes to arthritis and cancer, putting pressure on unpaid carers as well as health and social services.

Helping people remain healthier for longer is key to addressing these issues, and the Institute plays a pivotal role in advancing fundamental scientific knowledge and making it available to decision makers. Healthy ageing research spans and unites the Institute's scientific themes. Our aim is to understand how our bodies change as we age and how this impacts our lives so that science can inform lifestyle changes, policies and treatments to help people stay healthier as they get older.

For the past 30 years, the Institute has pioneered research into epigenetics – the mechanisms that control the way our genes function – revolutionising our concept of healthy ageing biology. In 2017, for example, Institute researchers identified a mouse epigenetic ageing clock and showed that lifestyle changes known to shorten lifespan, including a high fat diet, sped up the clock.

Doing ground-breaking science, however, is not enough. To maximise the impact of our research, we have to make it accessible to parliamentarians and policy makers, and last year Professor Wolf Reik and Dr Jon Houseley of the Epigenetics research programme contributed to a new POSTnote.

POST – the Parliamentary Office of Science and Technology – provides balanced, accessible overviews of scientific research. One of the tools it uses to put research into a policy context that can be used in Parliament is the POSTnote. These concise peer-reviewed briefings distil literature reviews and interviews with academic, industry, government and third sector stakeholders. In 2017, Sarah Worsley, a third-year PhD student at the University of East Anglia spent three months as a NERC-funded intern at POST, producing a POSTnote on the biological basis of ageing and how the ageing process can be manipulated to promote better health later in life.

"Collating 30 interviews into a four-page briefing and explaining complex science for an audience that has no knowledge of biology is challenging," Sarah explains. "Visiting scientists at the Babraham Institute, Newcastle University and the University of Southampton was vital to get the background to the biology of ageing. They told me about their work, and where they thought it fitted into policy and treatments for age-related diseases."

The POSTnote introduces the idea of biological versus chronological age, the epigenetic clock, and considers potential therapies and public health policy interventions opening up through this research. "Scientists

'Our research on healthy ageing has a direct impact on the nation's heath'

are beginning to understand the processes that occur in our bodies that cause ageing – the damage that accumulates over time which causes ageing and age-related disease. The interest now is to look for ways to reduce this damage, either via new drugs or changes in lifestyle," she says.

The POSTnote, published in February 2018, will be used by parliamentarians and policy makers who will be increasingly called on to regulate new drugs and set new directions in public health, ensuring that the Institute's research has a direct impact on the nation's heath. "Nutrition and other environmental factors influence the epigenome and can have long lasting consequences, not only for our health but that of future generations," says Wolf.

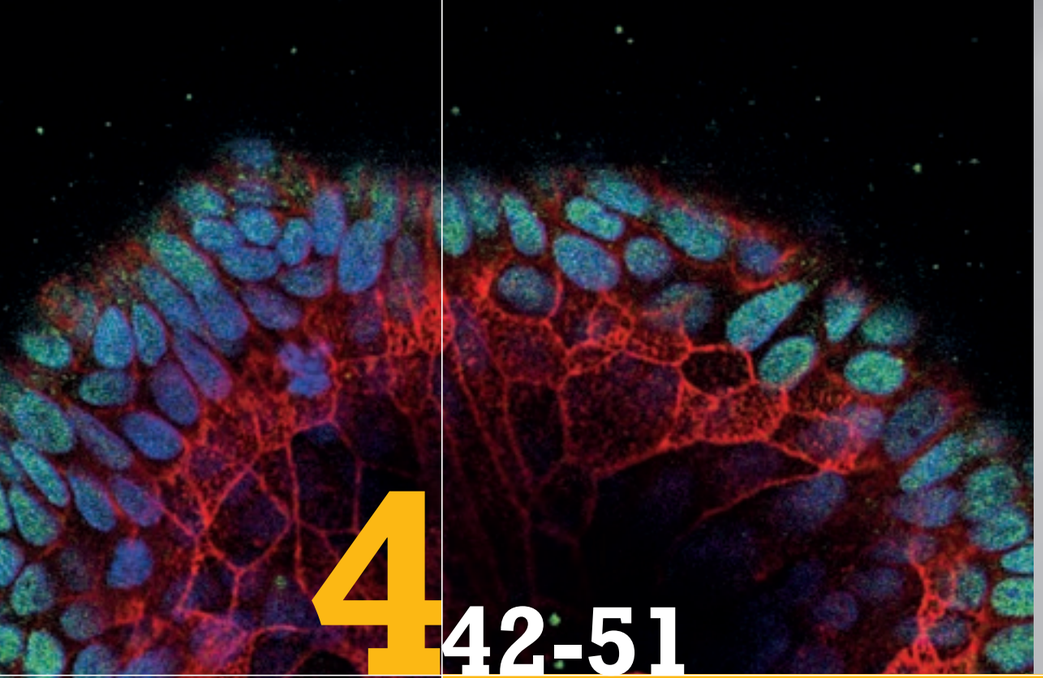
As well as public health and the development of new drugs, his research has other less obvious yet far-reaching implications, he adds: "Insurers might be very interested in people's biological age, which raises many policy questions. And if it's possible to influence the ageing process with drugs in the future, I think this has broader implications for population structure."

Being involved in research that's likely to have profound impacts on society as well as health makes him think about his science from new perspectives. "It makes us frame questions in a different way," he says. "It's important to inform parliament and our policy makers about scientific thinking, because new science raises so many new ethical and legal questions."

The POSTnote 'The Ageing Process and Health' is available online to download*

'It's important to inform parliament and our policy makers about scientific thinking, because new science raises so many new ethical and legal questions'

***https://researchbriefings.parliament.uk/ResearchBriefing/Summary/POST-PN-0571**



4 42-51

Nuclear Dynamics

Each cell contains a massive amount of genetic information stored on strands of DNA inside the cell nucleus. These strands are not randomly packed into cells but are highly organised. Different pieces of DNA are found in different places and often active genes are found together in specific locations. All of this means that physical changes in DNA organisation can affect how our genes, and our cells, behave.

Our research investigates how the physical organisation of DNA affects gene activity and how this changes in different types of cells and as we age. We do this by exploring:

- How DNA is organised inside different types of cells
- The location of active and inactive genes inside cells
- How different proteins reorganise the genome to alter gene activity
- 3D computer modelling methods to understand genome organisation

Group leaders

Peter Fraser

Anne Corcoran

Sarah Elderkin

Karen Lipkow

Mikhail Spivakov

Patrick Varga-Weisz

Peter Fraser
Programme leader

Group members

Postdoctoral researchers:
Tauanne Amarante
(Left in 2017)
Jonathan Cairns
Biola Javierre
Hashem Koohy
Wing Leung
Jorg Morf
Takashi Nagano
Stefan Schoenfelder
Sven Sewitz
Csilla Varnai
Steven Wingett

PhD students:
Stephen Bevan
Marco Michalski
(Left in 2017)

Visiting scientists:
Elad Chomsky
(Left in 2017)
Giuseppina Pisignano
(Left in 2018)
Gordana Wutz

Research assistant:
Clare Murnane

Professor Fraser is now primarily based at the Department of Biological Science, Florida State University

Structure and function of the genome

Our two-metre long genome is packed into a nucleus just a fraction of a millimetre across. Yet, what's truly astonishing is that our genomes are highly folded and organised inside the nucleus. Changes in DNA folding can control gene expression, affecting how cells develop and respond to the environment. The links between organisation and genetics could change our understanding of health, ageing and disease.

Current Aims

The spatial organisation of the genome is tissue-specific and has been linked to a range of processes in the cell nucleus. These include gene activation, gene silencing, genomic imprinting, DNA repair, DNA replication, and genome maintenance.

We study the interplay between genome structure and function both at the level of single cells and cell populations. We have developed a technique called single-cell Hi-C to gain insights into the variability and dynamics of chromosome organisation in cells, and Promoter Capture Hi-C (PCHi-C) to link regulatory elements across the genome with their target genes.

A visual representation of DNA molecules (chromosomes) within a cell. The packing of chromosomes into cells can affect the accessibility of different genes and chromosomes are packed differently inside different cells.

Progress in 2017

Using an improved single cell Hi-C method, we have captured thousands of genome conformations from individual cells. This has allowed us to connect complex features of chromosome architecture to changes as cells grow and divide. We have also been able to complete 3D virtual models of entire genomes.

We have generated detailed maps of contacts between genes and proposed gene regulatory regions using Promoter Capture Hi-C in a range of human and mouse cell types. Our goal is to enhance our understanding of gene expression control, and to understand how genetic changes outside of genes relate to human diseases.

Selected Impact Activities

- CHROMOS public displays at the Cambridge Science Festival (February 2017), London Science Museum (September 2017) and ZKM Karlsruhe (ongoing)
- We have provided training in Capture Hi-C methodology for visiting scientists from Florida and Vienna

Publications

https://www.bio.fsu.edu/faculty.php?faculty-id=pfraser

- Nagano, T *et al.* (2017) Cell-cycle dynamics of chromosomal organization at single-cell resolution. ***Nature*** 547: 61-67
- Rubin, AJ *et al.* (2017) Lineage-specific dynamic and pre-established enhancer-promoter contacts co-operate in terminal differentiation. ***Nat. Gen.*** 49: 1522
- Siersbaek, R *et al.* (2017) Dynamic rewiring of promoter-anchored chromatin loops during adipocyte differentiation. ***Mol. Cell*** 66: 420-435

Anne Corcoran

Group members

Senior research associate:
Daniel Bolland

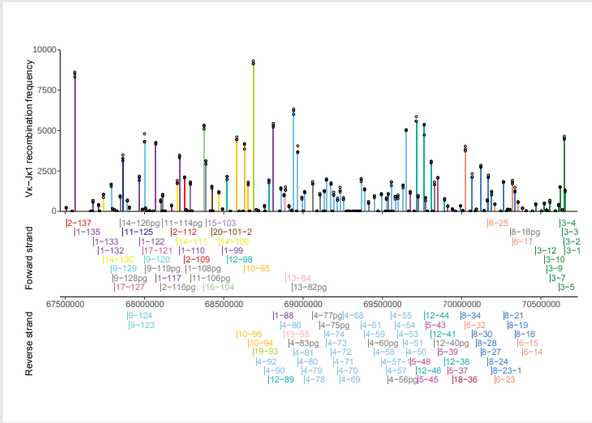
Postdoctoral researcher:
Lyubomira Chakalova
(Started in 2017)

PhD students:
Peter Chovanec
Olga Mielczarek
(Left in 2017)
Sam Rees
Carolyn Rogers
(Started in 2017)

Visiting researcher:
Jannek Hauser
(Left in 2017)

From April 2018, the Corcoran group will be part of our Immunology research programme

Making enough different antibodies to fight infection



This image shows the many different genes in the immunoglobulin kappa DNA region, colour coded by gene family. The length/height of each line indicates how often each gene is used to make antibodies.

The immune system creates antibody proteins to help fight diseases. Antibodies are made by white blood cells called B lymphocytes. By mixing and matching genetic information, these cells can produce billions of different antibodies to combat different diseases. We are interested in the mechanisms involved in the development of B lymphocytes and their ability to make antibodies. Reduced ability to produce effective antibodies is one of the reasons the immune system weakens as we age.

Current Aims

We aim to understand how the genes that make up antibody proteins come together in many different combinations to generate the enormous numbers of different antibodies we need to fight infections. This process involves epigenetic mechanisms at many different levels. We aim to understand how mechanisms like transcription factor binding and histone modifications affect which genes are more frequently used. We're also looking at how the large-scale 3D folding of these large DNA regions in the nucleus affects antibody production. This will increase our understanding of normal antibody production and help us to understand the events that cause leukaemias.

Progress in 2017

We have invented VDJ-seq, a method which detects multiple antibody gene sequences. VDJ-seq can show which genes are typically used the most to make antibodies and how this changes during disease. We have used this technique to study the genes used to make the immunoglobulin kappa light chain (Igk) protein. We have discovered that some Igk genes are used much more often than others. By examining transcription factors and histone modifications near the IgK genes, we found that frequently used Igk genes have very specific signatures. We are now investigating whether ageing affects the use of IgK genes and the corresponding signatures.

Selected Impact Activities

- New Epigenetics exhibit for Hills Road Biology Day and Cambridge Science Festival
- Patent granted in US and Europe on assay to detect antibody sequences
- Invited speaker at Successful Women in Science Symposium, Basel
- Talk at FASEB meeting, USA, on Gene Expression in the Immune System

Publications

www.babraham.ac.uk/our-research/lymphocyte/anne-corcoran

- Matheson, L.S. *et al.* (2017) Local chromatin Features including PU.1 and IKAROS Binding and H3K4 Methylation shape the repertoire of immunoglobulin Kappa genes chosen for V(D)J recombination. ***Front. Immunol.*** 8:1550
- Levin-Klein, R. *et al.* (2017) Clonally stable Vκ allelic choice instructs Igκ repertoire. ***Nat. Commun.*** 8:15575
- Collier, A.J. *et al.* (2017) Comprehensive Cell Surface Protein Profiling Identifies Specific Markers of Human Naive and Primed Pluripotent States. ***Cell Stem Cell*** 20: 874-890

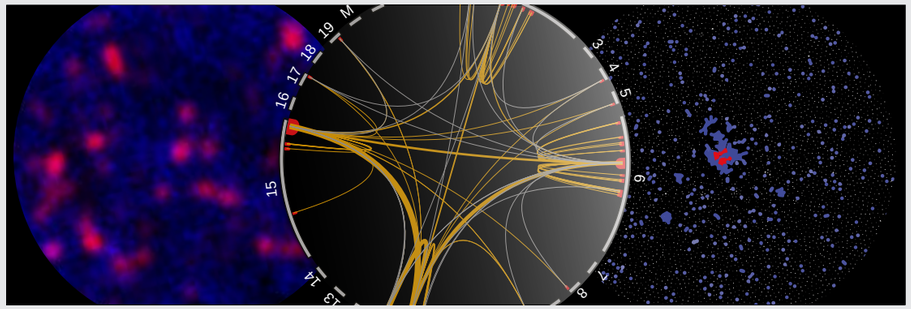
Sarah Elderkin

Group members

Postdoctoral researchers:
Louise Matheson
Salah Azzi
(Left in 2017)

In 2018, Sarah Elderkin becomes a Visiting Researcher at the Institute

Keeping genes silent



PRC1 protein complexes spatially restrain the genome in mouse stem cells. PRC1 staining as pink dots in the nucleus of an embryonic stem cell (left). A representation of contacts between different chromosomes (centre), line thickness indicates strength of interaction. Interactions of all 22,000 genes throughout the genome. Image: Dr Veronique Juvin.

We examine gene expression and how genes can be rapidly activated or silenced when cells change type. We are particularly interested in how stem cells are able to develop into a range of different types of cell through the process of differentiation. Precise control of gene activity is key to controlling these changes while helping different types of cell to remain healthy and perform specialised tasks.

Current Aims

We are particularly interested in groups of proteins called Polycomb Repressive Complexes (PRC), which reduce or silence gene expression. Although most genes affected by PRC are silent, some remain active. With colleagues at EMBL-EBI we recently showed that these genes are more noisy than normal, meaning that their activity varies between cells. Noise can be important in helping cells to make decisions and our findings indicate that PRC helps to generate this genetic noise.

Publications

www.babraham.ac.uk/our-research/affiliated-scientists/sarah-elderkin

- Kar *et al.* (2017) Flipping between Polycomb repressed and active transcriptional states introduces noise in gene expression. ***Nat. Commun***. 8:36

Karen Lipkow

Group members

Postdoctoral researcher:
Sven Sewitz

PhD students:
Latifa Aljebali
Zahra Fahmi

Visiting student:
Ema Etchegaray
(Left in 2017)

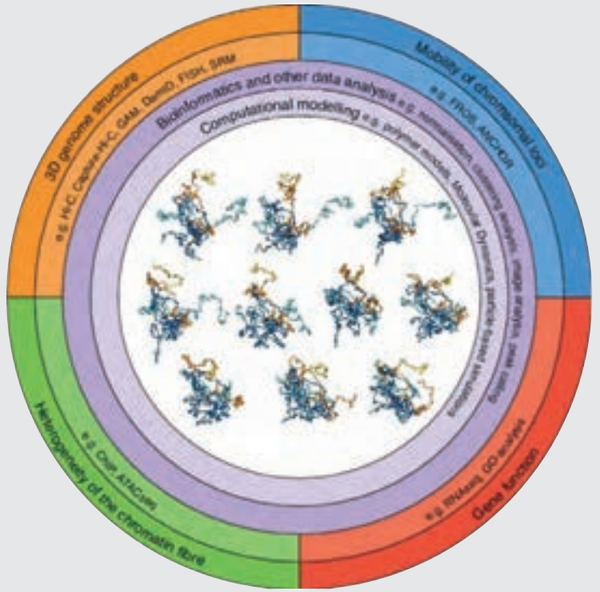
In 2018, Karen Lipkow becomes a Visiting Researcher at the Institute

Mechanisms of genome architecture

Each cell contains a huge amount of DNA packed into a small space inside the nucleus. Despite the crowding, the DNA is highly organised with active genes often found together in the same parts of the nucleus. By combining computing and biology, we're examining the physical and biological mechanisms responsible for organising DNA inside cells.

Current Aims

Inside cells, DNA is packaged with histone proteins to form chromatin. In our latest work we have been investigating how the mobility of different chromatin regions affects genome organisation. Using the yeast *S. cerevisiae*, and computer models of chromatin, we showed that the number of extra proteins attached to a section of chromatin affects its mobility. We went on to show that changing mobility helped the chromatin to organise into structures that aid proper gene regulation.



Methods for analysing the dynamic genome. The four aspects of studying genome organisation and the key techniques used in these areas (outer rings) are united through bioinformatics and computational approaches. This helps us to gain a more complete view of how DNA organisation changes within cells. The centre shows simulated movements of a yeast chromosome demonstrating the dynamics of chromosome conformations over a short period of time.

Publications

www.babraham.ac.uk/our-research/affiliated-scientists/karen-lipkow

- Sewitz *et al.* (2017) Heterogeneous chromatin mobility derived from chromatin states is a determinant of genome organisation in S. cerevisiae. ***bioRxiv*** (preprint)

Mikhail Spivakov

Group members

Senior postdoctoral researcher:
Hashem Koohy

Postdoctoral researcher:
Jonathan Cairns

PhD students:
Lina Dobnikar
Joanna Mitchelmore
Michiel Thiecke

Visiting students:
Pawel Bednarz
(Left in 2017)
Will Orchard
(Started in 2017)

Mikhail Spivakov will take up a new position at the Medical Research Council's London Institute of Medical Sciences in 2018

The logic of gene regulation from a distance

Many genes are controlled by pieces of regulatory DNA found elsewhere in the genome. Some of these regulators are close to the genes they affect but some are not. We are interested in understanding the relationships between different genes and their regulators and understanding how they impact on development, ageing and disease.

Current Aims

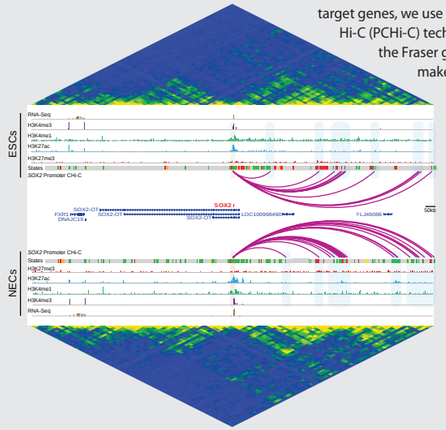
Our group studies the basic principles of gene regulation and their implications for ageing, development and disease. We combine experimental approaches with computational analyses using advanced tools, some of which we develop ourselves. Much of our work is focused on the logic of gene regulation by genomic elements that are found some distance away from the genes they regulate, such as gene enhancers. To link these elements to their target genes, we use the Promoter Capture Hi-C (PCHi-C) technique developed in the Fraser group. This method makes it possible to map the connections of gene promoters across the whole genome and at high resolution.

Progress in 2017

In collaboration with Peter Rugg-Gunn's and Peter Fraser's groups, we mapped the loops between genes and their regulatory elements in unspecialised human embryonic stem (ES) cells and in developing neurons derived from these cells. We found that these loops were extensively rewired when the ES cells went through the process of differentiation to become neurons. This is also consistent with the enhancer regions switching on and off. Additionally, we contributed to studies that identified possible target genes affected by non-coding mutations that are associated with human disease. This involved examining what gene promoters loop close to mutation sites.

Selected Impact Activities

- The CHROMOS project (see feature). Presented at Cambridge Science Festival, London Science Museum Lates and at venues abroad
- Valeriya Malysheva has taken part in the Roche Continents programme exploring the intersection of science and art



How the promoter of the SOX2 gene in human ES cells (upper; ESCs) and neural progenitor cells (lower; NSCs) interacts (purple arcs) with other parts of the genome. Also shown is information on gene expression (mRNA-seq) and the patterns of various epigenetic modifications (H3K27me3, H3K27ac, H3K4me1, H3K4me3). The accessibility of DNA in different parts of the genome is shown as chromatin states defined jointly based on these epigenetic patterns (active chromatin, green; poised chromatin, orange; Polycomb-associated chromatin, red; intermediate, yellow; background, grey). Heatmaps (top and bottom) show information on all interactions in the region (the promoter has most contacts with regions in yellow),

Publications

lms.mrc.ac.uk/research-group/functional-gene-control

- Freire-Pritchett, P. *et al*. (2017). Global reorganisation of cis-regulatory units upon lineage commitment of human embryonic stem cells. ***eLife*** 6: e21926
- Petersen, R. *et al*. (2017). Platelet function is modified by common sequence variation in megakaryocyte super enhancers. ***Nat. Commun.*** 8: 16058
- Burren, O.S. *et al*. (2017). Chromosome contacts in activated T cells identify autoimmune disease candidate genes. ***Genome Biol.*** 18: 165

Patrick Varga-Weisz

Group members

Postdoctoral researchers:
Juri Kazakevych
Anke Liebert
(Left in 2017)
Claudia Stellato
(Left in 2017)

PhD students:
Rachel Fellows
Elena Stoyanova

Visiting students:
Raquel Manzano
(Left in 2017)
Calvin Rodrigues
(Left in 2017)

Patrick Varga-Weisz will take up a new position at the University of Essex in 2018

How the environment changes genome function

The cells that line the gut form a layer called the intestinal epithelium that absorbs nutrients, supports good bacteria and protects against infections. How factors such as diet and bacteria impact on health, ageing and the immune system through changes in gene organisation and regulation is an important question.

Current Aims

Our lab studies how bacteria in the gut interact with the cells of the intestinal epithelium and control gene regulation in these cells, by affecting how the genome is packaged.

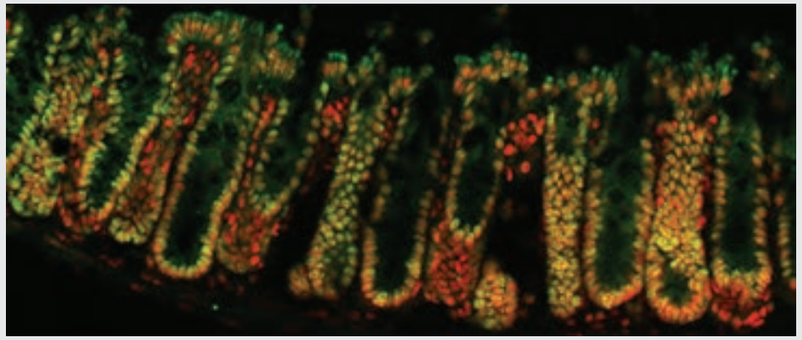
We also explore how ageing affects gene expression through chromatin dynamics – how the genome is arranged and moves within cells. We have worked in collaboration with the labs of Anne Corcoran, Peter Fraser, Mikhail Spivakov and Sarah Elderkin to do this for B cell precursor cells in the immune systems of mice and we are extending these kind of studies now to intestinal stem cells.

Progress in 2017

Fibre, such as pectin from apples, is an important part of our diet, yet the human genome doesn't include the genes needed to digest fibre. We can only digest fibre thanks to the bacteria in the gut which do have the biological machinery needed to break down fibre. By doing so the bacteria generate molecules called short chain fatty acids (SCFAs). These are taken up by the cells lining the gut, called intestinal epithelial cells, and provide an important energy source. We have shown that SCFAs lead to changes in gene expression. They do this by increasing the abundance of a certain type of epigenetic mark – a chemical modification that alters gene activity. This type of epigenetic mark is known as crotonylation and it is particularly abundant in the gut epithelium. Our work has shown how SCFAs affect crotonylation levels. Therefore, our study illuminated a new link between gut microbiota and the genome of intestinal epithelial cells.

Selected Impact Activities

- Rachel Fellows, was interviewed by BBC Radio Cambridgeshire about her research in the wake of the publication of her work
- Co-organiser, "The Ageing Cell" conference, Babraham Institute



Lining of the mouse large intestine. DNA in shown in red. Histone-crotonylation, an epigenetic mark involved in gene activation, shown in green. Yellow indicates both features together."

Publications

www.essex.ac.uk/people/varga22401/patrick-varga-weisz

- Fellows, R. *et al*. (2018) Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases. ***Nat. Commun.***
- Rodrigues, C. *et al*. (pre-pub) A Suv39H1-low chromatin state drives migratory cell populations in cervical cancer. ***bioRxiv*** 241398

The Sounds of the Genome

The Institute does world-leading research, and using public engagement to enthuse, excite and inspire is a key part of our mission. This year, we teamed up with two innovative artists to transform our data into a virtual reality experience. The result, CHROMOS, is allowing new audiences to discover the DNA drama that goes on inside the nucleus of a single cell.

From Twitter to CGI, new technology is re-shaping how we work, play and communicate. But when Dr Mikhail Spivakov from the Institute's Nuclear Dynamics research programme sent a tweet to music producer Max Cooper, neither thought that a 140-character message would evolve into a ground-breaking public engagement project.

Max – whose work spans dance-floor techno to fine art sound design – has more in common with Mikhail than meets the eye. With a PhD in computational biology but no formal music training, Max is fascinated by the rhythms of the natural world and the capacity of art and music for scientific storytelling.

"Mikhail tweeted Max inviting him to visit the Institute," recalls public engagement manager Tacita Croucher. "He'd seen some work that Max was doing, thought it was really cool, and wondered whether they could collaborate."

After meeting Mikhail and his team, Max decided that they should work together on a project inspired Dr Csilla Varnai's research, whose computer modelling has revealed the 3D organisation of DNA in single nuclei for the first time.

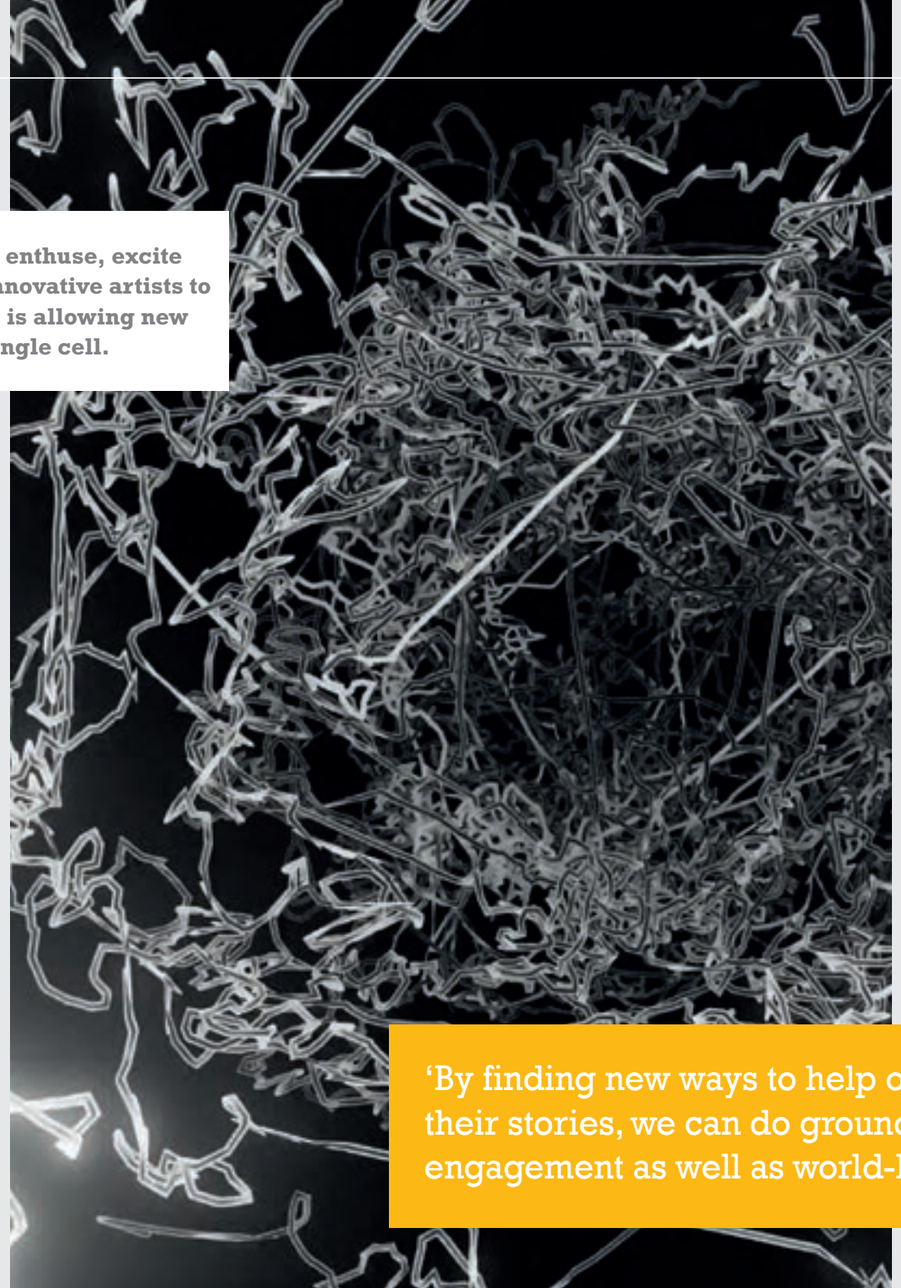
Our DNA is often represented as pairs of discrete X-shaped chromosomes, but the reality is altogether messier and more dynamic. With more than two metres of DNA packed into each cell's nucleus, our chromosomes usually resemble a tangled ball of wool rather than neatly twisted skeins of yarn.

This tangle of DNA is constantly moving, folding and refolding into different arrangements. When sections of DNA move from the centre to the periphery of the cell, meeting and parting company from others, they are effectively switched on and off in a way that enables the complex machinery of the cell to function correctly.

Because they can now study the relationship between DNA structure and function in single cells, researchers will be able to ask questions that would have been impossible to answer before – questions that should help them understand how the activity of the genes encoded in DNA affect health, disease and ageing.

While for scientists the findings have important implications for human health, for Max they provide artistic inspiration. "This process of simulated folding to create our best guess of real chromosome structure is a beautiful process, so this beauty became the focus of the project," he explains. And to bring out its full beauty, he decided to get CGI A-lister Andy Lomas – whose film credits include Hollywood hits from Avatar to the Matrix movies – on board.

Andy developed a way of transforming gigabytes of the Institute's raw data into video sequences and a virtual reality experience while Max produced a musical score. "We wanted to express the data in this unadulterated form, so you can experience the real science in action," Max explains. "It's a glimpse into the complexity and form of one of the most important molecular structures in all of life."



'We wanted to express the data in this unadulterated form, so you can experience the real science in action'

The result is CHROMOS: shimmering strands of DNA dancing to complex, layered melodies played on a sansula, a magical thumb piano made from small metal tines. The video has been viewed thousands of times on YouTube and the VR experience enjoyed by audiences at London's Science Museum, the Cambridge Science Festival and the Open Codes exhibition at ZKM Karlsruhe as well as in Berlin and Lisbon.

People's responses, says Tacita, have been amazing: "Our aim was to spark conversation, make people think differently and engage audiences who would perhaps not usually engage in science research. And we've achieved that. It's been a major success."

The project has also attracted attention from the public engagement community. "CHROMOS was a significant investment for the Institute and very different from anything we've done before," she says. "Its success shows that by finding new ways to help our scientists tell their stories, the Institute can do ground-breaking public engagement as well as world-leading research."

And for Institute researchers like Mikhail, it's been hugely rewarding. "As a biologist I'm passionate about finding ways to make our science more accessible, to help people understand what we do and why we do it," he concludes. "It was amazing to see how the project took real data from the lab and turned it into a multidimensional experience which allows people to get more closely acquainted with our DNA, what it does and how it looks, making it almost palpable."

To find out more about CHROMOS go to www.babraham.ac.uk/CHROMOS

'By finding new ways to help our scientists tell their stories, we can do ground-breaking public engagement as well as world-leading research'

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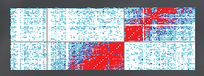
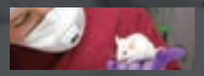
Facilities



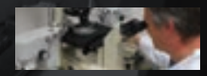
Bioinformatics

Biological Chemistry



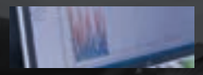
Biological Support Unit

Flow Cytometry

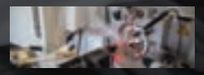


Gene Targeting

Imaging



Lipidomics



Mass Spectrometry

Sequencing

Simon Andrews
Facility head

Facility members

Biological statistician:
Anne Segonds-Pichon

Bioinformaticians:
Laura Biggins
Christel Krueger
Felix Krueger
Steven Wingett

Training developers:
Jo Montgomery
(Started in 2017)
Bhupinder Virk
(Left in 2017)

Bioinformatics

Research increasingly includes the creation of large amounts of data and the use of computers to manage and process that information. The Bioinformatics facility provides infrastructure to support the analysis of biological data. We provide guidance and training in data analysis, statistics and data management to both internal and external groups. We also develop novel tools, and administer the Institute's computing cluster.

Capabilities

- A group of six bioinformaticians and statistisiticians with biological backgrounds who can advise or practically help you with your analyses.
- A 700 node compute cluster to perform small- or large-scale data processing.
- A suite of tools developed in-house for the analysis of sequence data, designed to be used by both biologists and bioinformaticians.
- A comprehensive set of training courses to allow biologists to develop their informatics and statistical skills.

Progress in 2017

Over the last year the group has greatly expanded its training programme, running 34 courses on site in addition to those at Cambridge University, the EMBL-EBI and on other academic and commercial sites. We now have a modular set of statistics courses which cover all of the basic areas biologists are likely to need in their research. We have also expanded our sequencing training to cover more techniques, such that we now have an integrated set of courses to cover basic skills, application specific analysis and statistics.

Selected Impact Activities

- Helped organise the UK bioinformatics core facility meeting bringing together bioinformatics services from academia and industry
- Organised the first Cambridge Bioinformatics Hackathon to encourage new collaborative projects
- Presented at the Festival of Genomics on how biases in sequencing can produce misleading results

Publications

www.bioinformatics.babraham.ac.uk

- Hahn, O. *et al.* (2017) Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. ***Genome Biol.*** 18, 56
- Gahurova, L. *et al.* (2017) Transcription and chromatin determinants of de novo DNA methylation timing in oocytes. ***Epigenetics & Chromatin*** 10:25
- Wingett, S. *et al.* (2017) Cambridge Bioinformatics Hackathon 2017. ***F1000 Res***. 6-1942

Jonathan Clark
Facility head

Facility members

Postdoctoral research scientists:
Izabella Niewczas
Mel Stammers
(Started in 2017)

Biological Chemistry

The Biological Chemistry group provides support for scientists working at the interface between chemistry and biology at BI. We bring an understanding of chemistry and it's application to solving biological problems along with the capability to implement our suggestions using chemical and analytical tools.

In addition to our collaborations with the research groups we are investigating the chemical changes which occur in connective tissues as we age.

Capabilities

- Chemical synthesis of standards and reagents which are not commercially available
- Analysis of biological molecules by mass spectroscopy
- Development of new reagents and analytical methods
- Help and advice on any aspect of the application of chemistry/biochemistry to the exploration of biological problems

Progress in 2017

During 2017 we have supported groups throughout the Institute on a wide range of varied projects. These have ranged from synthetic chemical projects to make compounds which are not commercially available, through to developing new analytical methods to analyse lipids in cell extracts. In addition to these activities we have continued to run routine lipid analysis for a number of groups, both within the Institute and externally.

Selected Impact Activities

- Through 2017 we have run many commercial PIP3 analysis samples for a number of pharmaceutical companies studying the action of Pi3Kinase inhibitors in a clinical setting
- We have provided lipid analysis for a number of external academic groups through 2017

Publications

www.babraham.ac.uk/science-services/biological-chemistry

- Mouhannad Malek, Anna Kielkowska *et al.* PTEN Regulates PI(3,4)P2 Signaling Downstream of Class I PI3K, Molecular Cell, 2017, Volume 68, Issue 3, Pages 566-580

Biological Support Unit

Tim Pearce
Facility head

Facility staffing:

- 2 Deputy facility heads
- 2 Unit managers
- 2 Deputy unit managers
- 8 Supervisors
- 3 Deputy Supervisors
- 22 Experienced Animal Technicians
- 7 Junior Animal Technicians
- 4 Service Technicians
- 2 Veterinarians
- 1 Technical Services manager
- 1 Facility administrator/ Import and Exports manager
- 3 Apprentices

The use of animals in research continues to be key in helping to understand biology and disease. The Biological Support Unit provides state of the art housing and care for pathogen-free rodents used in both academic and private company research programmes. Our team of professionally qualified animal technicians provide expert technical support to researchers by undertaking regulated procedures, maintaining the animal health barrier and undertaking animal husbandry.

Capabilities

- The BSU is made up of four bio-science units, each performing a unique role in the provision of flexible services to meet the dynamic requirements of biological research. We have a mix of animal technicians and service technicians who perform daily husbandry duties and provide essential services to the facility.
- Our animal technicians hold Home Office Personal Licences enabling us to provide technical support for researchers. We have a commitment to up-hold the highest standards of animal welfare in all aspects of our work.
- The bio-science units surround the central services unit which utilises robotic cage-washing technology and automated sterilisation processes to provide equipment and consumables to each of the animal holding areas.

Progress in 2017

- Over the last year, the BSU has successfully implemented a centralised genotyping service using Transnetyx as the external provider. Transnetyx offers genotype results within 72hrs of the samples being sent with an accuracy of 99.97%, which allows for greater efficiencies with colony management and scientific research.
- As part of a continued career development programme the first class of apprentices have graduated with all three successfully being employed as qualified Junior Animal Technicians within the facility.
- The BSU provides rentable space and technical support to a number of commercial companies. Income from this venture doubled in 2017.

Selected Impact Activities

- As part of our recruitment initiative and commitment to the Concordat of Openness the BSU attended a careers fair at the Guildhall Cambridge promoting careers in animal technology
- In Nov 2017, the BSU conducted a virtual tour to a local community group offering members of the public a chance to understand how a modern animal facility operates
- A team of BSU managers gave a presentation entitled 'A holistic approach to building design' outlining the BSU concept including, design, construction, operation and future proofing

www.babraham.ac.uk/science-services/biological-support-unit

Rachael Walker
Facility head

Facility members

Attila Bebes
(Started in 2017)
Arthur Davis
Rebecca Roberts
Barbara Sobotic
(Started in 2017)
Lynzi Waugh
(Left in 2017)

Flow Cytometry

Flow cytometry allows cells to be identified, counted, analysed and sorted on the basis of specific physical or chemical features. For example, it can detect and separate different cells found in the immune system. The Flow Cytometry facility provides a world-class service to enable the research goals of the Institute. We help scientists from both the Institute and external companies with experimental design, training, troubleshooting and data analysis.

Capabilities

- Cell Sorting Service carried out by cytometry experts using state of the art cell sorters
- Training for scientists to use 5 High-End Analysers using up to 30 parameters
- Merck Millipore Amnis Imagestream MkII for analysing of cells using image cytometry
- Modular Theoretical Training Course which has already been attended by over 400 delegates including international delegates

Progress in 2017

In the past year, the Flow Cytometry Core has continued to provide an excellent service to Institute scientists, external companies and academics with utilisation of the high-end analysers and cell sorters. The three 5 laser, 20 parameter BD LSRFortessa analysers with in core facility, have continued to be heavily used and have played an important role in generating data for publications by Institute scientists.

Awarded a BBSRC ALERT-16 grant in April 2017 for an additional BD FACSAria Fusion cell sorter which will strengthen the cell sorting capabilities of Babraham Institute's Flow Cytometry Facility.

Selected Impact Activities

- Lectured on the EMBO Practical Course: The Fundamentals of High-Speed Cell Sorting at EMBL, Heidelberg
- Organised the flowcytometryUK meeting in London, exploring advances and interesting applications of cytometry
- Delivered a webinar on Data Management in a Shared Resource Laboratory (SRL) for the International Society for the Advancement of Cytometry (ISAC)

www.babraham.ac.uk/science-services/flow-cytometry

Publications

- Cossarizza, A. *et al*. (2017) Guidelines for the use of flow cytometry and cell sorting in immunological studies, ***Euro. J. Immunol***. 47(10), 1584-1797
- Collier, A.J. *et al*. (2017) Comprehensive Cell Surface Protein Profiling Identifies Specific Markers of Human Naive and Primed Pluripotent States. ***Cell Stem Cell*** 20: 874-890
- Frenk, S. *et al*. (2017) Aging yeast gain a competitive advantage on non-optimal carbon sources. ***Aging Cell*** 16: 602-604
- Kalkan, T. *et al*. (2017) Tracking the embryonic stem cell transition from ground state pluripotency. ***Development*** 141 (7) 1477-9129

Dominik Spensberger
Facility head

Dominik left the Institute in 2017, our future services are currently under review

Gene Targeting & Genome Editing

Our modern understanding of our genes makes it possible for researchers to alter individual genes to study their functions. The Gene Targeting facility can design and create specific genomic modifications by using techniques such as CRISPR/Cas9. We are able to produce genetically altered mouse models, embryonic stem cells and other cell lines. The facility can aid in the design, generation, targeting, screening and evaluation of genetic modifications.

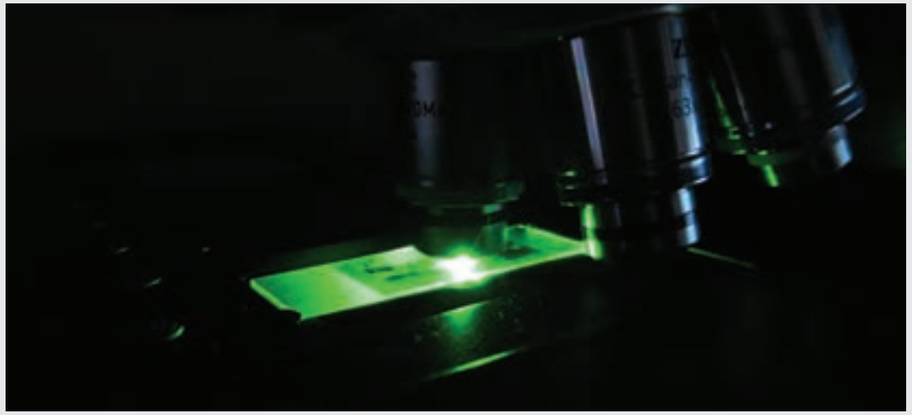
www.babraham.ac.uk/science-services/gene-targeting

Simon Walker
Facility head

Facility members

Deputy manager:
Hanneke Okkenhaug

Imaging



Green laser light illuminates a microscope slide using one of our confocal microscopy systems.

The Imaging facility provides a range of services to support the Institute's research. These include access to state of the art light microscopy technology, training and support for a variety of different imaging approaches. We provide advice on experiment design and offer an advanced image processing and analysis service.

Capabilities

- Super resolution fluorescence imaging (SIM & STORM)
- High content imaging and high content screening
- Image analysis software and training
- Focused Ion Beam/Scanning Electron Microscope (coming 2018)

Progress in 2017

Imaging remains a key investigative tool for Institute research and has contributed to a number of high profile publications this year (see below). We are also an important resource for commercial users and have an increasing portfolio of both campus-based and external companies accessing our facility.

We are continually looking to improve and expand our range of equipment and services, and have been fortunate to secure BBSRC funding for a new electron microscopy capability. This new instrument (due to arrive early 2018) will enable us to correlate 3D cellular ultrastructure with specific events of interest seen in living cells.

Selected Impact Activities

- Launched our Introduction to ImageJ courses. We anticipate adding an intermediate level ImageJ course and an Imaris course soon
- We welcomed two primary school visits this year, introducing children to the wonderful world of microscopy and discussing how imaging supports the Institute's research
- We hosted two undergraduate student visitors looking to increase their knowledge and experience of fluorescence microscopy

www.babraham.ac.uk/science-services/imaging

Publications

- Malek, M. *et al*. (2017) PTEN Regulates PI(3,4)P2 Signaling Downstream of Class I PI3K. ***Mol. Cell***. 68: 566-580
- Durgan, J. *et al*. (2017) Mitosis can drive cell cannibalism through entosis. ***eLife***, 6:e27134
- Diaz-Muñoz, M.D. *et al*. (2017) Tia1 dependent regulation of mRNA subcellular location and translation controls p53 expression in B cells. ***Nat. Commun***. 8:530

Michael Wakelam
Facility head

Group members

Qifeng Zhang
(Left in 2017)
Andrea Lopez
(Started in 2017)

Lipidomics

Lipidomics involves analysing the full compliment of lipid (fat) molecules found in cells, tissues and biological fluids. The aim is to provide a detailed yet complex view of molecules in a biological system. These methods can be used to understand cell structures, signalling and regulation and the data can be used in a system-wide approach to understand metabolic changes in health and disease. The Lipidomics facility can identify and semi-quantify a range of neutral, phospho- and sphingolipids.

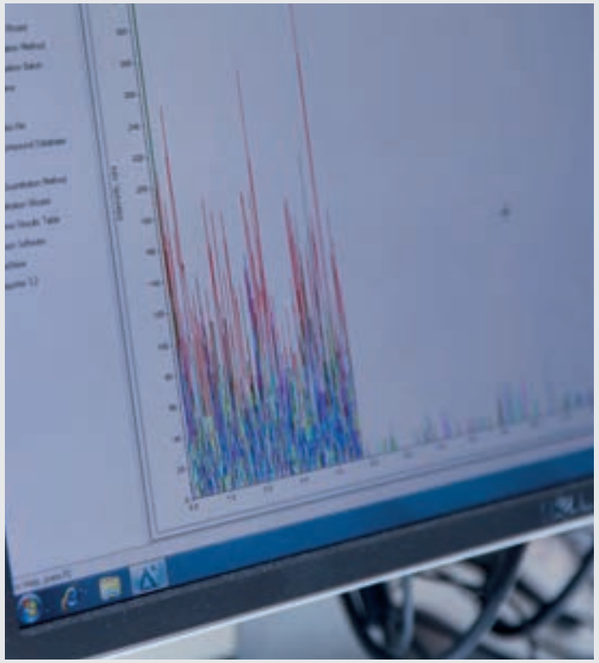
Capabilities

- Extraction, separation and measurement of neutral lipids, sphingolipids and phospholipids
- Bioinformatic analysis of lipidomics data to allow determination of biological pathways in which lipid molecules are modified
- Identification of novel lipids

Progress in 2017

The facility has undergone changes in personnel over the past year, which temporarily reduced our capability. New appointments Andrea Lopez and Greg West are now in place and have relaunched the facility.

In addition to our LC-MS capability we are now co-grant holders of LIPID MAPS with Cardiff University and UCSD in the USA, this has significantly expanded our lipidomics bioinformatics capability.



Selected Impact Activities

- Presented lipidomics data at the Keystone lipidomics meeting, the international Metobolomics and the Austrian proteomics meeting
- Together with colleagues in Austria, Germany, Singapore and the USA, developed bioinformatics methodology for platform-independent identification of lipid structures from MS data

Publications

www.babraham.ac.uk/science-services/lipidomics

- Nguyen, A. *et al.* (2017) Using lipidomic analysis to determine signaling and metabolic changes in cells. ***Curr. Op. Biotech***. 43, 96-103
- Hahn, O. *et al.* (2017) Dietary restriction protects from age-associated DNA methylation and induces epigenetic reprogramming of lipid metabolism. ***Genome Biol.*** 18, 56
- Hartler, J. *et al.* (2017) Deciphering lipid structures based on platform-independent decision rules. ***Nat. Methods***. 12:1171-1174

David Oxley
Facility head

Facility members

Senior research assistant:
Judith Webster

Postdoctoral researcher:
Katarzyna Wojdyla

Mass Spectrometry

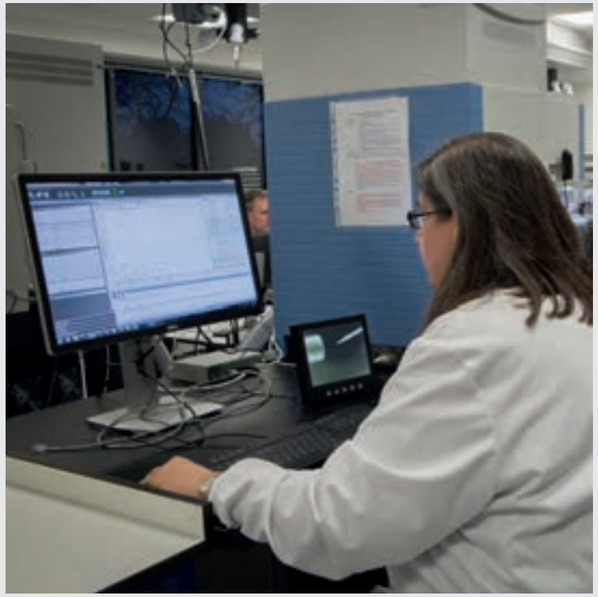
Mass spectrometry techniques can be used to analyse the structures of molecules. They have many applications in studying different biological molecules. The Mass Spectrometry facility uses the latest mass spectrometry approaches and develops new methods to support the Institute's research. We collaborate with colleagues across all of the Institute's research programmes.

Capabilities

- Three high resolution tandem mass spectrometers within the Facility, and shared access to a state of the art Orbitrap Fusion Lumos instrument located in the Biochemistry Department at Cambridge University
- Full range of high sensitivity mass spectrometric analyses for protein identification, quantitation and characterisation
- Quantitation of DNA modifications, particularly cytosine modifications 5mC, 5hmC, 5fC, 5caC
- Development of novel mass spectrometric analytical methods

Progress in 2017

We have successfully modified the tandem mass tagging (TMT) methodology to enable the multiplexed quantitative analysis of very low levels of affinity purified signalling complexes. In collaboration with Institute research groups, we have applied this to the analysis of PI3-kinase signalling in prostate, MEFs and T-cells. We have also developed an isotope-dilution mass spectrometric method for the accurate absolute quantitation of Erk1 and 2 phosphorylation, which we are using in collaboration with Simon Cook's group to monitor the response of cancer cells to various conditions.



Selected Impact Activities

- Collaboration with groups at Cambridge University on DNA modifications in cancer and in intestinal epithelial cells
- Commercial work for several campus companies
- Hosted two teachers from Manchester and Bury St Edmunds as part of the STEM Insight Programme

Publications

www.babraham.ac.uk/science-services/mass-spectrometry

- Langie, S.A. *et al.* (2017) The Ageing Brain: Effects on DNA Repair and DNA Methylation in Mice, ***Genes (Basel)*** 8(2). pii: E75
- Yang, J. *et al.* (2017) Establishment of mouse expanded potential stem cells, ***Nature*** 550, 393-397

Kristina Tabbada
Facility head

Facility members

Clare Murnane

Next Generation Sequencing

Sequencing large amounts of DNA from many samples – a process called high – throughput sequencing, has the potential to further our understanding of mechanisms for gene regulation. It can also help to enhance our knowledge of DNA organisation and structure. The Next Generation Sequencing (NGS) facility provides researchers with access to cutting edge sequencing technology to advance their research.

The NGS Facility now offers a start-to-finish library preparation service for specific library types, including standard RNA-seq and low-input RNA-seq. This includes RNA quality control (QC), sequencing library preparation and library quality control.

Capabilities

We offer a range of services that allow users to select platforms, read length and depth of coverage. Our instruments include:

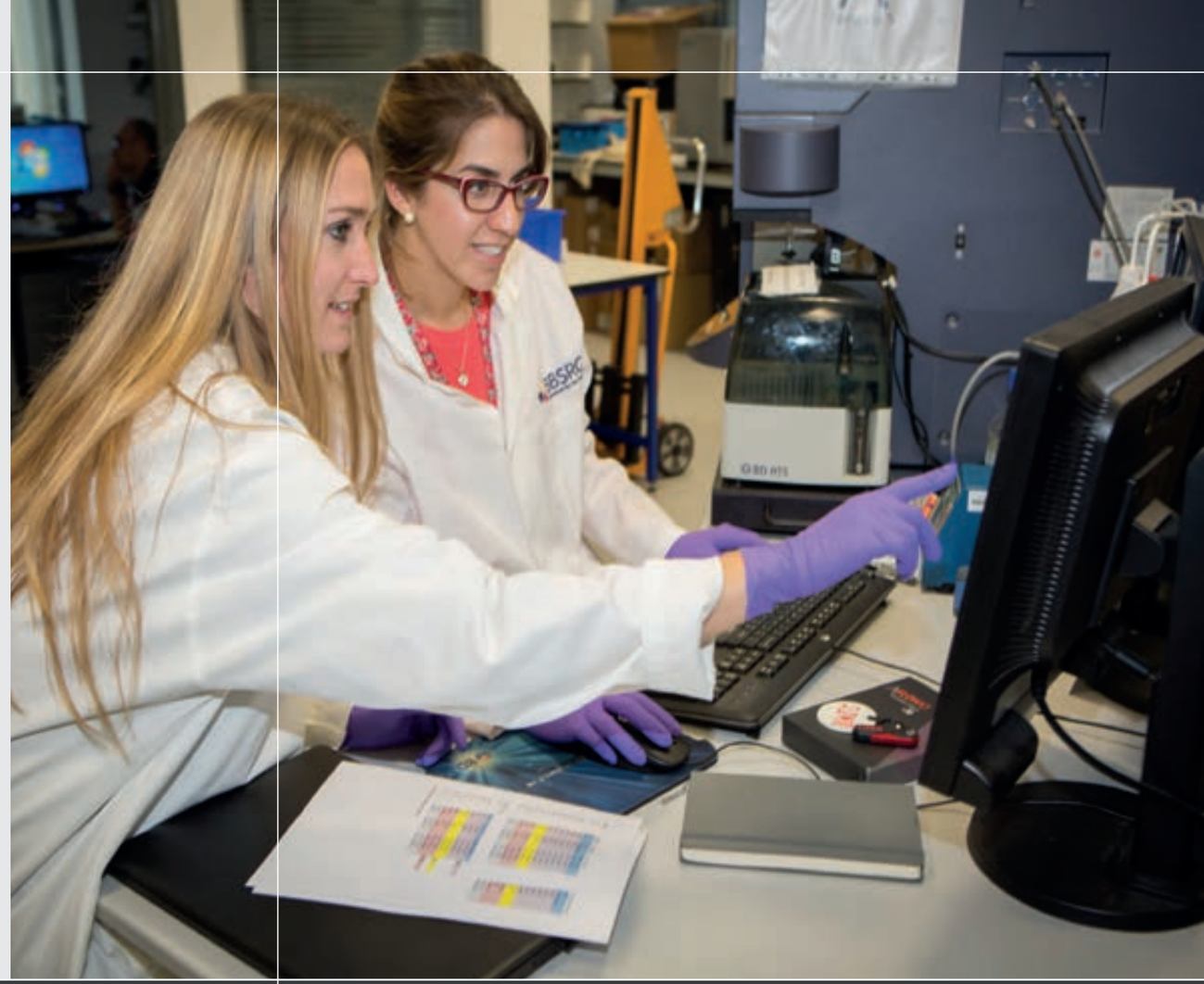
- HiSeq 2500 for high-throughput projects
- MiSeq for validation or long sequence runs
- NextSeq for sequencing depth with a fast turnaround

Progress in 2017

Whilst continuing to offer a state of the art sequencing service, the NGS Facility is developing an automated library preparation service using the high-precision fluidics of a Hamilton NGS Star. The facility team contributed to the successful grant application for this instrument. The Hamilton NGS Star has been fully installed, and protocols for running library preparation on the unit are being developed. The Hamilton NGS Star is expected to decrease the time required for library preparation, whilst improving consistency and eliminating the variation between users that occurs as a result of manual handling.

Selected Impact Activities

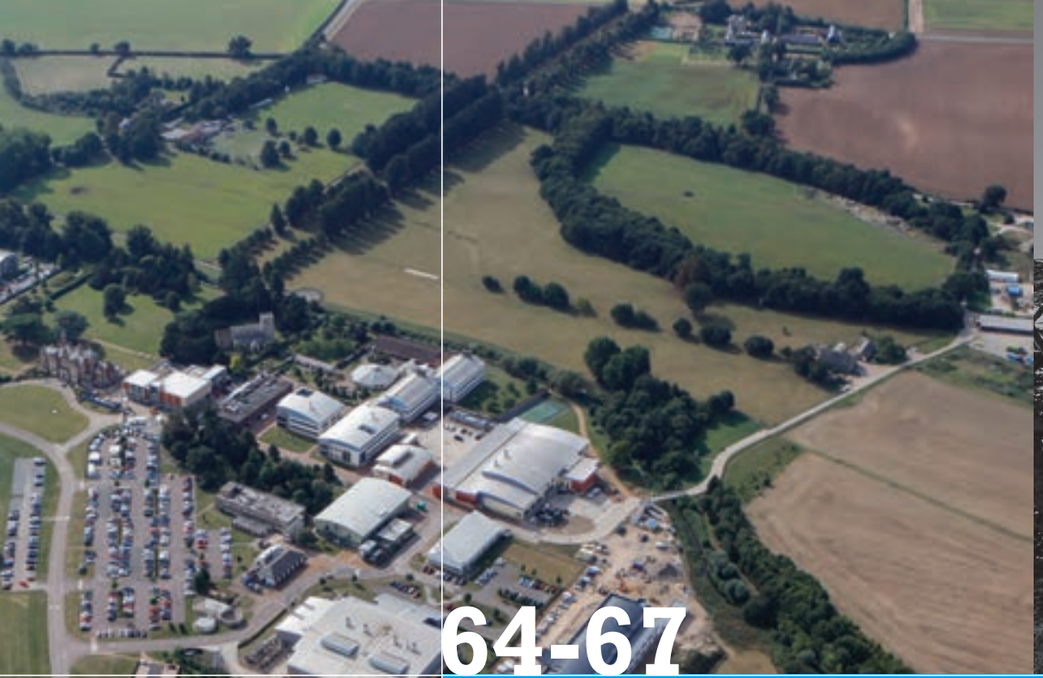
- Participated in the Facility Open Day 2017, in which the Babraham Institute Core Facilities welcomed visitors from around the Campus who were interested in their services and technology
- Hosted student tour groups
- Organised a Users Group Meeting involving NGS service users and Illumina representatives to discuss 'Index Hopping Effects and Mitigation Strategies'



Publications

www.babraham.ac.uk/science-services/sequencing-facility

- Matheson, L.S. *et al*. (2017) Local chromatin Features including PU.1 and IKAROS Binding and H3K4 Methylation shape the repertoire of immunoglobulin Kappa genes chosen for V(D)J recombination. ***Front. Immunol***. 8:1550
- Wutz, G. *et al*. (2017) Topologically associating domains and chromatin loops depend on cohesin and are regulated by CTCF, WAPL, and PDS5 proteins. ***EMBO J*** 36:3573-3599
- Stubbs, T.M., *et al*. (2017) Multi-tissue DNA methylation age predictor in mouse. ***Genome Biol***. 18(1):68



64-67

Impact

By working with organisations and communities in the local area and beyond, we help to ensure that the results of our research have greater impacts for society and the economy. Our goal is to help more people to live healthier lives by raising public awareness and rapidly transforming the latest science into new healthcare, policies and technologies.

Engaging with our research

Public Engagement and Science Communication (PESC) are an established part of our research culture. Institute researchers and scientific staff have a thirst for the curious and unknown, a passion for their work and an enthusiasm to share, discuss and consider public opinion. The Institute's PESC programme provides opportunities for all to be involved through discussions, exhibits, festivals and hands-on activities, student and teacher lab days, and community group talks and tours.

Our Goals

Our PESC programme is going from strength to strength, thanks to the commitment of both students and staff. We are developing a new PESC strategy with a vision to maintain an open and accountable approach, which ensures our research excellence contributes to culture, society, economic development and growth.

Through our European Commission-funded ORION project we will explore the concepts of Open Science with public dialogues and 'co-creative' research projects. In 2018 we'll be showcasing our latest ageing research, with a new exhibit 'Race Against the Ageing Clock' at the Royal Society Summer Science Exhibition in July. We'll also be providing new opportunities for students and teachers to learn about cutting-edge research through Schools' Day, BioscienceLITES, ethics workshops and more!

2017 Review

This year saw the launch of a new science-art project developed in collaboration with our researchers, CHROMOS – a virtual reality experience, video and music tracks offering a unique perspective on the genome (see Page 50).

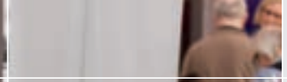
Schools' Day reached its 23rd year, community groups visited for virtual tours of our animal facility, and we hosted a number of events during Cambridge Science Festival. Our Royal Society Partnership Grant Projects with schools in Hitchin and Colchester, also came to an end with students showcasing their work at the Royal Society.

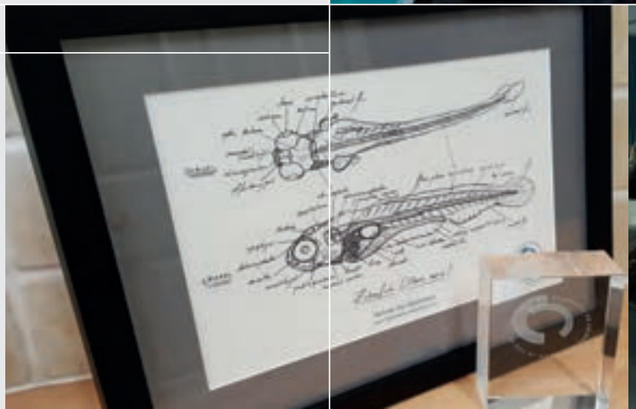
Finally, we were delighted to be awarded an Understanding Animal Research Openness Award, recognising our commitment to openness around the use of animals in research, particularly our work with the students at Sophianum School, in the Netherlands.

In total, over 130 staff and students participated in 50 events, engaging with 9000 people of all ages, from Cambridge, the UK and beyond.

www.babraham.ac.uk/about-us/impact/public

Look out for our new 'Race Against the Ageing Clock' exhibit launching in 2018.





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