Babraham Institute

2018

Babraham Institute
Annual Research Report

Life sciences research for lifelong health

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. To meet the challenges presented by an ageing global population, we must find ways to secure health in our later years.

To address these challenges, the Babraham Institute unites wide-ranging expertise in fundamental biology to gain a detailed understanding of ageing and lifelong health. Our research aims to uncover more about the role of the immune system in health and age-related changes, to investigate how the cells of our bodies respond and adapt to damage, disease, diet and ageing, and to chart epigenetic changes to gene regulation throughout development and ageing.

Contents

Director's welcome

As in previous years the Institute has continued to contribute to our understanding of the fundamentals of human biology. Much of this work is in line with the BBSRC Strategic Priority 'Bioscience for Health' within which one of our strategic missions is to tackle the challenges presented by an ageing population by making discoveries that have the potential to enhance lifelong health and wellbeing.

This Annual Research Report is a collection of the ground-breaking progress Institute scientists made in 2018 and our plans for the future. Through the included feature articles, we introduce the three new group leaders who joined the Immunology programme in 2018 (see Our People), share how the field of lipidomics is exploding and how the Institute is taking a leading role in uncovering the biological relevance of lipid changes, and reflect on how big data is revolutionising science. We continue to work to maximise our impact through working with industry, academia, politicians and the public to share our findings and promote the use of research findings to drive meaningful change and achieve wider scientific awareness. These interactions are summarised in the infographic overleaf.

Professor Michael Wakelam
Institute Director

Our Science

In 2018 the Institute began an exciting period of recruitment with some associated scientific redirection, nevertheless we continued to produce outstanding science as described in the following pages. Amongst the many highlights of the year was the development of scNMT-seq which enabled joint profiling of chromatin accessibility, DNA methylation and transcription in single cells (1). This simultaneous examination of three fundamental aspects of cell biology in the same single cell opens up the options of identifying changes in early development and in human disease. Institute scientists also identified placental defects key to prenatal deaths (2), and how ageing affects developing B cells including identifying the central role for insulin-like growth factor signalling (3). Additionally, developments in lipidomics identified lipid metabolic and signalling pathways critical for infections responsible for the common cold (4).

Our People

As I discussed in a Vision piece for the FEBS Network (5), an Institute is only as good as its staff. We are fortunate that the Babraham Institute has an outstanding cohort of staff at all levels and in all roles; our output is dependent upon the contributions of all. I am very proud that in 2018 we were awarded an Athena SWAN Silver Award for the second time recognising our total commitment to equality and diversity. We were very sorry to say goodbye to Myriam Hemberger who moved to a prestigious Professorial position at the University of Calgary, but during 2018 we recruited three new Group Leaders in the Immunology programme: Sarah Ross, Claudia Ribeiro de Almeida and Adrian Liston. Whilst Sarah and Claudia have been recruited as tenure-track Group Leaders, Adrian is already an established and internationally-recognised Group Leader and joined us from the University of Leuven. We look forward to each of these research groups making significant impacts over the years to come.

Our Impacts

The Babraham Institute's impact is presented through knowledge exchange, commercialisation, public engagement and communications. Notable examples from 2018 include our contribution to the Royal Society of Biology/ITN production: Addressing Global Challenges with a video outlining our research in 'Helping to turn back the ageing clock' (6). We were also pleased to be selected to contribute our exhibit: 'Race against the Ageing Clock' to the Royal Society Summer Science Exhibition (7). In addition to the Institute's many research publications we have made a number of contributions to the less specialised media, many of which have been highlighted on the Institute webpages.

Key Awards

- Silver Athena SWAN award under the expanded charter
- Professor Wolf Reik was awarded a Wellcome Trust Investigator Award for research into how to reprogramme the epigenome

113
VISITING RESEARCHERS

90
PUBLICATIONS

103
COMMERCIAL PROJECTS

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

Professor Michael Wakelam
Institute Director

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

Publications

1. New technique offers insights into early life www.babraham.ac.uk/news/2018/02/new-technique-offers-insights-into-early-life
2. Placenta defects key factor in prenatal deaths www.babraham.ac.uk/news/2018/03/placenta-defects-a-factor-in-prenatal-deaths
3. How does ageing affect developing B cells? www.babraham.ac.uk/news/2018/09/how-does-ageing-affect-developing-b-cells
4. Studying cellular fats reveals how to protect cells from the common cold www.babraham.ac.uk/news/2018/10/studying-cellular-fats-reveals-how-to-protect-cells-from-the-common-cold
5. One size doesn't fit all – the Babraham approach to achieving excellence. Visions piece for FEBS Network
6. Addressing Global Challenges: Helping to turn back the ageing clock https://youtu.be/cWEZJhdXvO0
7. Race against the Ageing Clock www.babraham.ac.uk/ageingclock

Performance in 2018

OUR COLLABORATIVE ACADEMIC PROJECTS
UK AND WORLDWIDE

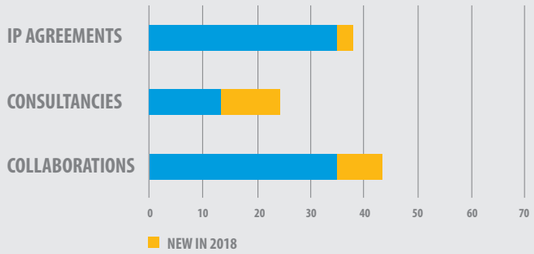
Working with others in 2018

47 ACTIVE PROJECTS

25 COUNTRIES

98 ORGANISATIONS

Working with commercial partners



People we've trained in our scientific facilities this year

1195

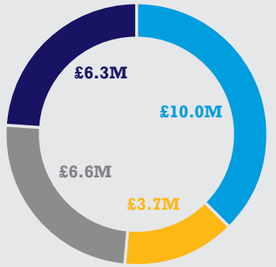
BIOINFORMATICS **899**

FLOW CYTOMETRY **209**

IMAGING **50**

ANIMAL FACILITY **37**

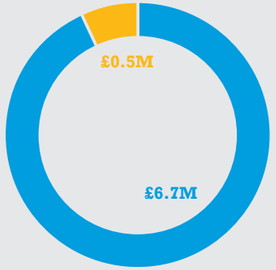
2018 income



£26.6M

- Core ISP grants & BBSRC non-grant income
- Competitively awarded grant income in 2018
- Income from services provided by the Institute
- Other

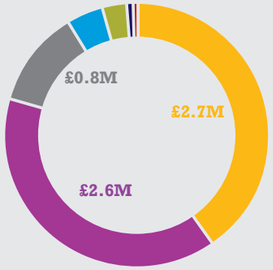
Value of all grants awarded in 2018



£7.2M

- UK funders
- International grants*

Value of UK grants awarded in 2018



£6.7M

- MRC
- Wellcome Trust
- BBSRC
- F-Star
- Plexxikon Inc.
- Centre for Trophoblast Research
- Royal Society

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

2018 successes

30
PUBLIC ENGAGEMENT EVENTS

INVOLVING

121
RESEARCHERS

14,800
PEOPLE ENGAGED

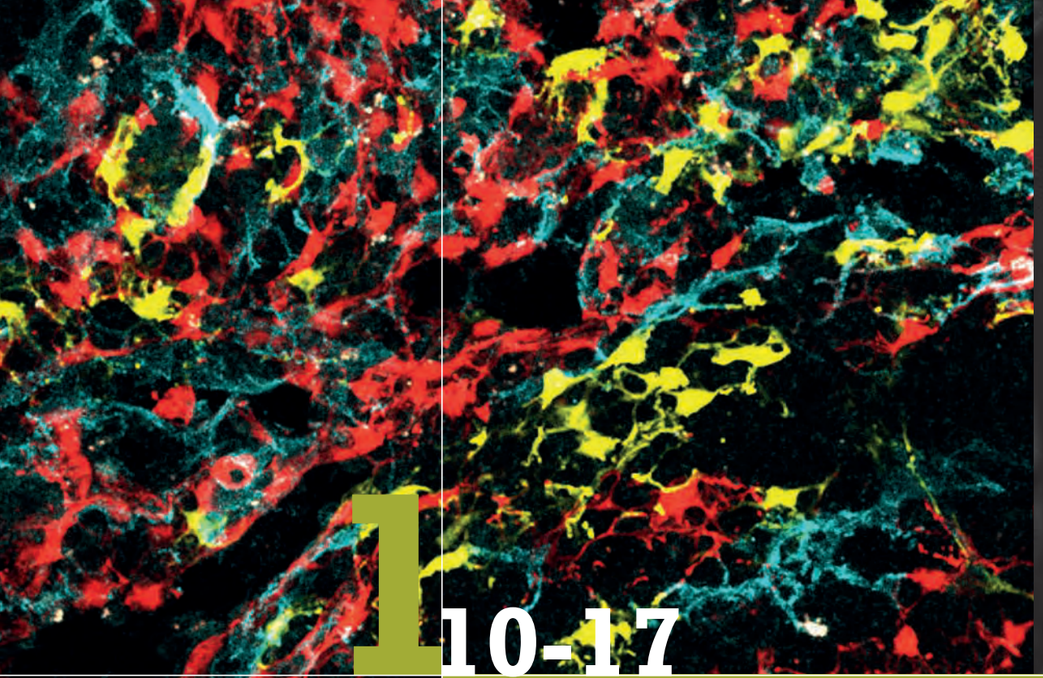
90
PUBLICATIONS

71
RESEARCH PUBLICATIONS

19
REVIEWS

Athena SWAN Silver Award
EC GENDER CHARTER

13
PhDs COMPLETED



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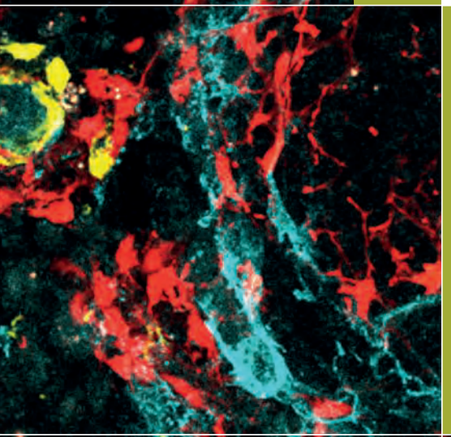
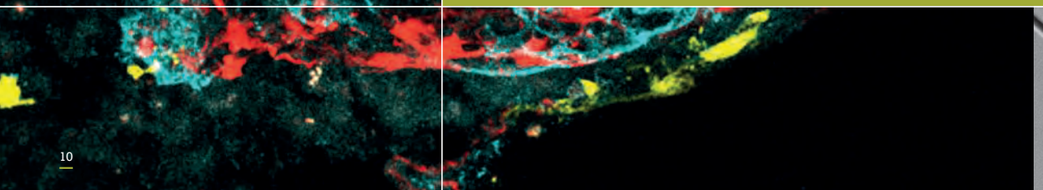


Immunology

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 tissues and organs of the body
- How different molecular signals influence gene activity and ultimately the growth and behaviour of lymphocytes



Group Leaders

Martin Turner

Anne Corcoran

Michelle Linterman

Rahul Roychoudhuri

Joined in 2018

Adrian Liston

Claudia Ribeiro de Almeida

Sarah Ross

Martin Turner
Programme leader

Group members

Senior research associates:
Sarah Bell
Elisa Monzón-Casanova

Postdoctoral researchers:
Georg Petkau (Started in 2018)
Beatriz Sáenz-Narciso (Started in 2018)
Fiamma Salerno
Michael Screen
Alexander Saveliev

Bioinformatician:
Louise Matheson

PhD students:
Oezge Gizlenci (Started in 2018)
Fengyuan Hu
Twm Mitchell
David Turner

Flow Cytometry assistant:
Barbara Sobotic (Left in 2018)

Visiting scientist:
Manuel Díaz-Muñoz (Left in 2018)

Molecular mechanisms of lymphocyte activation

We investigate the fundamental mechanisms regulating the changes in gene expression that promote lymphocyte development and activation. Our recent work has focused on RNA binding proteins (RBPs) that control messenger RNA post-transcriptionally. Our recent published work demonstrates RBPs play essential roles in lymphocyte homeostasis and in the selection of B cells in the germinal centre.

Current Aims

We study RNA binding proteins that control gene expression both by regulating the abundance of mRNA produced by a gene and by controlling the alternative transcripts of mRNA produced from a single gene through alternative splicing or polyadenylation. The activities of RBPs are regulated by signal transduction pathways that sense changes in the cellular environment. Moreover, they integrate signal transduction with epigenetic and transcriptional control (the rate at which mRNAs are produced) to enable both 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.

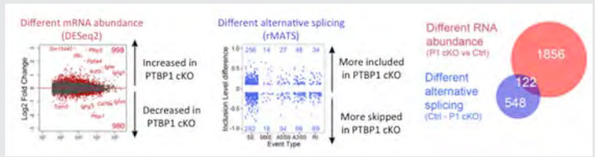
Progress in 2018

We reviewed the variety of means by which RNA binding proteins act to control the development and function of immune cells (Turner and Díaz-Muñoz, 2018). This class of regulators is increasingly appreciated to be deeply embedded in every aspect of development and function. As such their importance rivals that of transcriptional control. It is now a major challenge to understand how these different layers of control are integrated to bring about developmental and physiological responses.

In a significant body of work Elisa Monzón-Casanova showed that polypyrimidine tract binding protein (PTBP1) is critical for the selection of B cells in the germinal centre and regulates the abundance and alternative splicing of genes necessary for rapid proliferation (see figure) (Monzón-Casanova *et al*., 2018). PTBP1 was found to be an RNA binding protein induced by the transcription factor c-myc that is necessary for the full expression of the c-myc dependent gene expression programme.

Selected Impact Activities

- Invited participant at Keystone Symposia 'B Cells: Mechanisms in Immunity and Autoimmunity' June 2018.
- The lab hosted secondary school students for a week.



Visualisation of RNAseq data showing the effect of the loss of PTBP1 on the transcriptome of B cells in terms of mRNA abundance and RNA isoforms. Taken from Monzón-Casanova et al. (2018).

Publications

- Turner, M. & Díaz-Muñoz, M.D. (2018) RNA-binding proteins control gene expression and cell fate in the immune system. ***Nat Immunol.*** 19(2):120-129. Review. PMID: 29348497
- Monzón-Casanova, E. *et al.* (2018) The RNA binding protein PTBP1 is necessary for B cell selection in germinal centres. ***Nat Immunol.*** 19(3): 267-278. PMID: 29358707

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

Anne Corcoran

Group members

Senior postdoctoral researcher:
Daniel Bolland

Postdoctoral researcher:
Peter Chovanec

PhD students:
Lina Dobnikar
Sam Rees
Carolyn Rogers
Michiel Thiecke

Visiting scientist:
Lyubomira Chakalova

Visiting student:
Jasper Carmody (Left in 2018)

Making enough different antibodies to fight infection

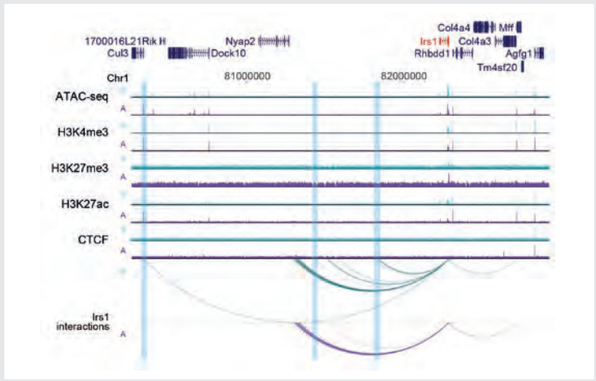
The immune system creates antibody proteins to help fight diseases. Antibodies are made by white blood cells called B lymphocytes. By mixing and matching genetic information, these cells can produce billions of different antibodies to combat different diseases. We are interested in the mechanisms involved 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 so many different combinations. 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 and impaired antibody production in ageing.

Progress in 2018

In ageing the bone marrow produces fewer B lymphocytes. With other groups at the Institute we compared genome-wide gene expression in B lymphocytes from young and old mice to discover genes dysregulated in ageing. We also investigated how ageing affects epigenetic mechanisms, including promoters that switch on genes, microRNAs that degrade RNA made by these genes, and 3D interactions of gene promoters with distal enhancers (activating sequences). We found that the insulin-like growth factor receptor signalling pathway that is required for B cell development and expansion is impaired in ageing B cells. Countering this impairment may provide a way to restore B cell numbers and reduce the age-related decline of the immune system.



Genome browser view of interactions from the irs1 promoter (in red) in young and old B lymphocytes. This gene encodes the insulin receptor substrate 1 protein, which is reduced in ageing. Y and A refer to young and aged B lymphocytes respectively. The tracks indicate enrichment for chromatin accessibility (ATAC-seq), histone modifications and CTCF. Blue shading indicates interactions that are lost upon ageing.

Selected Impact Activities

- Talk at Cold Spring Harbor, USA, 'Gene Expression and Signalling in the Immune System', April 2018.
- Group members designed, delivered and judged a new Launchpad science challenge activity for 12 year olds in three local schools.
- Contributed to an article by Tom Chivers published in the Wellcome Trust's online publication Mosaic and also in the Independent online: How big data is changing science.

Publications

- Koohy, H. *et al.* (2018) Genome organisation and chromatin analysis identifies transcriptional downregulation of insulin-like growth factor signalling as a hallmark of ageing in developing B cells. ***Genome Biol.*** 19: 126-150
- Chovanec, P. *et al.* (2018) Unbiased quantification of immunoglobulin diversity at the DNA level with VDJ-seq. ***Nat. Protoc.*** 13: 1232-1251

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

Michelle Linterman

Group members

Senior postdoctoral researcher:
Louise Webb

Research fellows:
Alice Denton
Danika Hill

Postdoctoral researchers:
Edward Carr
Ine Vanderleyden

PhD students:
Alyssa Silva Cayetano
Marisa Stebegg

Visiting students:
Janie Olver (Left in 2018)
Jaqueline Siu

Research assistants:
Sigrid Fra-Bido
Silvia Innocentin

The immune response 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

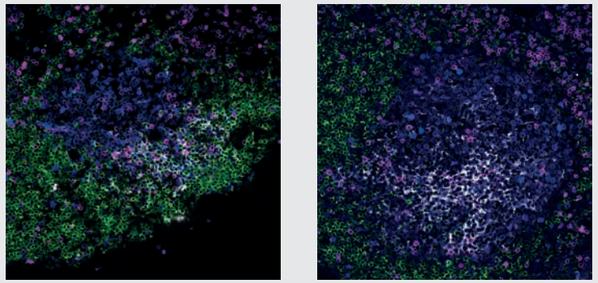
The germinal centre response generates protective immunity through the production of antibody-secreting plasma cells and memory B cells. Our research aims to understand why the magnitude and quality of the germinal centre response is impaired with advancing age. We also wish to identify tractable strategies to enhance the response to vaccination in humans.

Progress in 2018

In 2018 we discovered that the reduced size of the germinal centre response in the gut can be corrected in aged mice by microbial transplantation. This is a proof-of-concept study that shows the age-dependent defects in the germinal centre response are not irreversible. Further, we have identified that one of the next generation of adjuvants, GLA-SE, is able to stimulate the germinal centre response in humans. This works indicates that this adjuvant is a viable strategy to improving vaccine formulation.

Selected Impact Activities

- Hosted school students for work experience.
- Trained undergraduate summer students in the laboratory.
- Contributed to a film about the Institute's work, Helping to Turn Back the Ageing Clock, produced as part of the Addressing Global Challenges programme by ITN Productions in partnership with the Royal Society of Biology.



This pair of images depict the germinal centre response in mice 14 days after immunisation. Germinal centre B cells (Blue, Ki67) are seen within the B cell follicle (Green, IgD), follicular dendritic cells (White, CD35) are within the germinal centre, and T cells (Pink, CD3) are present both outside, and within the germinal centre.

Publications

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

@LintermanLab

- Wallin, E.F. *et al.* (2018) The calcineurin inhibitor Tacrolimus specifically suppresses human T follicular helper cells. ***Front. Immunol.*** 9:1184
- Stebegg, M. *et al.* (2018) Regulation of the germinal center response. ***Front. Immunol.*** 9:2469
- Poyntz, H.C. *et al.* (2018) Genetic regulation of antibody responsiveness to immunization in substrains of BALB/c mice. ***Immunol. Cell Biol.*** 97(1):39-53

Rahul Roychoudhuri

Group members

Postdoctoral researchers:
Teresa Lozano (Left in 2018)
Rabab Nasrallah
(Left in 2018)
Sarah Whiteside
(Started in 2018)
Jie Yang (Started in 2018)

PhD students:
Francis Grant
Charlotte Imianowski
Firas Sadiyah

Research assistant:
Panagiota Vardaka

Visiting students:
Carina Nava (Left in 2018)
Tihomir Todorov
(Started in 2018)
Nordin Zandhuis
(Left in 2018)

Uncovering the 'brakes' on immune activation

Immunoregulatory mechanisms are critical 'brakes' that constrain the activation of the immune system. Our research explores the immunoregulatory mechanisms that contribute both to immunological tolerance and immunosuppression and the immune cell types involved in these processes. This knowledge is of fundamental biological and medical significance, and the relevance of our research to immunotherapy has provided the laboratory with the opportunity to extend the impact of our work this year through the initiation of collaborations with the industrial sector.

Current Aims

T cells play a critical immunoregulatory function in addition to their better understood role in promoting immunity. Whereas conventional CD4+ and CD8+ T (Tconv) cells drive immune reactions and promote clearance of infections and cancer, regulatory T (Treg) cells suppress these reactions to prevent excessive inflammation and are critical to immunological tolerance. Treg cells also suppress Tconv responses in chronic infections and cancer and thereby contribute to immunosuppression.

Our programme of research is organised into three aims:

1. A fundamental focus of our research is to understand the gene regulatory mechanisms underlying the lineage specification of Treg and Tconv cells from common precursor cells, and their distinct functions.
2. Understanding the mechanisms that control the maintenance and function of Treg cells for immune homeostasis throughout the lifespan.
3. Investigating the mechanism by which distinct environments control T cell activation, development and function.

Progress in 2018

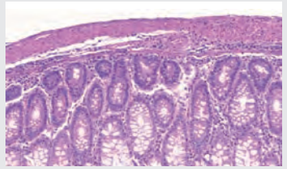
We have made progress in understanding the genetic basis underlying susceptibility to human inflammatory diseases by modelling the function of human disease-associated enhancers using mouse models. Our work shows that this type of genetic modelling, most frequently applied to understanding the function of protein-coding genes in the immune system, can also be applied to understanding the non-coding regulatory genome and the complex contributions it makes to controlling immunity.

We have also made progress in understanding mechanisms underpinning the maintenance and function of Treg cells following their lineage specification. We found that the transcription factor BACH2, which we know plays a critical role in early lineage specification of Treg cells (reviewed in Igarashi, Kurosaki and Roychoudhuri, *Nat. Rev. Immunol.* 2017), is repurposed following Treg lineage commitment. High levels of BACH2 expression in a subset of Treg cells is required to enforce their functional quiescence and this quiescence is important for Treg population maintenance.

Our collaborative work with the Stevens group at the Institute has identified new ways in which the function of the immune system is suppressed in cancer (Gyori *et al.*).

Selected Impact Activities

- We have initiated a collaboration with the Babraham Research Campus company F-Star Biotechnology to understand how new classes of tumour immunotherapies function.
- We hosted two groups of sixth form students for a day in the laboratory as part of the Institute's 2018 Schools' Day.
- International collaborations with researchers at the US National Institutes of Health have enabled us to gain new molecular insights into the stem cell-like behaviour of memory T cells (Gautam *et al., Nat. Immunol.* 2019) and their function in tumour immunity (Vodnala *et al., Science* 2019).



Gut inflammation in the large intestine of mice resulting from loss of an enhancer required for normal Treg function.

Publications

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

- Miura, *et al.* (2018) Bach2 promotes B cell receptor-induced proliferation of B lymphocytes and represses cyclin-dependent kinase inhibitors. ***J. Immunol***. 200:2882-2893
- Gyori *et al.* (2018) Compensation between CSF1R+ macrophages and Foxp3+ Treg cells drives resistance to tumor immunotherapy. ***JCI Insight*** 3(11) doi: 10.1172/jci.insight.120631
- Lim *et al.* (2018) Phosphoinositide 3-kinase δ inhibition promotes antitumor responses but antagonizes checkpoint inhibitors. ***JCI Insight*** 7;3(11) doi: 10.1172/jci.insight.120626

New horizons for immunology

New group leaders bring new skills, new expertise and new perspectives, and 2018 saw three new group leaders join the Institute's Immunology programme. Professor Adrian Liston, Dr Claudia Ribeiro de Almeida and Dr Sarah Ross talk about their research, their ambitions and what makes the Institute such a special place to work.

They come from VIB in Belgium and the universities of Oxford and Dundee, they focus on different areas of immunology and bring new interests and expertise, but Professor Adrian Liston, Dr Claudia Ribeiro de Almeida and Dr Sarah Ross are all hugely excited to have recently joined the Institute.

Liston, already an established group leader, works on the specialist population of immune cells known as CD4 T cells. These cells effectively coordinate and 'turbo charge' our immune response. They are also the cells that are targeted by HIV, explaining why the disease causes immune system suppression and illustrating how crucial CD4 T cells are to our overall health.

At VIB, Liston specialised in translational immunology, understanding and then developing ways to treat children with rare immune diseases. "These diseases are incredibly severe, but once you understand them mechanistically you can work out ways to treat them," he explains. "It was very rewarding because these kids that would otherwise often die can go on to lead long, healthy lives once you've found out what's wrong and how to fix it."

At the Institute, Liston wants to answer three key questions: how the millions of CD4 T cells in our bodies communicate and cooperate; how they switch between a ramping up and damping down cell type; and what they do in our tissues. Understanding how these cells modulate our immune system means that they can potentially be used as a tool to fine tune the immune system to help overcome age-related decline.

With its world-leading Immunology programme and cutting-edge facilities the Institute is a great fit for Liston's ambitions. But what sets the Institute apart is how it nurtures scientific innovation and champions equality and inclusion.

"Great research requires fantastic people who think as differently as possible, which means having an environment that celebrates equality and inclusion. The Institute has a great reputation for this internationally – it's setting the gold standard for equality and inclusion. You can feel the difference here," says Liston. "The Institute provides an environment where you're going to be stimulated and have the chance to explore the limits of your imagination."

Ribeiro de Almeida and Ross both believe the Institute's culture will help them build their first research groups. "It's a very friendly, supportive environment. Everyone is ready to help with time and feedback – they want you to succeed and that's really special," says Ross.

Ribeiro de Almeida's work centres on B lymphocytes and the rare ability they have to rearrange antibody genes by cutting and pasting DNA in order to fight the plethora of pathogens to which we are exposed. "I'm interested in understanding how this mechanism is regulated throughout cell development," she explains. "It's a fundamental question, because mistakes in this process can result in leukaemia and lymphoma. To understand these diseases and wider age-related immune dysfunction it's important to understand how these molecular mechanisms are regulated."

Dr Claudia Ribeiro de Almeida

Dr Sarah Ross

Professor Adrian Liston

'The Institute is setting the gold standard for equality and inclusion'

As a postdoc in Oxford, she worked in a lab that studied gene expression rather than B cells, so she brings a more molecular approach to the programme. She also discovered an RNA-binding protein that plays an important part in B lymphocytes' cut and paste process, something she's keen to follow up: "The research I want to do next is to identify which proteins are implicated in this mechanism of gene rearrangement and how they modulate B cell responses."

Ross specialises in T lymphocytes and the impact that hypoxia – or low levels of oxygen – has on the way they work. Because T cells commonly encounter hypoxic environments, they can adapt to low oxygen environments by changing the proteins they express. While this helps them survive, it can also make them less effective killers of disease cells.

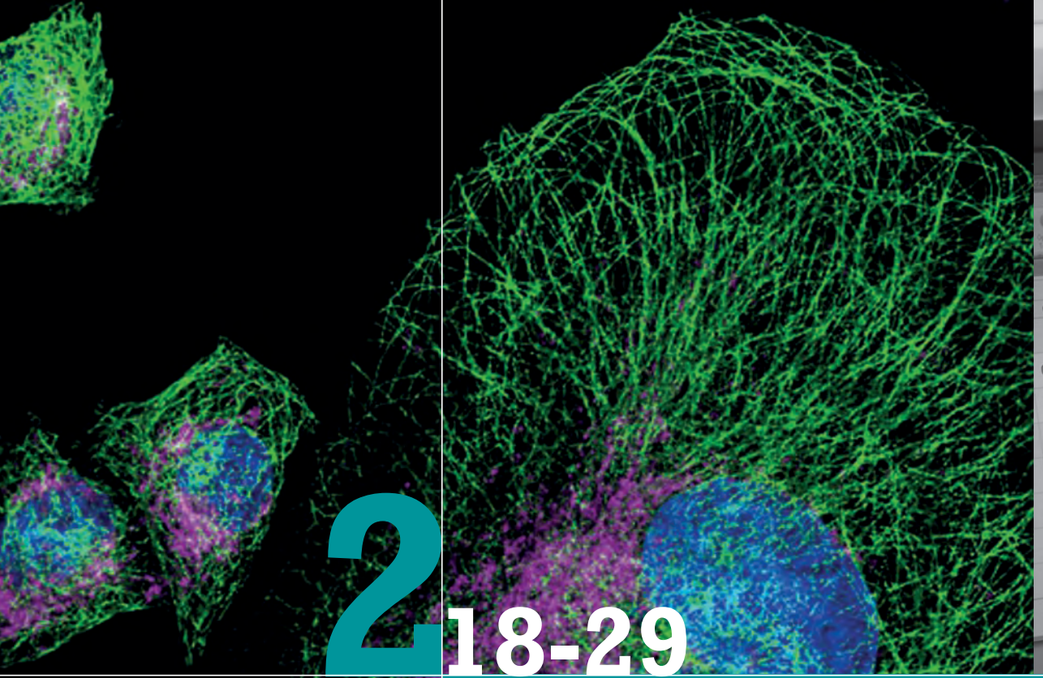
"I want to understand how oxygen regulates T cells from a signalling and gene expression perspective," she explains. "If we could identify factors that we could target therapeutically to overcome the effects of low oxygen and boost the ability of T cells to perform their protective function, that would be amazing."

We know that as we age, our immune system becomes less effective and poorer oxygenation is also connected with ageing, so what Ross discovers about hypoxia could have important implications, both for our understanding of the ageing immune system and in making immunotherapies more successful.

The arrival of all three is an exciting opportunity for the Institute, the Immunology programme and its three new group leaders. "It's amazing – I'm still pinching myself," Ross concludes. "It's great to be able to make new plans and work out how to turn them into reality utilising the know-how and the facilities we have access to here. And it's exciting to be here because my plans cover all three programmes – Immunology, Signalling and Epigenetics – adding my own to all the expertise here makes it hugely exciting."

'Great research requires fantastic people who think as differently as possible'

Image of Adrian Liston used courtesy of the Cambridge Independent.



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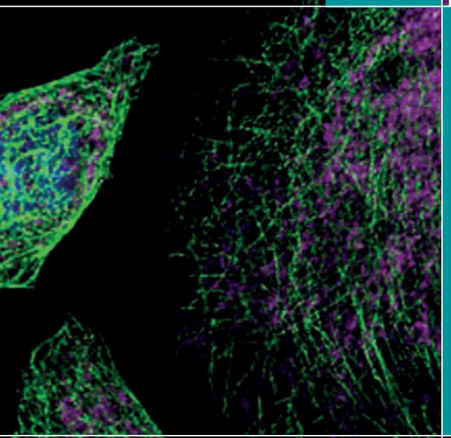
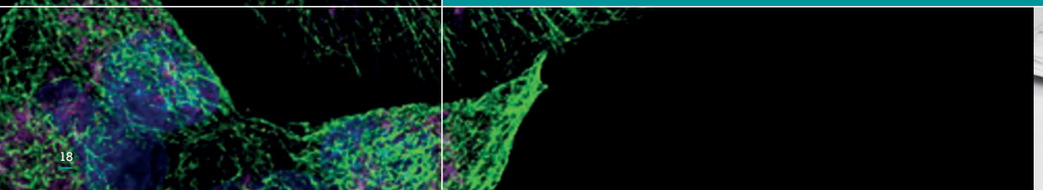
Signalling

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





Group Leaders


Len Stephens


Simon Cook


Oliver Florey


Phill Hawkins


Nicholas Ktistakis


Michael Wakelam


Heidi Welch

Len Stephens
Programme leader

Phill Hawkins

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Piotr Kobialka (Left in 2018)
Clement Pambrun (Left in 2018)
Marion Trebosc (Left in 2018)
Anna Wulf (Left in 2018)

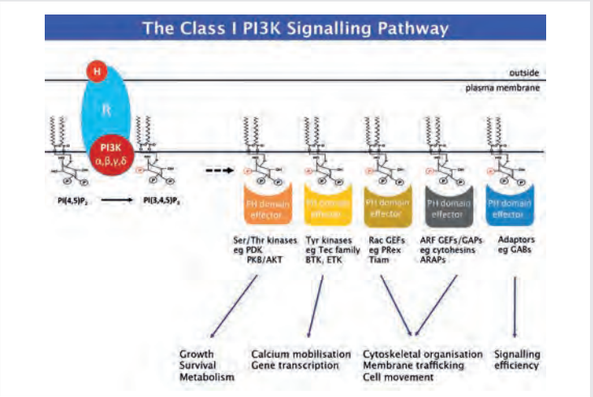
The regulation of cell signalling by PI3Ks

Cells communicate and respond to their environment through signalling pathways. These are molecular pathways that allow changes in the levels of hormones, growth factors or nutrients to be sensed by cell surface receptor proteins and then translated into defined changes in cell behaviour. One such signalling pathway involves the production of a chemical signal inside cells called PI(3,4,5)P3, by enzymes 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 several human diseases.

Current Aims

Our current work is aimed at:

1. Understanding how the PI3K signalling pathway allows certain immune cells (neutrophils and macrophages) to combat foreign invaders and how this capability declines with age.
2. Defining how different, closely related PI3K enzymes are used selectively to regulate cell growth and metabolism in response to changes in nutrient supply and growth factors. This work supports the pharmaceutical industry's attempts to target this pathway therapeutically.
3. Discovering new molecular mechanisms that drive activation of the PI3K pathway.
4. Discovering how the cell compartmentalises the synthesis of PI(3,4,5)P3 and related phospholipids from other, non-signalling molecules.



An overview of the PI3K signalling pathway. Hormones (H) bind to cell surface receptors (R) to activate one of four PI3K isoforms (α, β, γ, δ), which then convert a phospholipid called PI(4,5)P2 into one called PI(3,4,5)P3 (by attaching a phosphate group from ATP onto the 3-position of its inositol ring). PI(3,4,5)P3 then diffuses through the membrane and selectively binds to a conserved 'PH domain' that is present in 20-30 'effector' proteins (some examples are given). This interaction alters the location and activity of these effector proteins and thus passes the message from the hormone onto the proteins regulating cell growth, metabolism, movement etc.

Progress in 2018

We have defined some of the basic binding preferences between the regulatory and catalytic subunits of the different isoforms of Class I PI3Ks and started to establish how some of them are selectively recruited by growth factor receptors (1).

We have also revealed new mechanisms for how some tumours suppress immune cell function (2).

In addition, we have uncovered a new mechanism to explain how PI3K signalling is upregulated in neutrophils at sites of inflammation (3).

Selected Impact Activities

- We have collaborated with the pharmaceutical industry through joint grants, and served on scientific advisory boards.
- We have collaborated with academic groups in Japan, USA, Ireland, France, Spain and the UK, and presented our work at four international conferences.
- We have trained three overseas students (from Germany, France and Ireland).

Publications

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

- Tsolakos, N. *et al.* (2018) Quantitation of class IA PI3Ks in mice reveals p110-free-p85s and isoform-selective subunit associations and recruitment to receptors ***PNAS*** 115(48):12176-12181 doi: 10.1073/pnas.1803446115
- Gyori *et al.* (2018) Compensation between CSF1R+ macrophages and Foxp3+ Treg cells drives resistance to tumor immunotherapy. ***JCI Insight*** 3(11) doi: 10.1172/jci.insight.120631
- Suire, S. *et al.* (in press) Frontline Science: TNF-α and GM-CSF1 priming augments the role of SOS1/2 in driving activation of Ras, PI3K-γ, and neutrophil proinflammatory responses. ***J Leukoc. Biol.***

Simon Cook

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Matthew Sale

Visiting students:
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Charlotte Wright (Left in 2018)

Signals controlling cell fate and drug resistance

Environmental factors can determine how a cell behaves – these so-called cell fate decisions include whether to divide, change cell type or die. Proteins called protein kinases control cell fate decisions 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 2018

ERK1/2 signalling controls normal cell division but is also implicated in excessive or pathological cell division such as in cancer; consequently chemical inhibitors of ERK1/2 are being developed as anti-cancer drugs. Despite this, ERK1/2 signalling does not function as a simple 'on-off' switch. We have found that ERK1/2 signalling operates within a 'sweet spot' or 'Goldilocks zone' to maintain cell division. If cells activate too much ERK1/2 they will undergo a permanent cell growth arrest called senescence, a form of cellular ageing. This year work in the lab has demonstrated that this response to excessive ERK1/2 signalling even determines whether cancer cells adapt and acquire resistance to ERK1/2 pathway inhibitors. Thus, a hard-wired cellular ageing mechanism also determines whether cancer cell resistance to ERK1/2 pathway inhibitors is reversible or not.

Parental cells **Resensitised cells** **Resistant cells**

Parental COLO205 cells stained for chromosome 7 (red) and the BRAF gene (green), a critical activator of the ERK1/2 pathway. Cells made resistant to the ERK1/2 pathway inhibitor selumetinib amplify the BRAF gene (multiple green spots) to maintain ERK1/2 signalling. Resistant cells that have been deprived of selumetinib become resensitised to the drug because they lose the extra copies of BRAF.

Selected Impact Activities

- Two ERK pathway drug discovery collaborations with PhoreMost, separately funded by Innovate UK and Plexxikon.
- Industrial collaborations on ERK pathway inhibitors (with AstraZeneca and Astex Pharmaceuticals) and ubiquitylation (with MISSION Therapeutics).
- Hosted an undergraduate student (Charlotte Wright) for a summer research placement supported by the Biochemical Society.

Publications

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

- Kidger, A.M. *et al.* (2018) ERK1/2 inhibitors: New weapons to inhibit the RAS-regulated RAF-MEK1/2-ERK1/2 pathway. ***Pharmacol Ther.*** 187:45-60
- Hey, F. *et al.* (2018) Over-expressed, N-terminally truncated BRAF is detected in the nucleus of cells with nuclear phosphorylated MEK and ERK. ***Heliyon***. 4(12):e01065
- Prescott, J.A. & Cook, S.J. (2018) Targeting IKKβ in Cancer: Challenges and opportunities for the therapeutic utilisation of IKKβ inhibitors. ***Cells*** 23;7(9). pii: E115

Oliver Florey

Group members

Postdoctoral researchers:
Joanne Durgan
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(Left in 2018)

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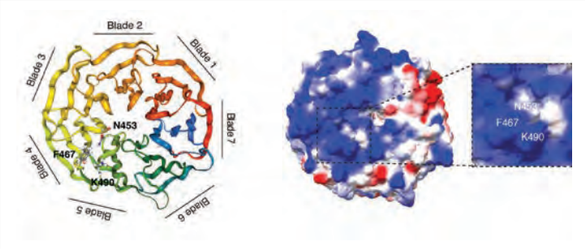
Katie Sloan

Understanding autophagy and cellular recycling



Ribbon model of the top face of Atg16L1 WD domain, with critical residues in ball and stick and a surface model coloured to electrostatic potential (blue positive, red negative).

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

Our goal is to understand the upstream regulation and downstream consequences of a 'non-canonical' autophagy pathway, which utilises some of the autophagic machinery to target external material eaten by cells, including pathogens and dead cells. This impacts many important processes within the cell. Using novel 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 molecular regulation.

Progress in 2018

We have continued to build on previous successes with the publication of several papers from collaborators and our own lab. These results, and the development of a new mouse model by our lab, will extend our understanding of how cellular eating processes are regulated. Based on this success we obtained grant funding from BBSRC-UKRI to extend our work with a focus on the immune system. Experimental evidence from our lab reveals that the 'non-canonical' autophagy pathway plays a key role in how specialised immune cells, called dendritic cells, identify pathogens and communicate their presence to the rest of the immune system, to mount a protective response. This ongoing work will investigate exactly how the non-canonical autophagy pathway regulates the immune system, with a focus on these dendritic cells, and explore how this declines over lifespan. To do this, we will take advantage of our recent work in developing unique models, using both cultured cells and mice, in which the 'non-canonical autophagy' pathway is specifically turned off. We will gain a detailed understanding of this pathway and how aging impacts it, opening up the potential to modify and manipulate the novel 'non-canonical' autophagy pathway for therapeutic benefit.

Selected Impact Activities

- Dr Oliver Florey, with the help of his lab, co-organised the 2018 UK Autophagy Network meeting held in Cambridge.
- Dr Florey presented recent work at a Gordon Research Conference in Italy and the 83rd Harden Conference on Autophagy in the UK.
- Students Katherine Fletcher and Katie Sloan helped deliver the Race Against the Ageing Clock exhibit at the 2018 Royal Society Summer Science Exhibition.

Publications

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

- Fletcher, K. *et al.* (2018) The WD40 domain of ATG16L1 is required for its non-canonical role in lipidation of LC3 at single membranes. ***EMBO J.*** 15:37(4)
- Bussi, C. *et al.* (2018) Alpha-synuclein fibrils recruit TBK1 and OPTN to lysosomal damage sites and induce autophagy in microglial cells. ***J Cell Sci.*** 30:131(23)
- Durgan, J. *et al.* (2018) Cancer cell cannibalism: Multiple triggers emerge for entosis. ***Biochim Biophys Acta Mol Cell Res.*** 1865(6):831-841

Nicholas Ktistakis

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Katerinai Kafka
(Started in 2018)
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(Left in 2018)
Vasiliki Spatharioti
(Left in 2018)
Jeremy Verbeke
(Left in 2018)

Dynamics of autophagy in animal cells

Autophagy is a conserved pathway among all eukaryotes that senses either nutrient levels or damaged organelles and proteins in the cytosol. In both cases, autophagy provides a positive response that deals with the stimulus. In the case of nutrient limitation, autophagy generates nutrients from self-digestion whereas in the case of the presence of unwanted components, autophagy eliminates them via delivery to the lysosomes. Autophagy is mediated by double membrane vesicles termed autophagosomes that engulf either random cytoplasmic material for nutrient generation or specific cargo for elimination.

Current Aims

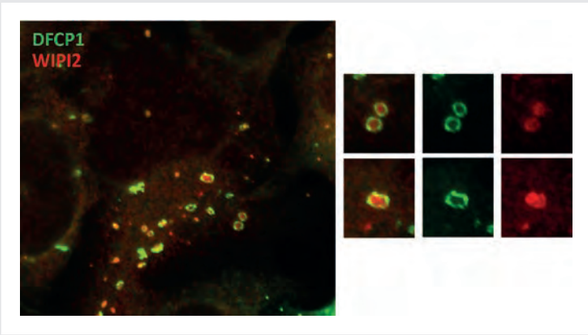
Our work aims to understand how autophagy is induced in mammalian cells, and the specific dynamics of the membrane re-arrangements required for the appearance of autophagosomes. Although we initially focused specifically on non-selective autophagy, we are now working on various pathways of selective autophagy, such as mitophagy (mitochondrial autophagy) and aggrephagy (autophagy of protein aggregates).

Progress in 2018

We have described a novel pathway of mitophagy in response to a well-used drug molecule. This pathway uses the known machinery of autophagy and some already known specific mitophagy adaptors. However, the dynamics of the response, and the early steps of selective autophagosome formation are distinct from what is known about non-selective autophagy. In other work done in collaboration, we have investigated the mechanism by which synuclein fibres, the key amyloidogenic proteins in Parkinson's disease, activate autophagy in brain microglial cells. We discovered that these fibres cause lysosomal malfunction, and, because of this, a pathway of lysosomal quality control involving autophagy is activated in order to repair the lysosomal damage. In other work, we examined how the early steps of autophagy are controlled by the kinase TBK1 as it phosphorylates the autophagy regulator syntaxin 17.

Selected Impact Activities

- Board Member, Autophagy Metabolism and Inflammation NIH Center, NM USA.
- With my colleague Oliver Florey we edited a 740-page volume on Autophagy protocols for the series Methods In Molecular Biology, Springer, Humana Press.
- Keynote speaker at two international conferences and invited speaker at several others.



Under conditions of stalled autophagy, early intermediate structures known as omegasomes accumulate.

Publications

www.babraham.ac.uk/our-research/signalling/nicholas-ktistakis

- Bussi, C. *et al.* (2018) Alpha-synuclein fibrils recruit TBK1 and OPTN to lysosomal damage sites and induce autophagy in microglial cells. ***J Cell Sci***. 131(23). pii: jcs226241. doi: 10.1242/jcs.226241
- Deretic, V. *et al.* (2018) Autophagy, Inflammation, and Metabolism (AIM) Center of Biomedical Research Excellence: supporting the next generation of autophagy researchers and fostering international collaborations. ***Autophagy*** 14(6):925-929. doi: 10.1080/15548627.2018.1465784
- Kumar, S. *et al.* (2018) Phosphorylation of Syntaxin 17 by TBK1 controls autophagy initiation. ***Dev. Cell*** (in press)

Michael Wakelam

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Senior research associate:
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Aveline Neo

LIPID MAPS web developer:
An Nguyen

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Research assistant:
Greg West (Started in 2018)

Visiting students:
Arsalan Azad (Left in 2018)

Lipids and their role in health and disease

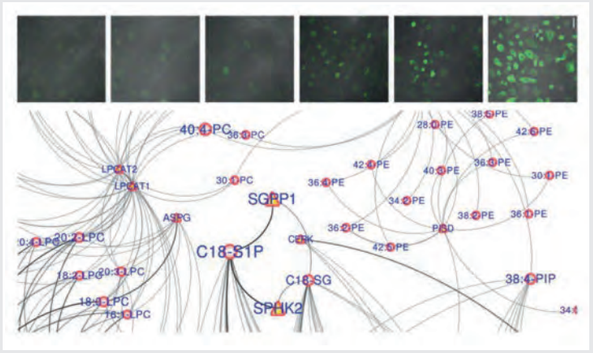
Lipids, also known as cellular fats, are highly dynamic structures with essential structural, metabolic and signalling roles. Our research aims to fully understand the physiological functions of lipids throughout the human lifespan. We use a multidisciplinary approach to identify the cellular signalling pathways and processes that individual lipid species regulate, and to investigate how the enzymes that determine the composition of the lipidome are regulated in response to changes in the environment.

Current Aims

Our present research is focused upon understanding the physiological importance of lipid molecular structures. By making use of cell and molecular biological methods coupled to lipidomics and bioinformatics we are determining the signalling and metabolic pathways that modify cellular lipids and how these are affected by ageing, viral infection and diseases such as cancer. This work utilises cell lines and model systems in mice and *C. elegans* and allows us to identify potentially novel therapeutic targets to treat such conditions. We are also exploring the regulation of a number of enzymes involved in lipid signalling, fatty acid biosynthesis and metabolism, notably autotaxin, stearoyl CoA desaturase and acetyl CoA synthase.

Progress in 2018

During 2018 we have continued to build upon our lipidomics expertise through our role in maintaining and developing the LIPID MAPS platform. We completed and published the determination of novel therapeutic targets to treat rhinovirus infection of human bronchial epithelial cells by integrating our novel pathway analysis of lipidomics data. We made further use of this to define lipid enzyme changes in the liver and adipose of ageing mice and to identify which enzymes respond to dietary restriction and its reversal. Our ongoing studies into the importance of autotaxin and stearoyl CoA reductase demonstrated the importance of both in hepatitis C infection of liver cells.



Optimal subnetwork analysis comparing the lipidomes of uninfected and rhinovirus virus infected primary human bronchial epithelial cells. This method identified infection-related changes in the activities of a number of lipid metabolism and signalling pathways, providing a number of potential anti-rhinoviral targets.

Selected Impact Activities

- Invited speaker at ASBMB, San Diego, USA; ESOF, Toulouse, France; International Mass Spectrometry Conference, Florence, Italy.
- Biochemical Society Morton Prize Lecture, Birmingham.
- Lab hosted a 12 month undergraduate sandwich student plus gap year and school student projects.

Publications

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

- Nguyen, A. *et al.* (2018) Host lipidome analysis during rhinovirus replication in human bronchial epithelial cells identifies potential therapeutic targets. ***J. Lipid Res.*** 59(9): 1671-1684
- Ezcurra, M. *et al.* (2018) C. elegans eats its own intestine to make yolk leading to multiple senescent pathologies. ***Curr. Biol.*** 28 (16): 2544-2556
- O'Donnell, V.B., Rossjohn, J. & Wakelam, M.J.O. (2018) Phospholipid signaling in innate immune cells. ***J. Clin. Invest.*** 128(7): 2670-2679

Heidi Welch

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Elpida Tsonou

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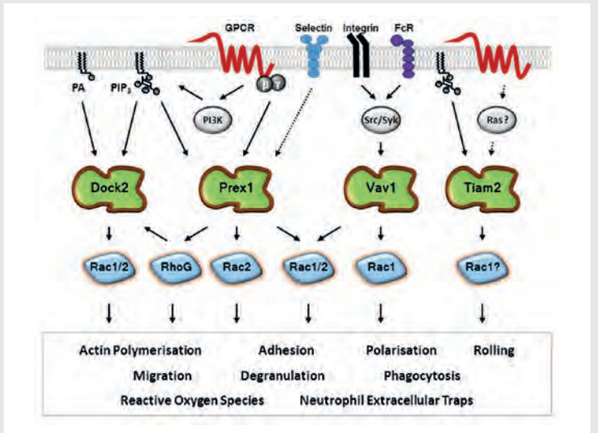
(Left in 2018)
Anna Mandel (Left in 2018)
Anna Roberts (Left in 2018)

Cell signalling through Rac-GEFs

Rac is a protein that enables cells to attach and move through their surroundings. We study how Rac is controlled, in particular by other proteins called GEFs that switch Rac on. Our recent research has identified new roles for Rac-GEFs in the immune system and in cancer. In addition, we have made progress in understanding how Rac-GEFs are controlled.

Current Aims

We previously discovered a family of Rac-GEF proteins that we called P-Rex. We described how P-Rex1 allows white blood cells to be drawn to the site of an infection and how it helps to fight disease (see figure and refs 1 and 2). Our current aims are to investigate the functions of other types of Rac-GEFs in the immune system, to study the roles of P-Rex GEFs in metabolism, to evaluate the importance of their catalytic activity, and to develop new methods for monitoring GEF activity. This knowledge will be valuable for understanding the basic biology of these proteins, how they contribute to maintaining lifelong health, and what diseases can arise when they do not work properly.



Signalling pathways of neutrophil Rac-GEFs. Many different Rac-GEFs are found within white blood cells such as neutrophils, which serve to protect us against bacterial infections. These different Rac-GEFs, which include P-Rex1 and Vav1, are all required in order to couple the various subtypes of Rac protein to a vast array of signals from the blood stream or tissues. These diverse Rac-GEF signalling pathways then lead to neutrophil responses such as adhesion and migration, and the killing of bacteria by neutrophils through various means. Figure adapted from (1) Pantarelli, C. & Welch, H.C. (2018).

Progress in 2018

We have been evaluating the importance of a protein called Norbin – a regulator of P-Rex1 which we identified (Pan *et al.,* 2016) – in controlling defence against infections. This work has begun to uncover surprising and important roles with implications for lifelong health. We have also made progress in identifying novel roles for Rac-GEFs in the immune system and in the maintenance of healthy blood glucose levels, and we have helped our collaborators at the Garvan Institute in Sydney develop a new method for monitoring the activity of proteins such as Rac (3).

Selected Impact Activities

- Members of the Welch lab gave three talks and two flash poster presentations at the 'Small GTPases' Biochemical Society meeting in Cambridge, July 2018.
- Heidi Welch was keynote speaker at the Cell Migration Retreat for Swiss PhD students, Bern, Switzerland in September 2018.
- Elizabeth Hampson from the Welch lab travelled to a secondary school in the Netherlands to help run a workshop on the 'Ethics of Animal Research' in November 2018.

Publications

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

- Pantarelli, C. & Welch, H.C. (2018) Rac-GTPases and Rac-GEFs in neutrophil adhesion, migration and recruitment. ***Eur J Clin Invest***. e12939
- Hornigold, K. *et al.* (2018) P-Rex1. Book chapter. ***Encyclopedia of Signaling Molecules***, 2nd Edition, Ed. S Choi. Springer, 4142-4154
- Warren, S.C. *et al.* (2018) Galene: Removing physiological motion from intravital and clinical functional imaging data. ***eLife*** 7, pii: e35800

SysBio
Reporting to Simon Andrews, Head of the Bioinformatics facility

Group members

Postdoctoral researchers:
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Senior software systems and database architect:
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Postdoctoral computational biologist:
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BioModels database curator:
Krishna Tiwari
(Started in 2018)

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Lars Ingerslev
(Left in 2018)
Vincent Knight-Schrijver
Maria Rostovskaya
(Started in 2018)

Visiting student:
Adrien Leroy (Left in 2018)

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

We are pursuing the use of mathematical modelling approaches to address fundamental questions relating to ageing. These range from highly focused models of specific interventions, such as the use of antibody therapy to treat rheumatoid arthritis, to more expansive projects modelling the entire ageing process of more simple organisms.

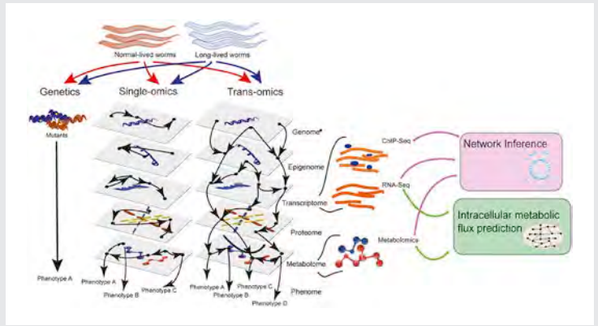
Progress in 2018

In collaboration with Dr Nicholas Ktistakis, we have built and analysed mathematical models of the autophagosome formation to gain insight into the mechanisms that regulate this process.

As part of the WormJam community we established a model of the entire metabolism of the nematode worm *Caenorhabditis elegans*. We used this model to study the metabolic changes that occur during ageing in this organism, and developed new methods which will be applicable to future ageing studies.

Selected Impact Activities

- Participated in the 2018 Computational Modelling in Biology Network meeting in Boston, USA.
- Contributed to the creation of a model of the entire metabolism of *C. elegans* which is available for use by the research community.



Graphic abstract from Hastings et al. (2) illustrating how trans-omics data can be harnessed for mechanistic systems biology tools such as flux balance and network inference analyses that are able to disentangle cause from effect during ageing.

Publications

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

- Dalle Pezze, P. *et al.* (2018) Dynamic modelling suggests differential mechanisms for initiation of non-selective autophagy and mitophagy ***bioRxiv*** (preprint)
- Hastings, J. *et al.* (2018) Flow with the flux: Systems biology tools predict metabolic drivers of ageing in *C. elegans* ***Curr. Opin. Sys. Bio.*** (Epub ahead of print)
- Glont, M. *et al.* (2018) BioModels: expanding horizons to include more modelling approaches and formats. ***Nucleic Acids Res.*** 46(D1):D1248-D1253

Welcome to the lipidome

Once neglected as too dull to study and too sticky to work with, lipids are at last stepping out of the shadows. Institute Director Michael Wakelam and lipidomics facility manager Andrea Lopez-Clavijo explain the challenges of working with these cellular Cinderellas and share their excitement of research in a field that's finally giving up its secrets.

For Professor Michael Wakelam, there's never been a better time to be studying lipids. On becoming the Institute's Director in 2007, he joined a thriving lipid research community. Things were very different, however, at the beginning of his career. "When I got my first lectureship in 1985 I worried that all the good stuff had been discovered," he remembers. "Now, I wonder how I can cram it all in before I retire. I wish I was just starting out again, because the things we can do are awesome."

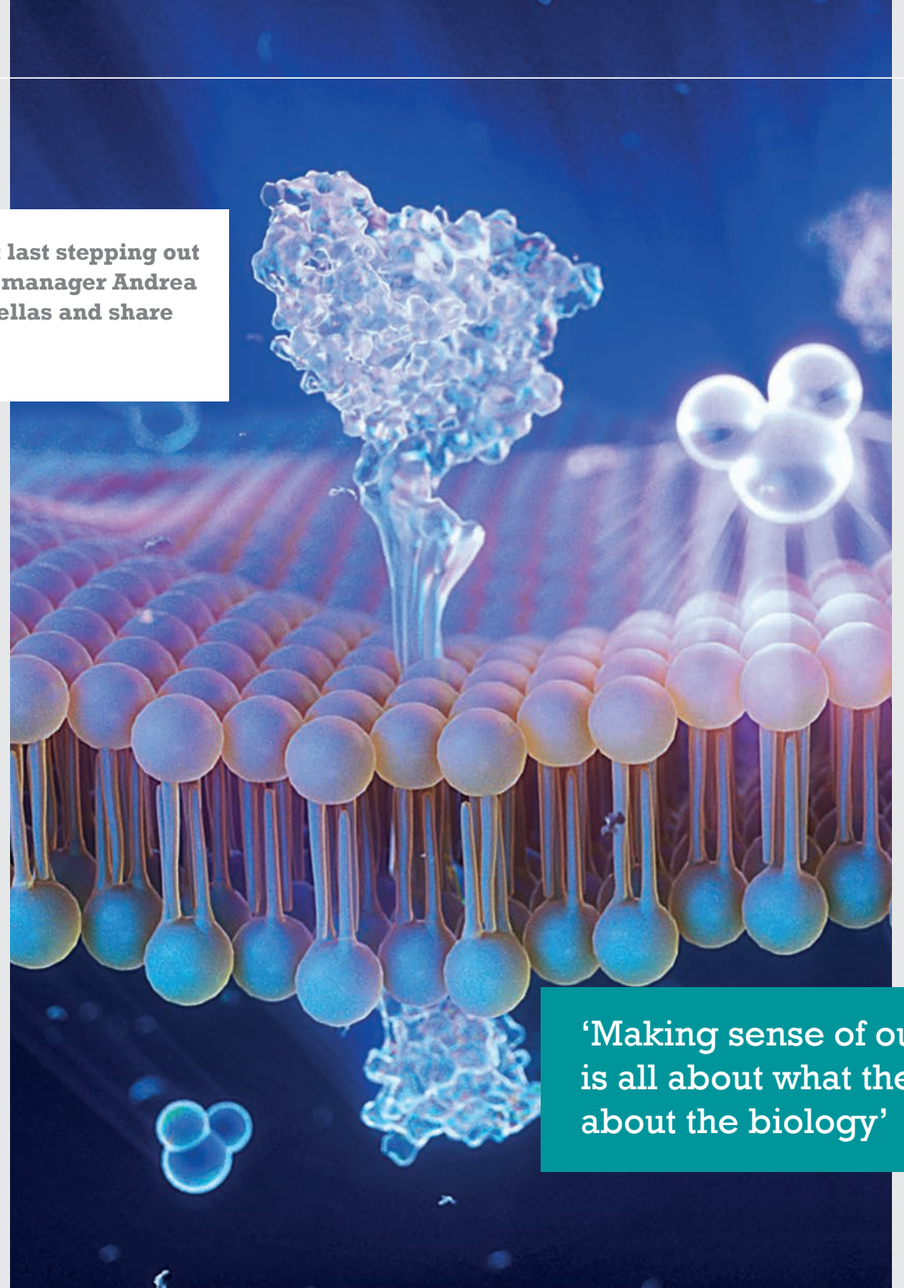
Lipids are essential components of all our cells, but were for many years neglected by many scientists because they were difficult to study and seen as less exciting than genes or proteins. "They aren't easy to work with," Wakelam says. "They're not water soluble and some lipids stick to plastic. It can be painstaking work and until recently they were incredibly difficult to analyse and quantify."

Today, all that has changed. The Institute has played a central role in lipid research since the 1950s, but it's been the development of bioinformatics and mass-spectrometry over the past 20 years, together with the decision in 2016 that the Institute would co-host LIPID-MAPS, the world's largest lipid database, which has opened up the field and fueled Wakelam's excitement.

We now know that as well as making up membranes and storing energy, lipids play a vital role in cellular signalling pathways. "They don't just hold things together and store energy. They're actually incredibly dynamic and regulate almost every function of the cell," he says. We have also discovered that the lipidome – which describes the total lipid landscape of our cells – is astonishingly complex and diverse. Thanks to new mass-spectrometry techniques, many of which were pioneered at the Institute, some 20,000 different lipid species from 30 distinct classes have so far been identified.

Structurally, lipids are proving fascinating too. Small differences in lipid structure and saturation have major impacts on cell membranes: whether they are thick or thin, straight or curved, rigid or flexible all depend on membranes' lipid makeup, with far-reaching implications for how immune cells work, how cancers spread and how viruses are able to infect our cells.

Lipidomics has exploded thanks to advances in mass-spectrometry. "It's allowed us to recognise an astonishing structural diversity in lipid molecules," says senior research fellow and expert analytical chemist Dr Andrea Lopez-Clavijo. "Without mass-spectrometry, we wouldn't have been able to determine what lipids were there and in what quantities. And without the bioinformatics capability to understand this data, all this would be pointless."



'Lipidomics can change what we know about our own cells'

But gaining a clearer view of the lipidome is only the beginning, Lopez-Clavijo explains: "Lipidomics is about finding connections between the data and its biological relevance. Making sense of our experiments is all about what the numbers tell us about the biology."

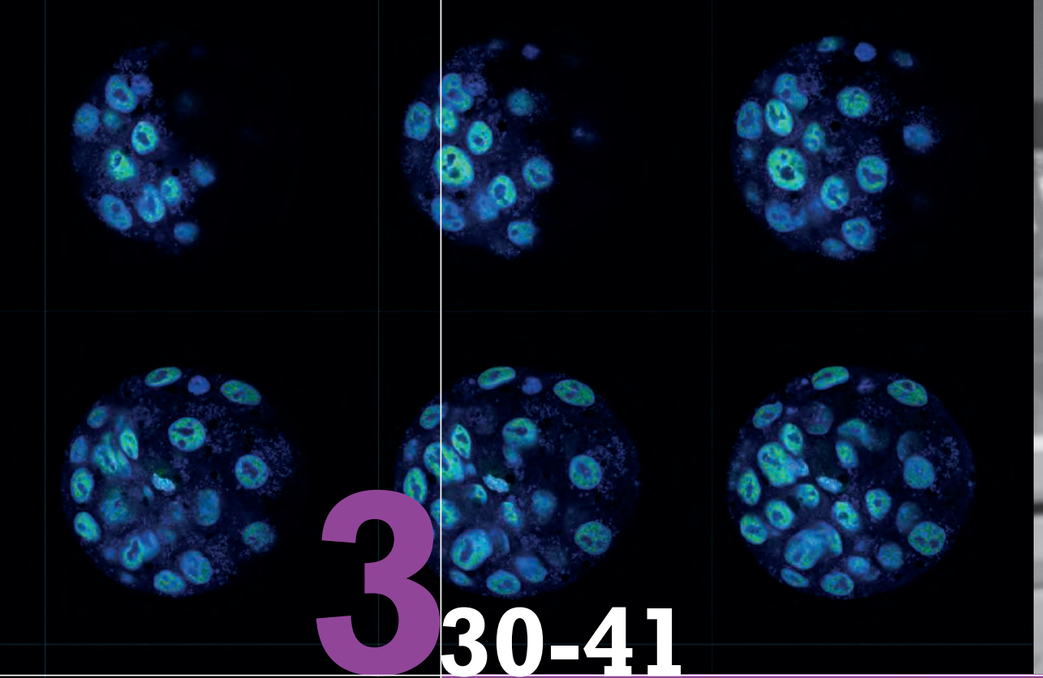
Now that we can start asking more interesting questions, the data is revealing some remarkable things. In 2018 Institute researchers published an important paper using lipidomics to unpick the common cold. The cold virus hijacks the cellular machinery in order to replicate and release virus, so membranes must be modified for this to occur; the implications, however, had been largely ignored. "How does catching a cold affect our lipid molecules during the first few hours of infection? It surprised me that no-one had asked this question," says Wakelam.

By culturing human bronchial epithelial cells, infecting them with the cold virus and then using mass-spectrometry and bioinformatics to examine changes in hundreds of lipids over the course of seven hours, they found that the infection caused changes in almost 500 lipids, a discovery that has allowed the team to identify pathways that could be new anti-viral drug targets.

More importantly, it shows that lipidomics has the potential to uncover new treatments for other previously hard to treat diseases from cancer to hepatitis. Recent studies with colleagues at Oxford, for example, revealed that the unsaturation of lipids affects the ability of hepatitis C virus to infect liver cells.

"Modifying the membranes modifies the viruses' ability to get into cells. Everywhere we look we find this – it's a completely understudied area," Wakelam concludes. "There are many more discoveries to be made with the help of lipidomics – and it has huge potential to change what we know about our own cells." For a former cellular Cinderella, the future for lipid research looks bright.

'Making sense of our experiments is all about what the numbers tell us about the biology'



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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

Group leaders

Wolf Reik

Olivia Casanueva

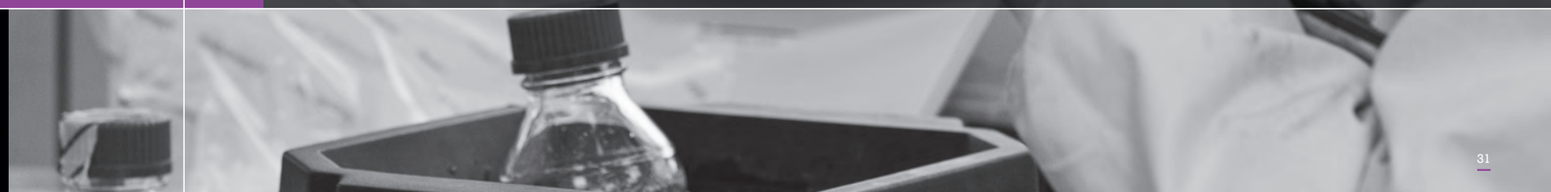
Myriam Hemberger

Jon Houseley

Gavin Kelsey

Peter Rugg-Gunn

Stefan Schoenfelder



Wolf Reik
Programme leader

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(Left in 2018)

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Single-cell epigenome landscape of development and ageing

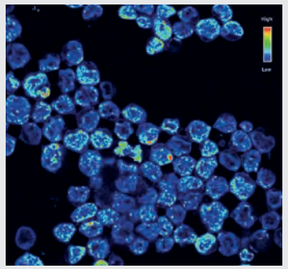
We are interested in epigenetic mechanisms in mammalian development and ageing. Epigenetic marks are able to regulate gene expression and can behave as a form of memory that records the history of a cell. These marks include chemical changes to DNA or DNA-associated proteins. We are particularly interested in the epigenetic rules that govern cell fate decisions in early development, and how cell fate degrades during ageing. Our research uses single-cell sequencing methods to investigate cell fate decisions at the level of individual cells.

Current Aims

The group's research focuses on understanding how cell fate decisions are first programmed or primed, and which epigenetic layers this involves. We would then like to know which cell signalling-induced epigenetic rearrangements occur during fate change. Finally, we are exploring whether epigenetic memory keeps cell identity of fully differentiated cells intact for the rest of our lives (or at least until we start to age). We are also working on identifying DNA binding proteins which are involved in epigenetic priming of enhancers or promoters for future lineage-specific gene expression.

Progress in 2018

In order to address these questions we are developing single-cell multi-omics sequencing approaches which can reveal molecular hierarchies involved in fate decision-making. Our most advanced method combines sequencing of the transcriptome, the methylome, and chromatin accessibility from the same single cell. Our collaborators have developed computational methods by which biologically meaningful relationships between the regulatory layers can be identified. In cells that exit from pluripotency and prepare for differentiation, we made the surprising observation that cells become hugely heterogeneous in their methylation patterns especially in enhancers, and this may be associated with transcriptional heterogeneity (or noise) which may help with cell fate decisions. We are also aiming to connect epigenetic marks in enhancers with histone dynamics which may be important for dynamic gene regulation.



Mouse embryonic stem cells (ESCs) stained for DNA methylation, and pseudo-coloured according to signal intensity (higher signal - red; lowest - blue), revealing the heterogeneity of this epigenetic mark.

Selected Impact Activities

- Members of the group formed a core part in developing and delivering the Institute's exhibit: Race Against the Ageing Clock at the 2018 Royal Society Summer Science Exhibition.
- Wolf Reik was featured in an article on big data 'How big data is changing science' for the Wellcome Trust's Mosaic platform, which was subsequently featured in the Independent online on 11th November, reaching over 22M people.
- A visiting employee from Shift Biosciences has been based in our lab over the past year to apply the lab's epigenetic ageing clock model to drug discovery.

Publications

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

@ReikLab

- Rulands, S. *et al.* (2018) Genome-scale oscillations in DNA methylation during exit from pluripotency. ***Cell Syst.*** 7(1):63-76
- Clark, S.J. *et al.* (2018) scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells. ***Nat. Commun.*** 9(1):781
- Raiber, E.A. *et al.* (2018) 5-Formylcytosine organizes nucleosomes and forms Schiff base interactions with histones in mouse embryonic stem cells. ***Nat. Chem.*** 10:1258-1266

Olivia Casanueva

Group members

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Other visitors:
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(Left in 2018)
Rob Jelier (Left in 2018)

Understanding the interplay between stress and metabolism during early stages of ageing

The discovery that genes control longevity has been quite significant for the understanding of ageing because it changed the view from a gradual stochastic process, to a genetically controlled process that we can interfere with and potentially slow down. Since then, thousands of genes and conditions have been found to influence lifespan, with many of them controlling the way in which organisms deal with external challenges brought by stress and nutrition. Such findings underscore the key interplay between genes and the environment and may explain the high degree of discordance among identical twins. Our lab's interest is to understand the non-genetic influences on lifespan and stress related phenotypes using genetically identical lab strains of *C.elegans* as a model organism.

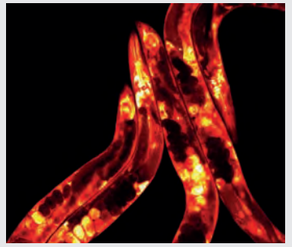
Current Aims

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 variability in the expression of genes that respond to external cues such as temperature and nutrients. We are interesting in finding how early molecular differences in the way worms respond to stress can influence and be predictive of lifespan.
2. How lipid and energy metabolism interplay with signalling pathways that mediate healthy ageing. Metabolism is a key mediator of longevity, however its complexity makes it difficult to study within the particular context of ageing. With this goal in mind, we have developed computational tools to study metabolic fluxes during ageing.

Progress in 2018

- We launched WormJam, a community-driven platform that improved the status of the existing model of *C. elegans* by reconciling and manually curating its metabolic pathways into a single consensus model (refs 1 & 3).
- We also discussed the relevance of these approaches in *Current Opinions in Systems Biology* (Hastings, in print), pointing at one of the key challenges that we face when studying ageing with these tools, namely that the modelling tools available are optimised for animals or cells that are in the process of growing, which is not happening in aged animals.
- Confronted with this challenge, we re-optimised the modelling tool by driving information from multi-omic sources (both transcriptomics and metabolomics) and were able to optimise this tool to study metabolic fluxes during ageing (2). This re-optimisation represents a significant technical advance for the field and will allow more accurate predictions of metabolic fluxes during the course of ageing.



C. elegans worms labelled with a fluorescent protein and imaged using a confocal microscope. C. elegans is a really useful system for our research because we can monitor fluorescent reporters of gene expression in vivo and study inter-individual variability in stress response gene expression in isogenic individuals.

Selected Impact Activities

- The group was involved in several public engagement events throughout 2018, including being part of the team that developed and presented the Institute's 'Race Against the Ageing Clock' exhibit at the Royal Society Summer Exhibition, and sharing the Institute's science at the Cambridge Science Festival and events held as part of the LifeLab project for European Researchers' Night.
- Lab members were involved in organising the second EU-LIFE postdoc retreat.
- The lab coordinates the organisation of local area Cambridge worm meetings.

Publications

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

- Witting, M. *et al.* (2018) Modeling meets metabolomics - The WormJam consensus model as basis for metabolic studies in the model organism *Caenorhabditis elegans* ***Front. Mol. Biosci.*** 5: 96
- Hastings, J. *et al.* Multi-omics and genome-scale modeling reveal a metabolic shift during *C. elegans* aging ***Front. Mol. Biosci.*** (in print)
- Hastings, J. *et al.* (2017) WormJam: A consensus *C. elegans* metabolic reconstruction and metabolomics community and workshop series ***Worm*** 6(2): e1373939

Myriam Hemberger

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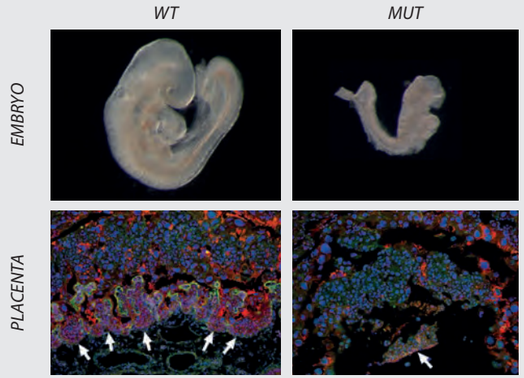
The placenta at the heart of development



Comparison of a normal (WT) and mutant (MUT) mouse embryo that lacks a functional Nubpl gene. The corresponding placentas are depicted underneath. The placenta associated with the mutant embryo is severely malformed and contributes significantly to the developmental defects of the embryo. The placentas are stained for the nutrient exchange surface (green) and for an essential placental progenitor cell type (red, highlighted by arrows).

A functional placenta is critical for normal embryonic development and lifelong health. The placenta is an integrated unit that develops from cells derived both from the embryo and from the mother. Our aim is to gain a comprehensive understanding of the collection of genes that contribute to normal placentation, as well as the maternal factors that affect this process such as advancing maternal age.

Current Aims

Our work focuses on gaining a better molecular understanding of placental development. We use genetic and stem cell models to identify critical factors and pathways involved in the early placentation process. This critical time window is when most defects occur that lead to common pregnancy disorders and developmental defects. We use state-of-the art technologies to manipulate gene function and correlate this with differences in placental cell differentiation and function. We are also integrating the impact of the maternal environment on placental development, and are specifically interested in the changes induced by advancing maternal age and how they affect placental development.

Progress in 2018

It has long been appreciated that development relies on a functional placenta. However, the extent to which the placenta potentially contributes to embryonic defects had remained vastly under-estimated. In 2018, we reported that the placenta is abnormal in about two-thirds of gene mutations that cause embryonic lethality. We also found that placental defects often correlate with abnormal heart and brain development. Thus, the placenta may be a frequent contributor to developmental and birth defects.

In parallel, we contributed to the establishment of a human placental stem cell model, a breakthrough advance that will greatly facilitate research into placenta-based pregnancy complications.

Selected Impact Activities

- Conference organiser: Reproduction and Development Meeting, Cambridge, UK (10-12 March 2018).
- Speaker at the British Society of Developmental Biology (BSDB) Meeting, Oxford, UK (10-13 September 2018).
- Received the Institute's Athena SWAN Best Practice Award 2018 for pioneering initiatives and commitment to women's careers in science.

Publications

www.babraham.ac.uk/our-research/affiliated-scientists/myriam-hemberger @HembergerLab

- Perez-Garcia, V. *et al.* (2018). Placentation defects are highly prevalent in embryonic lethal mouse mutants. ***Nature*** 555: 463-468
- Turco, M.Y. *et al.* (2018). Trophoblast organoids as a model for maternal-fetal interactions during human placentation. ***Nature*** 564: 263-267
- Chrysanthou, S. *et al.* (2018). A critical role of TET1/2 proteins in cell-cycle progression of trophoblast stem cells. ***Stem Cell Rep.*** 10: 1355-1368

Jon Houseley

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Fabiola Vacca (Started in 2018)

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

- To determine how novel mutations occur and whether these can be stimulated by the environment.
- To establish when and how drug resistance mutations occur in cancer cells.
- To understand the mechanistic link between nutrient environment and the ageing process.

Images of very old yeast cells that have been aged under unhealthy (left) or healthy diets (right). Red and green channels show two fluorescent markers of ageing that allow us to quantify ageing pathology. Images acquired using an ImageStream imaging flow cytometer (within the Institute's Flow Cytometry facility) by Dori Horkai.

Progress in 2018

Our optimisation of yeast ageing methods has finally borne fruit, allowing us to show that certain epigenetic marks become important as cells age to facilitate appropriate gene expression patterns. We are now able to functionally profile multiple epigenetic marks during the chromatin upheavals that are thought to accompany ageing in all eukaryotes, allowing new insights into the relationships between environment, diet and ageing. Work on non-random mutation is also progressing; we are elucidating new pathways of extrachromosomal DNA formation in response to environmental change and setting up industrial collaborations to address mechanisms of drug resistance acquisition.

Selected Impact Activities

- Members of the lab participated in the 2018 Royal Society Summer Exhibition 'Race Against the Ageing Clock' exhibit.
- Jon Houseley presented on extrachromosomal DNA formation at the EMBL Molecular Evolution and Ecology meeting.
- The lab opened a Twitter account - @HouseleyLab.

Publications

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

- Cruz, C., *et al.* (2018). Tri-methylation of histone H3 lysine 4 facilitates gene expression in ageing cells. ***eLife*** 7, e34081
- Frenk, S. & Houseley, J. (2018). Gene expression hallmarks of cellular ageing. ***Biogerontology*** 19(6): 547-566
- Cruz, C. & Houseley, J. (2018). Protocols for northern analysis of exosome substrates and other non-coding RNAs. ***Methods Mol Bio.***, in press

Gavin Kelsey

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Salah Azzi (Left in 2018)
Joomyeong Kim (Left in 2018)
Evelyne Oller (Left in 2018)
Laura Saucedo-Cuevas
(Left in 2018)

Visiting student:
Anna Townley
(Started in 2018)

Epigenetic legacies from eggs

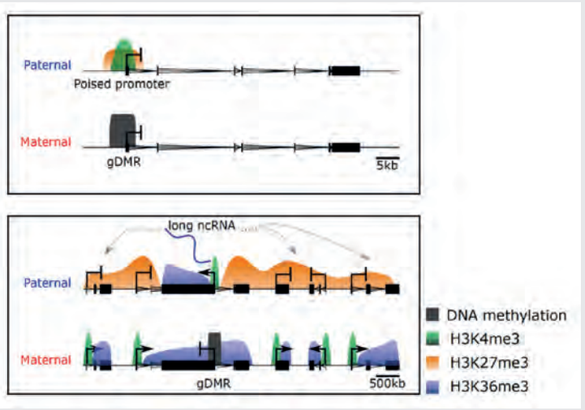
As well as genetic information, the egg and sperm also contribute epigenetic annotations that may influence gene activity both before and after fertilisation. We examine epigenetics during egg development and the effects of epigenetic marks on gene activity in the embryo. Our goal is to understand whether, 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 during oocyte development and influence gene expression in the embryo; for example, how repressive chromatin marks in oocytes lead to long-term silencing of maternal alleles particularly in cells that will form the placenta. We are also interested in how variations in DNA methylation can come about in oocytes and whether we can use methylation 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 cells or even single cells.

Progress in 2018

Using these sensitive methods, we have developed high-resolution epigenetic maps of mouse embryos shortly after implantation, in which we can separate the epigenetic information obtained on maternal and paternal chromosomes (alleles). This has allowed us to distinguish imprinted genes – genes that express a single allele – that depend on DNA methylation conferred in the oocyte from those that depend on repressive chromatin in oocytes. Importantly, we are beginning to see a pattern to explain how chromatin-dependent imprinting is controlled and why it persists selectively in extra-embryonic tissues.



Alternative roles for the repressive chromatin mark H3K27me3 in controlling genomic imprinting. In the upper panel, a paternal allele is silenced by H3K27me3 at its promoter but poised for later expression. In the lower panel, extensive domains of H3K27me3 dependent on monoallelic expression of a long non-coding RNA repress multiple genes.

Selected Impact Activities

- Participation of multiple lab members in the 2018 Royal Society Summer Exhibition 'Race Against the Ageing Clock'.
- Participation in the Cambridge LaunchPad partnership for STEM engagement (Hannah Demond).
- Co-organisation of 2018 EU-LIFE postdoc retreat, Wellcome Sanger Institute, November 2018 (Hannah Demond).

Publications

- Hanna, C. W., Demond, H. & Kelsey, G. (2018) Epigenetic regulation in development: is the mouse a good model for the human? ***Human Reproduction Update*** 24: 556-576
- Clark, S. J., *et al.* (2018) Joint profiling of chromatin accessibility, DNA methylation and transcription in single cells. ***Nat. Commun.*** 9:781
- Hanna, C. W. *et al.* (2018) MLL2 conveys transcription-independent H3K4me3 in the oocyte. ***Nat. Struct. Mol. Bio.*** 25: 73-82

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

Peter Rugg-Gunn

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(Started in 2018)

Visiting scientist:
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(Left in 2018)

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 biology.

Current Aims

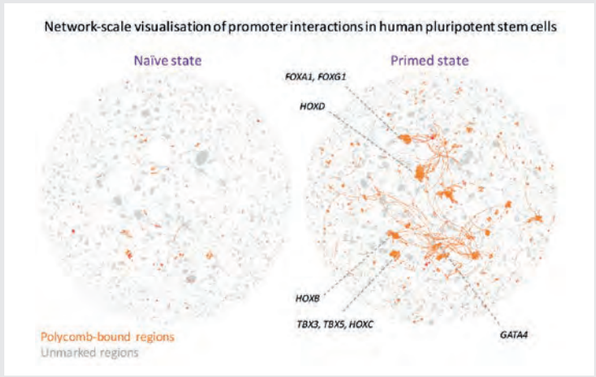
We seek to define the epigenetic and gene regulatory mechanisms that operate in unspecialised pluripotent stem cells and in cells transitioning towards more specialist cell types. We examine how these mechanisms are established in development, how they control cell state changes, and how their alteration can be helpful to reprogramme mature cell types back into an unspecialised form. Our current work also investigates how changes to epigenetic marks can alter the organisation of DNA interactions and associated gene activity. Applying this information will allow us to more precisely control cell fate decisions and to better understand the processes that shape human development.

Progress in 2018

One highlight was discovering that very active regulatory regions, called super-enhancers, are brought into close physical proximity to different gene promoters in different cell types through long-range DNA interactions (1). We further showed that the regulatory interactions connecting super-enhancers with their target gene promoters are controlled by cell type-specific transcription factors. Working with the Corcoran and Schoenfelder groups, we have now developed computational methods to study genome interactions at a network scale (see figure). Investigating chromatin topology and activity in pluripotent cells offers new insights into features of gene regulatory control during development and stem cell differentiation.

Selected Impact Activities

- We participated in several public events including Pint of Science and the Cambridge Science Festival, and we contributed to a podcast by the Naked Scientists.
- We all enjoyed being part of the Royal Society Summer Science Exhibition 'Race Against the Ageing Clock' – a very successful and rewarding team effort.
- Peter took over the co-organisation of the Cambridge Epigenetics Club (@EpigeneticsClub).



Visualisation of promoter-capture Hi-C data at a network-scale uncovers global changes in gene regulatory interactions as human pluripotent stem cells transition from a 'naïve' state to a 'primed' state. The example shown highlights the acquisition of long-range, Polycomb-associated DNA interaction networks that contain the majority of genes encoding key developmental regulators. The figure was produced by Peter Chovanec and Amanda Collier, as part of a collaborative project with Anne Corcoran and Stefan Schoenfelder.

Publications

- Novo, C. *et al.* (2018) Long-range enhancer interactions are prevalent in mouse embryonic stem cells and are reorganized upon pluripotent state transition. ***Cell Rep*** 22: 2615-2627
- Lupo, G. *et al.* (2018) Molecular profiling of aged neural progenitors identifies Dbx2 as a candidate regulator of age-associated neurogenic decline. ***Aging Cell*** 17: e12745
- Collier, A. and Rugg-Gunn, P. (2018) Identifying human naïve pluripotent stem cells - evaluating state-specific reporter lines and cell-surface markers. ***Bioessays*** 40: e1700239

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@RuggGunnLab

Stefan Schoenfelder

3D genome organisation in stem cells

The three-dimensional organisation of our genome is tightly linked to its function. Dispersed throughout the non-coding part of our genome, regulatory elements (such as enhancers and promoters) function as 'molecular switches' to turn genes on and off. These regulatory elements are brought into spatial proximity through cell-type specific folding of chromatin, which represents a key regulatory mechanism to control gene expression programmes during cell lineage specification.

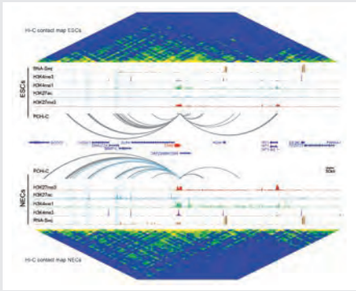
Current Aims

Our aim is to dissect 3D gene regulatory networks and enhancer–promoter interactions during normal development, and to understand how their function is perturbed in disease and ageing. Our research focuses on pluripotent stem cells, as they are a unique model to study early mammalian development, and hold great promise for applications in regenerative medicine, disease modelling and compound screening. We address three main questions:

1. How is the folding of the genome rewired during early mammalian development?
2. Which regulatory elements control cell fate decisions during lineage specification?
3. How do sequence variants in regulatory elements affect gene expression levels and thereby cell function?

Progress in 2018

We have mapped promoter–regulatory element interactions in mouse embryonic stem cells and trophoblast stem cells, demonstrating that profound differences in 3D genome organisation are already established after the first cell lineage differentiation process during early mammalian development. We have also shown that haematopoietic stem cells respond to growth factor signalling through widespread epigenome and transcriptome remodelling, but with very limited changes to promoter–regulatory element interactions. This indicates that priming of promoter–regulatory element contacts may contribute to efficient signalling pathway responses at the transcriptional level. We have further analysed how the 3D genome organisation changes during ageing in mouse B lymphocytes.



Developmental control of enhancer–promoter contacts during early human cell lineage specification. Transcriptional upregulation of PAX6 during the conversion of human embryonic stem cells (ESCs) into neuroectodermal cells (NECs) is accompanied by the formation of enhancer–promoter contacts in NECs (mapped by Promoter Capture Hi-C; PCHi-C), which involves both novel enhancer–promoter contacts and the emergence of the enhancer associated mark acetylation at lysine 27 of histone H3 (H3K27ac) at genomic regions that already interacted with PAX6 in ESCs (modified from Freire-Pritchett et al., eLife 2017).

Selected Impact Activities

- Presentation at EMBL-EBI Industry Programme workshop 'Epigenetics for ageing and disease' (November 2018).
- Participation in a STEM Insights teacher event hosted at the Babraham Institute (October 2018).
- Interview with Tom Chivers that contributed to an online article 'How big data is changing science' for the Wellcome Trust's Mosaic platform, which was subsequently featured in the Independent online on 11th November, reaching over 22M people.

Publications

www.babraham.ac.uk/our-research/epigenetics/stefan-schoenfelder

- Schoenfelder S. *et al.* (2018) Divergent wiring of repressive and active chromatin interactions between mouse embryonic and trophoblast lineages. ***Nat. Commun*** 9: 4189
- Schoenfelder S. *et al.* (2018) Promoter Capture Hi-C: High resolution, genome-wide profiling of promoter interactions. ***J. Vis. Exp.*** 136. doi: 10.3791/5732
- Comoglio F. *et al.* (2018) Thrombopoietin signalling to chromatin elicits rapid and pervasive epigenome remodelling within poised chromatin architectures. ***Genome Res.*** 28: 295-309

Riding the data wave

Big data is revolutionising science. But as well as changing physics, chemistry and biology, it's changing the nature of science itself. Institute researchers Wolf Reik and Stefan Schoenfelder and bioinformatics expert Simon Andrews reflect on how big data is re-shaping not only the way they work, but how they think. And we discover how bioinformatics – once considered a geeky corner of biology by some – has become central to scientific progress.

When Professor Wolf Reik, head of the Epigenetics programme, thinks about how big data has revolutionised his field he remembers the Swiss anatomist Karl Theiler. Theiler spent a lifetime creating 'The House Mouse: Atlas of Embryonic Development', painstakingly taking embryos at different stages of development and using staining and microscopy to identify each tissue type.

"Now, we take the same embryos and put them in a big machine which sequences up to 100,000 cells at a time. Through gene expression, it gives us an equally detailed atlas of development, but because we can now use multi-omics methods that link together different layers in a single cell – the epigenome and the transcriptome – we can ask much deeper questions about how these patterns arise mechanistically. That's what we really want to know," says Reik.

Despite being a relic of an earlier scientific age, Theiler's atlas remains on Reik's bookshelves: an illustration of how big data has transformed the scientific questions he can ask and an embodiment of how it's reshaped the way his younger colleagues think.

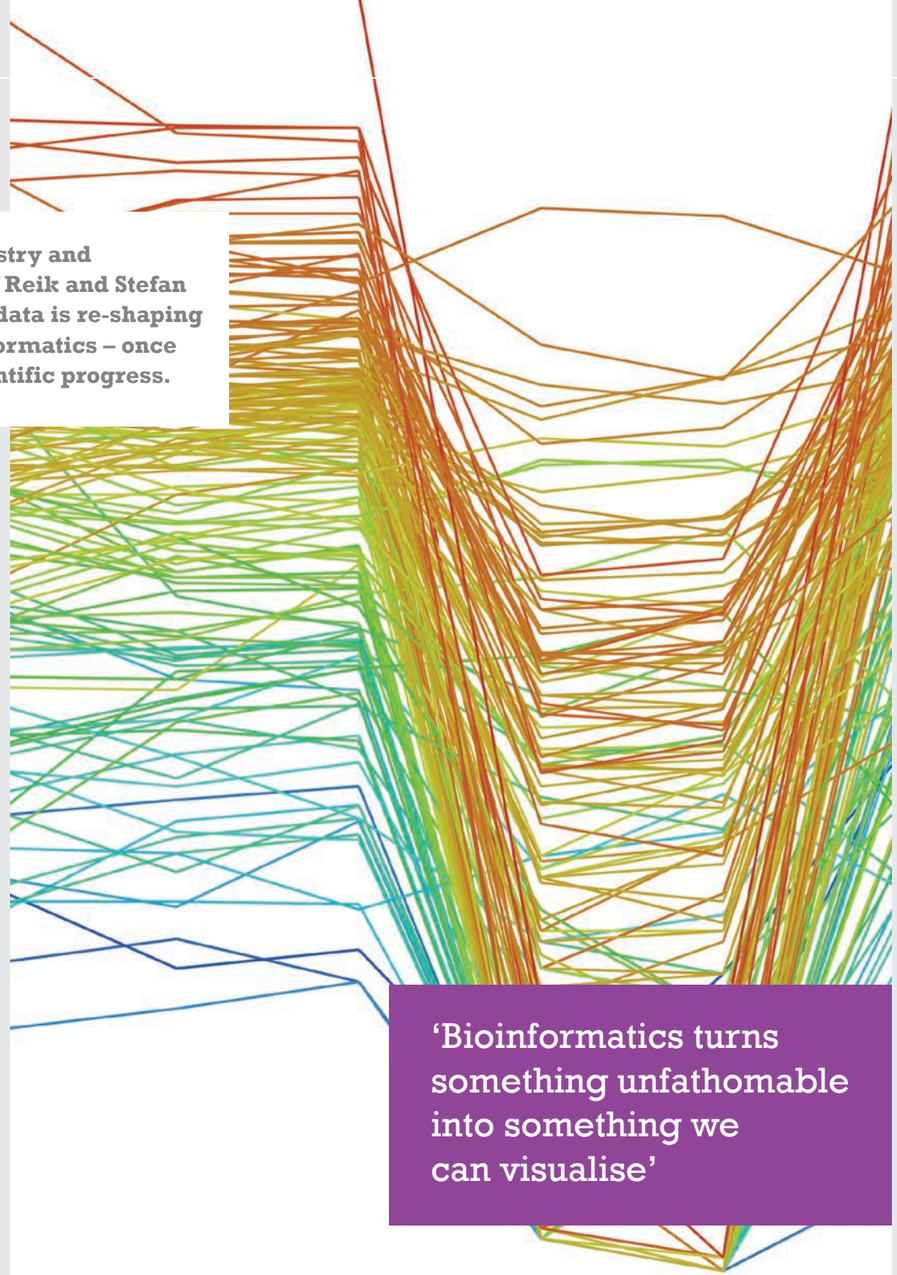
Before big data, researchers thought and worked on single genes – how they were regulated and their role in development, health and ageing. Now, thanks to the recent developments in next-generation sequencing, the focus is firmly on the genome as a whole. "We can now look at 20,000 genes or 20,000 promoters and get huge amounts of information. The younger members of my group get excited about the whole genome and what it's doing, whereas I was brought up in an era of asking what single genes do; it's a fundamental difference in thinking," says Reik.

Big data brings huge opportunities, but using techniques that generate massive amounts of increasingly complex data also presents huge computational challenges. So how do Reik and other researchers extract meaning from this deluge of data? The answer lies in bioinformatics, the science that has emerged at the intersection of biology, computer science and statistics.

Dr Simon Andrews, head of Bioinformatics, belongs to this new breed of experts. Since joining the Institute in 2001, he's seen the group expand from two to 10 staff, many of whom have their roots in biology.

"Lots of people in my group were once biologists who happened to play with computers for fun. My mother was a primary school teacher. Sometimes she'd turn up with a computer that had been donated to the school, point me towards it and say 'make this do something that I can take back into the classroom!'" Andrews recalls. "At university I built my own computers because we couldn't afford to buy them, and when I started research we were beginning to get electronically-generated data."

His PhD generated a respectable 1,000 bases of DNA sequence. Today, a single sample at the Institute yields 40 billion. "The fundamental change is that many experiments generate amounts of data that are



'Bioinformatics turns something unfathomable into something we can visualise'

'Big data changes how we think – and how we work'

impossible to understand without a computer. Before, computers were a nice add-on; now they are fundamental," he says.

One of the Institute's core facilities, the Bioinformatics group provides computational power and data analysis plus expert advice and bespoke development work. "What fires me up are computational problems that spring from biology," says Andrews, and what researchers often need most are ways of making their data more accessible. Over several years, Andrews' group has developed packages capable of visualising sequencing data sets with billions of data points. "These are unfathomable on their own, but we can turn them into billions of positions in a genome, and visualise what they look like," he explains.

Like Reik and Andrews, Dr Stefan Schoenfelder has lived through the revolution wrought by next-generation sequencing and big data. "It changes the way you think and changes the way we work," he says. "When I did my PhD 15 years ago I spent all my time doing experiments in the lab. Now it's the analysis that takes the time."

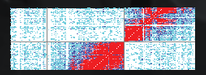
Schoenfelder is interested in how gene function and gene expression are controlled by non-coding bits of DNA known as regulatory sequences. In linear terms, genes and their regulatory elements may be some distance apart, so how the genome is organised in three dimensions is one of his key questions. "Whereas we used to look at individual examples, now it's possible to address those questions genome wide. We can get a complete picture of all the interacting sequences in a cell," he says. "When I came here after my PhD, it was something I thought might happen at the end of my career. That it's happened so quickly is incredible."

It also means that researchers need to learn how to interpret data, so the Institute's Bioinformatics group makes a major difference. "The skills I was equipped with in my PhD are not enough anymore. It's normal to keep learning in science, but this is a quantum leap," says Schoenfelder. "In a competitive field you need to work rapidly. I often work with dedicated bioinformaticians because it's almost impossible to be an expert in both."

The next scientific revolution is anyone's guess, but Schoenfelder is sure it will only underscore how much more we need to understand. "Sequencing and its impact on personalised medicine will continue to grow. High-resolution microscopy, observing live cells and even individual molecules, will be another game changer," he concludes. "We make contributions all the time, but we know so little. That's humbling – but it's also very exciting to be a part of."

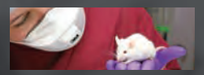
4 42-53

Facilities

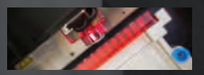


Bioinformatics

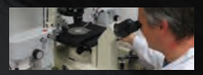
Biological Chemistry



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 developer:
Jo Montgomery

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

- An 800 node compute cluster with an extensive collection of bioinformatics software and pipelines.
- A range of custom software often focused on next generation sequencing, data visualisation and quality control.
- Experience in the processing, management and analysis of large biological data sets.
- An extensive modular portfolio of bioinformatics training courses targeted at biologists.

Progress in 2018

In 2018 the Bioinformatics group has greatly expanded its training programme. We have established a set of larger training bootcamps running over several days that provide an in-depth introduction to a number of relevant topics covering sequence analysis, programming and technical skills. As well as running these on site at the Babraham Research Campus, we have also run training courses for academic and commercial groups in the UK, Germany, Spain and Australia.

This year, we expanded our toolsets to support technologies such as NMT-Seq and single-cell RNA-Seq, BS-Seq, and RNA–interaction data.

Selected Impact Activities

- We established a new set of bioinformatics training bootcamps, covering next generation sequencing, R programming and Linux systems administration.
- We organised the Second Cambridge Bioinformatics Hackathon at the Centre for Computing History, bringing together over 50 bioinformaticians from around Cambridge and the surrounding areas.
- Two members of the group undertook an extended trip to the Hunter Medical Research Institute, Australia, to run a series of bioinformatics and statistics training courses and establish a longer term relationship between our institutes.

Publications

www.bioinformatics.babraham.ac.uk

@babraham_bioinf

- Clark, S.J. *et al.* (2018) scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells. ***Nat. Commun.*** 9(1):781
- Chovanec, P. *et al.* (2018). Unbiased quantification of immunoglobulin diversity at the DNA level with VDJ-seq. ***Nat. Protoc.*** 13(6):1232-1252
- Wingett, S.W. *et al.* (2018) FastQ Screen: A tool for multi-genome mapping and quality control. ***F1000Res.*** 7:1338

Jonathan Clark
Facility head

Facility members

Postdoctoral research scientists:
Izabella Niewczas
Mel Stammers

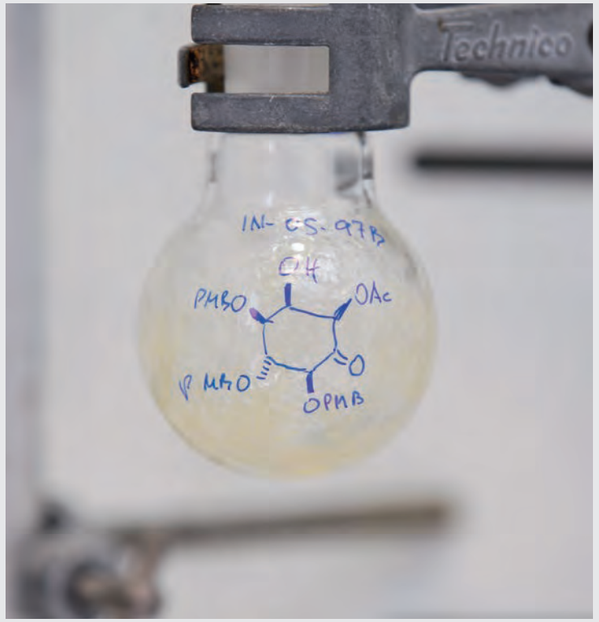
Biological Chemistry

The Biological Chemistry group provides support for scientists working at the interface between chemistry and biology. We bring an understanding of chemistry and its 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 Institute's 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 2018

During 2018 we have supported groups throughout the Institute on a wide range of varied projects. These have ranged from synthetic chemistry 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 also continued to run routine lipid analysis for a number of groups, both within the Institute and externally.

Separately in the connective tissue project, we have shown for the first time that the chemistry of collagen dynamically changes in response to stretching. In this work we have been able to describe the changes that occur to this chemistry with age and provide an explanation for the changes in the physical properties of tendons observed in ageing and in diabetes.

Selected Impact Activities

- Through 2018 we have run many commercial PIP3 analysis samples for a number of pharmaceutical companies studying the action of PI 3-kinase inhibitors in a clinical setting.
- We have provided lipid analysis for a number of external academic groups throughout 2018.

Publications

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

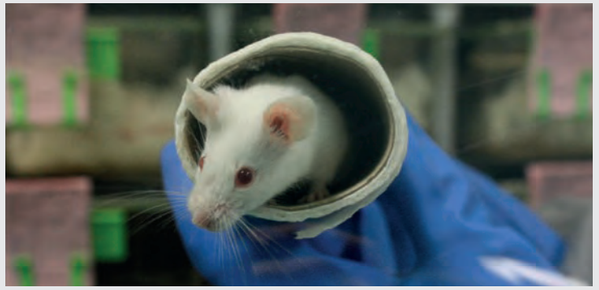
- Stark, A. K. *et al.* (2018) PI3Kδ hyper-activation promotes development of B cells that exacerbate Streptococcus pneumoniae infection in an antibody-independent manner. ***Nat. Commun.*** 9: 1-16
- Riento, K. *et al.* (2018) Flotillin proteins recruit sphingosine to membranes and maintain cellular sphingosine-1-phosphate levels. ***PLoS One*** 13: 1-18
- Chow, W. Y. *et al.* (2018) Essential but sparse collagen hydroxylysyl post-translational modifications detected by DNP NMR. ***Chem. Commun.*** 54: 12570-12573

Tim Pearce
Facility head

Facility members:

- 2 Deputy Facility heads
- 7 Managers
- 7 Supervisors
- 3 Deputy Supervisors
- 30 Experienced Animal Technicians
- 4 Trainee/Apprentice Animal Technicians
- 3 Support Service Technicians
- 1 Administrator

Biological Support Unit



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. Our team of highly trained animal technicians and service technicians perform daily animal 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 uphold the highest standards of animal welfare in all aspects of our work.
- Our Central Services unit utilises robotic cage-washing technology and automated sterilisation processes to provide equipment and consumables to the bio-science units.

Progress in 2018

- In 2018, the BSU successfully formed a collaboration and partnership with Agenda Resource Management creating an ongoing recruitment initiative for apprentice animal technicians, with the BSU fast becoming acknowledged as a centre-of-excellence for foundation training and beyond.
- The BSU continues to provide rentable space and technical support to commercial companies, with a 12% increase in income from this venture compared to 2017. Throughout the year the facility has continued to draw a high level of interest from new companies wanting to utilise the facility's services.

Selected Impact Activities

- A team of animal technicians and managers attended a LifeLab event held in Peterborough in September to promote careers in animal technology and engage members of the public in line with our commitment to the Concordat on Openness on Animals in Research.
- Facility tours and visits: All campus staff are invited to take a virtual tour of the Institute's animal facility to find out how our facility operates and how animals are used in our research. The facility ran three tours for campus staff in 2018. In addition, we continued to host visits from industry representatives, with respect to animal facility design for new builds and refurbishments, and to share technical expertise and guidance for their projects.
- The 2018 KEC prize (and also the Datesand group's Janet Wood Innovation Award) was awarded to a BSU Manager recognising their invention and development of an innovative animal enrichment device.

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

Rachael Walker
Facility head

Facility members

Flow cytometry specialist:
Attila Bebes
Rebecca Roberts

Flow cytometry technician:
Isobel Darlington
Aleksandra Lazowska

Flow cytometry assistant:
Arthur Davis

Flow Cytometry

Flow cytometry is a powerful technology allowing cells to be identified, counted, analysed and sorted on the basis of specific physical or chemical features, including using fluorescently labelled antibodies. 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

- State-of-the-art analysers: BD LSRFortessa and Propel Lab YETI analysers allowing up to 30 parameters to be simultaneously analysed.
- Image cytometry: The facility houses a Merck Millipore Imagestream MkII allowing quantitative flow cytometry data to be produced with images of each cell.
- Cell sorting service: The facility provides an expert cell sorting service for Institute and external users.

Progress in 2018

In 2018, the facility expanded with the acquision of a new, high-end BD AriaFusion sorter to strengthen our cell sorting capabilities. The facility also welcomed two new members of staff to support the sorting service.

Selected Impact Activities

- Flow cytometry training: Throughout 2018, the facility's modular courses continued to sell out with 240 delegates being trained in 2018 (178 unique delegates).
- The facility delivered bespoke flow cytometry training at the Pirbright Institute.

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

@babraham_flow

Our future services for this facility are currently under review.

Gene Targeting & Genome Editing

Introducing targeted changes to the mouse genome enables researchers to alter individual genes to study their functions. The Gene Targeting service is trialling new gene editing opportunities and technologies to produce genetically altered mouse models. Once up and running, the service will be able to aid in the design, generation, screening and evaluation of genetic modifications.

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

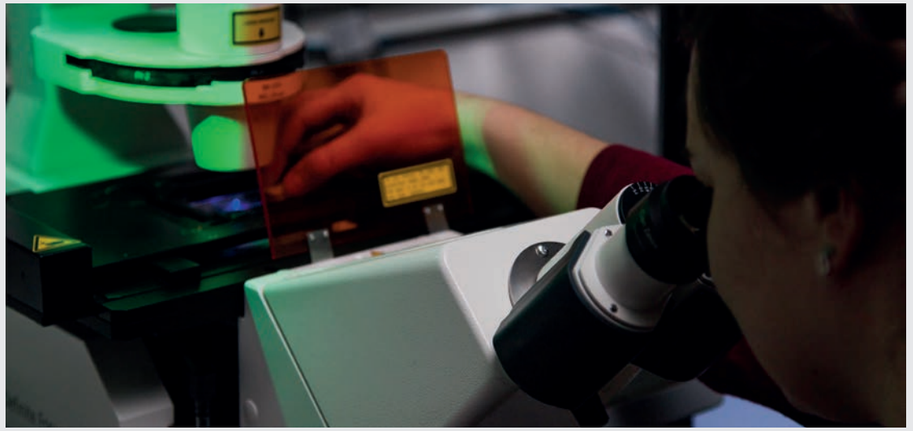
Simon Walker
Facility head

Facility members

Deputy manager:
Hanneke Okkenhaug

SEM specialist:
Chieko Itakura
(Started in 2018)

Imaging



The Imaging facility provides a number of services to support the Institute's research. These include access to advanced light microscopy technologies, an electron microscopy service, and an advanced image analysis service. Training is a key part of our remit, with users encouraged to learn how to operate our equipment independently, with expert advice on hand to help when required.

Capabilities

- Scanning Electron Microscope with Focussed Ion Beam (FIB SEM).
- N-SIM/N-STORM super resolution imaging system.
- Multi-photon microscope for intravital imaging.
- Image acquisition and data analysis for cell-based assays.

Progress in 2018

2018 has been a landmark year in the development of the Institute's Imaging facility as we can now offer an electron microscopy capability to complement our advanced light microscopy resources. The primary driver for this acquisition is a need to study cellular ultrastructure at high resolution in 3D, providing contextual information on organelle formation. Installation of the microscope was completed in April and a new member of staff joined our team in October to run the instrument and provide expertise on sample preparation. We anticipate this resource to be fully operational in early 2019.

Selected Impact Activities

- Simon Walker presented the facility's work at the first meeting of BBSRC-funded imaging facilities.
- Hanneke Okkenhaug hosted two GCSE school students on a week's work experience.
- Simon Walker attended a LabLife event in Peterborough, sharing STEM-related books that challenge gender stereotypes with children.

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

Publications

- Chrysanthou, S. *et al.* (2018). A critical role of TET1/2 proteins in cell-cycle progression of trophoblast stem cells. ***Stem Cell Rep.*** 10(4): 1355-1368
- White, M. A. *et al.* (2018). TDP-43 gains function due to perturbed autoregulation in a Tardbp knock-in mouse model of ALS-FTD. ***Nat. Neurosci.*** 21(4): 552-563
- Dautova, Y. *et al.* (2018). Calcium phosphate particles stimulate interleukin-1beta release from human vascular smooth muscle cells: A role for spleen tyrosine kinase and exosome release. ***J Mol Cell Cardiol.*** 115: 82-93

Michael Wakelam
Facility head

Facility members

Facility manager:
Andrea Lopez-Clavijo

Postdoctoral research scientist:
Aveline Neo

Research assistant:
Gregory West

Lipidomics

Lipidomics identifies and quantifies the large array of lipid (fat) molecules found in cells, tissues and biological fluids. The lipidome is separated chromatographically and comprehensively characterised by high-accuracy and high-resolution tandem mass spectrometry. 15 novel chromatography methods have been developed, tested and validated to identify and semi-quantify a range of neutral, phospho-and sphingolipids with the aim of providing a detailed view of the lipids in a biological system. This knowledge is then used to contribute to an understanding of cell structures, signalling and regulation in a systems-wide investigation of metabolic changes in health and disease.

Capabilities

- The facility uses liquid chromatography hyphenated to high resolution/high mass accuracy mass spectrometry for untargeted lipidomics (Orbitrap technology).
- Targeted lipidomics is performed by liquid chromatography or gas chromatography hyphenated to triple quadrupole mass spectrometers.
- Shotgun throughput analyses couples an Advion NanoMate to a high resolution /high mass accuracy mass spectrometer.
- Semi-quantitation of the lipids levels when compared to control samples prior to normalisation of the data to the weight/DNA/protein content.
- Hydrophobic extraction of the lipids present in cell lines and tissues from mouse, worm and human samples.

Progress in 2018

We have successfully re-established the Lipidomics facility adopting normal phase chromatography methods for the separation of phospholipids. The methods have been validated using targeted and untargeted approaches. In addition, reverse phase chromatography has been implemented for the separation of neutral lipids.

We are developing ion mobility methods for the separation of ceramides with similar elemental composition coupled with chromatography and targeted approaches. Methods to measure free fatty acids, cholesterol and cholesterol ester are also under development, to offer a comprehensive range of lipids to cover the lipidome. Finally, we have introduced a fast and reliable cold homogenisation of soft and bland tissue, including worms (*C. elegans*) using a Precellys homogenizer.

Selected Impact Activities

- Active collaborations with research groups from the University of Cambridge, King's College London, Birmingham University, Newfoundland University (Canada) and the University of Oxford.
- A service agreement for the analysis of commercial samples by the facility has been initiated with a company based in Oxford.
- Facility members promoted the science carried out in the facility at the British Mass Spectrometry Society annual conference.

Publications

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

- Sadej, R. *et al.* (2018). CD151 regulates expression of FGFR2 in breast cancer cells via PKC-dependent pathways. ***J Cell Sci.*** 131(21)
- Burla, B. *et al.* (2018) MS-based lipidomics of human blood plasma: a community-initiated position paper to develop accepted guidelines. ***J Lipid Res.*** 59(10): 2001-2017
- Nguyen, A. *et al.* (2018) Host lipidome analysis during rhinovirus replication in HBECs identifies potential therapeutic targets. ***J Lipid Res.*** 59(9): 1671-1684

David Oxley
Facility head

Facility members

Senior research assistant:
Judith Webster

Postdoctoral researcher:
Katarzyna Wojdyla

Mass Spectrometry

Mass spectrometry is unrivalled in its potential to identify, characterise and quantify almost any biological molecule, at very high sensitivity and in highly complex samples. The Mass Spectrometry facility uses the latest approaches and develops novel methods to analyse biological molecules, particularly proteins and nucleic acids, working with colleagues from across the institute and campus companies.

Capabilities

- Three high-resolution tandem mass spectrometers (Q Exactive Plus, Q Exactive and Orbitrap Velos Pro) situated within the facility, and the facility has shared access to a state-of-the-art Orbitrap Fusion Lumos instrument located in the Biochemistry department at the University of Cambridge.
- Full range of high-sensitivity mass spectrometric protein analyses including:
  - quantitative proteome analysis (label-free, SILAC, isobaric tagging);
  - identification/quantitation of proteins in purified complexes;
  - identification, localisation and quantitation of post-translational modifications;
  - detailed structural characterisation of individual proteins;
  - targeted protein quantitation.
- Quantitation of DNA modifications, particularly cytosine modifications 5mC, 5hmC, 5fC and 5caC.
- Development of novel mass spectrometric analytical methods.

Progress in 2018

During 2018 we worked with many of the Institute's research groups on a range of projects and also continued method development. For example, in collaboration with Wolf Reik's group, we extended our methodology for the analysis of cytosine modifications in DNA to measure uracil, a very rare base in genomic DNA, which may play a role in DNA demethylation. Working with the Kelsey lab, we used our low-level TMT method for quantitative proteome analysis of small numbers of mouse oocytes. We also initiated a new project using a cell-surface labelling technique to investigate the cell-surface proteomes of naive vs primed human pluripotent stem cells (with Peter Rugg-Gunn).

Selected Impact Activities

- Participated in the Institute's 'Race Against the Ageing Clock' exhibit at the 2018 Royal Society Summer Science Exhibition in London (July).
- Showcased the facility at the Babraham Research Campus science morning.
- Commercial work for several Babraham Research Campus companies.

Publications

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

- Tsolakos, N. *et al.* (2018) Quantitation of class IA PI3Ks in mice reveals p110-free-p85s and isoform-selective subunit associations and recruitment to receptors. ***Proc Natl Acad Sci USA.*** 115(48):12176-12181
- Olova, N. *et al.* (2018) Comparison of whole-genome bisulfite sequencing library preparation strategies identifies sources of biases affecting DNA methylation data. ***Genome Biol.*** 15;19(1):33
- Smyrnias, I. *et al.* (2018) Contractile responses to endothelin-1 are regulated by PKC phosphorylation of cardiac myosin binding protein-C in rat ventricular myocytes. ***J Mol Cell Cardiol.*** 117:1-18

Kristina Tabbada
Facility head

Facility members

Research assistant:
Nicole Forrester

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.

Capabilities

- A range of sequencing instruments (HiSeq 2500, NextSeq 500 and MiSeq) enabling researchers to select the sequencing depth and read length needed for their project.
- Library preparation services using the automated liquid handling technology of the Hamilton NGS Star. Protocols currently automated include the SmartSeq v2 protocol and NEB Next Ultra II RNA-seq library preparation.
- Quality control services to ensure optimal yield and sequence quality.
- Coming in 2019 – automated single cell library preparation using the 10X Genomics Chromium Controller.

Progress in 2018

The Next Generation Sequencing facility has continued to expand its range of services. In 2018, the facility began to offer automated RNA-seq library preparation services to make this powerful investigative tool available to a wider range of researchers. Library preparation using the Hamilton NGS Star liquid handling system with on-deck thermal cycling provides an integrated sample-to-sequence solution with enhanced reproducibility and throughput.

The 10X Genomics Chromium Controller single cell partitioning and barcoding system will allow researchers to study gene expression, copy number variation and chromatin accessibility as well as to profile the immune system repertoire at an unprecedented level of resolution.

Selected Impact Activities

- Attended the Core Technologies for Life Sciences (CTLS2018@VIB) Conference, Ghent, Belgium, 1-4 July 2018.

Publications

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

- Cruz, C. *et al.* (2018) Tri-methylation of histone H3 lysine 4 facilitates gene expression in ageing cells. ***eLife*** 7: 34081
- Koohy, H. *et al.* (2018) Genome organization and chromatin analysis identify transcriptional downregulation of insulin-like growth factor signaling as a hallmark of aging in developing B cells. ***Genome Biol.*** 19: 126
- Clark, S.C. *et al.* (2018) scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells ***Nat. Commun.*** 9: 781

5

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Impact

Our mission is to uncover knowledge that translates into healthier lifespans, securing health throughout life. The Institute is active in working with organisations and communities to ensure that our research has impacts for society and the economy. These interactions reach from the local area to raise public awareness of our research to working with global pharmaceutical companies where our research informs drug discovery and treatment regimes. Our research also feeds into policy development to ensure that the latest healthcare, technologies and policies incorporate the latest science.

Innovation at the Babraham Institute

At the Babraham Institute we value science-business interactions as a means to ensure that our research not only impacts on science but also delivers wider economy and social benefits.

As a contributor to economic development, the Institute plays a vital role as an employer and consumer, but also increasingly acts as a launchpad for entrepreneurial and business interactions. Our Knowledge Exchange and Commercialisation (KEC) team foster a culture of entrepreneurship and is always looking for the best routes to translate the Institute's science into products and services that deliver socio-economic impact.

The Babraham Institute has a strong track record of collaborative work through a variety of partnership models with academia, industry and charities. We are an active member of the Milner Therapeutics Consortium working alongside the University of Cambridge, the Wellcome Sanger Institute and seven major pharmaceutical companies.

Our scientists collaborate with biotech and pharmaceutical companies and also provide specialist expertise in the form of consultancy, to address specific problems and foster new ideas. Institute researchers participated in a total of 23 consultancy activities in 2018, with eleven of these being newly established.

In addition to providing access to expertise, the Babraham Institute also facilitates access to its cutting-edge science services and equipment, all managed by experienced staff.

We also develop our intellectual property assets through activities such as licencing and the formation of spin-out companies. The Institute benefits from its Cambridge and Babraham Research Campus location, the latter being home to over 60 commercial bioscience companies. Crescendo Biologics Ltd, is one of these campus companies, and an example of how the Institute's scientific discoveries can be successfully translated into a spin-out company.

Our KEC activities are supported by the BBSRC and underpinned by a strong governance framework, delivered by the KEC Committee (which reports to the Director and Executive Committee), and by the Institute's Translation Advisory Group consisting of biotech/ pharma and technology transfer professionals who advise on translational strategies.

Opening up our research

Our vision

The Institute is a fully open and transparent research organisation, where public engagement is embedded throughout our research ethos. Our engagement programme maximises the impact of our research by advancing understanding, supporting innovation and addressing societal challenges. Through the programme we aim to build trust, confidence, value and dialogue between our researchers and public groups and we strive to be inspirational, highlighting the role that our research and fundamental bioscience has in our everyday lives.

2018 highlights

Through 2018, over 100 staff and students from all parts of the Institute and from companies on the Babraham Research Campus were involved in a total of 30 engagement activities, discussing their research with nearly 15,000 people, across Cambridge, the UK and beyond.

Our fantastic new exhibit 'Race Against the Ageing Clock', which explores the speed of ageing and epigenetics and includes a number of interactive elements was showcased at the 2018 Royal Society Summer Science Exhibition, with the research made more widely through an online discovery element - Summer Science Exhibition Extra.

2018 was a year for collaboration and we worked with a number of organisations across Cambridge to launch a new project 'LifeLab'. Supported by the European Commission, this project is an international celebration of science in public. Taking place in September, we took our research across the wider region, working on a new schools roadshow, visiting Peterborough Cathedral Square, and different Cambridge locations.

Forward look to 2019

There's lots of opportunities to explore our research in 2019. In addition to our standard programme, we'll be hosting our 25th Anniversary Annual Schools' Day, launching a new Cell Signalling Escape Room, expanding LifeLab to include Ely, and discussing genome editing and our research across Europe – a very exciting year to come. We'll also be launching our new engagement strategy, which will see our programme develop to reach out to audiences who don't traditionally engage with the Institute or science.

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

In 2018:
30 engagement activities involving over 100 representatives from the Institute and campus companies reaching nearly 15,000 people

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Athena SWAN Silver Award

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