Whilst we’re living longer than ever before, our bodies still decline into old age at around the same point that they always have, a concept called healthspan. This decline brings with it challenges to the individual and to society as our final years are increasingly marred by chronic ill-health.

To address these challenges, the Babraham Institute unites wide-ranging expertise in fundamental biology to gain a detailed understanding of lifelong health and ageing. Our research aims to uncover the functioning of the immune system and its decline with age; to investigate how the cells of our body respond and adapt to damage, disease, diet and ageing; and to chart epigenetic changes to gene regulation throughout development and ageing.
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Director’s welcome

2020 was a challenging year for everyone as our lives were turned upside down by the Covid-19 pandemic. Here at the Babraham Institute we knew this too well as our Director and colleague Michael Wakelam was a victim of Covid-19-related complications in March 2020. This was a great trauma for the Institute as Michael was a dear friend to many, and cared passionately about the Institute, its staff and students.

In 2022 we will come together - in person - to celebrate Michael’s life, but for now we are reminded of a quote from Abraham Lincoln: “It’s not the years in your life that count. It’s the life in your years.” With great energy Michael packed a lot of life into his years.

Wolf Reik stepped into the role of Acting Director in early 2020 and was the ideal choice to steer the Institute during this difficult time. Whilst we were all delighted when he accepted the role of Director in early 2021 his tenure was sadly brief as he made the difficult decision to grasp an exciting new opportunity. On behalf of all staff and students I want to thank Wolf for his leadership and many contributions to Babraham over the years. We wish him well in his new venture and hope to work closely with him as a friend with the Institute.

Our People

I am delighted that our new Interim Director at a difficult time, but I remain optimistic about the future of the Institute for several reasons and at the heart of each of these reasons is my colleague, Dr Simon Cook.

Interim Director Dr Simon Cook, Publications 6

The pandemic brought huge challenges to the Institute and the fact that we were able to press ahead with our research – albeit at reduced capacity – and the articulations that both support and provide wider impact from was down to the hard work and dedication of staff from all parts of the Institute. This shows the rare determination and professionalism of our staff and our progress in knowledge exchange, training, funding and outreach is summarised on pages 12.

Following on from these recruitments in Immunology in 2016, we were joined by Hayley Hayne, Rahul Samant and Mario Christophorou in 2019-2020, marking the start of a recruitment phase for our Signalling research programme. Learn more about Hayley and Rahul in one of the Signalling features included in this report.

I am delighted that we will welcome new group leaders in 2021 and 2022 including Ian McGough (Signalling), Stella De Val (Signalling), Philipp Varg (Epigenetics), Teresa Rayon and Sophie Tewksbury (both joint leaders) in Signalling and Epigenetics. This represents a recruitment of eleven new group leaders since 2018 and is a strong statement of our aspirations for growth in the future.

Our Science

Through changes in leadership and global challenges, our research has stood firm and there have been some outstanding science produced across our three programmes; despite very obvious grief there was a determination to support each other and to do our best to progress our science.

To focus on a couple of examples from each, our Immunology research produced important understanding of the differences in immune system response with respect to age in a pre-clinical study of the Oxford/AstraZeneca COVID-19 vaccine (1) and identified a new role for white blood cells in the developing brain (2). The Epigenetics research programme applied the Institute’s expertise in single-cell techniques to explore the effects of age on the developmental competence of egg cells in mice (3), and in exciting collaborations contributed to the first comprehensive molecular map of early embryo development in mice (4) and explored the molecular mechanisms that drive ageing in humans (5). Finally, researchers in our Immunology programme applied their expert knowledge in cell signalling to better understand the mechanism of acquired resistance to anti-cancer drugs (6), possibly influencing treatment models in the clinic, whilst anthropophagy researchers from across the programme collaborated to show that autophagy is repressed during tumour cells’ drug addiction may be their downfall (7), the cellular recycling system is put on hold while cells divide (8). In 2020 and has achieved significant success over a very short timescale. Find out more in the Epigenetics feature on pages 50-51.

Recognitions and Key Awards:

Gavin Eley and Simon Cook became the Heads of the Epigenetics and Signalling research programmes respectively

Claudia Ribeiro de Almeida became a Sir Henry Wellcome Fellow

Hayley Sharpe received the 2020 Lister Research Awards

Michelle Linterman was awarded tenure in December 2019 and has achieved significant success over a very short timescale. Find out more in the Epigenetics feature on pages 50-51.

Career Development and Sustainability.

In November 2019 the Institute became a signatory to the Technician Charter; a sector-wide initiative signed by 100 organisations to support their technical workforce. Our technical specialists and their skills, experience, ability to develop and implement methodologies are critical to the Institute being able to perform world-class science. As a signatory, the Institute has developed a bespoke action plan to identify key areas of progress within the Commitment’s four core areas of Visibility, Recognition, Career Development and Sustainability.

Our Impact

The individual reports that follow share the progress made but I’d like to highlight a couple of significant developments and milestones:

Based on our pioneering research, EnhanceLD Genomics was formed as an Institute spin-out company in January 2020 and has achieved significant success over a very short timescale. Find out more in the Epigenetics feature on pages 50-51.

A Babraham Research Campus impact report recognised the Institute’s vital role in securing the Campus’s success, identifying the Institute’s discovery research and state-of-the-art scientific facilities as unique features of the Campus (9).

Our Public Engagement programme was part of the collaborative LifeLab public engagement project that brought an exciting programme of activities to Fly, Peterborough and Cambridge in 2018 and 2019 and the Institute also celebrated 25 years of our annual Schools’ Day event in March 2019.

Institute welcomes future vision for the Babraham Research Campus

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© LSHTM

1. Stephen Clark from the Reik lab was named as the Researcher of the Year in the Cambidge Independent Science and Technology Awards 2019

2. Michell Linterman was awarded tenure in October 2019 and received the 2019 Lister Prize.

3. The Institute was awarded the Leader in Openness status in 2019 by Understanding Animal Research

4. Michell Linterman was awarded tenure in October 2019 and received the 2019 Lister Prize.

5. The Institute was awarded the Leader in Openness status in 2019 by Understanding Animal Research

6. Michell Linterman was awarded tenure in October 2019 and received the 2019 Lister Prize.
Performance in 2020

Working with others in 2020

- **63** active projects
- **21** countries
- **96** organisations

Working with commercial partners

- **IP AGREEMENTS**
- **CONSULTANCIES**
- **COLLABORATIONS**
- **PATENTS**
- **INNOVATION OPPORTUNITIES DISCLOSED**

People we’ve trained in our scientific facilities this year

- **1,323**
- **1059** bioinformatics
- **230** flow cytometry
- **34** imaging

2020 income

- **£23.6M**
- Core EPSRC & BBSRC non-grant income
- Competitively awarded grant income in 2020
- Income from services provided by the Institute
- BBSRC additional income (including business cases, equipment etc.)

Value of all grants awarded in 2020

- **£6.9M**
- UK funders
- International grants*

Value of UK grants awarded in 2020

- **£4.4M**
- Wellcome Trust
- MRC
- BBSRC
- Cancer Research Technology Ltd
- National Institute of Preventive Medicine
- UKRI

*International grant sources: European Commission (EC)

2020 successes

- **180** students engaged with in-person school’s day 2020
- **83** staff and students involved
- **1097** number of people engaging with our online programme
- **126** publications
- **109** research publications
- **17** reviews

Diversity Access Programme launched hosting undergraduate students for virtual projects

- **15** PhDs completed
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

Immunology

Group Leaders

[Images of group leaders]
Characterisation of lymphocyte transcriptomes using long-read sequencing

Program in 2019 and 2020
By applying long-read sequencing to 8 lymphocytes, we detected transcripts from over 9,300 genes with a failure of supporting reads, which compares very favourably with the number of genes detected using conventional methods on the same samples. We were able to quantify the effect of the RNA binding protein polyadenylate tract binding protein 1 (PTBP1) on the alternative splicing of the Pkm gene and found the results to be consistent with a short-read sequencing method. Furthermore, the long-read sequencing data supported unambiguous assignment of reads to specific transcript isoforms arising from a gene with multiple variants, a feat that cannot be accomplished by short-read methods. This technology will give an unprecedented view into the dynamic regulation of gene expression.

Selected Impact Activities
- Martin Turner was invited speaker at the 2019 Keystone Meeting on Transcription and RNA Regulation in Immunology, and Immunity, Lake Tahoe, USA.
- Martin Turner was an invited speaker at the 24th Annual Haematology Congress in 2019, held in The Netherlands.
- PhD student David Turner presented his work on CRISPR screens for RNA binding proteins in 8 cell differentiation at the 2020 RNA VM meeting.

How we make enough antibodies to fight infection

The immune system creates antibody proteins to help fight infection. Antibodies are made by white blood cells called B lymphocytes, by mixing and matching genetic information, these cells can produce millions 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 appropriate 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, and how epigenetic mechanisms including transcription factor binding and post-transcriptional modifications affect which genes are more frequently expressed, or the expression level at how the large-scale 3D folding of these large DNA regions in the nucleus affects antibody production, and at gene expression and regulation in B cells. This will increase our understanding of normal antibody production and enable us to understand the events that cause leukemias and impaired antibody production in ageing.

Progress in 2019 and 2020
Aging bone marrow produces fewer B lymphocytes. With other institute groups we compared gene expression patterns in wide in B lymphocytes from young and aged mice to reveal genes dysregulated in ageing. We discovered that ageing affects epigenetic mechanisms, including promoters that make up genes, microRNAs that degrade splice RNA, and interactions of promoters with activating enhancers. Sequencing and functional data. The volcano plot depicts the change in gene expression between young and aged is B cells that make the antibody heavy chain, only young and aged is B cells that make the antibody light chain. Red spots or spots in the ‘volcano’ plot are genes that are dysregulated in ageing, which are the right hand expression in older in ageing. The genes with low expression encoded in red are components of the Igf1r signalling pathway.

Selected Impact Activities
- Anne Corcoran gave a presentation to the Cambridge Scientific Society; how we make a billion antibodies: genetics and development. March 2019.
- Immunology videos lecture for University of Malawian: MS students, Kamrul Uganda, organised for Cambridge for Africa.
- The group hosted a Welcome Trust Symposium for undergraduate student in 2019 and an online undergraduate project in 2020.

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

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

Martin Turner
Programme Leader

Group members
Senior research associates:
- Scott Bell
- Elia Montera Casasnovas

Postdoctoral researchers:
- Jia Lu
- Martin Turner
- Sarah Bell
- Vanessa D’Angeli
- Alexander Saveliev
- Fengyuan Hu
- Michael Screen
- Miriam Berry
- Lyobomira Chakalova
- Visiting scientist:
- Irina Ferapontova

PhD student:
- Elise French
- Yogita Suratwala
- Lina Dobnikar
- Daniel Bolland
- Michiel Thiecke
- Isabella Romano
- Emilia Camacho
- Cristina Cristofoletti
- Anna Granelli
- Elisa Giorgetti
- Thomas Noack
- Janna Nowak
- Gloria Holgado
- Ailbhe Duff
- Thomas Nowak
- Maximilian Zuckermann
- Evgeniia Sanina
- Maksim Tikhonov
- Christopher Church
- Selim Al Angel
- Georgia Patel
- Stijn De Block
- Dagmara Zgierska
- Alexander Saveliev
- Jana Krom"akova
- Ines Gisler
- Lizzy Ueland
- Josep Xavier
- Luiza Ribeiro
- Michiel Thiecke (Left in 2019)
- Fall 2020
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Understanding the germinal centre reaction

Our research focuses on the cellular and molecular mechanisms that underpin a robust germinal centre reaction. The germinal centre forms after antigen challenge and, because it is the only cellular source of long-lived antibody secreting plasma cells, it is essential for enduring antibody-mediated immunity after infection or immunisation.

Selected Impact Activities

- **Invited speaker, Keystone Symposium**: B cell/T cell Interactions, USA.
- **Virtual Symposium for Babraham Institute 2019 School’s Day in the Laboratory**.
- **Organised EMBO Young Investigator Immunology meeting, Cambridge, UK.**

![Image of a germinal centre in a lymph node 14 days after immunisation. Publishing germinal centre B cells: n=6, Indolic follicle centre B cells: n=6, Fractal follicle centre B cells: n=6.](image)

Intrafollicular Helper Cell Functions

1. We demonstrated that aged mice have a reduced immune response to the Oxford-AstraZeneca COVID vaccine which can be boosted by a second dose (Ref. 1. Silva-Cayetano, Foster, Innocentin et al., 2020).
2. We discovered that influenza infection remodels the lung to support the CXCR4-dependent recruitment of B cells to the site, enabling the formation of ectopic germinal centres (Denton et al., 1 Exp. Med. 2019).

3. In a human vaccine trial we discovered that it is possible to boost the T follicular helper cell response in humans, which supports long-lived antibody production after vaccination (Pipe, Li et al., J. Exp. Med. 2019).

T cells in our tissues

Lymphocytes are among the best studied cells in the body. We, therefore, know remarkably little about how they operate in the tissues - almost all our knowledge has come from studying blood- and lymphoid organs. Our research seeks to understand the generic programme that is intrinsic in the tissues, and how we can exploit this programme to maintain health.

Current Aims

We aim to understand how T cells, especially the anti-inflammatory regulatory T cells, interact with the tissues. We take a holistic approach to tissue immunology, looking across tissues to determine differences and shared biology. We seek to unravel the genetic and epigenetic programme that allows T cells to enter various tissue. We are actively developing genetic tools that allow us to track and manipulate T cells within the tissues. Finally, we seek to utilise the resident T cell population to enhance the robustness of the tissue to damage, injury and ageing.

Progress in 2019 and 2020

Over the past two years, we have made enormous strides into understanding the role of T cells in one particular organ - the brain. T cells enter the brain soon after birth, and in both health and illness the cells undergo a transformation aiding their survival in the brain environment. We have found that the entry of T cells into the brain is linked to a key maturation event during brain development: the differentiation of embryonic microglia into adult microglia. This event is required for microglia to gain the ability to prune neuronal synapses, a rewiring of the brain critical for learning.

Selected New Developments

- **Flow cytometry is one of the foundational tools in biomedical research, allowing single-cell profiling and functional assays.**

- **Despite decades of advances in the hardware of flow cytometers, the data processing side remained stagnant. We developed a new algorithm, called AutoSpill, which reduces the error in flow cytometry analysis by 100-fold.**

- **An industrial partnership allowed integration of this software into FlowJo, with a reach of ~80,000 users.**

- **To help children understand the COVID lockdown and the importance of vaccination, we produced two children’s books, “Just for Kids! All about Coronavirus” and “Battle Robots of the Blood”, translated into eleven languages and read by more than 5,000 children internationally.**

- **We developed a new technology allowing us to harness the anti-inflammatory properties of regulatory T cells in neuroinflammation. In animal models, this novel therapeutic can reduce brain damage by 50% following traumatic brain damage, stroke or experimental multiple sclerosis. This work has been patented and is being developed for human application.**

A T cell (green) and macrophage (red) collaborate in the brain. Blood work are shown in red.
We are interested in understanding how cellular mechanisms underpinning diversification of antibody genes, to gain insight into how B cells can effectively fight infections and the role this plays in age-related immune dysfunction. Emerging evidence suggests important roles for RNA and RNA-binding proteins (RBPs) in these processes, which constitute new opportunities for therapeutic intervention. Our ongoing research focuses on a class of RBPs known as RNA helicases, and how their activity in remodelling RNA and RNA-protein complexes regulates antibody gene rearrangements.

Current Aims
Our knowledge of how antibody gene rearrangements are regulated at the RNA level is limited, compared to the well-characterised function of transcription factors and chromatin epigenetic modifications. Therefore, much of our current effort goes into profiling protein–RNA interactions that characterise B cell developmental stages underlying antibody gene rearrangements. These analyses will provide important insights that will help prioritise RNA helicases for subsequent studies. We are also investigating how the RNA helicase DDX1 acts to modulate RNA–protein interactions that characterise B cells actively undergoing antibody gene rearrangements. Interestingly, we have found that many RNA-binding proteins (including RNA helicases) interact with RNA in response to DNA damage signalling, initiated by the protein kinase ATM. One example is DDX1 and we are currently investigating its role in B-cell activation in vivo. Possibly related to DDX1’s role in antibody isotype switching, we have discovered DDX1 is required for B cell differentiation in antibody secreting cells and impacts on the quantity and quality of antibodies produced during an immune response.

Selected Impact Activities
- Claudia Ribeiro de Almeida participated in the Malaria RNA Salon webinar series with a talk on the role of RNA helicases in modulating RNA structure during antibody gene rearrangements (May 2020).
- Claudia Ribeiro de Almeida presented at the BESIC Virtual Annual Visit at the Babraham Institute (November 2020).
- The lab hosted Guadalupe Müller as an Erasmus student from the University Grenoble Alpes for a three-month short-term research placement carried out remotely.
Oxygen makes up 21% of the Earth’s atmosphere and plays a pivotal role in biological systems. Despite this, huge gaps remain in our understanding of how this essential element regulates cell signalling pathways and affects our immune system – questions that Dr Sarah Ross aims to answer.

We all need oxygen. We breathe it in some 17,000 times a day. And although we might sometimes feel its lack – sprinting for a bus or travelling to altitude – oxygen levels in our tissues vary widely in health as well during disease.

We are still learning how cells sense and adapt to low oxygen, and how oxygen affects our immune system – knowledge that will be critical for developing new therapies for cancer and other diseases. In 2019, the Nobel Prize for physiology and medicine was won by a trio of scientists who uncovered how cells sense and adapt to low oxygen. At the Institute, Dr Sarah Ross wants to discover how low oxygen, or hypoxia – can prevent our immune system from working effectively.

Ross is studying killer T cells – a critical component of the adaptive immune system – whose job is to hunt down pathogens and protect against cancer by producing cytotoxic compounds. To do their job effectively, they must travel to altitude – oxygen levels in our tissues vary widely in health as well during disease.

“Hypoxia is relevant for multiple diseases. An obvious one is cancer, because we know it’s linked to hypoxia. But it might also play a role in how T cells function in inflammatory diseases like arthritis and Inflammatory Bowel Disease, which is something we need to investigate more,” Ross concludes.

“Oxygen affects our immune system is relevant for multiple diseases”

Since joining the Institute in 2018 she’s also been identifying common themes with her colleagues across the Institute. “What we are discovering in immune cells has importance for other cell types too, and we are always finding new connections with the work going on in Signalling and Epigenetics.”

Understanding which proteins are being regulated in T cells and how these might be controlling T cell function has important implications, because by working out which molecules are involved, researchers will be able to identify new therapeutic targets against a range of diseases as well as using existing drugs in different ways.

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Our tissues have different oxygen concentrations and this has implications for immune cells,” says Ross. “T cells usually reside in lymph nodes and the spleen, but when they are called on to fight infection or disease they often find themselves in foreign oxygen environments.”

Many factors influence oxygen levels in our tissues: some are normal variations that reflect the oxygen needs of particular tissues, while others result from disease or ageing. Bacterial infections can drive up oxygen demand when bacteria and immune cells compete for oxygen. Areas around tumours can also become hypoxic due to uncontrolled cell division in cancer. Apeing, too, affects the picture because diseases that affect the lungs or blood vessels reduce the supply of oxygen.

“Teasing out how these low oxygen environments hamper T cells’ work is central to Ross’s research. Her work focuses on three key areas: the role oxygen plays during an immune response, how oxygen is linked to age-related declines in the immune system and whether or not we can help T cells work better by targeting these oxygen-regulated pathways.

Answering such big physiological questions at a molecular level demands painstaking precision. Ross works in vitro with T cell cultures grown in standard conditions and, while her methods sound simple, they pose huge technical challenges. “Putting cells in different oxygen environments is easy. What’s really difficult is controlling the amount of oxygen that each of those cells will sense,” she explains.

This is because of the many variables involved. Different culture media will affect oxygen availability, as will biological variation among the cells. And variations in the density of cells in each culture also impact oxygen demand. “Some cultures use more oxygen than others, so we have to be very precise to avoid accidentally creating hypoxia,” says Ross.

It’s an observation that she believes has important implications for in vitro research well beyond her field. “Even if you’re not studying oxygen, changes in cell density could be triggering hypoxia in cell cultures and causing variation in your data. It’s across the board – in cancer cells, stem cells and immune cells – and while it’s rarely talked about it’s fundamental.”

Her first couple of years at the Institute have been busy ones: Ross’s group has been studying how duration of hypoxia affects T cells, how hypoxia alters the abundance of certain proteins and identifying which molecules are mediating these effects. Ongoing research is expanding this work to develop an understanding how the oxygen levels that a T cell experiences during an immune response defines their fate and function. The capability to do this research has been boosted by the acquisition of equipment to develop a hypoxia and physiological oxygen facility at Babraham, which was funded by the BBSRC.

“Hypoxia is relevant for multiple diseases. An obvious one is cancer, because we know it’s linked to hypoxia. But it might also play a role in how T cells function in inflammatory diseases like arthritis and Inflammatory Bowel Disease, which is something we need to investigate more,” Ross concludes.
Responding to the Covid crisis

As well as exposing weaknesses in healthcare systems and supply chains, the coronavirus pandemic has underscored the importance of fundamental research and collective effort. During 2020, scientists rose to the challenge of developing new vaccines and effective treatments for Covid-19. Institute immunologists Dr Michelle Linterman and Professor Adrian Liston describe how their labs responded and the lessons we must learn.

In the early days of the coronavirus pandemic, as lockdowns were introduced, workplaces closed and travel slowed to a trickle, Dr Michelle Linterman was certain of one thing – she wanted to make her group’s expertise available to the global vaccines effort.

Among those working on a vaccine against SARS-CoV-2 (the coronavirus that causes Covid-19) was Dr Teresa Lambe at the Jenner Institute in Oxford. “I already knew Tess, so once it became clear they had a vaccine candidate, my first instinct was to ask her what we could do to help,” Linterman recalls.

As an immunologist, Linterman’s work focuses on how the immune system responds to vaccines. In particular, she wants to understand why older people respond less well to vaccines, something she studies using human vaccination studies and in aged mice. “I thought the most useful thing was for us to offer something that nobody else could contribute quickly – and that was our ability to use aged mice as a pre-clinical test of how this vaccine is likely to work in an ageing immune system,” she says.

When Lambe said yes, Linterman set up trials to compare immunological responses to the Oxford/AstraZeneca vaccine in young and aged mice, and discovered that although aged mice responded more poorly than young mice to a single dose, after two doses of the vaccine, the immune responses were very good in both groups.

The study helped both institutes. For the Jenner, it showed two doses of the vaccine would give good protection against infection in all adults. For Babraham, it provided new insights into vaccine responses at a cellular and molecular level, expanded research into new vaccine platforms and led to new collaborations. Most importantly, it illustrated the value of publicly-funded research.

“Because we’re funded by the BBSRC – in other words the tax payer – it was incredibly important to use our knowledge and expertise to contribute to vaccine development in the midst of the pandemic,” she says.

Fellow immunologist Professor Adrian Liston also stepped up to the mark, using his research to help clinicians make the best treatment choices for Covid-19 patients and his communication skills to provide accurate information to journalists and the public.

“We need to develop good systems for treating emerging viruses before we know much about them, which is something my lab is working on,” explains Liston. “We are coming up with treatments that are vaccine agnostic, treatments that will work for most viruses with the potential to become pandemic, regardless of the actual virus.”

Liston’s group is also interested in systems immunology – exploring what makes people’s immune systems so different from each other. This variation has been graphically illustrated during the pandemic, some people experiencing mild symptoms while others died.

“Diversity is intrinsically important to the immune system. It’s the most genetically diverse system in the human body, and there are other factors at play, such as age, gender and weight,” he explains.

Being so close to events has taught Liston and Linterman many lessons – lessons, they say, that are vital for political leaders to learn. First, zoonoses (diseases spread between animals and humans) with pandemic potential are far from rare events.

“They occur every couple of years,” says Liston. “We’ve had coronaviruses outbreaks before, like SARS and MERS; they happen like clockwork. In the previous outbreaks we had better luck and better preparation. These are things we must prepare for.”

Secondly, we must guard against complacency. “If we put each other on the back for a job well done, and then slash science budgets, the next outbreak will be as bad as this one,” he warns. “We must fund surveillance as well as immunology and virology research, because if we scale back this science it takes a decade or more to rebuild that intellectual capital.”

It was incredibly important to use our knowledge and expertise to contribute to vaccine development in the midst of the pandemic – Michelle Linterman

We are coming up with treatments that are vaccine agnostic, treatments that will work for most viruses with the potential to become pandemic, regardless of the actual virus – Adrian Liston

LEARN MORE:
Watch an animated description of the Linterman lab’s research work on the Oxford/AstraZeneca vaccine.

This preparation extends to supporting fundamental research in a broad range of areas. “We need to fund fundamental research because you’re never sure which bit of it will save you in the future,” says Linterman.

Third, a global approach to research, and funding to support this is essential, because scientific discoveries are not bounded by borders, adds Linterman: “One of the reasons the Oxford vaccine was developed so fast was because of years of work on Ebola and MERS using the same adenoviral vaccine vector.”

As vaccines are rolled out, and countries emerge from lockdown, we might usefully reflect on what we would have done without a vaccine. It’s a scenario that frightens Linterman. “If we put each other on the back for a job well done, and then slash science budgets, the next outbreak will be as bad as this one,” he warns. “We must fund surveillance as well as immunology and virology research, because if we scale back this science it takes a decade or more to rebuild that intellectual capital.”

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We are coming up with treatments that are vaccine agnostic, treatments that will work for most viruses with the potential to become pandemic, regardless of the actual virus – Adrian Liston

We are coming up with treatments that are vaccine agnostic, treatments that will work for most viruses with the potential to become pandemic, regardless of the actual virus – Adrian Liston

Immunology
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, disease, 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
Signalling pathways in health and disease

Our goal is to better understand how protein kinase signalling pathways maintain health and how this may be deregulated in disease. Some pathways control the cellular recycling process known as autophagy whilst others control whether cells live or die. We also work with biotech and pharma companies to translate our knowledge to support the development of new drugs.

Current Aims

The ERK1/2 and ERK5 signalling pathway controls whether cells survive and divide or whether they senesce in a form of cellular ageing or die. We are interested in how these different outcomes are controlled and are seeking to identify novel regulators of these pathways. In addition, we are studying autophagy, the cellular recycling process that is activated when nutrients are scarce to keep cells alive. We want to understand how autophagy is controlled so that it is only activated at the right time, to support cell survival, and does not run out of control and kill cells.

Progress in 2019 and 2020

Ongoing collaborations with AstraZeneca have defined the role of an ERK1/2-regulated protein MCL1 as being crucial for the survival of melanoma cells, in so doing we have identified a novel drug combination that effectively kills melanoma tumour cells. We have also shown that autophagy is inhibited during mitosis, the process of cell division into two daughter cells. This repression of autophagy ensures that the non-selective autophagy machinery does not accidentally degrade kinetochore markers, that would otherwise cause generic damage to be passed on to daughter cells. We think this temporally distinct repression of autophagy is critical for lifelong health.

Selected Impact Activities

Simon Cook and PhD student Richard Odei gave talks at the 2019 mTOR congress and the 2019 Keystone Autophagy conference.

Our goal is to better understand lysosome degradation systems in both health and disease. We investigate autophagy and related pathways which we hope can be exploited to reverse the decline in lysosome function that is seen with increased age.

Current Aims

We are currently focusing on a non-canonical autophagy pathway, which utilises some of the autophagy machinery to target ATG8 lipidation to endolysosomal membranes. This pathway plays important roles in cellular responses to pathogens, including influenza A virus, and stress. A key open question we are addressing is: what are the exact functions of ATG8 proteins at these membranes? By understanding how the pathway is regulated, we hope to be able to harness it for therapeutic benefit.

Progress in 2019 and 2020

We have continued to make progress in our understanding of the non-canonical autophagy pathway by defining molecular signatures that are associated with it, and the development of tools to specifically manipulate it. Ongoing commercial collaborations have revealed a link between activation of the pathway and maintenance of the lysosomal system, which may underlie the functional role of non-canonical autophagy.

Selected Impact Activities

Oliveir Florey presented recent work at both Keystone and EMBO conferences.

The Florey lab has ongoing collaborations with Canada Therapeutics, a biotech company based in the US.

Maintaining the cellular waste disposal system

Selected Impact Activities

Dr Oliv Florey presented recent work at both Keystone and EMBO conferences.

The Florey lab has ongoing collaborations with Canada Therapeutics, a biotech company based in the US.

We aim to understand how autophagy is critical for lifelong health. By targeting these pathways we hope to be able to harness it for therapeutic benefit.

Progress in 2019 and 2020

We have continued to make progress in our understanding of the non-canonical autophagy pathway by defining molecular signatures that are associated with it, and the development of tools to specifically manipulate it. Ongoing commercial collaborations have revealed a link between activation of the pathway and maintenance of the lysosomal system, which may underlie the functional role of non-canonical autophagy.

Selected Impact Activities

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The Florey lab has ongoing collaborations with Canada Therapeutics, a biotech company based in the US.
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, which is a key player in a membrane phospholipid that is made by enzymes called phosphomonoesterases (PMEs). 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 the capability to do this is regulated by PI3K. The specific PI3K isoforms that drive activation of the PI3K pathway.

2. We have made progress in understanding the mechanism by which PI3K is regulated by nutrients to be sensed by cell surface receptors. 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.

3. We have identified a key molecular mechanism by which PI3K is regulated by cell surface receptors in neutrophils (ref. 3).

Progress in 2019 and 2020

Work in the group during this period has led to the following developments:

1. We have identified some of the key players in 'priming' the PI3K pathway during a neutrophil’s response to pro-inflammatory stimuli (ref. 1).

2. We have discovered the sequential translocation of PI3Ks inside cells called PI(3,4,5)P3, which is a key player in a membrane phospholipid that is made by enzymes called phosphomonoesterases (PMEs). 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.

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1. We have collaborated with the pharmaceutical industry through joint grants and serving on scientific advisory boards.

2. We have collaborated with academic groups in the USA, Ireland, Canada, Switzerland, and Germany and the UK and presented at five international conferences.

3. We have trained five overseas students (from Germany, France, Spain and the Netherlands).

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 response to the case of starvation, autophagy generates nutrients from self-degradation whereas the presence of damaged proteins or organelles triggers autophagy to eliminate them via delivery to the lysosomal machinery by double membrane vesicles termed autophagosomes that engulf various random cytoplasmatic 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 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.

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Published: www.babraham.ac.uk/our-research/signalling/len-stephens /philip-hawkins

Selected Impact Activities

We have modelled the process of autophagy induction prior to the appearance of autophagosomes. This model is the first to show that autophagosomes form at a site close to the cell surface 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). In addition to work on tissue culture cells, we are now working on PSC-derived neuronal cells trying to understand how autophagy modulates neurogeneration.

In 2019 and 2020

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Publications

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


Selected Impact Activities

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3. We have identified some of the key players in ‘priming’ the PI3K pathway during a neutrophil’s response to pro-inflammatory stimuli (ref. 1).
Cellular accumulation of misfolded proteins is a hallmark of ageing. In young cells, the protein clearance network efficiently clears new or emerging damage by activating one or more systems for misfolded protein clearance. We focus on how these clearance systems are integrated within the network to maintain protein homeostasis during youth, and how loss of this integration contributes to cellular senescence, another ageing hallmark with strong links to chronic inflammation and organismal frailty.

Current Area

We use two evolutionarily distant cell types, budding yeast and primary human fibroblasts, to identify conserved, conserved lines of communication between different clearance systems of the protein network, and investigate how these are preserved during replicative ageing (yeast) and senescence (fibroblasts). Our lab employs multiple-disciplinary approaches such as super-resolution imaging, flow cytometry, and mass spectrometry-based proteomics to measure proteostasis capacity and senescence phenotypes as quantitatively and robustly as possible. As proteostasis and senescence are regulated, particularly by reactive oxygen species, we use mass spectrometry in these experiments.

Signalling

Hayley Sharpe

Group members
Postdoctoral research scientist: G. W. Fearnley, I. M. Hay
PhD students: Kasia Wojdyla, Katie Mulholland, Gareth Fearnley (left in 2020)
Research assistant: Katherine Young
Visiting students: Oisharja Rahman, Iain Hay, Tiffany Lai
Research assistant: Debya Rahman
Selected Impact Activities

The reversible phosphorylation of protein tyrosine residues enables cells to dynamically respond to changes in their environment and is regulated by the antagonistic actions of kinases and phosphatases. We focus on the understudied phosphatases to understand how they signal, their roles in health and disease and how they are regulated, particularly by reactive oxygen species, which are implicated in the ageing process.

Current Area

Our overarching aim is to understand mechanisms of tyrosine phosphatase signalling in order to understand their fundamental functions but also to reveal new approaches to targeting them in disease, to overcome their undruggable reputation. Our current work is focused on a family of receptor tyrosine phosphatases that are present on the cell surface and form homophilic interactions at points of cell-cell contact. The receptor PTPRK is a tumour suppressor and had been suggested to mediate cell adhesion. To gain insight into its signalling we are working to identify its substrates and to understand its cellular function through promoter typing, structural studies, mass spectrometry and gqep profiling.

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Progress in 2019 and 2020

We have defined high confidence substrates for PTPRK, using unbiased interaction and phospho-proteomics. This revealed a key role for PTPRK in the regulation of cell--cell adhesion, and we found that deleting PTPRK leads to changes in cell morphology that we plan to further investigate (research described in ref. 1). We have also found that a related receptor, PTPN1, is in fact a pseudophosphatase. Using structural studies we found conformational features that explain its lack of enzyme activity. Curiously, despite being inactive, PTPN1 binds to PTPRK substrates. This led us to propose that this inactive receptor competes for substrates with its active paralogues and could even form a signalling scaffold (ref. 2). Pseudophosphatases are poorly studied but play an increasingly important role in cellular signalling events (reviewed in ref. 3).

The adhesive receptor protein tyrosine phosphatase PTPRK is expressed on epithelial cell sites as a result of cell--cell contact; we have identified key substrates that define cell adhesion (left). Transverse electron microscopy images revealed that PTPRK is secreted epithelial cell leads to disruption of adhesion and, as decreased cell--cell height, reminiscent of an epithelial to mesenchymal transition (right).

Selected Impact Activities

Industrial collaboration underway with Astrazeneca through a Collaborative Training Partnership.

Held a Wellcome-funded summer student.

Hayley Sharpe was profiled in the journal Cell as a young scientist in November 2020 as a cell scientist to watch.
Signalling

Rac is a protein that enables cells to attach and to move. We study how Rac is controlled 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 metabolism. In addition, we have made progress in understanding how Rac-GEFs are controlled and how they carry out many different roles within the same cell.

Current Aims
We previously discovered a family of Rac-GEF proteins we called P-Rex. We described how P-Rex1 allows white blood cells to fight diseases, and we found a new protein, Norbin, that controls P-Rex1. Recently, we found unexpectedly that Norbin suppresses the immune system, and our current aim is to uncover the underlying mechanisms. We also work towards a better understanding of the importance of P-Rex-GEFs and their catalytic activities in metabolism, and of the catalytic activities and roles of other Rac-GEFs in the immune system. 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.

Mice that lack Norbin protein in their neutrophils and macrophages (types of white blood cells) have tenfold increased immunity against bacterial pneumonia infections. This is dependent on neutrophils rather than macrophages. These images show neutrophils labelled with coloured dots depending on where they are in the lung, demonstrating that Norbin-deficient neutrophils get to the site of infection in a different manner to normal neutrophils. Norbin-deficient neutrophils are also better at killing bacteria than normal neutrophils. This study identified Norbin as a suppressor of the immune response to bacterial infections, which was surprising as the protein was previously only known for its roles in nerve cells.

Progress in 2019 and 2020
We showed that Norbin suppresses immune defense against infections through surprising and important roles in neutrophils, a type of white blood cell, with implications for lifelong health. We have also identified new roles for Rac-GEFs in the immune system and in the maintenance of healthy blood glucose levels, and this work is continuing. We found new cellular roles for P-Rex1 in nerve cells. Finally, we contributed to a study by the Mitchell lab in Melbourne, Australia, which identified that P-Rex1 is important for the initiation and metastasis of mammary tumours in mice (ref. 1).

Selected Impact Activities
- Ongoing collaborations with Bioscience Metabolism, Research and Early Development, Cardiovascular, Renal and Metabolism (CVRM), AstraZeneca, Cambridge, UK and with Vernalis (R&D) Ltd, Cambridge, UK.

Group members continued:
- Visiting students: Sarah Perrenot (Left in 2019), Paula Samso Ferre (Left in 2019)
- Continued from page 28

Publications
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Hedi Welch

Group members
Senior postdoctoral researcher: Kirsti Hornigold (Left in 2020)

PhD students:
- Stephen Chetwynd
- Elizabeth Hampson
- Polly Machin
- Chiara Pantarelli (Left in 2019)
- Elpida Tsonou (Left in 2020)

Research assistant: Laraine Crossland
Visiting students: Harriet Banks (Left in 2020), Abhi Gowda (Left in 2019), Borjan Venovski

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Publications
Back to basics

Setting up a new group is exciting and daunting. Two group leaders who joined the Signalling programme in 2019 – Dr Hayley Sharpe and Dr Rahul Samant – talk about their research and the supportive, collaborative and open environment that they say marks out the Institute.

Lots of ingredients go into building a successful new research group. Great ideas, a productive team and the right environment are all part of the mix.

A great illustration of the Institute’s ethos was a colleague’s reaction to news that Sharpe had been selected as an EMBO Young Investigator. “I was at my computer, saw the news and leapt up. One of the Principle Investigators happened to be passing and just walked in and gave me a big hug,” Sharpe remembers. “Everyone is so supportive – and everyone’s made a real effort to make us feel very welcome.”

Sharpe’s group works on a family of enzymes that – for the past two decades – has been largely ignored but which Sharpe believes is ripe for the next 30 years, hence the appeal of these enzymes, “she says. “But they proved very hard to drug, so the pharmaceutical industry fell out of love with these enzymes and abandoned them” Sharpe explains. Recent advances, however, have rekindled research interest. Big data, CRISPR and other new tools point to tyrosine phosphatases being important in many diseases – including some cancers and diabetes-related macular degeneration – as well as spinal cord injuries and skin ageing. “When you’re setting up a lab you want to go into an area where you can work for the next 30 years, hence the appeal of these enzymes,” she says.

In a neglected field, developing new therapies means going back to basics, which is part of Sharpe’s approach. She is working at a molecular level to discover how these enzymes help build up the layers of our skin and other tissues. She’s also using mouse models to understand their role in disease, aiming to translate new knowledge into future new therapies.

Basic biology is also what drives Dr Rahul Samant. Reflecting on his impressions as a new appointment at the Institute Samant says that what struck him most about the Institute was its openness. “The environment here opens up broader scientific thinking. Conversations are like relaxed brainstorming, and having people to bounce ideas off is important for me,” he says. “I do science because I want to know how things work. I want to be able to follow where the science leads me. And the Institute is one of the few research centres that has such a strong focus on fundamental, mechanistic biology.”

As a cell biologist, Samant is fascinated by misfolded proteins and the way our cells prevent them from building up. Our cells are complex machines with many moving parts, to work smoothly, proteins must be the right size, shape, and in the right place. It only takes one misfolded protein to trigger a chain reaction that can lead to disease, so our cells invest heavily in sophisticated quality control systems to deal with misfolded proteins before they cause damage.

“Recent advances, however, have rekindled research interest. Big data, CRISPR and other new tools point to tyrosine phosphatases being important in many diseases – including some cancers and diabetes-related macular degeneration – as well as spinal cord injuries and skin ageing. “When you’re setting up a lab you want to go into an area where you can work for the next 30 years, hence the appeal of these enzymes,” says Samant, we have known for the past 15 years that this is too simple to be true. “It’s very context dependent, and only now are we developing the tools to look at all the different type of ubiquitin tags in sufficient detail,” he explains. “I’m interested in using this increased resolution to go back to these basic questions that we’ve assumed to be true, but which the data now shows to be vague and hand-wavy.”

To study the process, Samant combines tools he honed during his time as a research associate at Stanford University with the state-of-the-art proteomics facility at the Institute. He also collaborates with the Institute’s world-leading experts in autophagy – another crucial cellular process for clearing up misfolded proteins. It’s work that could reshape our understanding healthy ageing and diseases, identifying new therapeutic targets and allowing us to treat neurodegenerative diseases and cancer much earlier. But only, Samant concludes, if we go back to basics. “We don’t yet understand how ageing affects the prevalence of misfolded proteins – and understanding these processes at a fundamental level is really important before we can start addressing the disease aspects.”
A remarkable partnership

Great science depends on teamwork, yet genuine partnerships are rare, especially those which sustain success over decades. Dr Len Stephens and Dr Phill Hawkins, both group leaders in the Institute’s Signalling programme, have worked together for more than 30 years. Here, they reflect on their research, their relationship – and their distinctly different approaches to fishing.

In 1980, Fred Sanger and Walter Gilbert won the Nobel Prize in chemistry for work on nucleic acid sequences. Polish workers set up the trade union Solidarity; and the Rubik’s Cube made its debut. It’s also the year that PI3K signalling pathways involving a sugar-like molecule called inositol were discovered. Lew Cantley’s lab in Boston had just discovered a new enzyme called phosphoinositide 3OH kinase, or PI3K for short, that made a new family of inositol-containing molecules in cells in response to growth factors. There was much to discover and while the science was challenging, there was a sense in the lab that they were hunting down something significant.

“At the beginning it was about correctly identifying the molecules that were appearing in cells and working out how they were made,” Stephens explains. “Our instincts told us they’d turn out to be a key piece of biology that controlled how cells behave, and that spurred us on to try and understand what was going on.”

We now know that cells monitor and respond to their environment by controlling the activity of a few key proteins, which in turn regulate a cascade of downstream events. Together, they orchestrate the complex behaviour that happens in cells, from cell growth and division to cell survival and movement. When these signalling networks go wrong, they can lead to a range of diseases, including cancers, chronic inflammation and autoimmune diseases. For instance, understanding the basic biology has opened up new treatments for these diseases.

“We thought our research would be a fundamental bit of cell biology, but at the time we didn’t know where it would lead,” says Hawkins. “There wasn’t a single eureka moment, many small step changes along the way allowed us to piece together the basics of what was going on. Then other labs discovered that mutations in PI3Ks are often associated with cancer. That’s when it became a much wider impact story, and attracted the attention of other researchers and pharmaceutical companies.”

Since then, Stephens and Hawkins have worked closely with industry, collaborating with Onyx Pharmaceuticals, UCB, AstraZeneca, GSK and Pfizer. By 2013, the pharmaceutical industry had invested £350 million in PI3K research and had more than 20 drugs targeting PI3Ks in clinical trials. In 2014 the first – Idelalisib – was licensed for treating chronic lymphocytic leukaemia.

Reflecting on their partnership, both agree that a natural friendship, shared values, and contrasting – but complementary – personalities have underpinned its longevity and success. Hawkins is more emotional, he says, his moods tracking the Y highs and lows in the lab, whereas Stephens is steadier and a battler, with a bold ambition for their science.

According to Stephens, having similar values is key. “The rest flows from there,” he says. “Are we similar in all respects? No, and that’s important. We have different strengths and weaknesses. It’s about your motives, the things that inspire you, the things you respect in others, what you find meaningful. And sometimes it’s about understanding – at a deep level – what can hack someone off.”

Both are eminent scientists and fellows of the Royal Society, but say that what matters most is a shared scientific curiosity, and a happy working environment. “Neither of us wanted success for its own sake or accolades,” says Hawkins. “We wanted to find out something fundamental about how the world works, and how cells work.”

And then there’s the fishing, which seems to encapsulate what they share, as well as their differences. Like their research and friendship, their fishing goes back to Birmingham. “When he invited me to Canon Hill Park, I saw fishing in a totally new light,” laughs Hawkins. “It’s a science for Len: what type of line to use, which home-made floats – he even made catapults with different types of elastic to deliver a certain number of maggots to a precise spot in the water! It’s fishing on a whole other level.”

Stephens agrees. “As far as I’m concerned it’s incredibly similar to doing experiments: I love trying to figure out what the fish are doing under the water, and doing experiments to work out how to catch them,” he concludes. “So yes, I can get very intense about going fishing.”
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 because cell 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 epigenetic differences influence cell diversity
- The impact of diet on epigenetics, health, and ageing
- The inheritance of epigenetic memory between generations
- How life events affect biological ageing through an epigenetic clock
- New approaches and technologies to drive further progress

Group leaders

- Glenn Kelkway
- Olivia Casasnovas
- Maria Christophorou
- Jon Houseley
- Wolf Reik
- Peter Rugg-Gunn
- Stefan Schoenfelder
- Martin Howard

Honorary group leader

38-51
EpiGeneics

Epigenetic legacies from eggs

As well as genetic information, the egg and sperm contribute epigenetic annotations that can influence how genes are activated after fertilization. We examine how epigenetic patterns are set up 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 for the health of a child.

Current Aims

A major aim is to understand how repressive chromatin marks in oocytes lead to long-term silencing – ‘imprinting’ – of genes from the mother, particularly in cells that form from the placentas. We are seeking to understand the genetic elements that carry this epigenetic memory between generations, how they control these ‘imprinted’ genes, and how important the epigenetic marks are for development and function of the placenta and consequently growth of the fetus. To investigate these questions, we develop methods to profile epigenetic information in small numbers of cells or even single cells, as well as using gene-editing methods.

Progress in 2019 and 2020

A highlight has been the discovery that newly-synthesized imprinting is controlled by genomic parasites – repetitive DNA elements that can be co-opted during evolution as mode gene control modules. They can act in a highly tissue-specific way, and are controlled by the epigenetic machinery, suggesting they could be influenced by environmental or nutritional factors (ref. 2). This discovery also provides clues about the conservation of the form of imprinting.

We also provided the first genome-wide assessment of DNA methylation and gene expression in eggs from aged female mice. As oocytes from older females had less active and less consistency in gene expression. Methylation in general correlated well between eggs from younger and older age groups, whereas transcription that age does not affect key sites of DNA methylation in the genome, but there were gene-specific changes coupled to gene transcription differences.

Oocytes (egg cells) from reproductive-age female mice have more variable gene expression than those from younger females. This is depicted as a 2D distribution of the distances between single oocytes based on inter-centre gene expression. From Carvalho et al., J. Med. Genet. (2020).

Selecte d Impact Actions

- Group representation for the Race Against the Ageing Clock’ exhibit at the Cambridge Science Festival, March 2019.
- Flyway speaker at the 16th International Conference on Pre-implantation Genetic Diagnosis Geneva, April 2019.
- Speaker at Royal Society of Medicine continuing professional development workshop on ‘Epigenetics June 2019.

Selected Publications

- Bircan, E. et al. (2020) Increased transcriptome variation and localised DNA methylation changes in oocytes from aged mice revealed by parallel single-cell analysis. eLife 9, e55516
- Laya, J. et al. (2019) Worm-align and Worm_CP, two open-source pipelines for straightening and quantification of fluorescence image data obtained from Caenorhabditis elegans. J. Vis. Exp. 159, 10.3791/61132
- Bircan, E. et al. (2020) Increased transcriptome variation and localised DNA methylation changes in oocytes from aged mice revealed by parallel single-cell analysis. eLife 9, e55516
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Using systems biology tools in C. elegans to extend life

It is estimated that more than 20% of the global population will be over 60 by 2050, the highest percentage of older persons in recorded history. (World Health Organization fact sheet on Ageing and Health, 2018). Over the last two decades studies have drawn a remarkable link between metabolism, stress and longevity and this line needs exploration in the face of current societal challenges. We use the nematode C. elegans to study this important question.

Current Aims

The specific problem that we look at in the lab is the interplay between stress and the oocyte during early ageing. To tackle this question, we have optimised new cutting-edge computational tools that bring new perspectives and insights into the problem. We have also used more traditional approaches to examine a more longevity pathway. This is a neuronal thermostat that senses and helps animals adapt to warming temperatures by modulating fat desaturation across tissues.

Progress in 2019 and 2020

My group used two very different and complementary approaches to explore key concepts that characterize longevity pathways. In one approach, we used classic genetics and lipids to discover that neurons can sense an environmental signal to help the body cope with a warming environment. We find that the neuronal thermostat regulates the membrane lipid composition and in doing so, extends lifespan. A similar neuro-hormonal axis may be key to healthy ageing in humans.

In a second approach, we took a highly systems-level view of the genetic interactions pathway and applied computational tools to understand how these long-lived forms of organisms are built within a network of gene interactions. This ‘bird’s eye view’ of a longevity pathway has a high predictive value for identifying the key genes that contribute to long life.

Selected Impact Activities

- The lab showcased the power of genetics using C. elegans as a model organism at the Cambridge Science Festival; part of the ‘Race Against the Ageing Clock’ exhibit.
- The lab hosted students as part of the Institution’s School’s Day events in 2019 and 2020.
- We also presented our work at the 17th Animal Science Meeting (2019), co-organised by the Royal Society of Biology and the Animals in Science Regulation Unit.

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Signalling to stem cell chromatin

Changes in the cellular environment, such as stresses and developmental cues, affect the epigenetic and transcriptional state of cells, thereby influencing cell identity. We aim to understand how environmental signals are translated into epigenetic changes through studying the biochemical regulation of epigenetic factors. We focus on one particular type of biochemical mechanism, the conversion of arginine residues to non-coded citrullines, or protein citrullination.

Current Aims

The citrullinating enzyme PADI4 modulates transcription and chromatin compaction and has well-established roles in innate immunity and the evolution and protein biochemistry, we demonstrated that animal PADI enzymes were introduced into animals through horizontal gene transfer from prokaryotes. This work has implications for how we think about the organizational roles of PADs, why they were retained and multiplied during animal evolution and how aberrant citrullination may promote the development of autoimmune diseases.

Progress in 2020

Our work towards understanding PADI4 activation led us to the unexpected discovery that the PADI enzymes, which were widely thought to be vertebrate-specific, are also present in some bacteria and fungi and have a highly unusual phylogenetic distribution. Through studies of phylology, protein structure, sequence evolution and protein biochemistry, we have discovered that PADI enzymes are retained and multiplied in invertebrates, plants, fungi and some bacteria. This work has implications for how we think about the evolutionary origins of the PADI enzymes and how they may have evolved to perform similar functions in different lineages.

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

1. To determine how conflicts between replication and transcription cause mutations in patients specific to the current environment, leading to both chromosomal changes and formation of extrachromosomal circular DNA.
2. To elucidate the contribution of DNA replication errors to the acquisition of novel mutations in cancer cells that underlie acquisition of drug resistance.
3. To understand how epigenetic marks contribute to gene expression changes during ageing, and the extent to which these age-linked changes are controlled by signalling of nutrient availability.

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3. To understand how epigenetic marks contribute to gene expression changes during ageing, and the extent to which these age-linked changes are controlled by signalling of nutrient availability.

Progress in 2019 and 2020

We have continued our work on extrachromosomal circular DNA – unstable DNA species that often host oncogenes and drug resistance genes in cancer cells. Circular DNA is implicated in cellular ageing, and we are investigating the accumulation of circular DNA during ageing and the impact of circular DNA on ageing phenotypes. This work is revealing how circular DNA can accelerate adaptation to challenging environments, promote drug resistance and mediate progressive changes in cell physiology. In 2020 we saw major advances in our work on mechanisms of adaptive genome change, as we learned more about how DNA replication defects caused by environmental change can form new adaptive mutations. The resulting publications will emerge next year, but some of the underlying methods, for example to improve genome-wide analysis of small, defined cell populations, have been released.

How cells interact with their environment

Selected Impact Activities

- We contributed a research spotlight article on epigenetics in ageing for The Physiological Society policy document ‘Genome older, better’.
- We have a new collaboration in place with AstraZeneca to recruit a PhD student who will study the acquisition of drug resistance during chemotherapy.
- Our work was featured in an article on extrachromosomal Circular DNA in Chemical and Engineering News: ‘The curious DNA circles that make treating cancer so hard’.

Publications

www.babraham.ac.uk/our-research/epigenetics/maria-christophorou

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

Single-cell multi-omics landscape of development and ageing

We are interested in epigenetic gene regulation in mammalian development and ageing. Epigenetic marks (such as DNA or histone modifications) act in concert with cell signalling and transcription factors to regulate cell fate. 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 decision at the level of individual cells.

Current Aims

A primary aim of the group is to examine the epigenetic genome activation, the sudden springing to life of transcription regulation of zygotic genome activation, and how their alteration can be helpful during human development and during human development and during stem cell ageing. Towards this goal, we have completed a genome-wide genetic screen that has newly identified many genes and pathways that are involved in establishing pluripotency in human cells. We identified that the factors have important roles in controlling gene activity and epigenetic modifications to DNA. Investigating these factors will help define the molecular mechanisms that control early development and will provide new insights into stem cell properties such as cell identity, differentiation and reprogramming.

Selected Impact Activities

- We identify new cell lineage regulators using CRISPR activation with a single-cell transcriptional read-out. We identified putative ZGA regulators. We have developed a protocol by which human embryonic stem cells are able to be reprogrammed to express a single transcription factor. This allows us to study the epigenetic and transcriptional regulation of zygotic genome activation.

- In mouse embryos in vitro, we also found that the two DNA binding proteins Dppa2 and Dppa4 are important for priming of pluripotent developmental genes. Brachyury gene activity is marked by both active and repressive histone modifications which keeps them poised for future activation. Dppa2 and Dppa4 were found to be important for targeting bivalency to enhancers or promoters for gene activation and activity. Dppa2 and Dppa4 are important for priming of transcription factors that are released from reprogramming to active and repressive histone modifications. We examined how these mechanisms are established in development, how they control cell state changes more generally, and how their alteration can be helpful during human development and during stem cell ageing. We are particularly interested in the epigenetic rules that govern cell fate decisions in early development, and how cell fate degrades during ageing.

- We have carried out a screen for regulators of genomic activation in the mouse. The screen was undertaken in embryonic stem cells by CRISPR activation with a single-cell transcriptional read-out. We identified several proteins such as Dppa2, Smarcl, and PAR1 as putative ZGA regulators. We are now testing the roles of these proteins.

- We c-authored a strategy report by the Regenerative Biology and Stem Cell Working Group commissioned by the BBSRC.

- We collaborated with Lonza and Plan to leverage our understanding of gene regulatory control to improve manufacturing processes.

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3D genome organisation and effect on genome function

The three-dimensional organisation of our genome is tightly linked to its function. Gene regulatory elements such as enhancers control spatiotemporal gene expression programmes in development by engaging in contacts with their target genes, sometimes over large genomic distances. Our research investigates how the three-dimensional organisation of the genome enables specific enhancers to control gene expression during stem cell renewal and differentiation.

Current Aims

Human induced pluripotent stem cells (iPSCs) hold great potential for cell-based applications in regenerative medicine and disease modelling. However, individual iPSC cell lines differ markedly in their ability to differentiate into specific cell types for applications in biomedicine. Non-coding genetic variants are emerging as key contributors to this functional heterogeneity between iPSCs, but their role is poorly understood. We combine functional genomics approaches with human genetics to understand how regulatory variants in the non-coding genome affect cell fate decisions during stem cell differentiation.

Progress in 2019 and 2020

We have mapped the gene regulatory landscape across a panel of iPSC lines large-scale chromatin accessibility, 3D genome organisation and long-range enhancer-promoter contacts to enhance genome-wide. This lays the foundation for our ongoing functional dissection of the gene regulatory networks in human pluripotent stem cells, using a combination of massively parallel reporter gene assays and CRISPR/Cas9 genome editing. Our aim is to identify non-coding genetic variants that contribute to functional heterogeneity between human pluripotent stem cell lines, and to understand how they exert their function in the context of the three-dimensional organisation of the pluripotent genome.

Selected Impact Activities

- Incorporation of a start-up company ‘Enhanc3D Genomics’ (as co-founder) commercialising business
- Talk at Masters’ student course ‘Genome Medicine: Epigenetics and Epigenomics’
- Participation in the Institute’s Schools’ Day 2020.

Our research explores how epigenetic memory is stably stored and propagated through the cell cycle. We take a theoretical approach using mathematical modelling in combination with experiments from collaborators, in an iterative cycle. This interdisciplinary approach helps to clarify underlying mechanisms in systems which are otherwise too complex to dissect with experiments alone.

Current Aims

My lab at the John Innes Centre is currently investigating epigenetics in the context of the stable gene silencing provided by the Polycomb system, vital to developmental transitions and environmental response. In particular, we are trying to understand how memory of the Polycomb-silenced state is propagated despite the perturbation of DNA replication. We are also investigating the dynamics of DNA methylation and how it is stably propagated. The group also has a long-standing interest in spatiotemporal protein dynamics and patterning processes, which we are currently studying through the phenomenon of crossover interference in meiotic crossover positioning.

Progress in 2019 and 2020

We uncovered a new state of Polycomb silencing [ref. 1] present after the apparatus that initiates the silenced state has disassembled, and chromatin stability is modulated through Single Nucleosome Polymorphisms (SNPs). The system we studied is epigenetically silenced by prolonged cold: we therefore investigated how the cold is preserved, which led us to a novel mechanism [ref. 2] where cold slows growth thereby allows the concentration of a stable protein to rise. Finally, we investigated the consequences of rapid cell cycles in the early Drosophila embryo [ref. 1], finding that rapid cycling may play a crucial role in keeping chromatin naïve. Collaborations with group leaders at the Babraham Institute are also now being developed, focusing particularly around the concept of bivalency (with the Flok lab).

Predictive genome editing

Profiting from precise genome editing approaches, the Polycomb system can be modified precisely to obtain desired experimental conditions.

Modelled Polycomb silencing dynamics. Tyrosine phosphorylation of Brm (a chromatin-remodelling ATPase) allows the concentration of a stable protein to rise. (left) Simulation of silenced state (high H3K27me3) periodically perturbed by DNA replication (middle) and of silenced state switching to an active state (right).
How yeast is reshaping ideas on ageing

Dr Jon Houseley is a heretic. Along with others in the field of ageing research, he is questioning long-established orthodoxies of ageing. For decades, ageing has been seen as inevitable, a paradigm that has so far failed to help us answer the basic questions about the nature of ageing.

If you rewind to the 1920s, however, alternative theories of ageing existed. Rather than simply a slow, inexorable process akin to a once pristine car rusting and breaking down, some argued that ageing is not, in fact, one single thing.

“Aging is really difficult to get your hands on, which is why we’ve started to revisit these old debates. But rather than argue about it intellectually, we have rolled up our sleeves and done experiments with yeast,” Houseley explains. “Using yeast, we are asking whether there are situations in which being old is an advantage – and it turns out that there are.”

One of Houseley’s central aims is understanding how organisms adapt to challenging – and changing – environments. “It sounds like a weird fit with our focus on ageing,” he admits. “But a major angle we have on ageing is that it could be a process that exists in basic eukaryotes like yeast to help them cope with stress.”

His studies provide persuasive evidence to support this idea. One focused on CUP1, a gene in yeast that allows cells to survive in high-copper environments. Some yeast cells make extra copies of the CUP1 gene, allowing them to survive and outcompete cells with fewer copies of the gene.

Surprisingly, the study revealed that extra copies of CUP1 result from an active process rather than random mutations. “We think of genomes as long-term, stable repositories of information but they change – and not only over evolutionary timescales,” says Houseley. “We know genome changes are hallmarks of cancer, but we’re discovering them in healthy cells too. Some parts of the genome are very prone to change, suggesting that organisms have more control over their genomes than once thought.”

But this raises a problem: cancer and ageing, alongside organisms care about the genomes they pass on to future generations and are careful to minimise mutation rates in their genes. This is where ageing can be useful, because genome changes can be restricted to old cells that only reproduce rarely, and to the strange non-chromosomal DNA elements that accumulate in old cells.

The Houseley lab examined how yeast forms circular non-chromosomal DNA elements in response to copper and how this differs between young and old yeast cells. The results revealed that older yeast cells had circular DNA containing extra copies of genes like CUP1. “It’s like a selfish insurance policy,” he says. “But while these extra genes might provide an evolutionary advantage, they might also come at the cost of ageing because these extra bits of DNA could hamper normal essential cell pathways.”

Understanding more about DNA circles, and how cells can change particular parts of their genomes in response to particular environments has important implications for both cancer and ageing. Cancers use DNA circles to carry cancer-causing oncogenes and to adapt in the face of chemotherapy, enabling them to develop resistance to anti-cancer drugs.

Houseley is at pains to stress that evidence for ageing being adaptive in yeast does not mean it’s also adaptive in higher eukaryotes. It does, however, explain how it evolved and may explain why ageing still occurs in higher organisms despite bringing no benefit.

As well as setting us on a new path to better understanding ageing, his research is also relevant to efforts to stop cancers from becoming drug resistant and could pave the way to healthier ageing. “Ageing is the biggest risk factor in a vast number of human disorders, but to come up with ways of dealing with ageing, we first need to understand it,” he concludes. “At the moment, we don’t understand how ageing works in any organism, so knowing how it works in one – even yeast – would be a major advance.”
Promoter Capture Hi-C: from academic tool to £1.5M startup

Fundamental research is vital for science and society. Many medical and technological revolutions are rooted in basic research, yet those roots can be hard to trace. Today, spinouts are key to turning academic bioscience into healthcare treatments. Dr Stefan Schoenfelder, a group leader in the Institute’s Epigenetics programme and co-founder of Enhanc3D Genomics, discusses taking a tool developed for fundamental research and building a business around it.

Setting up a new biotech spinout is a demanding business full of funding rounds, legal procedures and recruitment decisions. Doing so at the start of a global pandemic, however, adds a new set of challenges. Founded in January 2020, Enhanc3D Genomics secured its first round of funding the following month and by March 2021 had closed a second round of funding worth £1.5 million.

Being involved in a biotech spinout is somewhat surprising for Schoenfelder, who has worked at the Institute for 15 years, because it was never part of his career plan. “If you’d asked me five years ago, I’d have said that I wanted to focus solely on academic research,” he explains. “I’ve always hoped my research would help patients, but never saw myself as part of the commercial world. Now, I believe that I can play a more active role in making that transition from basic science to clinical application.”

The first fully sequenced human genome was published in 2003, with hope that this ‘operator’s manual’ for the human body would revolutionise our ability to treat, prevent and cure disease. During the past two decades, however, research has revealed that our DNA contains intricacy and complexity unimagined in 2003. Together with our genes, the non-coding sequences of DNA between the genes – once dismissed as ‘junk DNA’ – are just as important. And our DNA contains intricacy and complexity unimagined in 2003.

“Crucially, studies deciphering the 3D folding of the genome at high resolution also reveal how small mistakes in regulatory elements interfere with normal control of gene expression. According to Schoenfelder: “These regulatory elements function like molecular switches to control which genes are active, and thus produce proteins, in which cells. This process of gene expression control is vital to allow cells – which all contain the same genes – to specialise to carry out different tasks, and to help them respond to changes.” Identifying which regulatory elements act on which genes has been an epic challenge in genome biology, but thanks to an ingenious modification to the Hi-C technique called Promoter Capture Hi-C, research by the Institute and his colleagues has revealed how small changes in non-coding DNA implicate genes in rheumatoid arthritis, type 1 diabetes and Crohn’s disease.

“The vast majority of genetic variants associated with disease are located in non-coding parts of our genome,” says Schoenfelder. “That means we want to understand how most diseases arise – and find new targets for therapy – we need to be looking in the non-coding genome.”

Having pioneered Promoter Capture Hi-C as a tool for doing fundamental research into gene regulation, Schoenfelder and his colleagues soon realised it could be invaluable in understanding diseases and finding new ways to treat them, and that the best way to translate their fundamental research into clinical applications was through a spinout.

“The company’s vision is ambitious. “Our vision is to create 3D genome maps of all the cell types in the human body. If we succeed, it will be a unique database that will allow us to establish causal links between disease-associated regions and disease genes in almost every disease. Then, we will partner with experts in different disease areas to find new therapeutic targets,” Schoenfelder says.

Reflecting on a momentous year, he is enthusiastic about the spinout process and Enhanc3D Genomics’ potential: “The prospect of creating legacy that uses fundamental research to create a business and help patients is hugely exciting.”

“Covid-19 has shown the world what small, agile biotech firms can achieve. The most amazing research stories have come out of companies like Moderna and BioNTech,” he concludes. “I hope more people now see there’s lots of interesting research going on in biotech. The Institute and the many companies on the Campus create the ideal environment to foster these interactions. We need to get out of our ivory towers a bit more!”

‘To understand how most diseases arise – and find new targets for therapy – we need to be looking in the non-coding genome’

LEARN MORE: Find out more about the 3D organisation of the genome and how regulatory elements control gene expression.

Epigenetics
Facilities

- Bioinformatics
- Biological Chemistry
- Biological Support Unit
- Flow Cytometry
- Gene Targeting
- Imaging
- Lipidomics
- Mass Spectrometry
- Sequencing
Bioinformatics

The Bioinformatics facility exists to support the Institute’s research groups in the analysis, processing and organisation of their research data. We do this in a number of ways including providing a large compute cluster and an associated suite of software tools. We train scientists in the latest computational techniques and tools and we provide a consultancy service where we can either advise researchers or perform analysis on their behalf.

Capabilities:

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

Progress in 2019 and 2020

We have continued to work on a wide range of projects covering all of the major research areas at the Institute. We have developed new capabilities in the analysis of single cell data and in data from the Institute’s nanopore sequencer. These techniques allow for a more complete analysis of gene activity in biological systems. We have developed our existing suite of software to support new epigenetics techniques such as Smartseq and SingleCell and have worked on integrating results from more complex experimental designs covering a variety of different experimental techniques. Our training courses expanded to encompass bioinformatics developments to both the Institute and external organisations.

Selected Impact Activities

- We undertook a major programme of training for AstroZerica to add to our existing programmes for other commercial and academic groups around the world. Our courses can all now be taught remotely using cloud based computational infrastructure.
- We created a series of short online talks ‘Bioinformatics’ to present new and interesting python, R package development, source code management and machine learning.

A comparison of a published single cell dataset with data from Peter Rugg-Gunn’s research group, showing that both datasets contain similar cell subtypes.

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 research groups we are investigating the chemical changes which occur in connecive tissues as we age.

Capabilities:

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

Progress in 2019 and 2020

During 2020 we have continued to support groups throughout the Institute on a wide range of varied projects. These have ranged from synthetic chemical projects to make compounds which are not commercially available through to developing new analytical methods to analyse both small molecule and large molecules. In addition to these activities we have also continued to run matrix lipid analysis for a number of groups, both within the Institute and externally.

2020 saw the publication of key results from our research describing how the collagen changes dynamically during tendon stretching and the implications for this when considering changes in tendon with age.

Selected Impact Activities

- Through 2020 we have provided phospholipid insoluble analysis on samples for commercial and external academic groups.
- We collaborate with external academic groups studying the ageing of connective tissue.

Publications

@babraham_bioinf

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

**Facilities**

Facility members:
- 4 Facility managers
- 6 Supervisors
- 28 Experienced Animal Technicians
- 2 Trainee/Apprentice Animal Technicians
- 4 Support Services Technicians
- 1 Technical Services Technician
- 1 Veterinary Services Manager

**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 highly qualified animal technicians provide expert technical support to researchers by following regulated procedures, maintaining the health and welfare of animals used in research, 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 highly trained animal technicians and service technicians perform daily animal husbandry duties and provide essential services to the facility.
- Our animal technicians hold NVQ Level 2 qualifications. All technicians are current in their care in animal care within the commercial sector. Two further apprentice candidates are undertaking their training within the facility. The facility continues to provide advice to industry on best practice with regards to foundation training, evidence gathering and record keeping.

**Progress in 2019 and 2020**

- The BSU has formed a successful partnership with Anditex Science and become a recognised ‘Centre of Research Excellence’. This partnership allows the BSU access to the latest technologies and R&D discussions.
- The facility is currently training a new veterinary nursing trainee prior to global launch.
- Working in collaboration with Agenda UK, the first three apprentice animal technicians completed the programme and passed their Institute of Animal Technology (IAT) Level 2 qualifications. All three are now continuing their careers in animal care within the commercial sector. Two further apprentice candidates are undertaking their training within the facility.
- Having contributed to the latest IAT syllabus review in 2021, the IAT have now advertised the release of the updated syllabus with BBSRC support.

**Selected Impact Activities**

- The Flow cytometry service has been designated as a centre of excellence (COE) by the European Organisation for the Study of Cytometry (EOSC).
- The BSU is a centre of excellence (COE) in Flow Cytometry by the European Organisation for the Study of Cytometry (EOSC).
- The facility provides an expert cell sorting service for Institute and external users. A range of sorters in biosafety cabinets allows for a wide range of cell types and experimental designs to be accommodated.

**Flow Cytometry**

Flow cytometry is a single cell technology that allows cells to be identified, counted, analysed, and sorted on the basis of specific features including the expression of proteins labelled with fluorescent antibodies. The Flow Cytometry facility provides a number of services to support the work of scientists from both the Institute and external companies. These include an expert cell sorting service, analyser training, help with experimental design, troubleshooting, and data analysis.

**Capabilities**
- Flow cytometry service: The facility provides an expert cell sorting service for Institute and external users. A range of sorters in biosafety cabinets allow for a wide range of cell types and experimental designs.
- Analyser training: The BSU has a CellPad, a new cellulose producer of high quality feed and good health. The BSU is a supplier of animal welfare and animal health barrier and undertaking robotic cage-washing technology and automated sterilisation processes to easily sterilise and store. The BSU has a new computerised microscope system which will be rolled out in full.
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**Publications**


**Flow Cytometry**

**Selected Impact Activities**

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- The state-of-the-art analysers: BD LSRFortessa, Propel Lab VEST, and the Cytex Aurora spectral analyser allow high parameter analyser.
- Image cytometry: The Xenova Milipore ImageStream MX allows quantitative flow cytometry data to be produced with images of each cell.
- Training: The facility delivers modular training courses alongside practical training to enable scientists to use the analysers independently.

**Progress in 2019 and 2020**

- In 2019, the facility expanded with the acquisition of two BD LSR sorters. Three high-speed sorters have increased capacity and capability for cell sorts such as large CRISPR screens. A Cytex Aurora Spectral analyser was purchased through a BBSRC Aiken-18 grant in 2019, expanding the core’s multicolour capabilities. In August 2020, through a collaboration with Propel Labs, a new part of Thermo Fisher’s Bigfoot 80 parameter high-speed Spectral Sorter was installed in the facility. The interactive flow cytometry training programme is in its sixth year and has supported over 100 scientists. During 2020, the face-to-face training was adapted into an online virtual format.

**Selected Impact Activities**

- The Flow Cytometry facility hosted the 2019 FlowCytometryUK, a one-day meeting in November 2019, bringing together over 125 delegates from all over the UK.
- In September 2019, Attilla Bebes visited several flow cytometry core facilities in Belgium and the Netherlands, including two in EU- LIFES institutes, to share best practice.
- Rachael Walker organised and co-hosted three virtual flowCytometryUK facility meetings in May, June and July 2020 to establish safe working practices in the COVID-19 era. Each meeting was attended by over 150 delegates from over a dozen countries.

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**Publications**


**Flow Cytometry**

**Selected Impact Activities**

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**Publications**


**Flow Cytometry**

**Selected Impact Activities**

- The Flow Cytometry facility hosted the 2019 FlowCytometryUK, a one-day meeting in November 2019, bringing together over 125 delegates from all over the UK.
- In September 2019, Attilla Bebes visited several flow cytometry core facilities in Belgium and the Netherlands, including two in EU- LIFES institutes, to share best practice.
- Rachael Walker organised and co-hosted three virtual flowCytometryUK facility meetings in May, June and July 2020 to establish safe working practices in the COVID-19 era. Each meeting was attended by over 150 delegates from over a dozen countries.

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Gene Targeting Facility

The main purpose of the facility is to produce new mouse strains for use in the Institute’s research, editing in the design, genetic, genome, sequencing and evaluation of genetic modifications. The facility also provides expertise and guidance on the use of CRISPR/Cas9, including on the design and production of CRISPR-magnets such as sgRNA, Cas9 protein and long single-stranded DNA (ssSDNA).

Capabilities

- Generation of mouse models ranging from single nucleotide polymorphisms (SNPs), domain deletions, multiple gene knockouts and large knock-ins such as MiniTurbo.
- Guidance in CRISPR/Cas9-based technologies for producing transgenic cell lines and mice.
- High-throughput production of single-guide RNA with efficiency validated in embryos.
- Production of CRISPR/Cas9-magnets such as Cas9 protein and ssSDNA.
- Designing strategies for Gibson assembly and recombinase-mediated bacterial artificial chromosomes (BACs) for complex constructs.
- Analysis on magnets based on mechanisms of DNA repair, such as single-strand template repair, microhomology-mediated end-joining and homologous recombination.
- High-throughput screening of gene-edited cell lines using Next Generation Sequencing.

Progress in 2019 and 2020

Since re-establishing the facility in 2019, the facility has supported the Institute’s researchers in achieving desired genome modifications in cell lines and mice. The facility specializes in using Cas9-sgRNA ribonucleoprotein combined with electroporation to target various cell types, and we share our methodologies with users across the Institute to help optimize their gene editing experiments. Also, for generating mouse models, the facility has optimized electroporation and microinjection protocols for embryos. During 2020, the facility has made three new mouse lines and multiple loss-of-gene-function embryos. These new lines were made without using embryonic stem cells, meaning that mouse models can be delivered in a shorter time frame and overall using fewer mice in the process. We have also developed protocols to make in-house Cas9 protein and other Cas9 variants.

Selected Impact Activities

- Created the first mini-turbo gene-tagged mouse using promiscuous injection.
- Created a mouse with two SNPs on the same gene, where the SNPs are in different exons.
- Generated PCV-Cas9, which is a Cas9 variant that tetherers ssDNA to increase the efficiency of homology-directed repair.

Imaging Facility

The Imaging facility provides supported access to advanced light microscopy and electron microscopy resources. Our aim is to deliver a comprehensive solution to meet the imaging demands of our user base: whether it’s looking at dynamic processes in living cells, imaging cellular ultrastructure in 3D, or providing bespoke image analysis solutions, we aim to cover it all.

Capabilities

- High-resolution fluorescence imaging: We have advanced wide-field microscopes, point-scanning and spinning disk confocal systems and a super resolution imaging system, all of which can be used with both fixed and live samples.
- High content imaging: We have an InCell 6000 system which can image cells at high resolution in up to 1536-well format. We provide bespoke analysis solutions for high content imaging data.
- Focused ion beam-scanning electron microscope: Our dual beam Zeiss Crossbeam 550 can acquire nanometer resolution volumetric EM data and is also equipped with a STEM detector to provide TEM-like images.
- Image analysis: We provide access to advanced commercial image analysis software and can provide tailor-made image analysis solutions for demanding applications.

Progress in 2019 and 2020

The biggest challenge of 2019 was the full acquisition of this microscope. It facilitates correlative imaging workflows, ensuring that the facility’s light microscopy capabilities remain at the cutting edge.

Selected Impact Activities

- The facility continues to provide imaging solutions for a significant number of commercial organisations, and despite the challenges, researchers from five additional companies were trained during 2020.
- The facility showcased its resources at the Babraham Research Campus as part of the virtual 2020 Campus Science Week event.
- During extended periods of lockdown, our staff have continued to work productively from home, including helping external collaborators with their image analysis requirements.

Publications

Facilities

Lipidomics

The Lipidomics facility undertakes the detection and identification of lipid profiles, with the aim of providing a detailed understanding of lipid roles in cellular structure, signalling lipid-metabolic pathways, and the regulation in health and disease. Chromatographic methods developed in our lab allow the study of a wide range of lipid molecular species including neutral, phospho- and sphingolipids, and fatty acyl residues in tissues such as mouse and rat liver.

Capabilities

- The facility operates liquid chromatography hyphenated to high resolution / high accuracy mass spectrometry for untargeted Lipidomics (Orbitrap technology).
- Lipidomics is performed by liquid chromatography hyphenated to triple quadrupole mass spectrometers (SXC6000).
- Shigetaki throughput analysis is performed via an Agilent Nanofluidic coupled to a high-resolution/high mass accuracy mass spectrometer.
- Automated semi-quantitative of the lipid levels compared to control samples prior to normalisation of the data to the weight/DNA or protein content.
- Hydrophobic extraction of the lipids present in cell lines and tissues from mouse, worm and human samples.
- Bioinformatics pathway analysis of lipids and other biomolecules, especially proteins. We use (bio)chemical methods in combination with mass spectrometry to identify, quantify and obtain structural information on proteins.
- Mass Spectrometry

The facility’s expertise is in analytical biochemistry, and uses biochemical methods in combination with mass spectrometry to study a range of biotechnologies, especially proteins. We use methods to identify, quantify and obtain structural information on proteins that are involved in important biological processes, in order to help us understand how they function.

Capabilities

- The facility has three high-resolution tandem-mass spectrometers (Orbitrap Eclipse, Q-Exactive Plus and Q-Exactive), each interfaced to nanoLC systems.
- We can undertake a full range of high-sensitivity mass spectrometric protein analysis including:
  - quantitative proteomics analysis (label-free, SILAC, isobaric tagging);
  - identification/quantitation of proteins in purified complexes;
  - identification, localisation and quantitation of post-translational modifications;
  - targeted structural characterization of individual proteins;
  - targeted protein quantitation.

Selected Impact Activities

- Proteomics mass spectrometry provided to external companies and academics.
- Facility staff joined the Covid-19 Mass Spectrometry Coalition (https://covid19-msc.org), which is an international group whose aim is to use mass spectrometry skills/best practice to increase knowledge of the Covid-19 virus mechanisms and to drive therapeutic/vaccine development.
- Showcased the Mass Spectrometry facility at various campus events such as Campus Science Day and Babraham Campus Science Week (virtual event, 2020).

Publications

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

- Marshall, J. D. et al. (2020) THF-1, a macrophage cholesterol efflux is impaired by palmitolein through Akt activation PLoS ONE 15(5): e023318
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 Sequencing facility provides researchers with access to cutting-edge sequencing technology to advance their research.

Capabilities
- Sequencing service using a range of sequencing instruments (NextSeq500, HiSeq2500 and MiSeq) that enables researchers to select the sequencing depth and read length needed for their project.
- Quality control services for RNA to improve success in library preparation and for DNA libraries to ensure optimal sequencing quality and yield.
- Library preparation services using the automated liquid handling technology of the Hamilton NGS Star. Currently automated protocols include the SmartSeq v2 and NEB Next Ultra II RNA-seq library preparation protocols.

Single cell library preparation using the 10x Genomics Chromium Controller:
- Progress in 2019 and 2020: the Sequencing facility continued to improve automated RNA-seq library preparation services to make the 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-library solution with enhanced reproducibility and throughput.
- Introduction of the 10x Genomics Chromium Controller single cell partitioning and barcoding system allowed 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
- Facility participated in a public engagement event presenting to Chesterton Community College students, June 2019.
- The facility showcased its resources as part of the virtual 2020 Babraham Research Campus Science Week event.

Publications


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.
The Knowledge Exchange and Commercialisation (KEC) team works to maximise the impact of Institute science, by ensuring that our knowledge and skills are accessible to a wide range of professionals beyond the scientists in our own field, and to ensure that our research makes an impact on society outside of academia.

Knowledge exchange harnesses the formidable know-how and cutting-edge technical skills of Institute staff to aid professionals in academia, industry, the wider scientific community and beyond. We arrange training courses, fund scientific exchanges and provide opportunities for Institute staff to interact with professionals in other sectors. This encompasses the provision of expert advice to policy makers, as well as collaborations and consultancies for biotech and pharmaceutical companies to address specific problems and foster new ideas.

Commercialisation provides a revenue source for the Institute, but more importantly it is a pathway that translates our science into products useful in sectors such as healthcare. Examples from the last two years include Enhanc3D Genomics Ltd, a new company spun-out from Institute research aimed at discovering the function of disease-associated genetic polymorphisms, and the award of European Research Council (ERC) Proof of Concept funding in 2020 to Professor Adrian Liston’s team for developing a pioneering anti-inflammatory platform technology to treat CNS injuries and disorders.

Individual scientists and labs do not have the knowledge, skills or resources to span discovery science, product development, clinical trials and all the other steps necessary for capitalising on an exciting bioscience discovery, so partnering with industry, clinicians, learned societies and charitable organisations helps deliver real-world applications from our science. The Institute actively promotes collaborations between Institute scientists and pharma companies, particularly with those on the Babraham Research Campus, to develop ideas and undertake early-stage translational research, while also licensing discoveries and forming spin-out companies when clear pathways to market are available.

Our on-going commitment to furthering academic-industry connections on the campus promotes the commercialisation of life science research and the life science knowledge base, fosters collaboration, and enables the formation of entrepreneur-driven businesses. More widely, by facilitating the exchange of our knowledge and skills, and the translation of our science, KEC helps to deliver wider economic and societal benefits arising from our science and our scientific community.
Impact

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.

2019 and 2020 Highlights
Throughout 2019 and 2020 public engagement remained a key part of Institute work with 105 staff and students taking part in 2019, and a further 83 in 2020, to facilitate 47 events across the two years. The work of these teams, from all parts of the Institute, allowed discussions around our research to be had with over 9,000 people who joined from Cambridge, the wider UK and beyond.

2019 was a year for reaching out. We started the year off by hosting our 25th annual Schools’ Day – an event where staff and students guide secondary and sixth-form students through hands-on lab projects. Over the years this celebration of curiosity and discovery has reached nearly 3,000 students from across the UK offering them the chance to experience the work of our research programmes and facilities first-hand. We also launched our fantastic cell signalling-themed escape room experience and showcased it at a number of events including the Latitude music festival. In September, working with a number of organisations across Cambridge, we returned with ‘LifeLab’. Supported by the European Commission, this project was an international celebration of science in public and saw our research showcased across the region. We ran pop-up events simultaneously in Cambridge, Peterborough, and Ely, bringing science where people were not expecting to see it and allowing more people than ever to engage with our research. Public dialogue events were also held as part of the ORION Open Science project to better understand how citizens from across Europe view genome editing. Work from this and the wider project has gone on to produce a framework for better incorporating open science practices into our engagement work as well as that of the wider Institute.

2020 brought many challenges and our programme adapted accordingly. Members of our Epigenetics research programme developed a new, online escape room experience and we also launched our Science Spotlight series of online talks. Both these initiatives allowed audiences to participate remotely and even allowed people, who are often located too far from our in-person events, to engage with the Institute’s science.

2021 Forward Look
We will be continuing our work to reach out to audiences who have been traditionally excluded from engagement programmes with new partnerships forming in many of the rural areas of Cambridgeshire and East Anglia. We’re looking forward to reintroducing in-person events into our programme as this becomes more possible. Our aim is to offer opportunities for rich discussion around the Institute’s work whilst also maintaining many of our online events which have proven to make our science accessible to many more people.

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

In 2019 and 2020:
47 engagement events involving 188 Institute members reaching over 9,000 people

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

Public Engagement