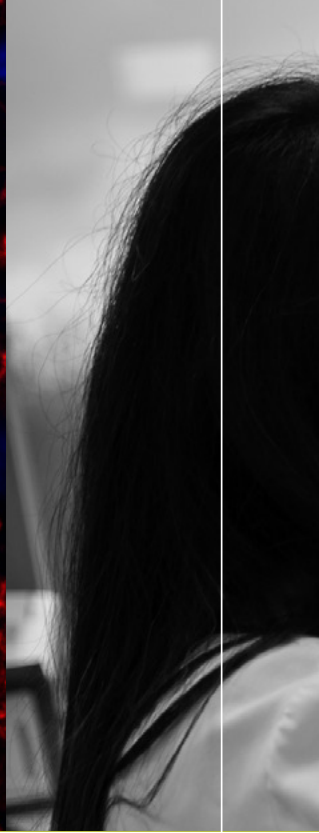
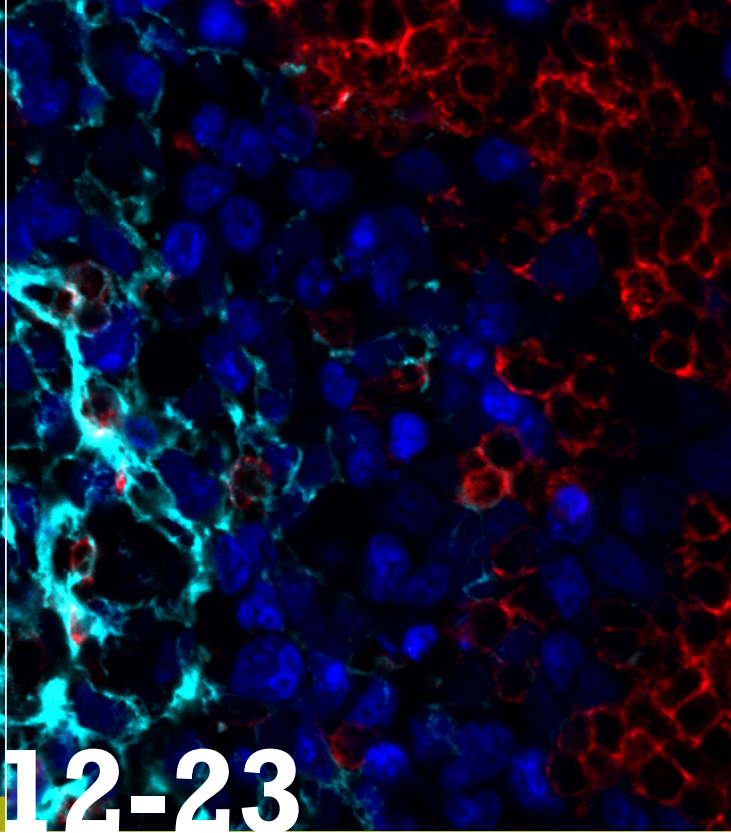
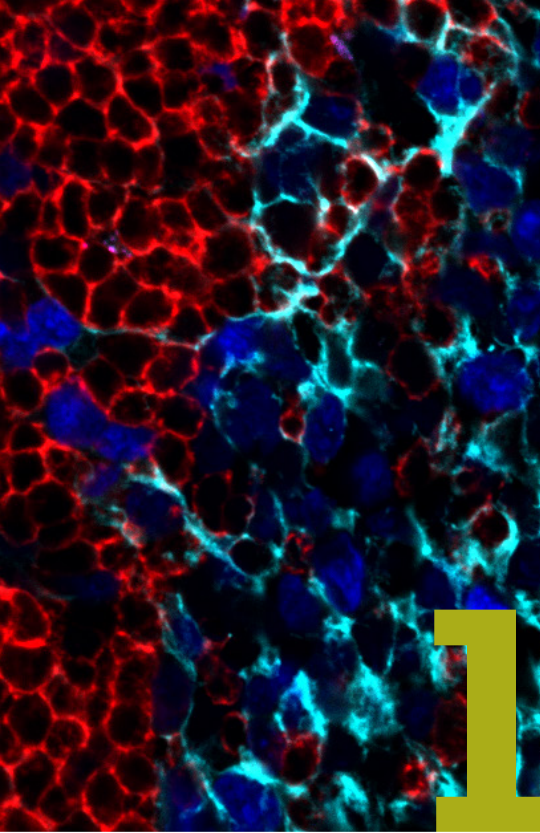


2019/20

Babraham Institute  
Annual Research Report  
Immunology



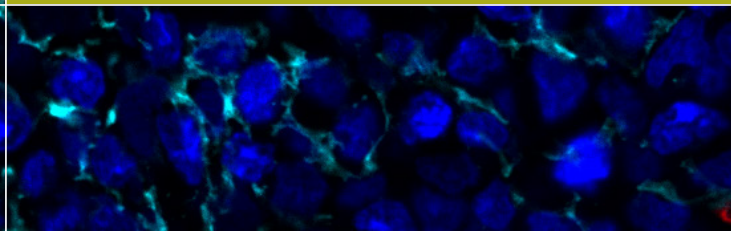
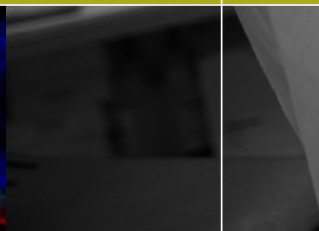
# 12-23



## Immunology

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

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

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





Group Leaders



Martin  
Turner



Anne  
Corcoran



Michelle  
Linterman



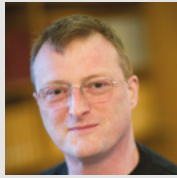
Adrian  
Liston



Claudia Ribeiro  
de Almeida



Sarah  
Ross



**Martin Turner**  
Programme leader

#### Group members

##### Senior research associates:

Sarah Bell  
Elisa Monzón-Casanova

##### Postdoctoral researchers:

Jia Lu  
Georg Petkau  
Beatriz Sáenz-Narciso  
Fiamma Salerno  
Alexander Saveliev  
Michael Screen

##### PhD students:

Vanessa D'Angeli  
Oezge Gizlenci  
Fengyuan Hu (Left in 2019)  
Twm Mitchell

##### Visiting scientist:

David Turner

##### Visiting students:

Miriam Berry  
(Left in 2019)  
Francesca Ippolito  
(Left in 2019)

## Characterisation of lymphocyte transcriptomes using long-read sequencing

**We study the differentiation of lymphocytes, immune cells that are critical for immune memory (and hence vaccine success) and also tissue homeostasis by limiting inflammation and promoting tissue repair. These cells utilise rapid and dynamic changes in gene expression to mediate their function and our work focuses on understanding the fundamental mechanisms controlling these changes.**

#### Current Aims

Most genes produce multiple molecularly distinct messenger RNAs that vary the amount or amino acid sequence of proteins. This is regulated by choosing alternative transcript start- and end-points and splicing of introns. Our recent work has investigated RNA binding proteins that regulate these choices. We are identifying the sequence of full-length mRNAs to discover how they vary between cell types, what controls this variation and how it contributes to cell function.

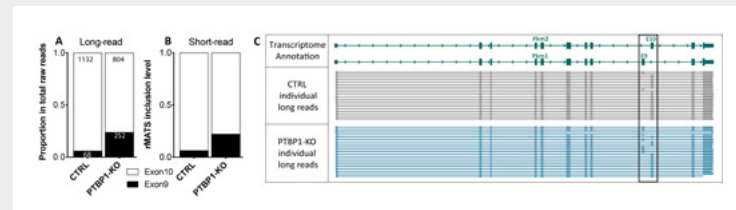
It is essential not only to measure gene expression quantitatively, but to understand how it is regulated qualitatively. We are using emerging technologies for long-read sequencing of full-length transcripts to identify alternative transcript isoforms and their variation in activated lymphocytes.

#### Progress in 2019 and 2020

By applying long-read sequencing to B lymphocytes, we detected transcripts from over 9,500 genes with at least five supporting reads, which compares very favourably with the numbers of genes detected using conventional methods on the same samples. We were able to quantitate the effect of the RNA binding protein polypyrimidine 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 allowed 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 insight into the dynamic regulation of gene expression.

#### Selected Impact Activities

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



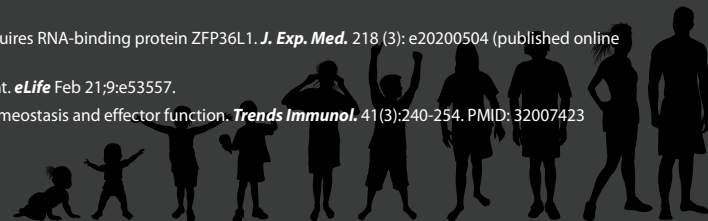
*PTBP1* suppresses inclusion of exon 9 and expression of *PKM1*. Quantitation of the usage of exons 9 and 10 in *Pkm* transcripts from *PTBP1*-sufficient (CTRL) and *PTBP1* knockout (*PTBP1*-KO) follicular B cells is shown.

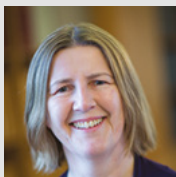
A) Individual long reads were counted for exon 9 and -10 containing isoforms; numbers are the absolute number of reads for each. B) Inclusion levels for *Pkm* exons 9 and 10 were quantified by rMATS analysis of Illumina short-read RNA-seq data where Percent of splice-in (PSI) values are scaled to 1. C) Top: annotated mouse *Pkm* transcript isoforms with exons 9 & 10 boxed in black; bottom: individual long reads for control *PTBP1*-sufficient (CTRL) and for *PTBP1* knockout (*PTBP1*-KO) cells.

## Publications

[www.babraham.ac.uk/our-research/immunology/martin-turner](http://www.babraham.ac.uk/our-research/immunology/martin-turner)

- Saveliev, A., Bell, S.E., Turner, M. (2021) Efficient homing of antibody-secreting cells to the bone marrow requires RNA-binding protein ZFP36L1. *J. Exp. Med.* 218 (3): e20200504 (published online December 2020). PMID: 33306108
- Monzón-Casanova, E. *et al.* (2020) Polypyrimidine tract binding proteins are essential for B cell development. *eLife* Feb 21;9:e53557.
- Salerno, F., Turner, M. & Wolkers, M.C. (2020) Dynamic post-transcriptional events governing CD8+ T cell homeostasis and effector function. *Trends Immunol.* 41(3):240-254. PMID: 32007423





**Anne Corcoran**

#### Group members

##### Sequencing Laboratory manager:

Paula Kokko-Gonzales  
Kristina Tabbada (Left in 2019)

##### Senior postdoctoral researcher:

Daniel Bolland (Left in 2019)

##### Postdoctoral researchers:

Sam Rees  
Maribel Lara Chica

##### PhD students:

Lina Dobnikar (Left in 2019)  
Elise French  
Carolyn Rogers  
Michiel Thiecke (Left in 2020)

##### Visiting scientist:

Lyobomira Chakalova  
(Left in 2020)  
Peter Chovanec (Left in 2020)

##### Visiting student:

Irina Ferapontova  
Joey Baxter (Left in 2020)

## How we make enough antibodies to fight infection

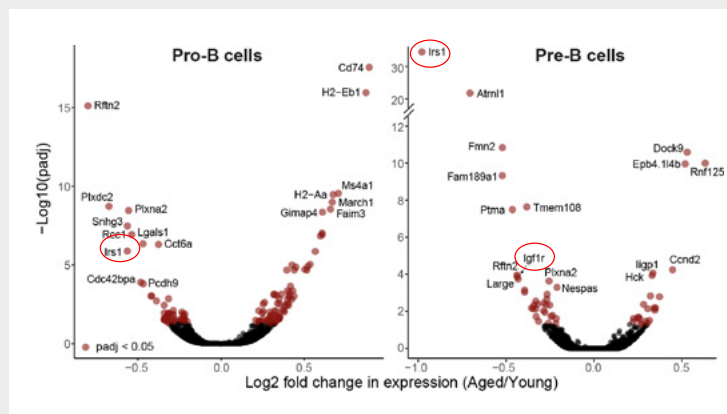
The immune system creates antibody proteins to help fight diseases. Antibodies are made by white blood cells called B lymphocytes. By mixing and matching genetic information, these cells can produce billions of different antibodies to combat different diseases. We are interested in the mechanisms involved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

#### Current Aims

We aim to understand how the genes that make up antibody proteins come together in so many different combinations, and how epigenetic mechanisms including transcription factor binding and histone modifications affect which genes are more frequently used. We're also looking at how the large-scale 3D folding of these large DNA regions in the nucleus affects antibody production, and at gene expression and regulation in B cells. This will increase our understanding of normal antibody production and help us to understand the events that cause leukaemias and impaired antibody production in ageing.

#### Progress in 2019 and 2020

Ageing bone marrow produces fewer B lymphocytes. With other Institute groups we compared gene expression genome-wide in B lymphocytes from young and old mice to reveal genes dysregulated in ageing. We discovered that ageing affects epigenetic mechanisms, including promoters that switch on genes, microRNAs that degrade their RNA, and interactions of promoters with activating



This 'volcano plot' depicts the changes in gene expression between young and aged pro-B cells that make the antibody heavy chain, and young and aged pre-B cells that make the antibody light chain protein. Red spots or 'sparks' to the left (below 0.0) are genes that are expressed less frequently in ageing, while those to the right are expressed more often in ageing. The genes with lower expression encircled in red are components of the Igf1r signalling pathway.

enhancer sequences. We found that the insulin-like growth factor receptor signalling pathway is impaired in ageing B cells. This important growth pathway is poorly understood and this work suggests an unappreciated role in B cell development and may help to restore B cell numbers in ageing.

#### Selected Impact Activities

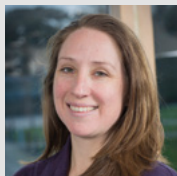
- Anne Corcoran gave a presentation to the Cambridge Scientific Society: How we make a billion antibodies: genetics and epigenetics, March 2019.
- Immunology video lecture for University of Makerere MSc students, Kampala Uganda, organised by Cambridge for Africa.
- The group hosted a Wellcome Trust Summer Bursary undergraduate student in 2019 and an online undergraduate project in 2020.

#### Publications

[www.babraham.ac.uk/our-research/immunology/anne-corcoran](http://www.babraham.ac.uk/our-research/immunology/anne-corcoran)

- Gonzalez-Garcia, S., *et al.* (2019) IL-7R is essential for leukemia-initiating cell activity of T-cell acute lymphoblastic leukemia. *Blood* 134 (24):2171-2182
- Ciccone, D.N., *et al.* (2019) The murine IgH locus contains a distinct DNA sequence motif for the chromatin regulatory factor CTCF. *J. Biol. Chem.* 294 (37):13580-13592
- Hill, D.L., Pierson, W., *et al.* (2019) The adjuvant GLA-SE promotes human Tfh cell expansion and emergence of public TCRβ clonotypes. *J. Exp. Med.* 216 (8):1857-1873





Michelle Linterman

**Group members****Senior postdoctoral researcher:**

Louise Webb

**Research fellows:**

Alice Denton (Left in 2020)

Danika Hill (Left in 2020)

**Postdoctoral researchers:**

Edward Carr

William Foster

Silvia Innocentin

Alyssa Silva Cayetano

Marisa Stebegg

(Left in 2020)

Ine Vanderleyden

(Left in 2019)

**PhD students:**

Xin Ge

Jia Le Lee

**Research assistants:**

Sigrid Fra-Bido

**Visiting scientists:**

Jelmer Vlasma (Left in 2020)

**Visiting students:**

Rachel Fellows

(Left in 2019)

Jaqueline Siu (Left in 2020)

## 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 antigenic 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.

**Current Aims**

Research in the Linterman laboratory aims to understand germinal centre function in the context of vaccination and infection. Our current research aims to address the following questions:

1. What causes poor germinal centre responses in ageing?
2. How do ectopic germinal centres form, and what is their function?
3. What are the biological mechanisms that support good germinal centre and vaccine responses?

**Progress in 2019 and 2020**

During 2019 and 2020 we made the following contributions to our scientific aims:

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.*, *Med.* 2020).
2. We discovered that influenza infection remodels the lung to support the CXCR5-dependent recruitment of B cells to this site, enabling the formation of ectopic germinal centres (Denton *et al.*, *J. Exp. Med.* 2019).

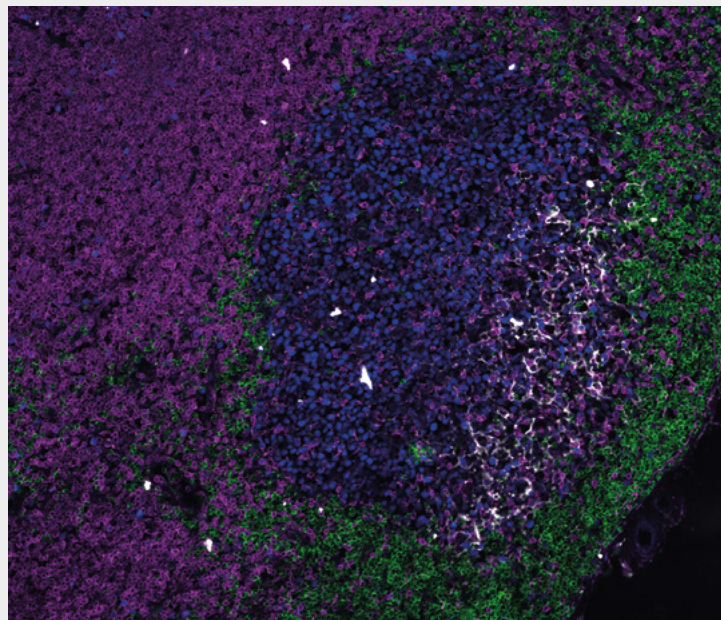


Image of a germinal centre in a lymph node 14 days after immunisation. Proliferating germinal centre B cells (Ki67, blue), Follicular dendritic cells (white), T cells (pink), B cell follicle (IgD, green).

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 (Hill, Pierson, *et al.*, *J. Exp. Med.* 2019).

**Selected Impact Activities**

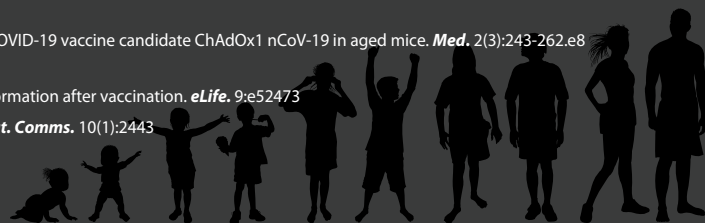
- Invited speaker, Keystone Symposia: B cell-T cell Interactions, USA.
- Hosted project for Babraham Institute 2019 Schools' Day in the laboratory.
- Organised EMBO Young Investigator Immunology meeting, Cambridge, UK.

## Publications

[www.babraham.ac.uk/our-research/immunology/michelle-linterman](http://www.babraham.ac.uk/our-research/immunology/michelle-linterman)

@LintermanLab

- Silva-Cayetano, A., Foster, W.S., Innocentin, S. *et al.* 2021 A booster dose enhances immunogenicity of the COVID-19 vaccine candidate ChAdOx1 nCoV-19 in aged mice. *Med.* 2(3):243-262.e8 [epub December 2020]
- Stebegg, M. & Bignon, A. *et al.* (2020) Rejuvenating conventional dendritic cells and T follicular helper cell formation after vaccination. *eLife.* 9:e52473
- Stebegg, M. *et al.* (2019) Heterochronic faecal transplantation boosts gut germinal centres in aged mice. *Nat. Comms.* 10(1):2443





**Adrian Liston**

#### Group members

**Senior staff scientist:**  
James Dooley

**Senior research scientists:**  
Oliver Burton  
Carlos Perez Roca  
(Left in 2020)

**Postdoctoral research scientists:**  
Pascal Bielefeld  
Orian Bricard  
Vaclav Gergelits  
Lubna Kouser  
Alena Moudra  
Samar Tareen  
Carly Whyte (Left in 2020)

**Research fellow:**  
Stephanie Lienart

**PhD students:**  
Magda Ali  
Julian Behr (Left in 2019)  
Amy Dashwood  
Ntombizodwa Makuyana

**Research assistants:**  
David Aaron Posner  
(Left in 2020)

**Honorary fellow:**  
Meryem Aloulou  
Kailash Singh

## T cells in our tissues

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

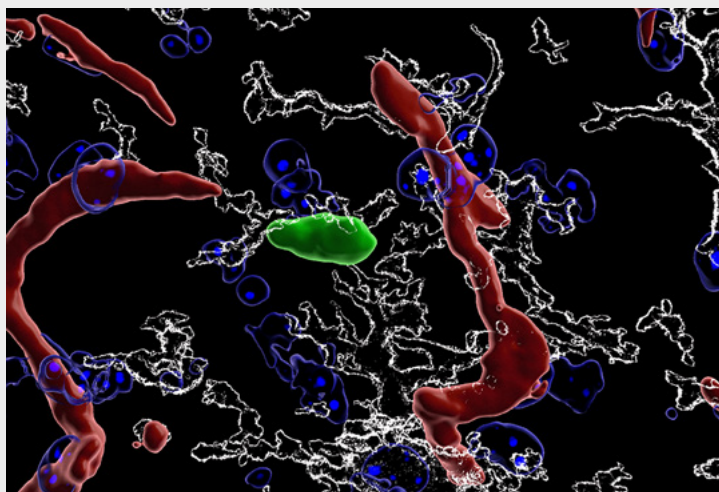
#### Current Aims

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 tissues. We are actively developing genetic tools that allows

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 tissues 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 mice and humans the cells undergo a transformation aiding their survival in the brain environment. We have found that this 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 Impact Activities

- Flow cytometry is one of the foundational tools for 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 100,000-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 a microglial cell (white) collaborate in the brain. Blood vessels are shown in red.*

#### Publications

[www.babraham.ac.uk/our-research/immunology/adrian-liston](http://www.babraham.ac.uk/our-research/immunology/adrian-liston)

@LabListon

- Pasciuto, E., Burton, O.T. & Roca, C.P. *et al.* (2020) Microglia require CD4 T cells to complete the fetal to adult transition. **Cell** 182(3):625-640
- Dooley, J. *et al.* (2020) Heterogeneous effects of calorie content and nutritional components underlie dietary influence on pancreatic cancer susceptibility. **Cell Rep.** 32(2):107880
- Neumann J, Prezzemolo T, Vanderbeke L, Roca CP, *et al.* (2020) Increased IL-10-producing regulatory T cells are characteristic of severe cases of COVID-19. **Clinical and Translational Immunology.** 9(11):e1204



**Claudia Ribeiro de Almeida**

#### Group members

**Postdoctoral research scientist:**  
Svetlana Sakhnevych

**PhD student:**  
Rachael Kimber

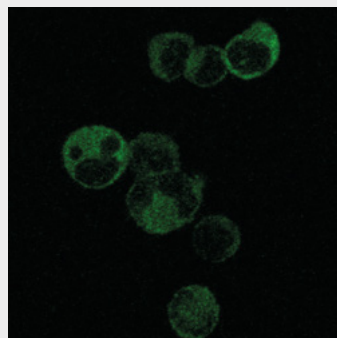
**Visiting scientists:**  
Isabel Leitch (Left in 2019)  
Gwendoline Muller (Left in 2020)

## Understanding how RNA helicase activity impacts on antibody gene rearrangements

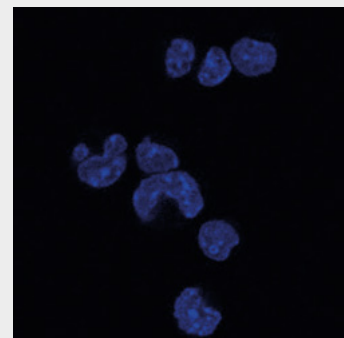
We are interested in understanding the molecular mechanisms underlying diversification of antibody genes, to gain insight into how B cells can effectively fight infections and the role this plays in age-related immune dysfunction. Emerging evidence suggests important roles for RNA and RNA-binding proteins (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-proteins complexes regulates antibody gene rearrangement.

#### 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 undergoing antibody gene rearrangements. These analyses will provide important insight that will help prioritise RNA helicases for subsequent studies. We are also investigating how the RNA helicase DDX1 acts to modulate RNA G-quadruplex structures, which are directly implicated in targeting the DNA mutator enzyme AID to the immunoglobulin heavy-chain locus, to initiate a DNA recombination mechanism that changes the antibody isotype B cells produce.



Confocal microscopy images of activated B cells showing cytoplasmic and nuclear staining for AID (green, left); nuclear area is defined using DAPI to stain DNA (blue, right).



#### Progress in 2019 and 2020

We have implemented state-of-the-art methodologies to capture the RNA-bound proteome, and are now identifying protein–RNA 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 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 Midlands RNA Salon webinar series with a talk on the role of RNA helicases in modulating RNA structures during antibody gene rearrangements (May 2020).
- Claudia Ribeiro de Almeida presented at the BBSRC Virtual Annual Visit at the Babraham Institute (November 2020).
- The lab hosted Gwendoline Muller as an Erasmus student from Université Grenoble Alpes for a three-month summer research placement carried out remotely.

#### Publications

[www.babraham.ac.uk/our-research/immunology/claudia-ribeiro-de-almeida](http://www.babraham.ac.uk/our-research/immunology/claudia-ribeiro-de-almeida) @cribdealmeida

- Ribeiro de Almeida, C. *et al.* (2018). RNA helicase DDX1 converts RNA G-quadruplex structures into R-loops to promote IgH class switch recombination. *Mol. Cell.* 70(4):650-662







**Sarah Ross**

#### Group members

##### Postdoctoral research scientist:

Jonathon Coates  
(Left in 2020)

##### PhD students:

Priota Islam  
Marian Jones Evans

##### Research assistant:

Rebecca England

##### Visiting student:

Lily Tan (Left in 2020)

## Oxygen-dependent control of T cell immunity

**Oxygen is vital for the ability of mammalian cells to survive and function. Oxygen-sensing signalling pathways underpin the ability of cells to adapt to conditions where oxygen is limited. Our research explores the impact of oxygen-dependent signalling on the activity of cytotoxic T cells, which are adaptive immune cells that play an important role in maintaining human health.**

#### Current Aims

During immune responses, cytotoxic T cells must attack and destroy infected, diseased or damaged cells in environments where oxygen availability is low.

Our goal is to determine how oxygen influences the ability of T cells to respond to the signals in their environment that direct their function. Our current research aims to elucidate the molecules and cellular processes that are regulated by oxygen in T cells and to establish how oxygen availability can determine how T cells become cytotoxic killer cells that can eradicate diseased cells.

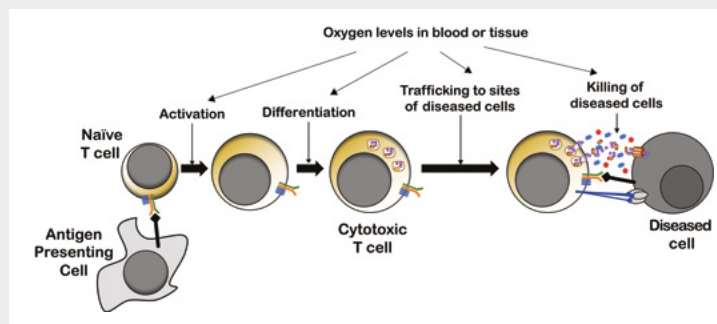
#### Progress in 2019 and 2020

Oxygen levels control the abundance of many proteins that are critical for the function of cytotoxic T cells. These include

metabolic enzymes; adhesion molecules that dictate how T cells migrate to diseased tissues; proteins that T cells use to kill cells; and receptors that determine how active T cells are towards diseased cells. Building on this work, through detailed analysis of cytotoxic T cells exposed to different oxygen environments, we have generated new insights into how oxygen controls the abundance of proteins in T cells. Our findings have important implications for understanding the activation, differentiation and function of T cells during an immune response.

#### Selected Impact Activities

- We hosted two teachers in the laboratory as part of the Institute's 'Teachers' Day' initiative (2019).
- Sarah Ross was part of the Internal Management Group that oversaw the ORION public dialogue on genome editing in the UK (2019).
- We hosted two school pupils in the laboratory as part of the Institute's virtual Annual Schools' Day (2020).



*Schematic representation of T cell differentiation and function, indicating where oxygen supply may be playing an important role in influencing the immune response.*

#### Publications

[www.babraham.ac.uk/our-research/immunology/sarah-ross](http://www.babraham.ac.uk/our-research/immunology/sarah-ross)

- Ross, S.H. & Cantrell, D.A. (2018) Signaling and function of interleukin-2 in T lymphocytes. *Annu. Rev. Immunol.* 36:411-433
- Rollings, C.M. *et al.* (2018) Interleukin-2 shapes the cytotoxic T cell proteome and immune environment-sensing programs. *Sci. Signal.* 11(526):eaap8112



# The essential element

**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 widely and work well in the myriad oxygen climates they encounter.

“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. Ageing, 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.

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.

"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.

**'Learning how oxygen affects our immune system is relevant for multiple diseases'**



# 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 loomed, 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.

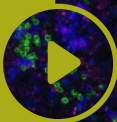
Fellow immunologist Professor Adrian Liston also stepped up to the mark, using his research to help clinicians make the best treatment choices for Covid-19 patients and his communication skills to provide accurate information to journalists and the public.

"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

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Watch an animated description of the Linterman lab's research work on the Oxford/AstraZeneca vaccine.



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

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 coronavirus 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 pat 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 you scale down this science it takes a decade or more to rebuild that intellectual capital."

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. "There wasn't another exit strategy," she says. "The vaccines are great, far better than we expected. But there are pathogens that we don't have good vaccines for. For me, that's the scary thing. We're lucky the vaccines are so effective – but that doesn't mean the same will be true for the next pandemic."

Confocal microscopy image of the spleen nine days after ChAdOx1 nCoV-19 immunisation in an aged mouse (22 months old). The image shows immunofluorescence staining to identify different classes of immune cell: IgD+ B cell follicle in green, CD3+ T cells in magenta, Ki67+ proliferating cells in blue and CD35+ follicular dendritic cells in white. Image: Sigrid Fra-Bido, Babraham Institute.

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Babraham Institute  
Babraham Research Campus  
Cambridge  
CB22 3AT  
UK

[www.babraham.ac.uk](http://www.babraham.ac.uk)  
Tel: +44 (0)1223 496000  
[babraham.contact@babraham.ac.uk](mailto:babraham.contact@babraham.ac.uk)  
 @BabrahamInst

The Babraham Institute

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Babraham Hall, Babraham,  
Cambridge, CB22 3AT  
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