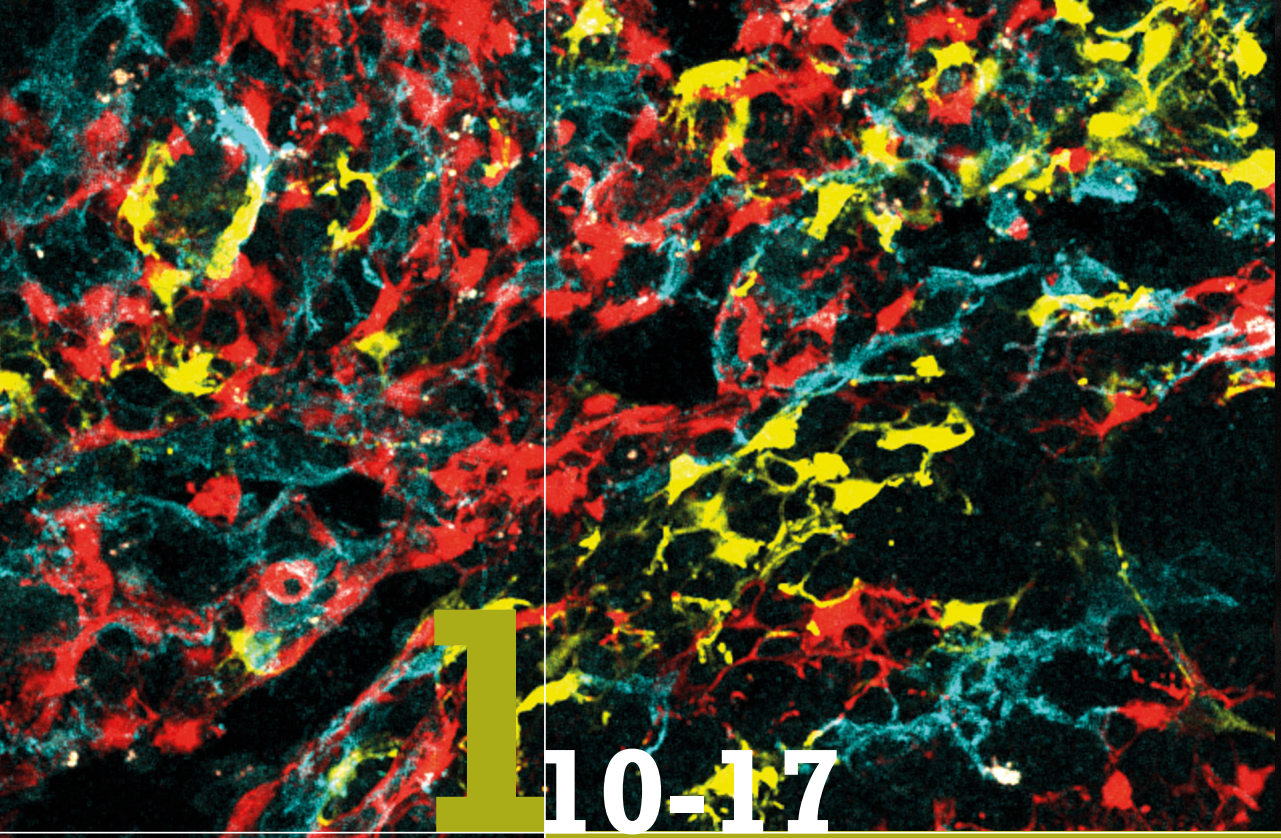
Babraham Institute

2018

Babraham Institute
Annual Research Report
Immunology



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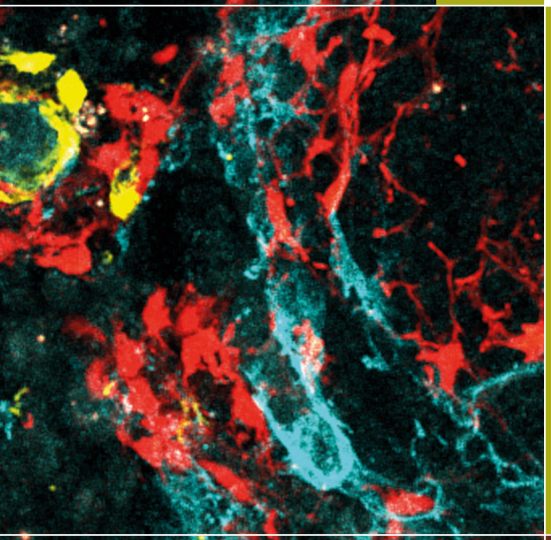
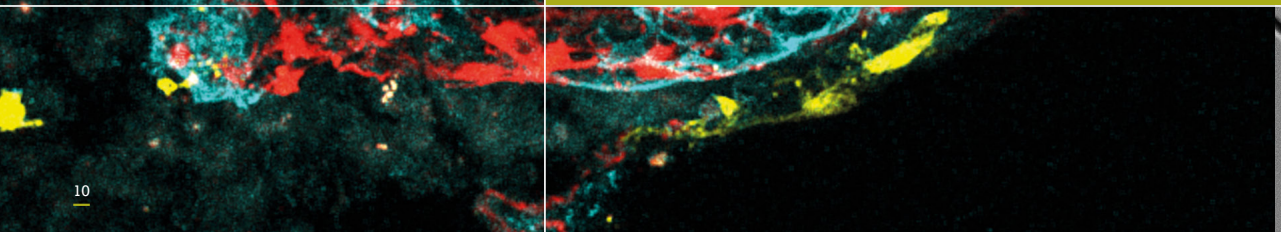


Immunology

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

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

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



Group Leaders

Martin Turner

Anne Corcoran

Michelle Linterman

Rahul Roychoudhuri

Joined in 2018

Adrian Liston

Claudia Ribeiro de Almeida

Sarah Ross

Martin Turner
Programme leader

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Visiting scientist:
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Molecular mechanisms of lymphocyte activation

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

Current Aims

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

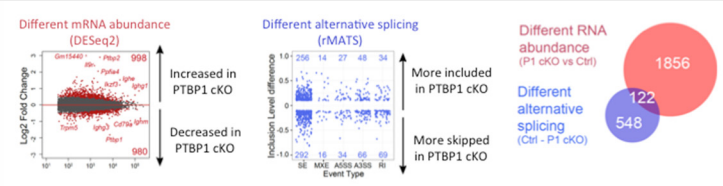
Progress in 2018

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

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

Selected Impact Activities

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



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

Publications

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

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

Making enough different antibodies to fight infection

Anne Corcoran

Group members

Senior postdoctoral researcher:
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Visiting scientist:
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Visiting student:
Jasper Carmody (Left in 2018)

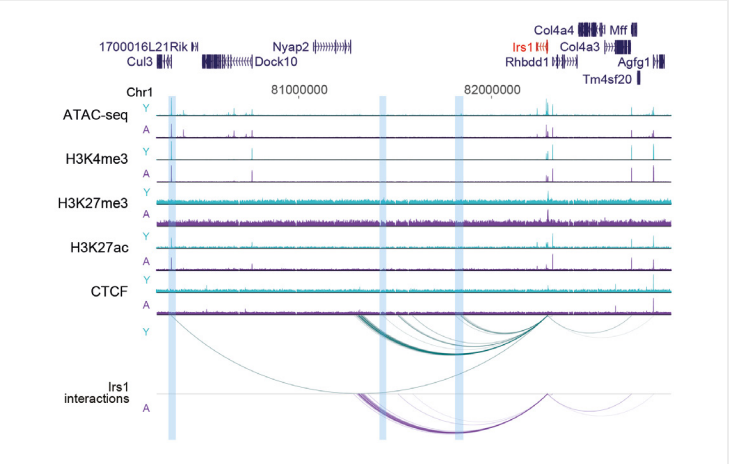
The immune system creates antibody proteins to help fight diseases. Antibodies are made by white blood cells called B lymphocytes. By mixing and matching genetic information, these cells can produce billions of different antibodies to combat different diseases. We are interested in the mechanisms involved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

Current Aims

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

Progress in 2018

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



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

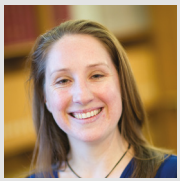
Selected Impact Activities

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

Publications

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

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



Michelle Linterman

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The immune response to vaccination

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

Current Aims

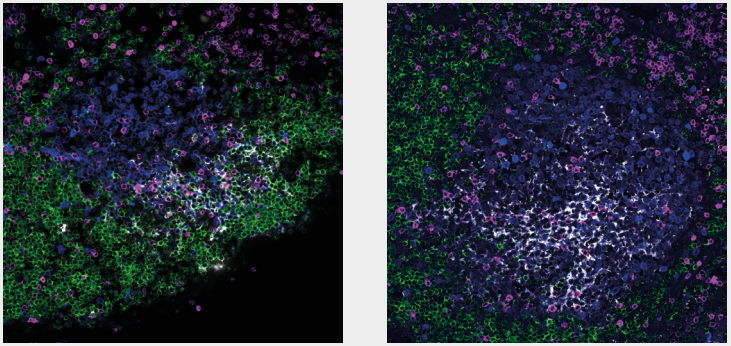
The germinal centre response generates protective immunity through the production of antibody-secreting plasma cells and memory B cells. Our research aims to understand why the magnitude and quality of the germinal centre response is impaired with advancing age. We also wish to identify tractable strategies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

Progress in 2018

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

Selected Impact Activities

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



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

Publications

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

@LintermanLab

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

Rahul Roychoudhuri

Group members

Postdoctoral researchers:
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Tihomir Todorov (Started in 2018)
Nordin Zandhuis (Left in 2018)

Uncovering the 'brakes' on immune activation

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

Current Aims

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

Our programme of research is organised into three aims:

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

Progress in 2018

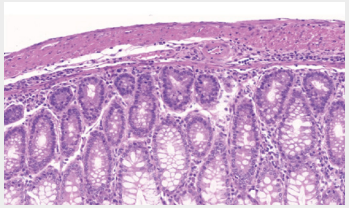
We have made progress in understanding the genetic basis underlying susceptibility to human inflammatory diseases by modelling the function of human disease-associated enhancers using mouse models. Our work shows that this type of genetic modelling, most frequently applied to understanding the function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

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

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

Selected Impact Activities

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



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

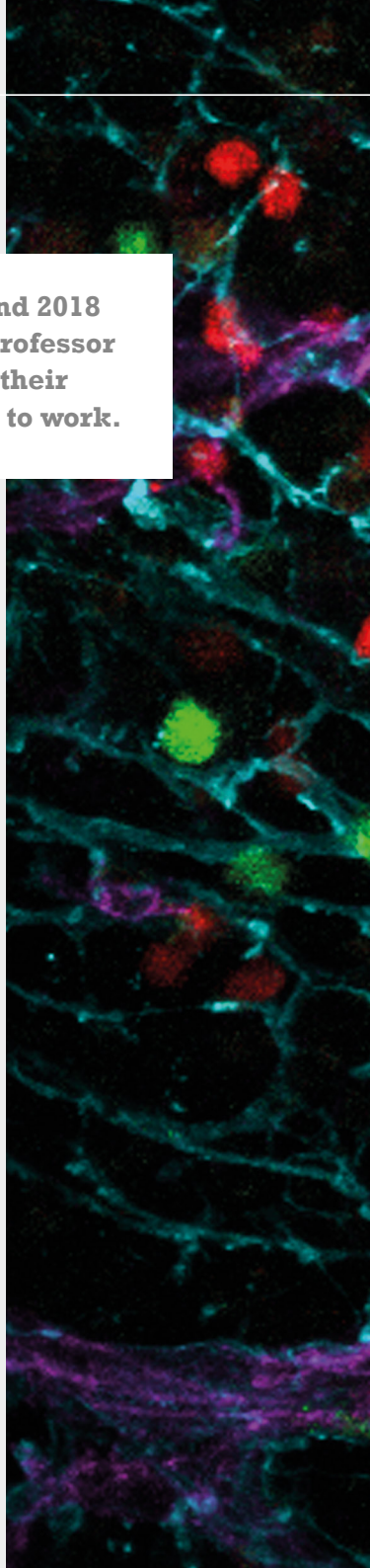
Publications

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

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

New horizons for immunology

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



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

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

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

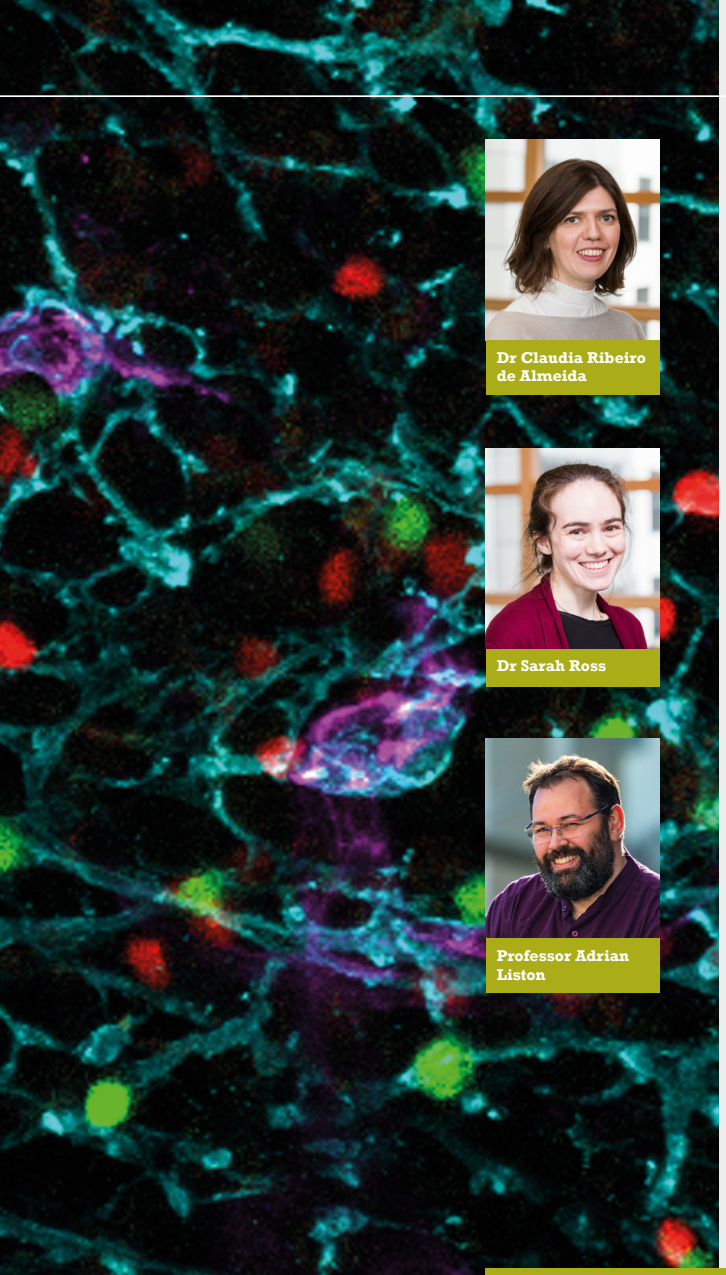
At the Institute, Liston wants to answer three key questions: how the millions of CD4 T cells in our bodies communicate and cooperate; how they switch between a ramping up and damping down cell type; and what they do in our tissues. Understanding how these cells modulate our immune system means that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

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

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

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

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



Dr Claudia Ribeiro de Almeida

Dr Sarah Ross

Professor Adrian Liston

‘The Institute is setting the gold standard for equality and inclusion’

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

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

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

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

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

‘Great research requires fantastic people who think as differently as possible’

Image of Adrian Liston used courtesy of the Cambridge Independent.

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Athena SWAN Silver Award

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