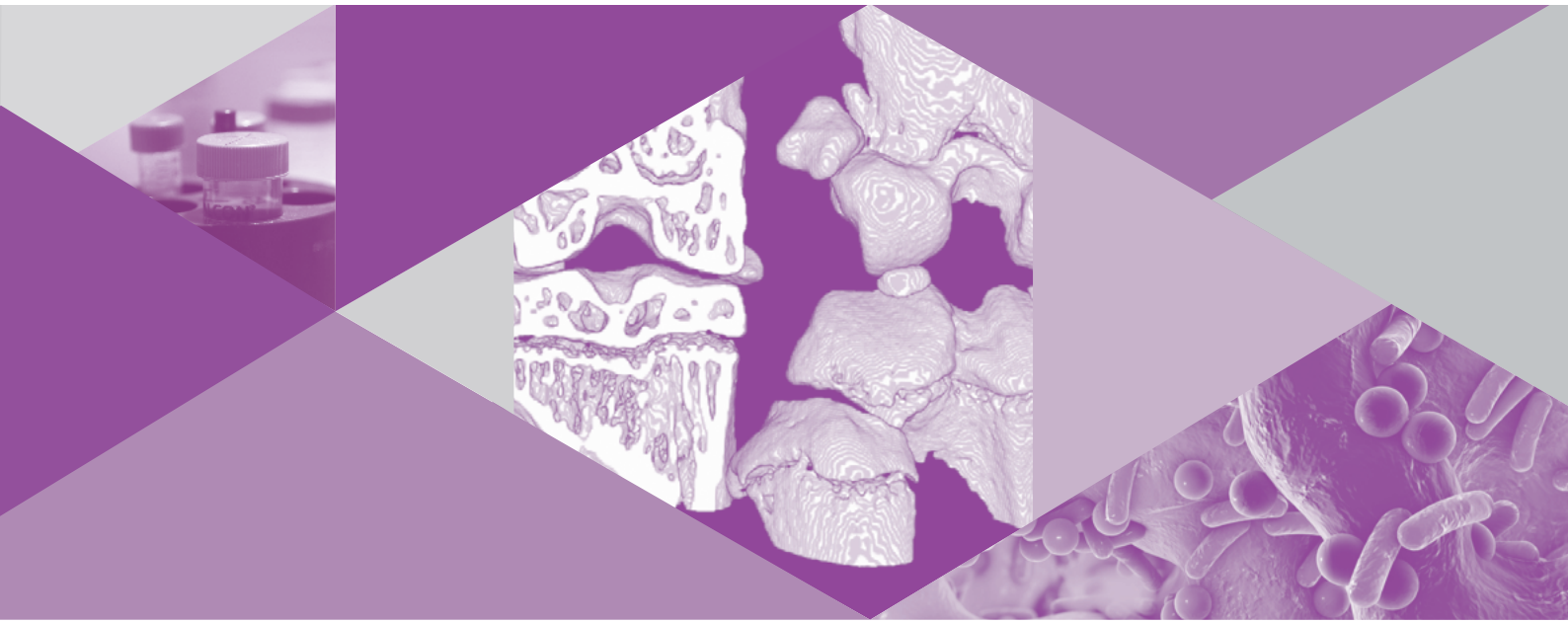
KENNEDY

INSTITUTE OF RHEUMATOLOGY | NDORMS


Kennedy
Institute of
Rheumatology

# Kennedy Institute of Rheumatology

## Report 2016



### Kennedy Institute

We are a world-leading basic and translational inflammatory sciences centre. The three major themes of our research - immunity and microbiome, inflammation biology, and tissue remodelling and regeneration - are relevant for a diverse range of chronic inflammatory disorders including arthritis, inflammatory bowel disease, tissue fibrosis and certain types of cancer. We apply state-of-the-art technologies in analysis of disease models and patient tissue samples to understand why disease develops and to reveal new diagnostic markers and targets for therapy. Strategic partnerships with nearby clinical centres such as the Nuffield Orthopaedic Centre and the John Radcliffe Hospital facilitate scientific translation from bench to bedside.

# Inside


Kennedy
Institute of
Rheumatology

# Director's Message

> The Kennedy Institute is a world-leading medical research centre where discovery research drives development of transformative therapies for chronic inflammatory and degenerative diseases.

## Professor Fiona Powrie

The Kennedy Institute is a world-leading medical research institute that carries out basic and translational research into chronic inflammatory and degenerative diseases. Kennedy Institute scientists and clinicians identified the role of the cytokine TNF in the pathogenesis of rheumatoid arthritis, and pioneered the use of anti-TNF antibodies in the clinic: a treatment that has changed the lives of millions of patients. Building on these successes, our goals are to identify fundamental mechanisms of disease and to apply this knowledge as a basis for the development and testing of transformative new therapies which help prevent, diagnose and treat a number of debilitating illnesses.

Under the leadership of the previous Director, Professor Sir Marc Feldmann, and with the support of both the Kennedy Trust for Rheumatology Research (KTRR) and the University of Oxford, the Kennedy Institute moved from London to Oxford in 2011. With the construction of a state-of-the-art new building, this visionary move ushered in a new era in the institute's history, offering the opportunity to expand the scope of our research within a world-class medical research environment. I am delighted to report that this move has been highly successful in paving the way towards the delivery of our strategic goals: to perform world class discovery research; to foster and develop talent; to integrate basic and clinical research; and to develop national and international collaborative networks to innovate, communicate and translate our work.

In this report you can read about our scientists' multi-disciplinary cutting-edge research. This ranges from understanding the nanoscale functioning of the immunological synapse, to the impact of the microbiome on chronic inflammatory disease and cancer, through to experimental medicine studies testing the efficacy of novel therapies in musculoskeletal diseases. Providing our scientists with access to the latest technologies is a key part of our research strategy. We have established sophisticated core facilities that support the study of disease processes, from bench to bedside. The quality and impact of our research is illustrated by more than 175 papers published by Kennedy Institute scientists since 2014. Investigators have received prestigious grants including Wellcome Trust Investigator Awards and European Research Council Advanced Grants. Kennedy Institute scientists are also recipients of major international awards including two recipients of the Gairdner Prize.

Recruiting and training the next generation of scientific leaders is vital for delivering our scientific mission. Over the past two years Professor Michael Dustin, Director of Research, has played a major role in driving the recruitment of junior investigators. In this report he outlines how the expertise and skills of our new recruits align with our vision for the institute as a world-leading centre for basic and translational research. With the support of the KTRR, we have established a KTRR Prize Studentship programme which attracts high calibre students from all over the world. We are delighted to have welcomed 19 of these students to the institute in the last three years, and we look forward to following their progress in the future.

The Kennedy Institute is uniquely positioned to bridge the gap between basic and clinical science. Our partnerships with clinical collaborators in Oxford and beyond provide a gateway to patient cohorts in inflammatory arthritis, osteoarthritis, cancer and inflammatory bowel disease. Use of patient tissue samples is a crucial component of our discovery science aimed at unravelling complex disease mechanisms to identify new drug targets or approaches for patient stratification. The power of our approach was recently recognised by large funding awards from Novo

Nordisk, Arthritis Research UK and the National Institutes for Health Research. The ambition now is to build infrastructure that will accelerate the uptake of early experimental trials in these patient groups, based on our observations from pre-clinical studies.

In 2016 the Kennedy Institute is truly integrated into its new home within the Nuffield Department of Orthopaedics and Musculoskeletal Sciences (NDORMS) at the University of Oxford.

We are very grateful to the KTRR and all the staff in Oxford who have smoothed our way and made us welcome. Kennedy Institute staff have shown great flexibility and resource during this transition. They are our greatest asset, and as illustrated in this report, we have together laid the foundations of our future vision and look forward to great progress in the future.

# A New Location – A New Era

> At Imperial we had run out of room for the Kennedy Institute to grow. Oxford has given us the opportunity to make a fresh start in a wonderful new campus with a state-of-the-art building, designed by the Kennedy staff to be optimal for our needs. The hard work has paid off and the future looks secure.
>
> Professor Sir Marc Feldmann

## The World's First Arthritis Research Institute

Founded in 1965 by Mathilda and Terence Kennedy, the Kennedy Institute was the first research institute dedicated to the causes and cures of rheumatic disease. The institute was initially located in Bute Gardens, Hammersmith, and later relocated to the Charing Cross Hospital. Working across the two sites, former institute Directors, Professor Sir Marc Feldmann and Professor Sir Ravinder Maini, pioneered the development of anti-TNF therapy, which was approved for use in rheumatoid arthritis in 1999.

In 2000, the institute's staff and research activities were transferred to Imperial College London as the Kennedy Institute of Rheumatology Division. The institute was then transferred to the University of Oxford in 2011, and the Trust changed its name to the Kennedy Trust for Rheumatology Research. The Trust and the University jointly funded the construction and fit out of the new building in Oxford, which opened in 2013, and continue to provide strategic support to the institute.

> A large and beautiful atrium offers the opportunity for researchers to meet and discuss their work away from the bench.

## The New Building

The new Kennedy Institute building was designed by Make Architects in collaboration with Nightingale Associates. Their aspiration was to create a modern and functional environment to facilitate high quality research, encourage interaction between research groups, and provide a place where researchers can enjoy their work. This interaction and strong sense of community is enhanced by the building's large and beautiful atrium, which offers the opportunity for researchers to meet and discuss their work away from the bench. The building has a total area of 7,300 square metres with four floors of laboratory and office space, and can house close to 200 researchers and support staff. Two further floors within the building are dedicated to the plant and equipment necessary to support such an advanced research facility.

> Progress in high quality research at the new Kennedy Institute is outstanding.

## Professor Andrew Carr, Head of NDORMS and Director of the Botnar Research Centre

The Kennedy Institute was incorporated into NDORMS in 2011 through the shared vision of the KTRR, Professor Sir Marc Feldmann, and the University of Oxford. Now situated on the University's Old Road Campus, the institute is embedded within a site of world-class biomedical research, in close proximity to a large programme of clinical research in rheumatology and musculoskeletal sciences.

The move to Oxford came with a change in leadership, and in 2014 we were delighted to welcome Professor Fiona Powrie to the department as the new Kennedy Institute Director. A second major addition to the leadership team is Professor Michael Dustin, a world-renowned immunologist who joined the institute in 2013 as Director of Research. The arrival of Fiona and Mike was quickly followed by major efforts in recruitment of new staff and investment in infrastructure to create a stellar environment for research into chronic inflammatory disease.

By bringing the Kennedy Institute together with the Botnar Research Centre and other Units that provide infrastructure for clinical science, the department is fully committed to supporting research across the translational spectrum from basic biology to clinical application. We aim to make a real difference to patient care for a wide range of disorders. Investigators at the two research institutes now collaborate extensively. For example, Botnar Research Centre investigators are incorporating the Kennedy Institute's immune monitoring platform into clinical trials to understand why some patients do not respond to treatment. Research at the Kennedy Institute linking certain immune molecules to the failure of anti-TNF therapy has also led to new clinical trials run by Botnar Research Centre investigators. The Arthritis Research UK Centre for OA Pathogenesis, directed by Professor Tonia Vincent at the Kennedy Institute, is another excellent example of added value through collaboration. The Centre receives a substantial amount of funding, which supports research programmes relying on the expertise of basic scientists, academic clinicians and surgeons from across the department.

With the tremendous pace of change under the new Kennedy Institute leadership this is an exciting time for the institute and department as a whole.

# A New Location – A New Era

## NDORMS

As the largest European academic department in its field, NDORMS runs a global competitive programme of research and teaching in a broad range of areas, including orthopaedic surgery, inflammation, immunology, rheumatology, medical statistics, epidemiology and clinical trials.

In addition to the Kennedy Institute, NDORMS hosts another internationally excellent institute – the Botnar Research Centre, on the Nuffield Orthopaedic Centre (NOC) site. The co-location with NHS services at the NOC allows the department's researchers to work alongside clinicians, which is essential for successful translational research.

By fostering collaborations between researchers of both institutes, the department promotes sharing of expertise to maximise the superb infrastructure for laboratory and clinical science.

## Old Road Campus

The Kennedy Institute is located on the University of Oxford's Old Road Campus – a site for internationally recognised biomedical research. The campus creates a hub for basic researchers and clinicians working in diverse areas including genomics, structural biology, vaccines, cancer biology and health informatics. Partnerships formed across the campus – and with other University research centres – allow investigators to rapidly adopt new ideas, techniques and approaches for application in the context of inflammatory disease.

The Kennedy Institute benefits from – and is also driving – scientific innovation across the University of Oxford. The institute's core technology platforms for human immune monitoring and single cell analysis complement research activities within the Oxford Single Cell Biology Consortium, Cancer Research UK Oxford Centre and elsewhere, creating new collaborations and funding opportunities. The Kennedy Institute also has a germ-free animal facility under construction. This will establish Oxford as one of the few UK sites with specialised facilities for microbiome research – a key area of research at the Kennedy Institute going forward.

## A Vibrant Research Community

At the heart of the institute's multidisciplinary approach is a diverse group of basic and clinical scientists who are working together to find new ways of investigating biological pathways that underpin disease. This team is expanding: the institute now houses approximately 200 staff, visitors and students representing over 27 different nationalities.

The research environment is open and collaborative, with investigators working across teams on shared interests in disease pathogenesis or to apply expertise in core technology platforms to new disease areas. The institute's expert core facilities managers provide training and advice to ensure core technology platforms are applied with maximum impact.

Regular 'Work in Progress' and 'Friday Forum' research meetings provide the opportunity for scientists at all career stages to share their data, leading to critical discussions and new perspectives. Researchers at the institute also engage with research outside their direct area of interest through a busy external seminar programme and weekly journal clubs in immunology and cartilage biology.

The Kennedy Institute also organises several international research meetings that are attended by institute staff and students as well as the broader scientific community. This includes the "From the Laboratory to the Clinic" translational research meeting, held annually in Oxford since 1984. This three-day meeting brings together basic scientists, clinicians, and industry researchers to explore how the latest discoveries in immunology and molecular medicine can be applied to improve clinical medicine. The meeting's small size and line up of world-class speakers creates an environment that stimulates exchange of ideas, facilitating new collaborations and scientific progress in the translational space.

# 2014–2016 Highlights

The exciting science underway at the institute has led to more than 175 publications since 2014. Investigators have also received a number of personal prizes and awards to recognise their research accomplishments, and have been awarded prestigious programme and strategic grants to support key areas of research at the institute. There has also been progress in clinical studies aimed at translating basic research at the institute to benefit patients.

## Funding and clinical translation

2014

- KICK study led by Dr Fiona Watt recruits the last of 150 patients for longitudinal follow up after knee injury
- Dr Tal Arnon receives a Wellcome Trust Investigator Award
- Professor Jagdeep Nanchahal receives a Health Innovation Challenge award from the Wellcome Trust and Department of Health, supporting a clinical trial to repurpose anti-TNF in Dupuytren's disease

2015

- Professor Michael Dustin receives a European Research Council Advanced Grant

2016

- Kennedy Institute receives a Wellcome Trust Multi-User Equipment Grant to support in vivo imaging in a germ-free setting
- Professor Fiona Powrie receives a MRC Confidence in Concept Award to support experimental medicine studies in colorectal cancer

## Personal prizes and awards

2014

- Professors Sir Marc Feldmann and Sir Ravinder Maini awarded the Canada Gairdner International Award for the discovery of anti-TNF therapy

2016

- Fiona Watt receives the Michael Mason Award for excellence in clinical rheumatology research
- Claudia Monaco awarded the Oxford-Harrington Scholarship to support research into drug discovery

## Publications

- Dustin lab show T lymphocytes communicate with other immune cell types through transfer of extracellular microvesicles to influence downstream immunity.

  Choudhuri et al. 2014. *Nature.* 507(7490):118-23

- Monaco lab show IDO metabolities stimulate B cell IL-10 production and are protective in atherosclerosis.

  Cole et al. 2015. *Proc Natl Acad Sci U S A* 112: 13033-8

- Powrie and colleagues show IL-33 enhances protective T regulatory cell responses after tissue damage in the gut, and find that this pathway is inhibited by the pro-inflammatory cytokine IL-23

  Schiering et al. 2014. *Nature* 513: 564-8

- Udalova lab identify the transcription factor IRF5 as a therapeutic target in inflammatory arthritis

  Weiss et al. 2015. *Proc Natl Acad Sci U S A* 112: 11001-6

- Midwood and colleagues identify protein tenascin-C as a biomarker allowing early detection of inflammatory joint disease.

  Schwenzer et al. 2016. *Ann Rheum Dis* 75: 1876-83

# Fostering and Developing Talent

> From University graduates at the very beginning of their research career to accomplished postdoctoral fellows seeking to establish their own independent laboratories, we are committed to providing outstanding training opportunities to develop the next generation of scientific leaders.

## DPhil Studies

The Kennedy Institute DPhil programme provides world-class scientific training in a supportive and collaborative environment. The Kennedy Trust Prize Studentships are a major component of this internationally competitive programme. By providing four years of funding and a generous stipend, these studentships allow the institute to recruit six high calibre national and international graduates each year. The institute also has students funded through other highly competitive programmes, including those run by the research councils and charities.

All students are introduced to research at the institute with a series of lectures in the areas of inflammation, immunology and musculoskeletal sciences. They also receive training in transferrable skills, as well as careers advice and mentoring. The ability to engage with the wider research community is fundamental for successful research; students get to hone their networking and communication skills by presenting their research internally and attending national and international conferences. As of 2016, students also organise and attend a Kennedy Institute Student Symposium that aims to foster a deep sense of community and collaboration.

> The Kennedy Institute provides an excellent environment for postdoctoral training and has hosted 21 fellowship awardees from 2013-2016.

## Postdoctoral Training

The institute offers several complementary support mechanisms to enhance the experience and training of its large community of postdoctoral researchers. Postdocs receive scientific training from Group Leaders, as well from staff at the institute's core technology platforms, and have access to University-run courses teaching transferrable skills. They can also take advantage of teaching opportunities within the Department and nurture their management skills by supervising undergraduate projects, or by formally co-supervising MRes or DPhil students. The Department's early career researcher training committee provides mentoring in the form of drop-in support sessions, assistance with fellowship applications, and an online forum for postdoc relevant issues and opportunities.

The institute also participates in several Oxford-wide postdoctoral fellowship programmes funded by industry partners. For example, Celgene Fellowships in translational research support postdoctoral fellows to work on areas with clear potential to advance therapeutics. These fellowships can be awarded to either basic or clinical scientists and provide postdocs the opportunity to spend time in Celgene laboratories to facilitate transfer of skills between academia and industry.

> We are committed to providing talented early stage scientists with all the support they need to become independent investigators.

## Early stage independent investigators

The institute offers a structured and competitive Career Development Programme for basic and clinicial scientists, which is tailored to individuals to provide them with the support to develop their scientific career. Within this programme we sponsor both Senior Fellows and Career Development Fellows.

The KTRR Senior Research Fellowship programme creates a platform for early stage scientists to launch an independent research career; it has also enabled the Kennedy Institute to recruit bright young investigators from across the globe. These five-year fellowships provide awardees with a generous funding package and strong mentorship, embedded within the institute's outstanding research environment. The first of these fellowships was awarded in 2013 to Dr Tal Arnon, who has subsequently received a Wellcome Trust Investigator award. Three more Senior Research Fellowships were awarded in 2016.

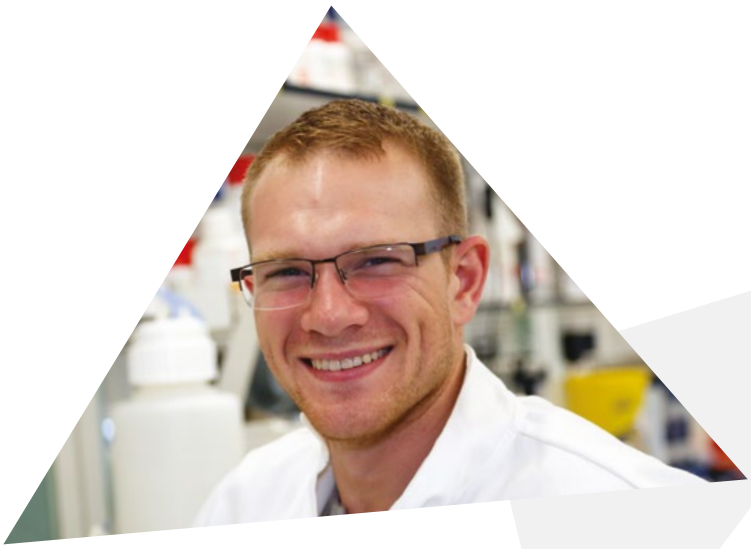
The institute sponsors a number of Career Development Fellows funded by external charities such as Arthritis Research UK. Sponsorship may include additional institutional support, and has a strong mentorship component with a mid-term review and structured discussions of long-term career plans.

> We work hard to ensure the institute is a truly welcoming and supportive environment for all staff and students.

## Athena Swan

NDORMS achieved an Athena SWAN Silver Award in October 2015 for good practice towards gender equality and diversity, as well as for supporting career progression pathways for NDORMS staff. The Athena SWAN Self Assessment Team, which includes Kennedy Institute staff from a variety of different roles, work to ensure continuing progress in improving processes related to equality and diversity.

# Fostering and Developing Talent



## Alastair Corbin
## 4th Year Kennedy Trust Prize DPhil Student

I graduated from the University of Manchester with a BSc (Hons) in Medical Biochemistry, which included a one year Industrial Placement at GSK Stevenage in the Immuno-Inflammatory department. I was attracted to the Kennedy Institute because it provides a platform to utilise cutting-edge technologies to understand inflammatory disease. Supervised by Professor Irina Udalova, I am applying low cell number RNA sequencing and CyTOF to characterise the role of IRF5 in monocyte and macrophage populations in the colon during colitis. My training at the institute will place me in an excellent position to pursue a career in academia.

## Dr Ahmed Hegazy
## Marie Skłodowska Curie Research Fellow

I am a clinician scientist and studied medicine at the Cairo University, Egypt, and Hannover Medical School, Germany. I received my PhD in Immunology and Infection Biology from Humboldt University of Berlin, Germany. I joined Professor Fiona Powrie's laboratory and the Kennedy Institute for postdoctoral studies because of the opportunity to conduct research at the intersection between basic and clinical science. My research is supported by an EMBO postdoctoral fellowship and a Marie Skłodowska-Curie Research fellowship. I have investigated microbiota-reactive $CD4^+$ T cells in the pathogenesis of human inflammatory bowel disease, using healthy and diseased tissue samples obtained from the Translational Gastroenterology Unit. Based on my successful and productive time at the Kennedy Institute, I was offered a Principal Investigator position at the German Rheumatism Research Centre, Berlin, which I have accepted starting in April 2017.

## Dr Jonathan Sherlock
## Senior Clinical Research Fellow

I studied pre-clinical medicine at the University of Oxford and clinical medicine at the University of Cambridge. My scientific background is in immunology, following work at the DNAX Research Institute in California on the role of interleukin-23 in spondyloarthropathy. The Kennedy Institute provides an ideal environment to combine basic immunology with translational research in the context of experimental medicine studies. Local availability of human tissue samples, the ability to interact and collaborate with a wide variety of specialists, and excellent laboratory and clinical infrastructure are central to this work. I work in close collaboration with Professors Fiona Powrie and Peter Taylor in the context of immune-driven rheumatic inflammation.

## Dr Anjali Kusumbe
## KTRR Senior Research Fellow

I gained my PhD from the National Centre for Cell Science, India, then moved to the Max Planck Institute for Molecular Biomedicine, Germany, where I worked on the bone vasculature. I was attracted to the Kennedy Institute because of its high quality research. My current research focuses on understanding the role and therapeutic potential of vascular niches in bone. The prestigious Senior Research Fellowship will support this program of research and will make a significant contribution towards the establishment of my independent research career. The fellowship is highly flexible and provides access to state-of-the-art facilities and a career development and mentoring program. The institute also provides excellent opportunities for new collaborations, allowing me to take my research into new disease areas such as tissue repair and osteoarthritis.

# Research

## Foreword from Professor Michael Dustin, Director of Research

Moving the institute to Oxford has created many new opportunities and we have already made great progress in broadening the scope of our basic and translational research programmes through recruitment of new Group Leaders at different stages of their careers.

The prestigious KTRR funded Senior Research Fellowships have enabled us to recruit four outstanding scientists: Dr Tal Arnon, Dr Audrey Gerard, Dr Jelena Bezbradica Mirkovic, and Dr Anjali Kusumbe. Tal and Audrey bring extensive expertise in molecular and in vivo imaging. Their innovative research programmes focused on understanding distinct aspects of adaptive immunity will make full use of state-of-the-art core microscopy facilities at the Kennedy Institute and elsewhere on campus. Jelena has a strong interest in innate immunity, and her work distinguishing downstream effectors of sterile versus microbe-induced inflammation is relevant to the pathogenesis of many chronic inflammatory and degenerative diseases studied at the Kennedy Institute. Anjali examines how vascular microenvironments shape bone development, homeostasis, and cancer metastasis, and her research aligns with basic research programmes within the Arthritis Research UK Centre for Osteoarthritis Pathogenesis. Our new Senior Research Fellows enrich established research programs at the institute and bring a wealth of new ideas and expertise for application in chronic inflammatory and degenerative disease research.

Dr Luke Jostins and Dr Jonathan Sherlock have also joined our team of Group Leaders, with support from the KTRR. Luke joins the Kennedy Institute officially in 2017, and together with Dr Stephen Sansom, brings crucial expertise in bioinformatics and computational biology.

Jonathan studies inflammatory arthritis, and together with Dr Fiona Watt at the Kennedy Institute and Professor Peter Taylor at the Botnar Research Institute, will play a key role in translational research programmes at the institute.

Professor Katja Simon also joined the institute in 2016. Katja's research has defined a fundamental role for autophagy in immune cell fate and function and her expertise in ageing brings a new perspective to the field of chronic inflammatory disease research and ageing.

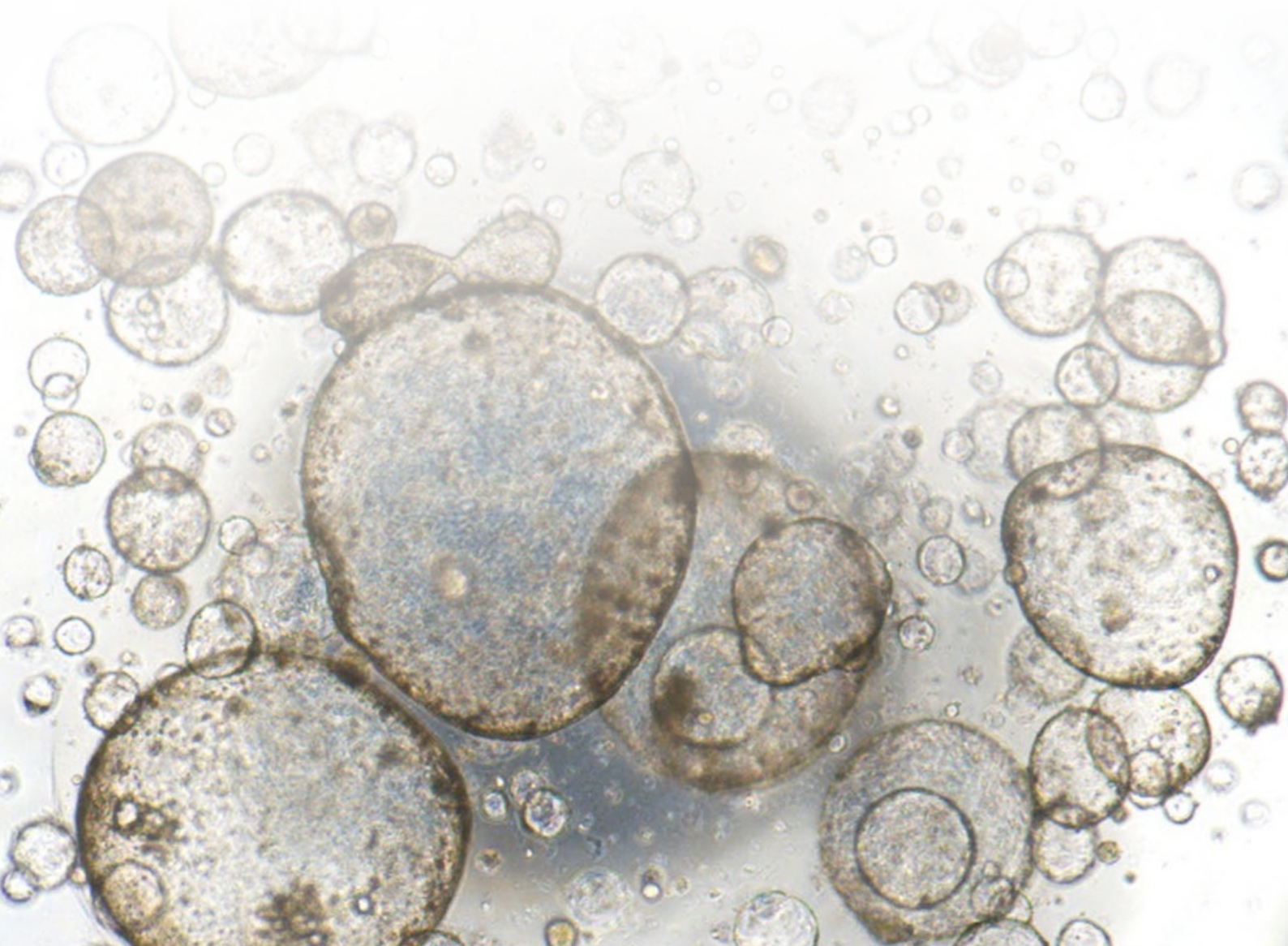
With a vibrant mix of established and new investigators combined with our outstanding core technology platforms, the institute has a brilliant future in Oxford.

> Our new recruits bring a wealth of ideas and expertise for application in inflammatory and degenerative disease research.

# Research Themes

Our discovery research seeks to uncover key biological processes that promote health and provide understanding of how these pathways malfunction in disease. We adopt a multidisciplinary approach incorporating molecular and cellular biology with analysis of disease models and interrogation of patient tissue samples.

A common goal is to define the molecular underpinnings of disease to guide the discovery of new drug targets or approaches for patient stratification. Strategic partnerships with nearby clinical centres and industry are crucial to advance translation of basic discoveries into new therapies for patients.



## Our research falls into three overlapping and complementary themes:

### Immunity and microbiome

The immune system employs a diverse range of strategies to protect the host against dangerous microbes and tumour growth. We investigate how the immune system distinguishes foreign invaders, and examine the cell types, receptors and signalling pathways that calibrate the response to the level and type of threat.

We are also interested in the mutually beneficial relationship between the immune system and microbes that populate the gut and other body surfaces, and in particular how these microbes exert control over immune cell development and function. These studies provide insight into the causes and treatment of autoimmune disease, and may help to guide the design of vaccines and other approaches to harness the immune system to treat chronic viral infection or cancer.

### Inflammation biology

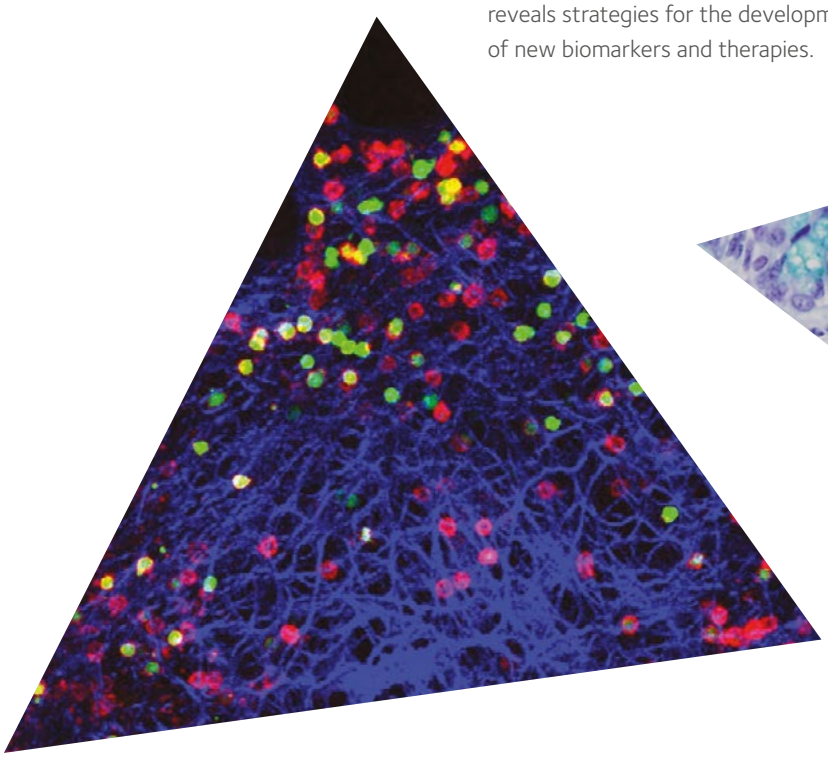
Inflammation is a crucial process that helps protect against infection and promote tissue repair after injury. Inflammatory responses are usually short-lived. However, if inflammation fails to subside it can contribute to the development of a wide range of chronic diseases including rheumatoid arthritis, cardiovascular disease, inflammatory bowel disease and certain types of cancer.

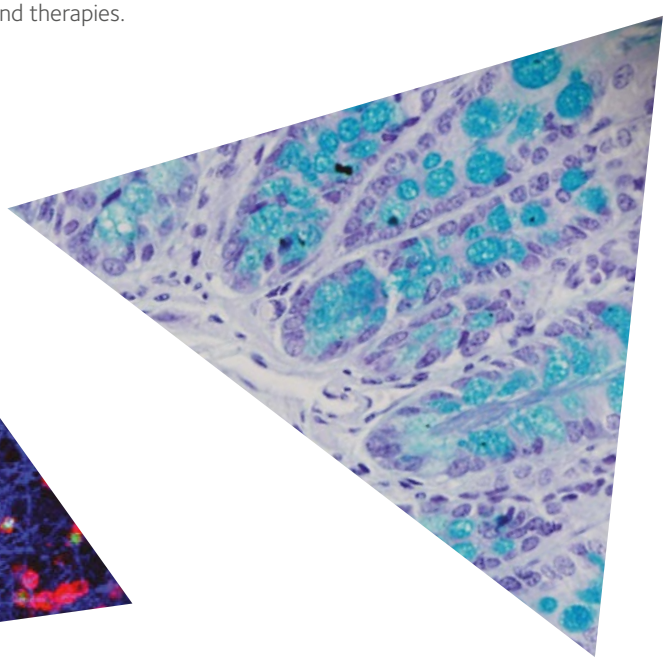
We investigate inflammatory cell types – and their functional plasticity – and the complex positive and negative feedback loops controlling initiation, progression and resolution of the response. In particular, single cell genomic and proteomic approaches are used to define signalling and regulatory pathways that underpin the behaviour of diseased tissue. Our research provides basic insight into the disease process and reveals strategies for the development of new biomarkers and therapies.

### Tissue remodelling and regeneration

An overarching aim is to appreciate how tissues respond to injury and how the inflammatory response this elicits drives tissue remodelling and regeneration. We examine the molecular and cellular mechanisms that drive healthy tissue repair and dissect how these activities become unbalanced in disease.

A major component of this work takes place within the Arthritis Research UK Centre for Osteoarthritis Pathogenesis and aims to understand the pathways that regulate cartilage wear and repair in joints. However, our research is also relevant for understanding many other processes including fibrosis and fibrotic disorders, tumour growth and progression, wound and fracture repair and application of stem cell technologies.





# Regulation of Humoral Immunity

## Tal Arnon

**Tal Arnon** has been a KTRR Senior Research Fellow at the Kennedy Institute since 2014. Previously she completed her PhD at the Hebrew University of Jerusalem, Israel, with Professor Ofer Mandelboim, and gained postdoctoral training at UCSF, USA, with Professor Jason Cyster. Her work is supported by a Wellcome Trust Independent Investigator Award.

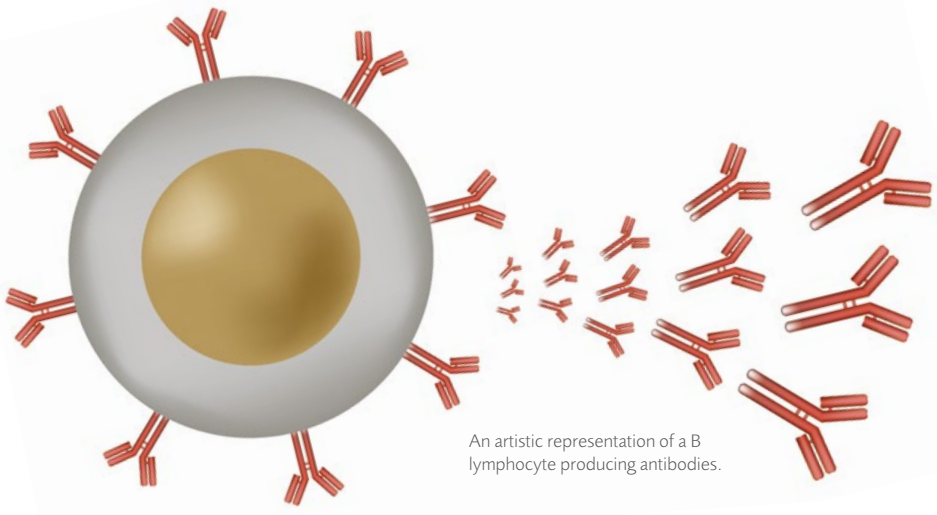
> We aim to understand fundamental principles that regulate antibody responses.

Antibodies are important for the clearance of pathogens and are critical for the ability of vaccines to provide long-term protection from many diseases. A better understanding of how B cells receive the necessary signals required for their activation and maintenance in vivo will inform attempts to develop broadly-neutralizing vaccines against pathogens such as malaria, HIV and influenza. Our lab uses genetic approaches combined with imaging techniques to directly visualize B cell responses within living tissue and to monitor their behaviour before, during and after immunological challenges.

The spleen is important for protection against pathogens that have reached the blood circulation, which pose a risk for systemic inflammation, a life threatening condition that can lead to septic shock and death. A major focus of my lab is to understand how tissue-resident macrophages regulate B cell responses in the spleen. Our goal is to define how macrophages regulate B cell migration and activation within the context of an intact splenic environment. We combine real-time imaging of B cell-macrophage interactions with the development of mouse models that permit targeted ablation of distinct macrophage populations. We anticipate that these studies will enhance our understanding of basic B cell and macrophage biology, and may also help to develop better vaccines against important blood pathogens.

A second focus is to understand memory B cell responses after influenza virus infection, which is crucial in order for the host to cope with secondary infections. Memory B cells can be found in the circulation, where they are thought to migrate between secondary lymphoid organs and scan the body for signs of pathogenic invasion. However, during certain pulmonary viruses, a large number of memory B cells can also be found in peripheral sites within the infected lung. These cells do not appear to circulate, but instead persist in the lung for prolonged periods of time. We aim to define the unique properties and importance of lung memory B cells to the clearance of influenza infection. These studies may help to develop improved ways to enhance B cell responses to viral infections in the lung, and possibly other peripheral sites.


1. Reboldi A, Arnon TI, Rodda LB, Atakilit A, Sheppard D, Cyster JG. 2016. IgA production requires B cell interaction with subepithelial dendritic cells in Peyer's patches. *Science* 352: aaf4822
2. Arnon TI, Horton RM, Grigorova IL, Cyster JG. 2013. Visualization of splenic marginal zone B-cell shuttling and follicular B-cell egress. *Nature* 493: 684-8
3. Arnon TI, Xu Y, Lo C, Pham T, An J, Coughlin S, Dorn GW, Cyster JG. 2011. GRK2-dependent S1PR1 desensitization is required for lymphocytes to overcome their attraction to blood. *Science* 333: 1898-903
4. Muppidi JR, Arnon TI, Bronevetsky Y, Veerapen N, Tanaka M, Besra GS, Cyster JG. 2011. Cannabinoid receptor 2 positions and retains marginal zone B cells within the splenic marginal zone. *J Exp Med* 208: 1941-8

An artistic representation of a B lymphocyte producing antibodies.

# Innate Immunity and Sterile Inflammation

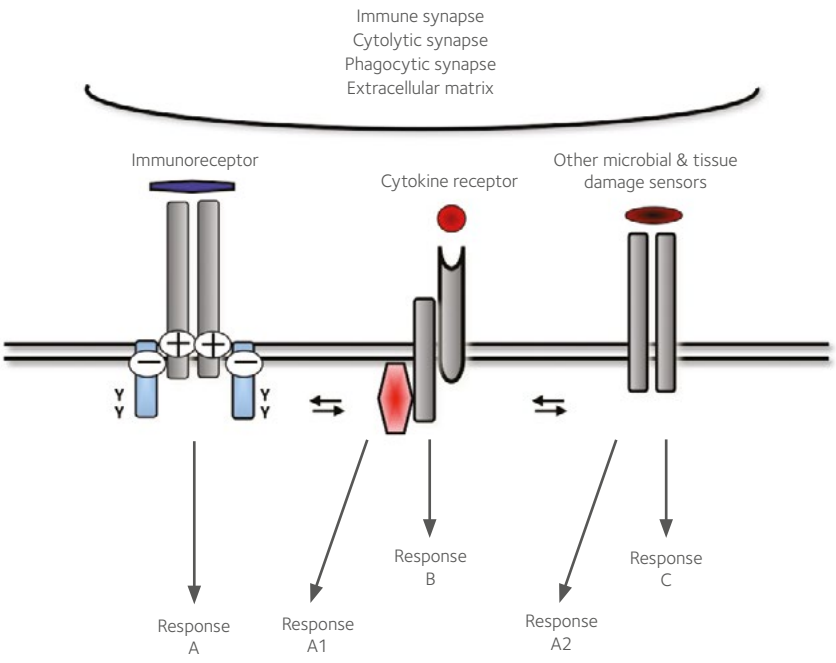
## Jelena Bezbradica Mirkovic

> The overall goal of our research is to understand inflammatory responses to sterile versus microbe-induced tissue injury.

During infection the innate immune response helps eliminate the pathogen and induce protective immunity, whereas inflammation triggered by sterile injury limits tissue damage and enables repair. In most cases, the same immune cells, receptors and signalling pathways control both types of responses, and the way that the type of response is tailored to its inducer is poorly understood.

My previous work has shown how tissue-resident immune cells, such as macrophages, integrate signals from cytokines (soluble mediators that report on tissue injury) with signals from microbial and tissue-damage sensors to direct a response that is best tailored to a specific pathophysiologic situation.

My research group now investigates a novel class of cytokine-regulated signalling adapters and their role in shaping the immune response to sterile and microbial tissue injury. I also seek to understand what exactly constitutes a macrophage response to sterile injury. The insights emerging from these studies will allow us to design therapies against inflammatory diseases caused by sterile injury without compromising the patient's antimicrobial defences.




The innate immune system activates distinct responses downstream of infectious stimuli and sterile injury.

**Jelena Bezbradica Mirkovic** joined the Kennedy Institute as a KTRR Senior Research Fellow in 2016. She earned her PhD under the tutelage of Professor Sebastian Joyce at Vanderbilt University, USA. She continued her research training as a Damon Runyon Cancer Research Foundation and Howard Hughes Medical Institute Postdoctoral Fellow with Professor Ruslan Medzhitov at Yale University, USA, and with Dr Kate Schroder at The University of Queensland, Australia.


1. Bezbradica JS, Coll RC, Schroder K. 2016. Sterile signals generate weaker and delayed macrophage NLRP3 inflammasome responses relative to microbial signals. *Cell Mol Immunol* doi: 10.1038/cmi.2016.11
2. Bezbradica JS, Rosenstein RK, DeMarco RA, Brodsky I, Medzhitov R. 2014. A role for the ITAM signaling module in specifying cytokine-receptor functions. *Nat Immunol* 15: 333-42
3. Bezbradica JS, Medzhitov R. 2009. Integration of cytokine and heterologous receptor signaling pathways. *Nat Immunol* 10: 333-9
4. Bezbradica JS, Gordy LE, Stanic AK, Dragovic S, Hill T, Hawiger J, Unutmaz D, Van Kaer L, Joyce S. 2006. Granulocyte-macrophage colony-stimulating factor regulates effector differentiation of invariant natural killer T cells during thymic ontogeny. *Immunity* 25: 487-97
5. Bezbradica JS, Hill T, Stanic AK, Van Kaer L, Joyce S. 2005. Commitment toward the natural T (iNKT) cell lineage occurs at the CD4+8+ stage of thymic ontogeny. *Proc Natl Acad Sci U S A* 102: 5114-9

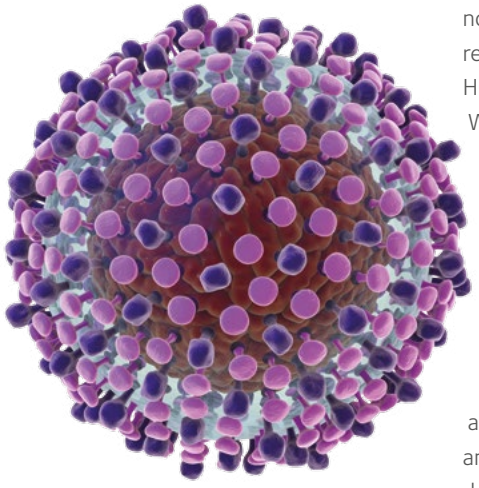
# Viral Infection and Immunity

## Lynn B. Dustin

**Lynn B. Dustin** is Professor of Immunology and Virology at the University of Oxford. She has a PhD in Immunology from Harvard University, USA and has led independent research groups at St. Louis University School of Medicine, USA, from 1996-2000 and at The Rockefeller University, USA, from 2001-2013. In 2013, she moved to Oxford for a joint appointment at the Kennedy Institute and the Peter Medawar Building for Pathogen Research.

> We dissect the relationship between beneficial and pathogenic immune responses to devise new strategies to combat chronic viral infection.

Despite the recent development of potent antiviral drugs, an estimated 130-200 million people worldwide remain persistently infected with hepatitis C virus (HCV), many unaware of their status. We study innate and adaptive immune responses to HCV infection, with the aim of defining mechanisms of defense and pathogenesis.



An artistic model of Hepatitis C virus

Antibody responses to HCV are delayed and inefficient, and patients with chronic HCV infection are at increased risk of the B cell disorders mixed cryoglobulinaemia and B cell non-Hodgkin lymphoma. To understand how HCV - a virus that primarily infects the liver - causes disordered B cell function, we have characterised abnormal B cells in clinical specimens. In mixed cryoglobulinaemia, memory B cells bear a stereotypical IgM antigen receptor, with highly similar IgM in different HCV patients. The IgM acts as a rheumatoid factor and at high concentrations may lead to the immune complex disease observed in mixed cryoglobulinaemia. We have found that these antibodies resemble broadly neutralising antibodies specific for HCV, HIV, influenza, and other human pathogens. Using arrays presenting thousands of self, HCV, and human pathogen antigens, we have now identified an unexpected target recognised by all antibodies cloned from HCV$^+$ mixed cryoglobulinaemia patients. We are now investigating the features that define an effective antiviral antibody response, and how these responses are affected by prior infection with unrelated pathogens.

We also investigate how innate host defenses control HCV and other viruses. HCV is known to antagonise an infected cell's virus recognition and antiviral machinery. However, we have demonstrated that primary liver cells acutely infected with HCV express type III interferons (IFNλ), TNFα, and a number of interferon-stimulated genes. Further work has shown that low amounts of IFNλ and TNFα can synergise to mediate potent antiviral activities. We are now characterizing the mechanisms underlying these synergistic interactions, with recent data suggesting that TNFα prevents viral spread by reducing viral particle production. We also investigate cell-to-cell variation in innate immune signaling, which we believe may underpin viral escape.


1. Dustin LB, Cashman SB, Laidlaw SM. 2014. Immune control and failure in HCV infection--tipping the balance. *J Leukoc Biol* 96: 535-48
2. Laidlaw SM, Dustin LB. 2014. Interferon lambda: opportunities, risks, and uncertainties in the fight against HCV. *Front Immunol* 5: 545
3. Cashman SB, Marsden BD, Dustin LB. 2014. The Humoral Immune Response to HCV: Understanding is Key to Vaccine Development. *Front Immunol* 5: 550
4. Charles ED, Orloff MI, Nishiuchi E, Marukian S, Rice CM, Dustin LB. 2013. Somatic hypermutations confer rheumatoid factor activity in hepatitis C virus-associated mixed cryoglobulinemia. *Arthritis Rheum* 65: 2430-40
5. Marukian S, Andrus L, Sheahan TP, Jones CT, Charles ED, Ploss A, Rice CM, Dustin LB. 2011. Hepatitis C virus induces interferon-lambda and interferon-stimulated genes in primary liver cultures. *Hepatology* 54: 1913-23

# The Immunological Synapse
## Michael Dustin

> We examine the role of the immunological synapse in dictating the balance between tolerance and immunity.

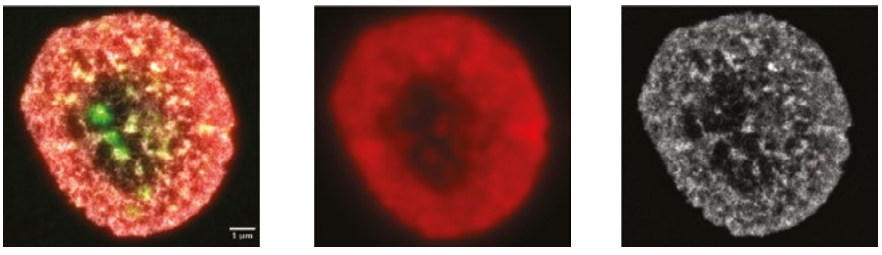
The immunological synapse is a highly conserved scaffold that allows communication between immune cells built around cooperation of antigen and adhesion receptors. We are focused on understanding how the immunological synapse contributes to decision making in the adaptive immune system.

We are developing a high throughput platform to identify molecular codes for immunological tolerance and response. This involves dendritic cell transcriptomics and surface proteomics to identify candidate molecules. These candidates are then generated as recombinant proteins and presented by supported lipid bilayers in a mobile or immobile form. These molecular signals are then isolated as recombinant proteins that are used to decorate supported lipid bilayers to test for functional effects and the structure of the resulting immunological synapses. This platform will also incorporate miniaturisation to reduce cell number requirements, to permit analysis of samples of patients in various disease states including rheumatoid arthritis.

A second project focuses on the function of T cell receptor-enriched extracellular vesicles – referred to as synaptic ectosomes – that are generated at the immunological synapse and transferred to antigen presenting cells. The potential for synaptic ectosomes and related exosomes to mediate T cell help, cytotoxicity and tolerance will be explored using human and mouse models. Alterations in diseases are also being investigated.

We also participate in an international collaboration aimed at understanding cooperation strategy and information processing in and between germinal centres. These are sites where high affinity antibodies are generated through cooperation of T cells and B cells. This project brings together experts in mathematical modelling, intravital microscopy and germinal center reactions and our group will focus on the role of synaptic ectosomes in germinal centre reactions.

The combined goal of these efforts is to work towards a complete understanding of T cell-mediated immune responses, with the ambition of engineering cures for autoimmune and inflammatory diseases.



The left panel shows a T cell (stained for actin cytoskeleton; red) interacting with an antigenic artificial lipid bilayer (green). Imaging with classical total interference microscopy (TIRFM) combined with Stochastic Optical Reconstruction Microscopy (STORM; left panel, grey) improves image resolution achieved with TIRFM alone (middle panel, red).

**Michael Dustin** is Professor of Immunology at the University of Oxford and Director of Research at the Kennedy Institute. He has a B.A in Biology from Boston University and a PhD in Cell and Developmental Biology from Harvard University. He has led research groups at the Department of Pathology at the Washington University School of Medicine and at the Skirball Institute of Biomolecular Medicine at the NYU School of Medicine. Supported by a Principal Research Fellowship from the Wellcome Trust, he moved to the Kennedy Institute in 2013.


1. Schmid EM, Bakalar MH, Choudhuri K, Weichsel J, Ann HS, Geissler PL, Dustin ML, Fletcher DA. 2016 Size-dependent protein segregation at membrane interfaces. Nature Physics. nphys3678.
2. Shaw TN, Stewart-Hutchinson PJ, Strangward P, Dandamudi DB, Coles JA, Villegas-Mendez A, Gallego-Delgado J, van Rooijen N, Zindy E, Rodriguez A, Brewer JM, Couper KN, Dustin ML. 2015. Perivascular Arrest of CD8+ T Cells Is a Signature of Experimental Cerebral Malaria. *PLoS Pathog* 11: e1005210
3. Kumari S, Depoil D, Martinelli R, Judokusumo E, Carmona G, Gertler FB, Kam LC, Carman CV, Burkhardt JK, Irvine DJ, Dustin ML. 2015. Actin foci facilitate activation of the phospholipase C-gamma in primary T lymphocytes via the WASP pathway. *Elife* 4
4. Grakoui A, Bromley SK, Sumen C, Davis MM, Shaw AS, Allen PM, Dustin ML. 2015. Pillars article: The immunological synapse: a molecular machine controlling T cell activation. Science. 1999. 285: 221-227. *J Immunol* 194: 4066-72
5. Choudhuri K, Llodra J, Roth EW, Tsai J, Gordo S, Wucherpfennig KW, Kam LC, Stokes DL, Dustin ML. 2014. Polarized release of T-cell-receptor-enriched microvesicles at the immunological synapse. *Nature* 507: 118-23

# Spatiotemporal Dynamics of T Cell Responses

## Audrey Gérard

**Audrey Gérard** joined the Kennedy Institute in 2016 as a KTRR Senior Research Fellow. She completed her PhD under the supervision of Dr Jacques Nunes and Professor Daniel Olive at the University of the Mediterranean, Marseille, France. She then undertook postdoctoral training at the Netherlands Cancer Institute in Amsterdam with Dr John Collard, and more recently in the laboratory of Professor Matthew Krummel at UCSF, USA.

> We are interested in understanding how the recruitment and differentiation of different CD8$^+$ T cell clones is organised in space and time to achieve the correct balance between tolerance and immunity.

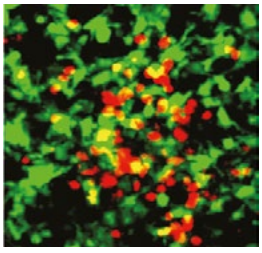
During an immune response, the production of CD8$^+$ T cell subsets by a polyclonal population of naïve cells results from averaging the diverse behaviors of individual clones, leading to a collective response. Although T cell clones with high affinity for their cognate peptide are sufficient to eradicate a given pathogen, low affinity clones are consistently recruited to a response. However, the benefits of generating this clonal diversity are elusive. The overall goal of our work is to understand how T cell clonal diversity elicited during an immune response is regulated and how it contributes to the balance between immunity and tolerance.

The fraction of T cells specific for any antigen is about $10^{-5}$ to $10^{-6}$ and T cells need to strategically survey lymphoid organs to favour encounter with their cognate antigen-presenting cells. We have previously found that T cells display discrete migration patterns allowing for both exploration of a large territory and efficient scanning of potential antigen-presenting cells. These migration patterns are required for eradication of infectious agents such as Listeria. We also showed that once T cells find their cognate antigen and get activated, they communicate with each other, in part through direct contacts. T cells form T-T synapses to privately and selectively share cytokines such as IL-2 and IFNγ, required for their own differentiation and efficient eradication of pathogens.

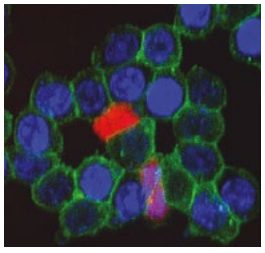
We are now interested in the relationship between migration patterns and the recruitment of diverse T cells into a response. In particular, we investigate how migration patterns regulate the activation of different T cell clones and subsets that have distinct inherent activation requirements. We are also investigating how direct communication between CD8$^+$ T cells shapes the breadth of a T cell response and which signals are involved. To understand the spatiotemporal development of endogenous T cell responses, we are developing imaging techniques based on fluorescent barcoding.

Our data will provide insight into how the immune system works as a whole and may lead to new therapeutic avenues by providing tools to manipulate the balance between tolerance and immunity.

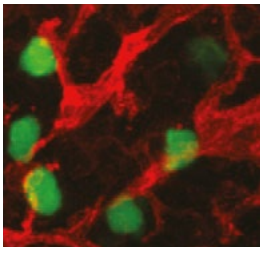

1. Headley MB, Bins A, Nip A, Roberts EW, Looney MR, Gerard A, Krummel MF. 2016. Visualization of immediate immune responses to pioneer metastatic cells in the lung. *Nature* 531: 513-7
2. Krummel MF, Bartumeus F, Gerard A. 2016. T cell migration, search strategies and mechanisms. *Nat Rev Immunol* 16: 193-201
3. Gerard A, Patino-Lopez G, Beemiller P, Nambiar R, Ben-Aissa K, Liu Y, Totah FJ, Tyska MJ, Shaw S, Krummel MF. 2014. Detection of rare antigen-presenting cells through T cell-intrinsic meandering motility, mediated by Myo1g. *Cell* 158: 492-505
4. Gerard A, Khan O, Beemiller P, Oswald E, Hu J, Matloubian M, Krummel MF. 2013. Secondary T cell-T cell synaptic interactions drive the differentiation of protective CD8+ T cells. *Nat Immunol* 14: 356-63
5. Gerard A, Beemiller P, Friedman RS, Jacobelli J, Krummel MF. 2013. Evolving immune circuits are generated by flexible, motile, and sequential immunological synapses. *Immunol Rev* 251: 80-96

T lymphocytes (red) interacting with dendritic cells (green) in lymph nodes after vaccination.



T lymphocytes (blue and green) clustering around a dendritic cell (red).



T lymphocytes (green) migrating in lymph nodes along conduits (in red).

# Haematopoiesis and Chronic Inflammation

Thibault Griseri

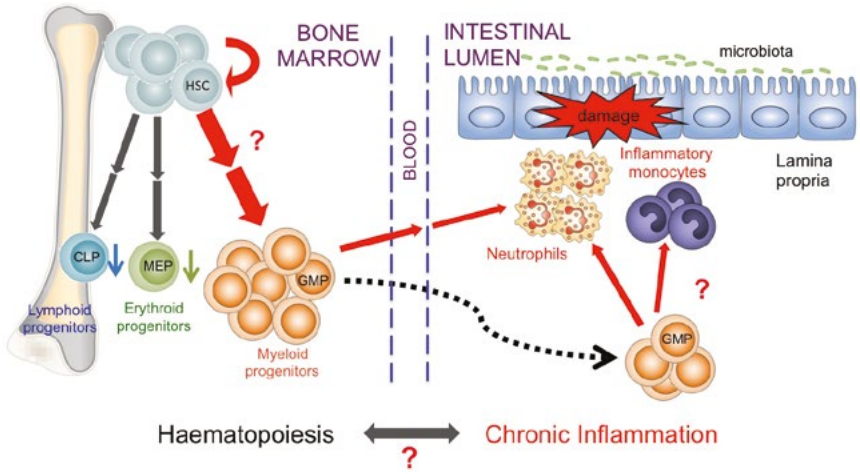
> We investigate abnormal haematopoiesis in the bone marrow as a pathogenic mechanism in chronic inflammatory disorders.

Substantial progress has been made in identifying the subsets of inflammatory leukocytes that cause tissue damage during autoimmune and chronic inflammatory diseases. However, we are still a long way from understanding the complex inflammatory network that leads to self-perpetuation and chronicity of disease.

My research group's aim is to understand the regulation of haematopoietic stem and progenitor cells (HSPC) during chronic inflammation, and to define how dysregulated haematopoeisis contributes to inflammatory disease. We have shown that highly proliferative granulocyte-monocyte progenitors accumulate in the bone marrow and periphery in models of colitis. Furthermore, in IL-23-driven colitis, eosinophil progenitors increase in the bone marrow through a GM-CSF dependent mechanism, and mature eosinophils contribute to colitis through release of inflammatory cytokines and tissue toxic cationic proteins.

We are now exploring how the HSPC compartment adapts to ongoing inflammation and participates in the pathophysiological network in inflammatory arthritis. We have observed that dysregulated haematoepoiesis correlates with severe accumulation of neutrophils in the inflamed joints and intestine in a model of spondyloarthritis. Intestinal inflammation is frequently observed in human spondyloarthritis, and future studies will investigate crosstalk between inflammatory pathways at these two sites and a possible role for the microbiota in regulating myelopoiesis during arthritis. We are also investigating whether the regulatory pathways that normally regulate balanced haematopoiesis are deficient in inflammatory arthritis.

The long-term goal of our studies is to identify targetable inflammatory pathways that promote dysregulated HSPC activity during arthritis.




During chronic intestinal inflammation haematopoietic stem cells (HSC) are hyperproliferative and their differentiation is skewed toward granulocyte-monocyte progenitors (GMP), which also accumulate at extramedullary sites (i.e. the intestine and spleen)

**Thibault Griseri** is a Research Lecturer at the University of Oxford. He gained his PhD working with Dr Agnès Lehuen at the Hôpital Saint Vincent de Paul, France. In 2007, he moved to Professor Fiona Powrie's laboratory at the University of Oxford as a postdoctoral researcher. He joined the Kennedy Institute in 2013 for a second postdoc toral position and was awarded an ARUK Career Development Fellowship in 2014.


1. Griseri T, Arnold IC, Pearson C, Krausgruber T, Schiering C, Franchini F, Schulthess J, McKenzie BS, Crocker PR, Powrie F. 2015. Granulocyte Macrophage Colony-Stimulating Factor-Activated Eosinophils Promote Interleukin-23 Driven Chronic Colitis. *Immunity* 43: 187-99
2. Schiering C, Krausgruber T, Chomka A, Frohlich A, Adelmann K, Wohlfert EA, Pott J, Griseri T, Bollrath J, Hegazy AN, Harrison OJ, Owens BM, Lohning M, Belkaid Y, Fallon PG, Powrie F. 2014. The alarmin IL-33 promotes regulatory T-cell function in the intestine. *Nature* 513: 564-8
3. Griseri T, McKenzie BS, Schiering C, Powrie F. 2012. Dysregulated hematopoietic stem and progenitor cell activity promotes interleukin-23-driven chronic intestinal inflammation. *Immunity* 37: 1116-29
4. Griseri T, Asquith M, Thompson C, Powrie F. 2010. OX40 is required for regulatory T cell-mediated control of colitis. *J Exp Med* 207: 699-709
5. Diana J, Griseri T, Lagaye S, Beaudoin L, Autrusseau E, Gautron AS, Tomkiewicz C, Herbelin A, Barouki R, von Herrath M, Dalod M, Lehuen A. 2009. NKT cell-plasmacytoid dendritic cell cooperation via OX40 controls viral infection in a tissue-specific manner. *Immunity* 30: 289-99

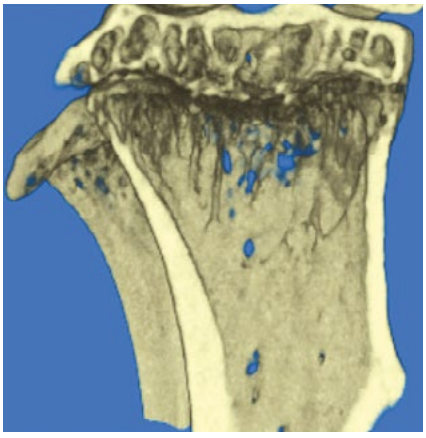
# Osteoimmunology
## Nicole Horwood

**Nicole Horwood** is an Arthritis Research UK Senior Research Fellow and an Associate Professor at the University of Oxford. She completed her PhD in 1999 at the University of Melbourne, Australia. She was subsequently awarded the Victoria Premiers Commendation for Medical Research in 2000, as well as a Howard Florey fellowship from the Royal Society for postdoctoral studies at the Kennedy Institute with Professor Sir Marc Feldmann and Professor Brian Foxwell. She was appointed to a lectureship in 2004 and moved with the Institute to the University of Oxford in 2013.

> We study the relationship between immune activation and bone turnover, with a focus on inflammatory arthritis and bone marrow cancer.

Current work in my laboratory focuses on understanding how inflammation drives aberrant bone formation in ankylosing spondylitis. In rheumatoid arthritis, inflammation leads to joint destruction, whereas in ankylosing spondylitis patients, enthesitis (inflammation at the site where tendons and ligaments meet bone) results in excessive bone formation in the vertebrae of the axial skeleton. This entheseal bone formation is a cause of disability and remains an unsolved problem, since inflammation generally has a catabolic effect on bone.

We are characterising novel mouse strains to understand inflammation-driven bone formation. We have also shown that oncostatin M produced by monocytes and macrophages is capable of driving new bone formation in vitro and in vivo, and we are now investigating the role of other cytokines and cell types in this process.



microCt image showing osteolytic lesions in the tibia due to multiple myeloma

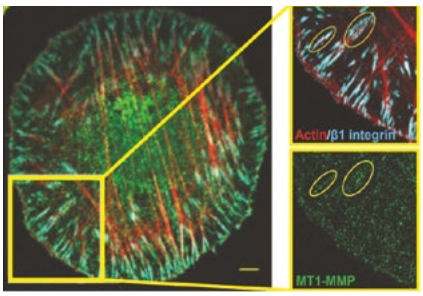
My group is also interested in understanding bone defects frequently observed in multiple myeloma, a malignancy arising from plasma cells. Multiple myeloma is associated with osteolytic bone lesions and skeletal complications in over 80% of patients due to inhibition of bone forming osteoblast activity and aberrant activation of bone destroying osteoclasts. Our work seeks to uncover ways of targeting both plasma cell expansion, as well as osteoclast activation and hence the associated bone lesions. Patients with multiple myeloma have an altered glycosphingolipid (GSL) profile, and we have shown that the inhibitor of GSL, Miglustat, leads to a reduction in both tumour burden and bone destruction in mouse models. Increased age and obesity are risk factors for multiple myeloma development, and we are now studying the effect of a new range of GSL inhibitors on multiple myeloma progression in old and young mice fed on different diets. These studies should provide insight into approaches to improve efficiency of GSL inhibitors prior to clinical translation.


1. Ersek A, Xu K, Antonopoulos A, Butters TD, Santo AE, Vattakuzhi Y, Williams LM, Goudevenou K, Danks L, Freidin A, Spanoudakis E, Parry S, Papaioannou M, Hatjiharissi E, Chaidos A, Alonzi DS, Twigg G, Hu M, Dwek RA, Haslam SM, Roberts I, Dell A, Rahemtulla A, Horwood NJ, Karadimitris A. 2015. Glycosphingolipid synthesis inhibition limits osteoclast activation and myeloma bone disease. *J Clin Invest* 125: 2279-92.
2. Espirito Santo AI, Ersek A, Freidin A, Feldmann M, Stoop AA, Horwood NJ. 2015. Selective inhibition of TNFR1 reduces osteoclast numbers and is differentiated from anti-TNF in a LPS-driven model of inflammatory bone loss. *Biochem Biophys Res Commun* 464: 1145-50.
3. Chan JK, Glass GE, Ersek A, Freidin A, Williams GA, Gowers K, Espirito Santo AI, Jeffery R, Otto WR, Poulsom R, Feldmann M, Rankin SM, Horwood NJ, Nanchahal J. 2015. Low-dose TNF augments fracture healing in normal and osteoporotic bone by up-regulating the innate immune response. *EMBO Mol Med* 7: 547-61.
4. Nicolaidou V, Wong MM, Redpath AN, Ersek A, Baban DF, Williams LM, Cope AP, Horwood NJ. 2012. Monocytes induce STAT3 activation in human mesenchymal stem cells to promote osteoblast formation. *PLoS One* 7: e39871.
5. Vattakuzhi Y, Abraham SM, Freidin A, Clark AR, Horwood NJ. 2012. Dual-specificity phosphatase 1-null mice exhibit spontaneous osteolytic disease and enhanced inflammatory osteolysis in experimental arthritis. *Arthritis Rheum* 64: 2201-10.

# Cell Migration
## Yoshifumi Itoh

> We examine the mechanisms behind uncontrolled cellular migration to develop new treatments that prevent progression of diseases such as inflammatory arthritis and cancer.

Cell migration is an essential process for the development and maintenance of multicellular organisms. It contributes to many aspects of normal physiology, including embryo development, wound healing, tissue repair and immunity. However, uncontrolled cell migration promotes progression of diseases such as cancer, inflammatory arthritis and degenerative arthritis. Our aim is to understand key mechanisms that control pathological cellular migration in the hope of developing new treatments that prevent disease progression.



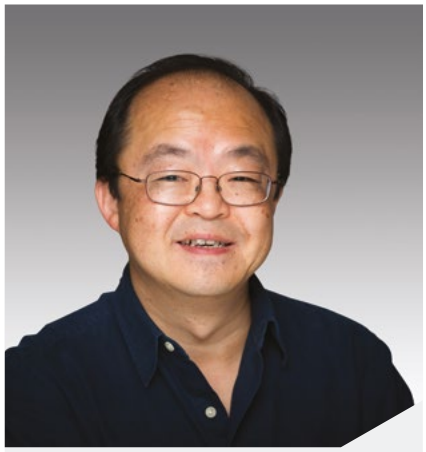

STED microscopy shows metalloproteinase MT1-MMP localises at focal adhesion sites (circled yellow) in human fibrosarcoma cells.

In order for cells to migrate through tissues, they must first recognise the surrounding extracellular matrix (ECM). We have been investigating the role of collagen-binding receptor tyrosine kinase DDR1 in sensing collagen during cellular migration. We have found that the ectodomain of DDR1 is shed by one of the ADAM metalloproteinases, ADAM10, and that this shedding event is crucial for regulating the half-life of DDR1-mediated collagen signalling and epithelial cell migration.

We are now investigating the role of both DDR1 and DDR2 in microenviroment recognition and crosstalk with other cell migration pathways.

ECM degradation is a second step in cell migration and the membrane-bound matrix metalloproteinases MT1-MMP plays a crucial role in this process. We have identified a region of MT1-MMP referred to as the MT-loop that ensures proper localisation of MT1-MMP at the plasma membrane, necessary for cellular invasion. Our work has also revealed how epithelial cells change MT1-MMP localisation to regulate ECM degradation. We continue to investigate the mechanisms that control MT1-MMP localisation at the leading edge of invading cells including focal adhesion site. The long-term goal is to develop approaches to specifically interfere with MT1-MMP-dependent cellular migration. The relevance of this approach is demonstrated by our recent work in a model of rheumatoid arthritis showing that specific inhibition of MT1-MMP activity prevents cartilage degradation and synergistically enhances the effects of anti-TNF. We are now investigating mechanisms of synergy.

Finally, we are also developing a non-invasive tool to monitor cartilage degradation for osteoarthritis. Our studies will provide insight into pathogenic mechanisms in cancer and inflammatory arthritis, leading to novel diagnostic tools and therapeutic strategies.



**Yoshifumi Itoh** is an Associate Professor at the University of Oxford. He received his PhD from Tokyo University of Pharmacy and Life Sciences, Japan in 1996. He was Assistant Professor at the Institute of Medical Sciences, University of Tokyo. He then moved to the Kennedy Institute in 2001 as a Group Leader and relocated with the Institute to Oxford in 2013.


1. Kaneko K, Williams RO, Dransfield DT, Nixon AE, Sandison A, Itoh Y. 2016. Selective Inhibition of Membrane Type 1 Matrix Metalloproteinase Abrogates Progression of Experimental Inflammatory Arthritis: Synergy With Tumor Necrosis Factor Blockade. *Arthritis Rheumatol* 68: 521-31
2. Shitomi Y, Thogersen IB, Ito N, Leitinger B, Enghild JJ, Itoh Y. 2015. ADAM10 controls collagen signaling and cell migration on collagen by shedding the ectodomain of discoidin domain receptor 1 (DDR1). *Mol Biol Cell* 26: 659-73
3. Weaver SA, Wolters B, Ito N, Woskowicz AM, Kaneko K, Shitomi Y, Seiki M, Itoh Y. 2014. Basal localization of MT1-MMP is essential for epithelial cell morphogenesis in 3D collagen matrix. *J Cell Sci* 127: 1203-13
4. Woskowicz AM, Weaver SA, Shitomi Y, Ito N, Itoh Y. 2013. MT-LOOP-dependent localization of membrane type I matrix metalloproteinase (MT1-MMP) to the cell adhesion complexes promotes cancer cell invasion. *J Biol Chem* 288: 35126-37
5. Manning HB, Nickdel MB, Yamamoto K, Lagarto JL, Kelly DJ, Talbot CB, Kennedy G, Dudhia J, Lever J, Dunsby C, French P, Itoh Y. 2013. Detection of cartilage matrix degradation by autofluorescence lifetime. *Matrix Biol* 32: 32-8

# Statistical Genetics of Immune Variation

## Luke Jostins

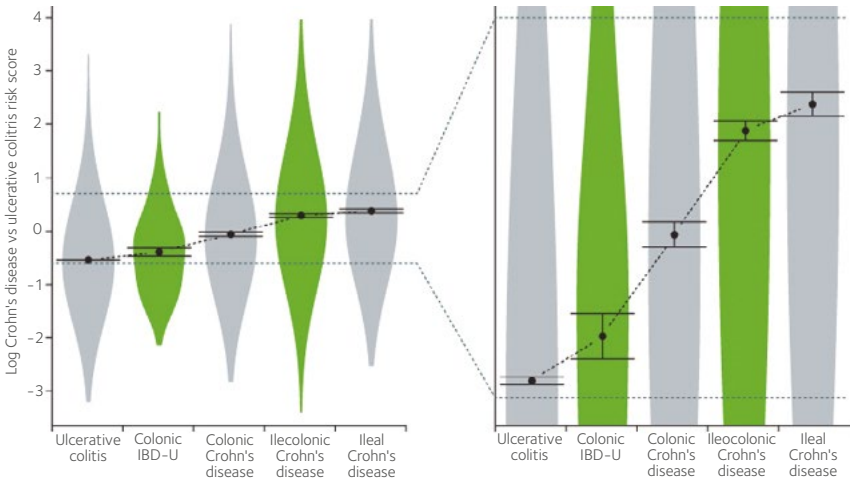
**Luke Jostins** is a KTRR Career Development Fellow and a Christ Church Junior Research Fellow at the University of Oxford. Supervised by Dr Jeff Barrett, he received a PhD in statistical genetics from the University of Cambridge and the Wellcome Trust Sanger Institute in 2012. He received a Sir Henry Wellcome Fellowship award to work at the Wellcome Trust Centre for Human Genetics at the University of Oxford, where he worked with Professor Gil McVean from 2013 to 2016. He will be joining the Kennedy Institute in 2017.

> We seek to identify multi-gene signatures of shared immune variation to better understand disease genetics and health outcomes.

My research to date has largely focused on identifying genetic associations with diagnosis or disease presentation in inflammatory bowel disease (IBD), and developing statistical techniques to understand the function of genetic risk variants. As a field, statistical genetics has been very successful at finding risk variants for a host of complex diseases of the immune system. These risk variants tend to be shared across multiple immune diseases, and many of them are in genes involved in relevant immune pathways or expressed in relevant immune cells (such as monocytes and $CD4^+$ T cells for IBD variants). However, we have had less success in identifying the impact of genetic risk pathways on the function of the human immune system, and cross-disease analysis implies that these risk variants fall into a great diversity of immune pathways. To translate disease genetics into real diagnostic, prognostic or treatment solutions we need to understand these pathways from genetic variation through healthy immune variation to disease risk. It is only through close collaborations between statistical geneticists, immunologists and molecular biologists that we will start to untangle these pathways.

My plan of research at the Kennedy Institute has three interrelated strands. The first is the analysis of large-scale human medical cohort data using statistical and computational techniques that are specifically designed to identify multi-gene signatures of shared underlying immune variation that drive a variety of different health outcomes. The second is to collaborate with other researchers to generate and analyse human immune variation data (including host immune function and exposure to both commensal and pathogenic organisms) in order to tie genetic risk of disease to variation in specific measurable immune phenotypes. The final strand is to collaborate with immunologists, cell biologists and clinical researchers to develop new ways of measuring the function of the human immune system in order to profile the specific pathways that confer genetic risk of chronic disease.

Violin plot showing the genetic substructure of inflammatory bowel disease location.





1. Jostins L, McVean G. 2016. Trinculo: Bayesian and frequentist multinomial logistic regression for genome-wide association studies of multi-category phenotypes. *Bioinformatics* 32: 1898-900
2. Moutsianas L, Jostins L, Beecham AH, Dilthey AT, Xifara DK, Ban M, Shah TS, Patsopoulos NA, Alfredsson L, Anderson CA, Attfield KE, Baranzini SE, Barrett J, Binder TM, Booth D, Buck D, Celius EG, Cotsapas C, D'Alfonso S, Dendrou CA, Donnelly P, Dubois B, Fontaine B, Lar Fugger L, Goris A, Gourraud PA, Graetz C, Hemmer B, Hillert J, International IBDGC, Kockum I, Leslie S, Lill CM, Martinelli-Boneschi F, Oksenberg JR, Olsson T, Oturai A, Saarela J, Sondergaard HB, Spurkland A, Taylor B, Winkelmann J, Zipp F, Haines JL, Pericak-Vance MA, Spencer CC, Stewart G, Hafler DA, Ivinson AJ, Harbo HF, Hauser SL, De Jager PL, Compston A, McCauley JL, Sawcer S, McVean G, International Multiple Sclerosis Genetics C. 2015. Class II HLA interactions modulate genetic risk for multiple sclerosis. *Nat Genet* 47: 1107-13
3. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, et al. 2012. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491: 119-24

# Tissue and Tumour Microenvironments

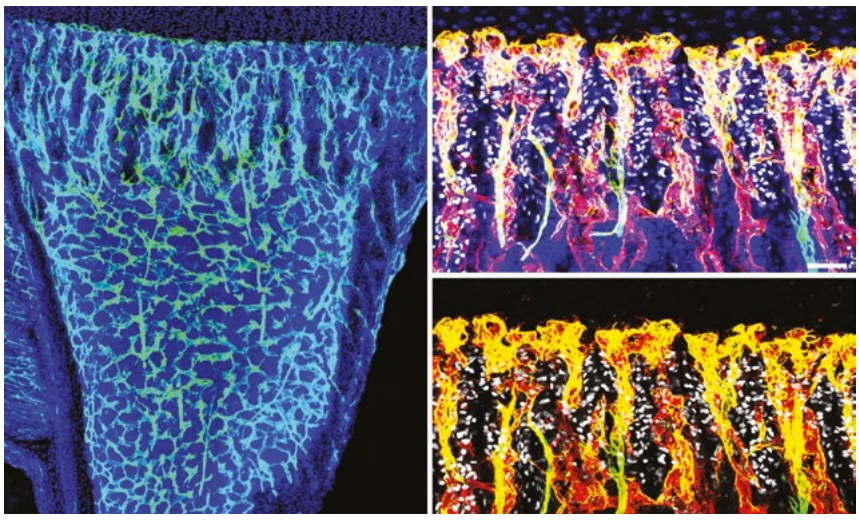
## Anjali Kusumbe

> We are interested in examining the contributions of endothelial-derived signals in defining tissue microenvironments and unravelling the changes occurring in vascular microenvironments during tumour growth.

Blood vessels play a pivotal role during organ development and regeneration, while pathological conditions are often associated with dysregulation of the vasculature. The vascular network extends into every organ and is implanted in a specific manner to ensure optimal delivery of oxygen and nutrients, together with instructive, paracrine and angiocrine signals. Therefore, endothelial cells play a key role in shaping and defining tissue and tumour microenvironments and present as a target for modulating tissue biology. However, to fully utilise the potential of endothelial cells in therapy, a detailed understanding of their role in tissue development, repair, regeneration and disease is required.

My recent work has identified a structurally and functionally distinct blood vessel subtype in bone that generates an active niche environment for bone forming osteoprogenitor cells. These blood vessels, referred to as 'type H' blood vessels due to high expression of specific markers, are composed of highly proliferative endothelial cells that gradually decline in numbers with age. Reactivation of type H endothelium in aged mice increases osteoprogenitor numbers and improves bone mass. In separate studies we found that complex niches involving distinct blood vessels and perivascular cells regulate hematopoietic stem cell maintenance, ageing and trafficking.

My group will further investigate the role of endothelial and perivascular cells during bone development, repair, and regeneration, as well as during skeletal metastasis and osteoarthritis. We will use bone imaging and mouse genetics to elucidate the functional role of vascular niches in bone. Our work will provide the first conceptual framework for the normal versus deregulated function of vascular niches in bone. It may also break new ground by analysing the role and therapeutic potential of vascular niche microenvironments in osteoarthritis and skeletal metastasis and in identifying novel strategies for the prevention and/or treatment of these bone pathologies.



Specialised blood vessels (green/yellow) form nurturing niches for osteoprogenitor cells (white) in bone.

**Anjali Kusumbe** is a KTRR Senior Research Fellow. She gained her PhD from the National Centre for Cell Science, India and then moved to the Max Planck Institute for Molecular Biomedicine, Germany for postdoctoral work with Professor Ralf Adams where she discovered a novel blood vessel subtype in bone. She joined the Kennedy Institute in 2016.


1. Kusumbe AP, Ramasamy SK, Itkin T, Mae MA, Langen UH, Betsholtz C, Lapidot T, Adams RH. 2016. Age-dependent modulation of vascular niches for haematopoietic stem cells. *Nature* 532: 380-4
2. Itkin T, Gur-Cohen S, Spencer JA, Schajnovitz A, Ramasamy SK, Kusumbe AP, Ledergor G, Jung Y, Milo I, Poulos MG, Kalinkovich A, Ludin A, Kollet O, Shakhar G, Butler JM, Rafii S, Adams RH, Scadden DT, Lin CP, Lapidot T. 2016. Distinct bone marrow blood vessels differentially regulate haematopoiesis. *Nature* 532: 323-8
3. Kusumbe AP, Ramasamy SK, Starsichova A, Adams RH. 2015. Sample preparation for high-resolution 3D confocal imaging of mouse skeletal tissue. *Nat Protoc* 10: 1904-14
4. Ramasamy SK, Kusumbe AP, Wang L, Adams RH. 2014. Endothelial Notch activity promotes angiogenesis and osteogenesis in bone. *Nature* 507: 376-80
5. Kusumbe AP, Ramasamy SK, Adams RH. 2014. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. *Nature* 507: 323-8

# Molecular Imaging
## Ngee Han Lim

**Ngee Han Lim** is an Arthritis Research UK/KTRR Research Fellow at the University of Oxford. He studied biochemistry at the University of Oxford and gained his PhD in 2008 working with Professor Hideaki Nagase at the Kennedy Institute, Imperial College London. In postdoctoral studies he continued to work with Professor Nagase and later with Dr. Ahuva Nissim at the William Harvey Research Institute Queen Mary University of London. He became a Group Leader at the Kennedy Institute in 2014.

> We aim to develop imaging agents for use as biomarkers for the diagnosis and quantitative, non-subjective assessment of OA in the clinical setting.

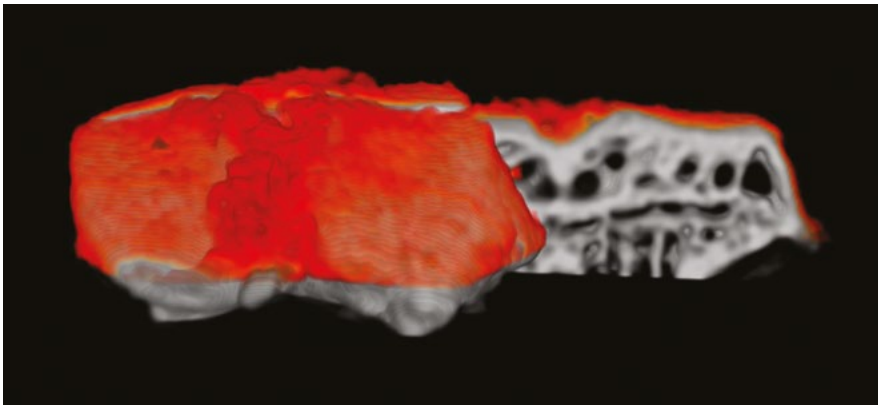
Patients with osteoarthritis (OA) and their physicians have no measure of the level of severity of the disease affecting their joint. This is because global serum and urinary biomarkers for OA are not robust and clinical imaging is limited to X-rays that detect late stage changes in joint space width. In the UK, 160,000 joint replacements are carried out yearly and this number will increase with the ageing population. Clinical trials examining disease-modifying OA drugs (DMOADs) accept both X-rays and patient reported outcomes as measures of efficacy. However, these outcomes are fundamentally flawed. By the time the decrease in joint space width is reliably measured, most cartilage in the joint has been lost, making it unlikely that any DMOAD would show a positive effect. Patient reported outcomes are subjective and weighted heavily on pain and quality of life as a poor surrogate marker for joint integrity. We aim to develop novel imaging agents for use as biomarkers for the diagnosis and quantitative, non-subjective assessment of OA in the clinical setting.

The first tissue to be damaged in OA is the articular cartilage. This tissue is composed primarily of type II collagen fibres, which provide tensile strength, and the highly negatively charged proteoglycan, aggrecan, which draws water into the tissue to provide compressive strength. Imaging agents that bind to these structural molecules would inform on the integrity of the cartilage.

We have developed di-iodotyrosinated peptide imaging of cartilage (DIPIC) that uses the natural modification of the amino acid tyrosine to label a type II collagen binding peptide with iodines to image and quantitatively assess the status of cartilage by X-ray based Computed Tomography (CT). We have successfully carried out DIPIC on tissue samples and we are in the process of optimising this method for use in vivo. A patent covering this technology has been filed through Oxford University Innovations and we are working to translate this method to the clinic.

We are also developing probes that are activated by aggrecanases (ADAMTS-4 and ADAMTS-5) or collagenases (MMP-1, MMP-13). We are testing these agents as tools to monitor molecular processes that lead to OA.

DIPIC imaging of a tibia within a knee joint showing cartilage (orange) and bone (white).




1. Hu H-Y., Lim N-H., Juretschke H-P., Ding-Pfennigdorff D., Florian P., Kohlmann M., Kandira A., von Kries JP., Saas J., Rudolphi KA., Wendt KU., Nagase H., Plettenburg O., Nazare M., Schultz C. 2015. In vivo imaging of osteoarthritic hypertrophic lesions. *Chemical Science* 6: 626-6261
2. Lim NH, Meinjohanns E, Meldal M, Bou-Gharios G, Nagase H. 2014. In vivo imaging of MMP-13 activity in the murine destabilised medial meniscus surgical model of osteoarthritis. *Osteoarthritis Cartilage* 22: 862-8
3. Lim NH, Meinjohanns E, Bou-Gharios G, Gompels LL, Nuti E, Rossello A, Devel L, Dive V, Meldal M, Nagase H. 2014. In vivo imaging of matrix metalloproteinase 12 and matrix metalloproteinase 13 activities in the mouse model of collagen-induced arthritis. *Arthritis Rheumatol* 66: 589-98

# Matrix Immunology
## Kim Midwood

> Our group investigates how the extracellular matrix – the component of tissue that lies immediately outside and between cells – contributes to inflammation.

Research in my group focuses on understanding how the cellular environment impacts cell behaviour, particularly how extracellular matrix molecules induced in response to tissue damage and infection help to orchestrate a successful immune response. We are investigating how these matrix molecules create a pro-inflammatory niche that enables cells to proliferate and thrive during inflammation and inflammatory disease, and how this information can be translated into new therapeutic strategies.

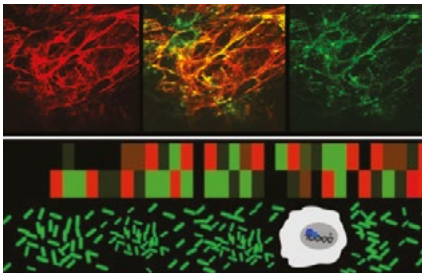
We have shown that the matrix molecule tenascin-C, which is up-regulated at sites of tissue injury, drives inflammation via activation of toll-like receptor 4 (TLR4). We found that persistent expression of tenascin-C is a key contributor to chronic inflammation in models of rheumatoid arthritis (RA). We also observed high amounts of circulating tenascin-C in RA patients, particularly in those with erosive disease, and found serum antibodies against modified forms of tenascin-C as a biomarker for individuals that will go on to develop RA.

Combining structural and biochemical approaches with single molecule imaging, we are now investigating how endogenous inflammatory stimuli such as tenascin-C activate pattern recognition receptors, and how this mode of action differs from activation of the same receptors by pathogenic stimuli. Insight into how cells detect different types of threat and direct specific responses to combat distinct dangers may allow the development of inhibitors that can block chronic sterile inflammation whilst leaving host defence intact.

We aim to use technologies such as single cell transcriptomics, high sensitivity proteomics and mass cytometry to reveal precisely how the microenvironment changes during inflammation, from the transcriptional to the post-translational level. In addition we will dissect the functional implications of these changes on cell behaviour.

We are also working with pharmaceutical partners, including our own spin out company, Nascient, to develop: 1) tenascin-C antagonists and test their efficacy in reducing inflammation in RA; and 2) assays that detect different forms of tenascin-C and anti-tenascin-C autoantibodies and to assess if these are useful diagnostic or prognostic tools for RA.

Finally, we are investigating whether aberrant matrix synthesis impacts inflammation in other diseases including asthma, fibrosis, diseases of the gut and tumours.



The extracellular matrix is a complex, 3D, network of secreted molecules that lies around and between the cells in every tissue of our bodies. Cells respond to signals from the matrix by modifying their behaviour to cope with changing conditions in the tissue. The Midwood lab studies global changes in the cellular microenvironment that occur during tissue injury and infection, as well as dissecting at the molecular level the mechanisms by which these changes drive inflammation.

**Kim Midwood** is Professor of Matrix Biology at the University of Oxford. She completed her PhD at Edinburgh University in 1999 and then moved to the laboratory of Professor Jean Schwarzbauer at Princeton University for postdoctoral work. She became a Group Leader at the Kennedy Institute in 2004.


1. Schwenzer A, Jiang X, Mikuls TR, Payne JB, Sayles HR, Quirke AM, Kessler BM, Fischer R, Venables PJ, Lundberg K, Midwood KS. 2016. Identification of an immunodominant peptide from citrullinated tenascin-C as a major target for autoantibodies in rheumatoid arthritis. *Ann Rheum Dis* 75: 1876-83
2. Piccinini AM, Zuliani-Alvarez L, Lim JM, Midwood KS. 2016. Distinct microenvironmental cues stimulate divergent TLR4-mediated signaling pathways in macrophages. *Sci Signal* 9: ra86
3. Midwood K. 2013. Startups on the menu. *Nat Biotechnol* 31: 490
4. Piccinini AM, Midwood KS. 2012. Endogenous control of immunity against infection: tenascin-C regulates TLR4-mediated inflammation via microRNA-155. *Cell Rep* 2: 914-26
5. Midwood K, Sacre S, Piccinini AM, Inglis J, Trebaul A, Chan E, Drexler S, Sofat N, Kashiwagi M, Orend G, Brennan F, Foxwell B. 2009. Tenascin-C is an endogenous activator of Toll-like receptor 4 that is essential for maintaining inflammation in arthritic joint disease. *Nat Med* 15: 774-80

# Cardiovascular Inflammation

## Claudia Monaco

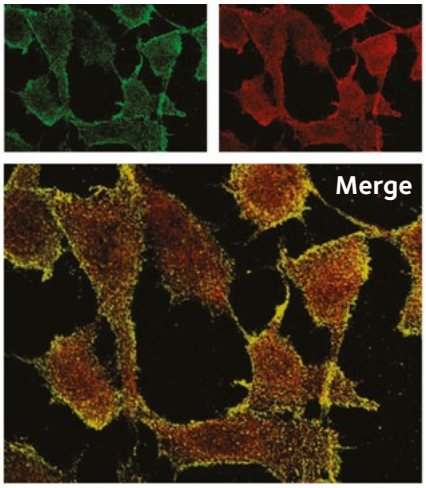
**Claudia Monaco** is Professor of Cardiovascular Inflammation at the University of Oxford and an Honorary Consultant Cardiologist at the University of Oxford NHS Trust. She trained as a Cardiologist (1998) and gained her PhD (2001) with Professor Attilio Maseri at the Catholic University of Rome, Italy. During her PhD, she worked with Professor Sir Marc Feldmann at the Kennedy Institute, Imperial College London. She became a Group Leader at the Kennedy Institute in 2003.

> We dissect how pattern recognition receptors regulate myeloid and stromal cells in the vasculature in health and disease.

Cardiovascular disease is associated with chronic inflammation of vascular tissues, which contributes to disease pathogenesis. Pattern recognition receptors (PRR) such as toll-like receptors (TLR), NOD-like receptors and C-type lectins are microbial and tissue damage sensors that detect microenvironmental cues and initiate downstream inflammatory responses. The precise role of PRR signalling in the vasculature and the therapeutic potential of interfering with, or exploiting, PRR signalling in cardiovascular disease is mostly unknown.

My group has established innovative methods for the isolation, culture and targeting of cells isolated from human atheroma lesions. Using this system combined with in vivo models we have shown that pattern recognition by TLRs can elicit either protective or detrimental effects in atherosclerosis, depending on the sensing pattern (extracellular versus endosomal).

TLR2 and TLR3 signalling has differential effects on the development of vascular disease depending upon whether these receptors are expressed on myeloid versus non-myeloid cells. My laboratory is now characterising myeloid and stromal cell populations in the vasculature, including responses to PRR stimulation. Recent advances in immune-monitoring, including multi-parameter flow and mass cytometry and single cell genomics, are being applied to define the cellular and molecular pathogenesis of atherosclerosis and other immunometabolic diseases. In particular, use of mass cytometry on dissociated murine and human tissues allows us to map the specific phenotype of mononuclear phagocytes, stromo-vascular cells and other inflammatory cells within arterial tissues in atherosclerosis. Moreover, we are studying the consequences of cell-specific PRR-mediated signalling in resident and inflammatory cell types using our well-established models of atherosclerosis, arterial injury and plaque rupture. These studies will provide insight into the tissue changes that accompany chronic inflammation and how these changes contribute to pathogenesis of immunometabolic diseases.




Confocal microscopy of epithelial cells labeled for TLR2 (green) and an endosomal marker (red).


1. Strom AC, Cross AJ, Cole JE, Blair PA, Leib C, Goddard ME, Rosser EC, Park I, Hultgardh Nilsson A, Nilsson J, Mauri C, Monaco C. 2015. B regulatory cells are increased in hypercholesterolaemic mice and protect from lesion development via IL-10. *Thromb Haemost* 114: 835-47
2. Cole JE, Astola N, Cribbs AP, Goddard ME, Park I, Green P, Davies AH, Williams RO, Feldmann M, Monaco C. 2015. Indoleamine 2,3-dioxygenase-1 is protective in atherosclerosis and its metabolites provide new opportunities for drug development. *Proc Natl Acad Sci U S A* 112: 13033-8
3. Cole JE, Navin TJ, Cross AJ, Goddard ME, Alexopoulou L, Mitra AT, Davies AH, Flavell RA, Feldmann M, Monaco C. 2011. Unexpected protective role for Toll-like receptor 3 in the arterial wall. *Proc Natl Acad Sci U S A* 108: 2372-7
4. Monaco C, Gregan SM, Navin TJ, Foxwell BM, Davies AH, Feldmann M. 2009. Toll-like receptor-2 mediates inflammation and matrix degradation in human atherosclerosis. *Circulation* 120: 2462-9
5. Monaco C, Andreakos E, Kiriakidis S, Mauri C, Bicknell C, Foxwell B, Cheshire N, Paleolog E, Feldmann M. 2004. Canonical pathway of nuclear factor kappa B activation selectively regulates proinflammatory and prothrombotic responses in human atherosclerosis. *Proc Natl Acad Sci U S A* 101: 5634-9

# Cartilage Biology and Repair
## Chris Murphy

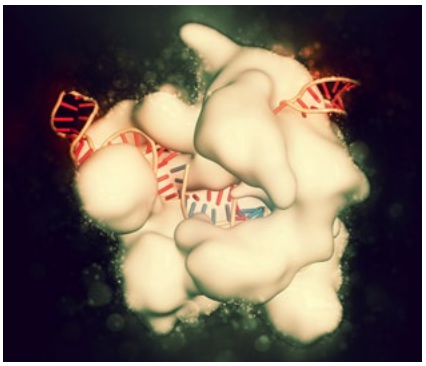
> My group specialises in understanding the transcriptional and post-transcriptional regulation of cartilage matrix turnover.

Cartilage is a connective tissue that lines bones in joints to provide support and allow flexibility of movement. My group addresses mechanisms of cartilage matrix turnover and repair with the aim of guiding development of therapeutics to induce repair of injured or diseased cartilage in the joints.

Cartilage is avascular and my early work showed that hypoxia drives cartilage-specific activities in the tissue. In particular, we discovered that cartilage master regulator SOX9 is induced by hypoxia and that hypoxia plays both a pro-anabolic and a chrondroprotective role in healthy human cartilage. We are now investigating whether these pathways are altered in the diseased state. Mouse cartilage and human cartilage respond differently to hypoxia and we therefore use human osteoarthritic tissue in our studies. Identifying key mediators in the hypoxia pathway in diseased tissue will pave the way for future clinically-relevant studies.

We have also identified several microRNAs that regulate SOX9 expression in cartilage. The process of developing therapies against microRNA-mediated pathways is complicated because a single miRNA can (and frequently does) directly target multiple (10-100s) genes. Thus for both clinical efficacy and safety reasons, it is crucial to identify and selectively interfere with only the relevant target sites to avoid potentially deleterious effects. We firmly believe that individual miRNA target sites, so-called miRNA response elements (MREs), and not the miRNAs themselves, need to be targeted for successful clinical application. To this end we are developing CRISPR-mediated site-specific genome editing strategies for assessment of MRE activity in human cells, crucially without perturbing endogenous levels of miRNAs. The overall goal is to target MREs that influence cartilage matrix turnover in the joint.

Induced pluripotent stem cells (iPSCs) could provide a much-needed source of cells for tissue engineering approaches to repair and regenerate cartilage. We also aim to enhance the chondrogenic differentiation capacity of human iPSCs through disruption of specific miRNA-target interactions using a genome editing approach.



CRISPR-CAS9 gene editing complex. The Cas9 nuclease protein uses a guide RNA sequence to cut DNA at a complementary site.

**Chris Murphy** is Director of Graduate Studies at the Kennedy Institute and an Associate Professor at the University of Oxford. He completed his PhD at Imperial College, London, in 1997, followed by postdoctoral work at the Georgia Institute of Technology. In 2000, Chris moved to the Tissue Engineering Centre at Imperial College, London, and joined the Kennedy Institute as Group Leader three years later. He was awarded the Michael Mason Prize in 2010.


1. Seidl CI, Martinez-Sanchez A, and Murphy CL. 2016. Derepression of MicroRNA-138 Contributes to Loss of the Human Articular Chondrocyte Phenotype. *Arthritis & Rheumatology* 68: 398-409.
2. Thoms BL, Dudek KA, Lafont JE, Murphy CL. 2013. Hypoxia promotes the production and inhibits the destruction of human articular cartilage. *Arthritis Rheum* 65: 1302-12
3. Martinez-Sanchez A, Dudek KA, Murphy CL. 2012. Regulation of human chondrocyte function through direct inhibition of cartilage master regulator SOX9 by microRNA-145 (miRNA-145). *J Biol Chem* 287: 916-24
4. Dudek KA, Lafont JE, Martinez-Sanchez A, Murphy CL. 2010. Type II collagen expression is regulated by tissue-specific miR-675 in human articular chondrocytes. *J Biol Chem* 285: 24381-7
5. Jones SW, Watkins G, Le Good N, Roberts S, Murphy CL, Brockbank SM, Needham MR, Read SJ, Newham P. 2009. The identification of differentially expressed microRNA in osteoarthritic tissue that modulate the production of TNF-alpha and MMP13. *Osteoarthritis Cartilage* 17: 464-72

# Tissue Fibrosis and Regeneration

## Jagdeep Nanchahal

**Jagdeep Nanchahal** is Professor of Hand, Plastic and Reconstructive Surgery at the University of Oxford. He completed his PhD in cell biology as a medical student and trained as a reconstructive plastic surgeon in the UK, with fellowships in hand and microsurgery in the USA and Australia. His clinical specialist interest is the management of severe open fractures. He was on the NICE guidance development groups on complex and non-complex fractures and chaired the group that wrote the Standards for the Management of Open Fractures of the Lower Limb. He joined the Kennedy Institute in 2006.

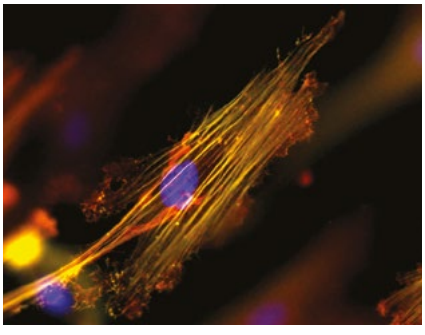
> We use human tissues to identify novel therapeutic targets and murine models to validate their efficacy.

Fibrosis represents a major unmet medical need and affects a variety of organs including the lung, liver and kidney. Localised fibrotic conditions including endometriosis, abdominal adhesions and frozen shoulder receive less attention yet cause considerable morbidity, and together affect more than 10% of the population. We have been studying Dupuytren's disease, a local fibrotic condition of the hand that affects 4% of the general UK and US populations. The cell responsible for the matrix deposition and contraction in all fibrotic diseases is the myofibroblast. Surgically excised specimens from patients with Dupuytren's disease provide an abundant supply of material to develop assays that can be applied to other fibrotic conditions where primary early disease stage human tissues are less readily available.

We found that TNF is the primary driver for development and maintenance of myofibroblasts in Dupuytren's disease. There is no approved therapeutic to prevent progression of early disease and we have commenced a phase II clinical trial to assess the efficacy of local injection of the anti-TNF drug adalimumab. We are also examining novel upstream regulators of TNF as potential targets in pre-clinical studies.

We also work with Somalogic and Celgene to identify novel therapeutic targets for fibrotic diseases using Somascan and Quanticel single cell RNAseq. In parallel, we are developing new assays to study the phenotype of primary myofibroblasts from clinical samples of early stage fibrosis. Our aim is to use these techniques to identify and validate novel therapeutic targets in a variety of fibrotic disorders including endometriosis and hepatic fibrosis, areas of significant unmet medical need.

Fibrosis results from failed tissue repair after injury. We also study the molecular mechanisms underlying tissue regeneration, and in particular the healing of fractures. We have identified an endogenous factor that transitions stem cells from a variety of human and mouse tissues into an alert phase and hence leads to accelerated repair following injury to several tissues including bone, muscle and blood. We are now investigating how this insight can be used to target endogenous stem cell recruitment and activation to accelerate tissue repair following injury, and to limit fibrosis.



Myofibroblasts form specialised junctions called fibronexi with the surrounding matrix (red). Cell cytoskeleton shown in green, nuclei in blue.


1. Nanchahal J, Hinz B. 2016. Strategies to overcome the hurdles to treat fibrosis, a major unmet clinical need. *Proc Natl Acad Sci U S A* 113: 7291-3
2. Chan JK, Glass GE, Ersek A, Freidin A, Williams GA, Gowers K, Espirito Santo AI, Jeffery R, Otto WR, Poulsom R, Feldmann M, Rankin SM, Horwood NJ, Nanchahal J. 2015. Low-dose TNF augments fracture healing in normal and osteoporotic bone by up-regulating the innate immune response. *EMBO Mol Med* 7: 547-61
3. Verjee LS, Verhoekx JS, Chan JK, Krausgruber T, Nicolaidou V, Izadi D, Davidson D, Feldmann M, Midwood KS, Nanchahal J. 2013. Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target. *Proc Natl Acad Sci U S A* 110: E928-37
4. Chan JK, Roth J, Oppenheim JJ, Tracey KJ, Vogl T, Feldmann M, Horwood N, Nanchahal J. 2012. Alarmins: awaiting a clinical response. *J Clin Invest* 122: 2711-9
5. Glass GE, Chan JK, Freidin A, Feldmann M, Horwood NJ, Nanchahal J. 2011. TNF-alpha promotes fracture repair by augmenting the recruitment and differentiation of muscle-derived stromal cells. *Proc Natl Acad Sci U S A* 108: 1585-90

# Mucosal Immunology
## Fiona Powrie

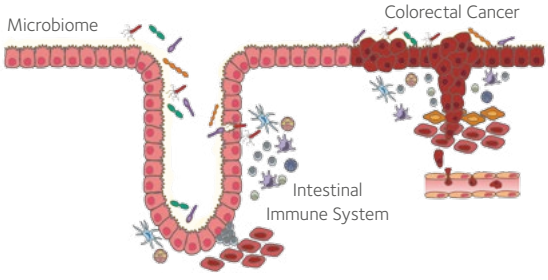
> My group focuses on understanding the interaction between the intestinal microbiota and the host immune system and how this mutualistic relationship breaks down in inflammatory bowel disease, arthritis and cancer.

The intestinal immune system is highly adapted to protect against invading pathogens while residing peacefully with the large number of diverse bacteria that inhabit the gut. This delicate balance between tolerance and immunity is achieved through complex interactions between the microbiota, intestinal epithelial cells and the host immune system. My group is interested in the molecular and cellular pathways that contribute to intestinal homeostasis and inflammation.

Our early studies identified the important role of regulatory T cells in controlling microbe-driven responses in the intestine. We have also identified a pivotal role for IL-23 in driving chronic intestinal inflammation. A major focus now is to better understand how microbial components influence immune homeostasis and inflammation.

We are using genomic approaches to profile the species composition and transcriptional activity of intestinal bacteria to identify changes that associate with chronic inflammatory disease onset and progression. This is combined with analysis of host factors such as genetic variation that may alter the microbiota to predispose to disease. We also perform mechanistic studies to assess how the microbiota and its products modulate the development and activity of specific immune cell subsets in the gut. Our interest in the microbiota extends to understanding its influence on distal inflammatory responses. My group leads the Inflammatory Arthritis Microbiome Consortium, an international team of multidisciplinary scientists working to characterise how the intestinal microbiome impacts on inflammatory arthritis.

A second major interest in my group is the role of inflammatory cytokines in inflammation-driven colorectal cancer. Patients with IBD are at increased risk of developing colon cancer, and inflammation is also thought to play an important role in non-IBD related colorectal cancer. We have shown innate lymphoid cell-derived IL-22 sustains tumour growth in a mouse model of colorectal cancer. We are now translating these findings in experimental medicine studies to assess whether inflammatory cytokines drive tumour progression in molecularly defined subsets of colorectal cancer patients. We also examine more broadly the mechanisms by which a lack of adequate T cell regulation in the gut can drive colon carcinomas.




Intestinal immune homeostasis is achieved through complex interactions between the microbiome, intestinal epithelial cells and the host immune system. An imbalance in these interactions can lead to chronic intestinal inflammation and colorectal cancer.

**Fiona Powrie**, FRS is Director of the Kennedy Institute and Professor of Musculoskeletal Sciences at the University of Oxford. She gained her DPhil at the University of Oxford and completed postdoctoral studies at DNAX Research Institute, California, USA. She returned to the University of Oxford as a WT Senior Research Fellow in 1996. She was previously the Sidney Truelove Professor of Gastroenterology and Head of the Translational Gastroenterology Unit (2009-2014). She was awarded the Louis Jeantet Prize for Medicine in 2012. She joined the Kennedy Institute in 2014.


1. Ilott NE, Bollrath J, Danne C, Schiering C, Shale M, Adelmann K, Krausgruber T, Heger A, Sims D, Powrie F. 2016. Defining the microbial transcriptional response to colitis through integrated host and microbiome profiling. *ISME J* 10(10): 2389-404
2. Griseri T, Arnold IC, Pearson C, Krausgruber T, Schiering C, Franchini F, Schulthess J, McKenzie BS, Crocker PR, Powrie F. 2015. Granulocyte Macrophage Colony-Stimulating Factor-Activated Eosinophils Promote Interleukin-23 Driven Chronic Colitis. *Immunity* 43: 187-99
3. Schiering C, Krausgruber T, Chomka A, Fröhlich A, Adelmann K, Wohlfert EA, Pott J, Griseri T, Bollrath J, Hegazy AN, Harrison OJ, Owens BM, Lohning M, Belkaid Y, Fallon PG, Powrie F. 2014. The alarmin IL-33 promotes regulatory T-cell function in the intestine. *Nature* 513: 564-8
4. Kirchberger S, Royston DJ, Boulard O, Thornton E, Franchini F, Szabady RL, Harrison O, Powrie F. 2013. Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J Exp Med* 210: 917-31
5. Buonocore S, Ahern PP, Uhlig HH, Ivanov, II, Littman DR, Maloy KJ, Powrie F. 2010. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature* 464: 1371-5

# Computational Genomics
## Stephen Sansom

**Stephen Sansom** leads the Computational Genomics Group at the Kennedy Institute. He gained a DPhil in Developmental Biology from the University of Cambridge and joined Professor Chris Ponting's Computational Genomics Analysis and Training program at the University of Oxford as an MRC Career Development Fellow in 2011. After a brief appointment as a Senior Genomics Fellow in the Ponting group, Dr Sansom joined the Kennedy Institute in 2014.

> In our research we analyse and interpret data from population and single-cell genomics experiments to investigate immune system development and dysregulation in disease.

The immune system is comprised of a dynamic and diverse cast of cell types that together defend and repair the body. Immune cells exhibit a remarkable degree of specialisation, both regionally in the different tissues of the body and locally in the responses they make to environmental cues. We are studying this heterogeneity at the single-cell level for insight into immune system development and the pathology of chronic inflammatory disease.

A principle interest of our research is the role of thymic epithelial cells (TEC) in T cell selection. En masse, T cells can recognise virtually any foreign antigen by virtue of a stochastically generated receptor repertoire. Critically, success of this 'catch all' strategy depends on the systematic elimination or education of T cells bearing self-reactive receptors. TEC guide this process by challenging developing T cells with a 'molecular mirror' of self-antigens. In collaborative work with Professor Georg Holländer, we are using single cell and functional genomics data to study TEC at the systems-level. Our initial analysis revealed the extent and nature of self-antigen expression in these cells, uncovering a strong association between the autoimmune regulator Aire and Polycomb-silenced genes.

A second major focus of our work is to identify and understand context-specific changes in immune cell abundance and phenotype during chronic inflammation. For instance, in inflammatory bowel diseases (IBDs) such as Crohn's Disease and Ulcerative Colitis, infiltrating monocytes rapidly become abundant in the intestine where they differentiate into macrophages and can adopt pro-inflammatory states. Together with the laboratories of Professor Irina Udalova and Professor Fiona Powrie, we are using single-cell RNA-sequencing to characterise immune cell states in a mouse model of IBD with the aim of identifying pathogenic factors and pathways as targets for selective therapies.

Our group also works with the Research Informatics team to manage the Kennedy Genomics high-performance compute facility (KGen), and together with Professor Irina Udalova's group we are leading efforts to develop a single-cell RNA-sequencing pipeline for the Kennedy Institute.

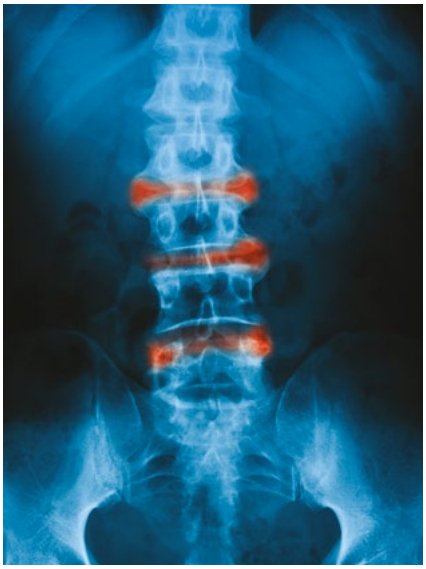

Population and single-cell RNA-seq reveals the relationship between self-antigen expression level and frequency in TEC.


1. Mayer CE, Zuklys S, Zhanybekova S, Ohigashi I, Teh HY, Sansom SN, Shikama-Dorn N, Hafen K, Macaulay IC, Deadman ME, Ponting CP, Takahama Y, Hollander GA. 2016. Dynamic spatio-temporal contribution of single beta5t+ cortical epithelial precursors to the thymus medulla. *Eur J Immunol* 46: 846-56
2. Seneviratne AN, Cole JE, Goddard ME, Park I, Mohri Z, Sansom S, Udalova I, Krams R, Monaco C. 2015. Low shear stress induces M1 macrophage polarization in murine thin-cap atherosclerotic plaques. *J Mol Cell Cardiol* 89: 168-72
3. Vance KW, Sansom SN, Lee S, Chalei V, Kong L, Cooper SE, Oliver PL, Ponting CP. 2014. The long non-coding RNA Paupar regulates the expression of both local and distal genes. *EMBO J* 33: 296-311
4. Sansom SN, Shikama-Dorn N, Zhanybekova S, Nusspaumer G, Macaulay IC, Deadman ME, Heger A, Ponting CP, Hollander GA. 2014. Population and single-cell genomics reveal the Aire dependency, relief from Polycomb silencing, and distribution of self-antigen expression in thymic epithelia. *Genome Res* 24: 1918-31

# Immunobiology of Systemic Rheumatic Disease

## Jonathan Sherlock

> We examine the immunological basis of systemic rheumatic disease, with an emphasis on the inflammatory cytokines that drive spondyloarthropathy.



Ankylosing spondylitis is associated with inflammation and new bone growth at tendon-bone attachments, particularly in the spine.

The spondyloarthropathies are a group of rheumatic diseases that are associated with inflammation of the spine and peripheral joints. The tendon-bone attachments (entheses) are particularly affected, and inflammation may also involve the intestine, skin, uvea, and aortic root. Current treatments for spondyloarthropathies target inflammation, but are not particularly effective at preventing abnormal bone growth. My previous work identified a population of resident immune cells in the enthesis that drive joint inflammation and bone changes in mouse models of spondyloarthropathy.

My group continues to research the cellular and molecular basis of rheumatic inflammation with the aim of further elucidating key drivers of inflammation and tissue destruction at diseased sites in diverse inflammatory conditions. Understanding the connections between inflammation at multiple sites will allow improved and coordinated treatment of these diseases and further possibilities for disease modification at a fundamental level.

**Jonathan Sherlock** is a KTRR Senior Clinical Research Fellow at the University of Oxford. He studied pre-clinical medicine at the University of Oxford and clinical medicine at the University of Cambridge. He subsequently trained in rheumatology under the supervision of Professor Christopher Buckley in Birmingham. During his training, he spent three years working in the group of Dr Daniel Cua at Merck Research Laboratories in California. Jonathan joined the Kennedy Institute in 2016.


1. Sherlock JP, Taylor PC, Buckley CD, Cua DJ. 2015. Spondyloarthropathy: interleukin 23 and disease modification. *Lancet* 385: 2017-8
2. Sherlock JP, Taylor PC, Buckley CD. 2015. The biology of IL-23 and IL-17 and their therapeutic targeting in rheumatic diseases. *Curr Opin Rheumatol* 27: 71-5
3. Sherlock JP, Joyce-Shaikh B, Turner SP, Sathe M, Grein J, Gorman DM, Bowman EP, McClanahan TK, Yearley JH, Buckley CD, Kastelein RA, Pierce RH, LaFace D, Cua DJ. 2013. Interleukin-23 is critical in the pathogenesis of spondyloarthropathy and acts on a novel population of interleukin 23R+ entheseal resident cells. *Lancet* 381: S14
4. Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, Gorman DM, Bowman EP, McClanahan TK, Yearley JH, Eberl G, Buckley CD, Kastelein RA, Pierce RH, Laface DM, Cua DJ. 2012. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. *Nat Med* 18: 1069-76
5. Cua DJ, Sherlock JP. 2011. Autoimmunity's collateral damage: Gut microbiota strikes 'back'. *Nat Med* 17: 1055-6

# Autophagy in Immunity and Inflammation

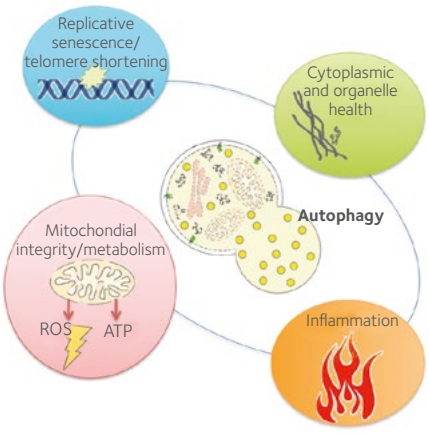
## Anna Katharina Simon

**Anna Katharina Simon** is Professor of Immunology at the University of Oxford. She trained under Avrion Mitchison at the DRFZ Berlin (EULAR award 1994) before completing a postdoc at the Centre d'Immunologie Marseille Luminy on thymic cell death. She then completed a second postdoc at the University of Oxford before going on to lead her own research group at the Weatherall Institute of Moelcular Medicine, University of Oxford, pursuing the topic of immune cell fate. She joined the Kennedy Institute in 2016.

> We focus on the role of autophagy in cellular differentiation, function and senescence, and investigate how this pathway can be targeted in disease.

Autophagy is a major degradation mechanism in the cell, responsible for the removal and recycling of bulk cytoplasmic material. Tissue-specific inactivation of autophagy proteins links the autophagy pathway to a range of diseases such as neurodegeneration, diabetes, inflammation and cancer. Much less is known about autophagy's role in healthy physiology. Hematopoietic and immune cells are ideal to investigate this as they are easy to identify and purify, well studied and readily accessible in mice and humans.

Over the last eight years we have found that autophagy contributes to red blood cell maturation, maintenance of the hematopoietic stem cell pool, and limits proliferation in acute myeloid leukaemia. We have also shown that T lymphocytes without autophagy fail to differentiate into memory cells. The autophagy pathway becomes less active with age, which may explain why the elderly are less able to form memory responses to de novo antigens. Indeed we were able rescue $CD8^+$ T cell memory responses in old mice with an autophagy-inducing compound.




Autophagy's impact on the cell biology of immune cells

We have also pioneered techniques using conventional and imaging flow cytometry to detect autophagy in primary human cells. This allowed us to link autophagy defects to primary immune deficiencies and T cell metabolism. We are now aiming to establish a more extensive immune metabolism platform at the single cell level for analysis of catabolic (autophagy, cellular respiration) and anabolic (building up of macromolecules) processes in both human and mouse cells.

Using our new tools, we aim to identify the mechanism by which autophagy allows differentiation of immune cells and hematopoietic stem cells. As differentiation of a variety of other cell types (e.g. osteoclasts, adipocytes) has been described to rely on autophagy, this should reveal a general mechanism. It will also help to identify ways to induce tumour differentiation, one of the goals in tumour therapy. A second long-term goal is to understand how the autophagic process is affected during ageing and the implications for cellular senescence. This is relevant because immune senescence is a risk factor for many age-related diseases, such as cancer and increased infections in the elderly. For both our major goals we will aim to identify novel pathways, drug targets and drugs.

1. Stranks AJ, Hansen AL, Panse I, Mortensen M, Ferguson DJ, Puleston DJ, Shenderov K, Watson AS, Veldhoen M, Phadwal K, Cerundolo V, Simon AK. 2015. Autophagy Controls Acquisition of Aging Features in Macrophages. *J Innate Immun* 7: 375-91
2. Puleston DJ, Zhang H, Powell TJ, Lipina E, Sims S, Panse I, Watson AS, Cerundolo V, Townsend AR, Klenerman P, Simon AK. 2014. Autophagy is a critical regulator of memory CD8(+) T cell formation. *Elife* 3
3. Phadwal K, Alegre-Abarrategui J, Watson AS, Pike L, Anbalagan S, Hammond EM, Wade-Martins R, McMichael A, Klenerman P, Simon AK. 2012. A novel method for autophag detection in primary cells: impaired levels of macroautophag in immunosenescent T cells. *Autophagy* 8: 677-893
4. Mortensen M, Soilleux EJ, Djordjevic G, Tripp R, Lutteropp M Sadighi-Akha E, Stranks AJ, Glanville J, Knight S, Jacobsen SE Kranc KR, Simon AK. 2011. The autophagy protein Atg7 is essential for hematopoietic stem cell maintenance. *J Exp Med* 208: 455-67
4. Mortensen M, Ferguson DJ, Edelmann M, Kessler B, Morten KJ, Komatsu M, Simon AK. 2010. Loss of autophagy in erythroid cells leads to defective removal of mitochondria an severe anemia in vivo. *Proc Natl Acad Sci U S A* 107: 832-7

# Metalloproteinase Dysregulation in Osteoarthritis

Linda Troeberg

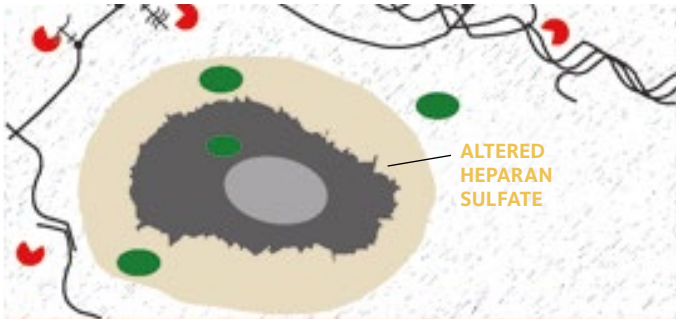
> We research what increases and decreases the loss of cartilage in osteoarthritis, to improve treatment solutions for the condition.

Osteoarthritis develops when the normal process of cartilage turnover becomes dysregulated. Weakening of the cartilage can occur, for example, as a result of increased expression of metalloproteinases and reduced expression of their endogenous inhibitor, tissue inhibitors of metalloproteinases 3 (TIMP-3). Strategies aimed at restoring healthy levels of TIMP-3 in cartilage thus have chondroprotective therapeutic potential.

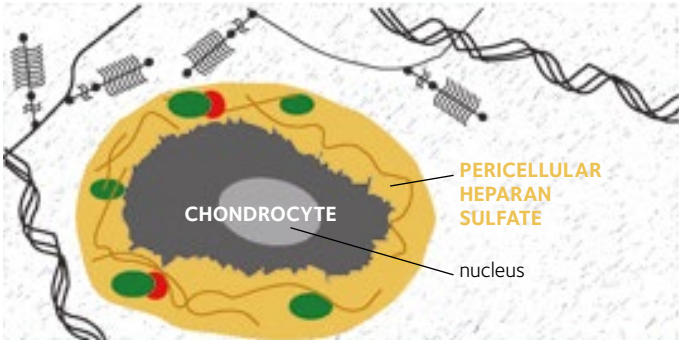
Our group established that TIMP-3 levels in cartilage are regulated by the equilibrium between its binding to heparan sulfate in the extracellular matrix and its cellular uptake by the scavenger receptor, LRP1. We have engineered LRP1-resistant mutants of TIMP-3 and shown that these have a longer half-life and improved ability to protect cartilage. These findings suggest that targeting the TIMP-3 trafficking pathway may have therapeutic potential in OA. We are currently developing small molecule inhibitors of TIMP-3 uptake as novel lead compounds for treating osteoarthritic cartilage loss.

Heparan sulfate also regulates the activity of numerous other homeostatic cartilage proteins, including protective growth factors such as TGFβ, CTGF and FGF2. Changes to heparan sulfate will thus affect the ability of cartilage to protect and repair itself. We are investigating whether the structure of heparan sulfate changes during the development of osteoarthritis, and comparing this with changes occurring naturally with age. Understanding this regulatory pathway will enable us to identify novel target genes associated with the development of arthritis.

**Linda Troeberg** is a University Research Lecturer, University of Oxford, and a Stipendiary Lecturer at St Hilda's College. After a PhD in Biochemistry, she carried out postdoctoral studies with Professor Richard Perham (University of Cambridge) and Professor Hideaki Nagase (Imperial College, London). She was awarded an Arthritis Research UK Career Development Fellowship in 2011.




In osteoarthritic cartilage, the structure of heparan sulfate changes, causing release of protective growth factors and inhibitors, and subsequent cartilage degradation.




In healthy cartilage, protective growth factors and inhibitors are kept near cells by heparan sulfate molecules.

1. Doherty CM, Visse R, Dinakarpandian D, Strickland DK, Nagase H, Troeberg L. 2016. Engineered Tissue Inhibitor of Metalloproteinases-3 Variants Resistant to Endocytosis Have Prolonged Chondroprotective Activity. J Biol Chem. Aug 31. *pii: jbc.* M116.733261
2. Troeberg L, Lazenbatt C, Anower EKMF, Freeman C, Federov O, Habuchi H, Habuchi O, Kimata K, Nagase H. 2014. Sulfated glycosaminoglycans control the extracellular trafficking and the activity of the metalloprotease inhibitor TIMP-3. *Chem Biol* 21: 1300-9
3. Scilabra SD, Troeberg L, Yamamoto K, Emonard H, Thogersen I, Enghild JJ, Strickland DK, Nagase H. 2013. Differential regulation of extracellular tissue inhibitor of metalloproteinases-3 levels by cell membrane-bound and shed low density lipoprotein receptor-related protein 1. *J Biol Chem* 288: 332-42
4. Troeberg L, Mulloy B, Ghosh P, Lee MH, Murphy G, Nagase H. 2012. Pentosan polysulfate increases affinity between ADAMTS-5 and TIMP-3 through formation of an electrostatically driven trimolecular complex. *Biochem J* 443: 307-15

# Genomics of Inflammation

## Irina Udalova

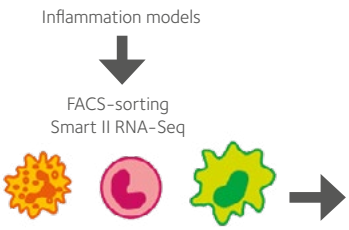
**Irina Udalova** is Professor of Molecular Immunology at the University of Oxford. She has a multi-disciplinary scientific background, based on a joint BSc/MSc degree in physics and mathematics with specialisation in molecular biology from Moscow Institute of Physics and Technology. She began her research career in Oxford in 1995, first as a Royal Society fellow and later on as a research scientist. She joined the Kennedy Institute as a Group Leader in 2004.

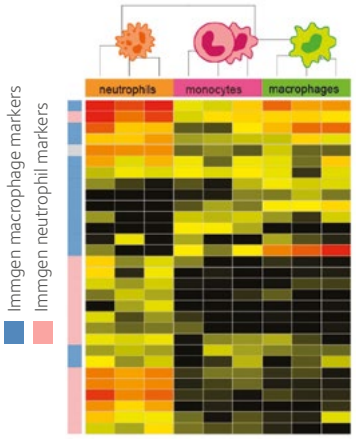
> Our research focuses on how myeloid cells contribute to inflammatory diseases and we aim to translate these findings into more effective therapies for inflammatory conditions.

Myeloid cells (e.g. macrophages, monocytes, neutrophils) are critical components of host defence, but under certain circumstances are major contributors to the pathology of inflammatory disease. Transcription factor IRF5 is linked by genetic-association to many autoimmune diseases. We identified IRF5 as a master regulator of inflammatory macrophages. Our work showed IRF5 activates key inflammatory cytokines and chemokines, promotes Th1/Th17 immune responses, suppresses Th2 immunity and plays an important role in tissue remodelling. Moreover, we have demonstrated that mice lacking IRF5 are protected from insulin resistance in a diet-induced model of obesity and have reduced knee swelling and pathology in a model of inflammatory arthritis. To further investigate the role of IRF5 in inflammatory disease, we are developing genetic approaches for better tracking, isolation and ablation of IRF5$^{+}$ cells. We are also searching for regulators of IRF5 activation with the goal of designing selective therapeutic strategies, which might be useful in a wide spectrum of inflammatory diseases.

A second goal of my laboratory is to understand the interaction between tissue-resident macrophages, infiltrating monocytes and neutrophils during sterile inflammation. We are combining advanced genomic approaches (single cell and small cell number population RNA-seq) with novel mouse strains to examine macrophage-neutrophil communication in established models of inflammation. We are specifically interested in understanding the transcriptional circuits controlling production of protein and lipid mediators that drive the neutrophil influx into the tissue.

We are also applying advanced genomic approaches to identify key regulators of neutrophil function in sterile inflammation using combined gene expression (RNA-seq) and chromatin (ATAC-seq) profiling, which represents a new tool for investigating subset specific immune-regulatory landscapes. These studies may guide strategies to target defined pathogenic neutrophil subsets in diseases. We are also dissecting the molecular mechanisms of specific modulators of neutrophil function such as IFN-λ, bioactive lipids and microbiota. This can lead to re-purposing of anti-viral therapeutics, i.e. IFN-λ, for the treatment of inflammatory conditions.





1. Weiss M, Byrne AJ, Blazek K, Saliba DG, Pease JE, Perocheau D, Feldmann M, Udalova IA. 2015. IRF5 controls both acute and chronic inflammation. *Proc Natl Acad Sci U S A* 112: 11001-6
2. Blazek K, Eames HL, Weiss M, Byrne AJ, Perocheau D, Pease JE, Doyle S, McCann F, Williams RO, Udalova IA. 2015. IFN-lambda resolves inflammation via suppression of neutrophil infiltration and IL-1beta production. *J Exp Med* 212: 845-53
3. Dalmas E, Toubal A, Alzaid F, Blazek K, Eames HL, Lebozec K, Pini M, Hainault I, Montastier E, Denis RG, Ancel P, Lacombe A, Ling Y, Allatif O, Cruciani-Guglielmacci C, Andre S, Viguerie N, Poitou C, Stich V, Torcivia A, Foufelle F, Luquet S, Aron-Wisnewsky J, Langin D, Clement K, Udalova IA, Venteclef N. 2015. Irf5 deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity. *Nat Med* 21: 610-8
4. Saliba DG, Heger A, Eames HL, Oikonomopoulos S, Teixeira A, Blazek K, Androulidaki A, Wong D, Goh FG, Weiss M, Byrne A, Pasparakis M, Ragoussis J, Udalova IA. 2014. IRF5:RelA interaction targets inflammatory genes in macrophages. *Cell Rep* 8: 1308-17
4. Krausgruber T, Blazek K, Smallie T, Alzabin S, Lockstone H, Sahgal N, Hussell T, Feldmann M, Udalova IA. 2011. IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. *Nat Immunol* 12: 231-8

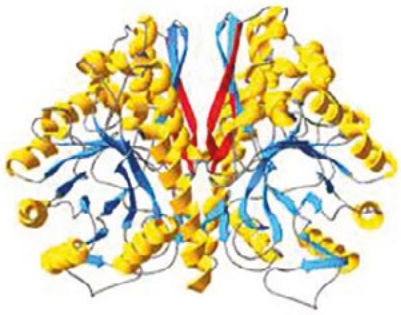
# Citrullination in Inflammation

## Patrick Venables

> My interests lie in understanding how conversion of the amino acid arginine to citrulline in proteins – a process known as citrullination – contributes to chronic inflammatory disease.

Antibodies against citrullinated proteins are highly specific for rheumatoid arthritis (RA). My group discovered citrullinated a-enolase and showed that it is a true autoantigen in approximately 50% of patients with rheumatoid arthritis. We went on to map its immunodominant epitope(s) to a peptide designated citrullinated enolase peptide-1 (CEP-1). Anti-CEP-1 is linked to a subset of RA patients in which smoking and the shared epitope are major interacting gene/environment risk factors. Antibodies to the CEP-1 peptide have also been linked to *Porphyromonas gingivalis* infection, and we have shown that immunising DR4 transgenic mice with *P. gingivalis* enolase induces an erosive arthritis and autoantibodies to mammalian enolase. More recently we have defined another major antigenic peptide from tenascin-C, whose antibodies are linked to another periodontal pathogen, *Prevotella intermedia*. All of these developments show that defining an autoantibody to a specific antigen in RA supports the gene/environment autoimmunity paradigm and provide indications of the upstream events in pathogenesis.

Citrulline residues are key components of autoantigens in RA. Therefore the enzymes that generate this post-translational modification, the petidylarginine deiminases (PADs), are the main focus of our current work. We have solved the crystal structure of *P. gingivalis* PAD and demonstrated how this unique bacterial deiminase could break tolerance to citrullinated antigens in the course of periodontal infection. We have also demonstrated that inhibition of PADs with small molecular weight inhibitors has a profound anti-inflammatory effect both in vivo and in vitro. Surprisingly much of this effect is due to the citrullination of key residues in histones and E2F-1, which regulate the transcription of proinflammatory cytokines. Thus PAD inhibitors may become a new class of treatments for chronic inflammatory disease.



Ribbon diagram of the a-enolase dimer showing the immunodominant epitope CEP-1 (red).

**Patrick Venables** is a Honorary Principal Investigator at the University of Oxford. He gained a Bachelor of Medicine and Surgery from the University of Cambridge in 1972, was awarded an MD (Cantab) in 1986, and became Senior Lecturer (London University) and consultant physician at Charing Cross hospital in the same year. He obtained his fellowship of the Royal College of Physicians in 1993 and was awarded a chair with the title Professor of Viral Immunorheumatology in 1999 at Imperial College. In 2012, he retired from clinical medicine and moved to the new Kennedy Institute in Oxford.

1. Montgomery AB, Kopec J, Shrestha L, Thezenas ML, Burgess-Brown NA, Fischer R, Yue WW, Venables PJ. 2016. Crystal structure of Porphyromonas gingivalis peptidylarginine deiminase: implications for autoimmunity in rheumatoid arthritis. *Ann Rheum Dis* 75: 1255-61
2. Kawalkowska J, Quirke AM, Ghari F, Davis S, Subramanian V, Thompson PR, Williams RO, Fischer R, La Thangue NB, Venables PJ. 2016. Abrogation of collagen-induced arthritis by a peptidyl arginine deiminase inhibitor is associated with modulation of T cell-mediated immune responses. *Sci Rep 6*: 26430
3. Ghari F, Quirke AM, Munro S, Kawalkowska J, Picaud S, McGouran J, Subramanian V, Muth A, Williams R, Kessler B, Thompson PR, Fillipakopoulos P, Knapp S, Venables PJ, La Thangue NB. 2016. Citrullination-acetylation interplay guides E2F-1 activity during the inflammatory response. *Sci Adv* 2: e1501257
4. Kinloch AJ, Alzabin S, Brintnell W, Wilson E, Barra L, Wegner N, Bell DA, Cairns E, Venables PJ. 2011. Immunization with Porphyromonas gingivalis enolase induces autoimmunity to mammalian alpha-enolase and arthritis in DR4-IE-transgenic mice. *Arthritis Rheum* 63: 3818-23
5. Mahdi H, Fisher BA, Kallberg H, Plant D, Malmstrom V, Ronnelid J, Charles P, Ding B, Alfredsson L, Padyukov L, Symmons DP, Venables PJ, Klareskog L, Lundberg K. 2009. Specific interaction between genotype, smoking and autoimmunity to citrullinated alpha-enolase in the etiology of rheumatoid arthritis. *Nat Genet* 41: 1319-24

# Molecular Pathogenesis of Osteoarthritis

Tonia Vincent

**Tonia Vincent** is Professor of Musculoskeletal Biology at the University of Oxford and Director of the Arthritis Research UK Centre for OA Pathogenesis. She studied medicine at UCL, qualifying in 1993. She then trained as a junior doctor in London, later specialising in Rheumatology. In 1998 she took time out to do a PhD at the Kennedy Institute under Professor Jeremy Saklatvala. She continued at the Kennedy Institute as a Wellcome Trust clinician scientist and is currently an Arthritis Research UK Senior Fellow. She continues to be clinically active, running a hand OA clinic in London and contributing to the multidisciplinary Marfan Syndrome clinic in Oxford.

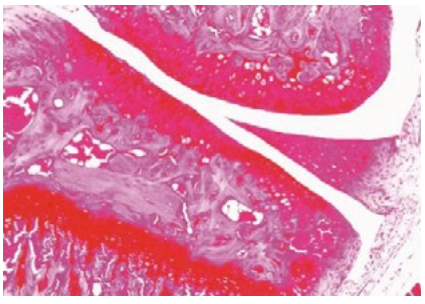
> We investigate pathogenic mechanisms of osteoarthritis with the hope of discovering therapeutic strategies to treat symptomatic and structural disease.

Our work is focused around three principal research themes: sequestered molecules of the pericellular matrix and their role in the response of articular cartilage to mechanical injury; molecular pathways that control intrinsic cartilage repair; pathogenic processes that drive pain in OA.

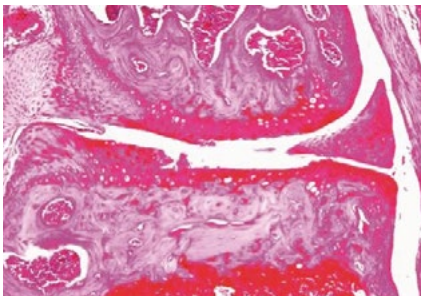
We discovered that matrix-sequestered growth factors are released upon cartilage injury and drive chondroprotective responses in the joint. FGF2 was the first growth factor that we identified; it is sequestered in the pericellular matrix (PCM) of cartilage, attached to the heparan sulphate chains of perlecan. Mice lacking FGF2 develop accelerated spontaneous and surgically induced osteoarthritis, indicating that its release is chondroprotective. By analysing the PCM of cartilage using a proteomic approach, we have identified three further growth factors of the PCM that are similarly released upon injury. We are currently investigating their function. One of them is a novel activator of TGFβ.

For a long time it was assumed that mechanical load induced osteoarthritis by 'wearing down' the articular surfaces. Matrix metalloproteinases, specifically ADAMTS5 and MMP13, are critical for the degradation of the articular cartilage in OA. We showed that these enzymes are regulated in the cartilage very rapidly when OA is induced in mice. Regulation is abrogated, and the joints protected from degradation, if the joint is immobilised after surgery. This points to the highly mechanosensitive induction of these enzymes in vivo and explains the strong epidemiological link between mechanical wear and OA.

Joint pain in osteoarthritis is poorly explained in patients and several tissues of the joint could contribute to its development. We were the first group to demonstrate painful behaviour in mice after surgical destabilisation of the joint. Mice remain symptom free for several weeks after surgery (apart from the immediate post operative period) and then develop pain at around 12 weeks post destabilistion. We discovered that nerve growth factor (NGF), a known pain sensitiser, was regulated in the destabilised joints at the onset of pain, and pain could be neutralized by the soluble receptor to NGF. In a recent publication we report the surprising finding that damaged cartilage is the principal source of NGF in the osteoarthritic joint. Multiple companies are investing in NGF neutralisation strategies for the treatment of painful osteoarthritis. Trials, thus far reported, have demonstrated excellent analgesic efficacy.



Normal joint



OA joint


1. Paul Potter, et al, Tonia Vincent, et al, Steve DM Brown. 2016. Novel gene function revealed by mouse mutagenesis screens for models of age-related disease. 2016 *Nat Commun.* In press
2. Driscoll C, Chanalaris A, Knights C, Ismail H, Sacitharan PK, Gentry C, Bevan S, Vincent TL. 2016. Nociceptive Sensitizers Are Regulated in Damaged Joint Tissues, Including Articular Cartilage, When Osteoarthritic Mice Display Pain Behavior. *Arthritis Rheumatol* 68: 857-67
3. Chong KW, Chanalaris A, Burleigh A, Jin H, Watt FE, Saklatvala J, Vincent TL. 2013. Fibroblast growth factor 2 drives changes in gene expression following injury to murine cartilage in vitro and in vivo. *Arthritis Rheum* 65: 2346-55
4. Burleigh A, Chanalaris A, Gardiner MD, Driscoll C, Boruc O, Saklatvala J, Vincent TL. 2012. Joint immobilization prevents murine osteoarthritis and reveals the highly mechanosensitive nature of protease expression in vivo. *Arthritis Rheum* 64: 2278-88
5. Vincent T, Hermansson M, Bolton M, Wait R, Saklatvala J. 2002. Basic FGF mediates an immediate response of articular cartilage to mechanical injury. *Proc Natl Acad Sci U S A* 99: 8259-64

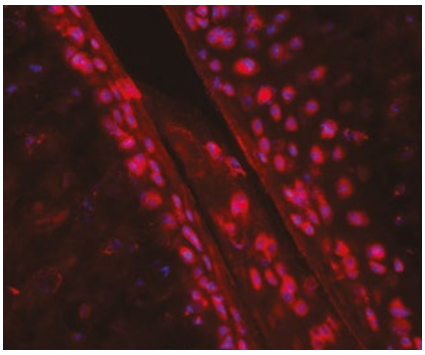
# Primary Cilia in Inflammatory Signalling

Angus Wann

> We examine a role for proteins associated with the primary cilium in tissue physiology and disease and the potential for exploiting this influence for therapies.

The primary cilium is a singular organelle assembled by the vast majority of cell types. Recent research has shown that the proteins associated with this organelle – referred to as the ciliome – regulate numerous aspects of cell biology. However, these studies have been conducted predominantly in the context of development and the influence of the ciliome in adult tissues and disease is largely unknown.

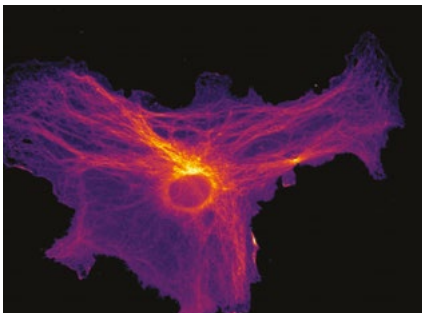
The principal disease focus of my group is towards osteoarthritis (OA). Previous work has shown that showed the ciliome is critical to how cells of the joint respond to mechanical cues and inflammatory cytokines. We are investigating how the ciliome regulates adult cartilage homeostasis and how this may be relevant or exploitable in the context of OA pathogenesis. We are perturbing the hierarchy of components that comprise the ciliome in healthy and diseased human chondrocytes, in vivo using transgenic models, as well as in pre-clinical models of disease. We are also investigating how the ciliome changes in disease and with ageing.



Immunofluorescent image of the articular surfaces of cartilage at the murine knee joint showing chondrocytes in both joint surfaces and meniscus.

Another core interest is how the ciliome may be regulating the signalling downstream of inflammatory cytokines and other pathological 'triggers'. We are particularly interested in how ciliary trafficking proteins may be encoding NFkB signalling. We mostly focus on ciliome-inflammatory signalling in musculoskeletal cells in the context of inflammatory arthritis, but are also are investigating other cell types, including sensory neurons. Related to this, we are interested in how cytokines alter cilia function and thus signalling-ciliome crosstalk.

The ciliome may represent an exciting set of new targets if we can define how it tunes cellular behaviour in context-specific ways. We are investigating the pathophysiological roles of the cilium from molecular interactions to whole animal physiology, and are trying to work from clinical data back down to the ciliome to pose translationally relevant research hypotheses.



Intracellular trafficking showing the nexus for traffic at the microtubular organising centre where the primary cilium is assembled.

**Angus Wann** joined the Kennedy Institute in 2015 as a Arthritis Research UK/KTRR Research Fellow. He received his PhD from St Georges University Medical School in 2009, where he worked on the mechanobiology of the synovial joint under Professor J.R Levick. From 2009 until 2014, he worked with Professor Martin Knight in the Institute of Bioengineering, Queen Mary University of London, studying the role of the primary cilium in mechanobiology and disease.


1. Wann AK, Chapple JP, Knight MM. 2014. The primary cilium influences interleukin-1beta-induced NFkappaB signalling by regulating IKK activity. *Cell Signal* 26: 1735-42
2. Wann AK, Knight MM. 2012. Primary cilia elongation in response to interleukin-1 mediates the inflammatory response. *Cell Mol Life Sci* 69: 2967-77
3. Wann AK, Zuo N, Haycraft CJ, Jensen CG, Poole CA, McGlashan SR, Knight MM. 2012. Primary cilia mediate mechanotransduction through control of ATP-induced Ca2+ signaling in compressed chondrocytes. *FASEB J* 26: 1663-71

# Translational Research in Osteoarthritis

## Fiona Watt

**Fiona Watt** is a University Research Lecturer at the University of Oxford and an Honorary Consultant Rheumatologist at the Nuffield Orthopaedic Centre. She has a PhD in cartilage biochemistry from Imperial College London and has completed specialist training in rheumatology. She won OARSI Young Investigator award in 2014 and the Michael Mason Prize in 2016.

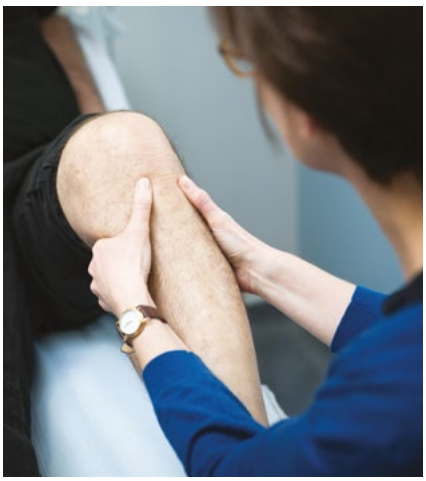
> Our group tests findings from the laboratory in human clinical studies, and runs clinical trials relevant to osteoarthritis within the Arthritis Research UK Centre for Osteoarthritis Pathogenesis.

My work is in clinical translation in osteoarthritis (OA): this includes academically-led cohort studies and clinical trials, but also facilitating human tissue access for many of our researchers in the Arthritis Research UK Centre for OA pathogenesis. My focus has been building 'intelligent' cohorts with associated bio-samples, allowing us to translate our pre-clinical findings. We also carry out interventional studies aligning with our laboratory work, which are likely to bring about patient benefit.

Joint injury is the single biggest risk factor for OA, yet we are unable to predict outcome at an individual level. The Knee Injury Cohort at the Kennedy (KICK) was designed to test whether we could measure in human joints the same responses seen after mouse experimental joint injury: some of this immediate molecular response to joint injury in the mouse appears necessary for subsequent OA. 150 individuals with acute knee injury are being followed over five years with clinical, imaging and biological sampling (synovial fluid, blood, urine). We have recently shown that this injury-related biomarker response translates to humans: an increased response is associated with more pain and symptoms at the time of injury, although interestingly appears to predict a greater clinical improvement in subsequent months. Our aim is to be able to predict risk of OA – currently we are studying the longer-term relationships between the measurable inflammatory response, pain, structural damage and OA in this, and other (newer) 'knee injury' cohorts here in the Centre (OxKIC, MenTOR).

We are also focused on targeting pain in OA. Our aim is to identify an effective medical treatment for osteoarthritis. As in rheumatoid arthritis, synovial inflammation is a potential target. Through our collaboration with Arthritis Research UK Clinical Studies Group and Professor Philip Conaghan (Leeds), I have led our participation in two large repurposing trials of anti-synovial therapies for pain efficacy in OA: HERO (hydroxychloroquine, hand OA) and more recently PROMOTE (methotrexate, knee OA).

Nerve growth factor (NGF) is produced by injured and osteoarthritic joint tissues and appears to be a key target for peripheral pain in both mouse and human OA. Studies of monoclonal antibodies to NGF have previously shown efficacy for OA knee pain. We are participating in two current commercial studies that test the effect of blocking this pathway on pain. Our participation in these clinical trials is pivotal in growing the Centre's capacity for investigator-led experimental medicine studies in OA.



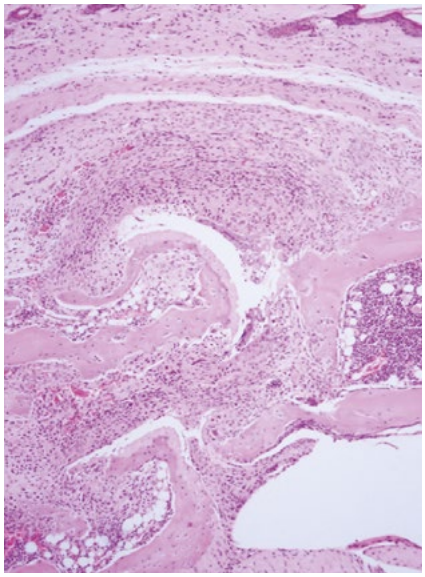

1. Watt FE, Paterson E, Freidin A, Kenny M, Judge A, Saklatvala J, Williams A, Vincent TL. 2016. Acute Molecular Changes in Synovial Fluid Following Human Knee Injury: Association With Early Clinical Outcomes. *Arthritis Rheumatol* 68: 2129-40
2. Kingsbury SR, Tharmanathan P, Arden NK, Batley M, Birrell F, Cocks K, Doherty M, Edwards CJ, Garrood T, Grainger AJ, Green M, Hewitt C, Hughes R, Moots R, O'Neill TW, Roddy E, Scott DL, Watt FE, Torgerson DJ, Conaghan PG. 2015. Pain reduction with oral methotrexate in knee osteoarthritis, a pragmatic phase iii trial of treatment effectiveness (PROMOTE): study protocol for a randomized controlled trial. *Trials* 16: 77
3. Watt FE, Ismail HM, Didangelos A, Peirce M, Vincent TL, Wait R, Saklatvala J. 2013. Src and fibroblast growth factor 2 independently regulate signaling and gene expression induced by experimental injury to intact articular cartilage. *Arthritis Rheum* 65: 397-407

# Targeting Disease Pathways in Rheumatoid Arthritis

Richard Williams

> The focus of our research is the development of novel therapies for rheumatoid arthritis, with emphasis on strategies to target the Th17 cell pathway and to promote regulatory T cell responses.

Our current research is based on two key findings. The first of these is the discovery that therapeutic TNF blockade causes a paradoxical increase in the number of pro-inflammatory Th17 cells in rheumatoid arthritis (RA), ankylosing spondylitis and psoriatic arthritis, as well as in animal models. A second area of discovery has been the demonstration that aberrant DNA methylation renders regulatory T cells non-functional in RA and that short-term treatment with DNA hypomethylating agents is able to reverse this effect and ameliorate disease in an animal model of rheumatoid arthritis.



Joints affected by inflammatory arthritis contain a large number of infiltrating immune cells (purple dots) and the bone (plain pink areas) becomes fragmented causing pain and stiffness

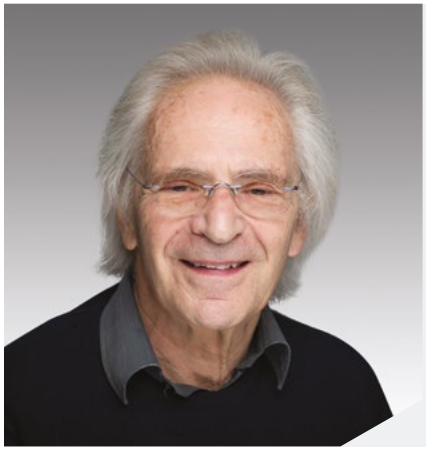
We aim to elucidate the mechanisms by which TNF inhibits Th17 responses and establish whether the expansion of Th17 cells observed following anti-TNF therapy contributes to poor response in some patients. To address these questions we have initiated a program to obtain blood samples from patients initiating anti-TNF therapy and to characterise T cell subsets and protein expression using a variety of platforms including CyTOF mass cytometry and Somalogic proteomic assay. It is anticipated that this research will reveal novel drug targets. Indeed a second objective is to assess the therapeutic potential in animal models of drugs that target the Th17 pathway, which could be used in RA, particularly for patients with a sub-optimal response to TNF inhibitors. A third objective is to develop a therapeutic strategy for promoting regulatory T cell responses based on the use of epigenetic modulators. This work involves the establishment of an assay of Treg induction in vitro and the use of predictive animal models of arthritis.

**Richard Williams** is an Associate Professor at the University of Oxford. He has worked at the Kennedy Institute since 1989. As a postdoctoral fellow he worked with Professor Sir Ravinder Maini and Professor Sir Marc Feldmann on development of anti-TNF for inflammatory arthritis. He was a Senior Lecturer (2007-2011) and then Reader (2011-2012) at Imperial College, London, before joining the University of Oxford. He is also a Visiting Lecturer at Queen Mary University of London and the London School of Hygiene and Tropical Medicine.

1. Cribbs AP, Kennedy A, Penn H, Amjadi P, Green P, Read JE, Brennan F, Gregory B, Williams RO. 2015. Methotrexate Restores Regulatory T Cell Function Through Demethylation of the FoxP3 Upstream Enhancer in Patients With Rheumatoid Arthritis. *Arthritis Rheumatol* 67: 1182-92
2. Cribbs AP, Kennedy A, Penn H, Read JE, Amjadi P, Green P, Syed K, Manka SW, Brennan FM, Gregory B, Williams RO. 2014. Treg cell function in rheumatoid arthritis is compromised by ctla-4 promoter methylation resulting in a failure to activate the indoleamine 2,3-dioxygenase pathway. *Arthritis Rheumatol* 66: 2344-54
3. Alzabin S, Abraham SM, Taher TE, Palfreeman A, Hull D, McNamee K, Jawad JA, Pathan E, Kinderlerer A, Taylor PC, Williams R, Mageed R. 2012. Incomplete response of inflammatory arthritis to TNFα blockade is associated with the Th17 pathway. *Ann Rheum Dis* 71: 1741-8
4. Notley CA, Inglis JJ, Alzabin S, McCann FE, McNamee KE, Williams RO. 2008. Blockade of tumor necrosis factor in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells. *J Exp Med* 205: 2491-7

# Emeritus Professors

In addition to full time Group Leaders, a small number of Emeritus Professors continue to be associated with the work of the institute after their retirement. They offer a wealth of experience and contribute to mentoring research staff, co-supervising DPhil students and advising on research in their areas of expertise. Their ongoing presence helps to ensure the continuity of our research.



**Sir Marc Feldmann, FRS**

Sir Marc Feldmann is an Emeritus Professor at University of Oxford. He trained in Medicine at Melbourne University and gained a PhD in immunology at the Walter & Eliza Hall Institute with Sir Gus Nossal. While working at the Kennedy Institute in the 1990s he developed anti TNF therapy together with Professor Sir Ravinder Maini. This led to election to the Royal Society, the National Academy of Sciences USA and the Australian Academy of Science, as well as the Crafoord Prize of the Royal Swedish Academy of Sciences and the Albert Lasker Clinical Research Award. He was Director of the Kennedy Institute for 12 years until 2014.

My research has focused on regulation of cytokines in autoimmune disease. My work together with Professor Sir Ravinder Maini and Dr Fionula Brennan in the 1980s showed a pivotal role for TNF in driving inflammatory cytokine production in rheumatoid arthritis (RA) synovial cell cultures. Subsequent clinical studies showed TNF blockade as both effective and relatively safe for use in rheumatoid arthritis, which has dramatically changed therapy for this disease, as well as for other chronic inflammatory diseases, such as Crohn's disease, ankylosing spondylitis and psoriasis. However, not all patients respond well to anti-TNF therapy and I continue to explore how anti-TNF as part of combination therapy might be used to get closer to a cure for RA. Another long-term goal is to usher in anti-cytokine therapy in acute diseases, such as acute respiratory distress or post-operative cognitive dysfunction. My ongoing research is in close collaboration with investigators at NDORMS, the Structural Genomics Consortium and industry.

### Hideaki Nagase

Hideaki Nagase is an Emeritus Professor at the University of Oxford. He was Professor of Matrix Biology at the Kennedy Institute, first at Imperial College, London, and later at the University of Oxford, until 2014. Prior appointments include Assistant Professor of Medicine at Rutgers Robert Wood Johnson Medical School, USA, and Professor of Biochemistry and Molecular Biology at the University of Kansas Medical Center, USA.

Extracellular matrix (ECM) remodelling is essential for many biological processes, but uncontrolled may cause diseases such as arthritis, atherosclerosis, cancer, and neurodegenerative disease. My research has examined the structure and function of matrix metalloproteinases and tissue inhibitors of metalloproteinases and their roles in cartilage matrix destruction during the progression of OA. My early work showed collagenase locally unwinds triple helical collagen before hydrolysing the peptide. More recent work has focused on exosites in metalloproteinases that are critical for collegenolytic activity as potential targets to inhibit cartilage degradation. I also collaborate with other groups to apply proteomics approaches to understand how low-density lipoprotein receptor related protein 1 (LRP1) regulates extracellular matrix degradation and tissue homeostasis in cartilage.

### Jeremy Saklatvala

Jeremy Saklatvala is an Emeritus Professor at the University of Oxford. He qualified in Medicine in London and trained as a Rheumatologist before obtaining his PhD at the University of Glasgow on the biochemistry of inhibitors of leucocyte proteases. He was based in Cambridge for 20 years, first at the Strangeways Research Laboratory and subsequently at the Babraham Institute, before joining the Kennedy Institute in 1996. He played an instrumental role in moving the Institute to Oxford in 2013, before retiring in 2014.

My research has examined the molecular mechanisms of inflammation, with a particular interest in destruction of cartilage and other connective tissues in rheumatoid and osteoarthritis. My group was involved in the early isolation of interleukin 1 and its identification as a multifunctional inflammatory mediator causing tissue resorption. We have since worked mainly on the intracellular signalling mechanisms by which inflammatory stimuli control cell behaviours. This includes the recent identification of a MAP kinase family member as crucial for control of aggrecan turnover in cartilage.

# Research Partnerships and Clinical Translation

Ambitious science aimed at tackling major challenges in biomedical research often requires diverse ways of thinking and complementary skill sets. Kennedy Institute investigators are leading a number of large multidisciplinary research programmes that bring together diverse partners for maximum impact in experimental medicine and clinical translation.

## Novo Nordisk Immunometabolism Consortium

Metabolic diseases such as obesity, insulin resistance, type 2 diabetes and cardiovascular disease are associated with low level inflammation in affected tissues that is thought to contribute to disease pathogenesis. In 2016, Professor Claudia Monaco was awarded £1.8M from Novo Nordisk to lead an international, interdisciplinary research programme to explore this relationship between metabolism and inflammation in metabolic disease.

The consortium brings together investigators from four different research institutes at the University of Oxford, as well as investigators from the University of Copenhagen and the Karolinska Institute. The team will study both patient tissue samples and disease models to examine how metabolic stressors activate inflammatory signalling in metabolic tissues, guiding the development of new therapeutic approaches. The Kennedy Institute's CyTOF mass cytometry immune monitoring platform is enabling key aspects of this research.

> By focusing on inflammatory drivers of metabolic disease, we hope to identify new treatment strategies that target causes rather than symptoms of disease.


## Arthritis Research UK Centre for Osteoarthritis Pathogenesis

There are currently no disease-modifying agents for osteoarthritis, and analgesic therapies are often ineffective at treating chronic pain. The Arthritis Research UK Centre for Osteoarthritis Pathogenesis was created in 2013 with the aim of identifying pathological processes in osteoarthritis, and to create a seamless transition from laboratory discovery through pre-clinical modelling to clinical translation.

The Centre is directed by Professor Tonia Vincent and incorporates the work of more than 20 Principal Investigators from the Kennedy Institute and Botnar Research Institute, as well as researchers and clinical scientists from the Nuffield Orthopaedic Centre (Oxford), MRC Mutagenesis Unit (Harwell) and other sites across the UK.

Current research areas include: healthy cartilage turnover and mechanisms of joint destruction; risk factors and biomarkers; intrinsic cartilage repair; pain mechanisms; and approaches for imaging cartilage and joint integrity.

Within the Centre, Dr Fiona Watt leads a team that interfaces with OA translational activities including provision of infrastructure for access to human joint tissues and capacity to follow cohorts of individuals at risk of, or with established, osteoarthritis. Her team also participates in trials of new medical or surgical treatments and provides a gateway for collaboration with Industry.

The Centre receives £2.5M from Arthritis Research UK with matched funding from the University of Oxford and the KTRR.

> The Centre is in an excellent position to influence what, until now, has been a largely impenetrable disease.


# Research Partnerships and Clinical Translation

## Inflammatory Arthritis Microbiome Consortium (IAMC)

Recent studies have linked changes in the large and diverse number of bacteria that inhabit the gut to a wide range of diseases associated with chronic inflammation, including inflammatory arthritis. It is unclear if and how these changes in the intestinal 'microbiome' cause disease.

Established in 2016 by Professor Fiona Powrie, the IAMC brings together an international, multidisciplinary group of scientists for in-depth analysis of the role of the microbiome in inflammatory arthritis. The consortium utilises cutting-edge technologies in DNA and RNA sequencing, as well as metabolomics, to identify specific species of bacteria and their products that associate with disease onset, progression and response to therapy. Follow-up experiments in a germ-free setting will assess the potential to manipulate the microbiome to influence host immunity and chronic inflammation.

The IAMC includes investigators from the Kennedy Institute and the Botnar Research Institute, as well as from the University of Birmingham and University College London, and US collaborators from Harvard University, New York University and Mount Sinai Hospital, New York. The consortium is supported by a £2M Strategic Award from Arthritis Research UK, together with funding from the KTRR and the Colton Centre for the Study of Autoimmunity at the NYU School of Medicine.

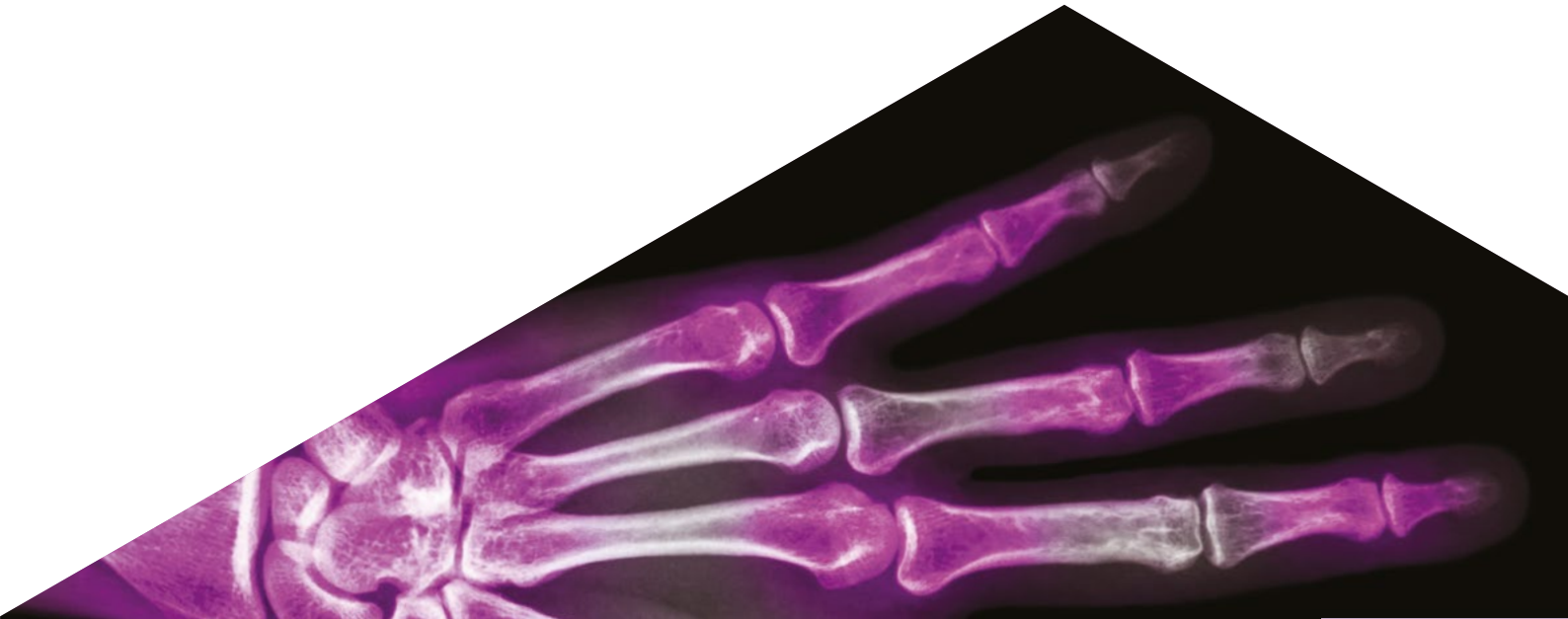
> The IAMC aims to bridge the gap between microbiome description and function, a key first step in unlocking the potential of the microbiome to yield new therapies for inflammatory diseases.

> Access to large, longitudinal patient cohorts in inflammatory bowel disease is a major strength of the OxBRC Gastroenterology and Mucosal Immunity theme, allowing investigators to test new therapies or stratified medicine approaches in the clinic.

## National Institute for Health Research Oxford Biomedical Research Centre (OxBRC)

OxBRC brings together the University of Oxford and the Oxford University Hospitals NHS Foundation Trust to accelerate translational research for the benefit of patients. The Centre runs more than 15 complementary research themes across a range of disease and therapeutic areas, two of which incorporate and support a range of research programmes underway at the Kennedy Institute. The 'Musculoskeletal Sciences' theme, led by Head of NDORMS Professor Andrew Carr, aims to drive development of new personalised therapies in inflammatory joint disease, degenerative joint disorders and rare bone diseases, and incorporates work from Kennedy Institute investigators, including Professors Michael Dustin, Sir Marc Feldmann, Jagdeep Nanchahal and Tonia Vincent.

Professor Fiona Powrie will lead the OxBRC 'Gastroenterology and Mucosal Immunity' theme from 2017. The theme brings together expertise in mucosal immunology, human immune profiling, single cell analysis, research endoscopy, and health informatics from across Oxford research centres, including the Kennedy Institute, the Translational Gastroenterology Unit (TGU), the Big Data Institute and the Department of Biomedical Engineering. Access to the TGU's large, longitudinal patient cohorts in inflammatory bowel disease is a major strength of this research programme. These and other well-characterised patient cohorts in inflammatory gastrointestinal and skin diseases allow investigators to probe novel disease drivers and apply this information for testing of new therapies or stratified medicine approaches in the clinic.



## Core Technology Platforms

> KIR investigators have access to key enabling technology platforms to innovate and advance their research.

With strategic support from the KTRR, we have invested in core technologies both within the Kennedy Institute and elsewhere on the Old Road Campus to enable new breakthroughs in inflammatory disease research. This investment has seeded state-of-the-art Small Research Facilities that include Flow Cytometry, Mass Cytometry, Imaging and Microscopy, Histology, Computational Biology, and IT and Informatics. The Old Road Campus provides cutting-edge proteomics facilities and screening technologies through the Target Discovery Institute and the Structural Genomics Consortium. Some of the KTRR funds have been used for a seed grant to facilitate the use of the Target Discovery Institute proteomics facility by investigators at the Kennedy Institute, which has been highly successful.

> We can now simultaneously interrogate cellular phenotype and function at the single cell level in unprecedented detail.

## Mass Cytometry

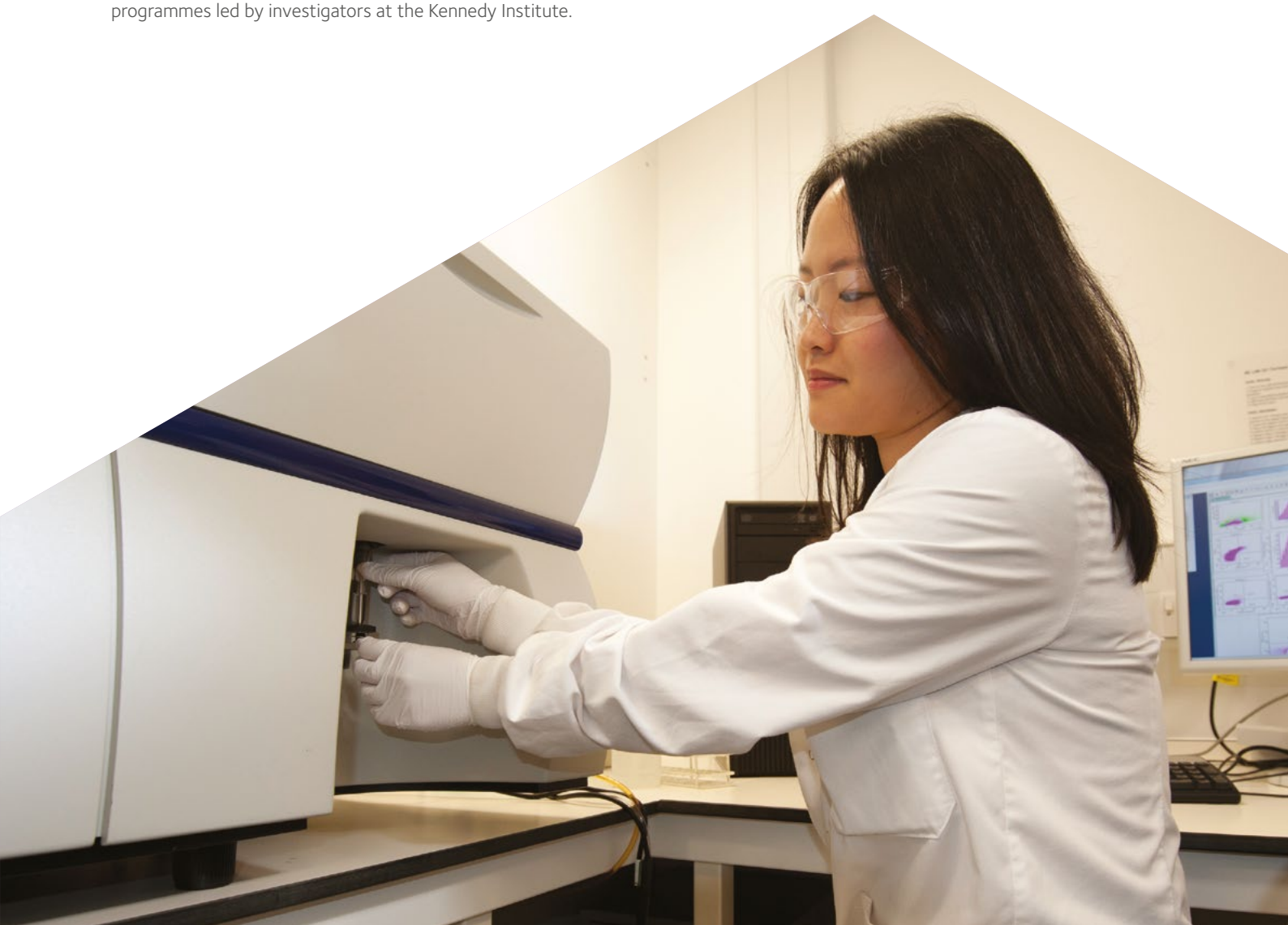
**Dr David Ahern**
Mass Cytometry Facility Manager

A better understanding of cellular responses in tissues in immune-mediated and chronic inflammatory disease is needed in order to identify novel disease drivers for design of better therapies. Mass cytometry has revolutionised the ability to profile a large number of parameters of immune cell function in tissues in health and disease. The cytometry time of flight (CyTOF) mass spectrometer provides the ability to quantitate tens of intracellular and extracellular parameters in single cells to simultaneously interrogate cellular phenotype and function in unprecedented detail. CyTOF mass cytometry is now being used at the Kennedy Institute and across NDORMS to unravel complex mechanisms underpinning disease in model systems, and to monitor the human immune response during chronic inflammatory disease progression and response to therapy. It is a crucial component of several large consortia and translational research programmes led by investigators at the Kennedy Institute.

## Flow Cytometry

**Dr Jonathan Webber**
Flow Cytometry Facility Manager

Flow cytometry is incredibly valuable for the discovery and definition of major and minor cellular subsets of the immune system, and for determining cellular subset abundance or signalling activity in healthy and diseased tissues. The Kennedy Institute Flow Cytometry facility has invested in several state-of-the-art analysers and sorters to support complex flow cytometry needs. The platform is also used for innovative assay development, for example optimisation of the cytokine capture method to isolate cells making up to three cytokines simultaneously. This has facilitated in-depth analysis of 'polyfunctional' cells, which are thought to be important drivers of autoimmune disease.



# Core Technology Platforms

> Completely new imaging and microscopy equipment used at the institute provides exciting opportunities for our investigators.

> We use state-of-the-art genomic approaches to accelerate understanding and treatment of inflammatory disease.

## Imaging and Microscopy

**Dr Volodymyr Nechyporuk-Zloy**
Imaging and Microscopy Facility Manager

The Kennedy Institute Imaging and Microscopy facility allows investigators to visualise biological processes from the localisation of single molecules in cells, to cellular activation in tissues, up to longitudinal measurements of disease progression in model systems.

The Imaging facility provides a small computational tomography system for tissue analysis and a system for correlating luminescence, fluorescence and CT imaging in vivo. This suite of instruments allows longitudinal analysis of disease models after genetic or therapeutic manipulation.

Microscopy equipment includes basic epifluorescence digital microscopes, live cell fluorescence microscopy, spinning disc confocal microscopy, point scanning confocal microscopy, two photon laser scanning microscopy and total internal reflection fluorescence microscopy. Many of the high-end fluorescent microscopes are set up for live cell or in vivo imaging to capture the immune response in real time. This equipment is being used to generate information about the location, dynamics, identity and functional state of molecular complexes within cells or of cells within tissues.

The Kennedy Institute is part of the Oxford-wide 'Micron' consortium and has forged strong alliances with the Wolfson microscopy facility at the Weatherall Institute. This has given Kennedy Institute investigators access to key technologies and is enabling the development of high-speed super-resolution microscopy in collaboration with Nobel prize-winning scientists. The Kennedy Institute is also collaborating with the Science and Technology Facilities Council in Harwell to build a novel microscope that measures inflammatory signatures in intact tissues without the use of any exogenous dyes or fluorescent proteins. This microscope will be located in Harwell, and will be accessible to Kennedy Institute investigators.

## Computational Biology

**Dr Stephen Sansom**
Group Leader, Computational Genomics

Recent breakthroughs in sequencing technology have driven a functional genomics revolution in experimental biology. Using genome-scale methods, researchers can now survey the entire landscape of cellular state and identity, short-circuiting traditional gene-by-gene methods. At the Kennedy Institute, cutting-edge genomic techniques such as single-cell RNA-sequencing and metagenomics (microbiome analysis) are being applied to accelerate understanding and treatment of inflammatory disease.

Analysis and interpretation of the wealth of digital data generated by genomics experiments is a computationally intensive task. The Kennedy Institute's Genomics High Performance Compute Facility - or KGen for short – is designed to provide virtual labspace for up to 20 skilled computational scientists. It is also vital for leveraging the fast-growing reservoirs of genomics and genetic data generated by the wider scientific community.

The KGen facility enables big-data, systems-biology approaches, which are expected to be important for disease stratification, patient monitoring and drug target discovery. Kennedy Institute investigators are using the facility to secure external funding for genomics-based studies, such as the £2M recently awarded to the Inflammatory Arthritis Microbiome by Arthritis Research UK.

## Histology

**Dr Bryony Stott**
Senior Research Technician (Histology)

Chronic inflammatory and degenerative disease is associated with underlying changes to tissue structure such as cell infiltration, fibrosis and bone remodelling. The Kennedy Institute's Histology facility allows researchers to accurately assess the composition of tissue samples to score osteoarthritis, gut inflammation and inflammatory arthritis. The facility provides an all-inclusive and high throughput service, supports routine histological stains and contributes to optimisation of immunohistochemistry protocols. It also provides expertise in specialised methods to work with calcified samples, such as bone. The Arthritis Research UK Centre for OA Pathogenesis provides substantial funding for the facility.

> We have developed the Scarab structured data capture platform to manage samples and anonymised patient information in clinical studies.

## IT and Informatics

**Dr Brian Marsden**
Principal Investigator, Research Informatics

The IT and Informatics team provides infrastructure and bespoke solutions to problems ranging from building management to the many aspects of institute administration, through to effective scientific data capture, processing and management.

The team works closely with many University departments and groups, for example collaborating with the Structural Genomics Consortium (SGC) Research Informatics team on development of the data capture platform Scarab, which underpins management of samples or anonymised patient information as part of clinical studies. The team also looks for new ways of making it easier for investigators to find, annotate and share particular datasets, as data gets bigger. The team also supports the Institute's high performance compute and storage platform, KGen, which allows researchers to investigate in great detail how genomic information has a direct impact upon disease.

**Jonathan Truslow**
Head of Operations

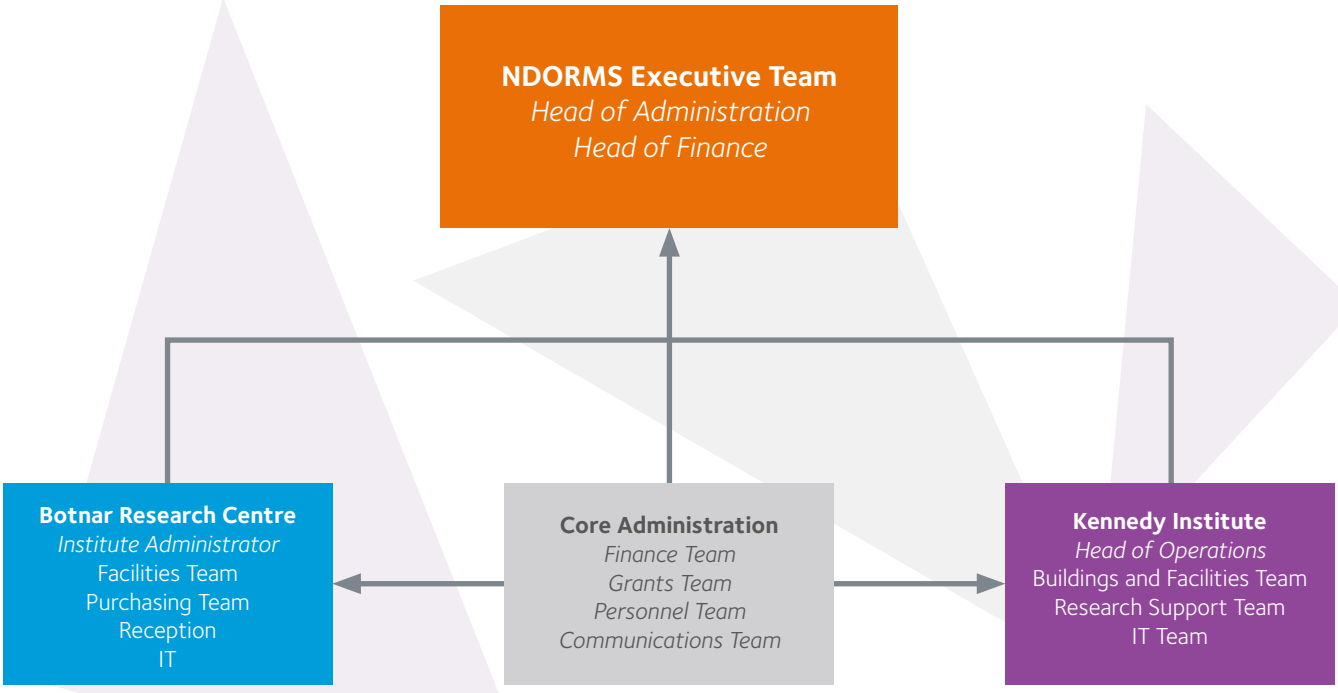
# Administration and Funding

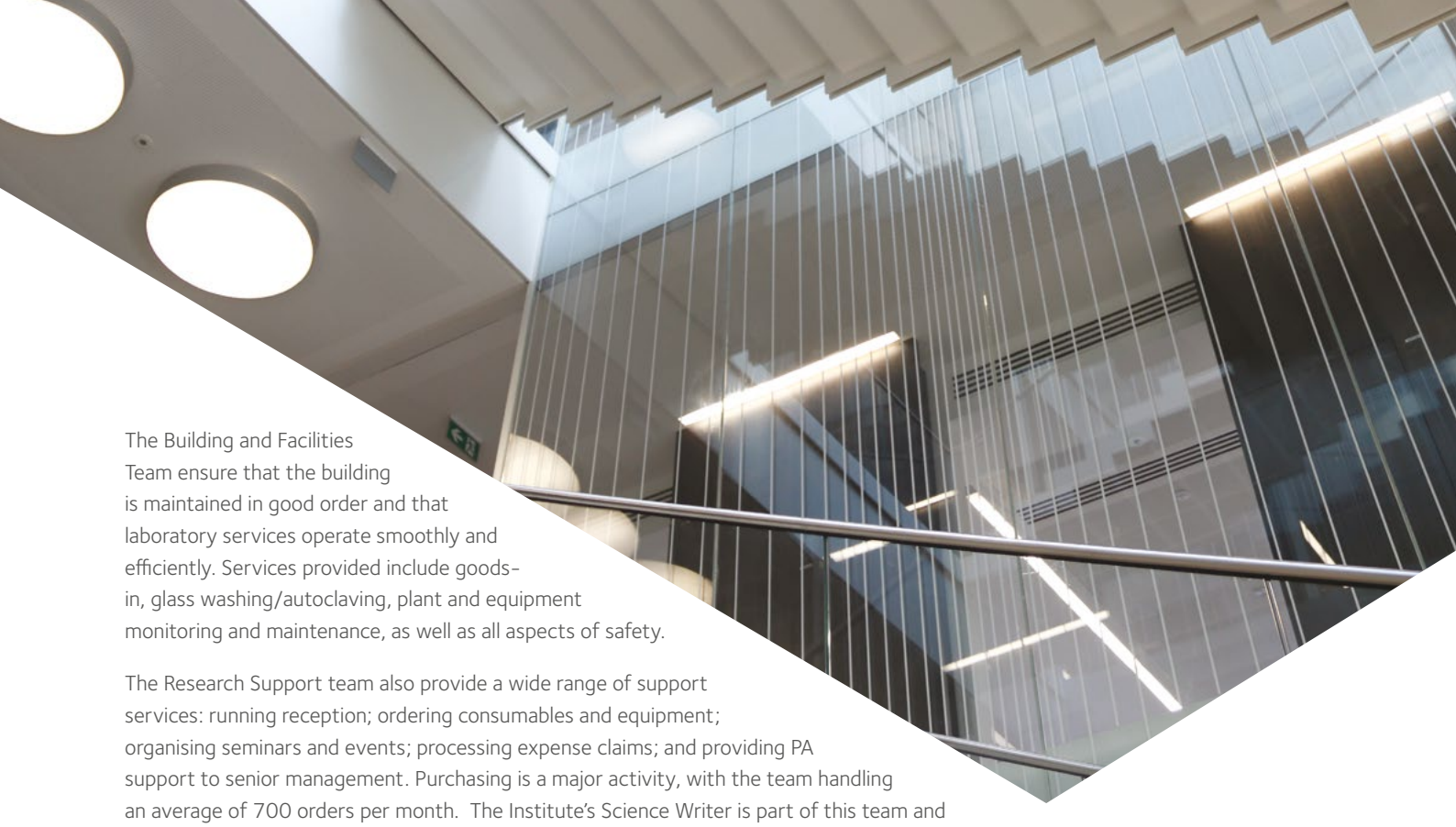
## Administration

Administration functions at the Kennedy institute are integrated within the departmental umbrella of NDORMS which supports the activities of both the Kennedy Institute and its sister unit the Botnar Research Centre. NDORMS core administration provides centralised support for finance, personnel, grant management and communications. NDORMS administration staff work closely with Jonathan Truslow, the Kennedy Institute's Head of Operations, through joint meetings and a regular presence at the Kennedy Institute.

Within the Kennedy Institute itself, three small teams provide a range of services to meet the day-to-day needs of the institute's researchers covering Buildings and Facilities, Research Support and IT.

### NDORMS Administration





The Building and Facilities Team ensure that the building is maintained in good order and that laboratory services operate smoothly and efficiently. Services provided include goods-in, glass washing/autoclaving, plant and equipment monitoring and maintenance, as well as all aspects of safety.

The Research Support team also provide a wide range of support services: running reception; ordering consumables and equipment; organising seminars and events; processing expense claims; and providing PA support to senior management. Purchasing is a major activity, with the team handling an average of 700 orders per month. The Institute's Science Writer is part of this team and assists in disseminating the Institute's work to a range of stakeholders.

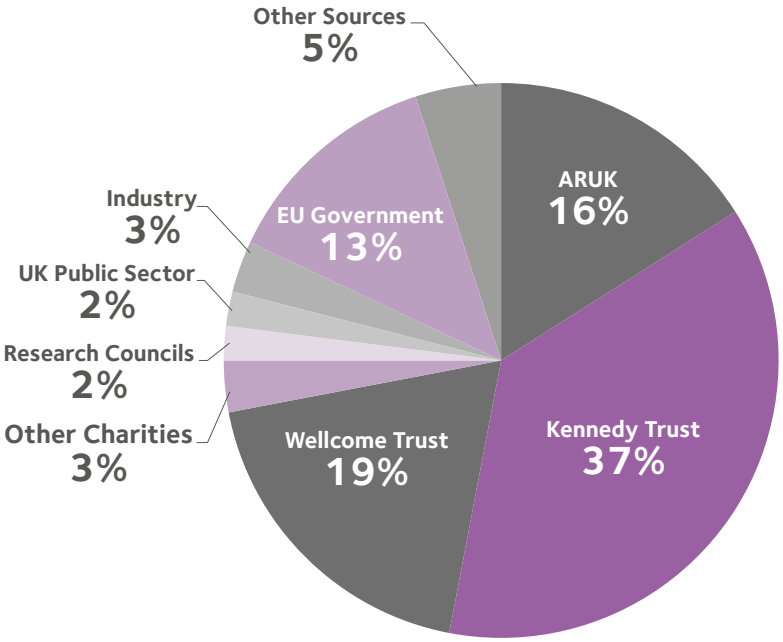
The IT team, which report jointly to Jonathan Truslow and Dr Brian Marsden (Principal Investigator, Research Informatics) keep all the Kennedy PCs, laptops and printers in top working order as well as managing any software development and assisting with any data management issues.

## Funding

The Kennedy Institute is a fully integrated part of the University of Oxford, but retains a special link with KTRR. The KTRR and the University jointly funded the new Kennedy Institute building. The KTRR also provided generous support for purchase of equipment for the new institute and continues to provide strategic funding to the director including a contribution to the costs of core services.

Our largest source of response mode funding is from the UK charity sector, particularly Arthritis Research UK and the Wellcome Trust. The EU represents our second largest source of funds and the University is making representations to the UK Government to ensure this funding can be maintained across the University long-term.

## 2015-2016 Grant Income



# Engaging the Public and Communicating Research

> NDORMS and the Kennedy Institute are committed to creating high-quality opportunities for the public and patients to engage with its research.

Supported by the NDORMS communications and public engagement team, the Kennedy Institute engages with a range of audiences at various stages of the research process and through different channels.

The vision across the Department is to empower patients and the public through a greater understanding of their own health, as well as to capture the imagination of primary and secondary school students.

In 2016 the Kennedy Institute joined NDORMS at the Oxfordshire Science Festival, which attracts up to 30,000 visitors per year. This provided staff and students with the opportunity to share their research with the public and inspire the next generation of biomedical scientists. The interactive stall included the Kennedy Institute's giant gut wall, as well as arthritis gloves, a microscope showing inflamed joint tissue, a table-top image card game and clubfoot surgery models.

Senior investigators at the institute also participate in Department-led and external speaking opportunities to educate the public on the latest research in chronic inflammatory and degenerative diseases, and what this means for patients.

Supported by the British Society for Immunology, Professor Fiona Powrie has given public lectures on the gut microbiome, including at the Edinburgh and Cheltenham Science Festivals. Within the Arthritis Research UK Centre for OA Pathogenesis, Professor Tonia Vincent and Dr Fiona Watt have given public talks and radio interviews on osteoarthritis, including on the BBC Radio 4 programme Woman's Hour. The Centre also launched the charity's 2016 Be The Difference Campaign in collaboration with the Daily Telegraph.

NDORMS runs various work experience programmes for GCSE and A-level students. In 2016 more than 10 students had the opportunity to spend time in the Kennedy Institute histology facility, gaining hands on experience in basic histology techniques and protocols.

## Kennedy Institute Artist in Residence

The Kennedy Institute is hosting an artist in residence, Francesca Corra. Funded by the Leverhulme Trust, this scheme promotes creative collaboration between artists and UK universities or museums.

Francesca will explore the disease process of hand arthritis and will produce a series of works focused on "arthritic diseases of the hand" and the "healing hands" of the physicians, therapists and surgeons who treat them.

Initially, the work will be exhibited at the Nuffield Orthopaedic Centre, Oxford. The series will then be displayed at the Kennedy Institute, as a reminder of the ultimate goal of arthritis research.

## The Giant Gut Wall

The Giant Gut Wall project was initiated to create an eye-catching exhibit that could be taken to science festivals and into schools to enthuse students about the growing area of microbiome research and explain why it is relevant to them.

A key part of the exhibit is a large magnetic wall depicting the structure of the gut at a microscopic level. Magnetised cuddly toys help researchers model what happens within the gut during health, as well as in inflammatory bowel disease and cancer. This is complemented by endoscopy videos to show what the gut actually looks like, as well as a microscopy challenge to identify diseased tissue, and an animated video to illustrate key concepts.

The interactive display was initially exhibited at the 2014 Royal Society Summer Science Exhibition, and has since been used at numerous outreach events, including the BBSRC Great British Bioscience festival, Brighton Science Festival and the 2016 Royal Society Science Exhibition, as well secondary and primary school visits.

**169** STAFF AND VISITORS

**25** GROUP LEADERS

**37** STUDENTS

**27+** NATIONALITIES

**£9m** ANNUAL INCOME

**£50m** TOTAL GRANTS PORTFOLIO

**120** TOTAL NUMBER OF GRANTS

**13** PATENTS FILED SINCE 2013

**7332 sqm** TOTAL KENNEDY SPACE

## Contact us

For more information about the Kennedy Institute of Rheumatology, visit our website at: www.kennedy.ox.ac.uk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Athena SWAN Silver Award

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