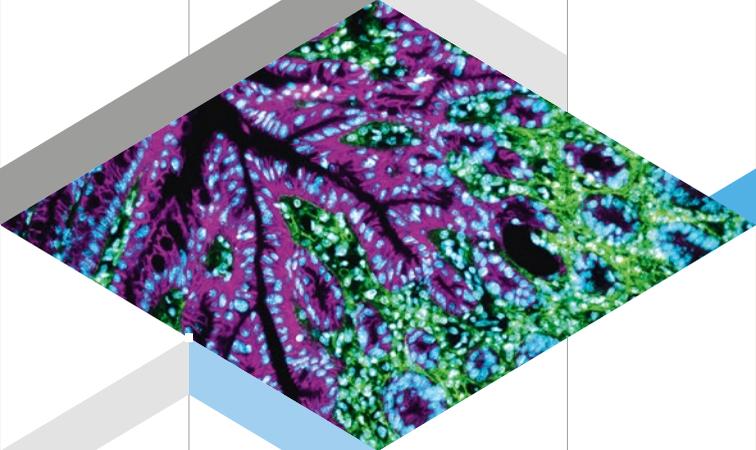




KENNEDY
INSTITUTE OF RHEUMATOLOGY | NDORMS



BRIDGING
THE GAP
Kennedy Institute
Report 2018

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Kennedy Institute Report 2018

A BOLD VISION

From discovery research that reveals basic principles of biology in health and disease, to the study of patient tissue samples and clinical trials, our ambition is to identify disease pathways for application in the clinic. By focusing on pathological processes across different types of disease, and in defined patient groups, our work is driving innovation in diagnostics and therapeutics.

At a glance

AT THE HEART OF IT

Just over 20 years ago, a unique combination of basic science, human immunology and experimental medicine at the Kennedy Institute led to the development of anti-TNF to revolutionise the treatment of rheumatoid arthritis.

This same collaborative spirit is just as important today. The Institute brings together diverse teams of researchers who apply state-of-the-art technologies across disciplines to make fundamental discoveries that help us understand what goes wrong in inflammatory and degenerative diseases.

But our work does not stop there. To accelerate our understanding of disease into the clinic, the Kennedy Institute partners with clinical units, research hospitals and industry for the development and testing of transformative new therapeutics.

This interactive approach leverages both the Institute's location on the University of Oxford's Old Road Campus, and its position within the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) within the Medical Sciences Division.

151

staff

43

students

30

nationalities

28

group leaders:
13 are female and
12 are early-stage
independent investigators

14

staff and DPhil
student clinicians





“The arrival of the Kennedy Institute in 2013 has reinvigorated research into inflammatory disease in Oxford. Under Fiona Powrie’s direction, the Institute has built upon its historical success in joint disease, and expanded its reach to address a number of immunological and inflammatory disorders affecting other organ systems. Whilst firmly rooted in basic science, the Institute is driven by the desire to translate its findings into new treatments, which is supported by extensive clinical trial activity on the Old Road Campus, and in collaboration with colleagues in Birmingham.”

Professor Gavin Screaton, Head of Medical Sciences, University of Oxford

“Much will be achieved by bringing together the Kennedy Institute and the Botnar Research Centre under the NDORMS umbrella. There is already evidence of strategic funding and publication successes, as well as positive trial data, as a result of collaboration between the two institutes. Looking ahead, we are strengthening ties between our basic and translational research programmes, including in the areas of tissue biology and bioengineering. Both institutes will also benefit from the newly created NDORMS Chair of Clinical Therapeutics that will seek to translate novel therapies quickly and sustainably from laboratory to clinic.”

Professor Andrew Carr, Head of NDORMS, University of Oxford



7,332

sqm total Kennedy space

£68m

total grants portfolio

£15m

annual turnover

17

fellowships in 2017/18

112

publications in 2017/18

BUILDING ON OUR FOUNDATIONS



Professor Fiona Powrie talks about the progress of the Kennedy Institute over the past two years.

Since our last report two years ago, we have moved from a period of laying foundations to one where we are gaining the critical mass and momentum to deliver our strategy. In these pages we highlight our science and scientists, as well as the approaches we are taking to enable discovery research that can be applied in the clinic to combat chronic inflammatory and degenerative disease.

Science has a history and culture, and this is very true at the Kennedy Institute. Although we have grown from 60 to over 200 staff and students since the new Kennedy building opened in Oxford in 2013, the Institute retains its strong sense of community. In true Kennedy spirit, many of our researchers work across research groups and themes to apply multidisciplinary science, and cross-pollinate basic and clinical research.

Our people are our biggest asset, and I am delighted we have been able to attract great scientists at all stages of their careers from around the world. To support our researchers, we have continued to develop our state-of-the-art core technology platforms, and there is now a real sense of excitement at what can be achieved. The combination of talented researchers and outstanding technology has led to significant success with grant funding, with many of our researchers obtaining prestigious awards from the Wellcome Trust, UK Research Councils, the European Research Council, and Versus Arthritis.

Science is becoming increasingly interdisciplinary, and we are using our technology platforms as a basis to develop collaborative networks within the Kennedy Institute, across Oxford and beyond to draw upon diverse expertise to catalyse scientific innovation. The new TIRF-SIM microscope, built here at the Kennedy Institute in collaboration with partners across Oxford and internationally, is a wonderful example of what can be achieved by working with others. One of the first of its kind, the microscope will allow researchers to track biological processes at nanoscale in living cells, and it will have many applications throughout the Institute.

OUR STRATEGY



Building on the Institute's new germ-free facility and capabilities in computational biology, we have also opened the Oxford Centre for Microbiome Studies this year. This provides Oxford researchers with a unique opportunity to decipher host-microbe cross-talk in health and disease, moving from correlative to functional studies that may help unlock the therapeutic potential of the microbiome.

From an ambition in 2016 to reality in 2018, we have built a number of links between discovery science and clinical medicine in the Institute to drive the application of our discoveries towards the clinic. Professor Christopher Buckley joined us last year as a joint appointment with the University of Birmingham. He leads the Arthritis Therapy Acceleration Programme (A-TAP), an innovative translational network to accelerate the testing of new therapies for immune-mediated inflammatory diseases.

A-TAP is complemented by two new initiatives in career development: a new PhD programme for clinician scientists funded by the Kennedy Trust for Rheumatology Research (KTRR); and a bespoke career development programme for clinician scientists as they embark on their independent careers. Our expansion into clinical translation is bearing fruit with promising early results from a Kennedy-run trial of anti-TNF in fibrotic disease.

We cannot undertake the translational journey alone, and we have established important clinical partnerships, as well as links to industry that bring commercial resources and expertise. We are now building capabilities in clinical informatics and machine learning to integrate large experimental and clinical datasets to understand how disease evolves over time, and in response to therapy in different groups of patients.

I am really impressed with the progress we have made towards our goals. This would not have been possible without the generous support of the KTRR and other funders. I have no doubt that the combination of our creative scientists and inspiring environment will continue to drive many exciting opportunities and discoveries in the future.



From new PhD students at the very beginning of their research career, to new Group Leaders, the Kennedy Institute provides outstanding training opportunities and tailored support to help talented scientists fulfil their potential.

NURTURING AND DEVELOPING TALENT

The Kennedy Institute provides a welcoming and scientifically stimulating environment for its large and vibrant community of trainees.

“There is the feeling of possibility, that we can ask the critical questions and have the support of the Institute to develop groundbreaking approaches to address them.”

**Dr Lilian Lam, EMBO Long Term fellow,
Powrie Group**

Students are offered a world-class, comprehensive DPhil training programme that includes rigorous scientific training, as well as the teaching of transferable skills, careers advice and mentoring. Each year, up to seven KTRR Prize Studentships are awarded to high-calibre DPhil students from across the world, and this now includes a tailored DPhil training program for clinician scientists. We also host students funded through other highly competitive programmes, including those run by the UKRI, Wellcome Trust, and charities including Versus Arthritis and Cancer Research UK.

A number of mechanisms are in place to enhance the scientific training and overall experience of postdoctoral fellows at the Institute. In addition to training from Group Leaders, postdoctoral fellows receive guidance from staff within the Institute's core technology platforms, and have access to University-run courses teaching transferable skills. They can also take advantage of teaching opportunities within the Department, and nurture their management skills by taking on supervisory responsibilities.

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.

To foster interaction and collaboration across the Institute, we organise a lively internal seminar programme, weekly journal clubs, and an annual Student Symposium, as well as a number of social events throughout the year.

Our people and talent continued



Profile

Clarissa Coveney

Clarissa is a fourth year KTRR Prize DPhil student at the Kennedy Institute.

She joined the Institute's DPhil programme in 2015 with substantial research experience, having previously worked in laboratories at University College London as a Biochemistry undergraduate and summer student, as well as at the Oxford Centre for Diabetes Endocrinology and Metabolism as a research assistant.

Within Dr Angus Wann's group, Clarissa examines a structure on the cell surface called the primary cilium and its ability to orchestrate signalling pathways that link to osteoarthritis development.

Speaking of the KTRR Prize Studentship Programme she says, "Thanks to the Kennedy Trust and the support of the Versus Arthritis Centre for Osteoarthritis Pathogenesis, I have received world-class PhD training, with access to fantastic supervision, facilities, career development programmes and leadership. The additional collaboration with clinicians within the department has also helped to elevate the translational relevance of my research, which was highly important to me."



Profile

Lilian Lam

Dr Lilian Lam is an EMBO Long Term Fellow working as part of the Inflammatory Arthritis Microbiome Consortium to decipher the interplay between gut microbes and inflammatory arthritis.

Lilian has a long-standing interest in microbial ecology studied through the lens of human disease. During her PhD studies at Stanford University, she additionally earned a Master of Science in Medicine Degree pursuing translational research to address how bacteria in the gut control the spread of Salmonella infection.

Drawn to the Kennedy Institute because of the emphasis on multidisciplinary approaches and translational research, Lilian explains, "Access to large patient cohorts through the consortium is invaluable. As a network of allied labs and physicians, we can maximize what we can learn from patients by combining our expertise in microbiology, immunology, and computational biology."

Lilian's research in Professor Fiona Powrie's group builds upon previous studies suggesting disease-causing bacteria in the gut are coated with large amounts of the antibody IgA. She is using special sequencing techniques to characterize IgA-coated bacteria in ankylosing spondylitis patients, with the hope of revealing clues into the microbial drivers of disease.

NEW GROUP LEADERS: A FOUNDATION FOR SUCCESS

Almost half of the Kennedy Institute's Group Leaders are early-career scientists. The Career Development Programme was launched to support these individuals as they develop their independent research careers.

"Our goal is to provide junior Group Leaders with a foundation for success, and to help them get the most out of being in this exciting research environment within one of the world's top Universities," says Professor Michael Dustin. As Programme lead, Mike oversees the tailored support provided to new investigators which involves a structured programme including mentorship and review.

This targeted support includes a distinct Clinical Career Development Programme, led by Professor Christopher Buckley, that takes into account the unique career progression and challenges of being a physician scientist. The clinical track was put in place to support an increasing number of clinician scientists in the Institute who bridge the gap between discovery and translational science.

There are two distinct entry points onto the Career Development Programme. Senior Research Fellows are recruited to the Institute, supported by a generous funding package from the KTRR, and current fellows have each gone on to secure highly competitive individual support from the Wellcome Trust and UKRI. The programme also attracts Career Development Fellows supported by various funders and charities.



Profile

Alexander Clarke

Dr Alexander Clarke is a Clinical Scientist and Consultant Rheumatologist, and the newest recruit to the Kennedy Institute's team of Group Leaders.

After training in Medicine and Rheumatology in London, Alex had his first foray into immune cell metabolism while studying for his PhD with Professor Tim Vyse at King's College London. "Taking a lead from genetic studies, our research led to one of the first reports of abnormal autophagy in autoimmune disease," he says.

To hone in on mechanism, Alex joined Professor Katja Simon's laboratory in Oxford as a Wellcome Trust Clinical Postdoctoral Research Fellow. Using a mass spectrometry approach to analyse metabolism in rare cell populations, he found certain B cell subsets rely on autophagy to adapt to their environment.

In 2018, Alex was awarded a Wellcome Trust Clinical Research Career Development Fellowship to launch his own research group examining how metabolism regulates damaging antibody responses in autoimmune disease.

This award represents a step towards the Kennedy Institute's expansion into clinical research. Alex's research will benefit from carefully curated patient populations and clinical networks made available through A-TAP. He will also receive a career development plan crafted for clinicians including a schedule for mentoring, feedback, evaluation, and progression to tenure.

A FOCUS ON DISCOVERY

Discovery research is a major focus at the Institute. Our work is revealing the biological processes that promote health – and how these pathways go wrong in disease. This goes beyond individual scientists working on their own research problem at the bench. Researchers at the Institute work collaboratively and across teams to adopt a multidisciplinary approach, enabled by our technology platforms, as well as through partnership with many other basic and clinical research centres.



Our discovery research spans three thematic areas: immunity and microbiome; inflammation biology; and tissue remodelling and regeneration. We believe a focus on specific research areas that are highly relevant for understanding chronic inflammatory and degenerative disease maximises the impact of our research for clinical translation – a cross-cutting theme across the Institute. Within these themes, we are expanding our research to incorporate new disciplines, such as physical sciences and mathematics, to facilitate innovation and scientific advance.

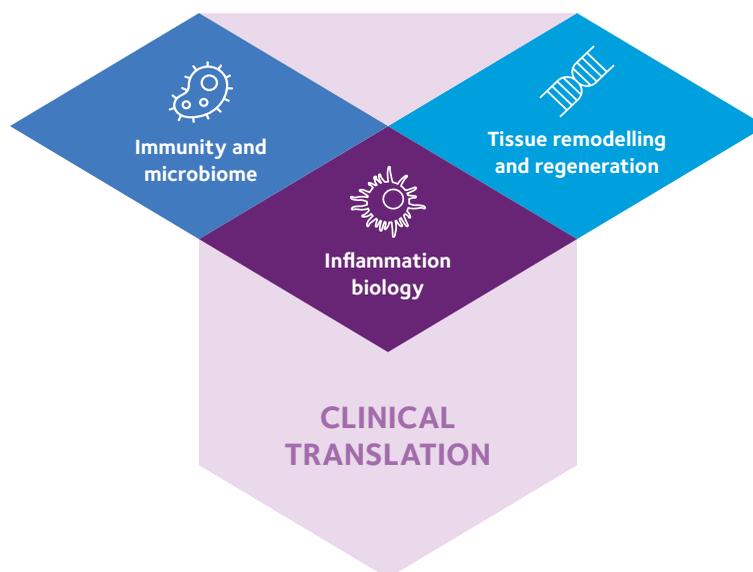
To deliver a breakthrough in each of our themes, we have built state-of-the-art technology platforms organised through a number of Strategic Programmes and Platforms that create a focal point for technology development. These initiatives also help build strategic networks for sharing insight, expertise and technologies across the Institute, throughout the University and both nationally and globally, to extend the reach and impact of our work.



Kennedy Institute Strategic and Platforms

- Cellular Dynamics Platform
- Oxford Centre for Microbiome Studies
- Tissue Biology Programme
- Computational Biology and Clinical Informatics Platforms
- A-TAP

RESEARCH THEMES



Immunity and microbiome

The immune system employs diverse strategies to protect the host against dangerous microbes and tumour growth. We investigate how the immune system detects foreign invaders, and examine the cell types, receptors and signalling pathways that tune the response to the level and type of threat. Aberrant activation of the immune response towards the host can lead to tissue damage and disease, and our work aims to identify the cellular, genetic and environmental factors that control this response. We are also interested in the mutually beneficial relationship between the immune system and microbes that inhabit the gut and other body surfaces, and how this changes in disease. These studies provide insight into the causes of autoimmune disease that can be used to develop new treatments, and may guide the design of vaccines and other approaches that harness the immune system to treat infection or cancer.

Inflammation biology

Inflammation is a complex biological process that – in combination with the immune response – is employed to clear infection and damage, and to initiate tissue repair. It is also a driving force behind many chronic diseases: arthritis, inflammatory bowel disease, atherosclerosis, and cancer, to name just a few. Recent research shows that many of the inflammatory pathways that protect against infection and injury are also active in disease. Our research is characterising inflammatory cells and the complex positive and negative feedback loops that determine whether inflammation is appropriately switched on or off in tissues. In particular, single-cell genomic and proteomic approaches are being applied to define signalling and regulatory pathways that underpin the behaviour of diseased tissue. This provides basic insight into disease processes and reveals strategies for the development of new biomarkers and therapies.

Tissue remodelling and regeneration

An overarching aim is to understand 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 mediate healthy tissue repair, and dissect how these activities become unbalanced in disease. A major component of this work takes place within the Versus Arthritis Centre for Osteoarthritis Pathogenesis, and focuses on the pathways that regulate cartilage wear and repair in joints. However, our research in this area also examines many other processes including fibrosis and fibrotic disorders, tumour growth and progression, wound and fracture repair, as well as the application of stem cell technologies.

PROGRESSING BASIC SCIENCE INTO THE CLINIC

We strive to apply our discovery research defining the molecular underpinnings of disease for the development of new drug targets or approaches for patient stratification.

Several exciting discoveries made at the Institute are now being tested in clinical trials, including studies to assess whether biologics to target inflammatory cytokines interfere with the disease process in patients with fibrotic disorders, and inflammatory bowel disease.

Central to our work is the application of immune phenotyping and molecular technologies for analysis of patient tissue samples. This is being used to redefine disease at a molecular level for the development of new treatments and biomarkers, and to understand how drugs affect the disease process in tissues. We are also developing innovative approaches for integration of molecular data sets with patient health records.

A-TAP was launched to bridge discovery research and clinical science and to build a translational research network enabling experimental medicine trials in the area of immune-mediated inflammatory disease.

► See page 26 for more about A-TAP

Our translational programmes and clinical research rely on strategic partnerships with the Nuffield Orthopaedic Centre, the Translational Gastroenterology Unit and other clinical departments within the Oxford University Hospitals NHS Foundation Trust, as well as with NHS Trusts that provide access to patients and create a network of clinicians and other healthcare professionals along the M40 corridor between Oxford and Birmingham.



TRACKING CELLULAR DYNAMICS ACROSS SCALES

The latest advances in microscopy and related methods are allowing researchers to visualise how cells function in unprecedented detail.

A DETAILED LOOK AT LIVE CELLS

Activation of T cells is the first step in generating targeted immunity against particular pathogens or tumour cells. But it is also a key process that goes wrong in autoimmunity. Kennedy Institute scientists are able to study cellular activation and other membrane events, in unprecedented detail, using super-resolution microscopy methods that have changed the limits of optical resolution.

The next step is to combine super-resolution microscopy with live cell imaging, which is “a dream of many biologists,” says Mike. To achieve this, his team have joined forces with Dr Marco Fritzsche at the MRC Weatherall Institute for Molecular Medicine, and Nobel Laureate Professor Eric Betzig to build a next generation of microscope that enables super-resolution microscopy of live cells.

This approach has allowed Marco to visualise the organisation and mechanical function of the cytoskeleton actin – a dynamic scaffold required for the active movement of cells that underpins successful immune responses. Several laboratories have been involved in the testing phase of the new system, and it is now open to all members of the Institute and Oxford community.

“Many investigators who would not have considered an imaging approach due to prior limitations, will now find these technologies useful for the first time,” says Mike. “It will now be key to educate researchers about the utility of the platform and the new system, in particular.”

The Cellular Dynamics Platform at the Kennedy Institute provides state-of-the-art technologies and know-how to explore the dynamics of the immune response, from analysis of single molecules in cells, to the visualisation of cellular activation in tissues and mapping of cellular networks in disease.

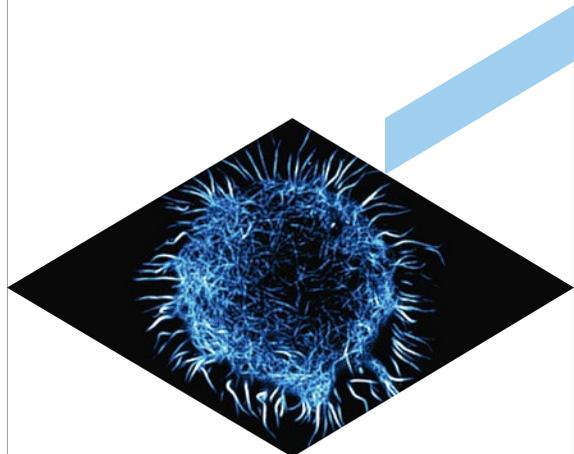
“The goal is to give our scientists an edge in addressing the most pressing questions about the function of cells in tissues, dysfunction in disease and corrective measures that can be taken,” says Professor Michael Dustin who leads the Platform. “To accomplish this, we must innovate on many fronts, both within the Institute and by joining forces with others, to gain greatest leverage to solve problems previously thought beyond reach.”

9

imaging systems

>8,000

hours spent using microscopy systems annually



Feature: Cellular Dynamics Platform continued

A CELLULAR RESPONSE IN 3D

Cells of the immune system travel extensively within tissues and throughout the bloodstream and lymphatic system as they seek out instructions on when and how to activate an immune response. Kennedy Institute researchers are using “intravital” microscopy to probe this movement and the natural dynamics of the immune response deep in tissues.

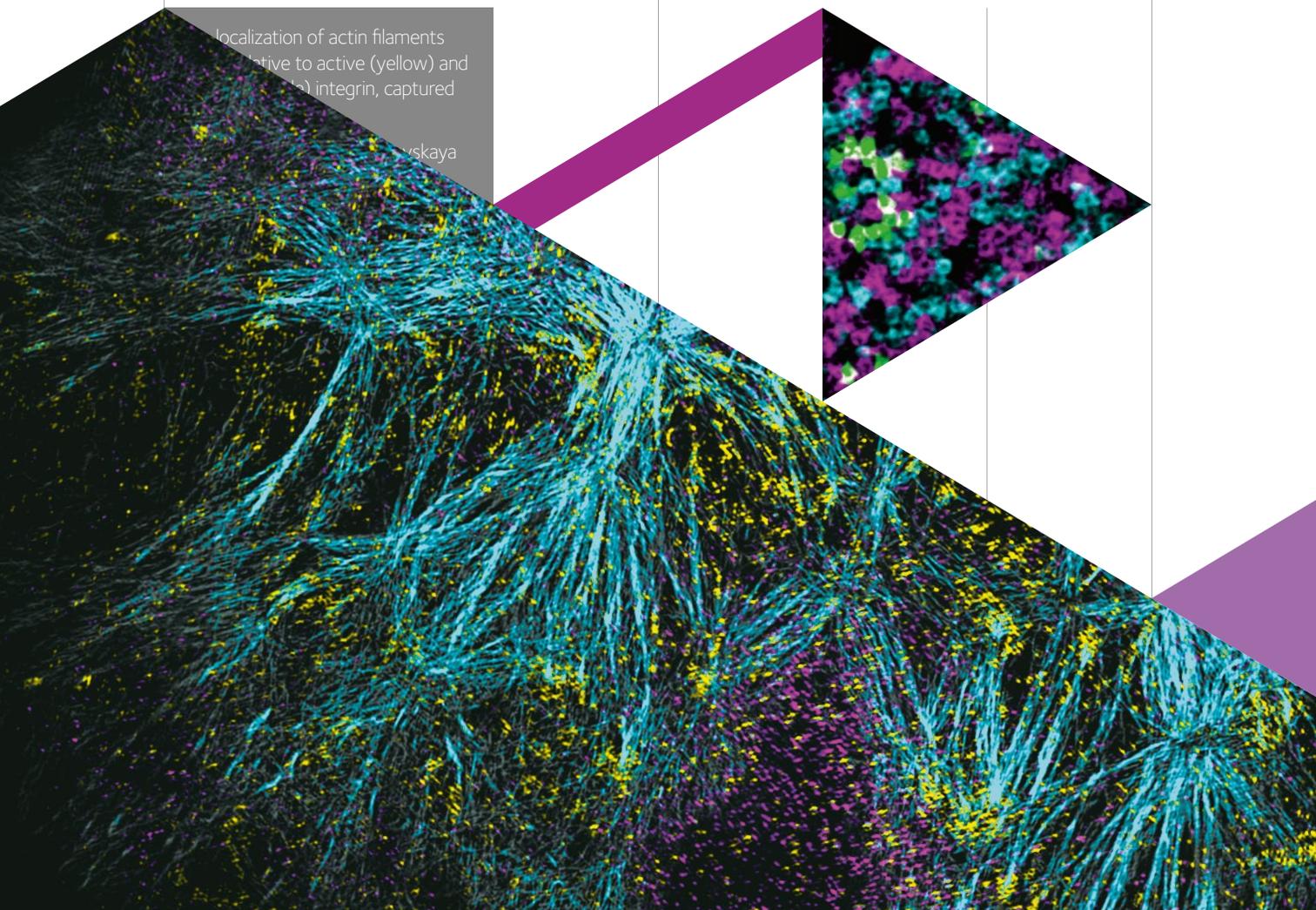
“Immune cells must position themselves in the right place at the right time,” says Dr Tal Arnon, a KTRR Senior Research Fellow at the Kennedy Institute. Tal’s research examines B cells in the spleen that defend against blood borne pathogens that could otherwise lead to sepsis.

By applying the latest advances in intravital imaging, together with genetic models, Tal can assess how B cells interact with their environment and other immune cells to support proper migration and activation. This insight could help guide the development of better vaccines against pathogens such as malaria and HIV.

KTRR Senior Research Fellow, Dr Audrey Gérard, also uses intravital microscopy to visualise immune cells across space and time. Her research examines a relatively unexplored area of immunology – how T cells organise themselves as part of an ecosystem.

Audrey believes that T cells communicate and co-operate with each other during infection to generate a collective response sufficient to fight off the pathogen without causing damage to the body’s own tissues. She hopes to understand the immune system as a whole to help develop new tools to turn off autoimmunity.

Through the Cellular Dynamics Platform researchers at the Kennedy Institute and across the University of Oxford are also able to explore how gut microbes impact cell signalling, migration and activation in tissues in real time. This will pave the way for a more precise understanding of how the microbes that inhabit our bodies influence health.



MAPPING CELLULAR NETWORKS IN TISSUES

Imaging studies allow researchers to track specific molecules inside, and on the surface of, defined populations of immune cells. The Kennedy Institute's CyTOF Mass Cytometry facility enables a complementary approach to map the different types of cells in blood and tissues at the single cell level.

"CyTOF represents a powerful approach to survey the immune landscape in inflammatory disease," says Professor Claudia Monaco, who leads the facility. Claudia has used CyTOF to show inflammatory myeloid cells build up at the expense of resident myeloid cells in arteries affected by atherosclerosis.

Having demonstrated the success of this approach for monitoring small cell populations, she is now extending these studies to analyse the composition of immune cells in the blood and arteries of patients with cardiovascular disease. "Single cell approaches like CyTOF are the start of a whole new opportunity to understand the function of immune cells embedded in vessel walls," she says.

The technology is also being applied to identify new subtypes of cells associated with autoimmune disease. "Using CyTOF, we have identified cell surface markers that can be used in FACS-sorting to isolate different flavours of neutrophils in the blood of patients with autoimmune diseases," says Professor Irina Udalova. This has spurred efforts to define neutrophil populations as biomarkers and targets for therapy.

The CyTOF platform is now an essential component of many of the translational research programmes underway at the Institute, including in the areas of inflammation, cancer and cardiovascular disease.



Profile

James Felce

Almost a third of all drugs target the G protein-coupled receptor (GPCRs) superfamily. Dr James Felce focuses on a subset of these receptors – chemokines – and how they influence T cell activation.

A biochemist by training, James gained his DPhil working with Professor Simon Davis, in Oxford, studying how GPCRs physically interact with one another to influence their behaviour.

"This involved the development and use of new techniques in biophysics and imaging, which encouraged me to move into a more imaging-focused field," says James. "Staying on in the lab as a postdoc, I also moved into the area of immunology, focussing on activation of antigen-recognition receptors."

James joined the Kennedy Institute in 2016 as a Sir Henry Wellcome Fellow. "I approached Mike as a potential sponsor of this fellowship application because he is a world leader in the use of microscopy and biophysics to study immune cell activation, yet is situated in a highly interdisciplinary environment."

"Thanks to direction by Mike and the rest of the leadership of the Kennedy Institute, we now have access to cutting-edge imaging technologies that allow us to tease apart the molecular mechanisms behind these vital immunological processes."

Publications

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Mayya et al. Cell Rep. 2018 22(2):340
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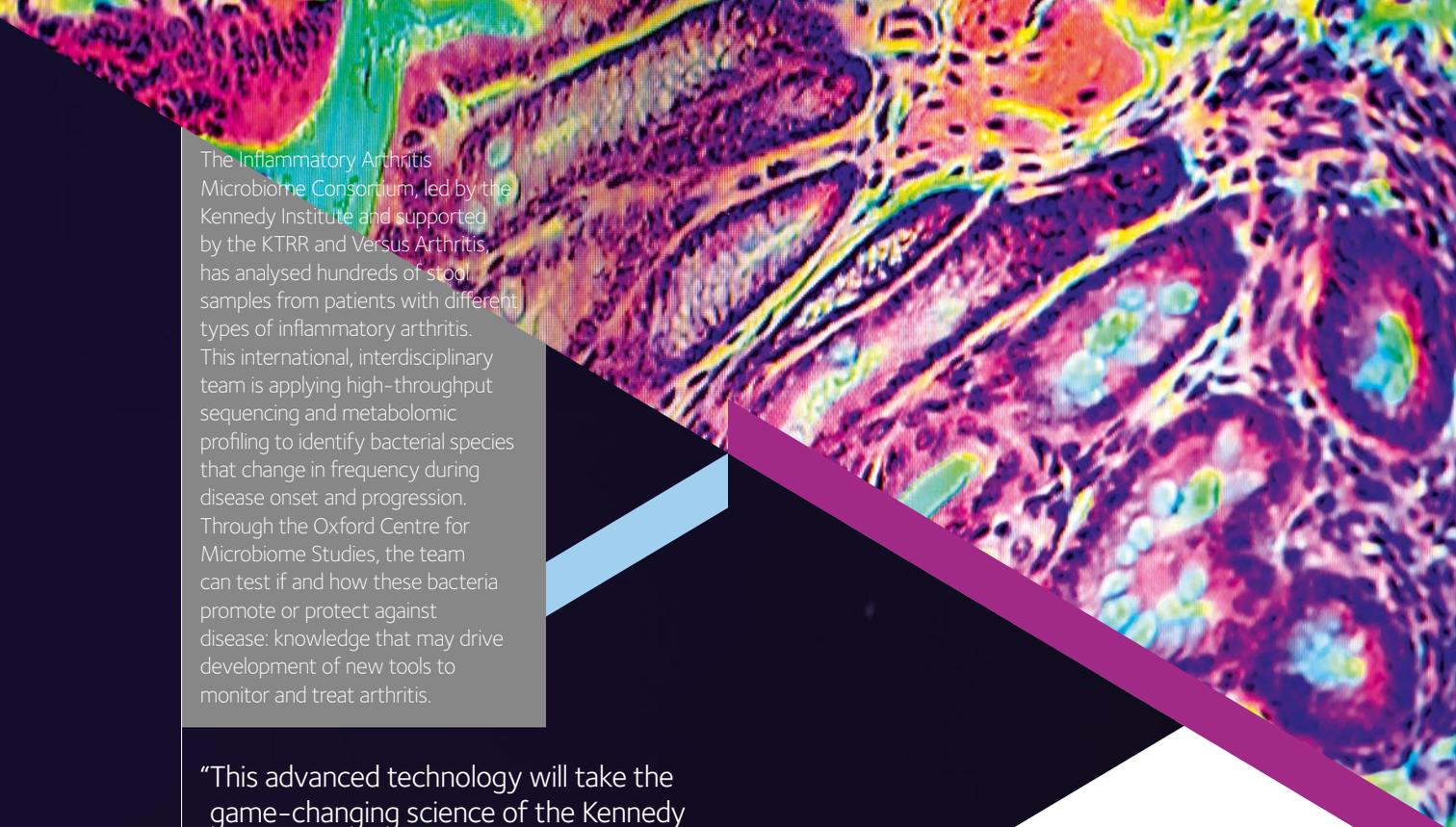
Feature: Oxford Centre for Microbiome Studies

MICROBIAL MATTERS

The human body is teeming with microbes. The gut and other body surfaces are covered in trillions of bacteria – the so-called microbiome – that promotes our well-being. Located within the Kennedy Institute, the Oxford Centre for Microbiome Studies seeks to accelerate research to unravel how these microbes underpin health and disease; from ageing and mental health to inflammatory bowel disease, arthritis and cancer.

Publications

Danne et al. *Cell Host Microbe*. 2017 22(6): 773
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The Inflammatory Arthritis Microbiome Consortium, led by the Kennedy Institute and supported by the KTRR and Versus Arthritis, has analysed hundreds of stool samples from patients with different types of inflammatory arthritis. This international, interdisciplinary team is applying high-throughput sequencing and metabolomic profiling to identify bacterial species that change in frequency during disease onset and progression. Through the Oxford Centre for Microbiome Studies, the team can test if and how these bacteria promote or protect against disease: knowledge that may drive development of new tools to monitor and treat arthritis.

“This advanced technology will take the game-changing science of the Kennedy Institute to another level, by allowing precise studies of the mechanisms that drive interactions between our bodies and the microbes that inhabit the gut and body surfaces.”

Professor Andrew Macpherson,
Director of Gastroenterology,
University Hospital, Bern,
Switzerland

Recent research links imbalances in the types of bacteria in our body to chronic disease. But how different types of bacteria interact with body systems to benefit the host or cause disease is largely unknown.

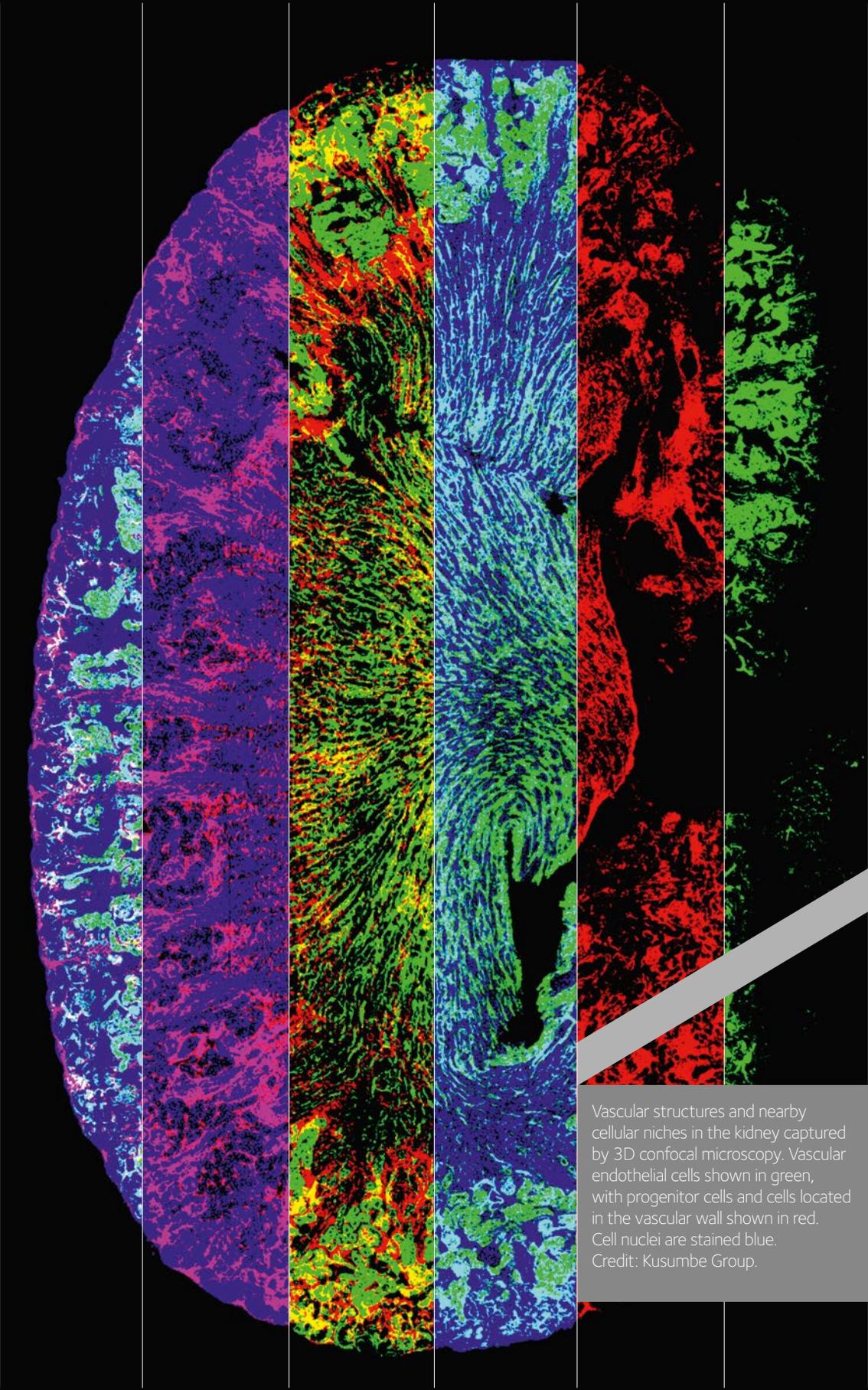
The Oxford Centre for Microbiome Studies opens up technology platforms at the Kennedy Institute for complete analysis of the microbiome. Using high-throughput sequencing and computational biology, researchers can pinpoint specific bacterial species – and their products – that associate with disease. The Institute’s new germ-free facility (one of only a few in the UK) offers the opportunity to directly test the impact of these bacterial species of interest on host physiology and pathophysiology. This represents a first and essential step towards harnessing the microbiome for new strategies to treat and prevent disease.

Work in the Centre covers a range of scales from cohort-based studies to identify changes in the microbiome in arthritis patients to the identification of bacterial products that have immune-regulatory properties.

Professor Fiona Powrie, who leads the Centre, says, “This initiative will galvanize and unite an interdisciplinary network of scientists to apply the most advanced technologies to uncover key features of the interplay between intestinal microbes and the host. Our new germ-free facility provides essential technology to move beyond association studies to identify functional pathways through which microbes communicate with their hosts. This knowledge will help us harness the power of the microbiome to promote health and prevent disease.”

Microbiome research is increasingly interdisciplinary, drawing on tools from ecology, environmental microbiology, immunology, computer science and engineering. By bringing together researchers from seven different University Departments, the Centre creates a collaborative network for innovation and sharing of expertise. The Centre also provides training through workshops on advanced genomics and computational approaches, and an annual Microbiome Symposium bringing local and international groups together.

Work at the Centre is supported through the Wellcome Trust Institutional Strategic Support Fund and the KTRR.



Vascular structures and nearby cellular niches in the kidney captured by 3D confocal microscopy. Vascular endothelial cells shown in green, with progenitor cells and cells located in the vascular wall shown in red. Cell nuclei are stained blue. Credit: Kusumbe Group.

SETTING THE SCENE FOR TISSUE REGENERATION

Understanding how cells interact with their surroundings to maintain tissue homeostasis could open up new approaches for stimulating tissue regeneration in chronic degenerative disease.

The space between cells is packed with structural proteins, enzymes and other molecules that provide cues allowing cells in tissues to sense and react to changes in their surroundings. Research at the Kennedy Institute is revealing how the tissue microenvironment dictates the behaviour of cells, and how this changes with injury, inflammation and age.

Extracellular matrix: from filler to function

Within the Versus Arthritis Centre for Osteoarthritis Pathogenesis, there is intense interest in the extracellular matrix – a molecular glue that holds tissues together – and its role in determining cartilage health or decline.

Cartilage consists of cells known as chondrocytes embedded within the extracellular matrix. Research by Professor Tonia Vincent, who directs the Centre, has shown that a specialised zone of “pericellular” matrix that surrounds chondrocytes is a storage site for growth factors released after joint injury to alter chondrocyte behaviour.

“We have found the extracellular matrix is more than an inert packing material,” says Tonia. “Rather, it is acting as sensor and effector of tissue injury, activating chondrocytes and promoting intrinsic cartilage regeneration. It is likely this is a common response to connective tissue injury and could contribute to over-zealous tissue repair in fibrosis.”

Another focus is how the extracellular matrix controls the activity of enzymes responsible for the breakdown of cartilage itself, and the team are also developing approaches to visualise the integrity of key structural proteins in the matrix to allow earlier detection of cartilage breakdown than is currently possible.

The team also examine how the cartilage tissue environment contributes to one of the major symptoms of osteoarthritis: pain. They have found nerve growth factor (NGF), a molecule currently being targeted with success in human osteoarthritis, is produced by cartilage at the onset of pain. Their research shows vaccination against NGF alleviates pain in models of osteoarthritis, suggesting a novel approach in patients.

Feature: Tissue Biology Programme continued

A danger alert

Beyond cartilage, Professor Kim Midwood is pursuing the extracellular matrix as a target for treating inflammatory disease and cancer. Her work has shown that the matrix protein tenascin-C propagates inflammation in inflammatory joint disease, and enables cancer cells to escape elimination by the immune response; she is now conducting pre-clinical studies to assess therapeutic antibodies that block tenascin-C in rheumatoid arthritis, fibrosis and cancer.

To cast a wider net, Kim also applies genomic and proteomic analysis, together with high resolution imaging, to characterise and map the content of the extracellular matrix in tissues. This will reveal more about how the matrix orchestrates beneficial immune responses or contributes to chronic inflammation.

Repair less, heal more

Connective cells in inflamed tissues ramp up production of matrix proteins in an attempt to heal damage caused by the triggers of inflammation. But over time, this leads to fibrosis and scarring, causing organs to work less effectively. To understand fibrotic pathways better, Professor Jagdeep Nanchahal studies patients with Dupuytren's disease, a fibrotic disorder of the hand often occurring with age.

Through analysis of patient tissue samples, Jagdeep has linked the inflammatory cytokine TNF to the development of myofibroblasts – the cell type that causes Dupuytren's disease. He is now leading clinical trials, early data from which shows the TNF blocking agent adalimumab limits fibrotic pathways in diseased tissues. Jagdeep's research also explores the drivers of uncontrolled myofibroblast activity using a special microscopy approach that measures the mechanical forces on cells.

Towards regeneration

By mapping the regulatory networks in tissues that promote homeostasis and disease, researchers at the Institute hope to develop new treatments to stop chronic inflammatory and degenerative disease in its tracks. There is also a growing interest in strategies to induce repair of damaged tissue.

Recent work from the Nanchahal Group has revealed a link between the inflammatory molecule HMGB1 and stem and progenitor cell activation, with the regenerative potential of HMGB1 now being investigated.

► See page 33 for more on HMGB1 and stem cells

Publications

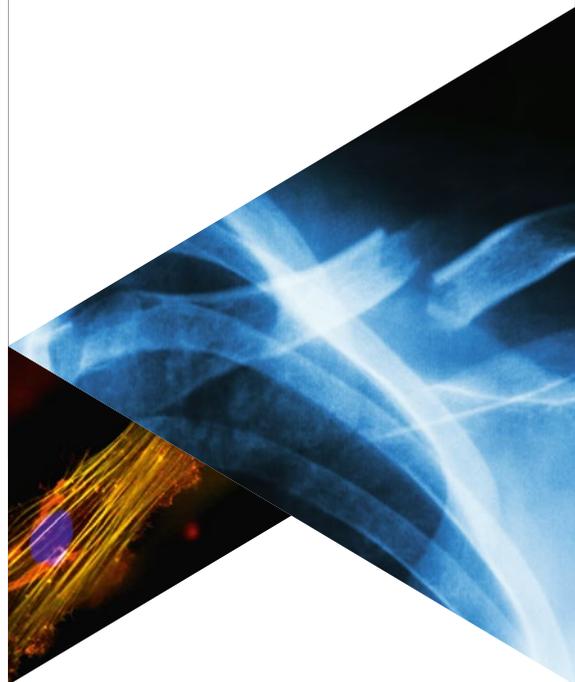
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Nanchahal et al. *EBioMedicine*. 2018 33:282
Zuliani-Alvarez et al. *Nat Commun*. 2017 8(1):1595
Driscoll et al. *Arthritis Rheumatol*. 2016 68(4): 857

Dr Anjali Kusumbe, a KTRR Senior Research Fellow at the Institute, also focuses on tissue repair. Her earlier research identified a cell type in blood vessels that coaxes mesenchymal stem cells in the bone marrow to make more bone. She now examines the communication between blood vessels and stem cells and how this might be targeted to stimulate new bone growth in bone disease or in elderly fracture patients.

Looking ahead, the ambition is to expand tissue biology research to include a greater focus on tissue stem cells and their interactions with immune and mesenchymal cells, as well as connective tissue.

“Deciphering cellular interactions in the tissue microenvironment, including stem cells, is key to tackling inflammation, fibrosis and tumorigenesis. With research programmes spanning immunology, inflammation and repair and regeneration, the Kennedy Institute is uniquely positioned to do this.”

**Professor Fiona Powrie,
Kennedy Institute Director**





Versus Arthritis Centre for Osteoarthritis Pathogenesis

There are currently no treatments to slow or prevent joint damage in osteoarthritis, and analgesics are often ineffective at treating chronic pain. The Versus Arthritis Centre for Osteoarthritis Pathogenesis at the Kennedy Institute was created in 2013 to identify the causes of osteoarthritis, and to create a seamless transition from discovery in the laboratory, to pre-clinical modelling to clinical translation. The Centre is directed by Professor Tonia Vincent and is supported by £2m from Versus Arthritis, with matched funding from the University of Oxford and the KTRR.

“We are hugely proud to have supported the Centre for Osteoarthritis Pathogenesis since 2013 based at the Kennedy Institute. Osteoarthritis dominates the total burden of musculoskeletal conditions with huge impact on the economy and on the lives of those who live with the condition. We have recently committed to a second five-year term harnessing the expertise within the Centre in understanding the underpinning mechanisms of osteoarthritis together with a strong programme in translation research and experimental medicine. Ultimately, there is huge potential for patients to benefit from the hard work being carried out by Professor Vincent and her team, and that’s something that we feel strongly about.”

Stephen Simpson, Director of Research and Programmes, Versus Arthritis

Profile

Fiona Watt

Dr Fiona Watt, University Clinical Lecturer at the Kennedy Institute, believes studying patients is key to unlocking the biology of osteoarthritis.

Osteoarthritis is a painful joint disease associated with cartilage degeneration, as well as inflammation and new bone growth. Fiona is interested in patients who have experienced traumatic injuries to their joints, who are at high risk of developing the disease.

By following patients immediately after their injury and for up to five years later, Fiona hopes to identify markers in the blood and joints that will predict which patients will go on to develop osteoarthritis. Fiona leads these cohort studies from within the Versus Arthritis Centre for Osteoarthritis Pathogenesis, although her research also involves contributions from data scientists, epidemiologists and clinical trials experts located elsewhere including at the Oxford Clinical Trials Research Unit, NDORMS.

“One of the reasons why attempts to develop drugs that slow osteoarthritis have floundered is that many patients entering clinical trials have advanced disease, or have earlier disease which is not destined to progress. By identifying predictors of disease in post-traumatic osteoarthritis we can think ahead about how to test interventions at the time of joint injury to prevent osteoarthritis,” says Fiona.

Fiona’s research into injury-related osteoarthritis could also provide clues as to why osteoarthritis develops with age. The Centre has set up and is recruiting to the Meniscal Tear and Osteoarthritis Risk cohort that will enable Fiona and her team to test whether predictors of post-traumatic osteoarthritis are also relevant in early osteoarthritis in the absence of traumatic injury.



DECODING INFLAMMATION THROUGH COMPLEX DATA

The Institute's Computational Genomics and Clinical Informatics platforms enable researchers to survey the genes, proteins, cells and microbes in our bodies and to integrate these datasets with patient data to understand better why complex diseases develop and progress.

Genetics, gut microbes and environmental factors and lifestyle choices all interact to influence the inflammatory responses in our bodies. To complicate matters further, inflammatory cells often take on new features in disease, and as a result, the precise drivers of inflammatory disease have been difficult to decipher.

Recent breakthroughs in sequencing and microfluidics technologies, however, are now allowing researchers to directly assess the contributions of both known and unknown cell types, biological pathways or genes to disease pathogenesis. Making sense of the vast quantities of data generated by these experiments relies heavily on computational approaches. To address this need, the Kennedy Institute has built Computational Genomics and Clinical Informatics platforms to support data-science-based research.

These platforms bring together skilled researchers and provide capacity for computationally intensive research. They also create a focal point to facilitate technology development, skills sharing, and training.

Mapping inflammation at high resolution

Leading some of the Institute's research in the area of computational genomics is Dr Stephen Sansom. His group applies single-cell genomic methods to build high-resolution maps of the cells and genes that are associated with immune and inflammatory disease. "By studying cells isolated from sites of active inflammation we are building new models of disease pathogenesis that will help to identify new therapeutic targets," says Steve.





This is also an area of focus for Professor Irina Udalova, who is using computational biology to examine the regulatory protein networks that drive reprogramming of myeloid white blood cells, such as monocytes and neutrophils, in inflammation. By mapping these networks in individual cells, Irina's research will identify specific combinations of proteins that support beneficial versus damaging white blood cells during inflammation that could be targeted in disease.

The power of high-throughput sequencing technologies can also be applied to understand microbial populations in the body. In Professor Fiona Powrie's laboratory, researchers use an array of sequencing technologies to reconstruct bacterial communities and their activity within the gut microbiome. By applying this approach to patient samples they aim to uncover novel microbial biomarkers and drivers of inflammatory disease.

“Researchers at the Kennedy Institute are transforming biomedical research through new approaches to collecting, integrating and analysing vast amounts of high-resolution biological data, from single cells to entire genomes. The combination of world-leading statistical and computational scientists, alongside clinical and experimental groups, enables the best designed studies and the greatest quantitative insights into the mechanisms underlying disease risk and progression.”

**Professor Gil McVean,
Director, Big Data Institute,
University of Oxford**

“Integrating these new single-cell and genomic techniques with patient genetics also opens up the possibility of understanding how disease risk genes drive inflammation,” says Dr Luke Jostins, a Sir Henry Dale Fellow at the Kennedy Institute. Certain variations in the DNA sequence of our genes are well known to confer risk, but in many cases the cause has been difficult to establish. Luke is developing statistical approaches to determine how groups of mutations that link to inflammatory disease affect certain types of immune responses. His goal is to track immune phenotypes that link with disease in patient cohorts to establish if and how they affect disease progression and clinical outcomes.

Managing, curating and mining patient data

The ambition is to relate complex experimental datasets with patient clinical data to inform new diagnostic and therapeutic strategies. “This requires integration of extremely complex and often large datasets, as well as novel ways of storing and processing them, including linking classical statistical approaches and machine learning (artificial intelligence) with bioinformatic approaches,” says Dr Brian Marsden who is leading efforts to support and develop clinical informatics capabilities. This includes the development of specific software for managing clinical samples and anonymized patient data, and deployment of the tranSMART database platform that brings molecular datasets and patient and clinical data together in one location.

This infrastructure is essential for managing, curating and mining data from several cohort studies led by the Kennedy Institute including the Inflammatory Arthritis Microbiome Consortium, the Knee Injury Cohort at the Kennedy (KICK), and A-TAP. In partnership with other nearby clinical and data science centres, the Kennedy Institutes Clinical Informatics platform will enable research to reveal patterns of biomarkers in patients at different stages of disease and overtime in large cohorts. These studies will guide stratification of patients to investigate new treatment approaches that are based on the underlying causes of disease.

BREAKING DOWN SILOS TO SPEED UP NEW THERAPIES FOR INFLAMMATORY DISEASE

The Kennedy Institute has joined forces with the Institute of Inflammation and Ageing at the University of Birmingham and seven NHS Trusts along the M40 corridor in a partnership that will pioneer innovative trial design to accelerate new drug targets into the clinic.

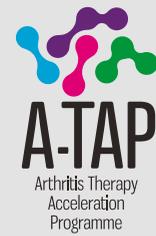
Talk to any two patients with rheumatoid arthritis and chances are they have had very different experiences of their disease. Rheumatoid arthritis, inflammatory bowel disease and other immune-mediated inflammatory diseases (IMIDs) often share common pathological processes that drive inflammation as the body's immune system mistakenly attacks its own tissues. But the immune cells and proteins that promote inflammation across different types of IMID often vary between patients with the same disease. As a result, these diseases can be unpredictable and difficult to treat.

A-TAP was launched to speed up the delivery of better treatments for IMIDs that target the underlying causes of disease. Initially, the programme will focus on four IMIDs

that affect the joints, eyes, skin and gut: rheumatoid arthritis, inflammatory bowel disease, Sjögren's syndrome and seronegative spondyloarthropathies.

Led by Professor Christopher Buckley, who is Director of Clinical Research at the Kennedy Institute, Oxford, and Director of the NIHR Clinical Research Facility in Birmingham, A-TAP will apply innovative trial design where repurposed or new drugs can be tried out across a range of IMIDs.

The success of a particular drug will be determined through tissue biomarkers rather than measurements of clinical symptoms only. The team hopes that their work will lead to a framework for selecting treatments based on the inflammatory signature in a patient's tissues.



A-TAP will bridge discovery research at the Kennedy Institute with clinical research at the Botnar Research Centre (Oxford) and the Institute of Inflammation and Ageing (Birmingham). It also forms an alliance with seven NHS Trusts along the M40 motorway to develop a network of consultants, nurses and clinical researchers and their patients.

Activating team science

In order to succeed, A-TAP requires collaboration between consultants from different specialities in a “bedside-to-bedside” approach, so that their primary interest becomes inflammation and not their own discipline. “It’s hard for physicians who have been brought up with an organ-focussed approach to adapt to process-driven pathology,” says Chris. “But that is what our patients want!”

The A-TAP partnership also brings expertise in machine learning and artificial intelligence that can be used to integrate molecular profiling of tissues with patient clinical data and treatment outcomes. This will help reveal tissue-based biomarkers to predict groups of patients most likely to benefit from a particular therapy. It will also highlight disease processes that are shared between different types of IMIDs, or unique to each one.

“Computer modelling has allowed us to identify drugs for repurposing to rheumatological disease, and this approach in the context of A-TAP trials has the potential to accelerate delivery of therapies to patients,” says A-TAP researcher Professor Mark Coles.

The close interaction between basic and clinical scientists will also spur exciting discovery research. Rheumatoid arthritis and Sjogren’s syndrome, two of the four diseases of initial interest are associated with autoantibody production. In collaboration with Professor Lynn Dustin and other immunologists at the Kennedy Institute, the A-TAP team will examine how B and T cells interact in IMIDs, and which of these interactions are shared or unique to particular diseases.

A-TAP is supported by a £7m investment from the KTRR, as well through funds from the Universities of Oxford and Birmingham.

OUR ACHIEVEMENTS

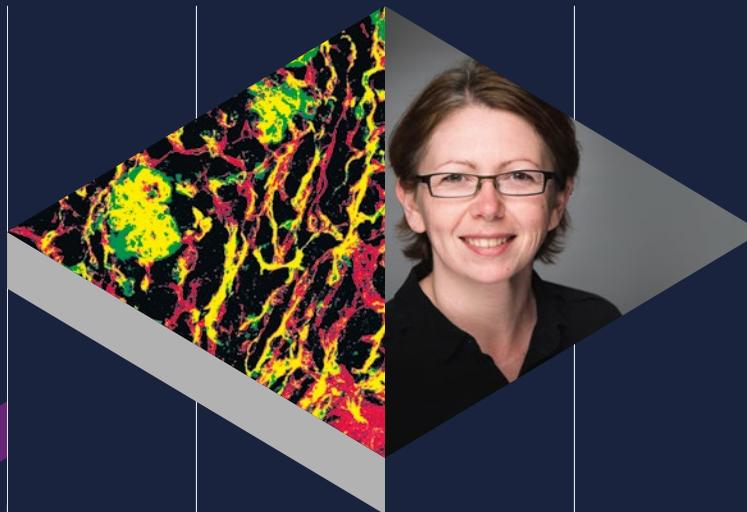
There has been a lot to celebrate at the Institute over the past two years. The outstanding contributions of our scientists to their research communities has been recognised with appointments and prizes, and a number of Group Leaders have been awarded prestigious fellowships that recognize the Institute's high quality. Kennedy Institute researchers have also led successful workshops and conferences to develop collaborative networks, and to communicate their research both nationally and internationally.

Events

- The Centre for Osteoarthritis Pathogenesis organises the second biennial Cutting-Edge Osteoarthritis Conference at Pembroke College (June, 2017)
- Kennedy Institute organises an inaugural Microbiome Symposium, attracting more than 200 attendees (January, 2018)
- Kennedy Institute leads the organisation of an NDORMS Imaging Symposium to showcase imaging studies in Oxford (January, 2018)
- A-TAP Launch held at the Academy of Medical Sciences, London and attended by representatives from a wide-range of organisations, including industry, major funders and patient groups (September, 2018)

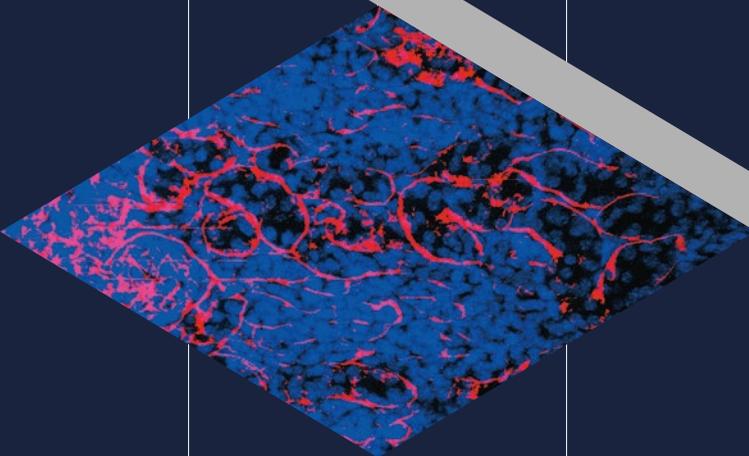
Prizes and appointments

- Professor Michael Dustin is elected a member of the European Molecular Biology Organisation (June, 2017)
- Professor Fiona Powrie becomes a Governor of the Wellcome Trust (January, 2018)
- Professor Fiona Watt becomes the Versus Arthritis Research Advisory Group Lead for musculoskeletal disorders (April, 2018)
- Professor Anna Katharina (Katja) Simon receives the EFIS-EJU Ita Askonas Prize for her contribution to immunology (September, 2018)
- Professor Irina Udalova joins Wellcome Trust Expert Review Group, Immune Systems in Health and Disease (October, 2018)



Fellowships and funding

- Dr Anjali Kusumbe is awarded an MRC Career Development Award to examine how blood vessels support bone growth and repair (June, 2017)
- Professor Irina Udalova is awarded a Wellcome Trust Investigator Award to study the molecular control of pathogenic neutrophil responses in chronic inflammatory disease (December, 2017)
- Dr Luke Jostins receives a Wellcome Trust/Royal Society Sir Henry Dale Fellowship for his work to decode how genetic variation predisposes to disease using statistical methods (January, 2018)
- The Centre for Osteoarthritis Pathogenesis receives a five year renewal from Versus Arthritis (April, 2018)
- Dr Audrey Gérard receives a Biotechnology and Biological Sciences Research Council (BBSRC) New Investigator Award to study the collective coordination of T cell responses (May, 2018)
- Dr Alexander Clarke receives a Wellcome Trust Clinical Research Career Development Fellowship to support his studies into metabolic control of antibody responses (June, 2018)
- Dr Jelena Bezbradica-Mirkovic receives a MRC New Investigator Award to study the innate recognition in myeloid cells (July, 2018)
 - Dr Anjali Kusumbe receives an ERC Starting Grant to investigate the link between ageing blood vessels and tumour metastasis in bone (July, 2018)



FUELLING NEUTROPHIL PRODUCTION IN THE BONE MARROW

Every second, the human bone marrow churns out more than one million neutrophils that protect against potentially lethal infections. A team from the Kennedy Institute shows that neutrophils use the cellular recycling pathway autophagy to maintain their energy levels as they mature.

Neutrophils help kill bacteria and fungi to protect against potentially life threatening infections. The blood contains large numbers of these short-lived cells that are constantly replaced by new cells from the bone marrow. The mechanisms that regulate this process are not fully understood, and dysfunctional neutrophil differentiation can lead to disease.

Research from Professor Anna Katharina (Katja) Simon and colleagues shows that a cellular process called autophagy is necessary to produce mature neutrophils. Autophagy is a self-eating mechanism that allows cells to remove toxic waste and recycle old or defective proteins. It can also be used to degrade lipid droplets to release free fatty acids that support neutrophil development, Katja's team reports.

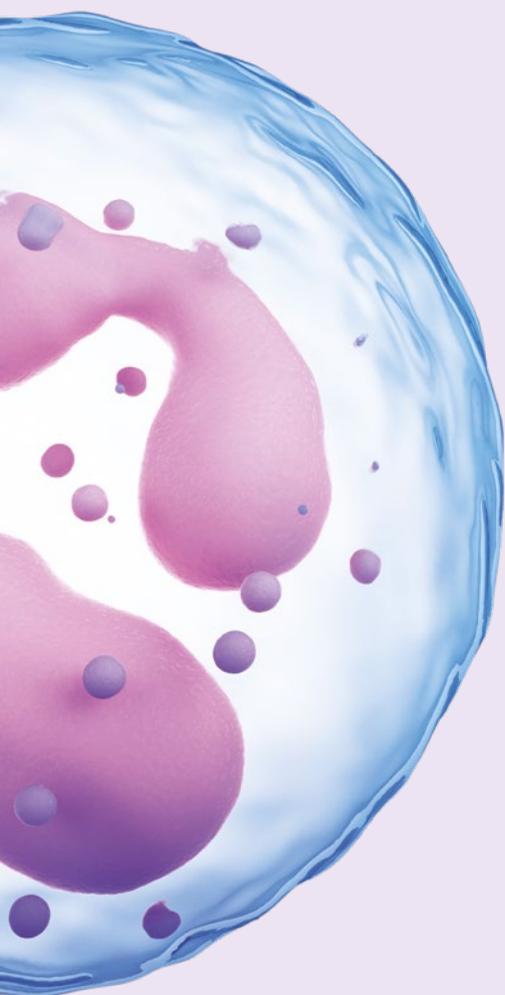
They found that the autophagy pathway becomes more active during neutrophil development, boosting free fatty acid levels. This turned on an alternative metabolic pathway, whereby neutrophils used free fatty acids rather than glucose to generate the cellular energy molecule ATP. This metabolic switch was essential for neutrophil maturation, and free fatty acids could restore stalled neutrophil development when fed to neutrophils that lack autophagy.

Many cell types, including stem cells, other white blood cells, and cancer cells rewire their metabolism to support cellular development or specialised cellular functions. The work by Katja and colleagues suggests autophagy could induce metabolic switching in a variety of different cell types to control diverse cellular processes.



“This work identifies the mechanism by which autophagy controls cellular differentiation. This is an exciting step forward, which can now be applied to other cell types.”

Katja Simon



The next goal for the researchers is to examine whether autophagy links to neutrophil defects in disease. For example, autophagy does not work properly in many acute myeloid leukaemia but whether metabolic defects contribute to features of the disease is unknown. The findings also raise the possibility that free fatty acids could be used to restore the production of neutrophils in patients receiving certain types of stem cell transplants to reduce the risk of lethal infection.

Publications

Riffelmacher et al. *Immunity*. 2017 47: 466

Research supported by the Wellcome Trust and the KTRR



Profile

Katja Simon

Professor Katja Simon joined the Kennedy Institute in 2016 and is a recipient of the 2018 Ita Askonas Award from the European Federation of Immunological Societies in recognition of her outstanding contributions to immunology in Europe.

Katja has a long standing interest in autophagy and its control of the immune system. “We quickly found there was a lot to learn – removing the autophagy pathway affected every cell type in different ways,” she says.

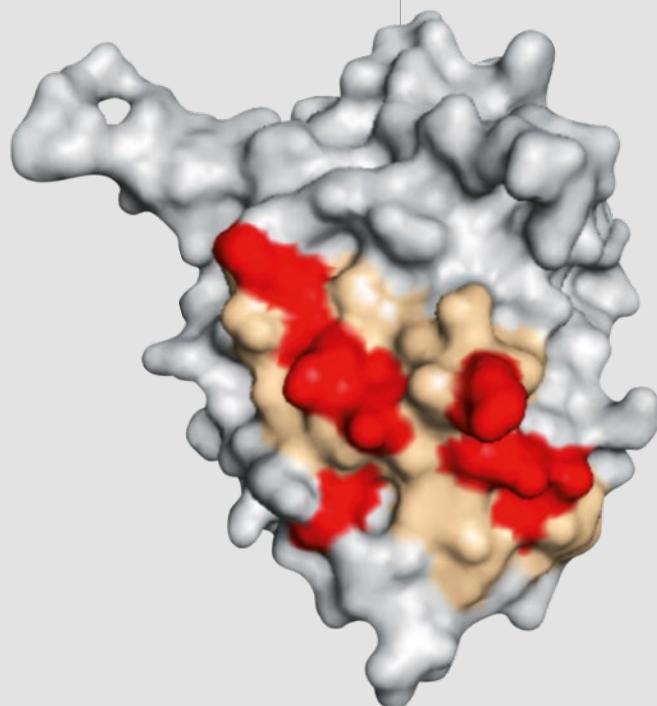
Her work has examined autophagy in a range of cells including stem cells, red blood cells and T lymphocytes, and includes recent findings that a natural decline in autophagy could explain poor vaccine responses in the elderly. She is now keen to identify drugs that target autophagy to boost the immune system.

Reflecting on her career, Katja is particularly proud of her role in mentoring students and trainees. Indeed, in just two years since joining the Kennedy Institute, four of Katja’s graduates and trainees have secured prestigious awards from funders including the Wellcome Trust, European Molecular Biology Organisation, and Elysium Health to support them in the next stage of their careers.

Katja tries to inspire those in her lab through her enthusiasm for scientific research. It was this passion for science that helped steer Katja through what she refers to as an “unusual” and sometimes “difficult” path to becoming a group leader. Katja had three children during her postdoctoral years, and it took her longer to build up her CV. “By the time I was ready to apply for independent fellowships, I was no longer eligible for most of them!” she explains.

Katja found a way around this by securing a small project grant that supported her early independent work; slowly she moved to larger funding as her publication record took off. She also helped set up the Oxford University Society for Females in Engineering, Science and Technology to help others in a similar situation. This brought discussions about gender equality to the forefront and “helped to get rid of the strict eligibility criteria for funding awards,” she says.

Although many funders now allow for career breaks, her advice to other scientists who find themselves in a similar position is “persevere, be determined and follow your own path!”



“This study paves the way for new drug discovery programmes designed to block the action of these dangerous proteins as they go out of control during a whole host of inflammatory diseases.”

Kim Midwood

SENSING DANGER WITHIN

A study led by Professor Kim Midwood reveals how tenascin-C, a danger signal released by the body after injury, is recognised by the immune system to trigger inflammation.

Although inflammation offers first line defence against harmful microbes, inflammation-related disease often develops in the absence of infection. Instead, the immune system is activated by danger signals released by the body's own tissues.

One of these danger signals, tenascin-C, is released in stressed or damaged tissues and activates the immune system via surface protein TLR4. This immune sensor is highly sensitive to components of the bacterial cell wall and other molecular patterns on microbes. Kim's research now reveals the exact sites exposed on the surface of tenascin-C that are responsible for triggering TLR4 activation.

She says, “we identified three different areas within tenascin-C, that come together to create a molecular tag that earmarks proteins for recognition by immune sensors. By removing the tag from tenascin-C, we could prevent its ability to activate TLR4, and by adding this tag to inert proteins, we could convert them into potentially pro-inflammatory proteins.”

This inflammatory tag was also found in a number of other proteins in the body known to drive inflammation in autoimmune diseases, such as rheumatoid arthritis, in fibrotic diseases and in aggressive or metastatic tumours. Understanding the structural details behind immune sensor activation by internal triggers may enable the design of drugs that can effectively block their activity.

Publications

Zuliani-Alvarez et al. Nat Commun. 2017 8: 1595

Research supported by Versus Arthritis and the KTRR

INFLAMMATION GETS STEM CELLS INTO GEAR

Injured or dying cells spill out molecules that alert the immune system to tissue damage and possible infection. Researchers at the Kennedy Institute show that one of these molecules – HMGB1 – also boosts the capacity of stem cells to induce tissue regeneration and healing.

Stem cells replace damaged or worn out cells and have the capacity to regenerate many, if not all, tissues. However, despite the success of stem cell transplants to correct blood disorders, stem cell therapy has had little impact on the treatment of solid organ injury and disease.

To overcome the limitations associated with stem cell transfer, Professor Jagdeep Nanchahal and colleagues focused their attention on the natural repair processes in tissues. They found that HMGB1 – a protein released from the nuclei of dying cells and elevated in the blood of fracture patients – could accelerate the healing of both bone fractures and muscle damage, as well as the regeneration of the blood system after chemotherapy.

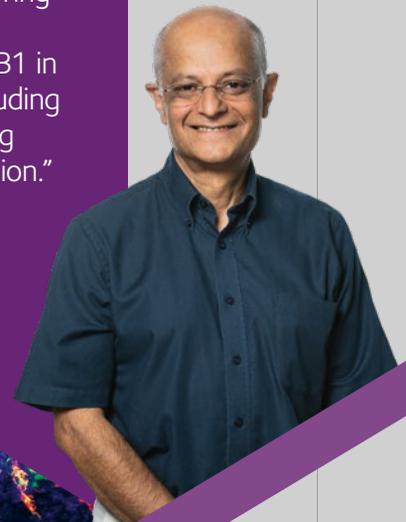
The team went on to show that HMGB1 acts on resident stem cells to promote tissue healing. At rest, stem cells adopt an inactive state to prolong their ability to self-renew without error. HMGB1 helped rouse stem cells from this dormant state by boosting metabolic signalling. This primed cells to enter into the cell cycle more efficiently and effect tissue repair on exposure to appropriate activating factors.

HMGB1 acted on stem cells in combination with another signalling molecule called CXCL12 via the CXCR4 receptor, which is found on the surface of multiple stem and progenitor cells.

Lead author of the study, Professor Jagdeep Nanchahal said, “HMGB1 promotes regeneration of multiple tissues when a single dose is administered soon after or even up to two weeks before injury. We are now looking forward to translating our lab findings to the clinic.” The finding suggests HMGB1 could be used in patients to speed up tissue repair post-injury or prior to surgery or other anticipated injury.

“We are now exploring the regenerative potential of HMGB1 in other tissues, including the heart following myocardial infarction.”

Jagdeep Nanchahal



Publications

Lee et al. PNAS. 2018 115: E4463

Research supported by the Medical Research Council, Versus Arthritis, Academy of Medical Sciences and the KTRR

A NEW BIOMARKER AND TREATMENT TARGET IN INFLAMMATORY BOWEL DISEASE

Anti-TNF therapy is very effective at easing the debilitating symptoms of inflammatory bowel disease, but in only a fraction of patients. Research led by the Kennedy Institute identifies immune molecule oncostatin M (OSM) as a potential biomarker to predict patients that respond poorly to anti-TNF treatment, and as a new therapeutic target for this difficult to treat disease.

“This is really exciting. Until now, no one has been able to predict who will or will not respond to anti-TNF therapy.”

Professor Simon Travis,
study clinical lead, Nuffield
Department of Medicine,
University of Oxford

The intestinal immune system goes into overdrive in inflammatory bowel disease. Excessive secretion of cytokines and other immune molecules participate in complex inflammatory cascades that are difficult to shut down once activated.

Anti-TNF latches on to and blocks one of these cytokines – TNF – and is very effective in treating disease. But up to 40 per cent of patients fail to respond, and many others develop resistance over time.

In a collaborative study between Professor Fiona Powrie's laboratory at the Kennedy Institute and the Translational Gastroenterology Unit, Oxford, researchers examined intestinal biopsies in a hunt for additional cytokines that drive disease. They detected increased amounts of the cytokine OSM in the intestines of inflammatory bowel disease patients, with very large amounts of OSM pre-treatment predicting those patients who did not respond well to anti-TNF.

But what does OSM do in the gut? The team found that OSM interacts with mesenchymal cells in the gut wall to increase inflammation – and that the gut is more sensitive to OSM in inflammatory bowel disease. Blocking these interactions between OSM and the gut wall dampened inflammation in a model of inflammatory bowel disease that responds poorly to anti-TNF.

The discovery of OSM as a potential biomarker paves the way for a more sophisticated approach to treating inflammatory bowel disease, whereby a test to measure this cytokine could guide the most appropriate therapies to the right patients. The team hopes to conduct clinical studies to test anti-OSM therapy in inflammatory bowel disease patients who have failed other types of treatment.

Publications

West et al. Nat Med. 2017 23: 579

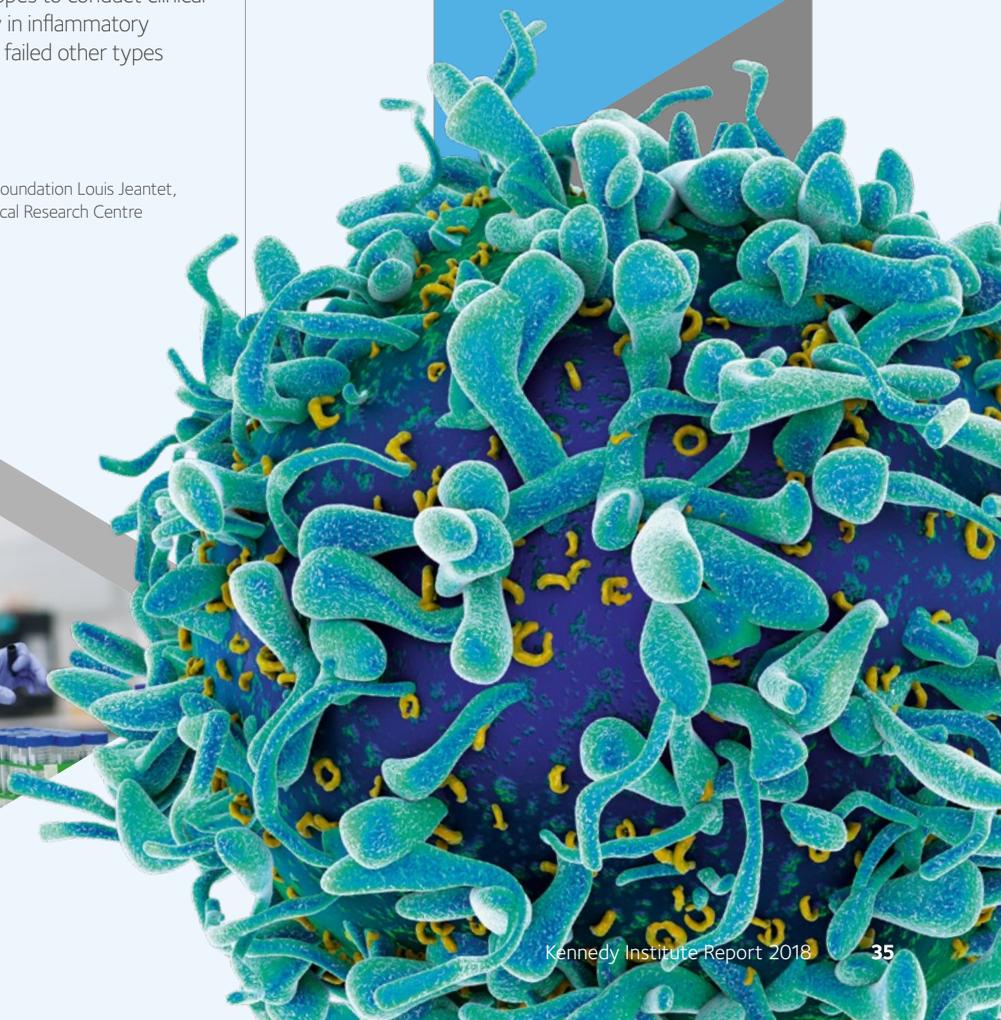
This research received support from the Foundation Louis Jeantet, Wellcome Trust and NIHR Oxford Biomedical Research Centre

Inflammatory bowel disease is a group of chronic painful diseases, which include conditions such as Crohns disease and ulcerative colitis. It is estimated around

5 million

people worldwide live with inflammatory bowel disease, with this number increasing annually, especially in East Asia, although it is most common in Europe and North America.

The Oxford IBD cohort at the Translational Gastroenterology Unit includes >3000 patients with ulcerative colitis or Crohns disease. New patients are diagnosed each week, providing access to patients with early-stage disease.



DEVELOPING STRONG PARTNERSHIPS

We are partnering with industry at all stages of the research process to facilitate drug discovery and experimental medicine trials, with the aim of getting new treatments to patients faster.

Our research takes place at the intersection of basic biology and clinical translation, opening up many opportunities for industry partnerships and innovation.

By incorporating analysis of patient tissue samples into our work we hope to identify disease-associated pathways that have high potential for drug discovery. Partnerships with industry bring commercial insight to our discovery research, and more than a tenth of postdoctoral fellows at the Institute are supported by industrial fellowships from partners including Celgene, Elysium Health, Roche and UCB.

Our work also attracts industry funding for strategic initiatives including a £1.2m Novo Nordisk Foundation award to Professor Claudia Monaco as she leads an international interdisciplinary team of researchers to explore the relationship between inflammation and metabolic disease.

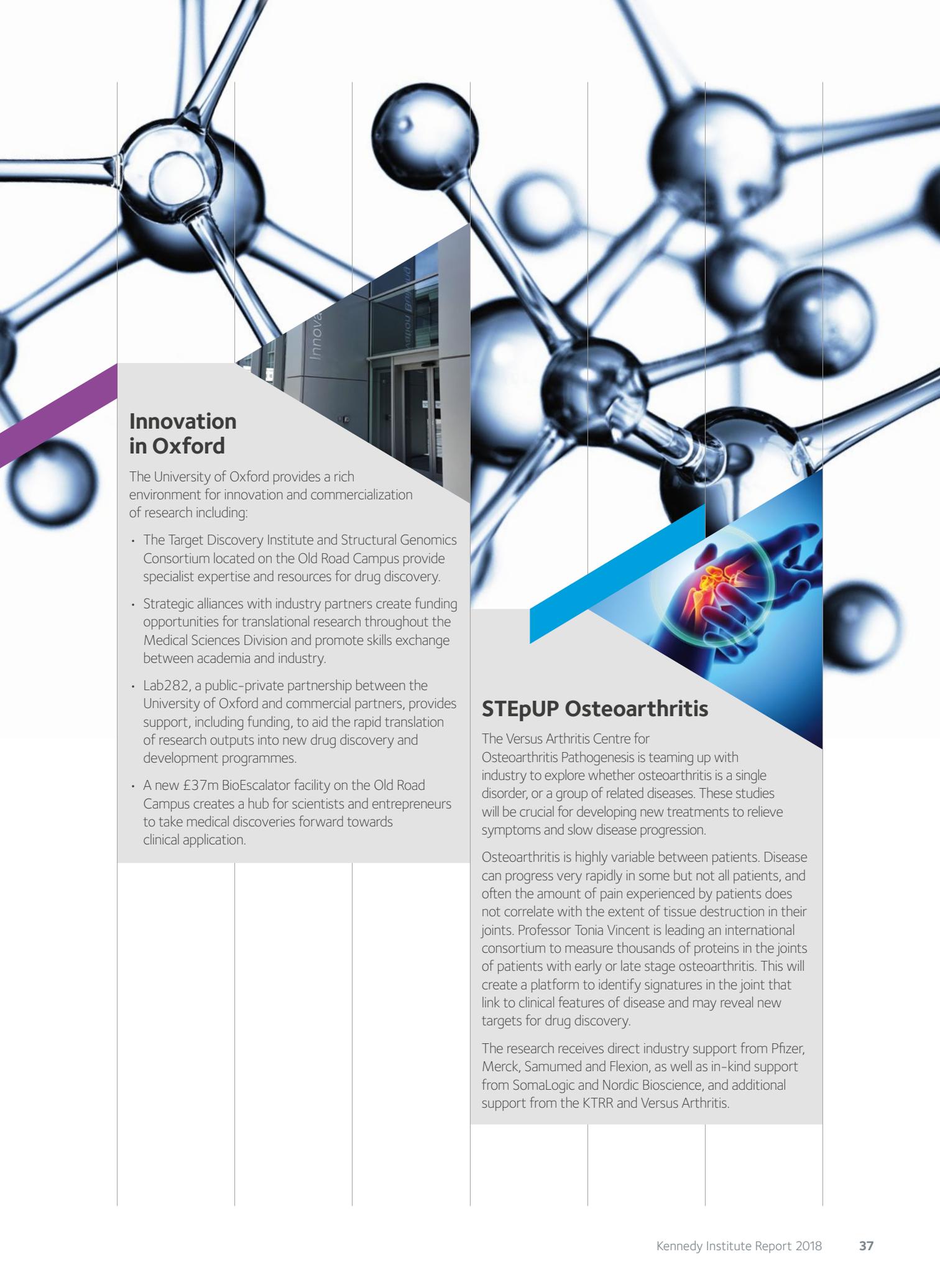
The Kennedy Institute is uniquely positioned to lead small experimental trials to explore if and how new and repurposed drugs affect both the molecules and cells driving disease. A-TAP creates a platform to engage industry, bringing commercial expertise and resources together with well-defined patient cohorts, technology platforms and innovations in trial design. The team is currently in discussion with a number of industry partners.

Spin outs

Kennedy researchers have launched a number of spin outs from their research including:

- 180 Therapeutics: a clinical stage company with a drug pipeline for fibrosis including anti-TNF for Dupuytren's disease. Founded by Professor Jagdeep Nanchahal.
- Nascent: developing therapeutics targeting the endogenous danger signal tenascin-C for the treatment of rheumatoid arthritis and other autoimmune inflammatory diseases. Founded by Professor Kim Midwood.
- Simomics: provides software for in silico virtual disease laboratories to reduce and replace the need for pre-clinical models in therapeutic discovery and development. Founded by Professor Mark Coles.
- Lightox: developed agents that can be conjugated to biomolecules without altering activity providing revolutionary diagnostic and life science tools. Founded by Professor Mark Coles.





Innovation in Oxford

The University of Oxford provides a rich environment for innovation and commercialization of research including:

- The Target Discovery Institute and Structural Genomics Consortium located on the Old Road Campus provide specialist expertise and resources for drug discovery.
- Strategic alliances with industry partners create funding opportunities for translational research throughout the Medical Sciences Division and promote skills exchange between academia and industry.
- Lab282, a public-private partnership between the University of Oxford and commercial partners, provides support, including funding, to aid the rapid translation of research outputs into new drug discovery and development programmes.
- A new £37m BioEscalator facility on the Old Road Campus creates a hub for scientists and entrepreneurs to take medical discoveries forward towards clinical application.



STePUP Osteoarthritis

The Versus Arthritis Centre for Osteoarthritis Pathogenesis is teaming up with industry to explore whether osteoarthritis is a single disorder, or a group of related diseases. These studies will be crucial for developing new treatments to relieve symptoms and slow disease progression.

Osteoarthritis is highly variable between patients. Disease can progress very rapidly in some but not all patients, and often the amount of pain experienced by patients does not correlate with the extent of tissue destruction in their joints. Professor Tonia Vincent is leading an international consortium to measure thousands of proteins in the joints of patients with early or late stage osteoarthritis. This will create a platform to identify signatures in the joint that link to clinical features of disease and may reveal new targets for drug discovery.

The research receives direct industry support from Pfizer, Merck, Samumed and Flexion, as well as in-kind support from SomaLogic and Nordic Bioscience, and additional support from the KTRR and Versus Arthritis.

Engaging the public and inspiring the next generation

ENGAGING AND INSPIRING

“Our research focuses on cells in the intestine and their interactions with gut bacteria, a subject area that is growing as we learn more about how the vast array of bugs living inside us link to human health. We find the subject fascinating and it has the added “yuck” factor, which is great for sharing our enthusiasm with the next generation! We have created a giant magnetic gut “wall” with moveable plush toys to represent our cells, in addition to an histology game, both of which appeal to a wide audience. Dr Sam Bullers and I regularly take these to science fairs with other volunteers, and have also visited local schools. This year Dr Lilian Lam and I also participated in Pint of Science where we had great fun sharing weird and wonderful gut facts with an audience in a pub.”

Dr Claire Pearson, Powrie Group

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 2017/18 the Kennedy Institute joined NDORMS at a number of science fairs and festivals, several of which attracted more than 10,000 visitors including the Oxfordshire Science Festival, Curiosity Carnival, and Big Bang Birmingham. Researchers from the Kennedy Institute took part in a drop-in week as part of Living Well Oxford 2017, a programme to encourage people to live well into their old age.

The events provide staff and students with the opportunity to share their research with the public and inspire the next generation of biomedical scientists. Interactive activities include the Kennedy Institute’s giant gut wall, microscopy, model cell crafting, and arthritis gloves.

Research Groups at the Kennedy Institute also host various work experience programmes for A-level students led by NDORMS. The aim is to give students a taste of laboratory life through a variety of activities including laboratory practicals, talks, workshops, and informal conversations.





Image taken at the Big Bang Fair

In 2017/18

42

staff and students
involved in outreach

23

work experience students

9

science festivals and other
outreach events

>1,000

direct interactions with the public

“Our cartilage is often taken for granted, but this clever stuff puts up with a lot! Members of the Centre go out into the community and beyond to describe how we work together to understand cartilage and the processes that start the most common, but not inevitable, of musculoskeletal diseases, osteoarthritis. The histology team shows how we watch as cartilage grows and fails, while clinicians describe how this affects our knees, hips and spines. At the 2018 Big Bang fair it was great to see our basic science students, clinical support staff, and academics teaming up to talk about joints to budding science, technology, engineering and mathematics students. We proudly placed cartilage research alongside mathematics of the genome, jump jets, cross-city tunnels, space research and brain surgery.”

**Dr Angus Wann, Group Leader, Versus Arthritis
Centre for Osteoarthritis Pathogenesis**

Going green

PROMOTING SUSTAINABILITY

To support this, a group of Kennedy Institute students and staff teamed up to increase sustainability and reduce environmental impact as part of the Green Impact environmental accreditation scheme initiated by the National Union of Students.

The Institute's Green Impact Team have now achieved Buildings Bronze and Silver Awards and the Laboratories Gold award for their efforts to reduce waste and promote sustainability. Activities range from monitoring waste routes and implementing the use of recycled paper to promoting sustainable transport and ensuring efficient use of existing equipment.

In 2011, the University of Oxford set an ambitious target to reduce carbon emissions by 33 per cent by the end of 2021.

Looking ahead, the Team wants to build on its success and take on larger projects including the installation of solar panels on the roof, consolidating ultra-low temperature storage into a sustainable central facility, and linking up with other research buildings to create a campus-wide green impact strategy.



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