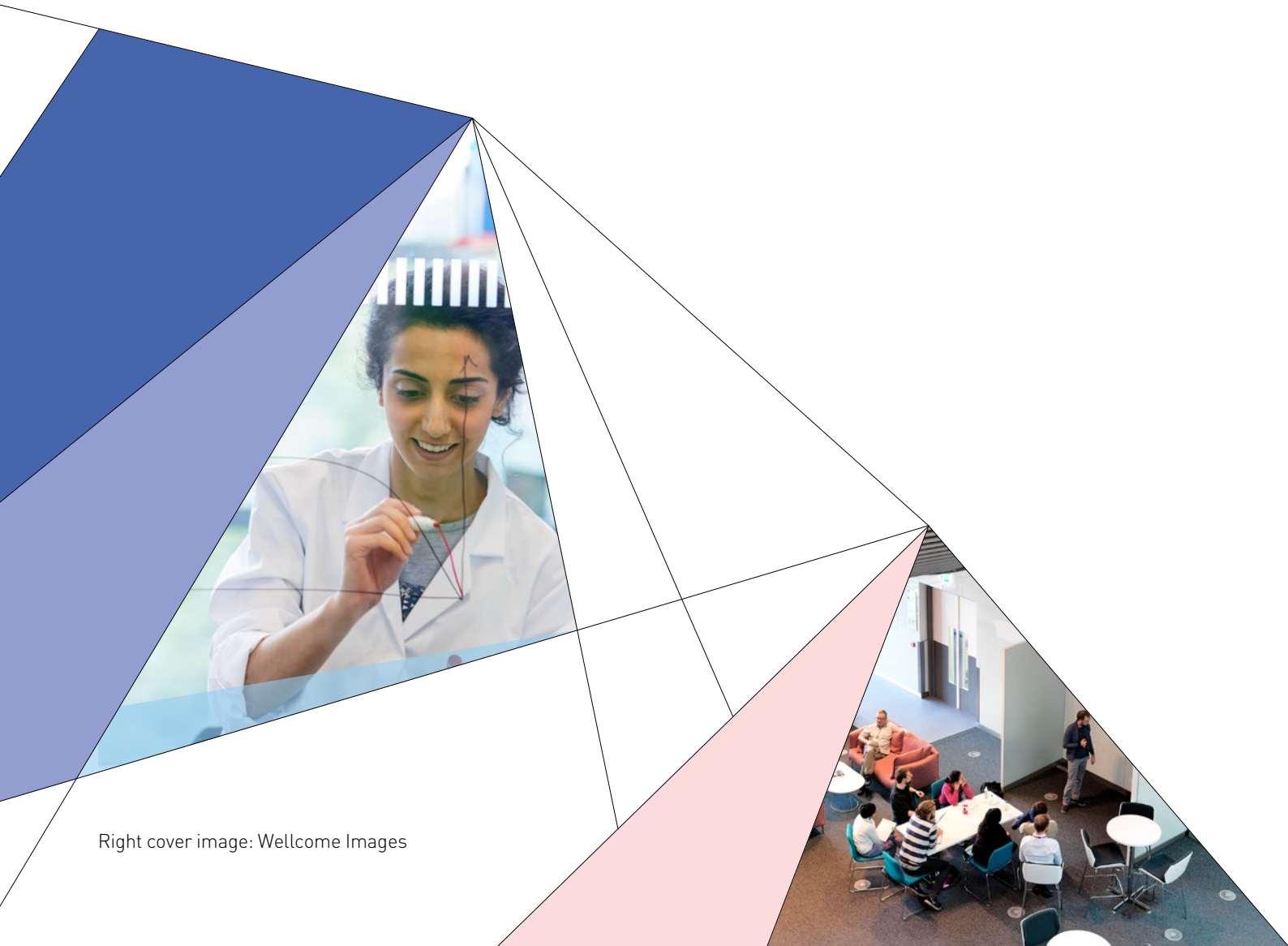
THE FRANCIS CRICK INSTITUTE

A NEW HOME FOR SCIENCE AND DISCOVERY

Annual Review 2016/17

The Francis Crick Institute is a biomedical discovery institute dedicated to understanding the fundamental biology underlying health and disease. Its work is helping to understand why disease develops and to translate discoveries into new ways to prevent, diagnose and treat illnesses such as cancer, heart disease, stroke, infections and neurodegenerative diseases.

For more information www.crick.ac.uk



Right cover image: Wellcome Images

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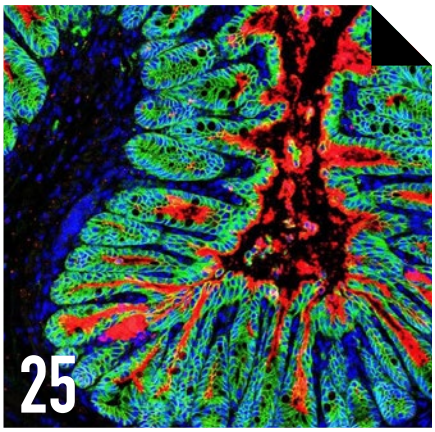
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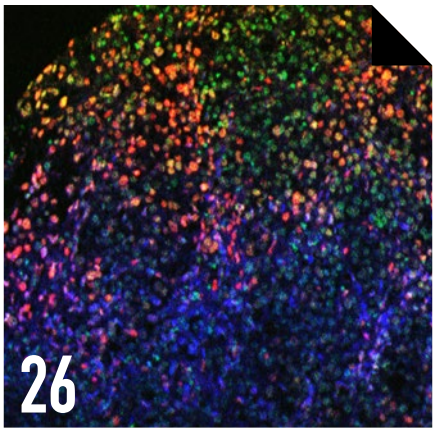
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INTRODUCTION BY PAUL NURSE

A BEGINNING

> Having most of our staff physically together for the first time does feel like the real beginning of what I hope will become a special place for science and discovery.

Welcome to our Annual Review for 2016/17: a year which saw the Francis Crick Institute – its research and its people – come together in the new laboratories at St Pancras, London.

Moving 94 research groups, 1,500 people, and many pieces of equipment and biological materials into our new purpose-built lab was no small job. It is a real achievement to be able to say that the Crick is successfully up and running, and my thanks go to all involved.

There still remains a lot of work to be done, but having most of our staff physically together for the first time does feel like the real beginning of what I hope will become a special place for science and discovery. We certainly had a good launch, with The Queen officially opening the Crick on 9 November.

Research has continued, despite the upheaval, and a number of our scientific advances in the last year are described on pages 17–29, covering a wide range of research topics.

Another advance has been the arrival of the first scientists from our three university partners moving in and joining their colleagues from the Crick's parent institutes. Interactions with clinical and physical scientists from the universities are important if we are to realise the Crick's multidisciplinary mission.

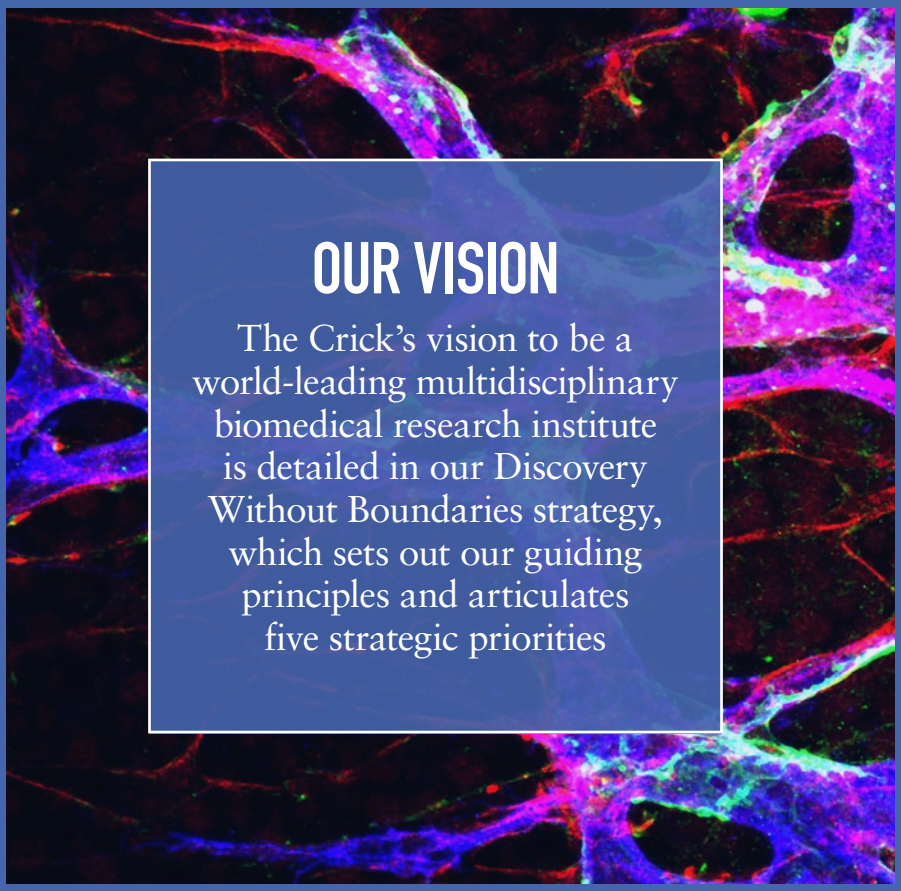
An exciting programme of seminars and lectures has been established, contributing to a lively culture of scientific interaction within the institute. The first recruitment drive for new early-career Group Leaders saw nearly 400 scientists from all over the world apply to establish a research group at the Crick. The first recruits will start later this year. There were also over 1,700 applicants to our PhD programme.

During the year we celebrated the announcement of the first Crick spinout companies, the first school children came to the Weston Discovery Lab, and the Living Centre became the first new community space in Camden for more than 15 years.

We are proud of what we have achieved this year, building on years of careful planning by the Crick and its founding partners to realise the vision of a major new biomedical research institute for the UK. We have a spectacular new home and we look forward to working together, making scientific discoveries that will bring new understanding of the biological processes that underpin human disease.

PAUL NURSE
DIRECTOR OF THE FRANCIS CRICK INSTITUTE

PROGRESS AGAINST OUR STRATEGY



OUR VISION

The Crick's vision to be a world-leading multidisciplinary biomedical research institute is detailed in our Discovery Without Boundaries strategy, which sets out our guiding principles and articulates five strategic priorities

We highlight progress we have made in the past year against the Crick's five strategic priorities, reflecting our commitment to the highest quality science.

1

PURSUE DISCOVERY WITHOUT BOUNDARIES

The Crick aims to discover the basic biology underlying human health and disease, taking an approach to biomedical research that fosters excellence, breaks down barriers between disciplines and works across institutions.

We created an important new group during the year, adding world-leading research management expertise to the Crick while also providing improved oversight. Our new Scientific Advisory Board comprises 14 internationally renowned scientific leaders, including three Nobel Prize winners, with extensive experience of running research institutes worldwide. The Board will advise on developing and implementing our scientific strategy and operations, support our aim to undertake biomedical research of the highest quality and reinforce the value of collaboration and a multidisciplinary approach.

The year saw us step up our search for early-career bioscientists with leadership potential. Following a rigorous selection process, we shortlisted 18 candidates from almost 400 applications. The coming year will see the successful few form their own research groups at the Crick.

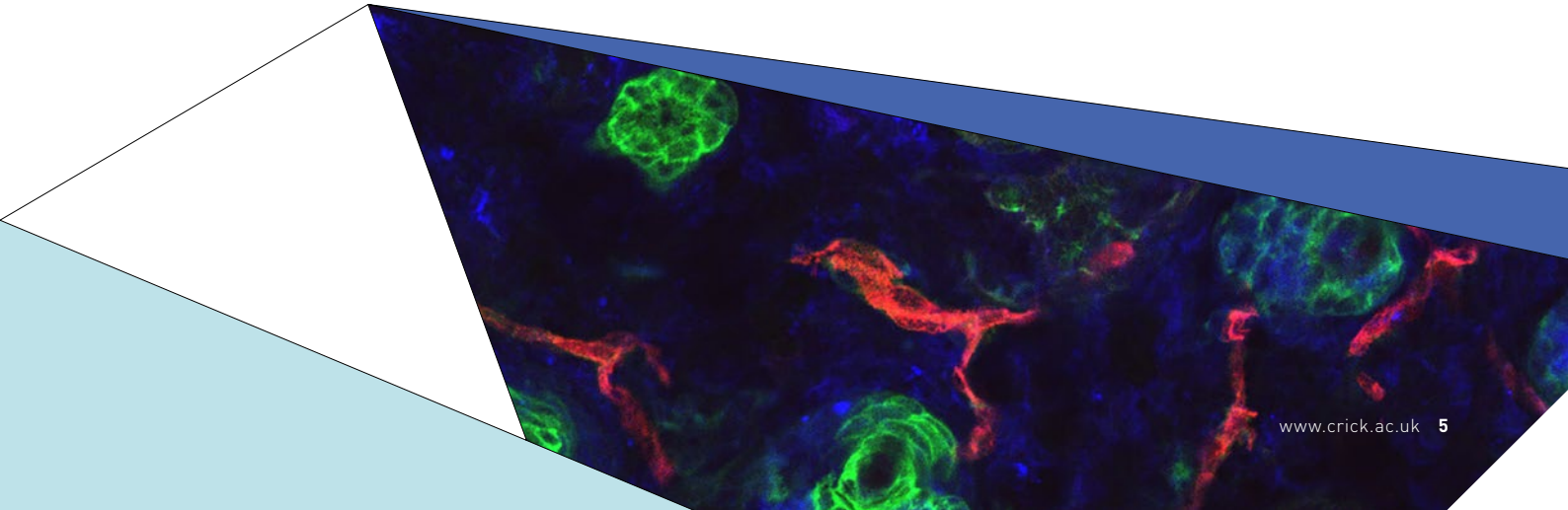
An extensive scientific discourse programme was launched in autumn 2016 (see page 7). This programme of seminars and lectures encourages the communication between researchers that is fundamental to the scientific process. It provides a platform for discovery and debate, enabling Crick scientists to interact with one another and with the wider scientific community.

GROUP LEADER APPLICATIONS

400

"We're looking for outstanding scientists from around the world who want to set up their own independent research programmes."

RICHARD TREISMAN,
DIRECTOR OF RESEARCH



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CREATE FUTURE SCIENCE LEADERS

The Crick aims to develop an approach to biomedical scientific training that maximises research excellence, dynamism and multidisciplinary activity, and in doing so to fulfil our national role by expanding the talent pool for biomedical research across the UK.

PhD APPLICATIONS

1,700

NEW PhD STUDENTS

52

The Crick aims to establish a global reputation as the place where the finest minds can do their best work. We want to encourage talented scientists to join us or collaborate with us, and also to nurture and train those individuals – enabling them to progress to become science leaders within the UK biomedical research endeavour.

Our PhD programme continues to train students in skills within and beyond research. For recruitment to the PhD programme starting in September 2016, we had more than 1,700 applications with 52 students subsequently joining us. As well as receiving scientific training, students are encouraged to attend non-scientific skills development courses both at the Crick and at their university.

Training for our 300 Postdoctoral Training Fellows (PTFs) has been enhanced through the establishment of a Postdoctoral Committee, helping to prepare our PTFs for the next stage of their careers (see page 36).

During the year we recruited to our new sandwich and summer student programmes for the first time, both of which form part of our commitment to creating the next generation of scientists. Eight undergraduate students from 197 applicants will join our sandwich student programme and 16 of 389 applicants will join our Crick–Calleva summer student programme in summer 2017. Both programmes are aimed at bright undergraduates who are considering a future in biomedical research, and are designed to give them the opportunity to gain insight into life in a research institute as well as valuable lab-based work experience.

Diversity is an important issue for all sectors of society and at the Crick we are committed to creating equality of opportunity and inclusivity for all, with several initiatives underlining this commitment during 2016/17. For example, around 40 people attended the launch of our black and minority ethnic (BAME) network, where guest Shami Chakrabarti, former Director of Liberty, gave an inspiring and passionate talk. In autumn 2016, we launched a new training programme to raise awareness of the unconscious bias that can have a negative impact on behaviour and decision-making.

FEATURE: SEMINARS

Putting the latest science at the heart of discussion

Launched in autumn 2016, our extensive programme of seminars, talks and lectures provides a platform for discovery and debate, and facilitates interaction between our researchers and scientists from elsewhere.

Weekly Flagship lectures are the centrepiece of our scientific discourse programme and provide a broad insight into biomedical research for everyone at the Crick, covering subjects that cross boundaries between different research areas. Our nine Interest Groups regularly bring together scientists working in particular fields, ranging from Computation and Physical Biology to Neuroscience. And our Opening Symposium, with presentations from outstanding researchers from all over the world, was one of this year's highlights.

> "Our broad scientific discourse programme facilitates discussion among scientists from different research disciplines, seeding new ideas and partnerships which we hope will lead to future discoveries."

ANNE O'GARRA,
ASSOCIATE RESEARCH DIRECTOR

3

COLLABORATE CREATIVELY TO ADVANCE UK SCIENCE AND INNOVATION

The Crick aims to develop and promote novel forms of partnership, both with its founders and the broader UK scientific community.

UNIVERSITY ATTACHMENTS

14

Attachments and satellite programmes encourage the multidisciplinarity that can stimulate novel approaches to the investigation of biological systems. Fourteen groups from our three university partners have now commenced their attachments. In March 2017, we launched our third call for expressions of interest for university attachments and at the same time invited Crick Group Leaders to establish satellite laboratories in the partner universities.

Following an executive governance review, we have established the University and Academic Partnerships Committee (UAPC) to maximise the value of links between the Crick and our academic partners. Led by Malcolm Irving of King's College London and the Crick, the UAPC will coordinate and advise on a number of areas of academic collaboration, including university attachments, strategic joint appointments, interdisciplinary research interfaces and interactions with the Wellcome Trust Sanger Institute and other UK universities.

A partnership of seven institutions led by the Crick and UCL, eMedLab benefited from the addition of a new state-of-the-art cloud computing environment during the year. eMedLab is funded by the Medical Research Council (MRC) and brings together clinician scientists and bioinformaticians to research advanced informatics methods in order to mine clinically relevant genomic, imaging and electronic health record data. Collaborations have been initiated with the Alan Turing Institute and with industrial partners Intel, IBM and BenevolentAI.

The Crick is involved in the new 4ward North Clinical PhD Academy, an initiative established by the universities of Manchester, Leeds, Sheffield and Newcastle, and funded by Wellcome. Academy students will benefit from our mentorship, advice and placements during their doctorate – and on completion of their PhDs, fellows may also have the opportunity to undertake a one-year postdoctoral programme at the Crick.

4

ACCELERATE TRANSLATION FOR HEALTH AND WEALTH

The Crick conducts discovery science that is open to translation. We focus on maximising the impact that can be generated from our science, measured in terms of improvements to people's lives and in economic opportunities.

IDEA TO INNOVATION PROJECTS

13

IDEA TO INNOVATION FUNDING

£500K

The process of translation involves taking scientific discoveries and translating them into practical treatments. The Crick has set up structures to identify a pipeline of research projects ripe for translation with seed funding available to carry out pilot investigations of ideas, and to accelerate their progression with partners in academic and commercial sectors to take them one step closer to patients.

We created a Translation Advisory Group to provide external peer review of translation projects at the Crick, as well as advice and support across a range of translational activities.

The Translation team was awarded £500,000 this year through the MRC Confidence in Concept award and philanthropic donations, and this will be used to fund our Idea to Innovation (i2i) initiative. i2i provides funding and support to early-stage translational projects, enabling researchers to address scientific questions that, if successful, would allow continued translational development funded by external grants or with commercial partners. Over the last 18 months, 13 projects have received funding. These range from understanding potential therapeutic targets in oncology to technology developments in neuronal recordings, with all projects having received clinical and industry input to accelerate their progression.

Early in 2017, almost 150 researchers from the Crick and GSK gathered together at the first GSK LinkLabs symposium. This event gave our scientists the opportunity to explore and discuss 12 projects from the LinkLabs portfolio. Established in 2015, the Crick/GSK LinkLabs collaboration provides a unique opportunity for scientists to work side by side on exploratory biology projects of relevance to human disease. This collaborative model matches GSK's capabilities and expertise with the Crick's deep biological insights and provides an environment for both industry and academic scientists to develop new skills.

▸ **FEATURE: SPINOUTS**

Translating discoveries into patient benefits

Fundamental discovery science lies at the heart of the Crick. But we also recognise the importance of turning those discoveries into practical treatments that benefit patients. This process is known as 'translation' – and it is both an important part of our strategy and a key aim for UK science generally.

Effective translation that converts discoveries into safe and effective new therapies is difficult and takes time. It also requires significant investment. One of the ways to achieve this is by forming a new company which can develop the technology

5

ENGAGE AND INSPIRE THE PUBLIC

The Crick aims to engage the wider world with its science through inspirational education, public and community engagement programmes, and through engaging in public dialogue about biomedical research.

Committed to playing an active role in our local neighbourhood, we have opened a brand new community space for people living close to the institute. The St Pancras and Somers Town Living Centre is a 450 m² facility within the Crick that aspires to improve health and wellbeing locally. Services include a job hub, activities for under-fives, courses in English as a second language, employability workshops, Citizens Advice services and healthy living classes.

We also launched our work experience programme during the year. Six young people have already spent time with our teams across the institute and another 51 are due to come by the end of the academic year. The programme aims to increase the aspirations of young people, improve their levels of scientific literacy and give them a useful insight into the world of work as well as an opportunity to develop transferable skills.

This initiative runs alongside our formal education programme, which aims to increase the number of young people going into careers involving science, technology, engineering and maths (STEM). The beginning of 2017 saw the first school groups come to a new dedicated space just for them inside the Crick – the Weston Discovery Lab (see page 39).

Public events are now increasingly important parts of our engagement work. In October 2016, more than 400 people filled the auditorium to participate in a joint Crick and BBC World Service debate on the possibilities, clinical applications and ethical issues arising from advances in genomic medicine. The debate was just one of a week-long series of programmes about the Crick broadcast to the World Service's 372 million weekly listeners. The following month saw members of the public visit our gallery for the first time to explore our exhibition titled 'How do we look?' (see page 39). This initial exhibition explored the what, why and how of scientific imaging through the eyes and thoughts of Crick researchers with a collection of images and videos created by our scientists to help solve a research problem.

NEW COMMUNITY SPACE

450 m²

"The Crick's mission is to help tackle some of the biggest health challenges facing humanity, from heart disease to cancer. Through our support for the Living Centre, we also aspire to improve the health of the local community."

KATIE MATTHEWS,
DIRECTOR OF PUBLIC ENGAGEMENT

and assemble a multidisciplinary team of dedicated scientists to take it forward. In recent months, two research initiatives from the Crick and our research partners have been spun out as new companies.

Achilles Therapeutics is a new company formed by Syncona LLP and Cancer Research Technology with backing of £13.2 million. It brings together research by scientists at the Crick and UCL. Charlie Swanton (below left) and colleagues discovered unique markers that are present on the surface of all cancer cells in an individual patient's tumour, but not on healthy cells. These markers can act as flags to the immune system. Achilles Therapeutics aims to design lung cancer therapies that target these markers with the aim of destroying tumours without harming healthy tissues.

GammaDelta Therapeutics, co-founded by Adrian Hayday (above left) and Oliver Nussbaumer at King's College London and the Crick, focusses on tissue-derived gamma delta (γδ) T cells – a unique population of immune cells – as a novel approach to immunotherapy. The new company received seed funding from investment group Abingworth this year and will seek to exploit the properties of tissue-resident γδ T cells in developing improved immunotherapies for cancer and potentially other diseases.

"Translation is one of our five strategic aims," says David Roblin, Chief Operating Officer and Director of Scientific Translation at the Crick. "We are pursuing an approach to translation that we think offers something new, offers the best chance of success in providing benefits to patients sooner and can play a role in demonstrating the way to boost innovation arising out of UK science."

THE BUILDING: THE CRICK LABORATORY

A MOVING EXPERIENCE

PEOPLE WORKING IN THE BUILDING
1,500

LABS MIGRATED
94

SCIENCE TECHNOLOGY PLATFORMS
14

PIECES OF EQUIPMENT MOVED
17,500

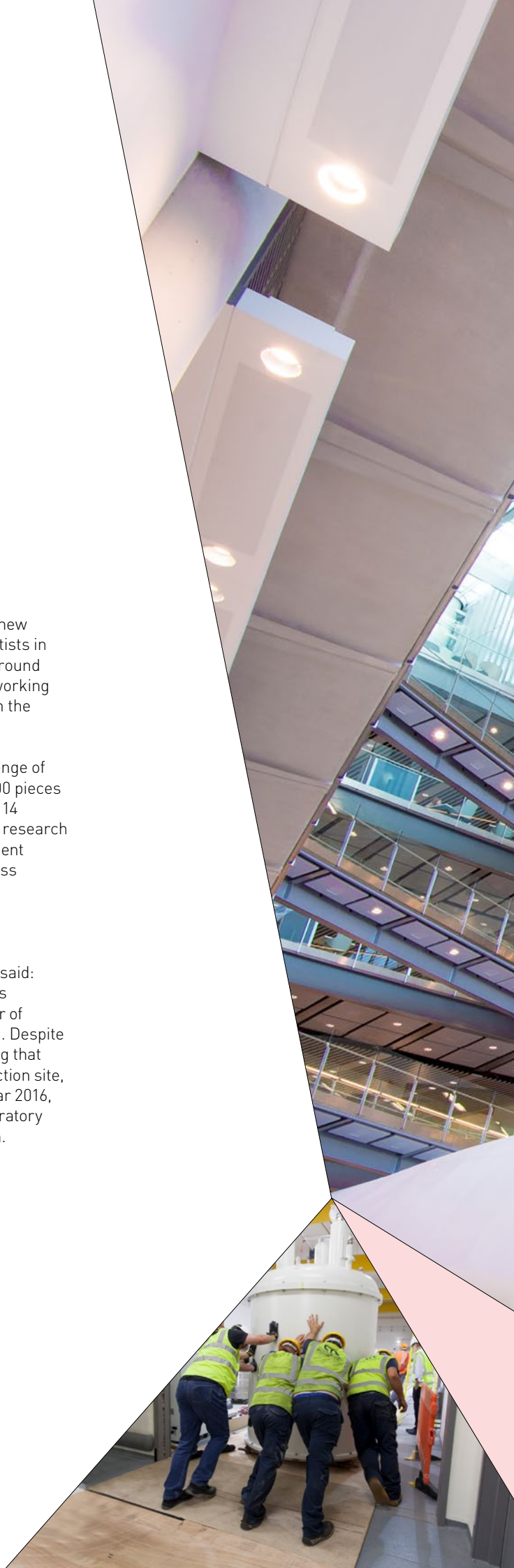
COMPUTERS AND ASSOCIATED ITEMS
3,107

After nine years of planning and anticipation, science is now hard at work inside the new Francis Crick Institute building.

We opened the doors of our stunning new £650 million building to the first scientists in August 2016 – and it is now home to around 1,500 people with 94 science groups working on hundreds of research projects with the potential to transform lives.

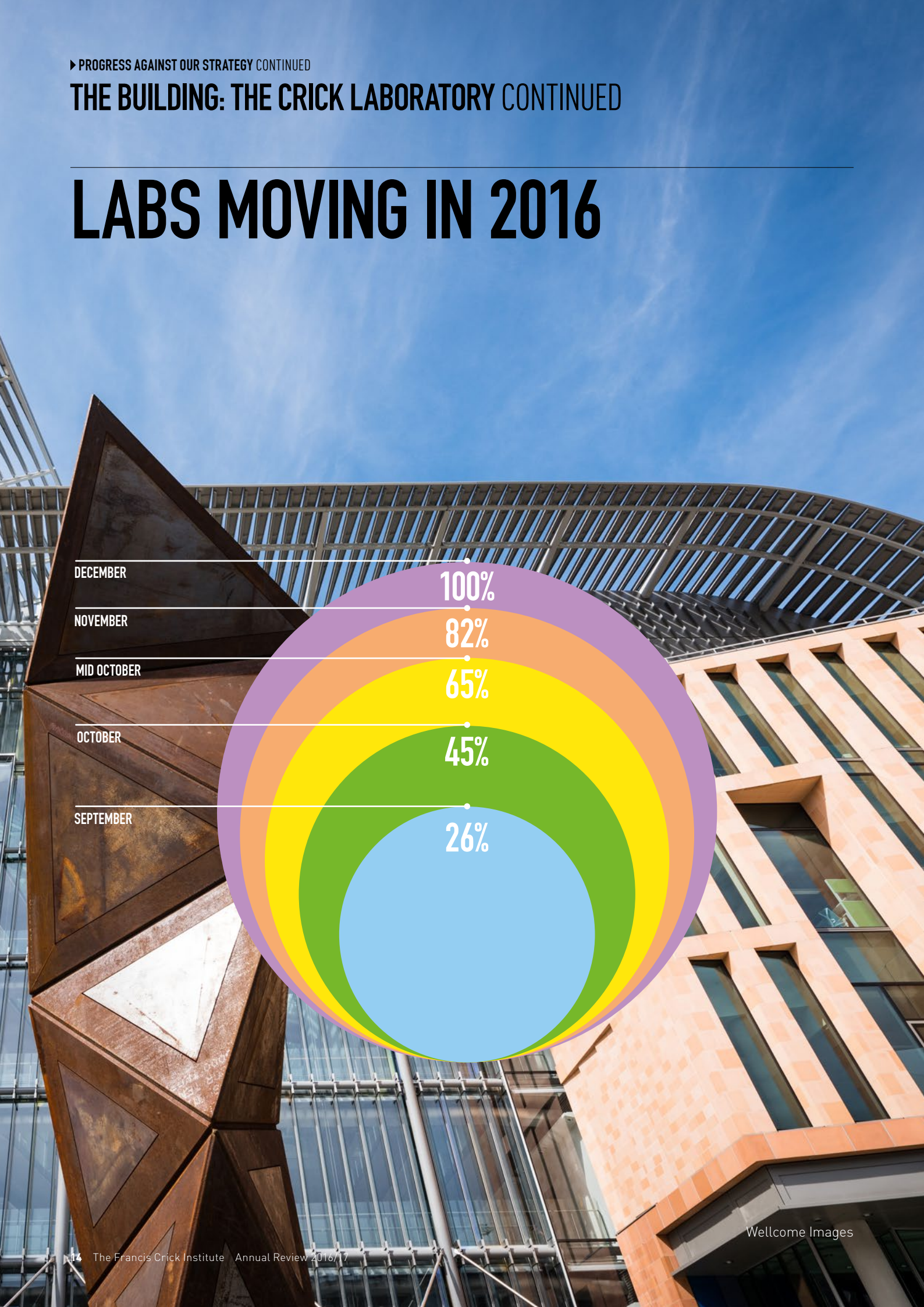
The move itself was a logistical challenge of the highest order. No fewer than 17,500 pieces of equipment were moved, along with 14 Science Technology Platforms (STPs, research facilities with state-of-the-art equipment such as election microscopes and mass spectrometers) and more than 3,000 computers and associated items.

David Roblin, Chief Operating Officer and Director of Scientific Translation, said: "Repeated delays in getting full access to the building created a great number of challenges for our migration planning. Despite the difficulties in moving into a building that was for a while still an active construction site, we were able to move in within the year 2016, within budget and in the planned laboratory sequence which minimised disruption.

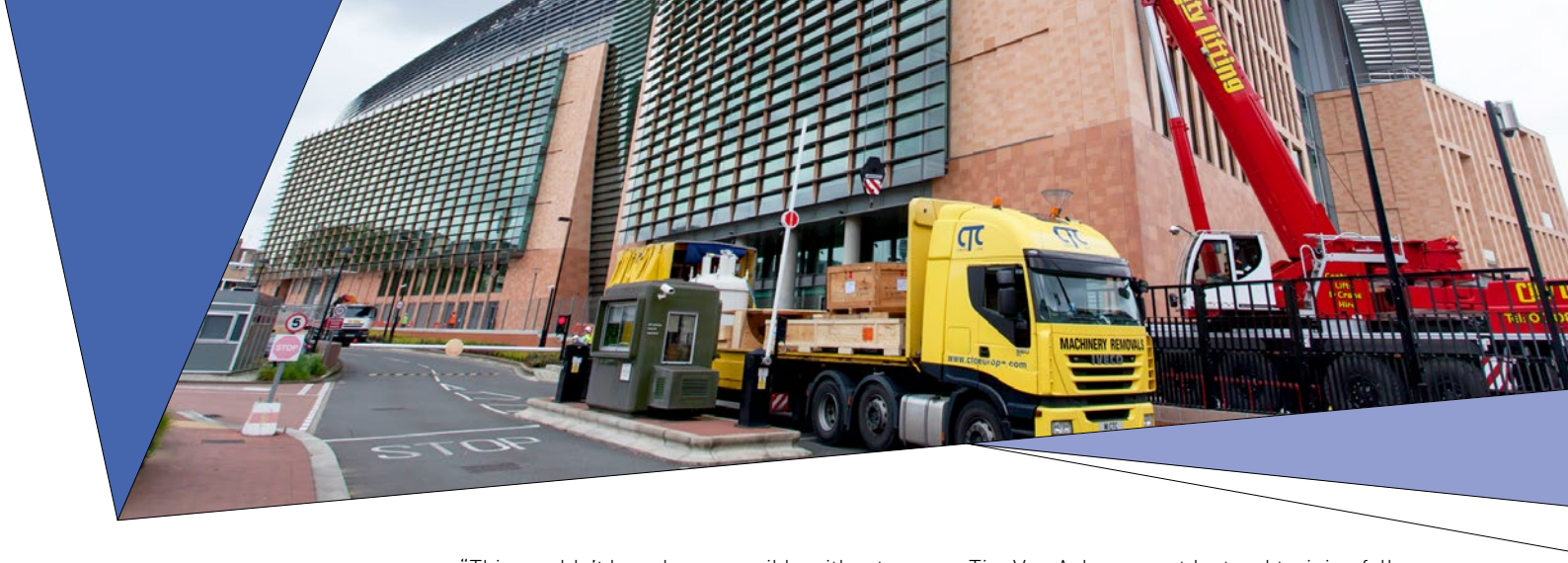


THE BUILDING: THE CRICK LABORATORY CONTINUED

LABS MOVING IN 2016



Wellcome Images



> Despite the somewhat painful preparations, the move itself went like clockwork, it was really a phenomenal success. It was fantastic to see the whole lab pull together, with everyone chipping in, and by day three we were already running bench experiments.
>
> **CAROLINE HILL, GROUP LEADER**

"This wouldn't have been possible without our phenomenal team, whom I would like to thank for their flexibility and professionalism in dealing with the extraordinary pressures of the move. Scientific discovery in the building started in 2016 and I am thrilled that we should be fully operational later this year. The Crick is beginning a new chapter focused on fully realising our innovative strategy of discovery without boundaries."

AN ENORMOUS UNDERTAKING

Caroline Hill, Group Leader at the Crick, said: "Years of planning, archiving and filing finally came to fruition with our move into the Crick. Decades' worth of experimental notes had to be sorted through, thousands of vials stored in liquid nitrogen reorganised and thousands of zebrafish embryos couriered by bike!"

David Hudson, Head of Operations for Science Technology Platforms, said: "The migration of around 30 different specialist facilities was an enormous undertaking that was extremely challenging but ultimately a success. Our move began with the lowering of nuclear magnetic resonance (NMR) and electron microscopy equipment into the basement by crane. The situation was exacerbated by unreliable telephones and, even more challenging, no toilets or lifts, which meant staff had to climb the stairs from the lowest basement floor to use toilets in the on-site portacabins.

"Maintaining essential research services across multiple sites was one of our major challenges but staff worked incredibly hard to ensure that the disruption on science was minimal. During periods of inactivity many took the opportunity to focus on other projects, for example software development and paper writing, as well as a having a good clear-out!"

A FRESH START UNDER ONE ROOF

It was an enormous effort and a logistical challenge in moving everyone into the new Crick building, but one that has ultimately been very successful. But now that researchers have moved in, what has their experience been like?

Tim Van Acker, a postdoctoral training fellow, said: "I regularly meet researchers from different fields in the canteen, collaboration spaces and on the stairs, and we end up helping each other out. Having 14 STPs under one roof is also amazing – when you need something doing, you only need to walk across the building!"

"Being located in the Knowledge Quarter is great for expanding our research network," says Aylin Cakiroglu, another postdoc. "We've already had meetings at Google's DeepMind, BenevolentAI and the Farr Institute, which are now just a stone's throw away.

"Our new and exciting surroundings are encouraging everyone to engage and share new ideas and expertise. It's like a new fresh start."

BUILDING AWARDS

- **THE CRICK WAS NAMED 'BEST NEW PLACE TO WORK' AT THE LONDON PLANNING AWARDS 2017**
  The category recognises developments that are well designed, provide high-quality public areas, encourage use of public transport, are energy efficient and provide good access to local amenities.

- **THE CRICK WAS AWARDED LONDON FIRST'S 'GREATEST RESEARCH AND DEVELOPMENT' PRIZE FOR 2017**
  The prize recognises organisations that undertake enterprising research or improve the city's science base.

- **GREEN APPLE AWARD FOR THE CRICK**
  In partnership with Bywaters, the Crick was crowned National Green Champion for our achievements in sustainable operations, with the highest scores being achieved for innovation, environmental awareness and best practice. The Crick was the only scientific institution to receive a Green Apple Award, a prize which recognises organisations for their environmental efforts.

RESEARCH HIGHLIGHTS

Crick researchers have published more than 450 peer-reviewed papers during the year. The following pages highlight a handful of the discoveries made, demonstrating the breadth of research undertaken at the institute and how our scientists' work is advancing understanding of health and disease.

NEW ANTIBODY MAY HERALD UNIVERSAL FLU VACCINE

Influenza remains a serious threat to global health due to the viruses' constantly evolving genomes and resistance to existing vaccines. Annual epidemics cause an estimated 3 to 5 million cases of severe disease and up to half a million deaths globally.

Flu viruses are especially deadly during pandemics, when there is not usually time to develop and produce enough vaccine. There are several types of flu virus, but influenza A is responsible for most hospitalisations and is the only type to cause pandemics.

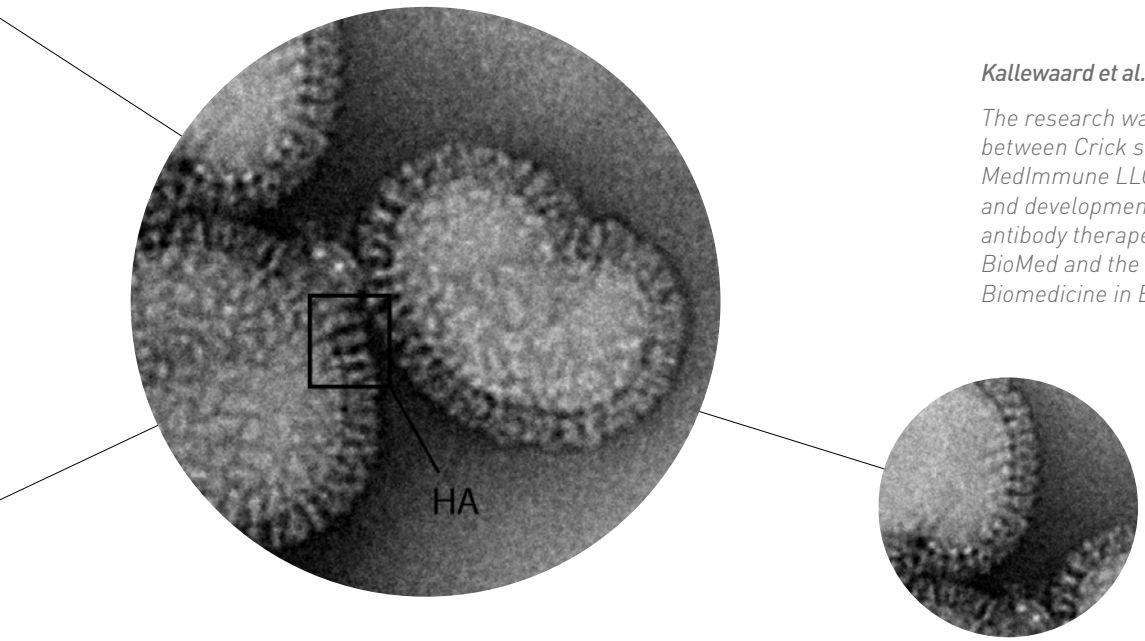
A new antibody, called MEDI8852, shows promise as a potential treatment for influenza A by fighting several strains on a number of fronts, including blocking essential steps of the virus's lifecycle and engaging the human immune system to eliminate virus-infected cells.

The antibody has been studied by scientists at the Crick with colleagues from academia and the pharmaceutical industry. Steve Gamblin, Group Leader and the Crick's Director of Science Operations, and John Skehel, Emeritus Scientist at the Crick, led the study. John said: "This research has implications for the design of a much-needed universal influenza vaccine, which could protect us against a future pandemic strain."

The antibody is now being tested as a possible flu treatment in early clinical trials.

Kallewaard et al., Cell 166 (2016): 596–608

The research was a collaboration between Crick scientists and colleagues at MedImmune LLC (the global biologics research and development arm of AstraZeneca), Swiss antibody therapeutics company Humabs BioMed and the Institute for Research in Biomedicine in Bellinzona, Switzerland.



PREVENTING STEM CELL LOSS IN THE BRAIN COULD STOP COGNITIVE DECLINE

Crick researchers studying adult stem cells in the brain's hippocampus, the area associated with memory, have discovered an important protein that could help stop our brains declining as we age.

> "In the brain, having fewer stem cells has been linked to memory impairment and cognitive decline.
>
> **FRANÇOIS GUILLEMOT**

Adult stem cells are found throughout our bodies. They can either remain dormant or become active, creating the different cells needed in that part of the body. The dormant cells are crucial for maintaining the stem cell population and for producing new brain cells over time.

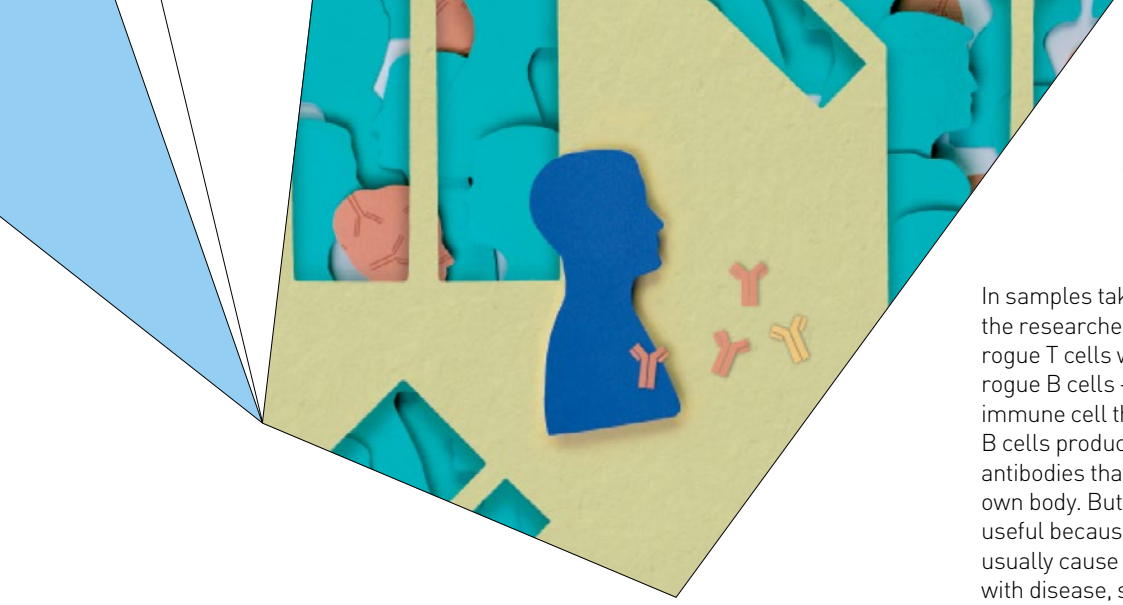
The scientists studied mice and selectively blocked genes involved in the replenishment of the pool of dormant stem cells in the hippocampus, and in the activation of these cells to create new brain cells. They discovered a protein which kick-starts a molecular process that enables active stem cells to return to the dormant state.

François Guillemot, Group Leader at the Crick, said: "In the brain, having fewer stem cells has been linked to memory impairment and cognitive decline. Understanding the mechanisms involved in regulating the maintenance of the adult stem cell population will help us find ways to prevent or even reverse their depletion and restore function during ageing. The discovery of a protein involved in this maintenance process is an important step forward."

The researchers also found that the stem cells that return to a dormant state have different properties from those that have always been dormant. They are now investigating whether there are differences in how these two types of dormant stem cell are regulated or in their functions.

Urbán et al., Science 353 (2016): 292–295

This research received additional support from Wellcome, the Medical Research Council and the Biotechnology and Biological Sciences Research Council.



HARNESSING HUMAN ANTIBODIES FOR NEW DRUGS

An international study into a rare and poorly understood autoimmune disorder has yielded unexpected results that could help researchers develop new drugs for other, more common autoimmune conditions such as type 1 diabetes.

The autoimmune condition in the study, called autoimmune polyendocrine syndrome type 1 (APS1), affects people differently but can cause hormone and thyroid problems, hair loss, digestion problems and liver inflammation, among other symptoms. It is caused by defects in a gene called the autoimmune regulator gene. When functioning properly, this gene helps purge the body of immune cells called T cells that, rather than targeting infections, instead attack our body's own proteins. In people with APS1, such 'rogue' T cells thrive due to the lack of the autoimmune regulator gene.

The defect in the gene should also put APS1 patients at severe risk of developing myriad autoimmune diseases, including type 1 diabetes, multiple sclerosis, lupus and rheumatoid arthritis – yet this is not the case. Working with international collaborators, a team of scientists from the Crick and King's College London set out to find out why.

In samples taken from 81 patients with APS1, the researchers found that those with more rogue T cells were also likely to have more rogue B cells – these are another type of immune cell that produce antibodies. The rogue B cells produced 'autoantibodies' – these are antibodies that target proteins within a patient's own body. But, in this case, the antibodies were useful because they targeted proteins that usually cause inflammation associated with disease, seemingly preventing many APS1 patients from developing type 1 diabetes, multiple sclerosis, lupus and rheumatoid arthritis.

Each patient studied had about 100 different autoantibodies in their blood. They all had different ones, so between them the patients had antibodies to thousands of different human proteins.

Adrian Hayday, Group Leader at the Crick and King's College London, led the study. He explained: "These findings provide novel and unexpected insights into human immunology, and are also significant clinically because antibodies make up one of the largest sectors of the pharmaceutical market, where one of the great quests is to be able to routinely generate many different antibodies that fight diseases.

"Rather than committing immense resources to drug discovery, which is at best a very uncertain path, the findings suggest that highly effective antibodies could be obtained from APS1 patients. The clinical information of each patient could guide us as to which diseases are most likely to benefit from their specific antibodies."

The team tested this theory in a mouse model of psoriasis, an autoimmune condition that causes red, itchy and scaly skin. They found that injecting the mice with antibodies from the APS1 patients reduced psoriasis symptoms.

The next step is to explore the potential of antibodies from APS1 patients to treat other autoimmune diseases, including type 1 diabetes, and possibly even cancers.

Meyer et al., Cell 166 (2016): 582-595

This research received additional support from ImmunoQure AG, a start-up biotech company established by the international team of scientists and clinicians involved in the study and the Finnish APS1 Patients' Association, as well as from Wellcome, Cancer Research UK and the European Union.

CELLS UNDER STRESS USE SAME GENES FOR DIFFERENT PRODUCTS

Scientists have long known that when DNA is damaged, such as by UV irradiation, cells respond by activating specific genes that help keep the genome intact. But less well studied is the fact that cells actually shut down the vast majority of their other genes after DNA damage.

Scientists at the Crick have analysed this genetic shutdown at the molecular level for the first time. They found that transcription across most genes slows rapidly and dramatically in response to DNA damage. Transcription is the first step in gene expression, where the genes are copied into molecules called RNAs. There are different types of RNA; the most common are known as messenger RNAs (mRNAs) and contain the instructions for building proteins.

Different transcript forms can be produced from the same gene, a phenomenon known as 'alternative splicing'. However, the Crick study led the researchers to an unprecedented example of a gene which encodes both an mRNA and a shorter RNA that doesn't contain the instructions for a protein (known as a non-coding RNA).

It was previously assumed that the purpose of alternative splicing is simply to enable one gene to encode several different protein forms. However, it has recently been argued that alternative splicing cannot be important, since only a single protein form can ever be detected from most coding genes. The Crick study now opens the possibility that some alternative transcripts function not as protein-coding mRNAs but rather as stable, non-coding RNAs.

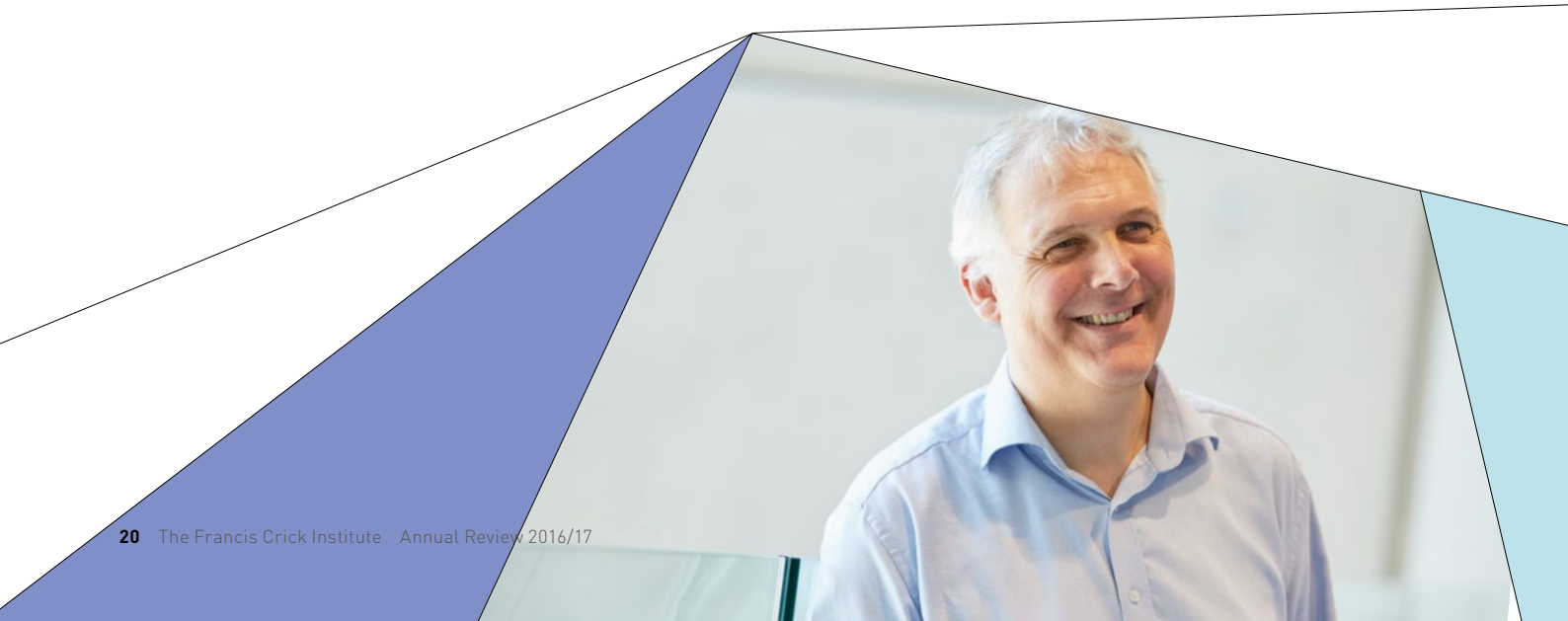
The Crick team discovered that, when faced with DNA damage, a gene called ASCC3 produces a non-coding RNA instead of its usual protein. Remarkably, the function of this RNA is to counteract the function of the ASCC3 protein, reversing its usual role in repressing transcription and allowing the cell to recover gene expression after DNA damage has been repaired.

Jesper Svejstrup, who led the study, said: "There may be many other genes like this; we certainly know there are scores of genes that appear to behave similarly in the DNA damage response. Such alternative non-coding RNA transcripts may also be up-regulated in response to other kinds of cellular stress.

"Now that we know that two RNAs – one that codes for a protein and one that doesn't but is still functionally important – can be produced from the same gene, researchers can start looking for functions for their short RNA transcripts in whatever physiological system they are working. It is also possible that a faulty switch between such transcript forms might underlie some human diseases, such as cancer."

Williamson et al., Cell 168 (2017): 843-855

The research received additional support from the European Research Council.



NEW UNDERSTANDING OF TREATMENT-RESISTANT LEUKAEMIA CELLS

Every year in the UK almost 10,000 people are diagnosed with leukaemia, a cancer of the blood. Almost half of them will die within 10 years.

This death rate reflects the high relapse rate for leukaemia, caused at least in part by some cancer cells surviving the initial treatment. These surviving cells are often resistant to treatment, allowing leukaemia to spread and become fatal.

Exactly how the treatment-resistant leukaemia cells survive initial chemotherapy is not well understood. One popular theory is that they sit hiding in special nooks within the bone marrow that usually harbour blood stem cells – immature cells that can form all other blood cells.

But research from the Crick, Imperial College London and the University of Melbourne in Australia has revealed that some leukaemia cells do not sit and hide. Instead, to the researchers' surprise, the cells are scattered throughout the bone marrow both before and after cancer treatment, and move around rapidly. This constant movement is likely to help them to evade efforts to kill them.

The research was carried out in mice and validated with human leukaemia samples. To investigate what happens at the cellular level, the scientists used a technique called intravital microscopy that allows fast, high-resolution imaging of live mice. They studied mice with a particularly deadly type of leukaemia called T cell acute leukaemia and tracked the movement of disease cells before and after chemotherapy.

After treatment, the leukaemia cells that survived were seen moving faster than the cells moving before treatment. The researchers suggest that the act of moving itself may help the cells to survive.

The team went on to test the findings in human leukaemia cells by imaging human T cell acute leukaemia cells that had been transplanted into mice. These results showed the same patterns of movement before and after treatment.

Study leader Cristina Lo Celso of Imperial and the Crick said: "Armed with the knowledge that these 'survivor' cells move rapidly throughout the bone marrow, it would be ineffective to target specific, limited areas to tackle treatment-resistant leukaemia.

"Our next step is to explore why these cells don't hide and how their movement helps them to survive. Ultimately we want to find out whether we can stop the movement, and whether this could kill the treatment-resistant cells, opening up new avenues in the development of novel, more effective leukaemia treatments."

> "Our next step is to explore how these cells' movement helps them to survive.
>
> **CRISTINA LO CELSO**

Hawkins et al., Nature 538 (2016): 518–522

This research received additional funding from the charities Bloodwise and Cancer Research UK, alongside contributions from the European Research Council, the Human Frontier Science Program and the European Hematology Association.

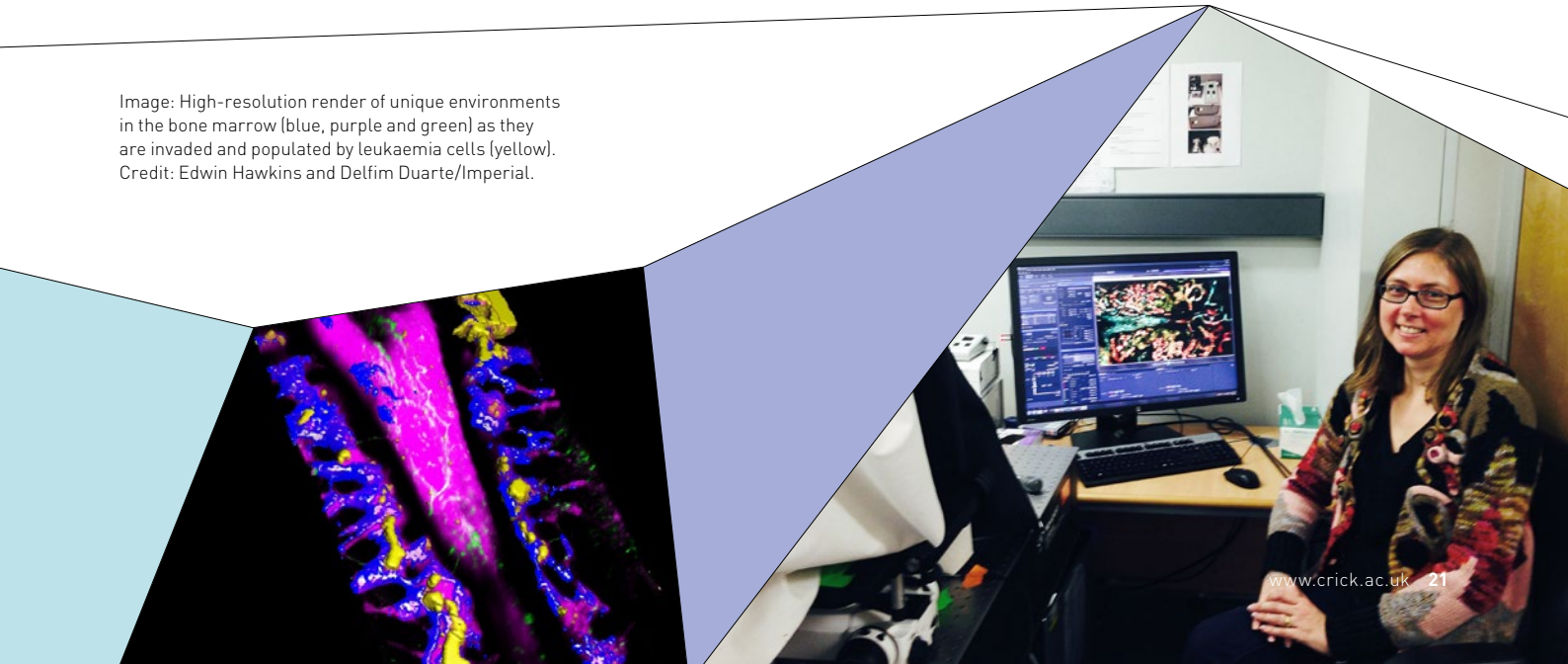


Image: High-resolution render of unique environments in the bone marrow (blue, purple and green) as they are invaded and populated by leukaemia cells (yellow). Credit: Edwin Hawkins and Delfim Duarte/Imperial.

> We now need to learn more about how cells regulate their metabolism to improve how we treat these conditions in the future.
>
> **MARKUS RALSER**

YEAST STUDY SUGGESTS A THIRD OF ALL GENES ARE INVOLVED IN METABOLISM

Crick scientists have grown around 5,000 strains of yeast, each missing a different gene, to determine each gene's function in relation to metabolism. This extensive piece of research allowed them to create an 'organisational chart' for the genes and attribute roles to around half of those genes whose function was previously unknown.

Unexpectedly, they found that metabolism is influenced by a large proportion – at least a third – of all genes in the genome. Metabolism is the name for the biochemical processes that occur inside a cell to maintain life. It includes the build-up and breakdown of nutrients to provide energy and to produce small molecules, including amino acids as well as sugars, fatty acids and vitamins. These building blocks are then used to create the proteins and other molecules our cells need to carry out their function.

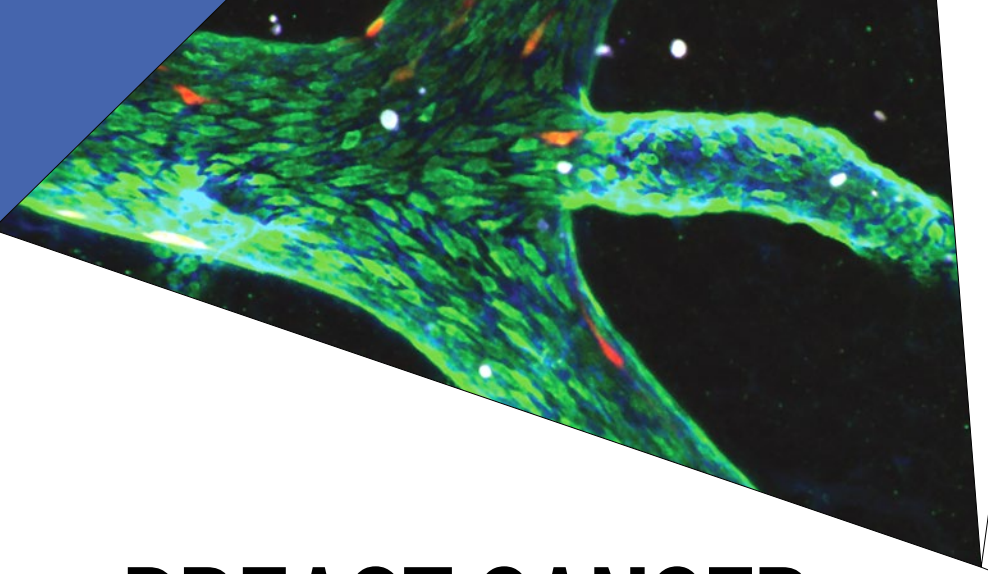
Markus Ralser, the Group Leader at the Crick who led the research, said: "The fact that around a third of the missing genes specifically impacted the metabolism of amino acids underlines the importance metabolism had in the evolution of our cells.

"In humans, amino acids are implicated in metabolic diseases such as diabetes, and their imbalance causes several rare medical conditions, many of those that depend on age. We now need to learn more about how cells regulate their metabolism to improve how we treat these conditions in the future."

Yeast cells have about 6,000 genes, compared with around 20,000 in humans. Because many yeast genes have human counterparts that also have unknown functions, identifying the roles of yeast genes can help scientists understand what human genes do. This can be the first step towards developing treatments for conditions caused by genes going wrong.

Mülleder et al., Cell 167 (2016): 553-565

The research received additional support from Wellcome and the European Research Council.



BREAST CANCER MARKER OFFERS NEW TREATMENT TARGET

Adult stem cells divide and maintain the different cells in each organ and tissue in our bodies. Mutations in stem cells are particularly dangerous because they can take advantage of stem cells' natural ability to reproduce, creating tumours.

The stem cell populations in the breast and the types of cell that give rise to breast cancer are incompletely understood. Now, Crick scientists have found a protein that identifies stem cells in the adult breast that are particularly prone to develop cancer in response to genetic mutations.

The discovery reveals how some kinds of breast cancer start, as well as a possible way to stop tumour growth by targeting cancer cells expressing this protein.

The team began by looking at a protein called Lrg6 that is found on the surface of stem cells of taste bud, lung and skin cells, as well as on an uncommon type of breast cell. To find out whether Lrg6 is also found in breast stem cells and whether it might play a role in cancer, they fluorescently labelled Lgr6-positive stem cells in healthy mice and in mice genetically engineered to develop breast cancer.

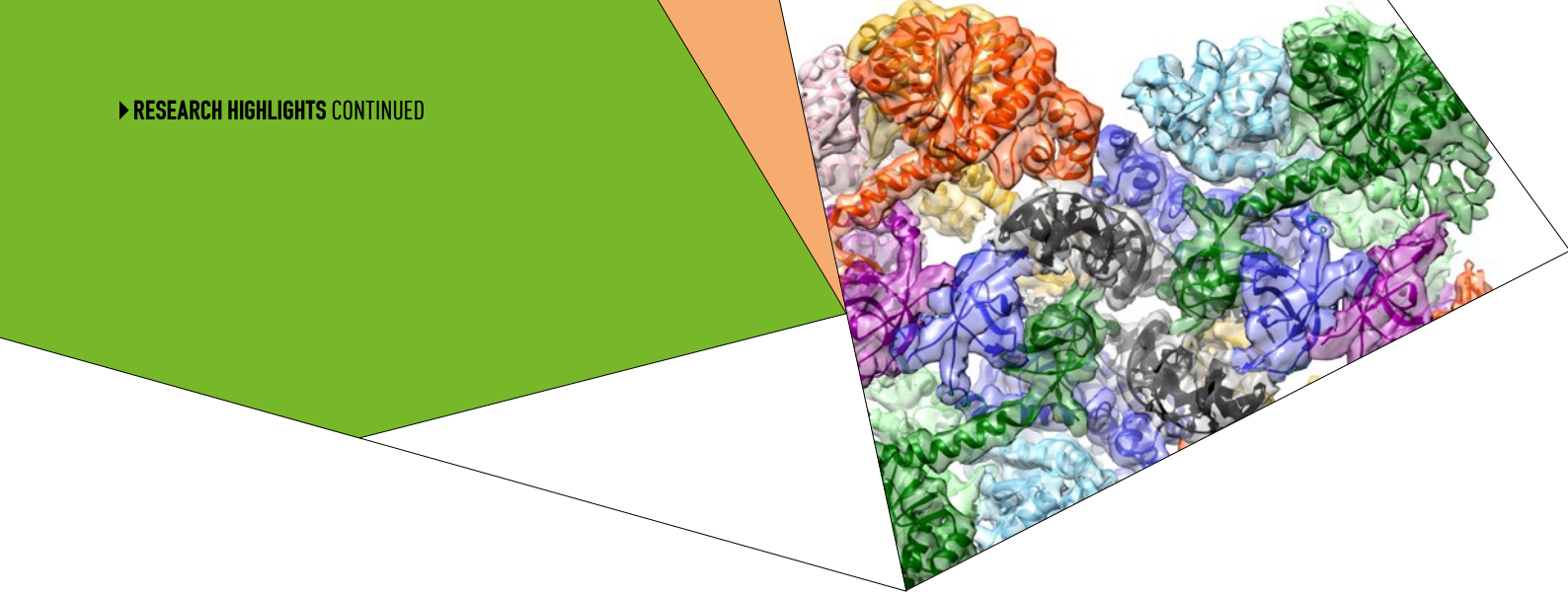
This revealed that Lgr6-positive cells are very active in the normal expansion of the breast during puberty and pregnancy, and when mutated can initiate breast cancer. Killing mutated Lgr6-positive cells in mice reduced cancerous tumour growth.

Axel Behrens, who led the work at the Crick, said: "We also found that around half of human breast cancers contain cells with this key marker. Tumours that contain this marker tend to be more aggressive. In the future, it might be possible to target mutated Lgr6 cells to reduce tumour growth."

Blaas et al., Nature Cell Biology 18 (2016): 1346–1356

This research received additional support from the Marie Skłodowska-Curie actions, the Wenner-Gren Foundation, the Swedish Cancer Society, the German Research Foundation (DFG), the German Academic Exchange Service (DAAD), the Knut and Alice Wallenberg Foundation, the Karolinska Institutet and the Swedish Research Council.

> "We found that around half of human breast cancers contain cells with this key marker.
>
> **AXEL BEHRENS**



SCIENTISTS DISCOVER SHAPE OF HIV 'SPEARHEAD'

Although HIV is no longer the death sentence it once was, 37 million people remain infected globally and over a million die from AIDS each year. Today, people receiving treatment for HIV can live more than 50 years after diagnosis, but there isn't yet a cure.

The success of the HIV virus relies on its ability to insert its genome into a host cell's chromosome in an irreversible process that makes it difficult to eradicate.

The viral component responsible for this is called integrase. Once the virus is inside a host cell, this deceptively small enzyme forms a highly stable structure on the viral DNA. This structure is called an intasome which, as it enters the host cell's nucleus, acts like a spearhead to insert the viral DNA into a host's chromosome.

Integrase inhibitors are a relatively new type of drug that stop the HIV virus spreading by preventing it from integrating its DNA into the host's chromosome. Deciphering the structure of the intasome should help to find weak points. Peter Cherepanov and Alessandro Costa, Group Leaders at the Crick, led research that set out to discover what this structure looks like in viruses such as HIV.

Alessandro explained: "Integrase proteins from HIV and related viruses are notoriously difficult to study in the lab, and the structure of the intasome they create to help penetrate the cellular genome has eluded biologists for over two decades. Years of research resulted in a collection of partial structures that did not explain how this viral protein protects the ends of the virus's DNA. Recent breakthroughs studying simpler viruses from the same viral family have revealed the intasome structure but seemed to contradict some of the previous results for the HIV virus."

The scientists used cryo-electron microscopy to take detailed images of thousands of individual biological molecules frozen at very low temperatures. This technique allowed them to visualise the structure. As well as solving the long-standing puzzle, their work reconciled years of data from structural and biochemical research into HIV.

The most remarkable and unexpected finding was that the intasome is much larger than expected; its formation involves as many as 16 integrase subunits, which assemble around a core structure.

Peter said: "The discovery of this complex structure is significant, as it may allow the virus to be more adaptable to the environment inside the host cell and more selective about where it integrates into the host genome. Understanding the structure of this spearhead might help us find weak points to target the virus with new drugs."

Ballandras-Colas et al., Science 355 (2017): 93–95

The work received additional support from Wellcome, the US National Institutes of Health and the Icelandic Research Fund.

> "Understanding the structure of this spearhead might help us find weak points to target the virus with new drugs.
>
> **PETER CHEREPANOV**

ANOTHER REASON TO EAT YOUR GREENS?

Nutrients found in certain vegetables boost the effectiveness of a protein that protects us from pollutants, toxins and pathogens, according to a study in mice by Crick scientists.

The protein, called the aryl hydrocarbon receptor (AhR), acts as a vital control centre to maintain our immune defences, particularly in our intestines, lungs and skin. These areas all have barriers to prevent bacteria and other pathogens from getting through. AhR helps to maintain these barriers, making sure that any holes are quickly repaired. If bacteria get through this barrier in the intestine, the resulting immune response causes severe inflammation and damage.

In the latest study, the Crick team led by Group Leader Brigitta Stockinger found that AhR activity is controlled by a delicate cycle. AhR can be activated by molecules of a specific shape, known as AhR ligands. When AhR is active, it produces an enzyme that then breaks down these ligands. When the system is working properly, this cycle keeps AhR activity at the right level to maintain our immune defences.

When the enzyme is hyperactive, however, it breaks down too many ligands so there is not enough AhR activity to support immune cells that keep bacteria out. When the team created mice with a hyperactive version of the enzyme, the mice were unable to fight off an infection with *Citrobacter* bacteria, the mouse version of human pathogenic *E. coli* bacteria. However, when the researchers fed these mice nutrients found in certain vegetables, their AhR activity and immune defences were restored. The nutrients helped in two ways, both reducing the activity of hyperactive enzymes and providing extra ligands to activate more AhR.

Brigitta said: "We could all benefit from eating more vegetables such as kale, broccoli and cauliflower, which contain nutrients that promote AhR activity. Maintaining healthy AhR activity helps to keep us safe from toxins, pollution and pathogens in our skin, lungs and intestines. It is possible that some people with inflammatory intestinal diseases have mutant enzymes with abnormally high activity. These people would be particularly sensitive to infections but could potentially improve their gut immunity by eating more of these vegetables."

Schiering et al., Nature 542 (2017): 242–245

This research received additional support from Wellcome, Cancer Research UK, the Swedish Research Council and the US National Institute of Environmental Health Sciences.

> "Maintaining healthy AhR activity helps to keep us safe from toxins, pollution and pathogens in our skin, lungs and intestines.

BRIGITTA STOCKINGER

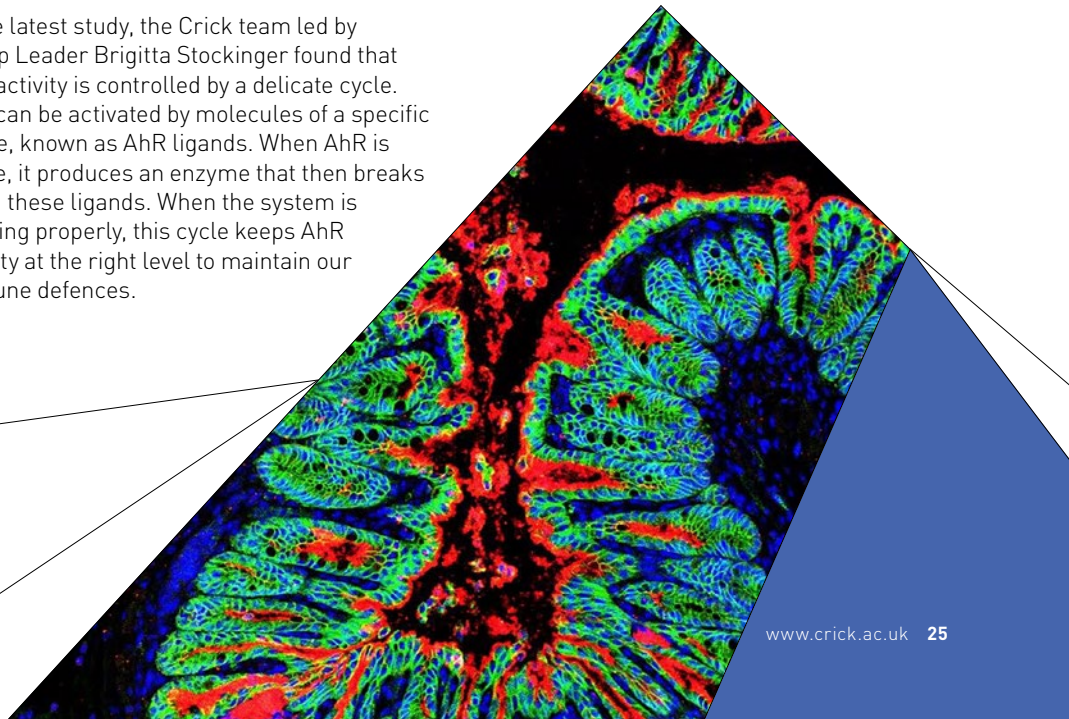


Image: Image of the colon (red is bacteria, green is epithelial cells and blue is cell nucleus).

GENETIC SWITCH MAY CONTROL CANCER CELL IMMORTALITY

A Crick team has found a possible way to turn cancerous tumours back into benign ones using a genetic switch.

Scientists led by Paola Scaffidi, Group Leader at the Crick, found that production of a protein called H1.0, which helps pack DNA tightly inside cells, is switched off in many types of cancer. Reactivating this protein may halt tumour growth.

Studying cancer cells lacking H1.0, the team found that DNA becomes uncoiled at key points, activating a series of genes that allow the cells to carry on dividing and expanding the tumour.

But as the tumour grows, H1.0 can spontaneously become switched back on in some cells. The researchers traced this back to a region of the DNA that acts as a control switch. With H1.0 back up and running, the cells return to a normal limited lifespan, stopping the tumour from growing.

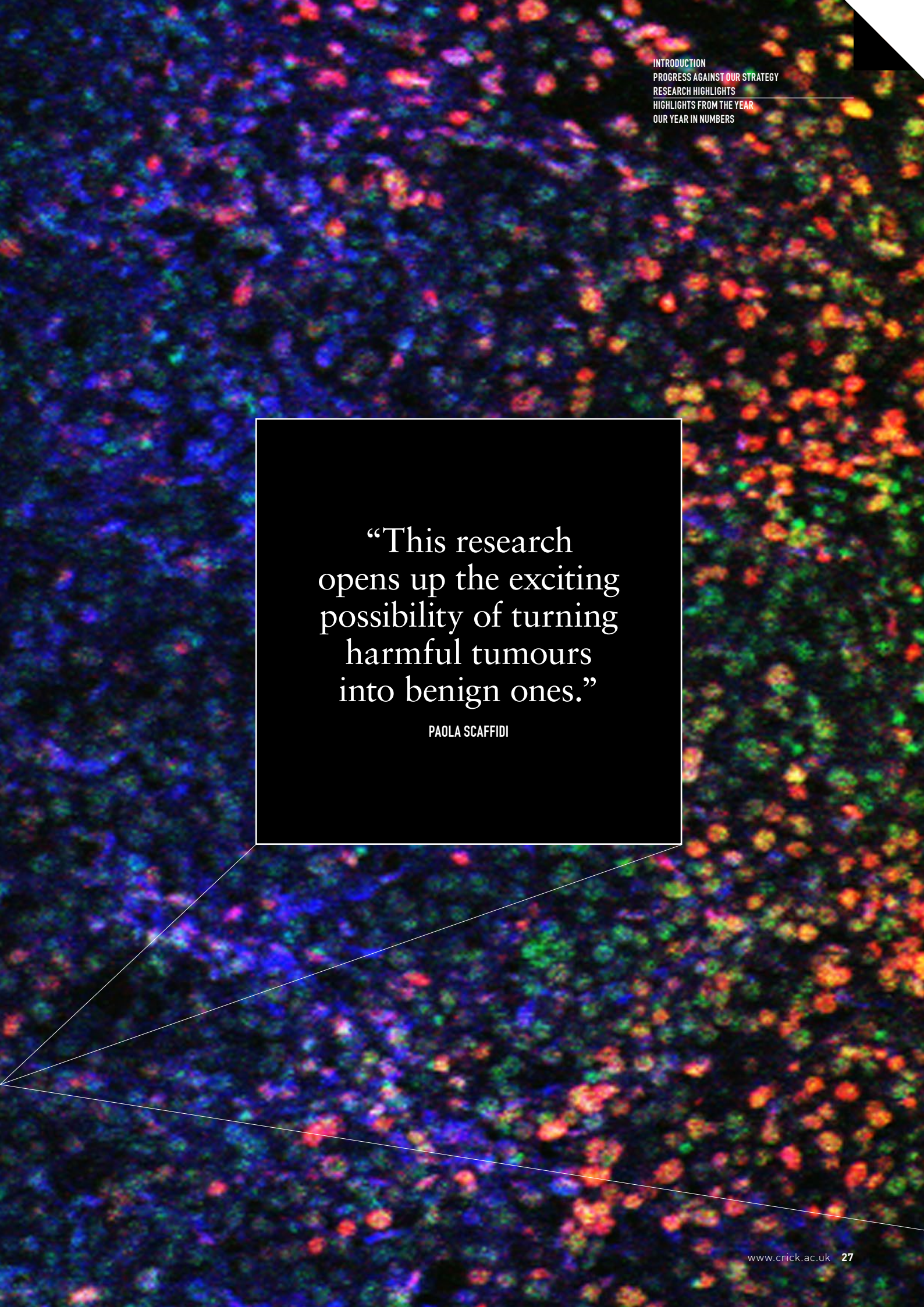
The scientists are now searching for drugs that could kick-start H1.0 production, providing a possible way to halt tumour growth.

Paola said: "This research opens up the exciting possibility of turning harmful tumours into benign ones by reverting cancer cells back to a limited lifespan, halting tumour growth."

Torres et al., Science 353 (2016): aaf1644

This research received additional support from Cancer Research UK, the US National Institutes of Health and National Cancer Institute, the Israel Science Foundation and the European Research Council.

Image (right): Breast cancer cells with variable levels of histone H1.0, shown in red.



"This research opens up the exciting possibility of turning harmful tumours into benign ones."

PAOLA SCAFFIDI

CELL CYCLE REGULATION THEORY PROVEN AFTER 20 YEARS

The discovery of a family of proteins called cyclin-dependent kinases (CDK) won Paul Nurse, Director of the Crick, a share of the 2001 Nobel Prize in Physiology or Medicine. Now after two decades, his research group has found convincing evidence for a theory, first proposed by his lab in 1996, about how CDK imposes order on the processes of cell division.

> “Understanding how CDK regulates cell division in yeast tells us a lot about how the same processes work in human cells.
>
> **MATTHEW SWAFFER**

The ‘activity threshold model’ proposes that the proteins needed at the beginning of the cell cycle are activated by low levels of CDK while those needed at the end are activated by higher levels of CDK. As a result, the natural increase of CDK over time activates the right proteins at the right time. But other scientists have proposed alternative models to explain how the right proteins are activated at the right time. This means that how CDK controls the order of cell cycle events has remained controversial.

When a cell divides, it has to replicate its DNA before it then separates the DNA into two daughter cells. The correct timing of these two events is critical, as incorrect replication or separation of DNA can cause dangerous mutations that can lead to cancer.

These events are controlled by CDK, the master-regulator enzyme, which switches the proteins on, in turn triggering replication and separation of DNA.

The researchers studied yeast, which is simpler and easier to manipulate than human cells, to re-engineer CDK and directly test their theory. They combined this with sophisticated technology that measures the activation of thousands of proteins in a cell at the same time.

They found that different proteins are activated at different times during the course of cell division, and that this is primarily determined by the activity levels of CDK. Proteins involved in cell replication are easier for CDK to activate and so are switched on earlier, when CDK activity is still low. Later in the cell cycle, after CDK’s own activity level has risen, the proteins involved in cell division are activated by the higher CDK levels.

Matthew Swaffer, from the Nurse research group at the Crick, said: “Understanding how CDK regulates cell division in yeast tells us a lot about how the same processes work in human cells. This is central to our understanding of cancer, which arises when cells divide uncontrollably.”

Swaffer et al., Cell 167 (2016): 1750-1761

This research received additional support from Wellcome, the Lord Leonard and Lady Estelle Wolfson Foundation and the Breast Cancer Research Foundation in the USA.

IMMUNE SYSTEM 'TEST LABS' PRODUCE HIGHLY POTENT ANTIBODIES

Our immune system is made up of a network of organs, tissues and cells that work together to protect us from infection and disease.

White blood cells play a key role in this process, and there are two types: T cells activate other cells to target pathogens, while B cells produce antibodies to fight the threats.

Researchers have discovered specialised properties in a group of B cells that act like our immune system's own 'test labs' – developing and refining the best antibodies for the job. The research helps to explain how highly potent antibodies are produced during an infection.

Studying this B cell group has been difficult in the past because the cells are uncommon and too fragile to survive normal lab procedures. But the researchers found a way to use high-resolution microscopy to study thousands of B cells at a time and so were able to look at the biology of these specialised cells for the first time.

Lead researcher Pavel Tolar of the Crick and Imperial College London explained his team's findings: "These B cell-based 'test labs' are special sites in our immune system that arise during an infection. They are dynamic groupings of B cells that are supported by specialised cells that capture pieces of the pathogen and deliver them to the B cells.

"Within these structures, the B cells multiply and mutate so they can produce and select an antibody with the strongest reaction against a particular pathogen. This provides our bodies with a more effective defence system."

Pavel added: "We hope this work might lead to the design of vaccines for human infections that promote the production of highly potent antibodies."

Nowosad et al., Nature Immunology 17 (2016): 870-877

This research received additional support from the European Research Council and the European Molecular Biology Organization.

> "We hope this work might lead to the design of vaccines for human infections that promote the production of highly potent antibodies.
>
> **PAVEL TOLAR**

Image: B cell 'test labs'.

NEW BUILDING OPENED BY THE QUEEN

Our new building was officially opened by The Queen and The Duke of Edinburgh on 9 November 2016.

Accompanied by The Duke of York, The Queen and Prince Philip toured our state-of-the-art facilities, including the advanced sequencing and peptide chemistry laboratories. She met scientists, representatives of each founding partner, major donors and staff before starting the sequencing of Paul Nurse's genome – all three billion letters in his DNA code.

The Royal party also met artist Robert Ballagh and unveiled his portrait of Francis Crick. The artwork was commissioned by James Watson, who worked with Crick on the structure of DNA. The visit concluded with The Queen unveiling a plaque to mark the opening of the building.

> It was a delight to welcome The Queen to our new building for the Francis Crick Institute and show her some of the science that we are carrying out to understand the human body better in health and disease.
>
> **PAUL NURSE**

HIGHLIGHTS FROM THE YEAR

OUR YEAR

Highlighting scientific excellence and outstanding achievements

In 2016/17 a number of our scientists received prizes, medals, fellowships and other honours in recognition of their world-class contributions to research. There were many other successes and new initiatives across the institute too, and they are celebrated here in our highlights from the year.

AWARDS AND APPOINTMENTS

PETER RATCLIFFE WINS THE 2016 LASKER AWARD

The Crick's Clinical Research Director, Peter Ratcliffe, won the 2016 Lasker Award for basic medical research – one of the most prestigious science prizes in the world.

Peter, William Kaelin and Gregg Semenza shared the award for their discovery of the pathway by which cells sense and adapt to changes in oxygen availability, a process that is essential for survival.

"I'm honoured to have won this award with Bill and Gregg," said Peter. "I hope that our work helps demonstrate the importance of curiosity-driven discovery research: investigating how the human body works, not with a specific aim in mind, but for the sake of understanding. It's this fundamental knowledge which opens the door for improvements in health."

The Lasker Awards, the USA's most prestigious biomedical research awards, recognise the contributions of scientists, clinicians and public citizens who have made major advances in the understanding, diagnosis, treatment, cure or prevention of human disease. Eighty-seven Lasker laureates have received the Nobel Prize, including 41 in the last three decades.

2017 LOUIS-JEANTET PRIZE FOR MEDICINE GOES TO CAETANO REIS E SOUSA

Awarded for fundamental biological research likely to have an impact in medicine and the treatment of disease, the 2017 Louis-Jeantet Prize for Medicine was won by Caetano Reis e Sousa. The award recognised Caetano's contributions to understanding how the immune system senses invading pathogens, and also detects damage to the body.

We now count eight Louis-Jeantet prize-winners among the current staff or alumni of our parent institutes – more than most European countries. In fact only the UK, Germany, Switzerland and France have seen more researchers win the award than the Crick.

"I'm delighted and honoured to be awarded this prize," said Caetano. "It stresses the importance of curiosity-driven research in developing innovative approaches to the treatment and prevention of disease. I'm very grateful to all the members of my research team over the years for their dedication and hard work, and thank all my colleagues, friends and family for their unwavering support."

KNIGHTHOOD FOR JIM SMITH

Jim Smith, Group Leader and until recently a Research Director at the Crick, was knighted in the Queen's New Year Honours for services to medical research and science education.

Jim was recognised for his research breakthroughs, his role in creating the Crick and his leadership in UK science across a breadth of disciplines. This includes his role in nurturing the next generation of scientists and promoting the careers of women in science.

Over the course of his career, Jim's work has transformed the understanding of embryonic development, giving insights into genetic defects in children and how stem cells develop into different tissues. Jim's current research interest is the molecular basis of mesoderm formation, a crucial part of early human and animal development.

▸ CHARLIE SWANTON AWARDED THE ROYAL SOCIETY NAPIER RESEARCH PROFESSORSHIP

Charlie Swanton was awarded the Royal Society Napier Research Professorship to further his study of the evolution of cancer cells within tumours. The Royal Society describes its research professorships as prestigious posts which usually run for up to 10 years and provide long-term support for internationally recognised scientists of exceptional accomplishments. Charlie is one of only six scientists receiving a professorship this year.

Charlie's research group investigates how cells in tumours change and adapt over time and in reaction to treatment. The group has found significant genetic diversity among cancer cells in a tumour, with cells having different mutations at different locations – and this has consequences for how best to characterise and treat a patient's cancer.

Charlie is chief investigator of the Cancer Research UK TRACERx clinical study which, through the UCL Cancer Trials Centre and UCL Cancer Institute, is tracking the evolution of lung cancer in patients undergoing treatment.

This last year also saw Charlie receive the Biochemical Society's GlaxoSmithKline Award which recognises research leading to new advances in medical science. It is specifically intended to recognise mid-career biochemists who completed their PhD less than 20 years ago.

Commenting on the award, Charlie said: "This prize is a testament to the amazing people who have worked so hard both in and with my laboratory over the last eight years. I am incredibly lucky to work with such a motivated team in this exciting field of cancer medicine."

▸ PETER JOHNSON APPOINTED AS DIRECTOR, CRICK CANCER RESEARCH NETWORK

Peter Johnson was appointed to a new part-time post as Director, Crick Cancer Research Network in January. A professor of medical oncology at the University of Southampton, Peter has held a part-time appointment as Chief Clinician for Cancer Research UK since 2008.

Peter will be supporting collaboration between the Crick and other Cancer Research UK-funded centres in both basic and translational research, and also fostering the development of the increasing numbers of clinical academic trainees with an interest in cancer research at the Crick.

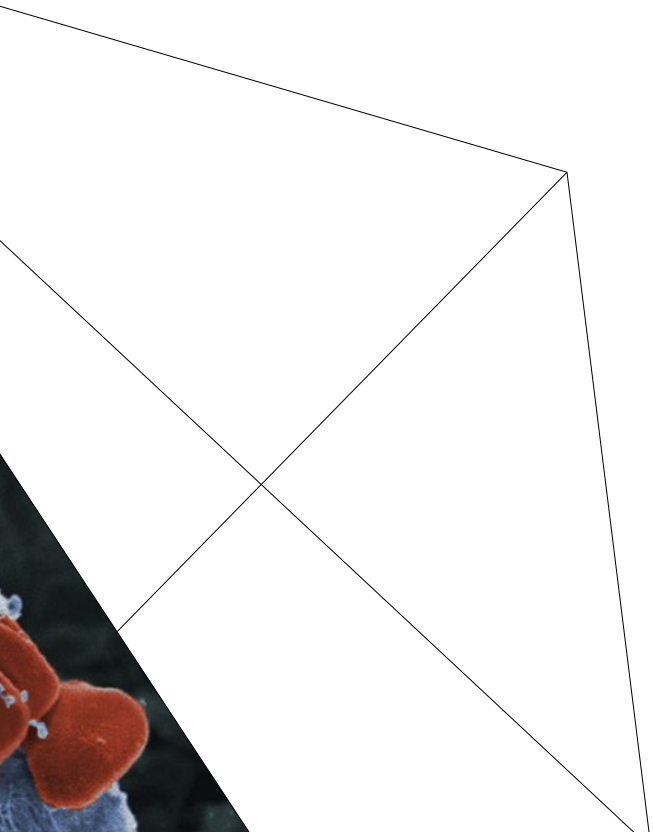
As leader of the Southampton Cancer Research UK Centre, Peter is responsible for bringing together a broad multidisciplinary group of basic, translational and clinical researchers, and for linking laboratory research to the extensive clinical practice in cancer treatment in the Southampton Cancer Centre. His research is focused on how the immune system deals with cancer and how an individual's own defence system can be re-targeted to allow it to attack cancerous cells.

▸ PAUL NURSE BECOMES CHANCELLOR OF THE UNIVERSITY OF BRISTOL

As Chancellor, Paul Nurse will be the ceremonial head of the University of Bristol and play an important ambassadorial role, both nationally and internationally. He succeeded The Right Honourable the Baroness Hale of Richmond, who had been Chancellor since 2004. Previous Chancellors include Sir Winston Churchill, Viscount Haldane and Nobel Prize-winning biochemist Dorothy Hodgkin.

FELLOWSHIPS AND MEMBERSHIPS

- Adrian Hayday became a Fellow of the Royal Society, in recognition of his work on epithelial immune cells.
- The National Academy of Sciences of the USA elected Steve West as a Foreign Associate for his contributions to the fields of DNA recombination and repair.
- Jean Langhorne was awarded the Lifetime Achievement Award at the 2016 Biology and Pathology of the Malaria Parasite conference.
- Tomas Lindahl, Nobel Prize winner and Emeritus Scientist at the Crick, and Karen Vousden, Cancer Research UK's chief scientist and Crick Group Leader, were named as Fellows of the American Association for Cancer Research (AACR) Academy.
- Paul Nurse became a member of the High Level Group of the European Commission's Scientific Advice Mechanism. He was also elected an Honorary Fellow of the British Academy, the UK's national body for the humanities and social sciences, and made an Honorary Distinguished Professor of Hiroshima University, Japan.



MAKING THE RIGHT CONNECTIONS

New funding is helping create closer links between the Crick and small and medium sized enterprises (SMEs). In February 2017, the MRC's Proximity to Discovery: Industry Engagement Fund awarded us £150,000 to pilot a new scheme known as Connect to Crick. This scheme is encouraging collaboration between our researchers and SMEs, and supporting the transfer of knowledge and skills by exchanging postdoctoral researchers.

The spirit of collaboration and partnership at the Crick delivered many success stories during the year, including two new collaborations. One will explore if inhibition of a particular biological mechanism could help in Alzheimer's disease, and the other aims to improve the quality of life as well as the survival of patients with breast cancer.

In Alzheimer's disease, clumps of misfolded proteins accumulate in the brain and are thought to contribute to the loss of nerve cells and memory loss. The early stages of the disease are characterised by the loss of synapses, specialised structures that allow nerve cells to communicate. One class of signalling proteins called Wnts has been shown to stimulate synapse formation, which could help counteract the loss seen in Alzheimer's. Jean-Paul Vincent, a Group Leader at the Crick, and Yvonne Jones, of the University of Oxford, have shown that Wnt signalling can be boosted by inhibiting a protein called Notum. They are now collaborating with UCL scientists to develop inhibitors of Notum, which could lead to a new therapeutic approach for Alzheimer's.

Breast cancer is the second most common cause of cancer death in women in the UK, largely due to cancer spreading to other parts of the body (metastatic disease). Currently no therapies are available to prevent or stabilise cancer metastasis. A partnership between Crick Group Leader Ilaria Malanchi and researchers at Imperial College London is investigating the observation that inhibiting the signalling molecule leukotriene prevents metastases. Under the leadership of principal investigator Charles Coombes at Imperial, the team is developing a clinical study to measure the effect of zileuton (which suppresses leukotriene formation) on the time to development of new metastases in patients with metastatic breast cancer.

NURTURING TALENT, CREATING OPPORTUNITY

Bringing together the brightest talents and the finest resources, postdoctoral training is part of the lifeblood of the Crick.

We currently have more than 300 Postdoctoral Training Fellows (PTFs) at the Crick. Around 20% are from the UK, half from elsewhere in Europe and the rest from further afield including Asia, Australasia, and North and South America. These postdocs, coming for a four-year training programme with the possibility of a two-year extension, broaden our capabilities across a wide range of subjects.

In the past year alone, postdocs have joined us to carry out research in: stem cells in health and disease; DNA replication, damage and repair; tuberculosis; signalling and cancer; cell diversity in the brain; immunology and cancer; cancer development; immunology and infectious diseases; biological clocks and sleep; retroviruses; cytoskeleton and signalling; and cell cycle regulation.

Our postdoctoral programme, developed in consultation with the PTFs themselves, aims to help postdocs make the most of their time at the Crick and prepare for the next stage of their careers. All postdocs attend an induction and introduction to the Crick's Science Technology Platforms and participate in at least one research Interest Group. They are encouraged to be proactive about their training and development, selecting from a broad range of scientific and transferable skills training and career development opportunities, to ensure that their training suits their ongoing scientific needs and future career aspirations.

Early in 2017, we established a new Postdoctoral Committee made up of postdoc representatives. The role of the committee is to facilitate communication between postdocs and the rest of the Crick, represent their needs and interests, provide ideas and feedback for training and career development activities, and help establish a PTF community.

▶ FEATURE: PROFILE

Greater collaboration, better science

The Crick Cancer Clinical Research Fellow (CCCRF) programme provides an opportunity for exceptional clinicians to gain broad and deep interdisciplinary research experience while performing innovative biomedical discovery research into cancer, all leading to a PhD. Maise Al Bakir was invited to join the programme in 2016.

"I knew I was applying for a very competitive programme at the UK's leading research institute, so when I got the news that I'd been selected I felt excited and extremely fortunate to have been given such an incredible opportunity.

"What makes the Crick so different is the multidisciplinary, collaborative approach. We have such a wide range of people and disciplines under one roof, with basic scientists, clinicians and translational scientists working together. Although I'm involved in cancer research, it's inspiring to interact with people from different areas, and to understand how knowledge gained in one field can be applied to another. Collaboration is very important in science – our group collaborates with lots of people, both within the Crick and beyond.

"Whilst my background is as a clinician, my work here is in bioinformatics, which involves the critical analysis of large-scale cancer genomic data. Doing research at this level has allowed me to better understand the biology of this disease and the future challenges we face. This experience will certainly make me a better oncologist.

"I'm privileged to be here for three years and hope that, ultimately, my research will in some way help us identify ways of improving patient care. After the CCCRF programme my aim is to become a clinician scientist."

▸ **FEATURE: INSIGHTS**

David Attenborough launches new lecture series

The Insight Lecture series aims to inform and inspire discussion beyond our immediate research. In January 2017, we welcomed Sir David Attenborough as the series' first speaker. His talk entitled 'Beauty and the Beasts' was delivered to a packed auditorium and also live streamed so that staff could watch at their desks.

LOOKING GOOD

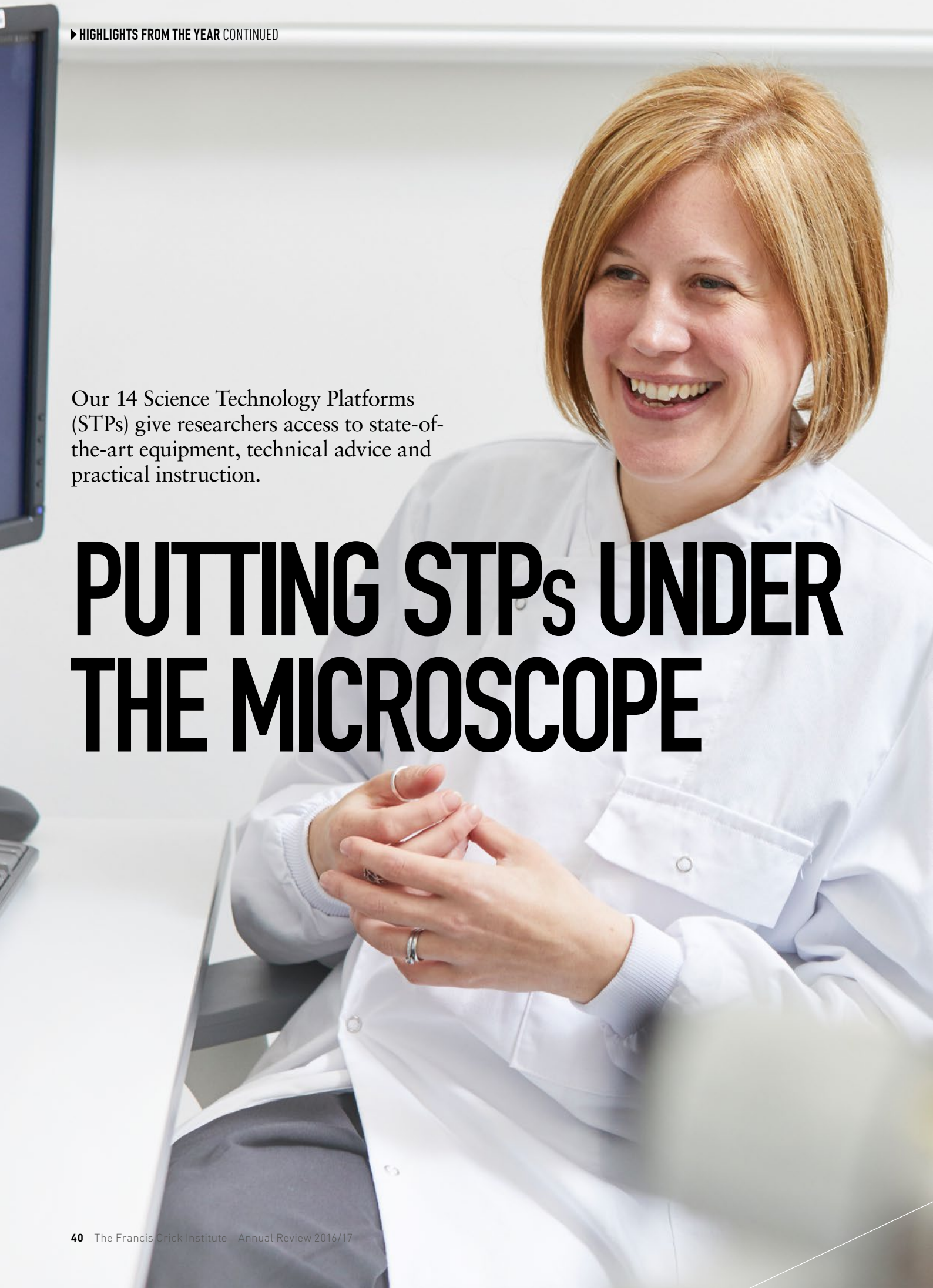
In November 2016, the Crick launched its public exhibitions programme in the Manby Gallery. 'How do we look?' explored the what, why and how of scientific imaging through the eyes and thoughts of Crick researchers. As a science exhibition it was almost unique, taking place inside the same building as the science on display was being undertaken.

The gallery is open to the public four days a week. In addition to free exhibitions exploring the Crick's research, live events and opportunities to meet Crick scientists take place throughout the year.

INSPIRING THE NEXT GENERATION

In early 2017, we opened a dedicated laboratory within the Crick building where children from schools in Camden can learn about science. The Weston Discovery Lab is named after the Garfield Weston Foundation, which supported the construction of the Crick.

"It's marvellous. Today has been really fantastic," said Kim Abraham, a teacher at Netley Primary School, as she watched her Year 5 pupils do a range of science activities with staff from the Crick's education team – from creating giant bubble eruptions to building electronic circuits that launch spinning discs high into the air. "There's not been a single moment when they haven't been fully engaged. They are loving it. It's something they can't get experience of at school."



Our 14 Science Technology Platforms (STPs) give researchers access to state-of-the-art equipment, technical advice and practical instruction.

PUTTING STPs UNDER THE MICROSCOPE

Run by separate skilled teams, STPs are core facilities which offer access to high-end, complex equipment and centralised resources for all research groups at the Crick. Scientists in the STPs and research groups work together to design, carry out and analyse experiments, often at the forefront of what is possible using the latest technology.

Lucy Collinson, Head of the Electron Microscopy STP, explains how her team supports the work of the Crick.

WHAT DOES THE ELECTRON MICROSCOPY STP ADD TO THE RESEARCH PROCESS?

In essence, we provide the equipment and expertise necessary to image the structure of molecules, cells and tissues at high resolution. Every imaging experiment is different, and so our team collaborates with the research scientists to design workflows unique to each research project.

I'd describe our facilities as world-leading. All our instruments are cutting edge, and some of our team members are designing and building new types of microscope that would be the first of their kind in the world.

WHAT ARE THE ADVANTAGES OF HAVING ALL THESE FACILITIES UNDER ONE ROOF?

Clearly, it wouldn't be practical to embed such specialist expertise and costly resources in each lab, so it makes both financial and operational sense to offer it as a centralised technology.

Our team comprises nine people – seven electron microscopists and two physicists. Although we are now technologists, we're also practical, experienced scientists with PhDs in different fields, and we're able to bring a different but complementary focus to projects across the Crick.

HOW DO YOU WORK WITH RESEARCHERS?

Researchers come to us when they need a specialist technique to answer a biological question. We get together and when they've explained their science and their question, we'll advise on the appropriate technique – and then we'll all work together to design the necessary experiments.

Right now we're working on around 80 projects with Crick researchers. This puts us in the privileged position of being able to take an overview of Crick science and identify emerging patterns. When we see three or four projects all looking at a similar issue, we can put those teams in touch with each other so they can share experiences, which can aid discovery.

WHAT ARE THE LATEST DEVELOPMENTS IN YOUR FIELD?

In recent years, the STP environment has delivered a huge range of innovations, from automated 3D electron microscopy of cells and tissues to integration of light and electron microscopes for correlative microscopy.

We cover a tremendous range of different projects. For example, we're currently working with several Crick groups on malaria, investigating how parasites invade red blood cells and how various mutations would stop that from happening. We're also working with research groups on the structure of protein and DNA molecules, how cancer cells spread, how immune cells function and how tuberculosis bacteria infect human cells.

MAKING IT

HAPPEN

Science Technology Platforms (STPs) have changed the way we work. Ravi Desai, Head of the Making Lab STP, provides the inside story.

WHAT'S THE KEY STRENGTH OF THE MAKING LAB STP?

One of the real advantages of the Crick is that housing so many disparate groups in one building promotes collaboration. The Making Lab STP is a hub that integrates people, ideas, projects, equipment and expertise to advance and accelerate scientific discovery by making customised devices that aren't available anywhere else. In addition, we can help researchers make their own devices using readily available technology such as a Raspberry Pi.

WHAT AREAS DO YOU SPECIALISE IN?

We offer three different types of fabrication. One of our main areas of expertise is microfabrication, particularly microfluidics. In other words, we make and customise plumbing devices on a miniature scale. We also make tiny micropatterns that can be used to position cells or tissues exactly where researchers want them in order to mimic how they're organised in humans or animals.

Our capabilities at a larger scale include computer numerical controlled (CNC) milling and 3D printing for making larger bespoke objects – for example, we could 3D print a scaled-up model in order to explain cells to school children.

We also use electronic fabrication techniques and tools to make sensors, actuators and control systems. A simple example would be LEDs that change colour when a specific temperature is reached.

HOW DOES YOUR STP INTERACT WITH RESEARCHERS?

In two different ways. Firstly, anybody can simply call in and see us – coffee and sandwiches always available! If they need to carry out a particular experiment, we'll do our best to build a device that will make it happen. Secondly, we work through longer-term, project-based collaborations.

Either way, the next step in our workflow is to design the device that we're going to be building, using computers and software. Fabrication takes place in fairly typical research-type labs – we have two at present, with a third under construction.

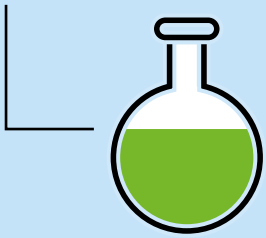
WHAT ARE YOU WORKING ON NOW?

Archaea are tiny microorganisms found in environments such as hot springs, where pH can be as low as 2.5 and temperatures up to 80°C. We're trying to come up with a microfluidic device to hold these cells in a fixed position and keep them alive for long enough for a high-resolution microscope to capture a good image. This is simply not possible in a traditional culture dish. By studying archaea, the researchers aim to gain insight into how basic cell division machinery operates, and how to potentially prevent it operating in cancers.

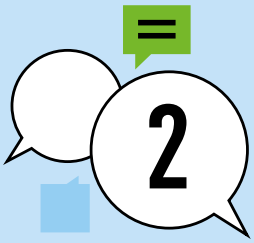
OUR YEAR IN NUMBERS

Income

£160.6m



New spinout companies formed



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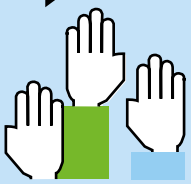
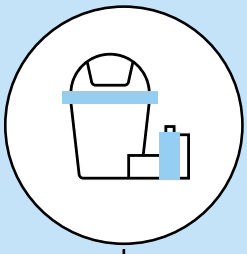
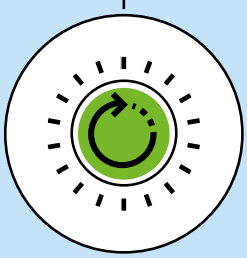


Primary school children reached with science activities

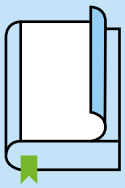


28%

Waste to energy

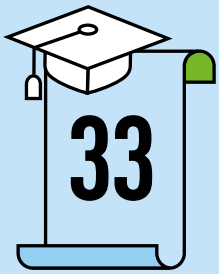


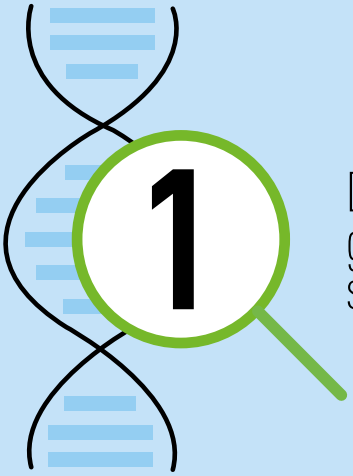
450+



Peer-reviewed papers published

PhDs submitted





Director's genome sequenced

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Design and production
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SCALING THE HEIGHTS

Jim Smith, Crick Group Leader (second from left), was among a group of fundraisers who abseiled 28m down the Crick building in March 2017 to raise £40,000 for Cancer Research UK.

The Francis Crick Institute
1 Midland Road
London NW1 1AT

Telephone: +44 (0)20 3796 0000
Email: info@crick.ac.uk

www.crick.ac.uk