THE FRANCIS CRICK INSTITUTE

FRANCIS CRICK INSTITUTE

DISCOVERY WITHOUT BOUNDARIES

ANNUAL REVIEW 2015/2016

INSIDE THIS REPORT

BRINGING IT ALL TOGETHER
OUR FIRST YEAR

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

INTRODUCTION
WITH PAUL NURSE

By bringing together scientists from many disciplines, the Crick will help to improve people's lives and keep the UK at the forefront of biomedical research.

Welcome to the first annual review of the Francis Crick Institute, a discovery institute dedicated to understanding the fundamental biology underpinning human health. Our work is furthering knowledge about why disease develops and how we can prevent, diagnose and treat illnesses.

We were founded by six of the UK's most successful scientific and academic organisations: the Medical Research Council (MRC), Cancer Research UK (CRUK), the Wellcome Trust, UCL (University College London), Imperial College London and King's College London. Collaboration with and beyond our founding partners is central to what we do, and part of our strategy, which we call 'discovery without boundaries'.

This review covers our first year of operations, 1 April 2015 to 31 March 2016. There is much to report: during the year we have been doing three things in parallel, each of which has been a considerable task in its own right.

The first is pursuing our core mission: the highest quality discovery science. This review offers a small selection from the more than 400 papers we have published during the year, but it gives a flavour of the range, depth and importance of our scientists' work – from understanding Down syndrome, to generating insights about cancer immunotherapy, to unravelling the fundamentals of life, such as how DNA replicates. The awarding of a Nobel Prize, a Louis-Jeantet Prize and a Brain Prize to Crick researchers during the year shows the quality of the scientific foundations we have inherited from our legacy institutes. Our ambition is to build on those foundations and make the Crick even more than the sum of its parts.

The second task has been establishing and embedding a new institute from the merger of our parent institutes, the MRC's National Institute of Medical Research (NIMR) and Cancer Research UK's London Research Institute (LRI). On 1 April 2015, this merger brought together nearly 1,200 staff. The practicalities of establishing a new, single institute have been numerous – from brand new online systems for finance, procurement, and HR to new logistical arrangements such as a unified delivery service. We have further been challenged to run the Crick across four separate sites. As these pages will show, this has not held back our progress either in research or in engagement with the wider world.

The third task has been completing the construction and commissioning of the Crick Laboratory – one of the most complex buildings in London and the biggest single biomedical laboratory in Europe. Our new home will not only be a scientific hub of the highest specification; it will be an iconic landmark at the heart of the greatest city in the world. The building speaks to our intention to reach beyond the science community, housing not only a Discovery Lab in which we will host schoolchildren, but a Living Centre for local residents, which is the first new community space to be built in Somers Town, one of the most deprived neighbourhoods in London, for more than 15 years.

In undertaking all three tasks in parallel, our staff, our founding partners and our supporters have shown drive, flexibility and determination. The achievements and discoveries outlined in this review speak to their success. The Crick's vision depends on effective collaboration, and as this year's teamwork has demonstrated, we can look forward to the future with great confidence.

The Francis Crick Institute was founded by six of the UK's most successful scientific and academic organisations, and draws on the distinctive strengths of each. Our founding partners reflect on our first year.

'Celebrating one year of operations of the Francis Crick Institute is testament to the outstanding commitment of all who have contributed towards delivering this remarkable new medical research institute. The partners' shared aspiration, a vision also held by the UK government, is that the Crick develops a new and even more effective approach to the clinical and commercial translation of discovery research, helping turn laboratory discoveries into treatments as quickly as possible to improve people's lives. I am confident this will be achieved through the combined specialist knowledge, expertise and resources of its scientists, working across many disciplines, and of all partners involved.'

Professor Sir John Savill, Chief Executive Officer, Medical Research Council (MRC)

'The Francis Crick Institute will revolutionise medical research. Through collaboration and sharing insights across many different disease areas, the Crick will make a unique global contribution to our understanding of their causes and drivers. This cross-pollination of knowledge, delivered through state-of-the-art facilities and the best scientific minds, will accelerate and deepen our understanding of how cancer starts, spreads and develops.'

Sir Harpal Kumar, Chief Executive, Cancer Research UK

'The Crick is one of the most important scientific developments in UK biomedical science for a generation, and one that Wellcome is proud to support in partnership with government, charities and universities.

Science is a global endeavour, and the spirit of international collaboration is central to the Crick's vision of attracting the most talented researchers from around the world.

I look forward to watching the progress of the institute as it moves into its second year and continues to make its mark as one the world's most progressive and innovative new research centres.'

Dr Jeremy Farrar, Director, the Wellcome Trust

UCL

‘The Francis Crick Institute is a once-in-a-generation opportunity for the life and biomedical sciences. Our commitment builds on UCL’s role as one of Europe’s largest and most successful centres for biomedical research and we are confident it will expand and enhance our already pioneering research. Having the Crick on our doorstep gives us the opportunity to form a world-class biomedical cluster for innovation and excellence in the heart of London. Being a founding partner of the Crick strengthens the translation of our remarkable research into new therapies that benefit human health.

The unique partnership working catalysed by the Crick allows us to make the whole more than the sum of its individually excellent parts, allowing us to tackle and overcome some of the biggest global healthcare challenges.’

Professor Michael Arthur, President and Provost, UCL (University College London)

Imperial College London

‘I congratulate the Crick team for the progress they have made, reflected in the milestone of this inaugural annual review.

Imperial College London’s mission to deliver enduring excellence in research and education for the benefit of society is advanced through collaboration with excellent partners like the Francis Crick Institute. Embedded in the Crick network, Imperial’s leading scientists, engineers and medics will further understanding, treatment and prevention of healthcare challenges like cancer, heart disease, infections and neurodegenerative conditions. The Crick will enhance the College’s impact in fundamental science and provide the impetus for new multidisciplinary and collaborative encounters with leading academic and industry partners.

We are proud to be a founding member and, working with our partner institutions, look forward to building on our collective strengths to shape the future of biomedical research.’

Professor Alice Gast, President, Imperial College London

KING’S College LONDON

‘As a founding academic partner King’s is delighted to play a key role in this world-leading institute, bringing experts from a wide range of disciplines to work collaboratively under one roof. King’s has an excellent track record in bringing scientists and clinicians together to translate research into innovative treatments as quickly as possible. Our expertise will strengthen further the institute’s ability to bring basic and applied science together with clinical knowledge, to benefit patients across the UK as well as society as a whole.’

Professor Edward Byrne AC, President and Principal, King’s College London

PROGRESS
AGAINST OUR STRATEGY

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:

- PURSUE DISCOVERY WITHOUT BOUNDARIES
- CREATE FUTURE SCIENCE LEADERS
- COLLABORATE CREATIVELY TO ADVANCE UK SCIENCE AND INNOVATION
- ACCELERATE TRANSLATION FOR HEALTH AND WEALTH
- ENGAGE AND INSPIRE THE PUBLIC

During our first year we have made progress across all these missions.

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.

Over 400 peer-reviewed papers have been published during the first year of operation. A small selection of the discoveries made, giving a flavour of the scope, range and possible long-term implications of our work, can be found on pages 24–35.

The excellence of the scientific foundation provided by the Crick's parent institutes was underlined not only by this ongoing research activity, but by the awarding of a number of honours and major international science prizes to Crick researchers in 2015/16, including a Nobel Prize (see page 11).

We aim to build substantially on this underpinning excellence. We have made a number of key appointments during the year (see page 12), and have been preparing to implement our ongoing senior scientific recruitment programme next year (see right).

CREATE FUTURE SCIENCE LEADERS

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

Our innovative '6+6' model will bring talented Group Leaders in for an initial period of six years, usually followed by another six years, after which they will be equipped to take up senior positions in other UK institutions, building the UK science base. During 2015/16 we have been developing and planning the Crick Group Leader recruitment programme, which will commence in late 2016, and will look worldwide for researchers of the highest quality in the early stages of establishing their independent careers.

At postdoctoral level we have an equally strong emphasis on career development, giving our Postdoctoral Training Fellows (PTFs) more structure both in terms of training and length of stay than most institutions. Crick PTFs will complete a four-year training programme with the possibility of a further two-year extension to undertake additional career development.

We welcomed 57 PhD students in September 2015, and recruitment for September 2016 revealed the profile and popularity of the Crick, with 1,300 applications for 44 places (see page 16). We are putting in place a programme to train our students in skills within and beyond research. They enjoyed a two-day 'introduction to public engagement' course in the autumn to get them thinking early about how science can be shared with the widest possible audience, and translation training that showed them how to turn discoveries into human impacts, supporting health and wealth.

Three cancer clinical fellows, funded by a Cancer Research UK Accelerator Award, will begin their PhD training in autumn 2016 (see page 15). The Crick will also be part of King's College London's and Imperial College London's applications for Wellcome Trust clinical PhD programmes, working with the universities in training the fellowship cohort and developing a joint annual symposium.

Ensuring that the science leaders of the future come from all parts of society is also important, and we established an equality, diversity and inclusion steering group during the year. The women in science committee is particularly active, and the year also saw the formation of an LGBT+ group.

400+

OVER 400 PEER-REVIEWED PAPERS HAVE BEEN PUBLISHED DURING THE FIRST YEAR OF OPERATION.

3,500

THE CRICK HAS DELIVERED INTERACTIVE SCIENCE SESSIONS TO OVER 3,500 CHILDREN.

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.

Collaboration across disciplinary boundaries and beyond the Crick itself is key to our vision. The intention is to develop novel scientific interactions with our three university founders and our other collaborators across the UK; to work with colleagues in the physical, as well as the biomedical, sciences; and to break down barriers between basic and clinical research.

To progress this we have established a Crick-university attachments programme (see page 13), helped to lead the eMedLab collaboration (see page 16), and developed industry partnerships (see right). There have also been numerous 'bottom-up' interactions involving joint grant applications and joint meetings and symposia.

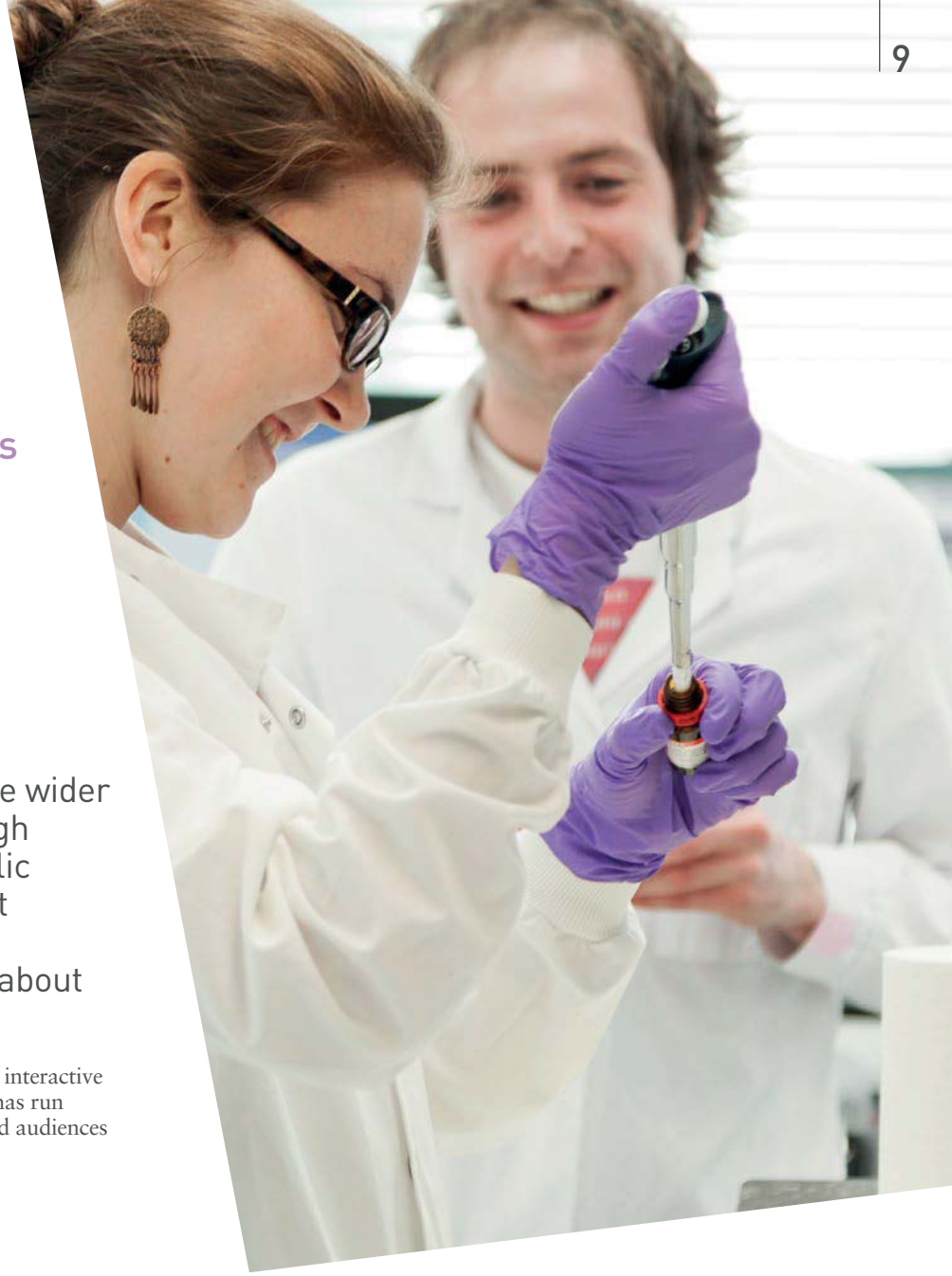
ACCELERATE TRANSLATION FOR HEALTH AND WEALTH

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

A translation team was established in 2015/16, with a number of key appointments, including a Head of Translation (see page 12). A translation advisory group has been established and will provide external peer review of the Crick's translation projects.

In July 2015, the Crick announced an open science collaboration with GSK, the UK's largest healthcare company (see page 15). We are establishing similar relationships with other pharmaceutical companies.

We welcomed 57 PhD students in September 2015, and recruitment for September 2016 revealed the profile and popularity of the Crick, with 1,300 applications for 44 places.



During the 2015/16 academic year over half of Camden's 65 schools, including the borough's special schools, have participated in the Crick's education programme.

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.

In its first year alone, the Crick has delivered interactive science sessions to over 3,500 children, and has run numerous events showcasing science to broad audiences of all ages. See more on page 18.

HIGHLIGHTS
FROM THE YEAR

CELEBRATING SCIENTIFIC EXCELLENCE

At the heart of the Crick's philosophy is a commitment to the highest quality science. In 2015/16, a number of our scientists received prizes, medals, fellowships and other honours in recognition of their world-class contributions to research.

1,500+

WHEN IT IS FULLY OPERATIONAL, THE INSTITUTE WILL HOUSE SOME 1,500 STAFF, MAKING IT ONE OF EUROPE'S LARGEST CENTRES OF BIOMEDICAL RESEARCH.

NOBEL PRIZE IN CHEMISTRY 2015

The Nobel Prize in Chemistry 2015 was jointly awarded to Crick emeritus scientist Dr Tomas Lindahl, with Paul Modrich and Aziz Sancar, for 'mechanistic studies of DNA repair'. The scientists received their Nobel for having mapped, at a molecular level, how cells repair damaged DNA and safeguard the genetic information. Their work has provided fundamental knowledge of how a living cell functions and is informing the development of new cancer treatments.

Tomas Lindahl was director of the Clare Hall Laboratories (part of the LRI) from 1986 to 2005. His Mutagenesis Laboratory at Clare Hall characterised different DNA repair pathways in a long-term project to provide better understanding of the cellular defence mechanisms against damage to the human genome. Tomas ran his lab at Clare Hall until 2009 and he remains a Crick emeritus scientist.

The Crick now counts three Nobel Laureates among its current scientists: Tomas, Paul Nurse and Tim Hunt.

LOUIS-JEANTET PRIZE FOR MEDICINE 2016

John Diffley, Associate Research Director at the Crick, was awarded the 2016 Louis-Jeantet Prize for Medicine, which recognises those conducting fundamental biological research that is expected to be of considerable significance for medicine. John received the prize for his contributions to understanding how DNA replication, a process essential to life, initiates. The Louis-Jeantet Foundation grants the sum of CHF 700,000 for the prizewinner, of which CHF 625,000 is for the continuation of their research. John will use the prize money to conduct further research into the mechanisms involved in the replication of chromosomes in yeast and human cells (see more about his research on page 34). The Crick now counts seven Louis-Jeantet prizewinners among its staff.

THE BRAIN PRIZE 2016

The Brain Prize, awarded by the Grete Lundbeck European Brain Research Foundation, recognises an outstanding contribution to neuroscience. Professor Tim Bliss from the Crick's Mill Hill laboratory and Professors Graham Collingridge (University of Bristol) and Richard Morris (University of Edinburgh) jointly won the prize in 2016 for their work on the mechanisms of memory. Their discoveries revolutionised our understanding of how memories are formed, retained and lost.

FRIESEN PRIZE 2015

The Crick's Director, Sir Paul Nurse, was awarded the 2015 Henry G. Friesen International Prize in Health Research by the Friends of Canadian Institutes of Health Research. The Friesen Prize, awarded annually, recognises exceptional innovation by a visionary health leader of international stature. Dr Aubie Angel, President of the Friends of Canadian Institutes of Health Research, said: 'Sir Paul Nurse has the uncanny ability to explain the most complex issues in science, research and health in ways that everyone can understand.'

The Crick now counts three Nobel Laureates and seven Louis-Jeantet prizewinners among its researchers.

Dr Peter Van Loo was presented with Cancer Research UK's Future Leader Award, for researchers who have demonstrated world-leading potential within 10 years of completing their PhD.

Dr Markus Ralser received the Biochemical Society's Colworth Medal, which is awarded to an outstanding research biochemist under the age of 35.

Dr Thomas Surrey was awarded the Hooke Medal of the British Society for Cell Biology, which recognises an emerging leader in cell biology.

FELLOWSHIPS AND MEMBERSHIPS

In our 2015/16 year, more Crick scientists were elected to distinguished scientific bodies.

Frank Uhlmann became a Fellow of the Royal Society. Royal Society Fellowship is made up of the most eminent scientists, engineers and technologists from the UK and the Commonwealth. Charles Swanton and Michael Way were elected as Fellows of the Academy of Medical Science. Fellowship of the Academy is based on exceptional contributions to the medical sciences, either in the form of original discovery or of sustained contributions to scholarship. Paul Nurse was elected to the Royal Spanish Academy of Sciences and the Chinese Academy of Sciences.

FURTHER HONOURS

Since the period covered by this review (which ends 31 March 2016), Crick researchers have won further plaudits: Adrian Hayday has been made a Fellow of the Royal Society; Steve West has been elected as a Foreign Associate at the National Academy of Sciences of the USA; Jernej Ule has been elected as a member of EMBO; Paul Nurse has been elected to the Royal Irish Academy; Sir Keith Peters has been awarded an honorary degree from Cambridge University; and Richard Treisman, Research Director, has been knighted.

RECRUITING FOR SUCCESS

The Crick has an ambitious vision for the future of biomedical research in the UK. To help fulfil this, a number of key appointments were made in 2015/16.

Professor Sir Peter J Ratcliffe was appointed to the new role of Clinical Research Director, starting in May 2016. Developing a culture of experimental medicine is a critical element of the Crick's strategy, Discovery Without Boundaries, enabling us to explore the opportunities for human physiological processes to inform basic biological models and vice versa. Sir Peter will continue to spend half his time at the University of Oxford, where he was previously Head of the Nuffield Department of Clinical Medicine.

Professor Akhilesh Reddy has been appointed as the Sir Keith Peters Chair of Experimental Medicine, which is a joint appointment between the Crick and UCL. Professor Reddy works as a Consultant Neurologist at the National Hospital of Neurology and Neurosurgery in London, and has established a laboratory at the Crick to work on fundamental aspects of circadian rhythms and sleep biology.

Malcolm Irving, Professor of Biophysics at King's College London, was appointed to a part-time position to develop liaison between the Crick and its university partners. The new role started in April 2016.

Three new independent trustee directors of the Francis Crick Institute were appointed: **Lord Willetts,** the former Science Minister and MP for Havant; **Professor David Lomas,** Vice Provost (Health) at UCL, Head of UCL School of Life and Medical Sciences and Head of UCL Medical School; and **Professor Doreen Cantrell,** Head of the College of Life Sciences and Vice Principal of the University of Dundee.

Another key appointment set in train during 2015/16, and due to be finalised in the coming year, is **Professor Karen Vousden,** who will take up a dual appointment as a Crick Senior Group Leader and the Chief Scientist at Cancer Research UK.

Accelerating translation for health and wealth is one of the Crick's strategic priorities, and a dedicated translation team was established in 2015/16. **Dr Veronique Birault** (above) joined the Crick on 1 September 2015 to lead the team as Head of Translation.

Stéphane Maikovsky joined the Crick on 1 February 2016 as Chief Financial Officer.

Ruth Collier joined the Crick as Director of Communications on 1 February 2016.

JOINING FORCES: WORKING WITH OUR UNIVERSITY PARTNERS

One of the great strengths of the Crick is that it brings together researchers from the institute and its partner universities to develop innovative research ideas and to undertake new collaborative projects. Over 200 researchers from the partner universities will ultimately be working at the Crick.

In 2015, a pilot of the Crick-university attachments programme was launched. We identified 19 university groups who will bring to the Crick complementary expertise in biomedical, physical, chemical, engineering, computational and clinical sciences. They will join the Crick through three different mechanisms: secondments, satellites and sabbaticals.

Secondments allow a scientist who is early in his or her career to move to the Crick, with his or her research group, for an agreed period (usually between three and six years). There is a particular emphasis on early career researchers who will benefit from the excellent training environment at the Crick.

Satellites consist of smaller numbers of university researchers (usually one to three) who will be embedded in a Crick research group for an agreed period (typically between three months and three years) to undertake a specific collaborative project. Satellites will usually include postdocs, PhD students and/or technical staff working at the Crick, while the lead scientist remains at his or her home institution. Satellites are an important mechanism for developing research in new multi-disciplinary areas.

Sabbaticals will enable a researcher to spend up to a year working in a Crick research group, perhaps learning new techniques or undertaking a hands-on collaboration.

There is a particular emphasis on early career scientists who will benefit from the excellent training environment at the Crick.

The groups selected in the pilot round include six secondments, 10 satellite groups and three sabbaticals – approximately 60 researchers in total. They will move into the Crick during 2016. A second round of recruitment for 2016/17 commenced this year.

University staff working at the Crick will remain full employees of their university, and will return to the university when they finish their work at the Crick.

CONSTANT COLLABORATION

The Crick-university attachments programme is just one of the ways in which we work with our university partners day-to-day. Our PhD students receive their degree from a partner university (see page 16), while many of our researchers have strategic joint appointments with a partner university. There are numerous ‘bottom-up’ interactions too, from joint grant applications to joint meetings and symposia.

Our university partners are critical to our multidisciplinary approach, providing bridges to the physical sciences and to clinical science, both through their research portfolios and through their extensive formal hospital links.

BREAKING NEW GROUND: APPROVAL AND RECOGNITION FOR GENOME EDITING APPLICATION

In February 2016, Dr Kathy Niakan's team became the first to receive permission from the Human Fertilisation and Embryology Authority (HFEA) to use the genome editing technique 'CRISPR-Cas9' in human embryos. The technique will allow her team to better understand the earliest stages of human development.

Genetic modification of human embryos in research has been permitted by UK legislation since 2009. The significance of the HFEA licence for this work is that it is the first time genome editing using CRISPR-Cas9, a specific and efficient genome editing technique, has been approved; and the first endorsement in the world of such research by a national regulatory authority.

The embryos used in the research project will be those left over from patients' fertility treatment and donated by patients. They will be surplus to the patients' treatment or family-building needs, and so would otherwise be disposed of. The embryos will never be used to establish a pregnancy. The research focuses on the first seven days of development after fertilisation.

Investigating early development could ultimately lead to improvements in infertility treatment, and a deeper understanding of the earliest stages of human life. It is important to note that these potential improvements in infertility treatment would not be delivered through genome editing: it is illegal to implant an embryo modified in this way into a human. Rather, a better understanding of this stage might allow, for example, the development of more successful human embryo culture conditions within IVF treatment.

Two months after receiving permission from the HFEA, Dr Niakan was named in the 'TIME 100', an annual list of the most influential people in the world in the past year, alongside the likes of Angela Merkel and Tim Cook.

She was nominated by Jennifer Doudna, co-inventor of the CRISPR-Cas9 genome editing technique, who said: 'Niakan's work will answer previously unanswerable questions about the earliest stages of human reproduction – what makes a healthy embryo, what factors contribute to infertility and what goes wrong when pregnancies don't progress as planned.'

David Roblin

SPEAKING THE SAME LANGUAGE: WORKING WITH INDUSTRY FOR PATIENT BENEFIT

In July 2015, the Crick announced a new open science collaboration with GSK, the UK's largest healthcare company, which will see GSK and Crick scientists working side by side both in the new Crick Laboratory and at GSK's R&D base in Stevenage. In the first partnership to be established between the Crick and a pharmaceutical company, the two organisations will explore new avenues of medical research across a broad range of diseases, with a view to achieving breakthroughs in the understanding of human health and disease.

One of the greatest challenges in developing new medicines is knowing where to start: scientists still have much to learn about the underlying biology of many diseases, which makes developing effective drug discovery programmes very difficult.

The GSK-Crick open science collaboration combines the specialised discovery science knowledge of the Crick's researchers with the pharmaceutical research and development expertise of GSK scientists, opening up possibilities for scientific discovery that would not be possible for either partner working alone.

> GSK is an outstanding first partner to work with and I am excited to see what we deliver together.
>
> *David Roblin*

David Roblin, Chief Operating Officer and Director of Scientific Translation at the Crick, said: 'The UK has historically not been good enough at translating discovery science into health or wealth benefits. At the Crick, we hope to change that, and this agreement truly represents a landmark in open science. We will have industrial scientists completely embedded within collaborating laboratories and fully integrated within the Crick as a whole. Together we will accelerate breakthroughs in the understanding of human health and disease.'

In the spirit of open innovation, research findings from the collaboration will be shared with the broader scientific community, via joint publication in peer-reviewed journals. This will enable important discoveries to be applied across the research community.

The first seven collaborative research projects are underway and, once the Crick is fully operational at St Pancras, more projects will commence.

ACCELERATING SCIENCE

In October 2015, the Crick was selected for a Cancer Research UK Centres Network Accelerator Award. This £15m scheme by Cancer Research UK is a new initiative that provides infrastructure support to research centres in order to encourage collaboration between different organisations and boost 'bench to bedside' science.

The Crick received £4.2m to support more experimental cancer research and create Clinical Research Fellowships to help unite different research centres in London. This will help turn innovation in the laboratory into tangible benefits for patients with the aim of saving more lives from cancer in the future. Three cancer clinical fellows funded by the award will begin their PhD training in autumn 2016.

HARNESSING THE POWER OF BIG DATA

Many current biomedical research projects involve 'big data' – a term given to data sets that are so complex that traditional data processing methods are inadequate.

To fulfil the potential of big data for human health, it is necessary to accumulate complex medical and biological data on an unprecedented scale, to coordinate it, to store it safely and securely, and to make it readily available to interested researchers.

To meet this challenge, the Crick has been instrumental in the formation of eMedLab, the first shared data centre for medical and academic research in the UK.

eMedLab is an off-site, high-performance computing and data storage facility which allows research teams to maximise the benefits from the huge amounts of data generated from large-scale genetic projects. It allows researchers to carry out powerful data analyses when researching cancers, cardiovascular conditions and rare diseases.

eMedLab should allow the researchers to address fundamental questions by searching across collections of data that cannot be combined in any other way. It represents a new level of collaboration between different research institutes, in line with the Crick's collaborative vision.

Funded by the Medical Research Council, the partnership also involves UCL and UCL Partners, the London School of Hygiene and Tropical Medicine, King's College London, the Sanger Institute, Queen Mary University of London, and the EMBL European Bioinformatics Institute.

It represents a new level of collaboration between different research institutes, in line with the Crick's collaborative vision.

The Crick's first intake of PhD students, 2015.

TOMORROW'S WORLD: TRAINING OUR FUTURE SCIENTISTS

In September 2015, we welcomed a record 57 new students to the Crick to embark on their four-year PhD programme. This was the first single Crick group of students, as in previous years the students applied to separate Crick-NIMR and Crick-LRI programmes.

This intake saw a broad range and balance of new students: 39 are women and 18 men; 29 are British, 20 from other EU countries, and eight from elsewhere, including Japan, Mexico and New Zealand.

The Crick PhD programme is designed to attract the brightest scientific minds from around the world and presents an opportunity for highly motivated and exceptionally talented individuals to embark on their career in biomedical research.

The popularity of this opportunity was confirmed when we received 1,300 applications for 44 places for the coming year's PhD students. Those selected begin in September 2016.

Our PhD students receive their degree from one of our partner universities, and the universities play a key role, contributing to the students' supervision. At UCL, Imperial or King's, students tap into a wealth of expertise in delivering generic as well as discipline-specific training.

The energy and enthusiasm of the student population are important parts of the Crick's research community, and the comprehensive Crick PhD programme ensures that all students have strong career prospects in science.

A RICH LEGACY, REMEMBERED

The Crick is a new institute built on a rich legacy, and in early 2015, we were awarded almost £20,000 to honour this legacy by preserving 150 historically important scientific objects. The Arts Council of England PRISM fund provided the money to help conserve our collection of scientific instruments, most of which were based at one of the Crick's legacy institutes, the National Institute for Medical Research (NIMR) in Mill Hill, North London. A smaller number of objects came from the former London Research Institute.

The objects in the collection include a microscope used by Nobel prize-winning scientist Peter Medawar; an infusion pump (invented at NIMR in the 1960s); an early model of a ribosome, signed by Peter Medawar and Francis Crick; and the protein analysis gel that first revealed cell cycle-dependent destruction of cyclin, leading to Tim Hunt's Nobel Prize.

The award will be used to assess, document and conserve the objects for future display and public engagement activities.

WE'RE ENGAGED! TAKING SCIENCE BEYOND THE LAB

Public engagement is one of the Crick's five strategic priorities, and our size, location and profile allows us to play an important role in generating excitement and interest in science. We also have an opportunity to help promote health and wellbeing in the local area.

Our engagement work covers a wide range of audiences: people living, working or studying within a mile of the Crick; people with an interest, but no specialist knowledge, in science; students and teachers from schools in Camden and neighbouring boroughs; and specialist interest groups, such as patients, funders, politicians and opinion-formers.

Our varied education, public and community engagement activities range from events and talks, through commissioned projects and appearances at festivals, to dialogues and debates which seek to involve the public in the future direction of our work.

Through our education outreach programme, we aim to increase young people's enjoyment of and aspirations in science. This year, we delivered interactive science sessions to more than 3,500 children at schools and colleges in Camden. We launched our Discovery Zone in collaboration with Regent High School, which gives us use of a science lecture theatre, a non-lab breakout area and a general science lab. This facility will be used to deliver the majority of our practical activities aimed at secondary school students.

We have been working with the local community since 2009, to keep our neighbours fully informed about the Crick's progress and how the institute can benefit the local area. This year, our community work included: a series of workshops and craft events in the Somers Town area; partnering with the Bloomsbury Festival, a three-day event in one of London's most vibrant cultural quarters; and supporting 11 projects through our Crick Community Chest, which provides grants of up to £3,000 for community-led initiatives that improve wellbeing locally.

We support our scientists to make public engagement an integral part of their research career. In 2015, we launched 'Crick Chats', a way of encouraging researchers and the public to interact on an informal level. A recent event brought together James Briscoe, a Crick developmental biologist studying how the central nervous system develops, Amy Congdon, a PhD student in textile design from Central Saint Martins, and Lucy Di Silvio, a scientist studying tissue engineering at King's College London. Their wide-ranging discussion explored the crossovers between design and science, the new insights provided by approaches to tissue engineering from art and science perspectives, and the implications of this emerging field.

> I believe it is important for Crick scientists to interact with students. I feel that I also benefit from the events – in the lab you get very focused on one question, but taking part in these activities reignites my passion for science in general.
>
> *Michelle Harreman, research scientist*

CAPITAL CELEBRATION

The Crick won the 2016 London First Investment in London's Future Award, for 'a visionary regeneration or development which reinforces London's competitiveness in the long term'.

As one of the major scientific hubs in the UK as well as an important new landmark in King's Cross, the Crick has an important role to play nationally, in London, and in our immediate locale, where we are contributing to the regeneration of the area – and the award recognised how seriously we take this role. The London First Awards celebrate the people, organisations or companies that have most contributed to making London the best city in the world to work, study, live and play in during 2015.

We are contributing to the regeneration of the area – and the award recognised how seriously we take this role.

Members of Cancer Research UK's Create The Change Development Board

Photo: © Simon Way

HUNDREDS OF DONORS SUPPORT THE CRICK

Cancer Research UK launched the ambitious Create The Change campaign in 2012 to raise £100m towards its contribution to the development of the Francis Crick Institute. The campaign set out to raise the money through philanthropic donations within five years and was the charity's boldest campaign yet.

Cancer Research UK brought together a board of high-profile philanthropists led by Charles Manby as chair, and held a number of unique fundraising events including auctions, science evenings and a gala dinner at Windsor Castle. The charity proceeds from the 2015 London Marathon also went to the Create The Change campaign.

The campaign has attracted many gifts from generous supporters and raised vital funds towards our development.

Find out how you can support the Crick's groundbreaking research at **cruk.org/crick.**

COUNTDOWN
TO THE CRICK LABORATORY

The construction of the Francis Crick Institute's building – what we call the 'Crick Lab' – has been a complex, challenging and exciting project, involving the expertise and collaboration of many specialist teams.

At the peak of the building programme, the Crick was the biggest single project of its kind in the UK, with more than 1,200 workers on site.

17,000

LIGHT FITTINGS HAVE BEEN INSTALLED

25,000

SENSORS ARE CONSTANTLY MEASURING HEAT, LIGHT, AIR PRESSURE AND HUMIDITY

65,000M^3

OF CONCRETE HAS BEEN POURED AND MORE THAN 9,000 TONNES OF STEEL HAS BEEN USED

For most of those involved, the design, engineering and construction of the Crick has been a once-in-a-lifetime experience. The building is, in terms of its technical requirements, one of the most complex to have been constructed in London. It will allow our staff to conduct world-class research for decades to come.

The institute was designed by HOK working with PLP Architecture and developed with input from scientists, local residents and community groups. Architecturally, there are strong links between the Crick and the historic buildings in the local area. Both the masonry and the distinctive vaulted roof recall features of the adjacent St Pancras International station.

To reduce its visible mass, one-third of the structure is below ground, with laboratories arranged over four floors above ground. A typical floor consists of four 'laboratory neighbourhoods', or 'quadrants', connected by two atria.

The design deliberately 'nudges' inhabitants towards collaboration by enabling serendipitous meetings between researchers from different groups and disciplines. The atria cross at the centre of the building to create a hub with break areas, informal collaboration space, and a large central stair. Walkways and informal meeting areas crisscross the main atrium and connect neighbourhoods.

Work on constructing the shell of the building started in June 2011 and was completed in autumn 2013. Since then work has focused on fitting out the interior, including all the plant and machinery needed to run the building as well as specialist scientific and computing equipment. When it is fully operational, the institute will house some 1,500 staff, making it Europe's largest biomedical research institute under a single roof.

Given the central location of the building and the residential areas to the west and north of the institute, we also focused our attention on landscaping the area around the Crick, including commissioning a major piece of public art, Paradigm (see right).

BUILDING FACTS

Our building is almost one million square feet in size (that's about 17 football pitches), has more rooms than Buckingham Palace, and has 25,000 sensors constantly measuring heat, light, air pressure and humidity (that's four times as many as in The Shard).

The amount of soil removed from the site would have filled the Royal Albert Hall – twice!

17,000 light fittings have been installed, 65,000m^3 of concrete has been poured and more than 9,000 tonnes of steel – equivalent to the weight of 1,200 double decker buses – has been used in the construction.

FOUR BECOME ONE

On 1 April 2015, we took a major step in the creation of the Crick, when staff from our legacy institutes – Cancer Research UK's London Research Institute (with labs at Lincoln's Inn Fields and Clare Hall) and the Medical Research Council's National Institute for Medical Research at Mill Hill in north London - transferred to the Crick to become employees of the new institute.

This meant that, in addition to overseeing the completion of our new building, we have also welcomed more than 1,200 staff as new employees of the Crick and taken over the operation of three existing research sites. The Crick's existing staff continued their work on a fourth site, at the Wellcome Trust's offices near Euston.

This was a major logistical undertaking, requiring extensive collaboration between staff, old and new, at all levels of the organisation.

PLANNING THE BIG MOVE

This year has also seen a major focus on preparing for the migration of all staff, equipment and resources from four sites into our new building at King's Cross.

Preparing a new scientific institute of the Crick's size is a major undertaking in its own right: our Building Services team has needed to procure all the management services and facilities required in the new institute, including maintenance, cleaning, reception, security and catering.

At the same time, we have been planning the big move, which will take half a year in total. Migration planning has to take into account the timelines of existing experiments as well as moving the large, complex scientific equipment used by research groups, so that ongoing research can continue with as little disruption as possible.

David Roblin, Chief Operating Officer, says: 'Many of our staff, particularly those in Science Operations, have effectively been doing two jobs this year: the day-to-day work and the planning for the move and the many new processes required. Everyone has risen to the challenge in an impressive way. If we can work together like this across four sites, the future is bright in the new building.'

In the space of one year, we have introduced a number of significant new systems to the Crick, from finance, HR and IT systems to our Cross Dock facility, which currently manages deliveries from suppliers to our Lincoln's Inn Fields and Mill Hill labs, and has delivered around 60,000 parcels over the year, with 99% on time.

Safety is of prime consideration in everything we do at the Crick. Our Safety, Health and Sustainability team has been maintaining standards at our current sites while developing systems to ensure we are equally safe and effective when working with hazardous substances at the new Crick Lab.

Our Information Technology and Services team has been working on more than 70 projects this year in order to support the new Crick Lab. One of the biggest individual projects has been the creation of the Data Centre in the new building, which was completed in January 2016. The team has also been installing 'big data' storage solutions along with high-performance equipment that will form a Crick analysis and data management platform for science.

Our Information Technology and Services team has also developed a 'wayfinding' app to help everyone find their way around the new building – believed to be the first wayfinding app for a private building in the UK.

810

PHOTOVOLTAIC MODULES ON THE ROOF CONVERT SUNLIGHT INTO ELECTRICITY, GENERATING ENOUGH ENERGY TO RUN 35 AVERAGE HOUSES

Paradigm by Conrad Shawcross is one of the tallest public sculptures in central London. It stands at an imposing 14 metres, comprising a twisting stack of 17 tetrahedra made of weathered steel, and weighs more than 25 tonnes – but the whole sculpture rises from a base of under one square metre.

Conrad's work weaves together the practicalities of geometry, mathematics and engineering with symbolism found in philosophy and metaphysics. Its material gives a nod to the industrial heritage of the area – which is also the area where Conrad grew up.

Paradigm, which was funded by a grant from the Wellcome Trust, provides a metaphor for potential: to grow; to advance; to discover. Its majestic form embodies boldness and courage, while its apparent precariousness reflects how easily old paradigms of knowledge can be toppled by new discovery. Fortunately, the 20-metre-deep piles sunk into the ground – precisely located so as to avoid underground transport – ensure that its precariousness is metaphorical only!

SCIENCE HIGHLIGHTS

DISCOVERIES FROM OUR FIRST YEAR

Our core mission is the highest-quality discovery science, and Crick researchers have published more than 400 peer-reviewed papers during the year. The following pages highlight just a few of their discoveries, giving a flavour of the range, depth and importance of our scientists' work.

ACTIVATING IMMUNE CELLS FOR **PERSONALISED CANCER MEDICINE**

Cancer treatments that harness the body's own immune system offer great hope in a field where progress can be slow and advances small. Cancer immunotherapies offer the most promise for new treatments since the first chemotherapies were developed in the 1940s.

The potential of the immune system can be unlocked in different ways. Checkpoint inhibitors release the brakes that usually restrain immune cells, allowing them to attack. Antibody treatments are designed to specifically target cancer cells. Cancer vaccines made from peptides derived from an individual's tumour are showing promise, as are approaches that extract, engineer and re-inject a patient's own immune cells.

Neoantigens pave the way for cancer immunotherapy by pointing the immune system to cancer cells. They are a type of flag that appears on the cell surface of a tumour, providing a marker for immune cells.

But as a tumour continues to mutate, different neoantigens develop and are flagged on the cell surfaces in different parts of the tumour. Chemotherapy can cause mutations to happen faster, resulting in even more neoantigens. These ever-changing antigens make it difficult for the body's immune system to track and target the tumour.

Charles Swanton's team at the Crick has been studying neoantigens. In research carried out jointly with Sergio Quezada of the UCL Cancer Institute, his team has discovered that even though neoantigens evolve and change with the tumour, those that represent the earliest mutations of the disease are likely to be present in every tumour cell and may provide an optimal target for the immune system. They made this discovery by analysing data from hundreds of patients who took part in previous studies.

In the next stage of the work, Charles's team studied samples from two patients with lung cancer. They were able to isolate specialised immune cells, called T cells, that could recognise these neoantigens encoded within every tumour cell.

These T cells have the potential to wipe out all cancerous cells within the tumour, but they are switched off by the tumour's defences. New therapies that specifically activate these T cells could target all the tumour cells at once.

Charles says: 'This is exciting. Now we hope to be able to prioritise and target tumour antigens that are present in every cell, that we hope will be the Achilles heel of these highly complex cancers.

'This opens up a way to look at individual patients' tumours and profile all the antigen variations to figure out the best ways for immunotherapy treatments to work, prioritising antigens present in every tumour cell and identifying the body's immune T cells that recognise them. Each patient would have a unique, bespoke treatment. This is really fascinating, and takes personalised medicine to its absolute limit.'

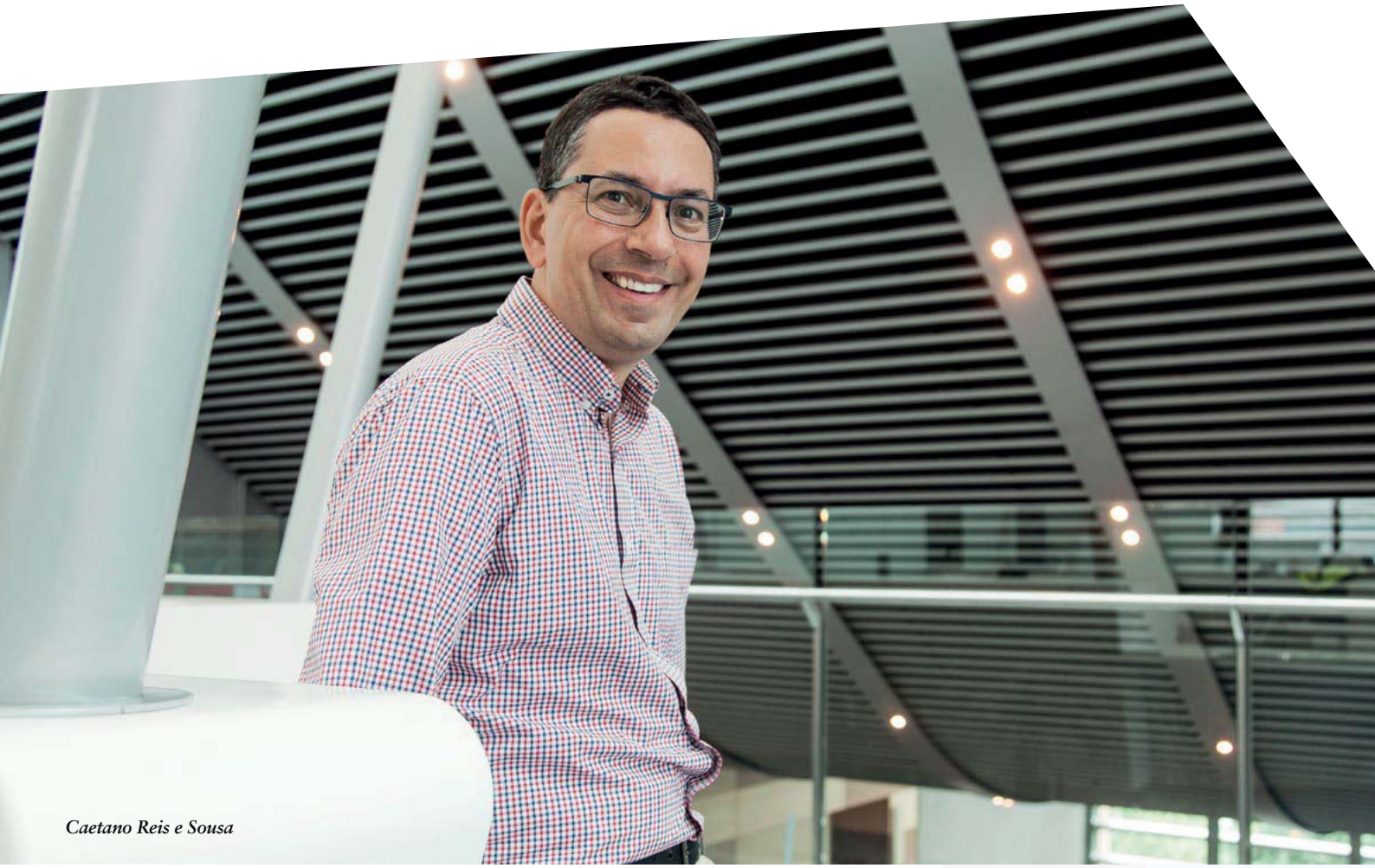
Science 351 (2016): 1463–1469

This research received additional funding from Cancer Research UK and the Rosetrees Trust.

As well as his position at the Crick, Charles Swanton holds a Chair in Personalised Cancer Medicine at the UCL Cancer Institute and is Consultant Medical Oncologist at UCL Hospitals. UCL is one of the Crick's founding partners.

This opens up a way to look at individual patients' tumours and profile all the antigen variations to figure out the best ways for immunotherapy treatments to work.

Charles Swanton



Caetano Reis e Sousa

ASPIRIN COULD HOLD THE KEY **TO SUPER-CHARGED CANCER TREATMENT**

Giving cancer patients aspirin at the same time as immunotherapy could dramatically boost the effectiveness of the treatment, according to research by Crick scientists.

The scientists showed that skin, breast and bowel cancer cells often produce large amounts of prostaglandin E2 (PGE2). This molecule dampens down the immune system's normal response, which helps cancer to hide. It's a trick that allows the tumour to thrive and may explain why some immunotherapy treatments have not been as effective as hoped.

Aspirin is part of a group of molecules called COX inhibitors, which stop the production of PGE2 and help reawaken the immune system. Research in mice showed that combining immunotherapy with aspirin or other COX inhibitors substantially slowed bowel and melanoma skin cancer growth compared to immunotherapy alone.

Caetano Reis e Sousa (above) says: 'We've added to the growing evidence that some cancers produce PGE2 as a way of escaping the immune system. If you can take away the cancer cells' ability to make PGE2, you effectively lift this protective barrier and unleash the full power of the immune system.'

Cell 162 (2015): 1257–1270

This research received additional funding from Cancer Research UK and the European Research Council.

As well as his position at the Crick, Caetano Reis e Sousa is a Professor of Immunology at Imperial College London, one of the Crick's founding partners.

MANIPULATING THE IMMUNE SYSTEM TO **STOP CANCER SPREADING**

Although the immune system is important in fighting cancer, one type of immune cell actually helps cancer to spread, Crick researchers have revealed. Blocking this part of the immune system's first response might help prevent cancer from spreading.

The team, led by Ilaria Malanchi (below), found that chemical messengers known as leukotrienes can help spreading cancer cells grow in a new environment. Leukotrienes are made by immune cells called neutrophils.

When the scientists looked at breast cancer in mice, they found that leukotrienes helped the disease to spread to the lungs. The leukotrienes homed in on the cancer cells with the highest potential to form a secondary tumour and helped them to multiply.

The work showed that blocking the production of leukotrienes with an inhibitor drug usually used to treat asthma reduced cancer spread in mice.

Dr Malanchi says: 'Neutrophils swing into action as soon as the body is injured or infected to kick-start the healing process. But in cancer patients, this can actually help the disease, and sometimes gives secondary tumours a better chance of taking hold.

'Our research uncovers the vital role played by neutrophils' chemical messengers. It suggests a way of targeting these messengers and stopping them from aiding cancer spread.'

Nature 528 (2015): 413–417

Ilaria Malanchi

UNDERSTANDING THE PART INFLAMMATION PLAYS IN **CLOGGED ARTERIES**

Fatty cholesterol-containing plaques can build up inside our arteries in the same way grease might build up on the inside of a kitchen drainpipe. This condition, atherosclerosis, can be symptom-free for decades, but can cause a heart attack or stroke if an artery becomes completely blocked. It is the biggest cause of death in developed countries.

Inflammation is the major driver of atherosclerosis. However, the events that cause inflammation in atherosclerosis and other chronic inflammatory conditions were not well understood. Inflammation in the absence of infection was an enigmatic process. Cholesterol crystals are produced when fats increase in our blood and this was known to be relevant, but the early events driving inflammation in atherosclerosis remained poorly defined.

Now, a Crick team led by Veni Papayannopoulos (below) has used a variety of techniques involving human cells and mice to reveal how cholesterol crystals can set off a chain of reactions involving web-like structures called neutrophil extracellular traps, or 'NETs'. These NETs activate other immune molecules to produce small proteins called proinflammatory cytokines that drive inflammation.

The scientists engineered mice that were unable to release NETs in response to cholesterol, and studied mice that were receiving treatments that degrade NETs. As predicted, these mice had lower levels of proinflammatory cytokines and smaller plaques in the main artery in their hearts.

Annika Warnatsch of the Crick says: 'Our work sheds light on how cholesterol crystals and the immune system work together in the absence of infection to promote inflammation and drive atherosclerosis and other chronic inflammatory diseases.'

Veni adds: 'At least 2.6 million people in the UK have narrowing of the arteries that can lead to atherosclerosis. Understanding the mechanisms behind this condition is vital if we are to learn more about how to prevent and treat it.'

Science 349 (2015): 316–320

At least 2.6 million people in the UK have narrowing of the arteries that can lead to atherosclerosis

Veni Papayannopoulos

AGE AND IMMUNE CELL PROFILE **PREDICT VACCINATION RESPONSE**

Just as everyone is good at different things and looks different, the way we respond to vaccines also differs.

Crick-led researchers investigating the role our immune system plays in responding to vaccination have revealed more about these differences, coming up with a number of surprise findings which may have important implications for vaccination and for cancer immunotherapy.

The team, led by Adrian Hayday, studied the reactions of 178 healthy people to a vaccine for the H1N1 influenza virus, which caused the major outbreak of 'swine flu' in 2009. They measured tens of thousands of immune parameters in the volunteers before and after vaccination.

'There were three unexpected results,' says Adrian.

'First, the strong and rapid immune responses that essentially everyone developed within 24 hours were very substantial and included the mobilisation of lymphocytes that the textbooks tell us are only likely to react around one week after vaccination. This is a clear example of what we learn from studying humans directly.

'Second, the nature of this early immune response was different in younger volunteers, up to around 35 years of age, than in those in their 40s and older. Although it has been known for many years that immune responses in the elderly are rather poor, this shift in response among relatively young adults was again not predicted by the textbooks and is a sharp reminder that age is a key factor in how people respond to vaccines and immunotherapies.

'Third, and most unexpectedly, individuals with increased levels of a particular type of immune cell – transitional B cells – were more likely to experience pain or fever or joint ache following vaccination. Transitional B cells have previously been linked to autoimmune diseases that affect joints or connective tissues, such as rheumatoid arthritis or lupus, but our volunteers were healthy. Nonetheless, these cells were present before vaccination in the blood of many of the individuals who went on to suffer adverse responses.'

About 30 of the participants in total reported side effects, but all recovered rapidly and there was no evidence that the vaccination caused any lasting harm. In fact, it rapidly induced strong antibody responses against swine flu in 80% of those immunised.

'While outcomes will vary from vaccine to vaccine and from vaccine to other forms of immunotherapy, these insights may help identify those people most likely to feel unwell following vaccination and other forms of immune intervention, such as cancer immunotherapy,' says Adrian. 'By providing rational explanations for this, we can counter the arguments made by some that vaccines are harmful, and thereby increase public compliance.'

Adrian worked with colleagues at King's College London, the Health Protection Agency, Porton Down, and Momenta Pharmaceuticals in Cambridge, Massachusetts, USA.

***Nature Immunology* 17 (2015): 204–213**

The research was supported by Cancer Research UK, the Wellcome Trust and the National Institute for Health Research Biomedical Research Centre at Guy's and St Thomas' Hospitals and King's College London.

As well as his position at the Crick, Adrian Hayday is Kay Glendinning Professor of Immunobiology at King's College London, one of the Crick's founding partners.

> These insights may help identify those people most likely to feel unwell following vaccination and other forms of immune intervention, such as cancer immunotherapy.
>
> *Adrian Hayday*

ZEBRAFISH EMBRYOS SHOW HOW CELLS COMMUNICATE

'How cells communicate with each other has fascinated scientists for decades because it is at the heart of how an entire organism can grow from a single fertilised cell,' says the Crick's Caroline Hill. Now, watching transparent zebrafish embryos develop in real time has shed new light on how cells communicate.

A key signalling protein called Nodal is responsible for generating the right number of cells that will become muscle, liver and other internal organs at the right time in an embryo. Caroline's team has discovered that this process is controlled by the timing of production of Nodal and its inhibitor protein Lefty.

The team visualised cells in zebrafish embryos where the Nodal signal was active. This showed them that Nodal signals to adjacent cells, causing more Nodal to be made and in turn to spread further.

It had always been assumed that Lefty was present wherever Nodal was – but the researchers discovered that in fact the production of Lefty is delayed relative to Nodal. This creates a window of opportunity for the uninhibited Nodal signal to spread to neighbouring cells.

But as production of Lefty increases, its levels become high enough to stop Nodal. This difference in timing is therefore what determines how many cells in a developing embryo become, for example, muscle or liver.

These findings not only shed light on early embryonic development, but are relevant for understanding how cells communicate in normal adult tissues and in disease.

Developmental Cell 35 (2015): 175–185

The research received additional funding from the European Commission Network of Excellence EpiGeneSys.

Caroline Hill

These findings not only shed light on early embryonic development, but are relevant for understanding how cells communicate in normal adult tissues and in disease.

FAT DROPLETS PROTECT BRAIN STEM CELLS FROM FREE RADICALS

Free radicals are molecules that contain oxygen with one or more unpaired electrons, which makes them highly reactive with other molecules. A free radical has been likened to a single person at a party looking for a partner – where taking someone else's partner can set off a chain reaction.

Our bodies normally cope with free radicals by using antioxidant substances to neutralise them. Oxidative stress occurs when a cell has more free radicals than it's able to neutralise. When these free radicals reach dangerously high levels they can damage or even kill cells and cause disease.

The polyunsaturated fats omega-3 and omega-6 are essential in the human diet. Omega-3 is primarily found in fish, while omega-6 is found in many vegetable and seed oils. But during conditions of oxidative stress, omega-3 and omega-6 are particularly vulnerable to attack by free radicals. This generates harmful chain reactions that can damage cells.

Alex Gould's team has discovered how neural stem cells – the cells that build the brain and nervous system – protect themselves from this dark side of polyunsaturated fats in our diet.

The scientists studied Drosophila fruit flies raised on a diet high in omega-6 polyunsaturated fatty acids. They then exposed the animals to chemicals that mimic the oxidative stress that occurs in human diseases.

They discovered that fat droplets accumulated in the brains of the flies and that these protected their neural stem cells from damage. When the scientists used genetic techniques to block the formation of these fat droplets, they saw a big increase in the damage caused by oxidised polyunsaturates.

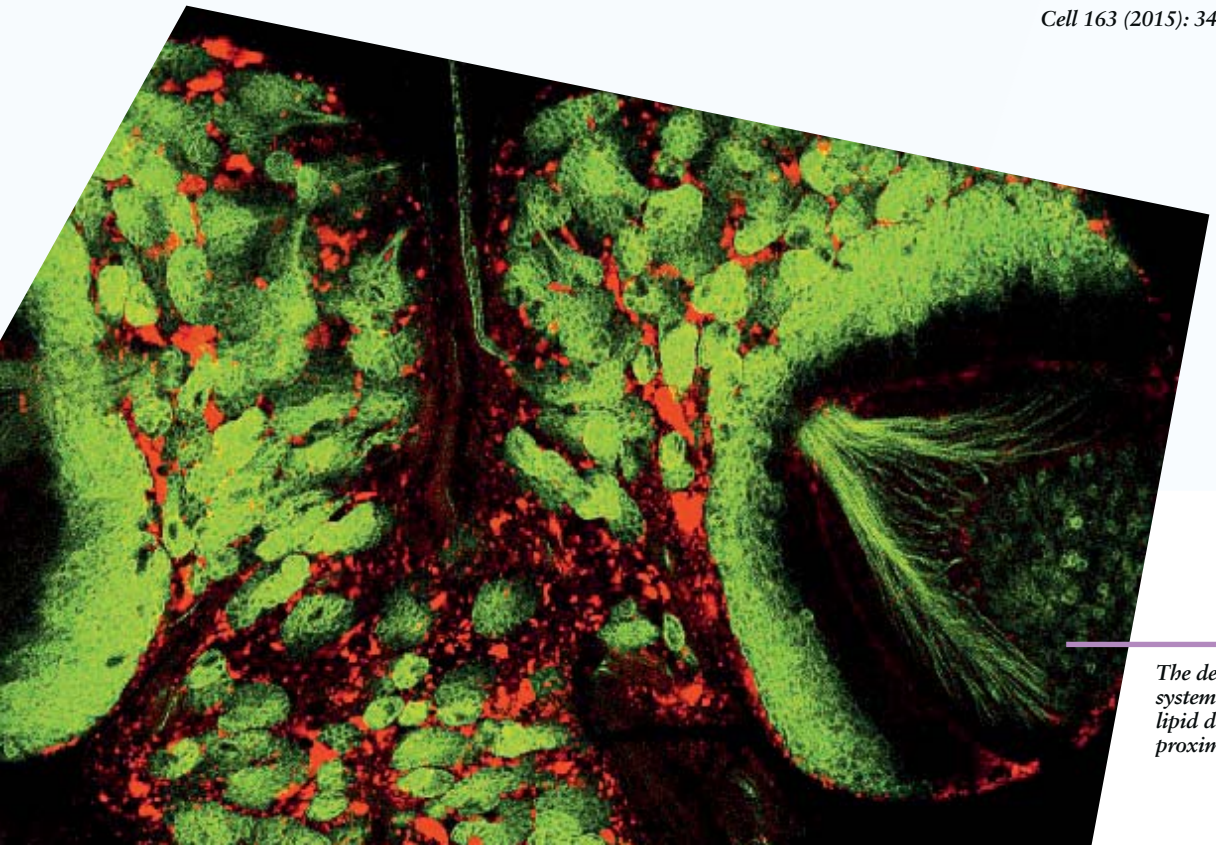
Further investigation revealed that these fat droplets perform their antioxidant role by hiding vulnerable polyunsaturates inside their protective core – similar to everyone at the party moving to another room that the single person is unable to enter. This helps to decrease the harmful chain reactions that would otherwise occur inside neural stem cells and damage them.

This discovery identifies an entirely new antioxidant process in cells and it may offer a future target for treating human diseases.

Alex says: 'It's well known that lipid droplets also form inside human cells experiencing oxidative stress in stroke, heart disease, neurodegeneration and cancer. Following on from the findings of this research, we now need to investigate whether lipid droplets also play a protective role in these disease contexts.

'Mostly, of course, that protective role is a good thing. But we do not want tumours to be able to protect themselves from damage. If we find that the lipid droplets inside tumours do turn out to have an antioxidant role, then it may be possible to use drugs that block the droplets as a new class of anti-cancer therapy.'

Cell 163 (2015): 340–353



The developing central nervous system of Drosophila, showing that lipid droplets in glia (red) are in close proximity to neural stem cells (green).

NEW INSIGHTS INTO HOW WE REPAIR DAMAGED DNA

Our DNA is under constant attack from things like UV light, free radicals produced as a by-product of metabolism, or errors made during DNA replication. Our cells experience DNA damage every minute of every day.

Damaged DNA is normally repaired by a special set of machinery in the cell. A protein called RAD51 is a key factor in a type of DNA repair called homologous recombination. This is a process where the damaged chromosome is repaired using its intact sister chromosome as a template – in the same way a broken part in a car engine might be replaced using the corresponding part from another car.

Women with faulty BRCA1 and BRCA2 genes, which directly regulate RAD51, are at higher risk of developing breast and ovarian cancer. Scientists already knew how RAD51 works to fix DNA damage, and why faults in this process can lead to disease.

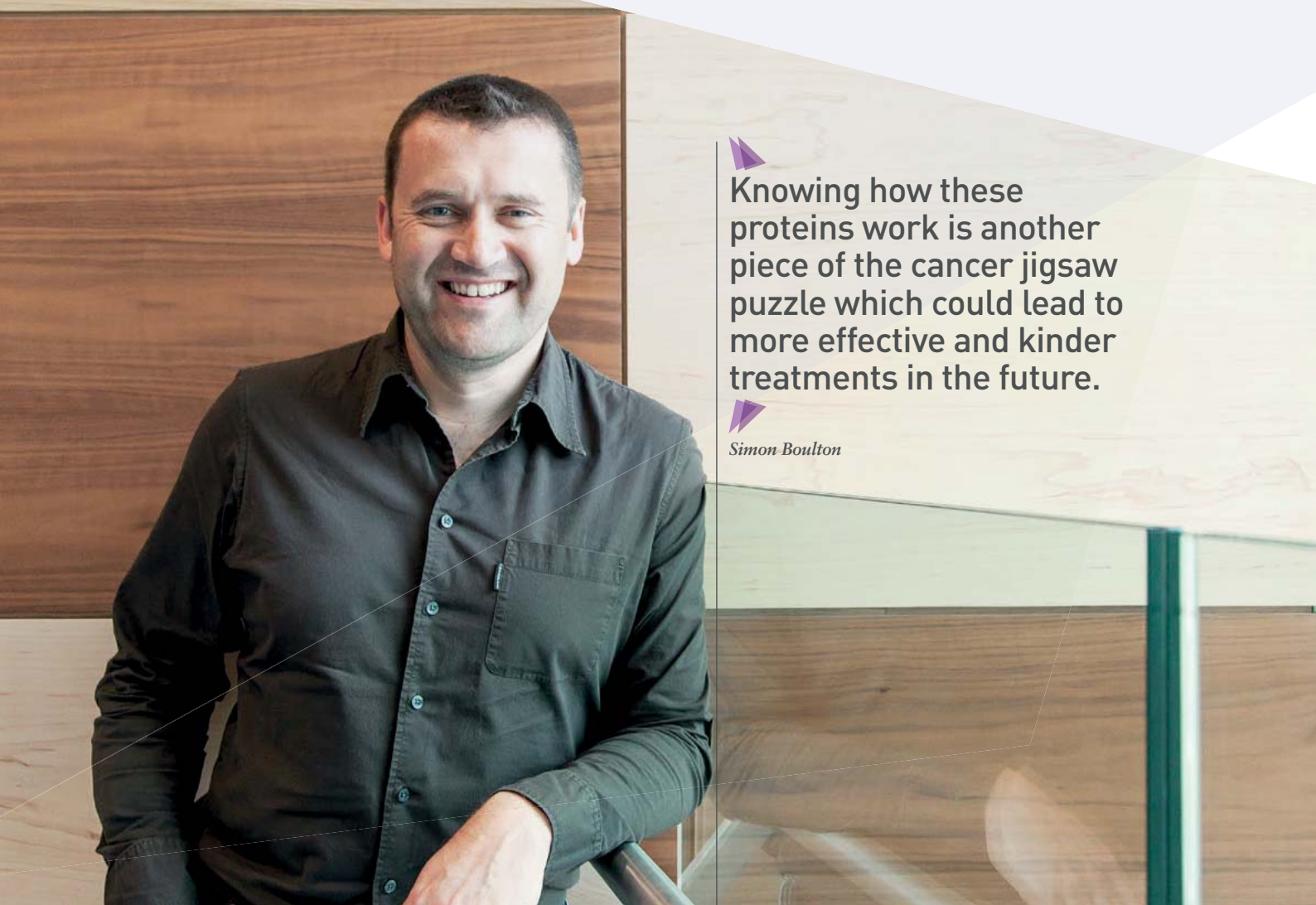
But defects in protein cousins of RAD51 – known as paralogs – also increase the risk of these cancers, and how these factors work in homologous recombination was unclear. Crick-led scientists have now solved this decades-old mystery. They used cutting-edge biophysical techniques, which showed that the RAD51 paralogs activate RAD51 when it is bound to single-stranded DNA, causing it to change shape. Once RAD51 has changed shape, it is primed and ready to start homologous recombination. By switching on RAD51, the paralogs dramatically boost the protein's DNA-repair activity.

Simon Boulton (below) says: 'The function of the RAD51 paralogs has been an enigma for about 30 years. But now we know they are right at the heart of repairing cell damage and helping to prevent breast and ovarian cancers developing. In fact they play as vital a role as the more well-known BRCA genes in preventing disease.

'Knowing how these proteins work is another piece of the cancer jigsaw puzzle, which could lead to more effective and kinder treatments in the future.'

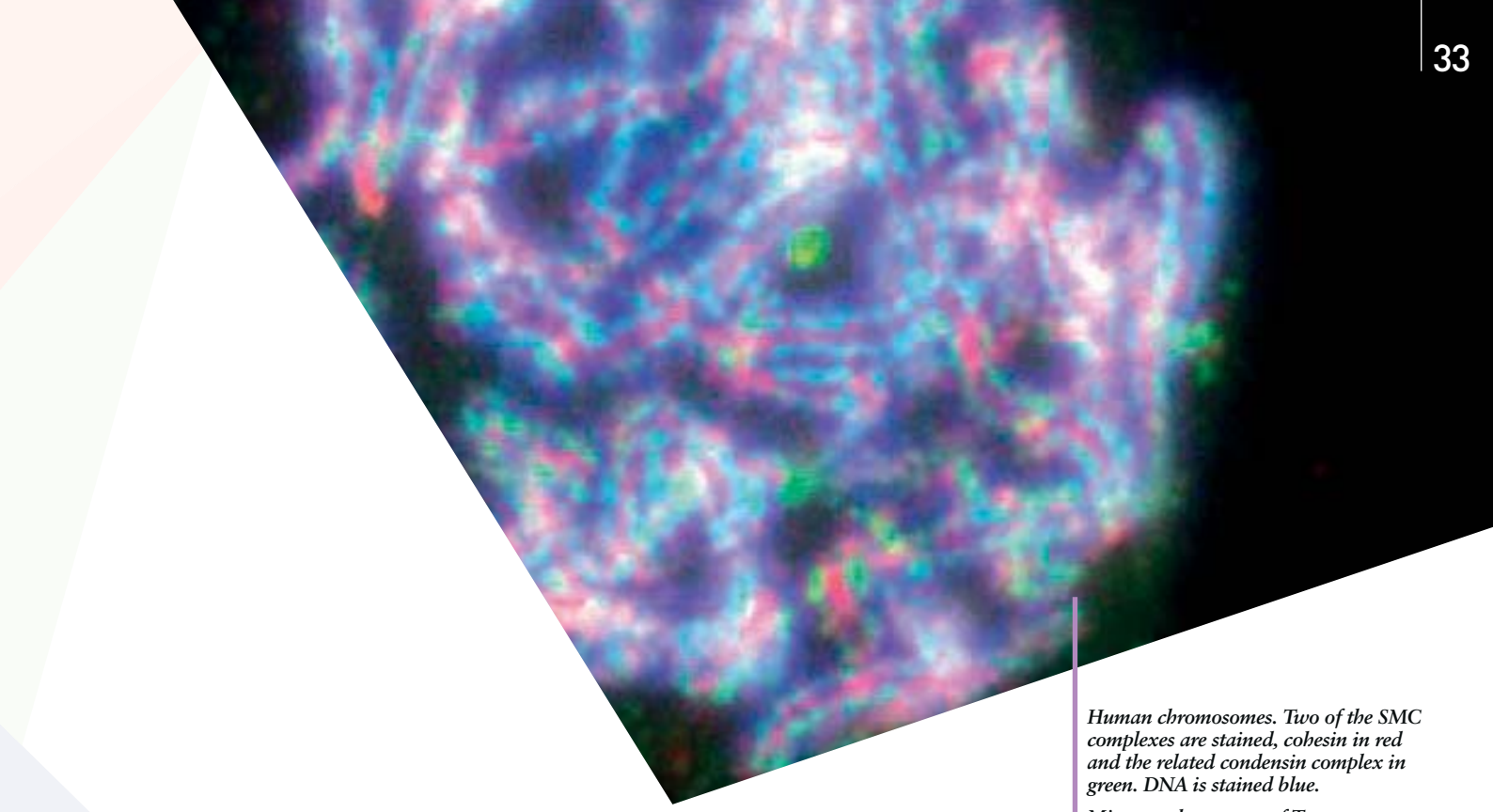
The Crick team worked with colleagues from Masaryk University in Brno, Czech Republic, Imperial College London and the University of Virginia School of Medicine in the USA.

***Cell* 162 (2015): 271–286**



Knowing how these proteins work is another piece of the cancer jigsaw puzzle which could lead to more effective and kinder treatments in the future.

Simon Boulton



Human chromosomes. Two of the SMC complexes are stained, cohesin in red and the related condensin complex in green. DNA is stained blue.

Micrograph courtesy of Toru Hirota, Japanese Foundation for Cancer Research.

THE LONDON UNDERGROUND IN A SUITCASE: **HOW DNA IS CRAMMED INTO CELLS**

Our genome consists of four metres of DNA packaged into the tiny nucleus inside each of our cells. This is equivalent to stowing the 401 kilometres of the London Underground network in a suitcase.

Exactly how this astounding feat of packaging happens has eluded scientists for years. But now Crick researchers Yasuto Murayama and Frank Uhlmann have described how DNA enters and exits the protein rings – called SMC complexes – that enable it to be packaged in this way.

SMC stands for Structural Maintenance of Chromosomes. SMC complexes are little ring-shaped protein machines in the nucleus of a cell. They encircle the DNA strand at specific locations and establish connections within and between DNA strands. This is how they organise the genome, enabling vital functions such as chromosome replication and cell division to happen.

The scientists carried out their work in yeast, which is commonly used as a model organism because it is quick and easy to grow and its cell cycle is similar to that of humans. The team began by purifying one of three SMC complexes found in yeast cells – known as the '6-subunit cohesin complex' – together with a related protein called the 'cohesin loader complex'. It was the first time that this has been successfully done.

The researchers then combined these purified proteins with DNA to biochemically reconstitute the loading and unloading of the cohesin rings onto DNA. This allowed them to define the path by which the DNA enters and exits the protein ring.

They found that DNA passes into and out of the cohesin ring through a set of two interlocking gates. The scientists went on to describe the molecular pathway by which these gates open to let DNA in or out.

Frank says: 'Chromosomes arguably are one of the most important biological structures and they have become an iconic symbol of the life sciences. To explain the molecular make-up and functioning of a chromosome is an important conceptual advance in its own right.'

The findings also have huge biomedical implications, as SMC complex mutations are among the most frequent mutations found in cancer and are implicated in a range of severe developmental disorders. Understanding precisely how SMC complexes work is essential to understanding what goes wrong when mutations occur, and how their consequences can be overcome.

Cell 163 (2015): 1628–1640

This research received additional funding from the Japanese Society for the Promotion of Science and the European Research Council.

DNA REPLICATION RECREATED IN TEST TUBE

DNA replication is essential for life. Without it, cell division wouldn't be possible and organisms wouldn't be able to grow, reproduce or function.

To accomplish this, the DNA double helix must first be unwound and then each strand must be copied. In eukaryotes – the most complex group of organisms that includes humans – replication starts at multiple sites throughout the genome. Initiation must be coordinated to ensure precise duplication of chromosomes. Mistakes during this process cause mutations, which can lead a cell down the path to cancer.

For the first time, scientists have reproduced the conditions needed to start eukaryotic DNA replication in a test tube.

A Crick team led by John Diffley purified 16 protein complexes made from 42 peptide chains needed for DNA replication. By adding these in the correct order, they were able to get these protein machines to replicate both strands of a piece of DNA. The process was regulated by the same enzymes that regulate it in real life inside cells.

John says: 'Much work has been done to identify the factors required for DNA replication. But understanding something well enough to be able to recreate it in a test tube is really the gold standard for comprehension. We've been able to reach this goal with the efforts of a team of tremendous scientists and with great support from the Crick.'

Nature 519 (2015): 431–435

HIV FAMILY HIJACKS HOST BY INSERTING OWN DNA **INTO HUMAN CHROMOSOMES**

HIV is the most notorious member of a family of viruses called retroviruses. These cunning pathogens hijack cells by inserting their own genetic material into host chromosomes. Then, in the way someone might hijack a plane and use it for his own purposes, the virus takes over a cell and turns it to its own means – the production of more virus particles, eventually destroying the host.

The difficulty of removing a hijacker who has taken control of a plane is obvious. Similarly, this ability of HIV to hide its genetic material inside human chromosomes is what makes it so difficult to eradicate.

Human DNA is first packaged into basic units called nucleosomes – which are like spools of thread with the DNA wound around them. These nucleosomes are then tightly folded into arrangements that make up chromatin, which in turn forms the structure of human chromosomes.

Now, powerful imaging has revealed exactly how retroviruses manage to open up these tightly wound packages of human DNA to insert their own DNA.

The retrovirus enzyme that enables the virus to irreversibly insert its own DNA into human chromosomes is called integrase. Every retrovirus carries multiple copies of this enzyme. The researchers used very powerful microscopy to visualise exactly how integrase captures nucleosomes so the retrovirus can insert its own DNA. They started from 2D images of individual molecular assemblies and used these to reconstruct a high-resolution 3D view of integrase attacking a tiny fragment of a human chromosome, 10 billionths of a metre in diameter.

The Crick's Alessandro Costa, who conducted the microscopy analysis, says: 'This pioneering achievement was inconceivable only four years ago. It was made possible by using a very sophisticated electron microscope, new-generation cameras and innovative software for data analysis. Biological nanomachines such as integrase can now be imaged in unprecedented detail as they perform their work. Thanks to these new tools we can rethink the way we ask scientific questions.'

Peter Cherepanov of the Crick, who led an international team of researchers in this work, says: 'The more we learn about the rules of engagement between the viral integration machinery and host cells, the easier it will become for us to break the chain of events that lead to persistent infection. This can lead to more effective antiretroviral drugs to treat HIV infection.

'There is also a potential benefit for gene therapy. The unique ability of retroviruses to efficiently integrate their genetic material into host cell chromosomal DNA means they could be used to deliver highly targeted drugs as part of gene therapy. However, uncontrolled integration by retroviruses carries the risk of serious side effects. Understanding how to selectively direct integration will potentially aid the development of safer gene therapy.'

The research team included scientists from the Crick, Imperial College London, the Dana-Farber Cancer Institute in Boston, USA, the Gorlaeus Laboratory in Leiden, Germany, and the Institute of Virology in Dresden, also in Germany.

Nature 523 (2015): 366–369

As well as his position at the Crick, Peter Cherepanov is Professor of Molecular Virology at Imperial College London, one of the Crick's founding partners.

MOUSE MODEL HELPS PINPOINT GENETIC CAUSE OF **DOWN SYNDROME HEART DEFECTS**

Down syndrome is the most common genetic cause of both intellectual disability and heart defects in humans and is triggered by an extra copy of chromosome 21. The condition results in delays in learning and development. As well as the risk of heart defects, it also increases the risk of other health problems such as epilepsy, leukaemia and early-onset Alzheimer's.

A decade ago, Victor Tybulewicz of the Crick (then at the Medical Research Council's National Institute for Medical Research) and Elizabeth Fisher of UCL inserted a whole copy of human chromosome 21 into a mouse to mimic Down syndrome. This was revolutionary research. The resultant mice had learning difficulties, congenital heart defects, and changes in their craniofacial skeleton. Since then Professors Tybulewicz and Fisher have collaborated with many groups in the UK and around the world to use this mouse model to better understand what goes wrong in Down syndrome.

Building on this work, the pair has now led a team of researchers to create a mouse model of the heart defects that occur in Down syndrome. Rather than inserting a whole copy of chromosome 21, this time they inserted extra copies of many of the genes that correspond to the human genes on chromosome 21.

Victor says: 'Each of the different symptoms of Down syndrome is caused by the extra chromosome, and presumably by an extra copy of one or more of the 230 or so genes on the chromosome. However it is not known which genes on chromosome 21 cause which defects.'

The scientists made seven mouse strains, each with extra copies of different sets of mouse genes corresponding to the human genes on human chromosome 21. This enabled them to narrow down the genes that cause heart defects to 39 of the 230 genes on the chromosome. These are known as dosage-sensitive genes, because the defect is due to an extra copy of the gene (on the third copy of chromosome 21) resulting in higher 'dosage' (or production) of that gene's protein.

The work revealed that at least two different genes contribute to Down syndrome heart defects.

The mouse model allowed the team to visualise the detail of how the defects occur during embryonic development. Unexpectedly, this showed that the congenital heart defects are not due to something known as the 'dorsal mesenchymal protrusion' failing to form in the embryo. This is a developmental abnormality that is linked to heart defects and was previously suspected to be the cause of these in Down syndrome.

Victor says: 'This work is a major scientific advance. It provides important insights into the genetic basis of Down syndrome, and our panel of seven genetically engineered mouse strains will help others to identify genes that cause other Down syndrome symptoms.'

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As well as his position at the Crick, Victor Tybulewicz is a professor in the Department of Medicine at Imperial College London, one of the Crick's founding partners.

Victor Tybulewicz

FACTS & FIGURES

OUR FIRST YEAR IN NUMBERS

£130m[1]
OPERATING INCOME

£107m[2]
OPERATING EXPENDITURE

400+
PEER-REVIEWED PAPERS PUBLISHED

3,500+
CHILDREN ENGAGED IN CRICK INTERACTIVE SCIENCE SESSIONS

178
STUDENTS

1,200+
STAFF

1. Operational income only: does not include income for construction and set-up costs

2. Operational expenditure only: does not include construction and set-up costs

KEEPING IT GREEN

We strive for environmental sustainability in the construction of our building and in our other operations.

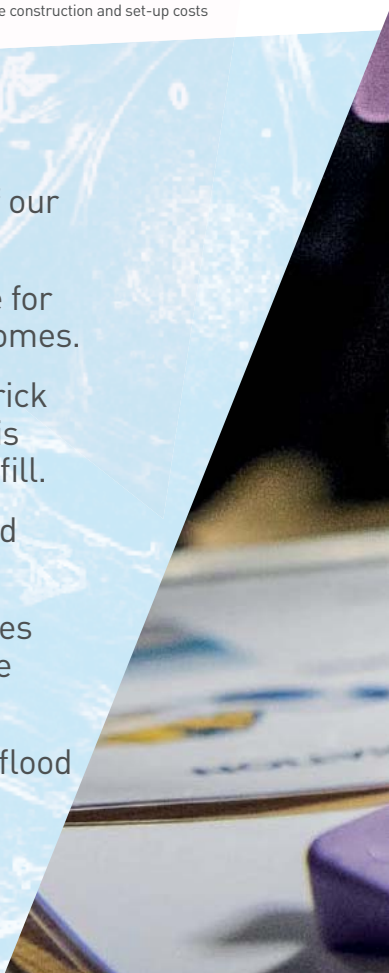
> We have funded an eco-friendly decentralised energy scheme for Somers Town, the local area, which will provide heat to 339 homes.

> Enough waste/soil was removed during construction of the Crick Lab to fill three Olympic swimming pools. However, 99% of this waste has been reused or recycled, and so diverted from landfill.

> The building incorporates brown roofs (where wild flowers and plants can grow) and bat boxes to encourage wildlife.

> There is no car parking for staff other than four disabled spaces – but there are 180 staff bike racks for staff, plus more outside for visitors.

> Extensive use of glass in the design will allow natural light to flood into the building, and all light fittings will be energy-efficient.



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