LIFE CHANGING SCIENCE

The Francis Crick Institute
Annual Review 2017/18

THE FRANCIS CRICK INSTITUTE

AN INSTITUTE FOR DISCOVERY

Our commitment to excellence, our emphasis on multidisciplinary research, our focus on young and emerging talent and our novel ways of partnership working are some of the factors that set the Crick apart.

Front cover
Vaccinia virus infection (green) disrupts a layer of epithelial cells (red/blue). Courtesy of Michael Way, Group Leader at the Crick.

Who we are

The Francis Crick Institute is a biomedical discovery institute dedicated to understanding the fundamental biology underlying health and disease. Our work is helping to build an understanding of 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.

Our vision

Our vision is to be a world-leading multidisciplinary biomedical research institute.

We bring together outstanding scientists from all disciplines and carry out research that will help improve lives and strengthen the economy.

Our strategy

At the heart of the Crick is a commitment to the highest quality science.

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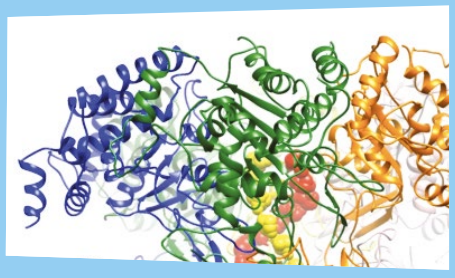
We have five strategic priorities:

— 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.

Our founding partners

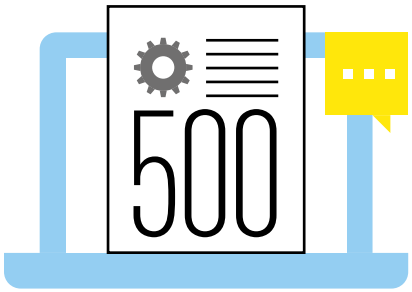
MRC Medical Research Council
wellcome
CANCER RESEARCH UK
UCL
Imperial College London
KING'S College LONDON

What's inside



OUR YEAR AT A GLANCE

The year in numbers



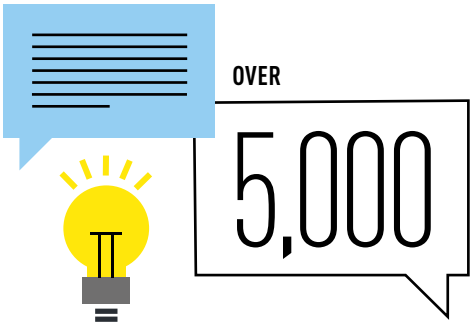
journal papers and preprints published

11

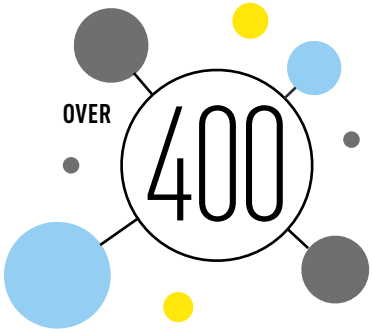
early-career scientists appointed as new group leaders. Three have already arrived

1,544

applications for around 45 PhD places starting in September 2018



delegates at scientific conferences

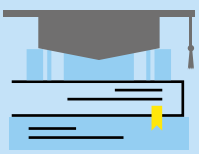


days staff have cumulatively spent in inspiring young scientists through work-experience placements

OVER

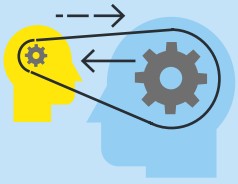
200

students on the Crick PhD programme



40

joint projects with pharma and biotech firms



8,400

people have visited the community centre attached to the Crick

The Crick highlights

Partnerships with industry

Joint projects with GSK and AstraZeneca are enabling scientists from the Crick and industry to work alongside each other, combining expertise and delivering scientific progress.

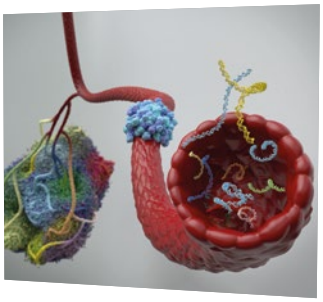
36 For more information

CryoEMs at the Crick

The biochemical processes of life are being revealed in atomic detail using sophisticated new microscopes called cryoEMs, which are revolutionising the field of structural biology.

32 For more information

Predicting lung cancer's return



Scientists have found that unstable chromosomes within lung tumours increase the risk of cancer returning after surgery. They have used this new knowledge to determine the risk of relapse up to a year before the cancer returns.

12 For more information

Deconstructing patterns

The latest exhibition at the Crick, Deconstructing patterns, explores different molecular and cellular patterns studied at the Crick – each one introduced by a unique artist commission.

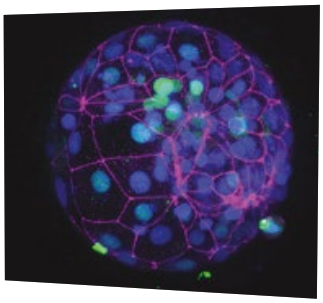
40 For more information

New group leaders

Three outstanding early-career scientists have arrived at the Crick. Selected from almost 400 applicants via a highly competitive process, they are establishing their new teams and new research.

27 For more information

Understanding embryo development



Crick researchers have used genome editing technology to reveal the role of a key gene in human embryos in the first few days of development.

14 For more information

INTRODUCTION BY PAUL NURSE

Our first full year in the Crick has seen us make significant advances, and we can look forward to broadening our research endeavour in the years to come, says Director Paul Nurse.

BUILDING FOR THE FUTURE

Welcome to our annual review for 2017/18, which focuses on our science, our people and our facilities as we work towards our goal of being a truly world-class institute.

Crick scientists have made a number of important findings this year, increasing our understanding of the biological processes underlying human health and disease. Many of the most significant advances can be found in the Research Highlights section on pages 10-25.

We welcomed the first three early-career group leaders to be recruited into our programme for training future science leaders. Silvia Santos, Lucia Prieto-Godino and Pontus Skoglund are early-career scientists who are now establishing research groups at the Crick (see p.27). Four more group leaders have been recruited this year. They will stay with us for up to 12 years, benefiting from the support, facilities and opportunities for collaboration available here. At the end of this period, they will take their established groups elsewhere, to establish a network of connections throughout the world. These are key parts of our national role.

> Central to the Crick's approach is that the best science is done where there are no boundaries between disciplines.

Looking forward

Central to the Crick's approach is that the best science is done where there are no boundaries between disciplines. We have been working with our university partners to appoint researchers to lead new groups in the physical sciences, which brings an interdisciplinary aspect that is crucial for today's biomedical research. Four researchers will arrive at the Crick over the next few months. We are also improving clinical links, providing more research training for clinicians and building closer collaborations with partner institutions on the medical implications of our research.

As this review demonstrates, it has been a year of significant advances, and we can look forward to broadening our research endeavour in the years to come. We are working to optimise our facilities, to support excellent science and to inspire the public with the latest science and its potential. Our aim is to make the Crick one of the most exciting places to be in biological and biomedical research.

Sir Paul Nurse
Director of the Francis Crick Institute

The Francis Crick Institute aims to improve lives through greater understanding of the biology underlying human health. We have made significant progress against our five strategic priorities in the past year, reflecting our commitment to the highest quality science.

PROGRESS AGAINST OUR STRATEGY

Cells in an early zebrafish embryo know to form distinct layers thanks to a network of signals (see p.21).

01

Pursue discovery without boundaries

Our approach to biological and biomedical research is to foster excellence, break down barriers between disciplines and work across institutions.

— Four researchers at the Crick were elected Fellows of the Royal Society, Academy of Medical Sciences and the American Association for the Advancement of Science, reflecting their outstanding contributions to their fields.

42 For more information

— Research highlights from last year include new insights into how tumours evolve and evade treatment, the use of genome editing to understand the role of a key gene in human embryo development and a step forward in our picture of the network of nerve cells that help maintain a healthy gut.

10 For more information

— Our Scientific Advisory Board held its first meeting in November 2017. The Board offers advice on implementing the Crick's scientific strategy and consists of eminent scientists from around the world, many of whom have led research institutes and helped formulate science policy.

— Lucia Prieto-Godino, Silvia Santos and Pontus Skoglund arrived at the Crick to establish new research groups following the 2017 recruitment of early career group leaders in biomedicine. A further eight group leaders have been appointed in 2018 and will arrive in the coming year. A total of 700-800 applications were received for the positions.

27 For more information

— There were 21 university research groups working at the Crick at the end of 2017/18, bringing their expertise and forming new collaborations. This follows another call last year for researchers at UCL, Imperial and King's to apply for these positions, with more to come this year.

30 For more information

Postdoc to Principal Investigator
The Crick Postdoc to PI programme provides training and support for postdocs interested in moving on to establish their own research groups. This includes practising chalk talks (above), an important part of applying for an independent research position.

02

Create future science leaders

The scientific training we provide aims at developing research excellence, dynamism and multidisciplinary activity, expanding the talent pool for biomedical science across the UK.

— Our training and development programmes for PhD students, postdoctoral fellows and laboratory research scientists are now well developed. There are training courses on presenting and writing about research, programming and use of scientific software. We've introduced careers talks, work placements for PhD students and undergraduate teaching opportunities for postdocs.

— The Crick signed up to the Technician Commitment, an initiative across the sector to ensure visibility, recognition, career development and sustainability for technicians working in higher education and research.

— We hosted the inaugural symposium of Equality, Diversity and Inclusion in Science and Health Research (EDIS), a new network formed by the Crick, Wellcome and GSK to make these issues a priority in research organisations.

03

Collaborate creatively to advance UK science

The Crick promotes novel forms of partnership with its founders and the broader scientific community.

— We launched a joint recruitment call with our three university partners for early-career group leaders in the physical sciences. The aim was to recruit chemists, physicists, mathematicians, computer scientists and engineers who wanted to apply their research to biomedicine. Four applicants will take up their positions during 2018. They will spend six years at the Crick before moving to an established position at UCL, Imperial or King's.
— The Crick African Network is a new partnership with five institutes in Africa. It received a five-year £6 million government grant to establish a fellowship programme that will train African researchers to tackle infectious diseases in their home countries.
— A new cryo-electron microscope is to be installed at the Crick alongside two similar machines thanks to funding from Wellcome. It will be owned and used by a consortium of London universities – Imperial, the Institute for Cancer Research, King's and Queen Mary University of London – making this equipment available to researchers across the city.

32 For more information

Collaborating with African scientists
The Crick African Network has held several workshops in Africa, like this one in Ghana, building research skills and supporting the best African scientists in tackling infectious disease.

04

Accelerate translation for health and wealth

We conduct discovery science that is open to translation, turning advances in understanding into new ways to prevent, diagnose and treat disease to improve lives and strengthen the economy.

— A new spin-out company called Ervaxx has been created to develop cancer vaccines. Based on research on human endogenous retrovirus in George Kassiotis' lab, the company has backing from investment group SV Health Investors.

— Researchers from AstraZeneca and the Crick are collaborating on early-stage research that could translate into new treatments and health innovations in the future, thanks to a five-year research agreement that was signed last year. This adds to our existing partnership with GSK, where joint projects are already delivering new insights into the underlying biology of disease.

36 **For more information**

— We are building closer links with partner institutions on the medical implications of our research. We also launched a new postdoctoral clinical fellowship scheme, complementing existing PhD level opportunities at the Crick for clinicians wishing to gain from a full training in basic science.

05

Engage and inspire the public

Our public, education and community programmes engage people in our science and encourage dialogue about biomedical research.

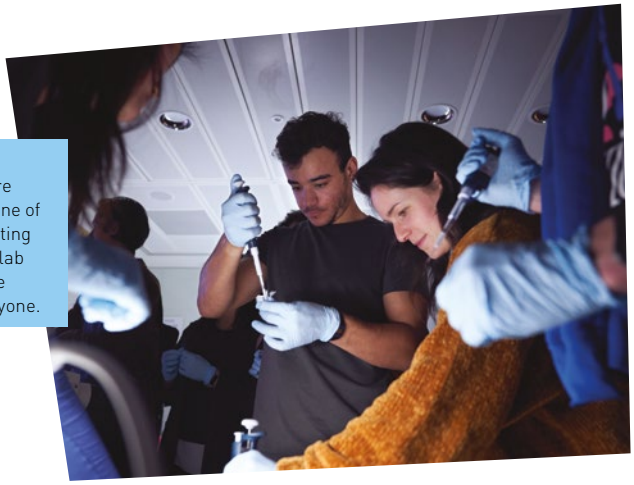
— Our exhibition *Deconstructing patterns: art and science in conversation* opened in the Manby Gallery in February 2018. In the first month, we welcomed over 2,000 visitors to the exhibition.

40 **For more information**

— Two Crick Late evening events and a Discovery Day for families were held at the Crick, part of a full programme of public events. Thousands of people got involved with the demonstrations and activities across the three events.

— Greg Clark, Secretary of State for Business, chose the Crick as the location to launch the UK government's Industrial Strategy.

— A local group of young filmmakers worked closely with Nate Goehring's lab in a collaboration with Holborn Community Association. The result is a film that offers a metaphor for the lab's research on growth and development.



The Crick Late events
People had the chance to explore many areas of our research at one of our Crick Late events. From getting hands-on with state-of-the-art lab equipment to inspiring talks, the events offer something for everyone.

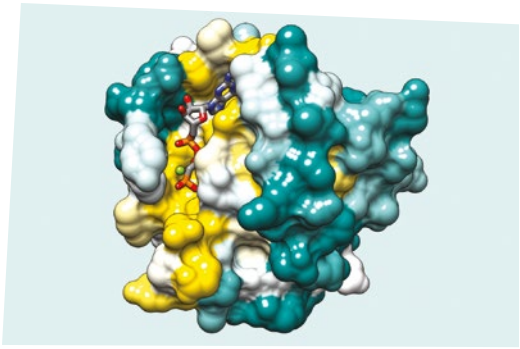
DISCOVERING THE BIOLOGY OF HEALTH & DISEASE

Our scientists made a number of significant findings last year, showing the breadth of research undertaken at the Crick and demonstrating how our research is advancing the understanding of health and disease.

A mouse tumour (grey/white areas) being infiltrated by cDC1 immune cells (yellow), triggering anti-cancer responses (see p.16).

Julian Downward lab

Cancer-causing mutation suppresses immune system



Mutations in *Ras* genes – which drive 25% of human cancers by causing tumour cells to grow, multiply and spread – can also protect cancer cells from the immune system.

Research, by a team from the Francis Crick Institute and Institute of Cancer Research (ICR) in London, shows that mutated *Ras* genes can suppress the immune system around tumours by increasing levels of a protein called PD-L1. Small amounts of PD-L1 exist naturally in the body to prevent the immune system from attacking healthy cells, but cancer cells can exploit this to protect themselves.

"Understanding how different mutations protect cancer cells from the immune system will help us to offer patients more precise and effective treatments," explains Matthew Coelho, a former postdoc at the Crick who was part of the team that led the work.

Developing better treatments

Antibodies that target PD-L1 proteins are currently used in the clinic, but it is hard to determine which patients might respond best to the therapy. By revealing the causal link between *Ras* and PD-L1 levels, the study offers new possibilities for combination therapies using different drugs.

"Our study highlights the fundamental role that *Ras* mutations play throughout the different stages of cancer," says Julian Downward, Group Leader at the Francis Crick Institute and Head of the Lung Cancer Group at the ICR. It was already known that *Ras* mutations played a key role in starting around a quarter of all human cancers, causing cancer cells to grow, multiply and spread. "We now know that they also help to protect the cancer cells from our immune systems, making them more difficult to treat," he says. "Understanding the mechanisms behind this will help us to develop better treatments in future, for example boosting immunotherapy approaches with drugs that disrupt cancer's defences."

Immunity (2017) 47, 1083

Ras protein (top). Julian Downward and postdoc Sophie de Carne Trecesson, members of the research team (bottom).

Charlie Swanton lab

Predicting lung cancer's return

Scientists at the Francis Crick Institute and UCL have found that unstable chromosomes within lung tumours increase the risk of cancer returning after surgery. They have used this new knowledge to determine the risk of relapse up to a year before the cancer returns.

"For the first time we've revealed new insights into how tumours evolve and evade treatment, a leading cause of cancer death," says Charles Swanton, the lead researcher on the Cancer Research UK-funded TRACERx lung cancer study.

The team analysed tumours from 100 patients with non-small cell lung cancer (NSCLC). They found that patients with a high proportion of unstable chromosomes in their tumour were over four times more likely to have their cancer return, or die from their disease, within two years.

Blood test

The researchers then investigated whether this genetic diversity could be tracked clinically. By looking for tumour DNA in blood samples taken from 24 patients after surgery for NSCLC, they accurately identified more than 90 per cent of those people destined to relapse – up to a year before clinical imaging could confirm the disease's return.

Christopher Abbosh of the UCL Cancer Institute, who led the work with Nicolai Birkbak and Gareth Wilson at the Crick, said: "Using circulating tumour DNA we can identify patients to treat even if they have no clinical signs of disease, and also monitor how well therapies are working. This represents new hope for combating lung cancer relapse following surgery, which occurs in up to half of all patients."

The TRACERx study involves more than 225 researchers and clinicians based at 19 centres across the country and is supported by Cancer Research UK, the Francis Crick Institute, UCL Cancer Institute, University College London Hospitals Biomedical Research Centre, the Royal Society, Achilles Therapeutics, illumina, Natera and the Rosetrees Trust.

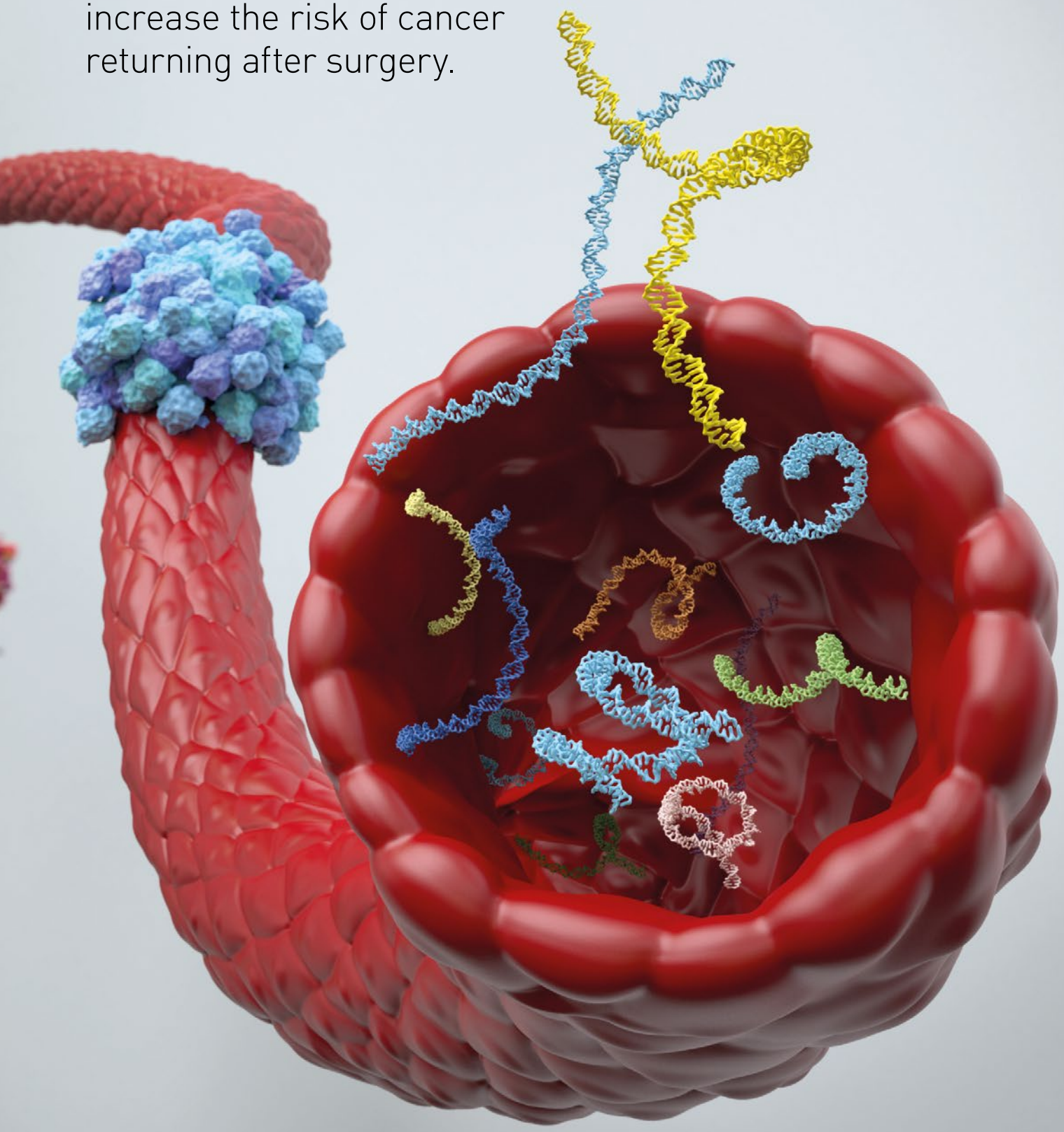
Nature (2017) 545, 446

PATIENTS ANALYSED
100

RESEARCHERS INVOLVED
225

Tumour DNA circulating in a patient's blood may be able to predict whether their lung cancer will come back after surgery.

Scientists at the Francis Crick Institute and UCL have found that unstable chromosomes within lung tumours increase the risk of cancer returning after surgery.



Kathy Niakan lab

New understanding of human embryo development

Researchers have used genome editing technology to reveal the role of a key gene in human embryos in the first few days of development.

> We were surprised to see just how crucial this gene is for human embryo development, but we need to continue our work to confirm its role.
>
> **Norah Fogarty**

This is the first time that genome editing has been used to study gene function in human embryos, which could help scientists to better understand the biology of our early development.

The Crick team used genome editing techniques to stop a key gene from producing a protein called OCT4, which normally becomes active in the first few days of human embryo development.

Crucial gene

After an egg is fertilised, it divides until at about five days it forms a ball of around 100 cells called the 'blastocyst'. The study found that human embryos need OCT4 to correctly form a blastocyst.

"We were surprised to see just how crucial this gene is for human embryo development, but we need to continue our work to confirm its role," says first author Norah Fogarty. "Other research methods, including studies in mice, suggested a later and more focused role for OCT4, so our results highlight the need for human embryo research."

Kathy Niakan, who led the research, adds: "If we knew the key genes that embryos need to develop successfully, we could improve IVF treatments and understand some causes of pregnancy failure. However, it may take many years to achieve such an understanding, our study is just the first step."

Lessons for stem cell biology

The team spent over a year optimising their techniques using mouse embryos and human embryonic stem cells before starting work on human embryos. To inactivate OCT4, they used an editing technique called CRISPR/Cas9 to change the DNA of 41 human embryos. After seven days, embryo development was stopped and the embryos were analysed.

As well as human embryo development, OCT4 is thought to be important in stem cell biology. 'Pluripotent' stem cells can become any other type of cell, and they can be derived from embryos or created from adult cells, such as skin cells. Learning more about how different genes cause cells to become and remain pluripotent could help us to produce and use stem cells more reliably.

The embryos used in the study were donated by couples who had undergone IVF treatment. The study was done under a research licence and strict regulatory oversight from the Human Fertilisation and Embryology Authority (HFEA), the UK Government's independent regulator overseeing infertility treatment and research.

Nature (2017) 550, 67

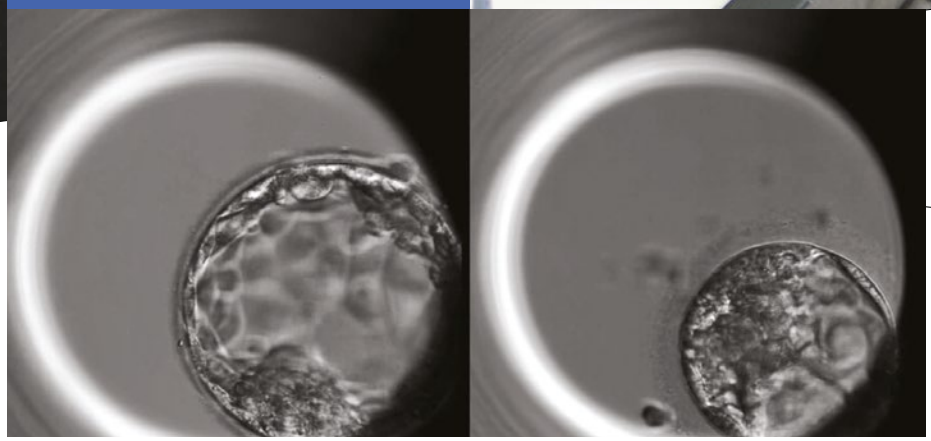
Kathy Niakan (top). Human embryos form a blastocyst (bottom left) after about seven days, unless OCT4 is inactivated (bottom right).

A HUMAN EMBRYO FORMS
A BLASTOCYST AFTER

5 DAYS

IT CONSISTS OF AROUND

100 CELLS



Caetano Reis e Sousa lab

Chemical attraction could improve cancer immunotherapy

Better immunotherapies for cancer patients could be developed using chemicals that attract specialised immune cells toward tumours, research suggests.

Scientists at the Francis Crick Institute have discovered that immune cells called Natural Killer cells accumulate in tumours and release chemicals that attract specialised dendritic cells (cDC1) – white blood cells known for triggering anti-cancer immune responses – to the tumour.

Genes associated with Natural Killer cells and cDC1 correlated with cancer patient survival in a dataset of over 2,500 patients with skin, breast, neck and lung cancers. A similar correlation was seen in an independent group of breast cancer patients, with a particularly positive outcome for women with triple negative breast cancer, which typically has a poor prognosis.

Opportunity for new treatments

"Our findings have given us a renewed appreciation of the importance of Natural Killer cells and cDC1 in the immune response against cancer," says Caetano Reis e Sousa, who led the study. "Attracting more cDC1 to tumours could be the basis of a new immunotherapy for cancer patients."

The team also showed that prostaglandin E2 (PGE_2), a molecule produced by some cancer cells, suppresses Natural Killer cell activity and reduces the responsiveness of cDC1 to the chemical attractants. This suggests that blocking PGE_2 with drugs might help boost the effectiveness of immunotherapies by restoring cDC1 levels in tumours.

"Now that we know better how this key anti-cancer response works, we can look at identifying other ways in which cancers get around it," says Caetano. "This understanding will ultimately help us to develop new immunotherapy approaches to help more patients."

Cell (2018) 172, 1022

> Now that we know better how this key anti-cancer response works, we can look at identifying other ways in which cancers get around it.
>
> **Caetano Reis e Sousa**

Jean Langhorne lab

Genes linked to malaria parasites' persistence

The ability of malaria parasites to persist in the body for years is linked to the expression of a set of genes from the *pir* gene family, scientists from the Crick and the Wellcome Sanger Institute have found.

The researchers showed in a mouse study that as few as 1 in 10 of the parasites that initially appear in the blood express this set of *pir* genes. But almost all the parasites found persisting in the body weeks later express the genes, and can be a source of further spread of the disease.

Malaria is caused by parasites which are passed between people by mosquitoes. The body's immune system will eventually destroy most of the malaria parasites, but some will continue to reside dormant in the body year after year without causing any symptoms.

The team hopes that a better understanding of the *pir* gene family will make it possible to destroy this reservoir of parasites that allows ongoing transmission of malaria.

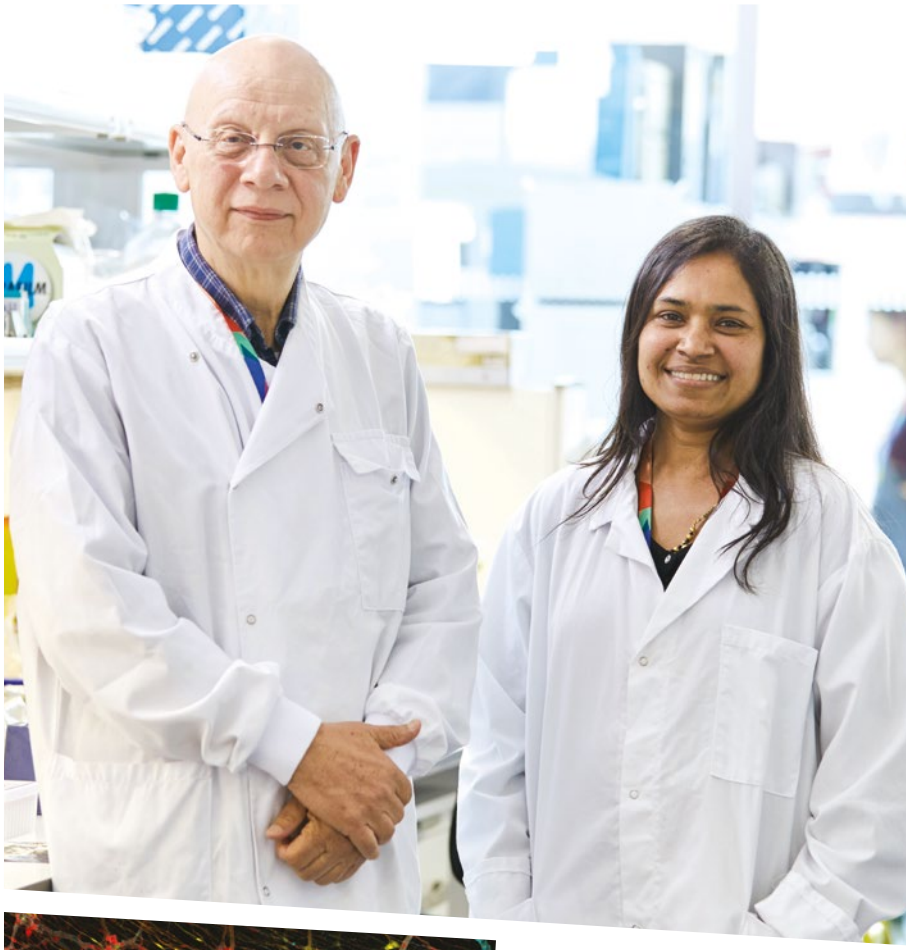
Jean Langhorne, who led the work at the Crick, says: "Understanding how certain parasites go on to establish chronic infection and determining how a particular set of *pir* genes are involved may provide us with a means to prevent chronic infection which could be applicable to all types of malaria in humans."

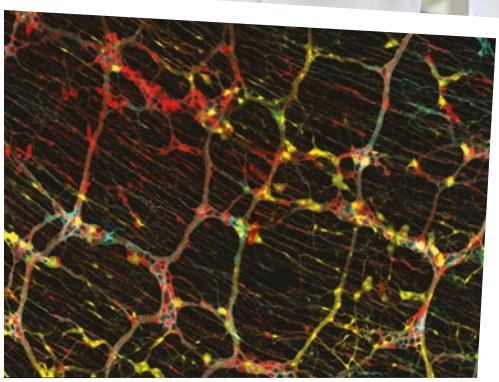
Nature Microbiology (2017) 2, 16276

Deirdre Cunningham, Irene Tumwine and Sarah Manni (left-right) in the Jean Langhorne lab.

Vassilis Pachnis lab

Architecture of our 'second brain'





> We uncovered a set of rules that control the organisation of the 'second brain'.
>
> **Reena Lasrado**

Scientists have made an important step in understanding the organisation of nerve cells embedded within the gut that control its function. The discovery could give insight into the occurrence of common gastrointestinal diseases, including irritable bowel syndrome and chronic constipation.

The researchers have revealed how the enteric nervous system – a chaotic network of half a billion nerve cells and many more supporting cells inside the gut wall – is formed during mouse development.

Often known as the 'second brain' for its vast number of neurons and complex connectivity, the enteric nervous system has a crucial role in maintaining a healthy gut.

"The neural networks of the gut are responsible for well organised and stereotypic functions such as secretion of enzymes that breakdown food, movement of food along the gut, communication with immune cells and bacteria, and the relay of information to the brain," says Vassilis Pachnis, Group Leader at the Francis Crick Institute.

Using genetic tools, the team labelled developing cells of the enteric nervous system with unique colours and followed their descendants through development and into the adult animal. By examining the type of cells produced by single progenitors, they could understand their properties.

"We uncovered a set of rules that underpin the organisation of the 'second brain' not just along a single gut layer but across the 3D space of the gut wall," says first author Reena Lasrado.

The research was led by the Crick in collaboration with the University of Leuven, Stanford University, the Hubrecht Institute and the Quadram Institute Bioscience.

Science (2017) 356, 722

Vassilis Pachnis and Reena Lasrado (top). Multicoloured families of cells in the gut wall (below).

James Turner lab

Cause of infertility side-stepped in mice

Scientists have created healthy offspring from genetically infertile male mice, offering a potential new approach to tackling a common genetic cause of human infertility.

Our sex is determined by the X and Y chromosomes. Usually, girls have two X chromosomes (XX) and boys have one X and one Y (XY), but approximately 1 in 500 boys are born with an extra X or Y. Having three rather than two sex chromosomes can disrupt formation of mature sperm and cause infertility.

Extra chromosome removed

Researchers at the Crick found a way to remove the extra sex chromosome to produce fertile offspring. If the findings can be safely transferred into humans, it might eventually be possible for infertile men with Klinefelter syndrome (XXY) or Double Y syndrome (XYY) to have children through assisted reproduction using this technique.

Working with researchers at Kyoto University, the team took small pieces of ear tissue from XXY and XYY mice, cultured some of the cells and turned them into stem cells. They noticed that in the process, some of the cells lost the extra sex chromosome.

Stem cell development

By guiding the stem cells to become cells with the potential to become sperm and reintroducing them to a male mouse to mature, they could use assisted reproduction to create healthy, fertile offspring.

However, the researchers caution that more work is needed before this approach could ever be used in humans as it is currently not possible to make mature human sperm outside the body.

Science (2017) 357, 932

Takayuki Hirota and James Turner (top), part of the research team that produced healthy mouse pups (bottom) from infertile male mice.

James Briscoe lab

Mechanism for spinal cord development discovered

Scientists have uncovered how nerve cells in the spinal cord are organised in precise patterns during embryo development – a finding that could give insight into regenerative medicine.

As embryos grow and develop they need the right cell types to end up in the right places inside forming organs. This is particularly important in the spinal cord, where different nerve cell types must be accurately positioned so that circuits can assemble properly to control muscle movement.

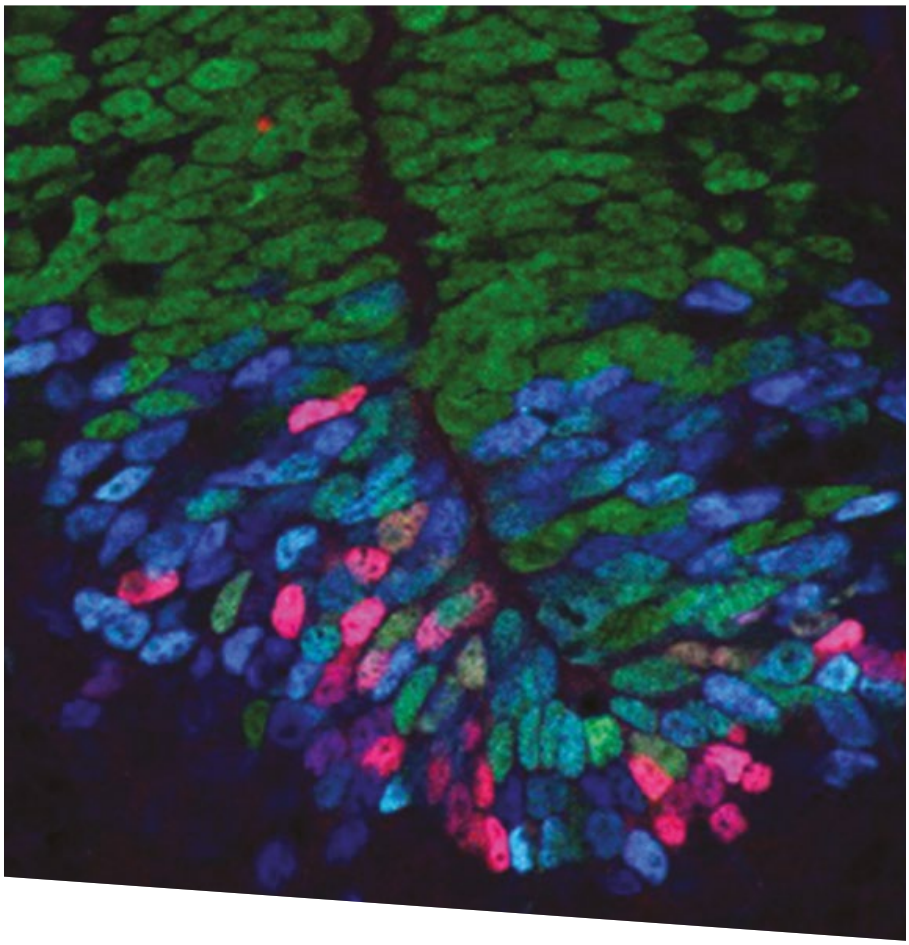
Two signals control gene activity

Researchers at the Francis Crick Institute, the Institute of Science and Technology in Austria and the Ecole Polytechnique Fédérale de Lausanne in Switzerland have found that cells destined to become nerve cells in developing mouse embryos use two different signals spreading from opposite sides of the spinal cord – the back and belly side – to measure their position accurately. Based on this map, they turn into the appropriate nerve cell type.

The team of biologists, physicists and engineers found that the strengths of the two signals originating from the back and belly sides of the body affect gene activity in developing nerve cells. Based on this gene activity in early development, the cells turn into the appropriate nerve cell type for that position in the spinal cord.

"We have shed light on the long-standing question of how developing tissues produce the right cells in the right place in the right numbers," says James Briscoe, Group Leader at the Crick. "In the long run this will help inform the use of stem cells in approaches such as tissue engineering and regenerative medicine. However, there is still much more to learn and we need to continue developing these interdisciplinary collaborations to further our biological understanding."

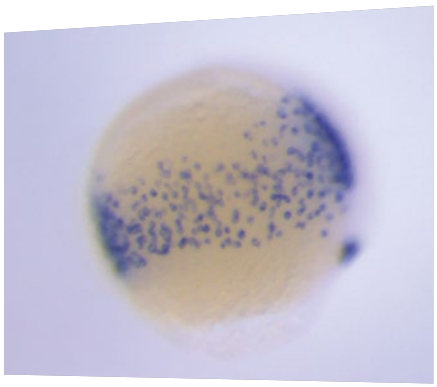
Science (2017) 356, 137



A developing spinal cord shows precise patterns of gene activity. The red, blue and green identify different types of cells.

Caroline Hill lab

A new layer of complexity in embryo development



New insights into how cells know what they should become in the zebrafish embryo have been revealed by Caroline Hill's lab at the Crick.

In vertebrates, a growing embryo begins as a simple ball of cells. All the cells look alike and have the potential to form any part of the body.

"It's a fascinating question," says Group Leader Caroline Hill. "How does a single fertilised egg go on to form a human body with all the different organs in the right place and the right size?"

An important early step sees a transformation of the embryo into three distinct layers: the ectoderm (where cells go on to form the skin and nervous system), mesoderm (blood and muscles) and endoderm (gut, pancreas and other internal organs).

Levels of a single protein called Nodal were thought to be responsible for determining where cells in the zebrafish embryo become endoderm and mesoderm. Nodal is present in different amounts across the early embryo, at high concentration where the endoderm forms and lower where the mesoderm forms.

"We knew this didn't fit the entire picture," says Andrew Economou, a postdoc in Caroline's lab, "because Nodal signalling didn't extend across all of the future mesoderm."

Network of signals

Andrew, working with another postdoc in the lab, Thijs van Boxtel, has shown that a more complex signalling network governs the process. This gives tight control over where the division between endoderm and mesoderm occurs. A second factor called Fgf extends the signal to become mesoderm, to all the cells in the layer, while a third protein drowns out the Fgf signal where the endoderm needs to be.

The understanding gained may be important for using stem cells in medicine in the future. If you know what prompts cells to become a certain type, you may be able to come up with cell therapies to replace lost function. For example, generating insulin-producing cells for the pancreas could one day help treat diabetes.

Developmental Cell (2018) 44, 179

Caroline Hill and Andrew Economou. Cells destined to become endoderm (blue) spread around the developing zebrafish embryo (bottom).

Frank Uhlmann lab

Two DNAs wedded with this ring

Crucial processes in our cells such as separating chromosomes in cell division, DNA repair and switching genes on and reading them out all require DNA molecules to be brought together in an organised way.

All organisms, from bacteria to humans, have rings of proteins that encircle DNA and are important in organising and packaging the long DNA molecules within cells.

But until now it remained unknown how the protein rings loop together two DNA molecules to allow processes such as chromosome separation to happen correctly. Frank Uhlmann and his former postdoc Yasuto Murayama, now with his own lab at the National Institute of Genetics in Japan, have shown how this happens in yeast with a protein ring called cohesin. The advance relies on Yasuto's success in recreating the binding of cohesin onto DNA in the test tube.

Molecular carabiners

Frank compares cohesin to the metal rings used in mountaineering called 'carabiners' which open up to clip onto a rope then use a slider to lock them on. "In binding one rope, you haven't achieved anything," he explains. "When you open up the carabiner and lock it onto a second rope as well, that's when you can go climbing."

Frank and Yasuto have shown that after binding one DNA molecule, the cohesin ring opens and binds a second. But the second DNA is single-, not double-stranded. DNA replication then occurs and makes the single-stranded DNA into double-stranded DNA.

"This was a total surprise. At first we couldn't believe it. But this is how it works. Cohesin binds single-stranded DNA. It's a really important mechanism," says Frank.

Cell (2018) 172, 465

Molecular model of a cohesin ring. Credit: Martin Singleton, Francis Crick Institute.

> This was a total surprise. Cohesin binds single-stranded DNA. It's a really important mechanism.
>
> **Frank Uhlmann**

John Diffley lab

Unravelling how DNA gets copied

> It's a big job. You can't just start at one end and copy the three billion letters in the human genome.
>
> **John Diffley**

How molecular machinery gets loaded onto DNA ready to create new copies of our genetic data has been revealed by Crick scientists.

New copies of our DNA are needed every time our cells divide, and it's the structure of DNA that allows this replication. The two strands in the DNA double helix are first unwound before each acts as a template for a new strand. The result is two new DNA molecules with the same genetic information copied in both.

Seeing the link between structure and replication is one thing. Understanding how a cell ensures complete control over the whole process is another.

"It's a big job. You can't just start at one end and copy the three billion letters in the human genome," says John Diffley, Group Leader at the Crick. "You start at tens of thousands of sites along the DNA, otherwise it would take forever."

Controlled unwinding

Replication has to start at all 50,000 sites at the same time, once and only once in each cell division. The control needs to be extraordinary: the error rate has to be less than 1 in 100 million or it is lethal for the cell. One main point of control is the initial unwinding of the DNA helix. This is done by a cellular enzyme called a DNA helicase.

John, and fellow Crick researcher Gideon Coster, have shown how helicases get loaded onto DNA. Two helicases pointing in different directions get clipped onto the double helix at the start sites of replication before setting off in opposite directions, unwinding the DNA. While the study was done in yeast, we know that similar proteins carry out the same role in humans.

A piece of the puzzle

They found that one helicase is loaded on at one replication site. However, unexpectedly, the other is loaded at a distant, previously unrecognised site. It then tracks along the DNA to join its partner and gets ready for action.

John explains: "It's a piece of the puzzle of how our genomes are replicated, a process that tends to become misregulated in cancer. We now want to look at whether helicase loading shows differences in cancer cells."

Science (2017) 357, 314

John Diffley, and with Gideon Coster (inset).

Simon Boulton lab

Telomerase's dark side discovered

> In order to translate science effectively into new treatments, you need to understand how systems work at this detailed mechanistic level.
>
> **Simon Boulton**

An enzyme called telomerase is crucial for maintaining the ends of chromosomes as our cells grow, divide and age over time.

Simon Boulton's group at the Crick has discovered a surprising activity of telomerase. It's surprising because it leads to the opposite outcome: the rapid loss of telomeres, a key structure that normally protects chromosome ends.

This 'telomere catastrophe' was known to occur when a protein called RTEL1 was missing. RTEL1 normally helps unwind a DNA loop present at the end of chromosomes to allow telomerase to do its maintenance job. Simon and his team wondered if getting rid of both telomerase and RTEL1 would accelerate the telomere crisis.

Confounding all expectations, they found that knocking out both RTEL1 and telomerase in mice rescued the situation. The telomere was maintained as normal.

"It was astonishing," says Simon. "It suggested that telomerase was actually toxic in cells lacking RTEL1. But why was unclear."

Carefully reconstructing what was going on, they found that in the absence of RTEL1's DNA loop unwinding activity, telomerase was blocking telomeres from being copied ahead of cell division. To relieve the blockage, cells had no other choice but to cut off the whole telomere.

Removing telomerase meant that telomere copying never got blocked and there was no catastrophe, explaining the rescue Simon's team had seen. It also reveals the biology at the root of the devastating rare genetic disorder Hoyeraal-Hreidarsson syndrome which is caused by RTEL1 mutations.

Cancer connection

When activated abnormally, telomerase is a driver of cancer as it allows cells to divide uncontrollably. Understanding more about telomerase and its functions is giving new insight into how some classes of anti-cancer drugs work.

"In order to translate science effectively into new treatments, you need to understand how systems work at this detailed mechanistic level," says Simon.

Cell (2018) 172, 439

First author Pol Margalef in the lab. Mouse chromosomes with telomeres labelled in red (right).

A YEAR IN SCIENCE

Our people, facilities and their achievements have helped advance research at the Crick this year.

New group leaders arrive

Three outstanding early-career scientists are setting up new research groups at the Crick.

NUMBER OF APPLICANTS

380

Three scientists arrived at the Crick in early 2018 to set up new research groups, having been hired in our first round of recruitment for early-career group leaders.

Selected from almost 400 applicants via a highly competitive process, Pontus Skoglund, Silvia Santos and Lucia Prieto-Godino have begun establishing their new teams and new research.

All three are keen to take advantage of the unique career structure we provide at the Crick, which has been specifically designed to provide opportunities for talented early-career researchers to develop themselves and their research.

Unusually, new group leaders remain with us for no more than 12 years before being supported to find scientific leadership positions elsewhere. This may be at other UK institutions or beyond, establishing links across the world.

This process is intended to develop future science leaders for biomedical science – a key aspect of our national role.

> I'm really excited to be at the Crick and I look forward to developing my lab and making the most of all the cutting-edge technology and supportive teams that are here.

Silvia Santos


Lucia Prieto-Godino

Lucia Prieto-Godino
Originally from Madrid, Lucia moved to the UK to study for her PhD at the University of Cambridge before taking up a five-year postdoc position in Lausanne, Switzerland.

The goal of Lucia's lab is to understand how evolution sculpts nervous systems, giving rise to new behaviours. Studying how neural circuits change over evolutionary timescales can provide important insights into how brains work and what goes wrong in disease. Her team is studying these issues using the fly olfactory systems, the neural circuits responsible for sense of smell. By comparing fly species that exhibit different preferences for the fruit they feed and breed on, Lucia and her team can start to tease apart how neural circuits responsible for odour-guided fruit preference behaviours have evolved.

"Observing animal behavioural diversity, I cannot help but wonder: how can brains' intricate neuronal connections evolve through random mutation and selection to produce all these different behaviours?" says Lucia. "I am absolutely fascinated about this question, and we know so little about it!"

Lucia's research requires a multidisciplinary approach, combining a variety of methods across fieldwork, bioinformatics, electrophysiology, imaging, behavioural analysis – such as looking at how the flies react to their favourite fruit – and genetic manipulation.

"I love the Crick's interdisciplinarity, and I immediately thought that there would be lots of opportunities for collaborations," she says. "I feel so fortunate to be part of such an amazing and welcoming community of researchers."

Pontus Skoglund
Following a PhD at Uppsala University in Sweden, Pontus undertook a postdoctoral research fellowship at Harvard Medical School, where he studied population history and historical admixture in the Americas, South Pacific, and Africa.

He now leads the Ancient Genomics Laboratory at the Crick and describes his field as currently one of the most interdisciplinary in science. Ancient genomics brings together a diverse range of research from areas including anthropology, archaeology, history, evolution, biochemistry, statistics and computational genomics, in order to understand our evolutionary past through fragments of DNA.

"You can think of ancient genomics as a kind of time-travel," he says. It involves examining the human genome through time and space, he explains, which helps us to understand the processes that have shaped our biology and that are still shaping our biology today. "For example,


Pontus Skoglund

through ancient DNA we are able to investigate the transition in human societies from hunting and foraging to agriculture. Furthermore, we can investigate the impact and effects of this transition on human diet and human biology. I'm particularly excited about the possibility of studying genetic variants that changed very rapidly, or at least rapidly on evolutionary timescales."

Pontus believes that the Crick's mission to understand the biology underlying human health and disease fits perfectly with his research. "Contemporary human biology is a direct product of evolution and ancient genomics is the best way to study human evolution directly," he says.

Silvia Santos

> You can think of ancient genomics as a kind of time-travel. For example, through ancient DNA we are able to investigate the transition in human societies from hunting and foraging to agriculture.
>
> **Pontus Skoglund**

Silvia Santos

Silvia's career path has exposed her to a variety of academic cultures. Originally from Portugal, she studied at the University of Glasgow and the European Molecular Biology Laboratory before working at Stanford University and the MRC's London Institute of Medical Sciences.

Her lab at the Crick is investigating control principles in cell decision-making by studying two important cell decisions which serve as paradigms for their research: cell division and cell differentiation (committing to a specific fate), using human embryonic stem cells as a model system.

Silvia and her team deploy a distinctive combination of theory (mathematical modelling and image analysis) and experiment (live cell imaging, quantitative molecular biology, biochemistry and chemical biology). This combination has been key to their ability to uncover regulatory principles in cell decision-making.

Silvia says that the Crick feels like her 'scientific home', because aspects of her PhD experience that shaped her as a scientist are explicit in the Crick's strategy and culture: the lack of departmental structures, the freedom to pursue curiosity-led research and the commitment to training scientists.

"I'm really excited to be at the Crick and I look forward to developing my lab and making the most of all the cutting-edge technology and supportive teams that are here," she says.

Joined-up thinking

Researchers from UCL, Imperial and King's are adding to the breadth of research at the Crick.

Thanks to the innovative way we work with our university partners, scientists from UCL (University College London), Imperial College London and King's College London are able to carry out and extend their research on attachments at the Crick.

This continues to generate new collaborations, bring specialist knowledge to the Crick and enable research across a wide range of disciplines.

Secondments allow a group leader to transfer all or part of a research group to the Crick for an agreed period, while satellites are small groups of university researchers embedded in a Crick research group for an agreed period.

Jernej Ule

> This close proximity has enabled rapid exchange of new insights and ideas.
>
> **Jernej Ule, UCL**

Jernej Ule
Seconded to the Crick from UCL, Jernej Ule's group is investigating how RNAs and proteins come together in our cells, and how this contributes to development or disease, with a focus on motor neurone disease (MND) – a fatal disease also referred to as amyotrophic lateral sclerosis (ALS). "Unless you know the primary cause of a disease, you are only ever going to be able to ameliorate the symptoms, not reverse the process."

"My group of nine researchers are all based at the Crick, where we have greatly benefited from work with different research facilities and initiated important new collaborations," explains Jernej. "Our lab is next to the computational biology and MND labs, and this close proximity has enhanced our collaborations and enabled rapid exchange of new insights and ideas."


Ed Tate

Ed Tate
Ed Tate manages a research group split between Imperial College and the Crick, and is an example of how university attachments can bring expertise in the physical sciences to collaborations at the Crick.

"We work with chemistry but we apply it to biology," says Ed. "When we see a biomedical or biological problem we think would be interesting to try to solve, we can decide to tackle it from a new perspective – and the Crick enables us to do that very effectively."

His satellite group at the Crick comprises six team members who each work on something different: one works on TB, one on malaria, three work on cancer and one works on chemistry.

"Over the last year or two, the research focus at the Crick has enabled us to make more progress on certain specific projects than in the previous five years or more," Ed believes. "At the Crick, we can work in a biology-focused environment and collaborate with other scientists to the benefit of all. To say that unexpected science comes from people talking to each other over coffee is a bit of a cliché – but it's absolutely what happens."

Snezhana Oliferenko
On a five-year secondment from King's College London, Snezhana Oliferenko's group of six researchers is studying the comparative biology of cell division – in particular the mitotic strategies of two different yeasts.

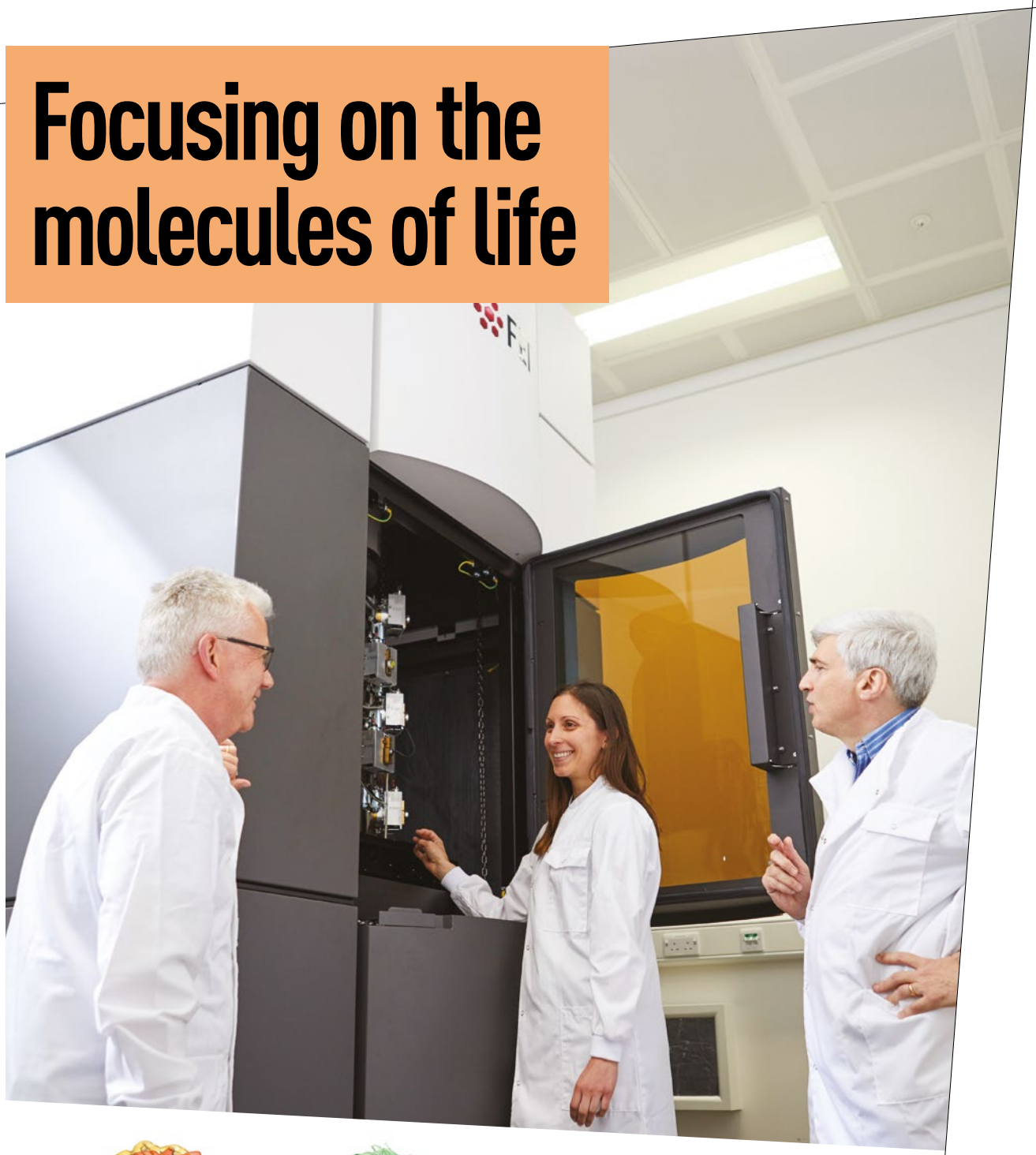
"Cell division is fundamental to all biological life on earth," says Snezhana. "If we can understand more about different strategies of cell division – as demonstrated by the two yeasts – we will gain greater knowledge of evolution, human development and disease."

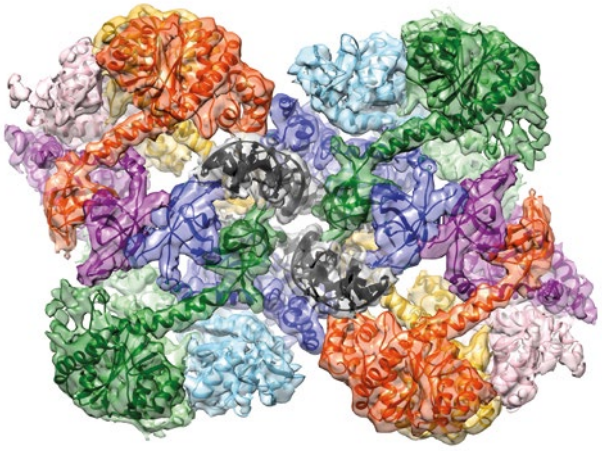
She explains that being at the Crick has given her team the opportunity to collaborate with others and to use research facilities to study areas beyond their core expertise. "You can always find the skills and knowledge you need here," she says. "It's a great environment for meeting like-minded people and talking science. It's also a very good experience for my team to be exposed to interesting and diverse thinking."

> It's a very good experience for my team to be exposed to interesting and diverse thinking.
>
> **Snezhana Oliferenko, King's College London**


Snezhana Oliferenko

Focusing on the molecules of life





The biochemical processes of life are being revealed in atomic detail using sophisticated new microscopes which are revolutionising the field of structural biology.

Scientists at the Crick are using a technique called 'cryo-electron microscopy' or cryoEM to image complex biological processes in atomic detail.

The multimillion-pound microscopes use focused electron beams rather than light, resolving greater detail. Using electrons, they can see down to the molecular systems at work in our cells and tissues. Flash-freezing samples to around -190°C using liquid nitrogen preserves biological structure and gives the technique its name: 'cryo' means cold or frozen.

CryoEM has improved significantly in the past few years, moving from seeing proteins as fuzzy blobs to resolving the full molecular structure. These advances were recognised in the award of last year's Nobel Prize for Chemistry to the three scientists who developed the technique. The Crick has a set of these microscopes available for research in its structural biology science technology platform, led by Phil Walker.

CryoEM at the Crick

The Crick's cryoEM facility is located in the basement, 20 m below ground. The 4 m high box enclosing the microscope manages the temperature, air flow and vibrations that could disturb the images collected.

The whole microscope is set on a base mounted on compressed air that actively dampens vibrations and disturbances, while metal in the walls of the room shields the microscope from stray magnetic fields.

Automated computer control of the microscope allows data to be continuously collected overnight and to be operated remotely.

The Crick has two of these state-of-the-art Titan Krios instruments, funded by the Medical Research Council, along with several smaller instruments to support a wide range of science at the Crick.

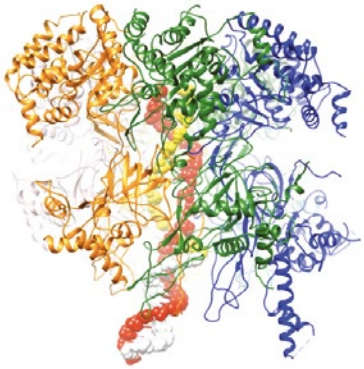
Thanks to related Wellcome funding, a third Titan Krios microscope will also be housed at the Crick for use by a consortium of London universities and institutes: Imperial, the Institute of Cancer Research, King's and Queen Mary University of London. This collaboration should see further sharing of skills and expertise in cryoEM among the research community in London. The large investment in these microscopes by the Crick, its founders and collaborating organisations reflects the depth of insight cryoEM can now give into biological processes.

Resolution revolution

The improvement in the microscopes has come from a range of developments. New cameras that are much more sensitive, better sample preparation and new data processing approaches have all come together to give a significantly greater level of detail with cryoEM.

Opposite: Phil Walker, Andrea Nans and Peter Rosenthal work on a Titan Krios cryo-electron microscope. Below: Structure of the integrase molecular machinery from a virus related to HIV. Courtesy of Peter Cherepanov.

Above: Molecular structure of a helicase as it begins to unwind DNA. Courtesy of Ferdos Abid Ali in the Alessandro Costa lab.



> CryoEM has allowed us to look at very large and very complex molecular machines in ways that would be really challenging if we were to use protein crystallography.
>
> **Alessandro Costa**

CryoEM at the Crick

RESOLUTION

0.1
NANOMETRES

MAXIMUM RATE OF DATA CAPTURE

10
TERABYTES/DAY

HEIGHT

4METRES

The Titan Krios instruments are managed by Andrea Nans, who has been working with cryoEM since 2005 when she did her PhD in the USA. She remembers the rigmarole of collecting data manually on photographic films before the new cameras came along. "It was very painful," she says. "It's easier now, especially as more people want to get into cryoEM."

More people are interested because of the unexpectedly rapid advances in what is now possible with the microscopes. "There's been a revolution in imaging biomolecules and more surprises are ahead," says Peter Rosenthal, a group leader and coordinator overseeing development of cryoEM research at the Crick.

Form and function

It is the jump in resolution that is changing what is possible for scientists. They can now use cryoEM to determine the position of atoms within large biological molecules.

The field of structural biology involves determining the three dimensional shape of biological molecules that carry out key processes in cells. Understanding how the biomolecules look is important because it gives information on how they function.

> If you know the structure, you know how to break it. You can design a precise drug or molecule to impede the process.
>
> **Peter Cherepanov**

Peter Cherepanov, Group Leader at the Crick, explains: "Everything in biology is based on chemical reactions and the interaction of molecules. If we can determine the atomic structures, very often it explains the mechanism through what contacts what." He says this offers important insight: "If you know the structure, you know how to break it. You can design a precise drug or molecule to impede the process."

For decades the method of choice to determine structures was X-ray crystallography. For this, you need to purify large amounts of your protein molecule of interest and find conditions in which it crystallises. You can then use X-rays to work out the protein's atomic structure when lined up in an ordered crystal. Crystallography has been tremendously successful in telling us how proteins carry out their role, in explaining the effect of certain mutations and in drug design.

But suddenly, in just the past three or four years, cryoEM is providing the same kind of detail without the need for crystals. And it can do so with large assemblies of proteins as they are when active in the cell – something unobtainable before. "Our job has suddenly become more exciting," says Alessandro Costa, another of the structural biology group leaders at the Crick. "CryoEM has allowed us to look at very large and very complex molecular machines in ways that would be really challenging if we were to use protein crystallography."

Watching biochemistry happen

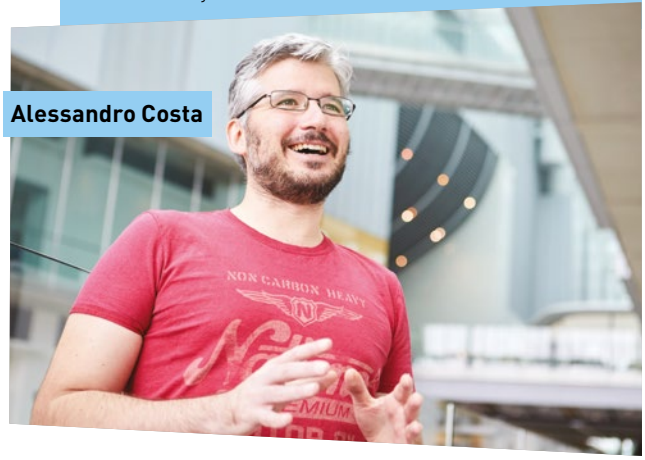
Peter Cherepanov has seen what is now possible with cryoEM. His group works on HIV and other members of the same virus family. They have been particularly interested in one viral protein called integrase which carries out an important stage in the virus' life cycle. It catalyses the insertion of the HIV genome into the DNA of our own cells where it can hide and stay dormant before re-emerging at a later time. A drug that stops this integrase step would be a useful addition in tackling HIV/AIDS.

The group had been using X-ray crystallography to study the structure of an integrase from a virus related to HIV. Now they have moved to use cryoEM, and they still get the same level of fine structural detail. They can see how the integrase works and see potential drug molecules bound inside. "This exceeded my expectations," says Peter. "I knew it was possible to see small molecules in the cryoEM. But this level of detail? People have been impressed: not everyone realises it is possible like this."

Alessandro Costa leads another structural biology group at the Crick. His team studies DNA replication, working on the structure of a molecular machine called a helicase. As described on p.23, this is a ring that encircles DNA and unwinds it for another machine called a polymerase to come in and duplicate the DNA. His group has been able to use cryoEM to capture the structure of a helicase bound to DNA in various states. From these images, it is possible to get insight into the mechanical steps involved as DNA is first unwound then replicated.

But Alessandro wants to move from static images to film a biochemical movie. His lab is currently carrying out experiments to understand the time resolution they would need to achieve to see the various steps in the duplication of DNA. That will enable them to tailor an experiment for the cryoEM to see the different events and time points in the process.

"We now want to visualise DNA replication as it is occurring, to see DNA as it is newly made – all at close to atomic resolution. This really is visual biochemistry."



Alessandro Costa

Bringing academia and industry closer together

Projects with GSK and AstraZeneca are combining expertise and delivering scientific progress.

Daniel Miller

Seeing scientific findings and discoveries develop into new treatments is a key priority for the Crick. We achieve this in many ways – such as by creating collaborative links with others who can help take ideas forward.

Our partnerships with GSK and AstraZeneca enable scientists from these companies to work alongside Crick researchers – sharing ideas, expertise and approaches while working together on promising early-stage projects. They also offer the scientists a chance to learn new skills, broaden their experience and develop their careers.

Industrial revelation

As a PhD student in Caroline Hill's lab at the Crick, Daniel Miller made a discovery that looked interesting. He'd been looking at a particular cell-signalling pathway in breast cancer in mice and found a related protein that was produced in high amounts. It appeared to help drive growth of the cancer cells.

Daniel spent nine months at AstraZeneca in Cambridge on a joint project to take these findings forward. "We came up with lots of ideas we would never have thought of on our own," he says.

Thanks to the collaboration, Daniel joined a team at AstraZeneca which uses a state-of-the-art platform to produce antibodies that bind tightly to proteins of interest. Having successfully made antibodies against the protein he discovered during his PhD, Daniel is now back at the Crick seeing if they neutralise the protein in breast cancer cells in mice.

The group's next step will be to see if the antibodies have the same effects in human cancers. "We're now collecting samples from biopsies of patients with pancreatic, breast and skin cancers," explains Daniel.

Daniel found the AstraZeneca experience immensely rewarding and is including pharma companies in his search for his next position. "During my PhD, I was drawn to the idea of working in an industry setting. I'm enthusiastic about taking the basic biology and turning it into new drugs," he says.

Hilary Eidam

New perspectives

A medicinal chemist by training and with more than a decade of experience at GSK in the US, Hilary Eidam is currently working in Barry Thompson's Epithelial Biology Laboratory at the Crick, through a partnership between the Crick and GSK.

The lab focuses on organ size control, and the pathway which tells a body when organs, such as the heart, have grown large enough during development. The hope is that the lab's work could ultimately provide insights into the possibilities of organ regeneration.

When Hilary's 18-month spell at the Crick ends and she returns to Philadelphia, she will take some valuable lessons home with her. "Although my 12 years in drug discovery have given me a deep knowledge of the challenges involved in taking a drug through from molecule to patient, and great experience of working on pharmacokinetics, I've never had deep biology expertise or training," she says. While her chemistry skills are valued by the team at the Crick, she feels she's gained significant biological insight during her time at the institute. "I'm now able to bring a different perspective to my work that will make a big contribution to projects back at GSK."

"I'll also be able to draw on the different ways of working I've experienced here," Hilary adds. She points to the fact that people rarely call or email each other at the Crick – communication is always face-to-face in real time. "That's a really collaborative approach and something that we can all learn from."

"Collaborations like this between academia and industry can be highly beneficial to mankind," Hilary believes. "To borrow a thought from Sir Keith Peters: academia and industry are both vital, and their areas of expertise have very little overlap – why on earth wouldn't we work together and rise to the challenges posed by human healthcare?"

The people making research happen

The latest research requires teams of people working together with high-quality equipment, all bringing their skills, expertise and dedication.

It's not just those working at the bench in science labs that keep research moving forward. People working in a wide variety of roles play an essential part in supporting science at the Crick.

Facilitating research
Alessandra Gaiba is a science support manager in charge of a quadrant of six labs.

"My role on the quadrant is to look after all the organisational aspects and allow the scientists to concentrate on science," says Alessandra. "They don't have to worry about equipment malfunctions, consumables or any aspect of the building's facilities – that's my responsibility."

Alessandra also has overall responsibility for all four quadrants on the floor, a total of 380 scientists in 30 research groups. This is more of a strategic, managerial role – beyond what lab managers typically do elsewhere. All the science support managers work together to identify how the Crick can best meet the needs of researchers.

Alessandra Gaiba

> It's about balancing communal and individual needs. You're part fixer, negotiator and concierge – the person to go to.
>
> **Alessandra Gaiba**

"It's about balancing communal and individual needs. You're part fixer, negotiator and concierge – the person to go to," says Alessandra. "For example, we'll have input into identifying the best location for a new lab, as well as where the equipment should be located," she explains.

Rekha Subramaniam

"I love the interaction with the scientists. Ultimately, the end goal is to make sure that the researchers are free to concentrate on what they do best: pursue the discoveries that could make a difference to humans everywhere."

Maintaining animal welfare

"It's really essential that animals are kept in the best conditions," says Rekha Subramaniam, a senior research scientist in the Crick's animal research facility. It's not just a moral imperative, she explains, you also get better data and better results if the animals are kept in an enriched, optimal environment. "Healthy animals mean better science."

Research at the Crick seeks to understand the biology underlying human health and disease. While standard lab-based techniques are used throughout the institute, animal research is necessary in some projects to understand why disease develops.

The overwhelming majority of animals at the Crick are mice. Rekha manages one of the mouse units, ensuring the highest standards of animal welfare are maintained at all times.

"We make sure all the animals are looked after, providing them with the best care," she explains. "All the staff in the facility and scientists from research groups using the animals need to be trained to a high standard and competency is regularly reviewed."

The mice are housed in individually ventilated cages and are health checked every day.

Researchers from groups working on cancer and developmental biology use the mice in the unit. The animals enable precise studies of gene function and the pathways involved in disease, as well as providing models for understanding human diseases like lung cancer and dementia.

> It's really essential that animals are kept in the best conditions.
>
> **Rekha Subramaniam**

Fermenting science

Ali Alidoust is co-lead of Fermentation Services at the Crick, working in a team with the other co-lead Namita Patel and scientist Damini Patel.

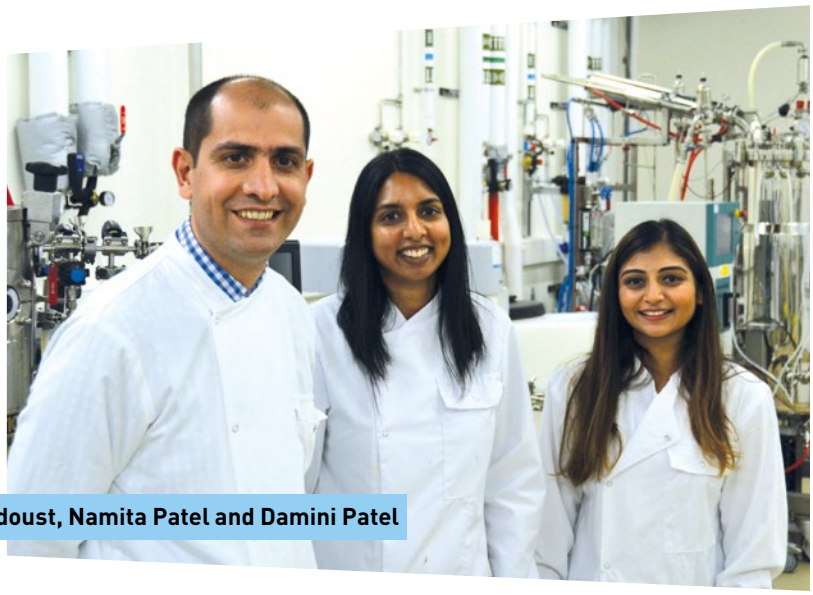
They grow yeast and bacteria in fermenters, providing large quantities of cells and proteins for research groups to use in experiments. Yeast and bacteria are standard organisms used in many biology labs. They can work as factories to produce proteins in order to study their biological role.

In small quantities, yeast and bacteria cultures can be grown overnight in flasks of nutrient-containing liquids. When more is needed, something else has to be done.

"We can save research groups time and cost with our specialist equipment and expertise," says Ali. "We can do 100 litres in one run, and we have produced 10,000 litres of culture for some postdocs in the past."

The Crick has five fermenters, each of which can control the temperature, acidity, aeration and other factors for optimal growth of the bacteria or yeast inside. Once the cells are ready, they are harvested through a continuous centrifuge in around an hour. The samples then go to the scientists for their experiments.

"For some groups, what we do is essential," says Ali. "We work with them all the time because, in order to assure the quality they need, we need to talk frequently, spotting and solving any problems."



Ali Alidoust, Namita Patel and Damini Patel

Patterns in art and science

The latest exhibition at the Crick showcases a series of unique collaborations between scientists and artists in the field of sculpture, film and spoken word.

The Crick's exhibition, *Deconstructing patterns: art and science in conversation*, provides a fresh perspective on the patterns found within our bodies.

Presented over three 'zones', *Deconstructing patterns* explores different molecular and cellular patterns studied at the Crick, each one introduced by a unique artist commission. The artworks offer an alternative way of visualising and describing the forms and functions that so intrigue our scientists. By taking patterns apart, deconstructing them, both the artists and scientists are seeking new insights into the puzzle of how the complexity of the human body arises.

In *Infinite Instructions*, DNA research and the search for the patterns amongst huge genomic data sets provide the starting point for an immersive sound installation by the award-winning poet Sarah Howe and sound artist Chu-Li Shewring.

For the *Transforming Connections* zone, artist Helen Pynor has created a mesmerising installation that combines light, photography and sculpture to explore the movement of patterns during the metamorphosis of the fruit fly. The commission is based on the work of Iris Salecker's lab, which investigates the development of the visual part of the fruit fly's brain.

Finally, *Breaking Symmetry* challenges our understanding of patterns even further, highlighting the creativity inherent in asymmetry, which is essential to the healthy development of all organisms. Nate Goehring's research group worked closely with young people on a summer filmmaking project at Holborn Community Association. The result is a wonderfully surreal fictional narrative created by the students which offers a metaphor for the lab's research into the first appearance of asymmetry in the nematode worm.

'Deconstructing Patterns' runs until 1 Dec 2018 in the Manby Gallery at the Francis Crick Institute.

Visitors find patterns in a sound installation by Sarah Howe and Chu-Li Shewring (far right), while another finds out about the science which inspired it (right).

Engaging and inspiring our visitors

Deconstructing patterns is the latest in a programme of exhibitions and events that aims to excite and inspire the public with science.

The Crick's size, location and profile means that we have a unique opportunity to share our work with the general public, schools, our local community and beyond.

Our programme gives people a rare opportunity to connect with our researchers, explore what goes on behind the scenes at the Crick and gain fascinating insights into our research.

Rewarding research

Our work was recognised by a host of high-level awards in 2017/18.

Jonathan Stoye

Royal Society Fellowship
Jonathan Stoye, Group Leader at the Crick, was elected a Fellow of the Royal Society in recognition of his work on genetic interactions between retroviruses and their hosts. Retroviruses, a family of viruses that includes HIV, are able to insert their genetic code into healthy host cells. Jonathan was one of the first virologists to look at natural mechanisms of immunity, and in 1996 cloned the first mammalian gene found to offer natural immunity to retroviruses, the Fv1 mouse gene. His work has helped to shape the field as we know it today.

Fellows of the Academy of Medical Sciences
Group Leader Robert Wilkinson and David Roblin, previously Chief Operating Officer and now our Senior Scientific Translation Fellow, were both elected Fellows of the Academy of Medical Sciences. David has made many contributions to translational medicine, turning research discoveries into treatments that directly benefit lives and the economy. Robert has worked on tuberculosis and HIV in South Africa and London while maintaining a first-class research programme.

Charlie Swanton

EMBO membership
Charlie Swanton was elected to membership of the European Molecular Biology Organisation (EMBO). This came just a few weeks after the announcement of his winning the 2016 San Salvatore Foundation award for research that is leading to new approaches to anti-tumour therapeutics.

Rafael di Marco Barros

Pontecorvo Prize
Cancer Research UK's Pontecorvo Prize for best PhD thesis was awarded to Rafael di Marco Barros, who completed his PhD in Adrian Hayday's lab. Rafael's research focused on the mechanism by which cells that line the intestinal wall may regulate the composition of immune cells in surrounding tissues, contributing to intestinal health and disease.

New Year's Honours
Three Crick scientists were recognised in the 2018 New Year's Honours list. Sir Keith Peters was appointed Knight Grand Cross (GBE) for his contributions to medicine and science, while Professor Robin Lovell-Badge was made a CBE for services to genetics, stem cell biology and the public understanding of science. DeepMind co-founder Demis Hassabis, who sits on the Crick's Scientific Advisory Board, was made a CBE for services to science and technology.

Sir Peter Ratcliffe

Buchanan Medal
The Royal Society awarded our Clinical Research Director, Professor Sir Peter Ratcliffe, its prize for distinguished contributions to the biomedical sciences. Peter was awarded the Buchanan Medal for his ground-breaking research on oxygen sensing and signalling pathways which mediate the responses of cells to low oxygen levels.

Appointments

Cristina Lo Celso

Foulkes Foundation Medal
Cristina Lo Celso, a stem cell biologist at Imperial College London with a satellite group at the Crick, won the Academy of Medical Sciences' Foulkes Foundation Medal. The prize was awarded in recognition of her work in using stem cells to study how leukaemia develops and relapses. The Foulkes Foundation Medal is awarded biennially to a rising star within biomedical research.

In addition, the year saw:

— The inaugural Sir David Cooksey Prize in Translation awarded to Lucy Collinson, Martin Jones, Lizzy Brama and Chris Peddie, who have pioneered new electron microscopy imaging techniques at the Crick.
— Emeritus scientist Tomas Lindahl was elected a Fellow of the American Association for the Advancement of Science (AAAS) for distinguished contributions to the study of DNA repair mechanisms.
— Our Chief Information Officer (CIO), Alison Davis, named the UK's CIO of the Year at the Women in IT awards.
— Our building beat 90 finalists to win the Silver Jubilee Cup for best overall project in the Royal Town Planning Institute's (RTPI) Awards for Planning Excellence.

Lord Browne appointed Chair of the Crick
Lord Browne of Madingley, the former BP chief executive, became the Chairman of the Francis Crick Institute in autumn 2017.

As Chairman, Lord Browne leads the Crick's Board of Trustees in its role overseeing the institute's activities and making sure the right strategy, resources and governance are in place to realise our vision for research excellence.

Lord Browne was chief executive of BP from 1995 to 2007, is a former President of the Royal Academy of Engineering and was Chairman of the Tate galleries for ten years. He sits as a crossbench member of the House of Lords and was the government's lead non-executive director from 2010 to 2015. He is currently Executive Chairman of L1 Energy and Chairman of Huawei Technologies (UK), and is a member of the board of a number of other private and not-for-profit organisations.

Sam Barrell becomes Chief Operating Officer
Sam Barrell is the Chief Operating Officer of the Francis Crick Institute, responsible for leading the operational management and running of the institute. She is driving efforts to ensure the Crick works as effectively as possible in supporting the science being carried out here.

Sam joined the Crick in September 2017 from a career in the NHS as a noted healthcare leader and former GP. As Chief Executive of Taunton and Somerset NHS Foundation Trust, she led a Global Digital Exemplar for the NHS rated "outstanding" for care. Previously, she was the Chief Clinical Officer leading the formation of South Devon and Torbay Clinical Commissioning Group at the time of the 2012 reforms of the NHS.

Sam sits on a number of advisory boards for science and healthcare networks and was made a CBE in 2014.

Supporting new discoveries

Help the Crick achieve its mission

To find out more, contact:

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> We're really proud to be supporting a scientist at such a dynamic, ground-breaking facility and thrilled to be part of the amazing work that the Crick carries out.
>
> **Alix Green, Josh Carrick Foundation**

We are grateful to the wide range of partners, funders and donors who come together to support the Crick.

With their help, we are training leading scientists and funding researchers as they collaborate across disciplines to pursue greater understanding of our biology, and improve the prevention, diagnosis and treatment of human disease.

Already, the Crick's approach is proving that research is better and moves faster when people work together, sharing their discoveries and expertise. We need to build on this momentum and ensure the Crick's community of leading researchers has the funding they need to carry out their work.

The Crick is now launching a fundraising partnership with Cancer Research UK to attract and secure philanthropic support to help further its mission of understanding human disease and accelerating the development of new treatments.

Investment from generous donors is vital for sustaining and extending our research programme.

One of these supporters is the Josh Carrick Foundation, which was set up in 2012 in memory of Josh Carrick, who died of testicular cancer at the age of 23. The foundation's trustees have developed a fundraising strategy to support research into cancer and raise awareness of testicular cancer.

The foundation's generous donations help to fund the work of Group Leader Erik Sahai, whose research focuses on how cancer spreads through the body.

"We have supported Erik since 2013 and believe the work he is doing to understand why cancer spreads and why existing therapies sometimes fail is fundamental to the fight against the disease," explains Alix Green, a trustee of the foundation. "We're really proud to be supporting a scientist at such a dynamic, ground-breaking facility and thrilled to be part of the amazing work that the Crick carries out."

Josh Carrick

Erik Sahai

King Felipe VI and Queen Letizia of Spain visited the Francis Crick Institute as part of their state visit to the UK.

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