NOVEMBER 2022

YOUR IMPACT

PREPARED FOR THE LORD LEONARD AND LADY ESTELLE WOLFSON FOUNDATION

THANK YOU FOR YOUR SUPPORT

We are delighted to present you with an update from the Francis Crick Institute, including a summary of the advances made in the Cell Cycle Laboratory, and how its new PhD students are settling into their projects.

This year, the Crick completed its first quinquennial review, which assessed the institute's performance over its first five years against its ambitious goals. The Crick received high praise from reviewers, who highlighted the exceptionally high standard of research being conducted there. As a result, the Crick's three major funders – the Medical Research Council, Cancer Research UK and Wellcome – pledged to continue their support for a further seven years.

In January, the Crick also launched a refreshed strategy, Discovery Without Boundaries, outlining the direction of the institute's research in the coming years. It describes five guiding principles: to accelerate discovery through a culture of scientific excellence; to support the biomedical research endeavour across the UK and beyond; to engage and inspire the public with discovery science; to build capability for outstanding science support; and, crucially, to make discoveries that improve human health.

We're so pleased with what the Crick has achieved since its formation. This success is in no small part thanks to visionary philanthropists like you, and we remain very grateful for your support.

A YEAR OF DISCOVERIES

DEC 2021

New Crick spin-out company Adendra Therapeutics launches, building on the work of Professor Caetano Reis e Sousa (pictured below). Adendra is applying Caetano's insights into how a specific type of immune cells, called dendritic cells, orchestrate immune responses to cell death. Their goal is to create a new kind of immunotherapy for cancers and autoimmune diseases.

DEC 2021

Dr James Turner and his team use gene editing technology to create female-only and male-only litters of mice with 100% efficiency for the first time. The technology could be used to improve animal welfare in scientific research – and potentially also in agriculture – by preventing the need to cull animals of unwanted sex.

JAN 2022

Crick researchers are recognised in the New Year's Honours. Dr Steve Gamblin, the Crick's director of scientific platforms, is awarded a CBE for his outstanding scientific leadership and contributions to the national COVID-19 effort. Paul Nurse is made a member of the Order of the Companions of Honour – a special award granted to those who have made a major contribution to the arts, science, medicine or government over a long period of time.

FEB 2022

Professor Adrian Hayday (pictured right) and his group uncover how gamma-delta T cells act as 'security guards', surveying our body's own tissues to assess their health, support their function and protect against cancer-causing DNA damage. This work challenges the assumption that immune cells simply detect and respond to threats and highlights an important role in the body's day-to-day function.

APR 2022

Professor Carola Vinuesa (pictured left) and her team identify a new genetic cause of the autoimmune disease lupus. The researchers discover the fault in the DNA of a seven-year-old child with severe lupus. They are now working with pharmaceutical companies to explore ways to develop treatments that target this gene to help not only people with lupus but also people with related conditions.

JUNE 2022

An international group of geneticists and archaeologists, led by Dr Pontus Skoglund and his team, finds that the ancestry of dogs can be traced to at least two populations of ancient wolves. This work moves us a step closer to uncovering the mystery of where dogs underwent domestication, one of the biggest unanswered questions about human prehistory.

JUNE 2022

A collaboration between Dr Alessandro Costa and Professor John Diffley's labs uncovers how the double helix structure of DNA is opened to allow DNA replication. The work could lead to further studies to better understand this process, including how it can go wrong in diseases such as cancer.

JULY 2022

Professor George Kassiotis (pictured below) and his team identify a promising target for a pan-coronavirus vaccine that could offer some protection against all current and future variants of the SARS-CoV-2 virus that causes COVID-19, as well as some common colds and future pandemic threats. This differs from current vaccines, which are more limited in the variants of virus they can protect against.

SEP 2022

A team led by Professor Charlie Swanton reveals how air pollution can cause lung cancer in people who have never smoked. The research found that exposure to tiny particles of pollution in the air promotes the growth of cells in the lungs that carry cancer-causing mutations. The research is part of the TRACERx Lung Study, Cancer Research UK's flagship study to understand how lung cancer starts and evolves over time, in the hope of finding new treatments for the disease.

THE CELL CYCLE LABORATORY

In the Cell Cycle Laboratory, Paul Nurse and his team study the complex molecular mechanisms that control the cell cycle, the process by which cells make a copy of their DNA and then divide in two.

This fundamental process lies at the heart of all life on earth, from the smallest microbes to the largest mammals. It underpins how a single fertilised egg cell can give rise to the trillions of intricately organised cells that make up a human being. Crucially, failure to control the cell cycle can lead to cell division spiralling out of control and the development of cancer. As such, understanding this process is invaluable to finding ways to better tackle the disease.

Over millions of years of evolutionary history, the mechanisms controlling the cell cycle have stayed strikingly constant. This is why Paul's Nobel prize-winning work has centred around using the simple, single-cell organism fission yeast to explore the molecular processes that carefully choreograph the cell cycle. Through this approach, Paul and his colleagues identified a molecule called cyclin-dependent kinase (CDK) as the master regulator of the cell cycle. This work has formed the foundations for other researchers to develop CDK-inhibitor drugs, which target uncontrolled cell division in cancer and are used in the clinic today.

RESEARCH HIGHLIGHT: SOLVING A CELL CYCLE PARADOX

This year, the Cell Cycle Laboratory published important new findings challenging the conventional understanding of how cells control their cell cycle. Former Cell Cycle Laboratory PhD student Dr Saz Basu led the study, which is published in the prestigious journal Nature. The findings solve a contentious debate within the field, centring on how cells use the same master regulator – CDK – to perform several tasks in the right order, first copying their DNA and then dividing.

Scientists had previously put forward two seemingly opposing models for how this works: one suggesting that different varieties of CDK specialise in controlling DNA replication or cell division, and another suggesting that CDK becomes increasingly active over the cell cycle – like a dimmer switch slowly being raised on a light – and that this change controls the order. Saz's research revealed a surprising and nuanced solution – it's actually a mix of both, with CDK's activity playing the leading role. The findings represent a fundamental shift in our view of the cell cycle and improve our understanding of an important target of cancer therapies.

As you know, Saz graduated from the lab last year and has now started a new position at the artificial intelligence company DeepMind, where he's applying their deep learning and artificial intelligence approaches to genetic problems. This coincides with the launch of an exciting new collaboration between the Crick and DeepMind, who this year established a research laboratory embedded within the institute, strengthening the bridges between the two organisations.

THE CELL CYCLE LABORATORY PHD STUDENTS

We are hugely grateful for your longstanding support of the Cell Cycle Laboratory PhD students, and for your renewed investment this year.

Your generosity is helping to support some of the world's brightest minds to take their first steps in their scientific careers, and to explore their bold ideas under Paul's mentorship.

We would like to congratulate Dr Clovis Basier and Dr Emma Roberts, who successfully wrote their PhD theses and passed their viva exams last year. The two former students have officially graduated, but are now spending some time at the Crick conducting additional experiments and writing up their findings for publication. Clovis is currently considering moving into life science consultancy, while Emma has secured a postdoctoral position at Oxford University. There, she'll be studying a structure involved in cell division – called the centrosome – and how it is linked to the cell cycle.

Joseph Curran and Theresa Zeisner are now entering the final year of their PhDs – an exciting and challenging time. They are both wrapping up their experiments in the lab and plan to begin writing their theses this spring, before submitting next September. Both currently hope to continue on in academia and undertake postdoctoral positions when they graduate.

Last year, we introduced you to three new PhD students joining the Cell Cycle Laboratory – Billy Whyte, Sarah Willich and Thomas Hammond. When we wrote to you, these students were still in the first few months of their projects and were deciding what their projects should focus on. Now we join them one year into their projects when they have refined their questions and have begun to take their first steps to answering them.

SARAH WILLICH

"My project centres around the question: how do cells know to first replicate their DNA before they undergo cell division? The master regulator of the cell cycle, CDK, is responsible for switching on both DNA replication and cell division. It does this by adding a tiny molecule called a phosphate to proteins, which acts like a switch to change the protein's function – activating or deactivating it. I'm interested in how CDK knows to switch on the systems that control DNA replication first.

"The project I'm venturing into is something that the lab has wanted to do for many years, but no one has attempted it because the technique it requires sits outside of the lab's usual expertise. So I'm attempting to set up this technique for the first time, working with Dr Tania Auchynnikava, who works between our lab and the Proteomics Science Technology Platform (STP). It involves bursting open cells to release their contents, and then examining how these molecular components operate in a test tube. Establishing this system will take a while, but once I have it working it will open many new doors for investigation.

"This year, I feel like I've taken a real leap into the unknown, exploring new things that nobody in the lab does. But it's been great for my independence, and I know overcoming this challenge will be worth it in the long run."

BILLY WHYTE

"I'm investigating how cells know how big they are and how much DNA they contain. The yeast we study can have one copy of each chromosome or two, and the amount of DNA they contain seems to determine how large they grow before they divide. The ability to divide at the right size is crucial to cells' normal function and health, and this can go wrong in disease. In cancer, for example, cells divide too rapidly and often become smaller in size. "My first experiments have involved a lot of observational work – looking at what the cells do in lots of different scenarios and then seeing if I can spot any clues pointing to intriguing lines of investigation. I've been examining cells with different amounts of DNA to see if I can observe interesting differences in the behaviour of the key molecules that control the cell cycle. I've also been studying yeast that have mutations in their DNA that cause problems with their size, and I'm also trying to create my own mutations. I plan to combine different mutations together into one cell to see what the cumulative effect is – for example, can I tinker with the yeast's genetics to make a cell that's twice the size it should be?

"I hope that this process will eventually enable me to unpick some of the molecular circuitry that's involved in how the cell senses its own size, and the role that DNA plays in this process."

THOMAS HAMMOND

"In my work, I'm interested in how cells decide when to divide. During the cell cycle, cells grow larger and larger until they eventually divide, so generally the earlier they divide, the smaller they are.

"Previously, a postdoc in Paul's lab studied how certain proteins accumulate during the cell cycle. He suggested that when the amount of these proteins reaches a certain threshold, they trigger a switch and initiate cell division. But we don't know for certain whether this theory is correct. "I'm currently testing that model by artificially varying the levels of these proteins in cells and looking at how that affects what size they divide at. I've seen a general trend that higher amounts of this protein trigger cell division to happen earlier, when cells are smaller. But I also made a puzzling observation. There's a lot of variation when you compare individual cells – some cells can have very similar levels of this protein and yet divide at very different sizes. So now, I'm trying to investigate why that is. Are there lots of other factors that are playing a role? And if so, which ones?

"I'm excited to follow up on these preliminary results. I'm also looking forward to travelling to some conferences this year – I'm going to a seminar in Austria, and hopefully also a big yeast-focused conference in Japan, both of which I'm excited for."

Q&A WITH THE NEW CELL CYCLE LABORATORY STUDENTS

What has been your experience of starting your PhDs together?

BILLY: It's nice having others who are in the same shoes as you. All of our projects are quite complementary so we can learn from each other – for example, if Thomas discovers something, it could inform my next steps too.

SARAH: There's a really nice collaborative environment here. The general vibe of the lab is if someone has some results, we all talk through it together.

BILLY: Yes, it's not uncommon to see a bunch of people all huddled around one computer screen for hours discussing someone's data that just came out of a microscope!

THOMAS: Personally, it's been really nice having people in the same position as you, so you can struggle through challenges together as opposed to being on your own. We were worried that the three of us might end up wanting to pursue the same project, but the way it worked out was nice. Eventually, we all found our own projects that we really identify with.

How has the Crick supported you?

BILLY: The support here is great. Everyone is really lovely and open to chatting with you. There's a great PhD student committee here that Sarah is on...

SARAH: Yes, I'm on the committee. For our year, we organised bi-monthly socials, like coffee mornings and drinks events.

THOMAS: Sarah and I also go to the institute's social club, the 'Cricksters', who hold a regular board games night, which is good fun. That helps to break down barriers too, because you get to meet people who are not just PhD students, but operations staff or postdocs too, for example.

SARAH: The support from the STPs is amazing too. We're especially lucky because we have Tania from the proteomics STP who works really closely with the lab. If you have an idea, it's easy to just email someone at the STP and they'll help you figure it out. Like today, I spoke to someone from scientific computing about data analysis. It's the perfect environment to do research. Discovery without boundaries!

How have you found working with Paul?

SARAH: It's great because he gives us a lot of independence as students. But if you need a meeting with him, he'll make the time. He also regularly walks around the labs and asks whether people have anything they want to show him or talk about. Or he might just come up to you and suddenly say 'I was thinking about your results...'!

THOMAS: He has a lot of enthusiasm in general for seeing data and really cares not only about your work but also about you as a person.

BILLY: He's a real ideas guy – so talking to him for five or ten minutes can really clear up your thinking about a project.

I hear you all went on a lab retreat recently – how was that?

BILLY: It was a lot of fun. The whole lab went to Bournemouth and stayed in a big manor house.

THOMAS: We were about a five-minute walk from the beach. A really nice beach actually!

BILLY: It was great for team bonding and for developing ideas scientifically.

SARAH: Everybody had 90-minute slot where you introduce a topic and then you bounce ideas around. And these were interspersed with even broader discussions about quite esoteric topics that the lab is thinking about. It felt like less pressure than last year's lab retreat when we were all trying to define our research questions.

BILLY: Definitely – and this year it felt more like we could contribute and so we could get a lot more out of it.

THOMAS: Also, Paul was there for the full five days, so we got a lot of time for discussion with him and to hear his thoughts.

What does the Lord Leonard and Lady Estelle Wolfson Foundation's support mean to you?

THOMAS: It's amazing because it shows that someone from outside of the scientific world understands and appreciates what you're doing and is willing to invest in it. And it gives you a real feeling of responsibility to work hard.

BILLY: It also reminds you of the importance of what you're doing. It's very motivating. If someone is willing to support your work because they think it's important then you must be on the right track!

SARAH: And without that funding, we might not even be here and get to do these projects, so it's really fortunate for us.

THANK YOU

On behalf of the Crick and Cancer Research UK, we would like to thank you for your support and belief in our vision.

As you have read, your generosity is helping to launch the careers of a cohort of exceptional young researchers, enabling them to take their first steps in understanding some of the most fundamental processes in biology. We hope you have enjoyed reading about their journeys and that you are proud of what your support is enabling us to achieve.

Veronica Hallas
Senior Philanthropy Manager
The Francis Crick Institute

020 3469 8293
veronica.hallas@cancer.org.uk

Cancer Research UK
2 Redman Place
London E20 1JQ
Tel: +44 (0)20 7242 0200
cruk.org

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