DECEMBER 2021

SUPPORTING WORLD-CLASS RESEARCH AT THE FRANCIS CRICK INSTITUTE

Impact report prepared for The Lord Leonard and Lady Estelle Wolfson Foundation

INTRODUCTION

Five years on from opening its doors, the Francis Crick Institute has established itself as one of the leading biomedical research institutes in the world. Since 2017, its scientists have been shaping our fundamental understanding of human health and disease.

In this short time, Crick researchers have published more than 2,000 scientific papers, providing significant new insights across the spectrum of biomedicine. Crick science has generated ten spin-out companies that aim to take promising discoveries from the lab bench into the clinic where they can benefit patients. The institute has become a global destination of choice for emerging research talent, recruiting 32 new early-career group leaders from 14 countries, and over 300 PhD students and over 600 postdoctoral researchers from around the world. Many of the Crick's faculty have been recognised through major scientific prizes, including the 2019 Nobel Prize in Physiology or Medicine.

The next chapter of the institute's journey will see us continue to embrace new opportunities to connect and collaborate to further accelerate our pace of discovery and to consolidate the Crick's status as a world-class biomedical research institute. It will be an honour and a pleasure to celebrate this anniversary of the foundation of the Crick with you, as friends who have supported the institute from the outset and whose continued commitment contributes to our ongoing success.

None of this would have been possible without the shared vision and commitment of supporters like you. We are delighted to present you with highlights of advances that the institute's researchers have made over the past year and update you on the progress of Sir Paul Nurse and his PhD students in the Cell Cycle Laboratory.

CANCER RESEARCH UK

THE FRANCIS CRICK INSTITUTE

RECENT RESEARCH FROM THE CRICK

JAN 2021

HIGHLIGHT

Professor Karen Vousden and colleagues discover a way to target cancer's nutritional needs, which could lead to a new way to treat the disease. The group found that restricting the amount of the amino acid serine in the diet of mice, when given alongside a drug that prevents the body from making serine, reduced tumour cell growth in several different models of bowel cancer.

APR 2021

HIGHLIGHT

Professor Stephen West and his team find that blocking a specific protein could increase tumour sensitivity to PARP inhibitor therapy, which is used to treat a subset of ovarian, breast and other cancers. In many cases, cancer eventually develops resistance to this treatment, enabling the tumour to start to regrow. Stephen's work suggests how PARP inhibitors might be combined with other treatments to kill cancer cells before this resistance develops, or re-sensitise the cells to treatment, which could offer people with cancer an improved chance of survival.

MAY 2021

HIGHLIGHT

A collaboration between Dr Samra Turajlic, Professor Charlie Swanton and Dr Paul Bates finds that cells at the centre of tumours have a less stable genome and a higher potential to spread to other parts of the body than cells at the edges of the tumour. The findings highlight a need to develop treatments that target the unique conditions found at the tumour core to eliminate the most aggressive tumour cells.

AUG 2021

HIGHLIGHT

Dr Naomi Moris publishes results showing how 3D models made from embryonic stem cells could be used as part of the testing process to assess whether treatments are safe for developing embryos. The models could help establish whether new drugs can be taken during pregnancy and improve the selection of compounds to move forward into further trials.

DEC 2020

HIGHLIGHT

Dr Paola Bonfanti and her team successfully rebuild a human thymus, an essential organ in the immune system, using human stem cells and a bioengineered scaffold, which supports tissue development. Their work is an important step towards being able to build artificial thymi, which could be used as transplants.

MAR 2021

HIGHLIGHT

Professor Rickie Patani and his team identify the trigger of a key cellular change in motor neurone disease. They reveal how a 'helper' cell in the brain, known as an astrocyte, changes its behaviour and can cause harm to neurons. The findings could aid the development of new treatments for this condition as well as many other neurological diseases with the same change, including Parkinson's disease and Alzheimer's disease.

MAY 2021

HIGHLIGHT

Professor Mike Blackman and his group design a molecule that effectively blocks a critical step in the malaria parasite life cycle. They are now working to develop this compound into a potential first-of-its-kind malaria treatment.

MAY 2021

HIGHLIGHT

A collaboration between Professor Jim Smith and Professor James Briscoe's teams examines the earliest point at which the heart forms during embryo development. They reveal, for the first time, that each of the four chambers of the heart has a unique origin. Their research has implications for understanding congenital heart diseases, which affect around 1 in 180 babies worldwide.

SEP 2021

HIGHLIGHT

GammaDelta Therapeutics, a biotechnology company co-founded by Crick group leader Professor Adrian Hayday, initiates its first Phase I clinical trial. This marks the first in-human tests of a novel cell therapy for the treatment of acute myeloid leukaemia. This cell therapy builds upon Adrian's pioneering work into the role of a type of immune cell known as gamma-delta T cells in tackling cancer.

THE CELL CYCLE LABORATORY

Every day, our bodies create billions of new cells to replace dead, depleted or damaged ones, with a staggering 10 quadrillion cell divisions occurring over the human lifetime. This fundamental biological process must be carefully choreographed by a network of molecular interactions, and faults can result in cell division spiralling out of control, resulting in the formation of cancer.

As you know, Paul Nurse has been studying the intricate processes that control cell division throughout his career. These processes are so fundamental to life that they have been conserved throughout millions of years of evolution, with similar systems operating in organisms seemingly distant from humans, such as yeast. Paul and his team take advantage of this similarity, using yeast as a simple model system to pick apart the details of cell division. At the centre of this work is a molecule called cyclin-dependent kinase (CDK), which Paul and his team identified in the 1980s to be the master regulator of the cell cycle. This initial discovery initiated a cascade of further discoveries, resulting in the development of CDK-inhibitor drugs that target uncontrolled cell division in cancer and culminating in the clinical approval of the first CDK inhibitor for people with breast cancer in 2015.

However, many mysteries remain around how the cell cycle operates that, if solved, could transform our understanding of how cells work. Today, the lab continues to ask questions such as: how do cells know what size they are? How do they know the correct time to divide? And what happens when certain elements of the cell cycle break down?

THE NURSE LAB PHD STUDENTS

We are incredibly grateful for your support of the Nurse lab PhD students over the past three years. Nurturing PhD students to become confident, thoughtful and independent researchers is a key priority for Paul and his lab. A PhD is one of the major milestones in a scientist's life that marks the beginning of their research journey and will shape the rest of their career. By providing strong support and role models at this pivotal time, the Nurse lab seeks to set students on the path to success, wherever their careers take them.

The past three years have seen the current cohort of students progress successfully through their PhDs. This year, Dr Tiffany Mak, who graduated from her PhD in the Nurse lab in 2020, secured an exciting position as a postdoctoral researcher at the Novo Nordisk Foundation Center for Biosustainability in Copenhagen, Denmark. She will be pursuing her passion for environmentalism and sustainability by exploring the use of micro-organisms such as yeast to create sustainable food sources to improve human nutrition. She also published results from her PhD in The EMBO Journal, showing the effects of inhibiting a protein called TOR, which you may remember is a key controller of cell growth that formed a focus of Tiffany's work. The paper provides a database of important molecular changes that occur in yeast when this protein is inhibited – this resource is now freely available for researchers around the world to use in their work.

In addition, Dr Saz Basu, who passed his PhD viva in December 2020, has secured an exciting new position at Google DeepMind, and is in the process of submitting several academic papers. Meanwhile, Emma Roberts and Clovis Basier are now writing up their theses and nearing the completion of their projects. We report in more detail on their progress below.

This year also saw the Nurse lab PhD student's contributions to COVID-19 research at the Crick come to fruition, in the form of seven papers published back-to-back in The Biochemical Journal. You may remember from our previous update that when the Crick temporarily closed to all non-COVID-19-related research during the first UK lockdown, the students teamed up with Professor John Diffley's lab to screen for drugs that inhibit key components of the SARS-CoV-2 virus that causes COVID-19. Altogether, the team identified 15 molecules that inhibit SARS-CoV-2 by blocking different enzymes involved in its replication. Four of these drugs were also found to improve the effectiveness of remdesivir – the only antiviral currently approved in the UK for people with COVID-19. Research teams at the Crick are now conducting further tests on the efficacy of these drugs in the hope that they can be developed into new treatments for COVID-19 or in preparation for future coronavirus outbreaks.

Since the beginning of your support, the Nurse lab has published a total of 26 papers, many of which have featured important contributions from the PhD students. No one could have foreseen the challenges that the COVID-19 pandemic would place on the Nurse Lab and its PhD students during this time. Yet, thanks to their determination, resilience and adaptability – and with the unreserved support of the Crick and Paul – they have found success in their endeavours and a bright future awaits them. We hope you are proud of what your support has enabled them to achieve.

Dr Saz Basu – graduating PhD student

Having completed his PhD and successfully passing his viva, Saz has spent an extra year in Paul's lab finishing some exciting new papers generated from his work.

In June 2021, Saz published a paper co-authored with former Nurse lab PhD student Dr James Patterson. The study addresses the mystery of how cells know what size they are. This information is crucial to enable cells to divide at the correct size – a process that goes wrong in cancer, where cells divide too rapidly and often become smaller in size. Researchers have debated whether cells determine their size by timing how long it has been since their last division, assessing how many new cell components they have manufactured, or by a means of physically measuring their own length. Saz found "it turns out that none of them are right, but it seems to be influenced by a combination of the three. The results open the door to further studies of this complex process."

Saz has also submitted two further papers for publication that are undergoing review. The first solves a question that has puzzled the field for decades. Many organisms, including humans, have multiple versions of the master cell cycle regulator CDK. Until now, it wasn't known whether each of these co-existing CDKs could independently trigger cell division. In the new paper, Saz and his co-authors finally show that they can – an important step forwards in understanding how cell division works. Further work is now needed to understand why some organisms have evolved multiple different versions of CDKs and what their specialist roles might be.

The second study examines what happens when we inhibit CDK – a topic that could inform how doctors harness CDK inhibitors to treat people with cancer. While most enzymes exist in a binary state of on or off, CDK is unusual in that its activity can be turned up or down like a dimmer switch. At the start of the cell cycle, it has very low activity, and this gradually ramps up until it has 50-fold higher activity at the point of cell division. However, Saz showed that cells can still divide even when we use inhibitors to block a large percentage of this activity. This raises interesting questions as to how we should best use CDK-inhibitor drugs to treat cancer.

Excitingly, Saz has now secured the next steps in his career. "I'm going to work for Google DeepMind," he explains. "I'll be applying their deep learning and artificial intelligence approaches to genetic problems – it's an unexplored interface between two very exciting topics." Saz believes that the collaborative culture at the Crick has played an important role in opening the door to this new endeavour.

"The Crick not only fosters collaboration between academics, but with all kinds of organisations, including tech giants like Google. Those connections helped me take the next step in my career, where I'll work in a different setting but the same goal: improving human health."

Dr Saz Basu

Emma Roberts – graduating PhD student

Emma has now completed the fourth year of her PhD and is nearing the completion of her project "I've been fortunate to get a five-month extension to my PhD to make up for some of the lost time in the lab due to the pandemic. That's been absolutely critical for me to get me a bit more time to collect data," she explains. "In the past month I've started writing up my thesis – it's been really nice to put everything from the past four years together and discuss it as a combined body of work."

Emma's project centres around CDK – the master regulator of the cell cycle that has been a key focus of Paul's research. Her main interest is how the location of this molecule within the cell affects its ability to control the intricate process of cell division. This year, she has been developing a new method to detect how active CDK is in different parts of the cell. The technique targets a fluorescent dye to molecules that have been switched on by CDK. This creates a map of CDK's activity within the cell, showing bright patches in areas of the cell where CDK is most active, and darker areas where it is not. "I've nearly finished developing this system, and the preliminary work has been promising." Emma comments. "Seeing results from experiments that have taken a lot of effort and time is always a highlight. Experiments don't work a lot of the time so when they do, it's a real boost!"

Emma thinks that the expertise that surrounds her at the Crick, from the STPs and other research labs, has been crucial to the success of her project. "Having that expertise on hand gives you the opportunity to try something that you haven't previously had experience with – such as the experiments I've done in human cells," she explains. "The quality of science and scientists at the Crick is very high and I've benefitted from that a lot. I'm surrounded by brilliant people who I'm able to learn from and go to for advice."

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Emma Roberts

Clovis Basier – graduating PhD student

Clovis also recently completed the fourth year of his PhD and has been awarded a five-month extension to complete his final experiments and write up his thesis. The past year has been an exciting time for Clovis' research. "I think the last years of your PhD are the most productive as by that time things have started to work a bit! So, for that reason, I've made a lot of progress this year."

Clovis is investigating how cells produce the correct quantities of their internal components to grow and divide healthily. This involves studying how cells manufactures proteins – a process called translation. This year, Clovis made a surprising observation in his yeast cells that took his research in a new direction. He found that some cells in a yeast culture radically increase the general amount of translation they do for a short period of time. But it's not clear why only some cells do this while seemingly similar cells in the same culture do not. Clovis discovered that faults in certain yeast genes eliminate this variation in translation, suggesting that it's not chance variation but a healthy feature that benefits the cells in some way. These results open up a previously unknown aspect of cell-cycle biology that deserves further investigation.

"I feel lucky that Paul gives us so much independence. His focus is asking interesting questions, so he encourages us to explore our own ideas. It's also really rare to have an environment like the Crick where you have so much support and so many resources. I can really focus on the science. I never had to worry about anything apart from my experiments not working!"

Clovis Basier

Joseph Curran – 3rd year PhD student

Joseph is now entering the third year of his PhD – a critical time for gathering experimental results now that he has set up some key experimental systems to generate the data he needs.

Joseph's project focuses on a protein called Suc1. This molecule is thought to be crucial in the cell cycle, but its function has eluded researchers for decades. It has proved very difficult in the past to turn off the function of Suc1 in cells, making it difficult to study which aspects of the cell cycle go wrong in its absence. This year, Joseph successfully created a way to inactivate Suc1 – this involved growing yeast that has a form of Suc1 that is stable at low temperatures, but that becomes unstable at higher temperatures. It also required Joseph to figure out the precise cocktail of nutrients and other chemicals to grow these fragile organisms in to keep them alive. Using his model, Joseph can now look for clues indicating which parts of the cell cycle go wrong when Suc1 does not work as normal, and how does this disfunction leads to cell death. This could produce new insights about an element of the cell cycle that has puzzled researchers for many years.

Joseph reflects that although the COVID-19 pandemic has impacted everyone's work, he feels lucky to have been based at the Crick during this time. "It's been quite intense – I think everyone would agree that – and we struggled to get things done for a while," he says. "But I think of any institute in the country the Crick has been the most open. We're really lucky that they set up testing and we were allowed in from about February. I have friends in other research institutions who weren't allowed in for six to eight months, so it's been really great to be able to come in to the lab while also feeling pretty safe, because people are being tested and the Crick is taking it seriously."

"We're really lucky that they set up [Covid] testing and we were allowed in from about February. I have friends in other research institutions who weren't allowed in for six to eight months, so it's been really great to be able to come in to the lab while also feeling pretty safe, because people are being tested and the Crick is taking it seriously."

Joseph Curran

“The Crick is a wonderful place to do a PhD, because it fosters collaborative projects like the one with Andrew. After working with social distancing and limited capacity for so long, it has been really exciting to see the Crick re-open and go back to normal. Being able to chat easily with my colleagues about experiments again is a really important part for me and helps me design better experiments.”

Theresa Zeisner

Theresa Zeisner – 3rd year PhD student

Theresa is also entering the third year of her PhD in Paul’s lab. “Being halfway through my PhD now I have a long list of experiments I’m excited to do,” she comments.

Theresa is focussed on understanding how a class of proteins called phosphatases influence the timing of the cell cycle. Dozens of these proteins work together in cells to turn different programmes on or off, like a molecular switchboard. They do this by removing a tiny molecule called a phosphate from proteins, which acts like a switch to change a protein’s function – activating or deactivating it. “Understandi¬ng how this intricate biological timer system works is important to get insights into how cancer develops, where cell cycle timings often spiral out of control,” Theresa explains.

This year, Theresa has worked with senior laboratory research scientist Andrew Jones, a member of Paul’s lab who is an expert in a technique called mass spectrometry. Together, they are using a new mass spectrometry method that allows them to look at thousands of phosphate sites in a single experiment. These results have begun to reveal a detailed picture of which molecules involved in the cell cycle are switched on or off by phosphatases at what time.

THANK YOU

On behalf of the Crick and Cancer Research UK, we would like to thank the Trustees of The Lord Leonard and Lady Estelle Wolfson Foundation for your support and belief in our vision. We are incredibly grateful for your commitment to this research.

As you have read, your generosity is enabling Crick researchers, including Paul and his students in the Cell Cycle Laboratory, to tackle some of biology's greatest mysteries and drive significant progress in their fields. We hope you have enjoyed reading about some of the institute's successes and that you are proud of what your support is enabling us to achieve.

CONTACT US

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