NOVEMBER 2020

# YOUR IMPACT

PREPARED FOR THE LORD LEONARD AND LADY ESTELLE WOLFSON FOUNDATION

## THANK YOU FOR YOUR SUPPORT

Since opening its doors in November 2016, the Crick is establishing its reputation as one of the leading biomedical discovery research institutes in the world. So far, Crick scientists have produced more than 2,500 research publications, which are advancing our fundamental understanding of human health and disease.

We are delighted to have your ongoing commitment to support Sir Paul Nurse and his team's work to understand the intricate processes controlling the cell cycle. Here, we are pleased to present you with an update from Paul and his team in the Cell Cycle Laboratory, as well as a round-up of some of the pioneering advances that the Crick's researchers have made over the past year.

Together we will beat cancer

THE FRANCIS CRICK INSTITUTE

CANCER RESEARCH UK

# HIGHLIGHTS AND ACHIEVEMENTS

**2,500+ research papers**
have been published since the Crick opened, sharing new discoveries and ideas that could transform the way we approach disease

**12 early career group leaders**
were appointed this past year, selected from a pool of 371 applications submitted from across the globe

**The Crick is 5th in the world**
for life sciences research outputs from nonprofit organisations, according to the 2020 Nature Index

**42 new PhD students recruited**
from a total of 1,642 applications, including four new clinical PhD students

**Almost 16,000 local residents**
have used the St Pancras and Somers Town Living Centre, which aims to improve local health and wellbeing

**25,000 people visited**
the Crick's Craft and Graft exhibition, which showcased the surprising roles of the institute's technicians, engineers and specialists who work around the clock to make life-changing research possible

## AWARDS IN 2020

**Professor Sir Peter Ratcliffe** and **Professor Charles Swanton** were elected to join the American Association for Cancer Research Academy in recognition of their significant contributions to innovation and progress against cancer

**Professor John Diffley** was elected to the US National Academy of Sciences in recognition of his distinguished and continuing achievements in cancer research

**Professor Markus Ralser** was awarded the EMBO Gold Medal, which recognises the outstanding contributions of young researchers to life sciences in Europe

**Dr Pontus Skoglund** received the Vallee Scholar Award, which recognises outstanding early career scientists conducting original and innovative work

**Professor Francois Guillemot** was elected to the Royal Society, the world's oldest independent scientific academy dedicated to promoting excellence in science

# A YEAR OF DISCOVERIES

## JAN 2020

New research by Professor Peter Cherepanov and his team uncovers the mechanism that HIV uses to become resistant to a widely prescribed group of drugs. The findings open the door to the development of more effective treatments.

## FEB 2020

Led by Dr Peter Van Loo and his team, an international collaboration spanning four continents finds that early genetic signs of cancer can appear decades before diagnosis. Developing tests for these genetic signs could provide new ways to spot cancer early.

## FEB 2020

A collaboration between Dr Vassilis Pachnis and Professor Gitta Stockinger finds that micro-organisms in the gut support healthy digestion by helping nerve cells within the intestine to regulate the contraction and relaxation of the gut wall. These findings could have implications for intestinal disorders, such as irritable bowel syndrome.

## MAR 2020

A new study by Dr Luiz Pedro Carvalho and his team shows that a key antibiotic widely used to treat drug-resistant tuberculosis does not work as expected – a finding that could be used to develop new drugs.

## MAR 2020

Dr Pontus Skoglund and his team publish the most comprehensive analysis of human genetic diversity to date after sequencing 929 genomes from 54 diverse populations across the globe. The findings shed light on the history of human evolution and reveal variations in DNA that might be linked to susceptibility to disease in particular populations.

## MAR 2020

Professor Andreas Schaefer and his team develop a new method to accurately record and stimulate brain activity. The technique could lead to new medical devices to help amputees or people with paralysis or neurological conditions, such as motor neurone disease.

## APR 2020

A new study by Dr Silvia Santos and her team identifies the point when stem cells in the human embryo irreversibly commit to becoming a specialised cell type, such as a brain, heart or liver cell. Understanding this process provides insights into diseases where cells forget what type of cell they should be, such as cancer.

## MAY 2020

The journal *Nature* features all eight of the TRACERx team's published papers in a special edition – each one shining a light on previously opaque areas of understanding. Led by Professor Charlie Swanton, the TRACERx study is already changing the way we view lung cancer, leading to new clinical trials and research projects aimed at tackling these hard-to-treat tumours.

## JUN 2020

Research by Dr Andreas Wack and his team finds that a protein that's initially helpful in the body's immune response to a virus can later interfere with the repair of lung tissue. The work highlights the need for careful consideration regarding the use of this protein to treat viral infection, including that caused by SARS-CoV-2.

## JUL 2020

A new study by Dr Steve Gamblin and his team characterises the structure of the spike protein on the surface of SARS-CoV-2, the coronavirus that causes COVID-19, as well as its most similar relative in a bat coronavirus. The structures provide clues about how the spike evolved and could help inform vaccine design.

## AUG 2020

Professor Adrian Hayday and his team identify three immune signalling molecules in the blood of people with COVID-19 that could be used to predict how severely ill they will become, aiding patient management.

## SEP 2020

Dr Vivian Li and her team report their success in growing mini versions of the human intestine in the laboratory using stem cells from patient tissue. This technique could one day lead to personalised transplants for children with intestinal failure.

## SEP 2020

Dr Steve Gamblin and his team show that the spike protein on the surface of the SARS-CoV-2 coronavirus can adopt at least 10 distinct structural states when it comes in contact with the human virus receptor ACE2. This new insight could inform studies into vaccines and treatments.

## OCT 2020

Research from Professor Victor Tybulewicz and his team reveals that signals from two key proteins are essential for the survival of our 'immunological memory'. This insight could help with the development of future vaccines and treatments for disorders of the immune system, such as autoimmunity.

# THE CELL CYCLE LABORATORY

As you know, Paul and his team study the cell cycle – a carefully orchestrated sequence of chemical reactions in which one cell copies its DNA and divides into two. This process is the basis for the growth and development of all organisms – from the largest mammals down to single cell organisms, such as *Schizosaccharomyces pombe (S. pombe),* the yeast model that has been at the heart of Paul's award-winning scientific career for decades.

This year has been incredibly eventful for the Crick. When the COVID-19 crisis hit the UK in March 2020, Paul and his colleagues took the decision to repurpose some of the institute's laboratory space into a virus testing facility, a transformation which took place in less than a fortnight. For over seven months, they have been working with University College London Hospitals Trust and their diagnostic partner, Health Service Laboratories, to test NHS staff and patients from 10 London hospitals, the London Ambulance Service and 150 care homes across the capital. Currently, they are carrying out 10,000 tests a week, with samples going through the pipeline in eight hours and test results returned in 24 hours – and they have plans to at least double this in the near future.

In parallel, Paul oversaw the establishment of a new COVID-19-related research effort, in which Crick researchers working across disciplines – including infectious disease, virology, immunology, molecular biology, computer science and genetics – united under the common goal of increasing our understanding of COVID-19 and the virus that causes it, SARS-CoV-2, in order to uncover ways to combat the pandemic. Paul's PhD students were among the volunteers who joined this research effort, as we report below.

Despite this upheaval, Paul and his team have still made great progress in their research into the cell cycle, with several new discoveries made and papers published. What's more, in September 2020, Paul published a book for the general public titled *What Is Life? Understand Biology in Five Steps*, an absorbing and accessible exploration of five key ideas that form the basis of biology. The book has received critical acclaim, including from physicist and science communicator Brian Cox, who described it as "a beautifully written exploration of perhaps the most important question in science".

Below we share some of the progress from the PhD students and recent graduates in Paul's lab, both in unravelling the mysteries of the cell cycle and in supporting the Crick's COVID-19-related research efforts.

# THE NURSE LAB PHD STUDENTS – TACKLING COVID-19 TOGETHER

When the COVID-19 pandemic first struck the UK in March 2020, the Crick was forced to temporarily shut down its usual research activities, including the cell cycle work underway in Paul's lab. But the institute and its population of exceptional biomedical researchers saw an opportunity to apply their strengths to the urgent challenge posed by COVID-19. More than a hundred Crick researchers from across disciplines pivoted their focus to the virus, with the aim of finding better ways to test for it, treat it and stop it spreading.

All six of Paul's PhD students – Emma, Clovis, Joseph, Theresa, Saz and Tiffany – eagerly volunteered their time and skills to help with COVID-19 research at the Crick. "Paul was very supportive and encouraged us to help where we could," Clovis comments.

The students teamed up with Professor John Diffley's lab, situated just next door to the Nurse lab, who are experts in DNA replication and study the protein 'machines' that carry out this process. When the pandemic hit, John realised they could use their experience in purifying proteins to find new ways to tackle the virus.

The genetic code of SARS-CoV-2 contains instructions to make around 15 proteins, which carry out tasks crucial to its survival and spread. John and his team planned to purify the virus proteins and test an existing library of more than 5,000 drugs on each one to identify agents that disrupt the protein's function. This information could then be used to develop new drugs to tackle COVID-19.

Members of John's lab helped to train the Nurse lab students in the techniques they needed to purify and test the activity of the virus proteins, then each student took responsibility for working with one protein. "We got to know John's lab really well," says Theresa. "It felt like the spirit of the Crick – everything was really collaborative." Excitingly, several of the students successfully identified chemical compounds that blocked the function of the virus proteins.

Once their experiments were finished, John's team and the students passed the project along to Crick group leader Dr Rupert Beale and his lab, who are testing these drugs further in cells infected by the virus to examine whether they can tackle the infection in a living cell. John, Rupert and their teams are now working to publish the results in several academic papers, which will feature the Nurse lab students as co-authors.

"It was really interesting and I learnt a lot working with them," Emma comments. "It's really good to have a chance to get all this training in a different project just for a short amount of time and work with people who are in a slightly different field to us and so might think differently."

In addition to working in John's lab, Saz volunteered to work on the Crick's SARS-CoV-2 testing pipeline. In this role, he learned how to process sample swabs in a containment level 3 facility – a laboratory specially designed to contain dangerous infectious pathogens. He helped the team to process thousands of samples, preparing them for the high-throughput screening robots that would carry out the next steps in the testing procedure.

From May 2020, Crick researchers were able to return to the institute and resume their usual research, alongside the continuing COVID-19-related research efforts. This re-opening was significantly more rapid than many other institutes, many of which are still only able to operate at a low capacity. The Crick is now able to operate safely and confidently at nearly full capacity, largely thanks to its virus testing service, which provides weekly tests for all staff to help identify any infections and stop the spread of the virus through the institute.

# PROGRESS IN THE NURSE LAB PHD PROJECTS

## EMMA ROBERTS
*4TH YEAR PhD STUDENT*

Emma is now entering the fourth and final year of her PhD project in Paul's lab. As you may remember, her project focuses on a molecule called CDK – the master regulator of the cell cycle that has been at the centre of Paul's research since the 1970s. Emma wants to understand how the location of this molecule within the cell is tied to its ability to orchestrate the complex process of cell division.

During normal cell division, CDK goes to a structure within the cell called the microtubule organising centre, which controls the cell's internal scaffolding system. This scaffolding maintains the cell's shape and helps to pull it into two parts when it divides. Working with Saz, Emma studied the fission yeast *S. pombe* with a genetic fault that stops CDK from going to the microtubule organising centre. Interestingly, they found that CDK didn't work as normal when it's in the wrong place due to the genetic fault, and that these cells were unable to divide.

While Paul and his lab do most of their work in *S. Pombe*, Emma also studied human cells to see whether their findings held true within our own bodies. Although yeast and humans diverged from a common evolutionary ancestor around one billion years ago, Emma confirmed that a similar process occurs at the microtubule organising centre in human cells, illustrating what a fundamental part the same cell cycle processes play across a large proportion of life on earth.

In March 2020, Saz and Emma successfully published these results in the journal *Current Biology*. "That was quite a big thing for me because it's the first paper I've ever had published!" says Emma, who is now finishing off her experiments to complete her story about CDK. She will then shift her focus to writing her thesis in the coming months.

Having thrived during her time at the Crick, she is keen to continue her journey as a biomedical researcher. "The Crick has been a pretty amazing place to work. If you're not an expert in something, you can go and find someone who is, and I think that has been absolutely brilliant here," she explains. "I really love science and I'm hoping that I'll go into a postdoc after this."

# CLOVIS BASIER

*4TH YEAR PhD STUDENT*

Clovis is also entering the fourth and final year of his PhD in Paul's lab. He is continuing to explore the question of how cells maintain the right size and how they manufacture the right quantities of internal components as they grow and divide.

Every second, our cells are mass manufacturing proteins – crucial molecules that perform a vast array of functions. When the cell needs to make a protein, it first makes a copy of the instructions written in its DNA by making a matching molecule called RNA – a process called transcription. These RNA molecules then travel to protein-making factories called ribosomes, which manufacture the protein according to the RNA's instructions in a process called translation.

Clovis is studying how cells change the amount of transcription and translation they do to ensure they are manufacturing the perfect quantities of different proteins to enable them to function properly as they grow. As you might remember, Clovis was using a technique called flow cytometry to examine transcription and translation in thousands of individual yeast cells. In the past year, he has also been using microscopy to capture pictures of individual cells at different stages in the cell cycle using a special fluorescent dye that marks newly made RNA molecules and newly made proteins, which he can see and measure down the microscope. This allows him to determine how much transcription and translation is happening in cells at different stages of growth and division.

The results of the experiment surprised Clovis. There are currently two conflicting theories in the field regarding levels of transcription: one that they increase gradually as cells grow, and another that they increase suddenly when cells copy their DNA. "But what I found is that it's a bit of both," Clovis explains. "It's still unclear why. And it's the same for translation, which is even weirder. I don't think anyone would expect that! That's something I'm trying to understand now."

Clovis says that the supportive environment at the Crick has been crucial to his success and enjoyment of his PhD so far. "I think it's a very encouraging environment to do science, and to think and ask questions in general," he comments. "I don't think many people have the luxury of looking forward to going to work every day, so I'm thankful for that."

# JOSEPH CURRAN

*2ND YEAR PhD STUDENT*

Joseph is now entering the second year of his PhD in Paul's lab. His project focuses on a mysterious protein called SUC1, which was discovered by Paul's first PhD student in the 1980s and plays a crucial role in the cell cycle – but we still don't know exactly what it does.

What we do know is that it interacts with CDK – the master regulator of the cell cycle – and seems to be incredibly important to normal cell function. "It's essential," Joseph explains. "If you get rid of it, cells die. So I'm trying to understand what it does and why it's essential." Joseph thinks that SUC1 might be playing multiple roles, which could explain why its function has been so difficult to pin down.

Because SUC1 is so essential, researchers can't use the common approach of deleting its gene from the cell to see what happens, as the cells die almost immediately. Instead, Joseph is working with a temperature-sensitive form of SUC1 in yeast, which functions normally when the cells are grown at 25°C, but stops working at 36°C. This means that Joseph can increase the temperature of the yeast to rapidly deactivate SUC1, enabling him to see how the cells respond without instantly killing them. He is also testing systems that use a particular drug to switch the gene for the protein on or off in yeast and hopes that these tools will enable him to uncover details about SUC1's function that have so far eluded other researchers.

So far, Joseph has theories about the true function of SUC1 that he is eager to test: "It would be interesting if it did multiple things at different times in the cell cycle," he says. "It might be regulating the process in a way that we don't quite understand yet."

Joseph is particularly glad Paul encourages him and the other PhD students to explore their ideas and try new things. "I really like the freedom that Paul gives you to be independent – at least when you want to be," he comments. "Paul never says 'you absolutely must do this experiment', instead he says 'you can think about this and you can try this'. When I have an idea, I'm free to try it, which is different to other labs I've been in."

# THERESA ZEISNER

*2ND YEAR PhD STUDENT*

Theresa is also entering the second year of her PhD in Paul's lab. As you may remember, she is interested in how a class of molecules called phosphatases are involved in the cell cycle.

One of the main ways that our cells turn proteins on or off is by adding a tiny molecule called a phosphate to them, which acts like a switch to change a protein's function by activating or deactivating it. One class of enzymes – kinases – attach phosphates to proteins, whereas an opposing class – phosphatases – take the phosphates off again. Together, these molecules work as conductors to orchestrate events inside cells, switching key cellular programmes on and off. It is an incredibly intricate and carefully controlled process that involves hundreds of different kinases and phosphatases performing countless reactions each second.

One kinase of special interest to Paul's lab is CDK – the cell cycle's master regulator. While we know a lot about how and when CDK adds phosphates to different proteins involved in the cell cycle, Theresa is interested in the interplay between CDK's effects and phosphatases in the cell. She thinks that phosphatases might help to control the timing of when different processes are activated within the complex sequence of events that make up the cell cycle. "We still don't know how this timing is achieved – how the master regulator ensures that everything is activated at the correct time and then initiates the very different processes of genome duplication and then cell division," Theresa explains.

This year, Theresa studied *S. Pombe* cells with faulty versions of different phosphatases and has identified a number that lead to problems with the cell cycle, suggesting they play an important role in the process. She's now working to expand on these findings with the help of Andrew Jones, a senior laboratory research scientist in Paul's lab who is an expert in a technique called mass spectrometry. This technique will enable her to take a kind of molecular snapshot of cells at different stages of the cell cycle to see which proteins have phosphates attached to them and which don't, giving a birds-eye view of the entire process.

Looking back on the first months of her PhD, Theresa is thankful for the support that Paul and the rest of the lab have given her to help get her project off the ground. "Paul was always there to talk to, especially at the beginning when I was finding my project," she says. "Everyone in the lab has been really incredible with teaching me different experiments."

# SAZ BASU

*GRADUATING PhD STUDENT*

After completing the fourth year of his PhD, Saz has now written and submitted his thesis and will undertake his viva in December 2020 – a final rite of passage where he will need to engage in an intense discussion of his work with respected experts in the field.

Saz is fascinated by the cell cycle and is studying how CDK controls this complex process. As you have read, he and Emma worked together to publish a paper in March 2020, which explored how the location of CDK within the cell was important for cell division. "It was a real highlight when we managed to publish that paper," Saz recalls. "It's my first lead-author publication and it meant a lot that my research was accepted and that the peer reviewers commented that it was a good quality piece of work."

In addition to his work with Emma, Saz has been studying how CDK is able to control two separate, yet equally complex processes within the cell cycle: replication of our DNA and cell division. To carry out its role, CDK forms partnerships with a class of molecules called cyclins, which act like specialised adaptors for CDK and help it to carry out different functions. The conventional view in the field is that cyclins are very different from one another and cannot perform each other's jobs – for example, a cyclin that helps CDK control DNA replication cannot also help it initiate cell division.

Saz set out to understand what made these cyclins different, but his experiments revealed an unexpected result. "What I found is that actually they are incredibly similar, which is really surprising," he explains. "It suggests that there's some adaptability within the system that we didn't really understand or expect." Saz found a way to make cyclins that normally appear early in the cell cycle, when DNA replication is due to happen, instead appear later when cell division was due to occur. Intriguingly, he found that these out-of-place cyclins could assist CDK in initiating cell division, therefore carrying out a completely different role to normal.

"This has implications for our understanding of disease as well," Saz comments. "It suggests that there might be multiple pathways to a disease such as cancer, where the cell cycle spirals out of control. Because if many things can do the same job, then many things can malfunction and lead to disease."

Saz now has plans to submit his results as two new papers. After an intense year of finalising his experiments, writing his thesis and helping with the Crick's COVID-19-related research, he is as passionate about science as ever and says that he cannot wait to get back into the lab. "In the front of my thesis I have an acknowledgement to Paul, thanking him for making his lab a place I always wanted to be," he says. "The past four years have been an absolute treat."

# TIFFANY MAK

*GRADUATING PhD STUDENT*

Tiffany passed her PhD viva in December 2019. "I was surprised – it seems weird, but I really enjoyed it!" she recalls. "Everyone's nervous for their viva – you're going to be grilled for three hours straight! But it was really nice being able to discuss my work with two people in the field who have been thinking about similar problems for a really long time. They were very engaged and complimentary of the approach I took, which was really nice."

After her viva, Tiffany returned to Paul's lab to conduct some final experiments to complete a paper she plans to submit. As you might remember, her project explored the complex network of interactions that cells use to control their growth. She has particularly focused on a protein called TOR, which sits at a major crossroads in this network of interactions and integrates inputs from lots of different sources to control cell growth – for example, carrying information about the cell's oxygen and nutrient levels.

As proteins make up a large proportion of cells, Tiffany is interested in how cells adapt the amount and types of protein synthesis they perform depending on cell growth. She added inhibitors that blocked part of the cell growth network involving TOR and then examined the effect on the rest of the network over time, generating a vast amount of data describing what happened to protein synthesis across the entire cell – including which types of proteins were affected and how rapidly these changes took place. Now, she is planning to publish her dataset as a valuable, accessible and useful resource for the rest of the scientific community to reference. "Over the years, I've taken some programming courses and after talking to a few people, I realised I could develop a tool that visualises the data," Tiffany explains. "Eventually, I wrote a mini application to go along with my data to make it easier for people to use."

Tiffany is now looking towards the next steps in her scientific career and would like to continue her journey in academia as a postdoctoral researcher. After four years embedded in the Crick's culture of cross-disciplinary working and collaboration, her ambition is to switch fields and apply the skills she has learned in Paul's lab to an entirely new challenge. "There are many things I have learned that I can apply to other problems," she says. "I've been analysing how this whole, closed system within a cell works. But I've always been interested in questions about the environment and sustainability – you can think of our world as a closed system, it's just a matter of scale. I'd really like to work on multispecies interactions – like how microorganisms in the soil interact with plant roots and then influence the rest of the ecosystem. So I think that's where I'm going."

# THANK YOU

## We hope this report leaves you feeling inspired and motivated by the scientific advances being made by Paul and his team, which you are helping to drive.

COVID-19 aside, we have never seen such a rapid pace of progress. This is all thanks to the Crick's distinct environment: the focus on excellence, the availability of state-of-the-art technology and facilities, the convergence of disciplines, the emphasis on collaboration and the translational ecosystem.

The pandemic has impacted biomedical research in significant and dramatic ways, and yet its importance has never been more evident.

Thank you for your ongoing commitment to the Nurse laboratory and to biomedical endeavour.

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