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# THE FRANCIS CRICK INSTITUTE

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PREPARED FOR LORD LEONARD AND LADY ESTELLE WOLFSON FOUNDATION

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## THANK YOU FOR YOUR SUPPORT

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Without the support of visionary donors like you, the Francis Crick Institute would not be the success it is today. Since the Crick officially opened its doors just three years ago, we have gained a major international profile and we are making good progress in our bid to become one of the world's best research institutes.

In this report, we are pleased to share the news from the Cell Cycle Laboratory and the students you are generously supporting.



Sir Paul Nurse  
Director, Francis Crick Institute

Together we will beat cancer



# THE FRANCIS CRICK INSTITUTE: DISCOVERIES THAT CAN CHANGE THE WORLD

For almost three years, Crick researchers have profited from the institute's state-of-the-art facilities and highly collaborative environment. The Crick brings together the world's best scientists, regardless of discipline, and gives them the space and creative freedom to make discoveries with potential to change the world. By breaking down barriers between disciplines and connecting diverse fields of expertise, the Crick aims to accelerate progress in addressing fundamental questions about human biology to prevent, diagnose and treat disease.

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## HIGHLIGHTS AND ACHIEVEMENTS TO DATE

### 1,946 research papers

have been published, noting new discoveries and ideas that could transform the way we approach disease.

### Nearly 1,000 applicants

for group leader positions since the Crick opened. This past year, three early-career group leaders were appointed from 304 applicants.

### 2/3 of Crick's research labs

now engage in translational activities to help accelerate discoveries into clinical interventions. 62 new projects with pharmaceutical and biotech firms have emerged and the Crick has supported the development of six spin-out companies, three of which are developing novel cancer therapeutics.

### Nearly 20,000 schoolchildren

have learned about science and careers in STEM (science, technology, engineering and mathematics) through the Crick's education programme in the past year alone.

### Over 11,000 people

have used the St Pancras and Somers Town Living Centre, which aims to improve local health and wellbeing. The centre is the first new community space in 15 years in what is one of London's most deprived areas.

## AWARDS

Over half of the Crick's senior group leaders are Fellows of the Royal Society and Academy of Medical Sciences. Senior faculty regularly receive some of the world's most prestigious prizes to recognise outstanding contributions to their field.

- **Peter Ratcliffe**

Just last month (October 2019), Director of Clinical Studies, Peter Ratcliffe, was awarded the Nobel prize in Physiology or Medicine for his contributions to understanding how cells sense and adapt to the availability of oxygen. The Crick now counts four Nobel Prize-winners on its faculty.

- **John Diffley**

Earlier this year, John Diffley won the prestigious 2019 Canada Gairdner International Award for his pioneering research which has advanced our understanding of DNA replication. Many scientists who have previously won this prize have gone on to win a Nobel Prize.

- **Caetano Reis e Sousa**

Crick scientist Caetano Reis e Sousa – whose exploration of the immune system aims to contribute ideas for better vaccines and cancer therapies – has become the eighth member of the staff to receive the prestigious Louis-Jeantet Prize for Medicine.

## THE CELL CYCLE LABORATORY

Cell division is the act of one cell, the biological unit of all organisms, becoming two during a heavily regulated process called the cell cycle. This process of cellular reproduction underlies much of life as we know it. The goals of Paul Nurse's laboratory are to understand the networks within cells that control the cell cycle and the growth and shape of cells. These cellular controls are fundamental to the development and reproduction of all living organisms – from the single cell organism *Schizosaccharomyces pombe* (*S. pombe*), which has been at the heart of a number of groundbreaking developments in Paul's laboratory, to multicellular organisms such as humans.

Paul's work has helped to lay the foundation of our current molecular understanding of cancer, which is now thought of as a condition in which these cellular controls are defective, leading to unrestricted proliferation and spread of cells through the body. This work has been built over decades of research – in many cases driven by PhD students in Paul's laboratory.

### AN ENVIRONMENT IN WHICH TO FLOURISH

An important aim of the Cell Cycle Laboratory, and something that you've been kindly supporting throughout the years, is to train and develop the next generation of researchers – to give them the tools and resources to tackle complex scientific questions combined with the freedom to grow into independent, curiosity-led scientists. This all starts with Paul encouraging newly arrived PhD students to explore scientific questions and areas they find fascinating, as long as they are within the realm of the laboratory's interests. Though not always an easy feat, this process gives students the opportunity to drive, shape and take ownership of their projects at an early stage, with Paul's guidance. It allows students to develop the skills that equip them to become successful scientists, laying the foundations for future pursuits and perhaps preparing them to run their own laboratories one day.

Saz Basu, who is most of the way through his PhD studies, comments:

"We're independent but we have Paul's support, so even if our idea could be refined, it's still an idea that we've had independently and it's something that Paul will help us build on. The fact that it is intrinsically ours means that we all care about it a lot more. And I think that is something that Paul does really well – he always encourages individual thought and choosing a project that really inspires you as a person."

Interestingly, this approach also makes for a dynamic, fascinating and collaborative research environment in which students flourish. PhD students often have different interests. Some are driven by their curiosity to explore broad scientific concepts, which allows them to refine and shape their projects. Others are motivated by using a particular approach or technique – for example, one that may leverage their quantitative skills – which then guides them towards finding a scientific question to explore. This variety allows a diverse set of research projects to be carried out simultaneously in the lab, supported by wide-ranging tools and technologies, and it creates a strong peer group that feeds the students' enthusiasm, keeping them motivated through the challenges that are inevitable in any project. Although everyone works on their individual project, scientific paths often cross through shared data or techniques, allowing students to build on each other's success and head off in new directions. Paul's laboratory truly encapsulates the Crick's ethos.

While supporting the new generation of scientists and running an exciting research programme, Paul is continuously recognised for his wider contributions to science. In just the past 12 months, he has received numerous awards. These include becoming a Fellow of Goodenough College and receiving: the Capo d'Orlando Prize; the Order of the Rising Sun, Gold and Silver Star; the Duvel Moortgat Prize; the Genetics Society Centenary Medal; and an Honorary Degree from Rockefeller University.

Below we share some of the progress and work of the six PhD students currently in Paul's lab who are at different stages of their studies – some having just started and others about to graduate.

## 1ST YEAR PHD STUDENT THERESA ZEISNER

Theresa is one of two new PhD students starting in Paul's lab this year. Originally from Bremen in Germany, she studied Natural Sciences and Biochemistry at the University of Cambridge before moving to the Crick to begin her PhD. Her longstanding interest in the biology that governs how cells divide naturally led her to apply for a position within Paul's lab.

"I think it's an immensely fascinating phenomena, how cells divide," remarks Theresa. "It's a really fundamental problem in biology that we still haven't fully understood, so I've always wanted to go in that direction."

At this early stage in her project, Theresa is working to define the direction that her PhD research will take over the next four years. "One of the things that is really great about Paul's lab is that he gives you so much freedom to choose your own project," she explains. "Paul wants you to explore what you're really interested in. Having that freedom at the beginning to really take control of your own project is a great feeling."

Theresa is currently most interested in how a class of molecules called phosphatases are involved in the cell cycle. These molecules work as conductors that orchestrate events inside cells, switching key cellular programmes on and off. But it isn't clear how phosphatases know how to turn particular processes on or off at the correct time within the intricate sequences of events that control the cell cycle. What's more, humans have around 200 different types of phosphatases, all of which control different cell functions, creating an incredible degree of complexity.

To examine this intricate process in a simple system, Theresa is studying how phosphatases control the cell cycle in *S. pombe*. She's looking at how switching off the genes for each of the different phosphatases in this organism affects its shape and size – information that will give her clues about how each molecule affects the cell cycle. She can then identify which phosphatases have the most interesting effects and design further experiments to study these in more detail.

So far, Theresa is excited to be in such a collaborative and supportive environment at the Crick. "It's great," she says, "Even though Paul obviously has so many things to do, he always takes the time to check-in with me to see if I'm generally happy in the lab, and if he can help with anything. All the members of the lab help me so much. I think it's a very supportive environment."

## 1ST YEAR PHD STUDENT JOSEPH CURRAN

Joseph is the second new PhD student starting in Paul's lab this year, having recently completed his master's degree in the Laboratory of Molecular Biology at the University of Cambridge. With multidisciplinary research interests spanning biology and engineering, Joseph describes himself as a 'molecular tinkerer'.

"I'm a biochemist by training but I like to develop little tools, like biosensors or neat little systems that allow you to study very precise biological processes without disrupting the system too much," Joseph explains. He is planning to use this approach to study how a tiny molecule in *S. pombe* called SUC1 affects cell division. Interestingly, this molecule was discovered by Paul's first PhD students and now years later Joseph is interested in building on that work. Researchers know that this molecule has an important impact on cell division, but so far no one has been able to understand how it works. "SUC1 is this tiny little molecule that appears as though it could be really inconsequential, but it turns out to be absolutely essential for cells to survive and grow," says Joseph, "So the question is: what's it doing?"

By switching off the gene that manufactures a particular molecule, researchers can examine how the cell acts without this molecule to gain clues about its role. The problem with SUC1 is that cells die when its gene is switched off, so its function remains a mystery. Rather than completely eliminating the gene, Joseph is looking for ways to more subtly compromise the activity of the protein so that he can determine its role without killing the cell.

The Crick's vision to encourage collaboration and innovation that defies the boundaries of conventional disciplines provides an ideal environment for students like Joseph who want to try new and creative approaches. "I like how open and collaborative it is at the Crick. People talk a lot and it's a very friendly environment," Joseph comments. "As a result, it feels possible to set up discussions and collaborations with experts in a wide range of disciplines, which is a very exciting, innovative and productive way to do research."

Joseph says that he is most excited about the freedom that being a PhD student in Paul's lab affords him. "I like Paul's group a lot," he remarks. "Everyone is really nice and the atmosphere is great and really productive. It's supportive rather than pressured. Paul is quite open – if you have an idea, I can't see him saying no unless it's really, really expensive! So I have the freedom to try cool things."

### 3RD YEAR PHD STUDENT CLOVIS BASIER

Clovis has just started the third year of his PhD studies. Coming from a physics and mathematics background, he completed his earlier scientific training in France and later carried out research in the US. Driven by his interest in systems biology – an approach to understand the big picture of biological phenomena by thinking about how all the pieces of a problem fit together rather than by taking them apart and studying them individually (a reductionist approach) – he was able to identify the perfect project to explore in Paul's lab.

Clovis is exploring scaling: how do cells maintain the right size? Cells that are too small or too big develop problems. In order to understand how cells maintain the right size, it's important to study how they grow and how they produce the right amount of their internal components as they get bigger. For example, if cells double their size, do they simply double the amount of their components?

The central dogma in biology states that DNA is used to make RNA, which is used to make protein molecules, the molecular building blocks of the cell. Despite the formulation of this dogma more than a century ago, we still don't know how the amount of protein or RNA scales with the amount of DNA. Because the number of copies of each gene doubles during the cell cycle, Clovis is using it as a way to test whether doubling the amount of DNA causes a doubling in the amount of RNA and protein.

Excitingly, Clovis' project builds on research published by Paul himself in the 1970s. This subject is something that few have been able to tackle since then, owing to limitations in the tools and technologies available. But during the first half of his studies, Clovis has been able to develop an impressive system that allows him to measure the rate of production of all RNA in a given cell by using an extremely sensitive technique called flow cytometry. This technique enables him to study single yeast cells – up to 400,000 in a given experiment – and monitor their size, amount of DNA and amount of RNA simultaneously.

"Being at the Crick is a big advantage – firstly, because being in a fission yeast lab that has been in the field for so long means that we have a collection of yeast strains at our fingertips," Clovis explains. "And the imaging machine that we have in house is very useful. There are very few places that have this kind of flow cytometer that you can use for imaging yeast. It's really convenient. I don't have to wait to do my experiments, I can just try something, pick the yeast strain, try it and see what happens."

Moving forward, Clovis' goal is to use his quantitative skills to model and test this biological problem of scaling using computational tools – linking back to his interest in systems biology.

### 3RD YEAR PHD STUDENT EMMA ROBERTS

Emma has also just started the third year of her PhD in Paul's lab. Her project is examining how the location of particular molecules within the cell is important in the cell cycle and what happens if these molecules end up in the wrong place.

Cells are not simply tiny bags of molecules; they contain a complex system of different compartments, tubes and mini-organs known as organelles. Each of these components carry out different specialised tasks and require a very specific subset of molecules to perform these functions. If important molecules end up in the wrong place in the cell, it can cause major disruption to fundamental cell functions such as cell division.

"When I started, I knew I wanted to work on the cell cycle, but I did a lot of reading, and got really interested in localisation," Emma explains. "I'm looking at the localisation of one of the main master regulators of cell division, called CDK."

Emma is particularly interested in a cell structure known as centrosomes in humans, which are critical for organising the internal skeleton of cells, particularly during cell division, when they help pull DNA into opposite sides of the cell as it divides into two new cells. A similar structure is found in *S. pombe*, and Emma is studying a type of *S. pombe* cell with a genetic fault that prevents CDK from getting to the centrosome. Interestingly, these cells are unable to divide, but it isn't clear if this defect is due to the incorrect location of CDK or another unknown factor. To solve this question, Emma is genetically modifying these cells to add a molecular chain that will shackle CDK to the centrosome. This method should reveal whether forcing the molecule back into its proper place enables the cells to divide again.

This work requires sophisticated microscope techniques to examine the internal structures of cells in exquisite detail. Fortunately, Emma has access to expert technical advice through the Crick's Microscopy Science Technology Platform (STP). "I hadn't had much experience in microscopy and I use it very heavily in my PhD, so I learnt a lot from the Microscopy STP here," Emma explains, "You can just go to the STP and they can give you training and help you out with your particular experiment. It opens up a wider range of experiments that you can do."

#### 4TH YEAR PHD STUDENT

### SAZ BASU

Saz is in the final year of his PhD in Paul's lab, with just a year left to complete his experiments and finish writing his thesis. He is fascinated by the cell cycle and a firm believer of the importance in gaining a deeper understanding of this process to unlock new insights into human health and disease. "Our understanding of how one cell becomes two effectively underpins our understanding of, I'd say, about 99% of biology," Saz remarks. "It's a really important problem because so many diseases result from a defect in cell division – the primary one being cancer, which is uncontrolled cell division."

Saz is studying the molecule CDK – a master regulator of the cell cycle. He wants to understand how this molecule is able to control two separate yet equally complex processes within the cell cycle: replication of our DNA and cell division. "How has life evolved this Swiss army knife of machines? That's my question," says Saz.

Previous research has shown that CDK can form partnerships with a class of molecules called cyclins. These molecules come in many different types, and act like specialised adaptors for CDK, helping it to carry out different functions. But it's still unclear how these different cyclins affect how CDK works.

Saz's approach to this problem is to use sophisticated genetic engineering techniques in *S. pombe* to force the cell into unusual situations. This tactic enables him to tease out how the biology is working and what its limitations are. For example, his experiments have included switching off the genes that manufacture different cyclins, or permanently welding a particular cyclin to CDK.

These experiments revealed that cyclins work in two different ways: they can control which other molecules CDK interacts with, and they also can affect the location CDK inhabits within the cell. Together, Saz and Emma have written a new paper describing their insights into the biology of CDK, which is currently in the final stages of review at an academic journal.

Saz is now looking towards the next steps in his scientific career and reflecting on the value of his time spent at the Crick. "I worked at other institutes before here, but the Crick is a completely different beast entirely," he explains, "Science is rapidly changing from an individual pursuit to one that requires collaboration, and I think that the Crick really addresses the science of the future in that way."

#### 4TH YEAR PHD STUDENT TIFFANY MAK

Having submitted her thesis recently, Tiffany has just completed her PhD studies and will have her viva in December.

Her project has revolved around the understanding of cellular growth control, with a particular focus on the regulation of protein synthesis within a cell. 60% of a cell is made up of proteins, accounting for the largest proportion of dry mass within a cell. At the same time, cells are subjected to constantly changing external environments, and therefore it is important for them to be able to respond to signals to coordinate protein synthesis as a means of growth control. They have evolved programmes that coordinate these processes and Tiffany has been studying the molecular events and the timings of events associated with such processes.

She has focused on a molecule called TOR – a major regulator of growth in both yeast and mammalian cells. When TOR is shut off, it signals the cell to stop growing and Tiffany wants to understand what happens during this process. Her aim was to figure out precisely how and in what order the creation, destruction and activation of proteins changes when she switches off TOR. In this way, she systematically mapped how the cell implements the decision to stop growing. Tiffany plans on staying in the lab for another year to write up her findings in scientific papers and present her work at conferences.

In addition to her PhD research, being at the Crick opened the door for Tiffany to get involved with a number of inspiring projects outside the lab. "It's not only the Crick's research that makes the institute an exciting place, it's also having the opportunities to get involved with science beyond the bench," Tiffany comments. "For example, I undertook a short internship in the policy development team at CRUK, which was eye opening and made me realise that I should be more proactive in giving my opinion because informed policy benefits from scientists' involvement.

"And within our institute, I've been involved with the Crick's education team by helping out with a genetic engineering workshop that's offered to 16-17-year-old students in Camden in our dedicated teaching lab. I then hosted a student for a short period of time in our lab who had attended the workshop and found it inspiring. It's nice to see how as PhD students we can also encourage the next generation to pursue science. That's very important to me, especially encouraging women in science, so it's great to be part of the Crick's efforts in this area."

# CREATING THE FUTURE

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On behalf of the Francis Crick Institute, thank you very much for your continuing friendship and ongoing commitment to our work.

We are so grateful to have you stand by our side as we create the future science leaders who will go on to change the world, just as Paul has done.

We hope this report leaves you feeling inspired and motivated by the progress being made in the Cell Cycle Laboratory.

Thank you.

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