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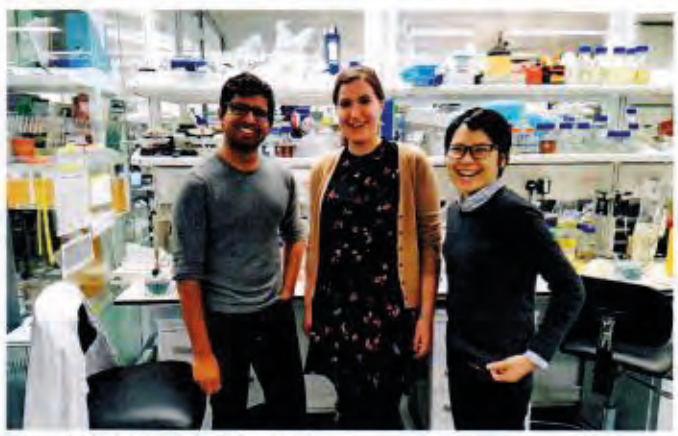
PROJECTUPDATE

PREPARED FOR THE LORD LEONARD AND LADY ESTELLE WOLFSON FOUNDATION

CANCER RESEARCH UK

YOUR IMPACT ON BEATING CANCER SOONER

We are delighted to present you an update on the Francis Crick Institute, in recognition of your generous donation towards our Create the Change campaign for the capital build of the institute. In this report, we will cover the latest Crick news, as well provide an update on the research being conducted by the PhD students you support in Sir Paul Nurse's lab.



Left - Sir Paul Nurse. Bottom right - PhD students Saz Basu, Helena Cantwell and Tiffany Mak in the Cell Cycle Laboratory.

UNDERSTANDING CELL CYCLE CONTROL

It's been a year since the Cell Cycle Lab transferred to the Francis Crick Institute, and life in the lab is as exciting as ever. Following the ground-breaking work of **Sir Paul Nurse** are **Helena Cantwell**, **Tiffany Mak** and **Saz Basu**, all PhD students whose work is supported by your generosity. Here we met up with them to find out how their work is going.

The three students are all deep into their studies on the cell cycle, but at different stages of their PhDs. Saz and Tiffany are entering their second and third year, respectively, while Helena handed in her dissertation on the last week of October. She will stay at the lab for another year, before heading off to either Europe or the United States to complete her postdoctoral studies.

The cycle of cell growth and division is a complicated process that is essential for life, but also fundamental to cancer development. While all three PhD students are investigating how cells grow and divide, they are researching different elements of how it is controlled.

SIZING UP THE NUCLEUS

The cell's DNA, which acts like an instruction manual for the cell during growth and division, is tightly packaged into part of the cell called the nucleus.

For the past three years, Helena Cantwell has been studying the relationship between the size of the nucleus in relation to the total size of the cell. "I've been trying to understand how, as a cell grows, it makes sure that its nucleus is the right size," Helena explains.

"A while ago, I showed that if you have a nucleus that's the wrong size, the cell has a mechanism to correct it, something which had never been shown before. I'm now looking at how and why this happens."

Size matters when it comes to the nucleus of a cell. In healthy cells this ratio is always the same, but in cancerous cells it can differ widely. Cancer cells are known to have larger nuclei, therefore nuclear size has long been used clinically as a diagnostic tool.

We don't know yet whether the enlarged nucleus develops in the early stages of the disease or is a later consequence. However, it has been shown that the cells around a tumour quite often have enlarged nuclei as well, even if they don't have many of the other properties of cancerous cells, so it's quite possible that this happens early on.

> IT IS ESSENTIAL THAT WE UNDERSTAND THE UNDERLYING CORE MECHANISMS BEFORE WE CAN START LOOKING AT THE CLINICAL RELEVANCE BUT IT'S A VERY EXCITING AREA TO BE WORKING ON
>
> Helena Cantwell
> PhD Student, Cell Cycle Lab

TO GROW OR NOT TO GROW

Tiffany Mak is studying the global control of cell growth – cells need to grow, but the process is very tightly controlled to avoid things going out of control. **"Even though cell growth feels like a very simple concept, we don't really know much about the direct cause, whether there is a master regulator or whether there is a host of different networks and pathways that feed into this one signal of a cell deciding to grow or not"** she explains.

Tiffany is using classical genetics to look at this problem, investigating what happens to the process when you get rid of certain genes. She also suspects other molecules within the cell are central to controlling cell growth, and she is using techniques called 'proteomics' to investigate this. By interrupting key parts of the process, Tiffany can see what happens and whether it has an effect on how fast the cell grows – helping her to understand which molecules are the most important for cell growth. Importantly, when cell growth processes get out of control it can lead to complications like cancer, so Tiffany believes her work will have clinical potential in cancer.

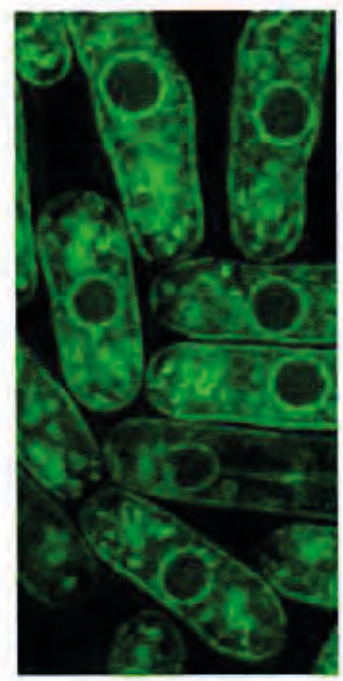
HOW ONE BECOMES TWO

The principle of the cell cycle is how one cell divides into two. Before dividing, first a cell needs to perfectly replicate its DNA, then separate it accurately into two new 'daughter' cells. The order in which that happens is absolutely critical. Saz Basu is focusing on a molecule called CDK1, the 'master regulator' of the cell cycle. His work takes over from former Cell Cycle Lab PhD student, Matthew Shaffer, who found that CDK1 is an enzyme able to control both the processes of DNA replication and then division.

"That's a bit of a problem," Saz explains. **"Normally one enzyme is meant to be associated with one function, they are very highly specialised proteins that can only really do one thing. When you have an enzyme that's able to effectively orchestrate the entire cycle of a cell, there's something really special about it."** Saz's work consists of taking apart little bits of this enzyme to try to figure out how one molecule is able to control both tasks. "Hopefully, with a greater understanding of how this works, we'll move towards a more targeted and rationalised approach to making cancer therapeutics."

All three PhD students carry out their important work in Schizosaccharomyces pombe, the fission yeast used in traditional brewing ("pombe" means "beer" in Swahili). They take very different approaches to their experimentation, and use an array of techniques, such as screening, genetics or proteomics. Saz explains that this is thanks to the fact **"S. pombe is an incredibly powerful model organism to work with. You can basically manipulate its entire genome and it's super easy to do."**

Helena adds that, **"Historically, Paul's lab has had a role in making a lot of the resources for the S. pombe community. We've got a freezer where we have all the S. pombe strains, and in each strain one gene is deleted. We basically have the whole genome of S. pombe pretty much sat in our freezer!"**



Wild type S. pombe cells with lipophilic dye

A VERY SPECIAL LAB IN A VERY SPECIAL BUILDING

An important aim of the Cell Cycle Lab is to train and develop the next generation of researchers, giving them the methods, techniques and reasoning to crack complex problems in cellular and molecular biology and eventually move on to set up labs of their own. "Paul loves PhD students, there are more of us than postdocs in the lab!" laughs Helena. "And it's such a privilege... He sees it as his responsibility to train us and he's obviously an incredible source of knowledge."

Doing your PhD in Sir Paul's lab is quite a different experience from the get-go as well, according to Tiffany. "Paul gives us the liberty to get started without a specific project in mind. We get the freedom of reading, talking to people and trying to come up with a question we're interested in asking. That, in a way, gives you the freedom to have crazy ideas, but also teaches you how to take charge of your own project. We go through a much steeper learning curve than most PhD students."

All three agree that even though this feels slightly terrifying to begin with, they become much more responsible for their work and take special pride in discussing the projects they come up with.

Saz chimes in, "Everyone is very passionate in what they do. And because we're all interested in different things, it gives the lab a breadth of knowledge and experience that's quite unique... Our lab is incredibly diverse in the sort of ideas we have, but they all link together in some way."

And it's the links between different, novel ideas that allow researchers to look at their questions in a new light, encourage them to solve problems in a collaborative way and, ultimately, lead to scientific progress. It's a scientific truism that one of the best ways to have new and innovative ideas is by talking to other people – and, by housing the combined brainpower of over 1200 of the world's brightest scientific minds, the Crick provides the perfect backdrop for this.

"The whole building was conceived around the principle of collaboration and it's true – you do end up chatting and sharing ideas with so many more people than you normally would," says Tiffany. Saz agrees, "Because everyone is here, you're way more likely to go talk to someone somewhere else in the building. At the Crick, you interact a lot more with the labs around you, it's unlike any other place."

But there are also other advantages. According to Saz, "In terms of facilities, it also means everything is under one big building. Having your DNA sequencing in house, your bioinformatics in house, your proteomics and metabolomics in house... It's so conducive to getting your work done, and it's phenomenally good for productivity."

SCIENCE ISN'T FINISHED UNTIL IT'S COMMUNICATED

Communication between researchers is also [illegible] fundamental to the scientific process. The Crick runs an extensive programme of seminars, lectures and symposia designed to enrich the institute's scientific environment, foster collaborative work and encourage the exchange ideas and multidisciplinary research. Together, these events provide an opportunity for the PhD students to share their ideas with other researchers and scientific leaders from around the world. Helena, Tiffany and Saz all agree that it's one of the best things about working at the Crick. "The quality of speakers you can attract with a building this size is phenomenal" says Helena. "There are so many talks and seminars... Every week there's something you really want to go to!"

In terms of communicating their own work to their peers, the PhD students at Sir Paul's lab are a prolific bunch. This year, Helena published her first paper in the prestigious PLoS Genetics journal, and is currently preparing her second one. And former Cell Cycle Lab PhD students, Lizzie Wood and Matthew Swaffer, published three papers each during their time at the lab. Lizzie is now on the NHS Clinical Genetics training programme in Oxford and Matthew is a postdoctoral researcher at Stanford University.

But the PhD students are also aware of the importance of communicating their work and engaging with the general public. "So much funding here comes from charities... When your research is so dependent on people giving money, you have a responsibility to talk about the work that you do" says Helena.

Both Cancer Research UK and the Crick offer them additional training to improve their oral and written communication skills. That way, the students feel better prepared to explain their work and engage, enlighten and inspire people of all ages. Helena continues, "It's our responsibility to encourage the next generation to do the things we're doing. And as woman especially, it's really important that we give girls role models, that we show them they too can be scientists if they want to."

THANK YOU FOR YOUR SUPPORT

"A research institute like the Crick doesn't exist anywhere else in Europe, arguably nowhere else in the world. We are so lucky to be here, we absolutely love what we do," concludes Saz. "Even though our work is quite basic, fundamental research, we really do think it will have a significant impact in people's lives down the line.

That someone like Lady Wolfson has the vision to support the work we do, to support us at the earliest stages of our careers, it means the world to us."

Every step we make to beat cancer sooner relies on the extraordinary donations we receive from people like you. Without you, there is no research. And without research, there are no cures.

"KNOWLEDGE IS OUR MOST POWERFUL WEAPON, AND THANKS TO THE RAPID DEVELOPMENT OF NEW TECHNOLOGIES, THIS IS A TIME OF EXCEPTIONAL OPPORTUNITY"

Iain Foulkes
CEO of Cancer Research Technology & Executive Director, Research & Innovation CRUK

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