

CELL SCIENTISTS TO WATCH

Cell scientist to watch – Hayley Sharpe

Hayley Sharpe graduated from the University of Bath, UK, with a degree in biochemistry. She then joined the laboratory of Sean Munro for her PhD in cell and molecular biology at the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) in Cambridge, UK. There, she investigated the properties of protein transmembrane domains embedded within the organelle membranes of the secretory pathway. She next moved to San Francisco, USA, for postdoctoral work at Genentech, where she studied clinical resistance mechanisms to a Hedgehog pathway inhibitor in skin cancer. In 2016, Hayley returned to the UK to establish her own research group at the Cambridge Institute for Medical Research, and in 2019, she moved to the Babraham Institute, also in Cambridge. Her laboratory works on understanding how protein tyrosine phosphatases function in signalling and cell–cell communication, with a particular focus on a family of cell surface receptors. Hayley became part of the EMBO Young Investigator Programme in 2019 and was awarded the Lister Institute Research Prize in 2020.

What inspired you to become a scientist?

I didn't grow up in a scientific household. I just followed what I was really interested in at school. I always liked science, and when I was deciding what to study at university, I was reading a lot of popular science books and 'New Scientist' magazine; that led me into biochemistry. I really enjoyed lab work at university and I knew that was what I wanted to do. So I guess it wasn't just one event that inspired me – I always take things one step at a time. I didn't know much about the career of a scientist or even the concept of academia. I still get really excited when talking about our research or the latest discoveries.

What questions are your lab currently trying to answer?

Fundamentally, we're trying to understand how cells communicate and respond to cues such as damage. We study phosphatases that counterbalance the activity of kinases to regulate tyrosine phosphorylation. Although they have opposing enzyme activities, their activity is not always antagonistic. And even though it's a relatively low abundance modification in cells, phosphotyrosine has really important effects on protein function and, ultimately, cell behaviour. And, of course, it's dysregulated in several diseases. So we want to understand how phosphatases function at the molecular level – addressing their signalling mechanism, their roles in disease and whether there is the opportunity to exploit them therapeutically. One of the most recent areas we're getting into, after we had some unexpected results in the lab, is the crosstalk between phosphatases and redox signalling pathways. So, we focus on the biology of the phosphatases, which is an understudied area.

How did your interest in phosphatases come about?

I came across phosphatases while I was doing my postdoc [at Genentech]. A group at Genentech identified receptor-type tyrosine-protein phosphatase kappa (PTPRK) as a recurrent gene fusion partner with the Wnt pathway agonist RSPO3 in colorectal



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cancers. It was also found in a screen for modulators of mouse intestinal mutagenesis. We're all familiar with the receptor tyrosine kinases, but these tyrosine phosphatases localised in the plasma membrane were more enigmatic. In fact, the whole PTP family is important in several aspects of cell biology, but is also in need of greater understanding. Because I worked on membrane trafficking (during my PhD in the lab of Sean Munro), I'm usually drawn to processes that take place at cellular membranes. Making use of my background and of what I learned at Genentech about cell signalling, I thought it was a really good opportunity to delve into this family a bit more. I also think combining the different aspects of academic and industrial research has helped shape my line of research. With Sean [Munro] at the LMB, I learned how to take systematic approaches to understanding fundamental biology; then, when I got to Genentech, it was all about physiological relevance and how this could inform us about pathologies and disease. I think both of those elements come through in the research questions I address and how I approach them.

Was it difficult adjusting to the differences between academic fundamental research and the focused translational research in industry?

I did find the transition quite difficult because it was not only a new field, it was also a new environment. I think Genentech is unique

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Hayley cycling in the Corsican mountains with her husband Rob.

amongst other companies in that it has a very ‘academia-like’ postdoc programme. You are in this intermediate or hybrid position of being in both academia and industry. So in that sense, you are still surrounded by people who just want to answer research questions; they still publish their research, but it has a different slant, with a focus on the translational aspects. And things could be done on such a massive scale. It’s very inspiring in many ways, but just a very different environment. I believe that both academia and industry have massive value but with distinct emphasis and purpose.

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What drove you back to academia?

I really wanted to go back to academia because I was more motivated by figuring out how things work – being able to look at protein sequences, develop questions and decide which technology would best address a problem – that’s what I really love doing. I had come up with an area I wanted to explore, and only academia offers the relative freedom to do that; although hearing from patients and being at the cutting edge of drug discovery was incredibly inspiring. The worlds of industry and academia are certainly blurring more as there is a push towards more translational research and collaborations. There’s certainly a career angle to changing fields; when you’re obtaining funding, one aspect they look for is your independence from your past supervisors. I think a change in field can really build the confidence that you need to become independent and think for yourself, or even to develop your own niche of research. But there are certainly risks. I just never got to the risks part! [laughs] I think the main risk is that no one knows you in the field; you may not be taken seriously by those that are already established in the area, because you don’t have the track record. And I had to do so much reading to just get on top of things. I took the time to go to conferences. I think now [in the context of the SARS-CoV-2 pandemic] it would be much harder, being unable to go to

conferences and get to know people, to really understand what the next questions are in the field.

What challenges did you face when you started your own lab?

There were challenges, mostly around administration and logistics, but overall I loved it, and I really enjoyed the whole process. I met so many people who said ‘it’s just the hardest thing’. Maybe I was just really fortunate that the Cambridge Institute for Medical Research was so supportive. It was a great place to be, and I got plenty of encouragement. I appreciated the challenge of setting up the lab in a way I hoped would be sustainable. I think probably the most difficult thing was recruiting people. I got lots of advice on recruitment and the importance of recruiting well, so I put a lot of effort into it. There’s always going to be an element of risk there; after your first hire, it’s just going to be the two of you in the lab. On top of hiring, there is the constant switching between tasks. You’re still at the bench, but you have all of these higher-level things to do. One minute you have to worry about how many microlitres to put into a tube and the next minute you’re picking out racking for a -80°C freezer, while trying to write a grant. I’ve taken management very seriously, and try to be efficient in order to juggle the different tasks that fall onto my plate.

How are the challenges that you’re facing now different?

I think the recruitment is a constant challenge. You’re always sort of worried because you want to hire the right people who are going to make sure your lab keeps running smoothly and effectively. So far, funding has gone quite well, but I am already nearing the end of my first major grant and I am applying for more funding. There is also the worry that, as the lab grows, I feel like losing touch with projects could be a real risk, because I will have less time to spend on each individual project.

What characteristics do you look for when you’re recruiting new group members?

We’ve been thinking a lot about the lab philosophy. I just did the EMBO leadership course, and one of the things we discussed was thinking about the values of the lab. The things I look for reflect those values: being honest, engaged, creative and respectful. All of those things are important, but I think engagement is crucial. You want to invest in people who are excited about what you’re doing. Hiring is a really difficult task, because that ‘fit’ aspect is so subjective. And it works both ways – I wouldn’t want to take somebody on and it not be good for them either. It’s an extra challenge to find people using Zoom interviews, but we’ve just recruited two great people over Zoom, and I’m really optimistic.

“... there is no such thing as a safe project in research.”

What was the best science-related advice you’ve ever received?

When I was a PhD student, I was in a really amazing environment at the LMB. We had a dinner, and Peter Lawrence was there. He sat with us and explained how there is no such thing as a safe project in research. On one hand, you can do something you think is safe, but somebody else will be doing it and scoop you. On the other hand, you can take a risk and then it may not work out, but you might find something important. I think that encouraged me to be brave. I do see science as collaborative, but competition is inevitable. So maybe focusing on this different direction has steered me away from direct competition, in the short term at least!

What would be the most important advice you would give to someone starting their lab?

I got lots of advice! I mean, you will always get lots of advice. It's why I don't know whether giving it out is the best thing [laughs]. There are two pieces of advice I got that did stick in my mind: 'you are your best postdoc' and 'spend your money'. For the first, the message is that you've (typically) got by far the most lab experience (with no disrespect to those joining the lab!), so you need to be in the lab. I certainly was in the lab a lot in the beginning; it was just me and a postdoc for about 16 months. I actually ended up hiring a really good postdoc who had fantastic lab skills, so that took a lot of pressure off in terms of me having to be the main driver of the lab work. Regarding the second piece of advice, if you're very fortunate and get five years of funding, actually spend it. Go for it! I also have some advice from my experience too, such as getting a system in place to be organised and to also really care about your people. Oh, and keep your focus; it's very tempting when you start your lab to go off in several different directions. But in the end, you'll be measured on what you produce, and the best way to do that is to focus on one or two things that you think are going to pay off.

What is your advice on establishing good collaborations?

I guess collaborations shouldn't be exploitative in any way. It should be a mutual benefit. You need to fully engage somebody in a project. And find somebody you can really have an open and frank conversation with. You don't want to be in a situation where things get hidden or conflicts can arise because of differing interpretations. If you're not open from the very outset, things could really go the wrong way. Fortunately, I haven't had that happen yet. But I could be speaking too soon [laughs].

How did you and your lab cope with the lockdown due to the SARS-CoV-2 pandemic?

Where to start? I'm adjusting to working from home, and I think it's okay. My husband is also working from home, and we're fortunate in that we have a house where we can be relatively separate [laughs].

But I really miss the informal chats with colleagues and members of the lab. We had one socially distanced outdoor lab meeting, which was really nice. I really feel for those who have kids at home, which has made things much more challenging. I think it will really impact students who are just about to start their PhDs; it's not going to be the same experience. I think there is a huge social aspect to research, especially during training and just absorbing experience from other people. On the upside, we've increased all of the ways that we communicate; we do Zoom meetings, we have Slack and we have WhatsApp, so we can have more informal communication as well. After some time, I think everyone in the lab was pretty desperate to get back in. The Babraham Institute was very supportive and have been very proactive in seeking out what limitations and bottlenecks we might be experiencing. Also, the whole lab has been really good at adjusting to the new rules and at negotiating with each other to arrange different shifts. I have focused on helping them with their priorities, and then they organise their time, and it's worked out well so far. Overall, we have been very fortunate. We all have to adjust expectations for productivity. It possibly just means that projects have to be well-planned and focused.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

Sport has always been a massive part of my life. I used to play a lot of hockey, and during my postdoc I also played soccer and got into road cycling up mountains. A favourite of mine is ultimate Frisbee. I started playing at university. During my PhD, I actually got a half blue from Cambridge University for ultimate Frisbee after playing a varsity match against Oxford. For all the sports they award blues, but for ultimate Frisbee, they only award a half blue, because it's not a 'proper' sport [laughs]. I think because it's self-refereed.

Hayley Sharpe was interviewed by Inês Cristo, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.