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SPOTLIGHT

An interview with Christiana Ruhrberg

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Christiana Ruhrberg is Professor of Neuronal and Vascular Biology at the UCL Institute of Ophthalmology in London. Her lab investigates the relationship between nerve and blood vessel development in the central nervous system. In 2018, she was awarded the British Society for Developmental Biology's Cheryll Tickle Medal, which recognises outstanding achievements of mid-career female scientists in the field. In advance of her medal lecture at the society's spring meeting, we met Christiana to find out what the award means to her, how she settled on neurovascular development after many changes in direction early in her career and her thoughts on what makes a good scientific mentor.

You're attending the upcoming BSDB meeting as winner of the Cheryll Tickle Medal: what does the award mean to you?
First of all, it means a lot to be invited – it's one of my favourite meetings, particularly because of the breadth of the research you encounter there. As a student and postdoc I would go regularly, and recently I've been trying to attend more often, as I remember how much I loved it. I will particularly cherish the opportunity to present the wide scope of my team's research – normally, a conference lecture covers one topic and contains mostly unpublished data, but this talk will be different. I'll have to synthesise all the different research projects we've completed over the years, which is going to be a challenge, but also great fun! This lecture will provide a very special opportunity to take stock of what we've achieved.

What do you think of the situation for women in research today? Have things changed a lot since you were getting your training in the '90s?
Although not everything is perfect, the situation for women in research has changed a lot and in hugely positive ways. I think the efforts made to support female researchers have brought benefits to all young researchers, male and female alike, because initiatives to increase equality (like the Athena Swan Charter) make a difference to everyone – it's about fair recruitment, career establishment, nurturing individuals and maintaining a work/life balance.

When I was a student, it was pretty depressing for women in academia, and I felt it. When I recount some of the stories of sexual prejudice and harassment that I experienced at that time, younger people are quite outraged and astonished that this sort of thing was possible. It wasn't an issue amongst peers; rather, it was academics in positions of power abusing that power, because they knew that there would be no consequence. Of course it was a minority of academics who acted that way, but because they got away with it, they felt that their unacceptable behaviour was going to be tolerated. There wasn't really any disciplinary network at the time – but after sexual harassment and discrimination legislation was finally put in place, it gave the right messages and the situation began to improve.

Let's go back to the beginning: what first got you interested in science, and biology in particular, in the first place?
Originally, I didn't want to be a scientist. I actually thought that I would become a translator of modern languages: I learned English, French and even some Latin at school, and was always pretty good at them. My ambitions changed when I started my A level studies – we had an amazing biology teacher, Herr Heppenstiel, who was inspirational because he just loved his subject. He used to run around the classroom gesticulating, jumping on his desk to illustrate activation energy or other interesting concepts, and carried us along with his enthusiasm. That was also the time when molecular biology started blooming, which was hugely exciting. So I was converted to the idea of studying biology and there was really no way back, although having learnt English to a high standard certainly came in handy after I moved to the UK!

Your first publication was as a co-author of a 1993 study on ovarian cancer – how did this work come about?
At my German university (the University of Giessen), a first degree in Biology required me carrying out an extensive, 15-month research project as the basis for my final year thesis. At the time, however, there was no option for me to carry out a molecular genetics project, so instead of working in another subject area, I decided to do a year

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abroad at the University of Sussex. During this time, I started working in a cancer genetics lab, and I then also carried out my research project there with permission from my German university. My thesis research formed the basis of the paper you mention – publishing a paper was really exciting and convinced me that I wanted to stay in scientific research. However, there was a disappointing aspect to publishing this paper – I was second author on the study, even though it actually comprised my whole thesis research. My supervisor at the time said not to worry, because, as an undergraduate, I was lucky to have a paper published at all! The upshot of this experience is that nowadays, when it comes to authorship debates, I try to be compassionate and understanding, and firmly stand up for junior people so they will get the credit they deserve.

Did you plan to stick with cancer research for your PhD?

I had initially wanted to do cancer genetics for my PhD thesis research, but fortunately ended up working with Fiona Watt, whose team studies epithelial differentiation and epidermal stem cells. In Fiona's lab, I felt a little like the odd one out – I had a molecular biology background, but, at the time, most people in the lab were cell biologists. But Fiona had a leftover project that no one had wanted to tackle, because it involved cloning two massive proteins at a time when we still did manual Sanger sequencing with ^{35}S. I decided that this project was perfect for me, and I spent the first year cloning the first protein and then moved on to the second one. Fiona gave me a lot of freedom, she really let me get on with it, and I think this experience was very useful, because it taught me to be independent quite early on.

By that time, I had abandoned the idea of working on cancer – technically, it wasn't much fun at the time, being dominated by Southern blotting and a lot of sequencing. Combining molecular and cell biology seemed much more attractive, particularly because of the variety of research questions and techniques, for example using cell culture models and carrying out biochemistry to identify protein interactions. From then on, my research was no longer driven by my initial ambition, but rather by the work I enjoyed doing in the lab on a daily basis.

You then moved to the National Institute for Medical Research in Mill Hill for a postdoc with Robb Krumlauf – what led you to make the switch to developmental biology?

We named the two proteins I had cloned in Fiona's lab envoplakin and periplakin because they were related to another protein called desmoplakin. We had some ideas about where they were positioned within the cell in tissue culture models of epidermis, but we could not be sure how they functioned in a real organ context. In order to establish this, we would have needed to knock them out in a mammalian model. Fiona's lab had at the time never done anything like that, and, in fact, few labs in those days had mouse knockouts. Robb's lab was one of those few – they had a knockout mouse line for a transcription factor that controls brain stem development, and I heard that he was a great boss too. So Fiona put in a good word for me, and I started in his lab just after I had completed my PhD research. Again, it was a daunting switch in topic – now I was working on neural development, so I had to start completely from scratch again. When you knock out a gene, you quite often end up with developmental defects, so I knew that I had to learn about developmental biology, no matter which field I was going to end up researching. And in Robb's lab, I definitely fell in love with developmental biology research – there was so much to learn about brain development, neural crest cells, tissue interactions, how genes patterned whole organs – it was just fascinating. Again, there was no way back for me: I knew then that I wanted to be a developmental biologist.

You then had a second postdoc with David Shima and another switch in your focus: what attracted you to blood vessel growth?

In Robb's lab, I was looking at hindbrain development, and became interested in neuronal migration and axon guidance. But then Robb was offered a chance to start a new cancer research institute in Kansas City and left to take up this fantastic opportunity. For family reasons, I couldn't follow him there, and so I had to find another postdoc position. Speaking to David Shima, we reasoned that how neural networks form and how vascular networks form would follow some of the same principles, in terms of signalling molecules as well as cell biological behaviour. So we convinced the MRC that I should be able to transfer my fellowship to a vascular biology lab, and I became Dave's first postdoc. In his lab, I applied my neural development model to vascular biology research, and at the same time began to examine how vascular growth factors might affect neurons – this turned out to be a good move, as it kick-started my independent career.

You started your lab at UCL in 2003: what did you hope to achieve in your early years as a PI?

I wanted to try and synthesise my two postdoc areas – developmental neurobiology and vascular biology – into something we could consider a new research field. I developed the hindbrain as a system to look at vascularisation of an organ that is driven by the needs of the neural progenitors. At the time, people were mostly using the retina to study vascular development, but this vascular bed develops postnatally, so for any embryonic lethal knockout mouse was not informative; for embryonic lethals, the hindbrain provided a useful alternative model. At the same time, the neurons I had studied in Robb's lab turned out to respond to the vascular endothelial growth factor (VEGF), the very molecule I had studied in Dave's lab, and so we continued pursuing that finding as well. We showed, for example, that VEGF is important for neuronal migration, axon guidance and neuronal survival. These discoveries certainly made a big splash in the field, and together with the work of others pursuing similar ideas, have impacted on how we think about treating neurodegenerative diseases. Along the same vein, we and other teams looked more recently at how the vasculature feeds back on neurogenesis to regulate neural progenitor self renewal.

It was a good thing to start a career in a new field – there wasn't too much competition, and a lot of big labs were happy to give me their mouse knockout models, because they weren't going to use them in the same way I wanted to. When I started my lab, crossover between vascular biology and developmental neurobiology was practically non-existent. But now studying the crosstalk between neural cells and blood vessels is a growing area – we even have our own dedicated conferences! The crossover is increasingly obvious for those doing adult brain research (for example, on conditions such as vascular dementia), but there's also increasing interest in the development of the blood-brain barrier, a process that involves crosstalk between glial cells and blood vessels, and in the vascular regulation of neural stem and progenitor cells.

And in terms of vascular-neural signalling crosstalk, what sorts of questions are you tackling now?

The same signal can mean one thing to a developing neuron and another thing to a developing blood vessel; the big challenge now is to figure out how these two different systems read the same signal

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and why they read it differently. A lot of this work is carried out at the level of receptors and signal transduction. There are a limited number of building blocks – the signalling molecules and their receptors – available to build the signalling relays that orchestrate the enormous complexity of the animal body; different cell types have to use the same type of molecules throughout development, and somehow they are combined in unique ways to enable a variety of unique and appropriate responses. For instance, we have found that facial brachiomotor neurons respond to VEGF via the neuropilin receptor in the migrating cell body but, at the axonal end, the same cells use neuropilin to pick up semaphorin signals via plexin co-receptors. We still do not know, for these neurons, what the VEGF co-receptor is – it's not the typical vascular co-receptor – so there's obviously something unique going on in these cells. This observation illustrates the complexity of signalling in a biological system, and this complexity makes developmental biology research fascinating.

This complexity makes developmental biology research fascinating

Where do you see the next decade taking the Ruhrberg lab?

We are certainly going to stay with mouse reverse genetics, which is getting more and more sophisticated, to answer our questions. We also want to take full advantage of the transcriptomics and bioinformatics revolution, and recently started a project on understanding vascular progenitor lineages. As well as mining existing datasets for useful information, we would like to use single-cell transcriptomes to better understand diversification within the lineages. The bottleneck with this research at the moment is personnel: we need people with the right bioinformatics background to join a developmental biology lab. It's our challenge to convince these experts to become interested in answering developmental biology questions.

For one particular research project, it's clear that the single-cell data will help us progress a lot. We want to understand the origin of the vasculature, whose formation is intimately linked to the development of the hematopoietic system. There has been a long-standing debate, for instance, about whether angioblasts have dual endothelial and hematopoietic potential but then become fate-restricted, and whether there is a cell that could be called a hemangioblast. We might be able to resolve these long-standing questions of how the hematopoietic and vasculature systems are linked by applying modern transcriptomic approaches to classical developmental biology studies.

More broadly: where next for developmental biology as a field?

One thing that developmental biologists excel at is thinking about the bigger picture. It is possible to drill down to understand the interaction of molecules, without thinking too much about cells in the context of tissues and organs, and this work can get published well. But I think, yes, these interactions are interesting, but where and when do they take place in the organism, and how and why? Developmental biologists can step beyond thinking about interacting molecules and signalling pathways – we more often view these molecules as tools that can be manipulated to understand what makes cells move or why cells need to talk to each other. For us, it's not just about molecules interacting: we need to understand the processes that take place in tissues to build a body. We probably have to re-convince some journal editors of the value of this approach, as identifying new molecular interactions seems to be what is required to get published in some journals – though Development, fortunately, doesn't have this view at all. For instance, when you take a molecular interaction that has been shown in one cell type and manipulate this pathway to answer a developmental biology question, you don't want to hear 'well, that's not novel, we know that these molecules interact' from an editor. Actually, it is novel when you're showing why they interact. There's a larger scale purpose to that interaction, and finding this purpose is what current developmental biology research excels at.

How did your experiences working in different labs influence your own mentorship style as a PI?

Fiona was definitely a big influence during my formative years as a PhD student. She was always extremely constructive and positive: when you didn't get the results you had expected she'd advise you not to be disappointed, and to appreciate that seemingly 'bad' results force you to rethink the question you want to answer and the approach to take. So I learned from her to always see the value in all kinds of data, positive or negative. I was also influenced by her ability to let the people in her team work as independently as they wanted to. She was the opposite of a controlling PI – she'd nurture her team members according to their individual needs, and this is something I try to do as well. Research is a lot about us as individuals: it is driven by our individual skills, ideas and thought processes. It's really important for me to know that everyone in the lab is enjoying themselves in an environment where they will be able to develop to their best abilities. Not everyone wants to pursue the same type of research question – you can see that in my lab in terms of topics we pursue – and similarly, not everyone wants to be an independent group leader – some people only like to work on the bench as part of a team. I felt privileged in Fiona's lab to work on a topic that wasn't her mainstay, and so when talented young researchers ask to work on their favourite topic in my lab, I always try to accommodate them, even if it is different from what we do already. With the right amount of passion, enthusiasm and commitment, there's nothing to stop them following their own idea and making a career that way. Finally, I think team work is vitally important: in our lab, everyone has their own dedicated, main project, but also has a side project that involves collaboration with another team member. This gives everyone a back-up plan if the main project doesn't progress well or fast enough, but it also means that the team members are more tied together, which promotes team spirit and a vibe in the lab where people care for each other and each other's research.

The most important quality a young researcher needs is an unwavering enthusiasm for discovery

Do you have any advice for young researchers weighing up a career in science?

I think the most important quality a young researcher needs is an unwavering enthusiasm for discovery – if you have that, it is definitely worth trying to pursue an academic career. But even if you decide to go into a science-related area like publishing or policy making, I think doing a PhD and even a postdoc can really be useful: there are so many different careers in which you can apply what you learned in the lab environment. Of course you learn your specialised

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technical skills that only apply to bench research, but at the same time you practice verbal and written communication, project management, leadership and problem solving. So if you love scientific research, I would suggest not to worry too much about the rest of your career, but give it a shot, as you can always use the skills you accumulate in many different ways thereafter.

Finally, is there anything Development readers would be surprised to find out about you?

I went out for dinner the other week for a leaving do, and one of the guests said to me: 'Christiana, I would never have thought that you would be listening to Kerrang Radio!' That gets me thinking about your question – maybe others find it surprising how passionate I am about new music. I have a Spotify subscription, and my favourite pastime at the weekend is to browse through the new releases – I don't always like the commercial stuff, but there are a lot of new bands experimenting with novel concepts, which I find very exciting, and I also particularly like the evolving alternative rock scene. When I go to the BSDB meeting, I love the disco on the last night. The young people are very good sports, dancing so enthusiastically to all the '80s music that is probably played for the people in my age bracket, but I'm just thinking 'please, not another '80s song!' I've always liked listening to current music, but these days, with three teenage children, I also need to keep an interest in what they're listening too, because music is very important to them.