© 2023. Published by The Company of Biologists Ltd | Development (2023) 150, dev201553. doi:10.1242/dev.201553

INTERVIEW

An interview with Christopher Wright

Helen L. Zenner[*,‡]

Christopher Wright is Professor of Cell and Developmental Biology and the director of the Program in Developmental Biology at Vanderbilt University. His lab works on pancreas organogenesis and how it relates to disease, using techniques spanning from single-cell technology through to high-resolution imaging. Chris was awarded the 2022 Society for Developmental Biology (SDB) Victor Hamburger Outstanding Educator Prize and we talked about what winning this award means to him, as well as discussing his career and his hopes for the future of developmental biology.

Let's start at the beginning, when did you first become interested in science, and biology in particular?

As a school kid, I was top in my class in most subjects, from French to mathematics, sciences to history. I tended to become extremely fascinated with particular topics, often to a point of exclusion, but then I'd move onto something else. Funnily enough, this doesn't fit with the other part of my personality, which is to procrastinate! Within sciences, while I was good at chemistry and physics, it was the beauty of biology that struck me. I still remember a biology class when I was 13 years old; we were looking down a microscope for the first time and my teacher, Mr Parry, said, 'I want you to draw what you see down the microscope'. I enjoyed drawing the details and Mr Parry told me that my drawing was pretty accurate and really good. It was probably a 10-min interaction but that is where my interest in biology really started from! I have an inherently three-dimensional and picture-oriented way of thinking, and I think that this contributed to my interest in biology. I went on to study at the University of Warwick in the UK, which had set itself up as a pre-eminent, forward-looking university, looking at the horizon, the vision of where biology is going. I didn't realise how privileged I was to be going there – I was taught by some phenomenal lecturers, who were all part of the [Nobel Prize winner] John Gurdon family: Hugh Woodland, Alan Coleman, Liz Jones and Bob Old. Back in the late 1970s, we were just entering the molecular era. I remember being told 'we've got tadpoles that are making their own milk', and comments like that really pique your interest. They had made plasmids that express casein and they could see the protein on the gel!

It almost sounds like it was an opportunity to play!

Yes, and I think that permeates my entire life, I still see biological discovery research as pure magic and I'm amazed at what we can learn. I try to pass on that there's so much to be fascinated with, and it's the magic moments that drive us. I still get excited when I do *in vitro* fertilisation of *Xenopus* eggs, all becoming two cells in synchrony – I love to share the excitement.

I still see biological discovery research as pure magic and I'm amazed at what we can learn

How did you choose the Knowland lab in Oxford for your DPhil (PhD)?

While I was still at Warwick, I told Alan Coleman that I was fascinated by developmental biology and asked if I could join his lab as a PhD student. He told me that staying at Warwick was a bad idea and that I should move to another lab. He suggested a few people, including John Knowland. I remember going to the interview with Knowland and I found his work interesting. He worked in *Xenopus*, but back then no genes were sequenced and we were far from even conceptualizing having complete genome sequences. My job was to purify a protein from *Xenopus* liver, with the aim of injecting it into oocytes to trick them into making liver proteins. I got taught hardcore biochemistry during my PhD and this is where my love of quantitative biology is from. Knowland would build me up, telling me I was too self-deprecating and needed more confidence, but at the same time saying that I'd better get a fundamental assay to work, or I wouldn't get my PhD. That taught me pretty big independence values and, as I'm not the sort to shrink away from a challenge, I just

*Online Editor, Development.

‡Author for correspondence (helen.zenner@biologists.com)

H.L.Z., 0000-0002-8578-9797

Development (2023) 150, dev201553. doi:10.1242/dev.201553

worked at it for about three to five months. This was his way of teaching, little steering, real old-school training. I thought I would fail my DPhil, because I couldn't get the assay to work and there was no plan B. Eventually, it worked, I could move forward, and it taught me to be responsible for my own career. It was a fascinating time to be at the biochemistry department at the University of Oxford. I think we were the first people to purify plasmids and run them on electrophoresis gels. With the soon-after advent of cDNA libraries and molecular biology, it was a new level of magic!

You made a switch from biochemistry to developmental biology for your postdoc. How did you choose Eddy de Robertis' lab for your postdoc and what did you work on?

Eddy de Robertis, who was working on the new-fangled homeobox genes just being found in vertebrates, was recommended to me. When I dug deeper, I thought it sounded really interesting and we arranged to meet in the Kings Arms pub in Oxford. After my interview, he sent me a preprint of his work on the new homeobox genes in *Xenopus* and how they control body patterning in *Drosophila*. At the time this was anathema, no-one really believed that genes that controlled fruit fly development would be so similar engaged in *Xenopus*. So, I went in having no idea if it would work out, we only knew that the genes existed. Cue the nightmare re-starting where I thought I would fail in my postdoc! We were tasked with making antibodies to the proteins, because at that time *in situ* hybridization wasn't working in either *Xenopus* or mouse. We first wanted to know where the homeodomain proteins were produced because we didn't know any of the rules. Nothing was working for a while, but this was where my training from John Knowland kicked in, and eventually we had high-quality antibodies that worked. Finally, we could see the remarkable expression patterns of these proteins, recognised with publications and review articles in Cell, Nature and Science in this age of 'homeobox madness'. It was an exciting time and the collinearity of chromosomal location and expression domain of homeobox genes in *Drosophila* being conserved with vertebrates was amazing. I did a five-year postdoc in the end, one in Basel, four in Los Angeles, which I thought was maybe too long, but I was having way too much fun, and publishing like a maniac! My postdoc set me up with a fascination with multiple species, because as soon as we saw that our antibodies would work in *Xenopus*, we started testing them in salamanders, chicken embryos, zebrafish and so on. It was discovery science at its best. Then, I had to choose whether to stay in the USA or come back to Europe and, although I was offered positions back in England, I realised that I couldn't be a fully independent assistant professor and would possibly only be offered a corner in a lab. In contrast, in the USA I had found a mentor and a supportive advocate in Brigid Hogan at Vanderbilt. She pushed really hard to get me a great start-up package and lab space. Another aspect that drew me to Vanderbilt was Brigid's relationship with Liz Robertson and Rosa Beddington, who were establishing mouse knockouts. This made it a perfect move for me. I was lucky in my early career because, although I had some frights with experiments not working, nothing has ever gone really terribly wrong for me. I grew up during exciting times for molecular biology, genetics and developmental biology, and could achieve a lot of my goals.

You mentioned Brigid Hogan as a mentor, do you think mentoring is important and what is your own mentoring style?

I learned from this period that it is incredibly important to find a single senior mentor or advocate that you trust for candid conversations. I think our common British heritage helped with the tone of these conversations. For me, finding someone like Brigid, who was just a lover of high-quality science, strengthened my belief that science is a worthwhile scholarly pursuit. Brigid invited me to write several news and views articles with her, and because of that association I was invited to the Cold Spring Harbor mouse course. I met Liz Robertson, Rosa Beddington, Richard Behringer and many other people and became sort of an honorary member of the mouse club. Now, I like to tell people at all career stages that they just need to find someone they can talk to candidly about science. To have a supporter who will look you in the eye and say, 'it's just not good enough', and it can be a two-way relationship.

I try to bring that style to my mentorship. I think that it is important for people to remember that you can question the conclusion that someone draws from their data without it being personal – it's about the data. Once people get to know me, they understand that I am in it for them, but they must get past my titles and get to know me as a scientist. So, the first thing I do if I'm on a PhD committee is invite the student to come and talk to me. We'll chat about science, why they are here and what the PhD is about, trying to really break it down. Eddy de Robertis was great for talking about things at microscopes, looking at data and just talking it through.

What are the main questions that your lab is trying to address?

For a long time, we've been interested in pancreas biology because we discovered genes that when you knock them out, there is no pancreas. It doesn't kill the cells, instead the cells transfer stemness to adjacent tissues, for example duodenum or stomach. I'm particularly fascinated with whether or not the endoderm is the most plastic of all germ layers. For example, in a number of situations in humans and in strange chemical treatments of model organisms, you have pancreas tissue emerging in the middle of a stomach, or hepatocytes in the middle of the pancreas. We tried to understand the rules of that: Why is it so plastic? Why does it happen? And ultimately, why does it happen in some humans – for example, when patients have pancreas in the stomach, it's not resistant to acid and they get terrible ulceration.

What we're trying to understand, in broad terms, is how cells actively maintain themselves in their cell state, whether that's epigenomics or combined with transcription factor talk. Then we go on to consider the insults that can be given to that system and how things become shaken up, resulting in the gene regulatory networks being shifted into a different state. And so, I hypothesise that there may be cell states in adult tissues that are never visited during embryogenesis. 'Cell space' is another interesting thing that I like to think about, especially considering single-cell omics. I started to think about quasi-cell space, a new cell space that isn't accessed until you do something unusual. For example, when you get insulin cells suddenly changing to become somatostatin-producing. We're trying to understand how cells are maintained in fate and what happens in metaplasia, or in progression to neoplasia. What are the best models to study such issues? Can we watch the niches in which these things happen in real time? There's nothing better to me, than using timelapse imaging to discover what is happening at the cellular level – you can't argue with a timelapse movie, when you can see the biology happening quite directly. There is so much information in a movie; we once made a single movie that opened up probably five or 10 new biological questions!

As I've gotten older, and I had enough discretionary funds, I felt we needed to reconceptualize everything, so I took a step back and

Development (2023) 150, dev201553. doi:10.1242/dev.201553

said, there are data in my field of pancreas biology that just don't sound right, it just doesn't look that way in reality! This meant going back to basics and re-describing pancreas organogenesis. The pancreas is formed in a completely different way to many other organs. It doesn't go through classical branching morphogenesis but through a plexus-like epithelial growth period. In several papers we have described how the plexus expands, while concurrently producing differentiated cell types, such as the islet cells that must cluster together. The plexus grows and the organ expands 500- to 1000-fold in volume but, in the end, you also end up with a relatively rational epithelial tree. How does the expansion phase followed by branch pruning, coalescence, or selective cell death actually work? In my lab, we've now tried to turn pancreas organogenesis into a set of engineering questions. We ask, are there some building rules, do these rules go wrong sometimes or not, and are the same rules used in the much larger human pancreas? That is, are there scaling issues in building a pancreas in human versus mouse? These scaling and engineering issues have been in my mind over the last five or six years, allowed because of taking a step back and seeing the field in a bit of disarray. I also strongly believe in the importance and the beauty of doing descriptive biology.

As a visual person, do you still enjoy looking down the microscope with your colleagues?

Yes, it's wonderful to look down the microscope, but also as a group leader I am responsible for the primary data, so it's important for me to see the result. Having said that, it's often just for pure excitement! For imaging, we are now using a lot of lightsheet microscopy and tissue clearing to image large tissue volumes. This means we can create surface rendered images of pancreas tissue and quantitatively analyse them, and even step inside it using an Oculus viewer! At Vanderbilt, we have great imaging centres, with completely novel lattice lightsheet microscopes. Such facilities keep us on the front of the curve regarding imaging technologies.

You have been awarded the 2022 SDB Victor Hamburger Outstanding Educator Prize for your contribution to teaching and mentoring, what does winning this award mean to you?

Maureen Gannon had nominated me in 2021, but quite sensibly they gave the award to Michael Barresi. But Maureen was pretty determined and nominated me again for 2022. I told her not to worry, because I'm okay with not having awards, I just want to have some impact on upcoming generations. But in the end, it was fantastic to hear that I'd won and I would like to thank Maureen enormously for steadfastly putting together the nomination. It was a great feeling to discover that people have noticed what we are doing at Vanderbilt. It is recognition of what I feel is the most important thing that I do now, mentoring and advocating for faculty and postdocs, trainees and research staff. I try to keep people excited about what we are doing, and although that can sometimes be difficult and disappointing, it is important. Winning the Outstanding Educator prize reinforces that I've been doing the right things and I hope to be able to leverage the award to improve teaching and mentoring in the future, especially here at Vanderbilt.

Can you tell us a little about the Program in Developmental Biology at Vanderbilt?

I run the Vanderbilt Program in Developmental Biology, a cross-institutional forum between Vanderbilt Medical Center and the university. One main goal is to set up opportunities for people to talk and think about science and the future. We have developmental biology 'research in construction', which is for graduate students only, and they decide what they want to talk about, whether it's horrible experiments that aren't working, new techniques that everyone should know about, practice their talks, or anything like that. We also have a fantastic journal club, where we insist that anybody from the program – faculty, postdocs and grad students – appear in the roster. In addition, we have something call 'Sip'o Science', inspired by British teatime (although ours is early evening wine and crackers), which gives faculty, postdocs and trainees the opportunity to discuss all aspects of research and careers in a different way, with much less formality. Scheduled for an hour, most last almost 2.5 h, and we discuss all different aspects of science. All these activities are designed to get us thinking and talking.

What will be the big questions for developmental biologists to address over the next decade?

I was talking about this recently and I would say, while incredibly challenging, there has to be some way of moving into carbohydrate biology and the extracellular matrix because that is the milieu through which so many things happen. And it's complicated, with multiple levels of protein decoration and many enzymes carrying out modifications. I don't know how we are going to do it, but that is a huge challenge in my mind. I also think that understanding the dynamics of how a cell is moving through cell states will be important. We need to know the push points on a gene regulatory circuit; if you push here, then cells will fall out and adopt a new state. We should be looking for crucial push-pull points through a biology-oriented, but also disease-oriented, lens. Finally, perhaps the biggest challenge for the developmental biology community is to come together to address similar questions, especially between communities working on different organs. Currently, everything is too individualised, and data floods without cogent and multi-level curation just compound the issue. Within this context, I believe we need to challenge each other more at meetings, be provocative, but about the data or interpretations, not personal attacks.

I believe we need to challenge each other more at meetings, be provocative, but about the data or interpretations, not personal attacks

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

I don't know if people would be surprised, but I have depression, which is being clinically treated. In the past, this has led me to push myself hard, almost to exhaustion. I think that people might not be surprised to know that a lot of scientists have an association with a depressed state. I am also an avid cyclist with three Tour de France quality bicycles at home. I love long-distance solo rides, which help my brain unwind and wonder with the metronome of pedalling.