

## INTERVIEW

# Transitions in development – an interview with Kate McDole

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Kate McDole is a Group Leader at the MRC Laboratory of Molecular Biology (LMB) in Cambridge, UK. Using the mouse embryo as a model, Kate's research group studies how mechanical forces can shape complex three-dimensional structures out of simple populations of cells. We met with Kate to find out more about her career, the challenges of setting up a lab during the pandemic, and her thoughts on mentorship and transitioning to a group leader position.

## Let's start right at the beginning – how and when did you first become interested in science?

I've pretty much been interested in science my entire life. I grew up in a really engineering and 'sciencey' household; neither of my parents were scientists per se but my father was an engineer and my mother was a botanist turned science teacher turned engineer. As kids, we were always running around out in the desert and finding creepy crawlies to bring home. Fortunately, my mother was always very enthusiastic about this. I remember bringing home the largest, ugliest toad I had ever seen and, when she met me in the doorway of the house, she just thought it was fantastic! We put it in the bathtub while we made a house for it in the garden. So, we were always building something, dissecting something, repairing something or finding some strange animal to bring home.

## How did you then become interested in developmental biology in particular?

For a while in high school, I thought I was going to go into medicine because I had so many teachers tell me that's what I should do. They said: 'You don't want to be a scientist – scientists don't make any money. Unless you're a Nobel Prize winner, you'll never have any kind of success.' They were actually very discouraging. I guess I thought the same about science until I wandered into a lab within the first couple months after starting my undergrad at the University of Washington. A friend of mine was doing some work in the lab and, while I was waiting for him, a postdoc in the lab was sitting at his bench giggling about something and he waved me over. He was doing an experiment with a *Xenopus* frog, injecting GFP or something into it; I can't remember what. But on the back of this rather grumpy frog were glowing letters that spelled out 'FROG'. I remember thinking this is so much cooler than working with patients, so I started working in a lab as an undergrad and never looked back.

I mostly worked in the cancer field before I went to graduate school. However, the first lab I worked in as an undergrad is where I was exposed to mammalian development for the first time. I would

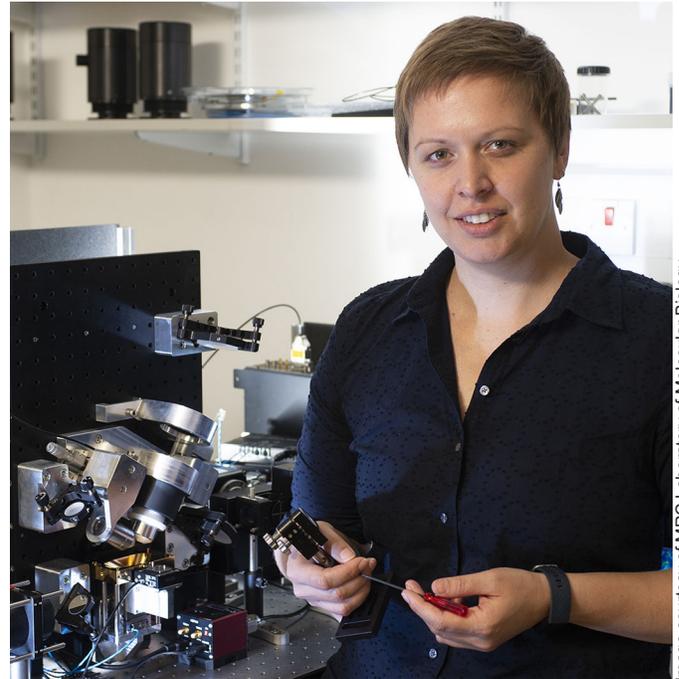


Image courtesy of MRC Laboratory of Molecular Biology

dissect out very early mouse embryos and remember being stunned by just how fast and how much embryos would change over the course of a single day. Developmental biology was fascinating to me, not only scientifically but also in terms of engineering, i.e. how do you build an embryo; how do you go from this simple, single cell to a complex, moving, functioning thing? I realised that the embryo has to do some pretty amazing physics.

## And what led to your interest in imaging techniques?

I started doing a lot of imaging in graduate school while I was studying preimplantation embryo development. I realised that, for me – maybe it's just my simple mind – I really like to be able to see things. Doing things in a test tube just isn't good enough for me; I need to actually see what the embryo is doing. What is the cytoskeleton doing? How is that shape changing? I need to watch it and poke it to figure out what is going on. I used multiphoton microscopy to visualize preimplantation embryo development and that really got me started. It made me realise the power of being able to use these imaging technologies to answer questions that people hadn't really been able to address in the past, simply because they hadn't been able to look at them properly before. I met Philipp Keller during my graduate work and we started talking about the light sheet microscope he was using, and I remember thinking: 'You have to do this on mouse next – that's the next obvious thing.' So when he opened up a postdoc position in his lab, it seemed like the perfect next step for me. I remember my graduate advisor telling me: 'You need to find a job in which you can always tinker with things because

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otherwise you're going to be very unhappy,' and I guess she was right!

Fortunately, there was plenty of tinkering to do in Philipp's lab. No one had ever imaged the post-implantation mouse embryo with single-cell resolution for as long as we were trying to do. We needed a microscope that could image the whole embryo and not fry it, a culture system that could keep it alive, and a computational pipeline that could handle the whopping great datasets we were going to throw at it. It was a lot of hard work that involved a lot of amazing people, but it was also some of the most fun I've ever had in science. Every day was different – you could be ogling over some new developmental process you'd never seen before, crawling around under an optical table to align a laser, hunkering over a bench in the machine shop assembling some fiddly new part, or wading through the massive amounts of data, trying to make sense of it all.

### **What were your most important considerations when you were looking for group leader positions?**

By that point, I had worked in academia and in biotech, and I had worked in large universities and smaller institutes like the Fred Hutchinson and the Carnegie Embryology Department. I really liked the institute way of doing things, with smaller teams and more of a focus on the science (versus, say, teaching). Working at the Carnegie was a lot of fun because everyone knew what everyone else was doing, and you could just wander down the hall and ask somebody for an antibody or their advice on something. It was a really interactive environment compared with some of the university departments I had worked in, where you were in your lab in your own little bubble. I knew I wanted to be in that kind of interactive and collaborative environment, where I could just go banging on people's doors, and the LMB certainly fit those criteria.

### **How was the transition to becoming a group leader?**

I have to say that it was very disorienting, but I guess that's largely due to circumstances; I moved to the UK at the end of January 2020, and started in the lab in beginning of February 2020, around a month before the UK went into lockdown due to the COVID-19 pandemic. It was very lonely and a lot more challenging than I had expected, but not necessarily in a scientific way. The LMB and especially my department were extremely supportive, checking in and making sure I had what I needed. I was also very fortunate that the ordering process was very smooth, so most of the parts that I needed for my microscope were already here before lockdown. And because I could do it in isolation in the building, my lockdown project was then building up the microscope. In some sense it worked out well – I could blast my 'Build Party' playlist without bothering anyone and there weren't any witnesses when I did something stupid like wiring something up wrong! When I needed to debug the software, the mouse facility wasn't really able to handle requests so I couldn't get any embryos to image; however, just down the hall there were a couple of people coming in to feed their brain organoids. I asked them if they had any fluorescent samples I could put on the microscope, and they were more than happy to provide me with some brain organoids so I could get all the kinks in the system worked out. In the end, the imaging worked out so well that they started doing experiments using the microscope and generated some data for a paper. So I guess that worked out nicely despite the circumstances. Overall, it's been weird and it's been disorienting but so many people have had it so much worse that I really can't complain! I always knew it would be challenging, just not quite like this. Someone actually got me the book *At the Helm: Leading Your Laboratory*; however, nowhere in that book does it mention how to

start up your lab during a pandemic! We should suggest a new chapter.

### **What's been the best thing so far about starting up your own group?**

That's actually really hard to decide. But I guess it was the moment when I recruited – I finally had people to work on the different projects that I had in mind. One of the biggest motivations for me to start my own lab was that I realised that there was just too much for one person to do, so it was really great to finally have people in the lab working on the various problems I wanted to address. Being able to introduce the light sheet microscope to other people has also been really exciting. Lots of people haven't visualized their samples in such a way so seeing them being really excited about what the technology can do for them has been fun.

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Being in Cambridge has also been great, although due to the pandemic I haven't been able to get out and about much and there are lots of people in Cambridge that I still haven't had the chance to interact with. But on the other hand, I have to say that Zoom has made it much easier to interact with collaborators. Before, it always felt a little rude to have a virtual meeting with your collaborators and it was harder to just cold call someone. But now it's super easy for me to just write to somebody say 'Hey, do you want to Zoom over a beer and chat about projects?' It's just more acceptable now and I think it will change things going forward.

### **What are the main research themes and aims of your group?**

The main aim of our group is really to understand how an embryo gets its shape. We do this using advanced microscopy, biophysical techniques and computational tools. We want to actually try and figure out how you shape complex three-dimensional structures out of an initially homogeneous, simple ball of cells. How do you actually get a beating heart? How do you form a brain? How do all the different germ layers coordinate and work together to shape these different tissue structures? In the past few years, we've gotten very good at making round balls such as organoids and spheroids. And sometimes we can make crypts and folds and get them to be things that kind of look like structures. But we haven't really been able to build an embryo or structures that are very complex. We don't really understand how this whole process gets started, even at its most basic level. To address this, we're looking at the stage of mouse development when all of that starts happening. This stage of development is fairly accessible, it's easy to image, and it's amenable to lots of manipulations and perturbations. We use a multidisciplinary approach to try and understand how physical forces shape the embryo, where these forces come from, how they drive cell and tissue shape changes, and how they influence gene expression and cell fate. There's just so much out there that we don't understand about these questions but we finally have the technology to start looking at them.

### **In your opinion, what's the most exciting thing that's happening in the field at the moment?**

I think it's got to be the technology really. That's the thing that's going to help us answer so many questions. But what's also exciting is the development or intertwining of so many different fields. Developmental biology has been driven by a lot of classical descriptive or genetic work that has just been amazing. However, things just kind of stalled there for a while; we couldn't do some of the experiments and measurements that we really wanted to do simply because we didn't have the technology. I don't want to use the cliché phrase that 'developmental biology is going through a renaissance'... but it really is! Not only do we now have new interests in stem cells and organoids, and the physics of living matter, but we also have computational tools that we can use to analyse the massive amounts of data that we're getting. All of these different disciplines coming together are providing us with new approaches to tackle long-standing questions. It's an exciting time to be in developmental biology.

### **What's been your approach for hiring people in your in your team?**

Because we're a very interdisciplinary lab, there's no one type of person that I'm looking for when I'm hiring. There are some people who may be more interested in the biology side of things, whereas others are more interested in the imaging or the physics or the computer science. I'm mostly looking for people who aren't afraid to take on large challenges or tackle very big unknowns. We're using techniques and approaches that have not been tried in the mouse embryo before, so the projects are a little more high-risk. But they're also a lot of fun! For these types of projects to succeed, I also think we need people who can wear multiple hats; we need biologists who understand Python, and computer scientists who aren't afraid to get their hands dirty in the lab and who also understand how biology works. I remember we were once trying to image the mouse embryo but had to stop at a certain stage because the heartbeat makes the embryo shake too much, so that you can't track cells, and the theoreticians asked 'Well, can you make it stop?'...!

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I think it's also important to have people who are very collaborative and can help each other out. So, biologists who can get the computer scientists the data they need, and computer scientists who can help the biologists analyse their data. When everyone works together it makes for a fun environment. That's how Philipp ran his lab and I really enjoyed it so that's what I'm trying to set up here.

### **How important do you think mentorship is in navigating an academic career, and what's your approach to mentoring?**

I've been fortunate that my advisors have always allowed me a very high degree of independence and freedom (probably more than they should have in some cases!). But Janelia Research Campus (Howard Hughes Medical Institute) had an excellent mentoring program for postdocs on the job market. They walked us through research proposals and held grant writing workshops with us. We also did practice chalk talks. They helped us to prepare for the job market and think about how we would start up a research program. It was an extremely valuable experience and I think it's good to have these sorts of mentorship programs available to everyone, regardless of what career trajectory they want to take.

When it comes to individual mentorship and one-on-one mentoring, I think that really depends on the person; some people get more out of it than others. Having had a lot of freedom myself, I guess I try and find people who can be independent and are willing to take ownership of their project. I like to give people the freedom to think and tinker! But it's also important to know when you're stuck, and when you need to find someone to get unstuck.

### **What advice would you give to people who are on the job market now looking to start up their own their own lab?**

I guess, first, don't do it in a pandemic! But more seriously, I think you just have to find a good fit; you have to find a department and colleagues that you can work with. I now appreciate that you're quite isolated when you first start up your own lab (even when it's not a pandemic!) so having colleagues you can easily interact with is very important. It needs to be a good fit and you really need to like the area you're in, not just in terms of the lab and the science but also in terms of the place you're actually living in.

Some advice that another group leader gave me, which I also think is really important when you start up your own lab, is to pay attention to your own mental health. You need to be at the top of your game and if you're not taking care of your poor little brain, which can become stretched to its limits, your science is going to suffer. So find a place where you're not isolated scientifically, with good colleagues and senior PIs who keep an eye out for the more junior ones, with as few barriers to doing your science as possible, and somewhere that's also a fun and enjoyable place to live. It sounds like a tall order, but when you find a good fit, you'll know it.

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### **Did you ever consider an alternative career path?**

Not really. Once I got from out from under the bad advice of some high school career guidance counsellors, and once I started playing around in the lab, I soon realised that this – science – was what I wanted to do. I did work in industry for a little bit but I didn't really enjoy it. Even though I was in a place where I had the freedom to do basic research, we were still thinking about 'products' and would have the management team sit in on meetings and try to tell you, sometimes in not so subtle ways, to make the data fit the marketing strategy. The focus was less on the science and more on making money.

### **One last question: is there anything that our readers would be surprised to learn about you?**

Well, maybe it's not something surprising, although it is something I need to apologize for, but we recently learned that face blindness runs in my family. We didn't figure this out until a few years ago, when we started sharing embarrassing stories. I'm not as bad as some people in my family (who will literally walk past their own children without recognizing them!), but the odds are if I haven't seen you in a while, or you've changed your hair, or you're somewhere out of context, I probably won't recognize you. So, sorry about that.