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INTERVIEW

Transitions in development – an interview with Daniel Grimes

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Daniel Grimes is an Assistant Professor in the Institute of Molecular Biology at the University of Oregon, USA, and a recipient of the National Institutes of Health (National Institute of General Medical Sciences) MIRA Outstanding Research Award. His lab studies the consequences of ciliary mutations including left-right patterning defects and scoliosis, primarily in zebrafish. We spoke to Daniel over Zoom to hear more about his career path, his experience of becoming a group leader and the influence of Jurassic Park.

Let's start at the beginning, can you take me back to the moment you became interested in science?

I can probably trace it back to Jurassic Park. I was about six when that came out and I remember feeling really enthralled by it. I never had any academics or scientists in my family, so I didn't really know what scientists were like. I don't know how accurately Jurassic Park portrayed science at the time, but something about that combination of ferocious dinosaurs and Mr DNA definitely called out to me. I became interested in geology and earth science, which were my earliest interests in science. In my teens, I went through a phase of reading popular science physics books. But I ended up in biology, though I'm not exactly sure how that happened!

You completed your PhD at the Medical Research Council, Harwell Institute, UK, with Dominic Norris. Could you tell me a bit about what you worked on during that time?

I was in the Mammalian Genetics Unit, which has closed recently. It was a mouse genetics institute and everyone in the department was using mouse forward genetics to study all sorts of different things, from development and metabolism to neuroscience. I had done a 6 month project, in a different lab, during my undergraduate degree and I wanted to go back to Harwell for my PhD. The Norris lab work on cilia and left-right asymmetry. They had recently isolated and mapped a new mutant line from a screen that had organ symmetry defects. The mutation was in a gene called *Pkd1l1*, which encodes a polycystin protein. The student that helped map the mutation was finishing their PhD, so it was a good time for me to pick up the project. It seemed like a perfect project; my job was to characterise the mutation and to try and figure out what Pkd1l1 was doing to establish left-right organ asymmetry. We knew that motile cilia generate an asymmetric fluid flow that breaks symmetry and, during my project, we figured out that PKD1l1 is involved in transducing that flow signal to give rise to the first asymmetries in gene expression in the embryo (Field et al., 2011). Although we didn't know it at the time, the mutation we originally isolated in the screen was not a null mutation, so we published a second paper changing some of the initial ideas and building a more complete model of how Pkd1l1 works (Grimes et al., 2016a). I think that shows the power of genetic screens; that you don't just discover a gene involved in a process, you can isolate interesting alleles that tell you more about the underlying biology than simply creating standard loss-of-function alleles. Unsurprisingly, I'm still a big fan of screening approaches.

You then moved to Princeton University, USA, for your postdoc with Rebecca Burdine. What drew you there?

I owe a lot of that decision to Dominic. He had made a similar move where he went from the UK to the US for his postdoc as well. He always spoke so positively about the experience. Over time, it just became something that I felt like I wanted to do. Having a mentor who had done it, with whom I spoke every day, made it seem possible and feasible.

I decided on Princeton for the Burdine lab. I wanted to change model system and work on zebrafish. TALENS, and even early CRISPR, was becoming available with zebrafish so it felt like a good time to get involved as a geneticist, as well as to enjoy the other advantages of the fish system, such as imaging. I wanted to keep working on left-right asymmetry, but move away from the early embryonic patterning aspect into organogenesis. Becky had just published a few nice papers on heart symmetry so I planned to work on the heart, but those projects didn't take off, though we did

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eventually put out a small story (Grimes et al., 2020). Then, we noticed fish with dramatic spinal curves in our fish facility. Maybe it was my history of working at Harwell, but I thought that was a great phenotype and I wanted to try and figure out what was going on. So, I switched to these 'scoliosis' projects (Grimes et al., 2016b). Looking back, all of my PhD and postdoc projects are connected by cilia because the mutations I've worked on in both labs have been in cilia genes, whether studying left-right asymmetry, the heart or scoliosis. But I wouldn't say I directly work on cilia biology; I work more on the roles cilia play in development. That's what fascinates me.

How was your experience moving from Oxford to the USA?

Immigration is a complex process with a big administrative burden and time commitment, and with that comes lots of anxiety. Ultimately, I was pretty privileged. Immigration is hard for everyone, but it's harder than what I went through for a lot of other people; there was no real cultural difference, no language barrier for me. I didn't have kids coming with me or other family members. I rented a studio apartment in Princeton from the UK without visiting it first. When I arrived, fresh off the plane, I was surprised that the apartment wasn't furnished, which is less common in the UK but apparently normal in the US. Those first few days when I had no bank account, no mobile phone, no social security number and no bed – I think I slept on a pile of clothes – were tough. But, I soon got on my feet and settled in; I found people to play soccer with and it was a great opportunity to meet new people, see new places and do some science.

When did you start to look for independent positions?

In 2016, I put in two or three applications because I considered that as being a practice year on the faculty job market. I didn't get any interviews, but it was useful for preparing the materials and getting into the process mentally. I would recommend a practice year if there is time because redrafting and expanding the materials the following year was a lot easier than writing from scratch. Then in 2017, I applied to maybe ten places, which was actually quite a small search. Although I still had another year of funding in the Burdine lab, I did end up, very fortunately, getting a job that year.

How did you decide where to apply?

I made a list of all the adverts when they came out in journals like Nature and Science. The advice I now give to those going on the market is to apply broadly, to as many places as you can imagine yourself being, but I actually didn't follow that advice. I thought I should go to a medical school and applied to about five or six, but just a few months after my applications I realised that a medical school wouldn't be the right fit for me. I had three interviews, and one of them was here at the University of Oregon. It just seemed like the perfect place for me.

You became a group leader at the University of Oregon, USA, in 2019. Why did you decide to move there?

The University of Oregon is strong for zebrafish research; the model was founded here by George Streisinger. In fact, the building I'm in now is called the Streisinger building. A lot of the early pioneers, Chuck Kimmel, Monte Westerfield and Judith Eisen, are still here in active research. We also have excellent core facilities, which about 11 labs share, and joint meetings. It's a great place to do fish work. In Princeton, we were the only fish lab in the university and that was lonely at times. I wonder if that drove me towards a place where there was a long history of fish research and loads of labs working with fish. Ultimately, I believe in trusting your gut. When I came here, I got good vibes from people at all positions, from the department head to the students and the administrators, everyone seemed happy and that was key. When I got the offer to come here, it was quite an easy decision.

How was the transition to becoming a group leader and what has been your best moment?

I've liked nearly every aspect of it. It's such a good opportunity and I'm really enjoying it. I was originally excited by the challenge of having different roles and responsibilities from what you typically have as a postdoc. There's no formal training in many of those other roles, so there's lots of on-the-job learning but, at least initially, I liked that challenge. For example, writing NIH grants and getting feedback on them has really helped me to hone my work and think about it more deeply. It's a stressful business with so much money on the line, but it's been a great and useful exercise. Getting that first NIH grant was a big relief.

I've not had just one 'best moment'. Any successes in the lab by all lab members add up, whether it be getting a fellowship, getting a paper accepted, giving a talk, getting an experiment to work or even just asking a question at a seminar. We have a Slack channel called 'declarations of victory' where people can share these things and everyone else piles on congratulations and support. Celebrating the people I work with in the lab every day and helping them explore whatever they're curious about has been my favourite part of the job.

Can you summarise the research themes of your group now?

We're interested in how anatomy is built through the process of development and growth, and then maintained during adult phases. This includes how the organs become positioned correctly in the body, but also the overall shape of the body. There are links to various human diseases; mispositioning of the organs is a condition called heterotaxy, which can be very severe and a life-threatening birth defect, but can also lead to congenital heart disease in more mild cases. In particular, we're interested in the long axis of the body, the spine, and how it forms during development and then is maintained as the organism grows, or how this breaks down to cause scoliosis. We think about these problems across size scales, from molecular (gene expression and protein interactions) up to how tissues behave and interact with each other. I think most of the answers to these questions are going to exist in the communication between different scales and the interactions in both directions. These topics unite the things I worked on as a PhD student, left-right asymmetry, and then as a postdoc, the spine and scoliosis, but we're now taking a broader approach, no longer focusing only on the roles of cilia.

In your opinion, what are the exciting areas in your field?

The zebrafish spinal shape field is really taking off. It's still a relatively new field, there are only about five or six labs working in this area and every paper is an interesting step forward. The field is really coming into its own and I hope it's going to be helpful for understanding conditions like scoliosis. There's a long way to go, of course, but I think that's what I'm most excited by; the fact that it's still a young field and there are lots of big discoveries to be made in the near future.

You've already mentioned your team and their success. How did you go about hiring people?

I've hired one postdoc to date, Beth Bearce, and it's been – by far – the best decision I've made. We initially met through Twitter (I'm not a heavy user of Twitter but it's definitely helped me make

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some important connections in academia); Beth had written on her Twitter profile that she was looking for a postdoc and so I messaged her. She interviewed during the worst snowstorm Eugene's had in decades, but that didn't put her off. She's really helped get the lab up and running, and she's a great source of mentorship and knowledge for other lab members. It was useful to have a confident postdoc in the lab early on as a model for some of the graduate students and I think it's worked out for Beth – she's been publishing like crazy!

Pretty much everyone else in the lab is a graduate student and my philosophy is that if someone wants to do a rotation project I'll accept them – unless it's terrible timing or something. After that, it's about deciding whether I think I'm the best mentor to help them through their journey or whether they'd be best served by another mentor. Part of that answer comes from me and part of the answer comes from them – we just try to figure that out. I also regularly get hiring advice from other people. That's essential, because I recognise that I'm not experienced in it and it is a challenging part of the job.

How important do you think mentorship is in academia?

I've had some excellent mentors with different styles. It's important for people to find mentors beyond the obvious ones. Everyone has their advisors, but if you can try and expand that circle, it's going to be beneficial for you. Not only do you then experience different styles – and diversity, of course, is always a big asset – but having lots of different people at different career stages and in different places to give you their thoughts is valuable. You can assemble some kind of 'meta-advice' from that varied feedback. In my lab, we actively discuss strategies for how to find mentors and cultivate the mentor-mentee relationship long-term. Of course, that's easier for some kinds of people than others, and we have to be aware of that. Having lots of mentors yourself also helps you support your own mentees in more ways, simply because you've experienced a diversity of styles as a mentee and you can draw on those to fit the particular needs of your mentee. Good mentorship is essential at all career stages; everyone is a mentor and everyone is a mentee. Understanding the dynamics of that relationship is one of the big challenges, and exciting aspects, of academia.

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What advice would you give to people starting their own labs?

Always have in mind what your primary goals are and learn how to say 'no' to things that aren't going to further them. My goals are to do the best science we can, to support mentees, their work and their careers, and also try to use any leverage I have to help shape the department, the university and professional associations into places where historically marginalized people can thrive. Those are my big goals and I regularly check that I spend 80-90% of my time on them and I'm not getting taken away by other things. I also recommend getting a standing desk.

What approaches have you taken to help improve equality, diversity and inclusion (EDI)?

As I mentioned, improving EDI is a primary goal of mine. I was on the graduate recruitment committee and took courses on how to improve recruitment to make it more holistic and fair. I'm applying for funding to start a summer programme for students from traditionally underrepresented backgrounds. I also try to bring EDI issues into my biology courses because I think these issues should be front and centre. It's hard to change the status quo; it's a slow process, but it should be people like me that really put their time and effort into it as well.

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You were also an early contributor to preLights. Why did you decide to get involved and what are your views on preprints?

There are lots of issues surrounding publishing and science, as we all know, and some of those are gradually being tackled. The biggest improvement, for me, has been the rise of bioRxiv and preprint servers. I don't see a downside to preprinting, but I do see lots of advantages. We put out a preprint a few weeks ago and received instant feedback from the community (Bearce et al., 2022). We then sent the paper to Review Commons for peer review, which came back in about three weeks. After that, we went straight to a journal and got a response in a couple of days. The whole process has taken five weeks, which has not been my experience with traditional publishing. This idea at Review Commons, that even if the first journal doesn't like your paper, you can take it to another journal straight away with the same reviews, saves everyone's time. The best thing, of course, is preprints allow you to get your work out to the community straight away. So, I wanted to do my bit for the preprinting community and that's why I got into preLights. It's a really good resource and I'm sure preLights has been important for the growth of preprinting in cell and developmental biology.

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You recently co-organised The Company of Biologists Workshop on The Biology and Physics of Left-Right Patterning. Why did you decide to apply?

I applied because the left-right patterning field is small, and we do not have a meeting dedicated to asymmetry. We decided on 'the biology and physics' because left-right patterning involves fluid flow and so quite early on the field embraced mathematical and physical modelling-type studies. It seemed a natural fit. I'm a big believer in bringing different types of people together who think about problems in different ways. That's the beauty of the workshop – we could do that and get a deeper understanding of the system and, hopefully, foster collaborations that will push the field forward. It was easy and fun to organise and that meant we could focus on the science and the people.

Having had a number of editorial and committee roles, how important do you think such opportunities are for career development?

I've definitely enjoyed the committees I've been on and you learn something new every time but, if I was to redo my time again, I would have done fewer of these things. Although I believe everyone should do their fair share of service in the university and the academic community, I don't think editorial committee roles are especially important for early-career scientists – not compared with the other roles junior PIs have, such as building the lab, writing papers, getting funding and learning how to be a good mentor.

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Did you ever consider an alternative/non-academic career path?

I don't think I strongly thought about my long-term career until I was a postdoc, and I decided I wanted to try the academic job market. It's probably a privileged position to be in, but it's also kind of my personality; I wasn't too worried about the long term. I was lucky that that approach worked for me in the end. I do almost cringe a little bit thinking back, I probably should have been more proactive in exploring other opportunities as well. At the University of Oregon, we have a career opportunity seminar series for graduate students, in which people with biology PhDs that have taken various different kinds of routes after that come in and talk about their career paths. I think that's important and the graduate students here like that. I think that if something similar existed when I was training it would have influenced me to think more deeply about my career.

So, my last question: is there anything Development readers would be surprised to learn about you?

This is a tough question because readers probably don't think about me at all! Well, I did biochemistry as an undergrad and, in my first year, I almost changed to geology. I had all the paperwork signed. My transfer was delayed because the administrator was away for a few days and, over that weekend, I changed my mind again and stuck with biochemistry. I sometimes think back at that moment and how close I was to completely changing my future life. I could have been a geologist, and maybe that would have made more sense for hunting dinosaur fossils like I wanted to do when I was six.

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