© 2019. Published by The Company of Biologists Ltd | Development (2019) 146, dev176016. doi:10.1242/dev.176016

INTERVIEW

An interview with Cassandra Extavour

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Cassandra Extavour is Professor of Organismic and Evolutionary Biology and of Molecular and Cellular Biology at Harvard University (www.extavourlab.com). Recently appointed an editor at Development, her lab works on the evolution and development of germ cells in animals, the genetic control of reproductive capacity, and the evolution of the arthropod body plan. We met with Cassandra at the 2018 Santa Cruz Developmental Biology meeting and heard about her scientific history, her thoughts on the future of research at the intersection of evolution and development, and her lifelong passion for music.

Image courtesy of Erica Derrickson

Taking things back to the beginning, what got you into science in the first place?

I was not interested in science as a child, and only got interested in it very accidentally, towards the end of secondary school. I was talking to one of my friends who said he wanted to be a psychologist because, at 16, he felt he had great insight into people's minds. That got me thinking – I'd always found human behaviour fascinating, and thought the extent to which behaviour was controlled by the brain would be interesting to understand. I gradually turned that into deciding that I should train to be a neurosurgeon – surely they must be taught how brains work to operate in an intelligent way? (Of course now I know that no one really knows how brains work.) People sometimes ask me today why didn't I study neuroscience – the reality was that I didn't know that neuroscience was a field of research; I didn't even know that research was a profession. My parents didn't go to college – this is a very esoteric profession practised by such a tiny fraction of the population, and unless you know someone in an academic workplace, it wouldn't even occur to you that this kind of thing was happening.

But by the time I was finishing my undergraduate studies in Toronto, I had learned about the world of research labs. It still seemed quite vague, but it did seem to be a place where I could get advanced information about what I was learning in lectures. So I decided to get a summer internship and ended up in a developmental genetics lab, Joe Culotti's, where I helped map mutations that had come from a screen for axonal pathfinding mutants in worms. So the science interest was kind of late, kind of random, not very directed, and developmental genetics was also kind of random, but I found it interesting.

And what led you to move to Spain for your PhD?

I had heard about Antonio García-Bellido's work on *Drosophila* development in my studies, and I thought that I would like to learn to think about genetics like that. I was also interested in moving to another country and learning another language. So I wrote to Antonio, and he said that while he couldn't support foreign students, if I found money he'd be happy to advise me. I found a short-term fellowship programme and was able to go over, and then that year the Consejo Superior de Investigaciones Científicas (the National Science Foundation equivalent in Spain) opened up their graduate training fellowship to anyone who was a legal resident of Spain, and I applied and was awarded 4 years of funding.

What was your experience of Madrid, scientifically and culturally?

The science was fantastic. Antonio is the only person I've ever met who I would call a genius. It's hard to say what his teaching style was: I can't say exactly that he taught by example – he wasn't in the lab a huge amount. I learned so much because there was constant discussion and constant questioning. No one took anything you said at face value, ever, which was and is good practice. Why are you claiming that? Why do you think this? How many clones did you look at? Antonio wouldn't even talk about a phenotype until you had a few tens of clones, and so the bar was very high to even get him to engage with your data. I appreciated that – on the one hand, I see the utility of training in a style that allows your students to come to you with the minutiae at the beginnings of an experiment, but there's also value in saying that, however you're going to do it, I expect you to figure out the first 90% by yourself, and then I'll talk to you about the last 10%. Now he didn't say I needed to do this by myself; he said I had to learn from other people: read these books, talk to these people, share your data. It wasn't a message that you

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Development (2019) 146, dev176016. doi:10.1242/dev.176016

were on your own, it was a message that this is a stage of your learning that you must take responsibility for, by getting other people to show you, and thinking about it yourself. So that was the most formative scientific experience of my career, no doubt.

And culturally, I had a wonderful time in Madrid. I had never lived outside of Canada before, and the only countries I had visited were the United States and Argentina. I didn't know anyone in Spain, spoke Argentine Spanish (which turned out to be quite different), and didn't know anything about the country or its history. It was fantastic to learn all of this – people would even invite me to their villages to meet their grandmas! The biggest culture shock to me was that Spain was a monoculture – I was born in downtown Toronto, one of the most multicultural cities in the world, with multiple cultures within my own nuclear family, so to go to a place where everyone and every generation of their family for as long as they could remember was born in Spain, ate the same things, had the same names even, was quite a striking experience. It wasn't negative – I just didn't know to expect it before I moved.

After Spain you crossed the Mediterranean for Greece – what were you doing there?

I had a four-month Cretan interlude, thanks to a short-term EMBL fellowship in Michalis Averof's lab. For the first time I was working on a non-traditional model organism, trying to find germ cells in the brine shrimp *Artemia*. The experience really was helpful: it helped me learn how to find a gene when there's no genome, how to do experiments without previous protocols to rely on, all these different tricks to get round the various roadblocks such research presents. It was a great experience and introduction to doing research outside of established models.

Moving to Michael Akam's lab in Cambridge, what were you aiming to achieve?

I went to Michael and said I'd like to find germ cells in lots more organisms – for most animal phyla, someone had looked for and found germ cells, but it might not have been for 150 years. With molecular markers, I could identify germ cells and their precursors in embryogenesis, interrogate the mechanisms by which they are being specified, and generate a comparative view that's better than the one we currently have, which is based on three vertebrates, a nematode and a fly (which can't be the whole picture). Michael gave me a great deal – he said come to the lab, I can support you, but my funding is to study Hox genes, so you should try to get your own funding to work on germ cells; if you don't get it, you'll have to do something to do with Hox. It was a very good and fair deal, and I ended up getting a Biotechnology and Biological Sciences Research Council grant to study comparative germ line specification. An upshot of getting the grant was that I was able to be very independent in Cambridge.

When you set up your lab at Harvard, was the aim to continue this project?

I wanted to see if I could find molecular mechanistic evidence for a cell signalling pathway that was required and potentially sufficient to induce germ cells in arthropods. Because of the fly example, and other developmental models that had been looked at, there was a very strong feeling that germ plasm – cytoplasmic determinants inherited from the mother – specifies germ cells. But I thought that it was more likely that an inductive signal, the specifics of which I was agnostic about, was the ancestral mechanism, and therefore should be more commonly found across animal species. We started to look in a bunch of different arthropods: the cricket turned out to be one of the most tractable systems, and we tested the role of BMP signalling in them, inspired by how specification works in mice. We collected strong evidence that BMP signalling was necessary and potentially sufficient for at least germ cell maintenance and development, and we think specification too. So that was my main goal in setting up my lab – let's see if we can find evidence for this hypothesis I generated a while ago. I wasn't particularly invested in the hypothesis being correct or not – I was invested in finding evidence one way or another. It's not going to change my life if it works one way or another!

And we had other side projects – for example, the project looking at what determines ovariole numbers and hence fecundity in different *Drosophila* species, which I talked about in this meeting. I'd been interested in this for a long time without having done anything about it, and managed to convince a couple of my first graduate students to lay the foundations for that. We also ended up working on a gene called *oskar* completely serendipitously after one of my first graduate students found an *oskar* orthologue in the cricket, which led to a whole new focus on its evolution. *oskar* was discovered in *Drosophila* about 30 years ago, and it has the amazing characteristic of being the only animal gene ever discovered to be both necessary and sufficient to induce germ cell fate. Our discovery of *oskar* in a cricket was unexpected, because it was previously thought to be exclusive to a much smaller group of insects, and it was significant because we showed that cricket *oskar* was not needed in the germ line at all, but instead, played a role in the nervous system.

How did you find the postdoc-to-PI transition in terms of managing projects and people?

It was very challenging. I had been trained in labs where I'd never co-authored anything with anyone else in the lab – you were the sole author, or it was you and your advisor. My advisors expected a high level of independence, and were also very senior in their positions so just weren't around a lot (though were available to discuss the project's progress). I thought that I would do the same thing with my students, but I realised early on that it wasn't going to work like that. I was at a different stage in my career – I needed something different from my students than my advisors had needed from me. I also realised that my advisors had had an unusually homogenous population of people in their labs in terms of work habits, and that I did not have, at that stage of my career, the option to choose among large numbers of applicants that they had had, so I was going to have to find a different way of doing things. It was a new experience being responsible for manuscripts that I had not done all of the work for – that's very challenging. I don't like to micromanage, but if I feel like something isn't correct, then I will get in and micromanage it.

For the first five or six years of the lab, for every paper we published I generated some of the data – the cloning, the staining, the statistics – so I felt I was intimately involved in the data for all of our first important publications. That was helpful for me, and I hope it was helpful for the people involved, as I could be closer to what they were doing. I said to my first group of students and postdocs: you will get more of my attention than any other generation of the lab ever will, and it may feel like more pressure, but the upside is that for this lab to continue to exist, you will all need to be successful, so I'm going to make sure that all of your projects are successful.

The evo-devo field is very exciting at the moment: how can it continue to thrive in the next decade?

I think evo-devo should continue the practice of generating high-quality evidence, as close to functional or perturbational as possible,

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for specific hypotheses at the intersection of development and evolution. It will be important to continue to do this on a case-by-case basis – why is this one green and this one red? How come this has four fingers while this has five? Those kinds of stories, supported by strong functional evidence, will continue to be important and we shouldn't stop pursuing them. At the same time, we're at a point where we can take a step backwards and say: Are there any patterns to this? Are there certain types of evolutionary changes that have a higher probability of occurrence than others? Is the tendency via changes in cis versus trans regulation? I think we should keep adding our case studies to the pile, but also take more of a systems approach to the genetic basis of evolutionary change.

Lots of evolutionary biologists work on micro-evolution, looking at within-population variation for example. I think people coming at this from an evo-devo perspective can come closer to their traditional developmental biology colleagues, who are in fact in the best possible position to tell us about variation within a population. Everyone knows that when you report the expression pattern of a gene, for example, you've done *in situ* hybridisation on 30 or 100 embryos, but you know they didn't all look like the one you published! You picked the most representative, prettiest one that was developing in the way that you consider most normal, and that is a totally legitimate choice. That kind of variance – which might also be accentuated for instance if you shake the cage or switch the lights – is the kind of variance that evolutionary biologists are looking for, that they want to know about! Developmental biologists seeing high-throughput data sets know more about the details of within-population variation than many ecologists or evolutionary biologists. High-profile evo-devo has focused on macro-traits, which is fantastic and accessible, but I do think we can use traditional developmental biology expertise to bridge that macro/micro gap.

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You've recently joined Development as an editor: what do you hope to achieve in your new position, particularly with regard to evo-devo?

I do hope to further increase the appeal of Development for the evo-devo community. A common concern I hear from people considering submitting to us is that you'll get a *Drosophila* person asking you to make clones in your organism, be it an elephant or whatever, without understanding the specific attributes of the model. Another aspect is that while they'd like their paper to be in Development, many of their peer group, those in the evolutionary biology camp, won't necessarily see it, which might put some people off. Part of what I am going to try hard to do is to get the most appropriate expertise in the field as reviewers – people who will be able to appreciate works at the crossroads that have the potential to contribute to many different fields. I hope that as someone with developmental genetics experience in the premier genetic model organism who has also experienced really quite intractable models in the lab, I can help authors make it clear to reviewers and readers in more diverse fields what the importance of their work is. Development's practice of having reviewers talk to each other after submitting their reports is so helpful for us as editors, particularly when reviewers don't necessarily agree, and this fantastic feature is particularly helpful for evo-devo.

Development is the top specialist journal in developmental biology, but evo-devo is one step over. Coming from that perspective, authors need to make it crystal clear to all readers of Development, not just those in evo-devo, why it's really important that they know about the advance. It's the same thing we have to do when we ask for grants, or submit applications for fellowships – the reality is that we are in a privileged profession, using enormous amounts of resources, and we should be able to justify very clearly why we are doing what we do, why we get paid what we do. We recently had a session on grant writing with the lab and I stressed how important it is to be clear why your proposal is interesting – the fact that it's interesting to you isn't enough; the fact that you are exploring the unknown also isn't enough. I'm not saying that evo-devo is especially bad at this at all, but any time you try to cross a bridge – between cultures, between countries, between scientific fields – extra effort is required, and we need to continue to make that effort. The community has been great at doing this – evo-devo has been spectacularly successful in the last few decades, so we're in a great position.

Do you have any advice for a student considering a career in research?

If at 22 you feel absolutely sure that you want an academic career, a PhD is an entry pass, and you must have it, so you should do it. But what if you are not sure what your career will look like? This is of course more realistic, and also absolutely fine. I had no idea what I would be doing after my PhD and it didn't bother me, but I was really interested in learning how genes made cells do things, and I thought, and was willing to gamble on it, that I was not going to be bored learning about that for the next five years. I was also going to get paid, so I wouldn't need to find another job; I didn't have any dependents, so could afford to live on a student salary and just get to learn things. So if you think your interest is strong enough, that it is going to sustain you for five years, then do it, you can't go wrong; it has to be self-contained. That's my best advice, because nothing is guaranteed – not an academic job, not any other job based on your PhD.

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

Outside of the lab, I'm a soprano singer. I started performing when I was four, and music is essential to my life – it's not hard for me to imagine my life without science, but it's not possible to imagine my life without music. I started singing seriously at about 18 or 19 – before that I was mainly a flautist – and in graduate school got a teacher and started singing professionally more often. Singing is similar to science in a way. There's the creativity and the drive, and also the solitude – no one can do it for you, you have to do it yourself. Plus there's the networking, and the luck, and being introduced to the right people. Like science it's not a pure meritocracy, so it took me a few years to break into the Boston circuit, but I have been fortunate since then, getting quite a bit of professional singing work.