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INTERVIEW

An interview with Debby Silver

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Debby Silver is an Associate Professor at Duke University Medical Center and the Duke Institute for Brain Sciences, in Durham, North Carolina. Debby's research focusses on mammalian cortical neurogenesis, and on how RNA metabolism controls cell behaviors in the developing brain. Earlier this year, Debby became an Academic Editor at Development, and we met over Zoom to discuss her career path and research interests, as well as her motivation for joining the Development team.

Let's start at the beginning – what first got you interested in science?

I was one of those kids who always gravitated towards science and math. Towards the end of high school, I was thinking about engineering, but I took a biology class in my last year and got particularly excited about that direction. I majored in biology at college, but I really cemented my passion and excitement for biology when I had the opportunity to work in labs and learn molecular biology. It was just amazing to me to be able to apply what I'd learned in the classroom to the bench. I think my parents also influenced my career path: my dad was an engineer and my mom an artist, and I like to think that I got something relevant from each of them – analytical thought and creativity.

During your PhD, you worked with Denise Montell on cell migration in the *Drosophila* ovary. What drew you to this topic and to Denise's lab?

After I graduated from college, I worked in a lab at the National Institutes of Health for several years before starting my PhD. I chose to do this because I wasn't really sure what I wanted to do and I wanted a full time lab experience before jumping into graduate school. I had the opportunity to work with Jim Sellers on the biochemistry of myosins, and Jim basically treated me like a grad student, which was amazing. This period really taught me how to do science – I had originally planned to stay for one, maybe two years, but I got so into my project that I stayed for four!

So that is how I got interested in the cytoskeleton, and when I was looking for graduate programs I wanted to move from *in vitro* reconstitution to *in vivo*. My favorite class in college was developmental biology, and so I was drawn to Denise's lab. Her border cell model is just amazingly beautiful, and simple, and I loved being able to manipulate genes and look at cell migration. Denise also gave me the space to translate what I had learned in flies to study questions in human cancer cells. I got so many great foundations in her lab – not just learning how to do rigorous science, but also about asking bold and interesting questions, taking risks and pursuing the unexpected.

You then switched fields for your postdoc, moving from flies to mice, and working initially on neural crest derivatives. What was your motivation for this move?

The dabbling I did with human cancer cells at the end of my thesis got me thinking that it would be useful to learn an *in vivo* mammalian model. I got really excited about Bill Pavan's lab because they were pursuing forward genetic screens for neural crest phenotypes in mice and I thought it was so cool having come from the fly world to be able to apply some of these same approaches to mice.

The logistics of screening in mice are so much more complicated (and expensive) than in flies – do you see forward genetic screens as a useful route to discovery in mammalian systems today?

Absolutely. It is really about having good design and a robust readout. In Bill's lab it was a dominant screen, and they were using pigmentation as a readout of neural crest defects, which were really easy to spot (no pun intended). Mapping mutants is even easier now than when I did it – as folks can sequence exomes. As a research community, we are also only studying a small fraction of

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the genes in our genome – the ones we have tools for – so I definitely think there is a place for unbiased gene discovery through forward genetics – as long as you have the right screen design, and the funding!

How did you then become interested in the development of the central nervous system?

I was interested in studying the nervous system when I started my postdoc. But studying the cortex was somewhat serendipitous – the mutant that I decided to focus on from the screen had, in addition to a neural crest phenotype, a really severe microcephaly. This got me excited about cortical development, because it seemed to me to be a microcosm of so many different developmental processes: migration, polarity, cell division, cell fate choice and so on. So I redirected my efforts in that direction during my postdoc, and Bill was super supportive of this. He and I both agreed that I would need to get some additional advisors to help me make this transition. I developed key relationships and collaborations, and working on this project helped give me confidence in my ability to work independently, as well as excitement to create my own scientific journey. And, of course, the fact that I had developed my own line of research really helped once I started my own lab because I wasn't in a position where I was competing with my postdoctoral supervisor.

You set up your own lab at Duke in 2010. What were the questions you initially set out to address?

The mutant I identified in my postdoc was in an RNA binding protein (Magoh), which we showed had clear roles in cortical neurogenesis and mitosis. So, this was a foundation for me to start to think about RNA metabolism in cortical development, about which there wasn't much known at the time. I decided to focus on Magoh and more broadly on how RNA binding proteins control brain development – I felt like this could give us a unique angle on understanding cortical development, particularly in the context of cell division and cell fate. From the RNA metabolism direction, I also became interested in subcellular RNA localization.

From the cell perspective, what do you think are the advantages of regulating expression at the level of RNA rather than the level of transcription?

RNAs can prime cells for rapid and spatial gene expression in response to extrinsic or intrinsic signals. As a field, we rely a lot on transcriptomic data, but there can be discordance between RNA and protein levels. RNA is quite fascinating, requiring different levels of post-transcriptional control and having functions beyond simply making a protein.

What is your lab working on now, and what are you getting excited about in terms of possible future projects?

We are continuing along many of the same lines that were the foundations of my lab. Initially, we were mostly using mouse models, but we have increasingly started to incorporate human induced pluripotent stem cells (iPSCs) and organoids to complement our understanding of cortical development. We are still focusing on post-transcriptional control, including RNA binding proteins that are related to neurodevelopmental disease. RNA localization is still a fascinating research direction for the lab, and one that has also led us to become interested in the subcellular architecture of the cortex. We are excited to understand subcellular gene expression, but also how signaling and communication at different niches can influence how a progenitor behaves, what type of neuron it makes and when.

And one of the projects that I started working on pretty early on in my lab is cortical evolution, which began with a collaboration with Greg Wray, an evolutionary biologist here at Duke. This is something we are continuing to work on, and we are increasingly thinking about how to bridge interests in the lab – beyond studying evolution from the perspective of non-coding elements, but also thinking about how post-transcriptional control may shape species differences.

Brain evolution is an innately fascinating topic, because it leads into thinking about what makes us human. I am interested in the extent to which you think it will be possible to really understand human-specific brain development and function

I think we can characterize developmental differences and now start to manipulate them. But of course holistically it is a much bigger challenge, and we are always going to be limited by the systems we use. It is a really cool time to be studying cortical evolution with lots of comparative genomics data, CRISPR and iPSC technology; there has been some great work in the field to catalog genomic differences, but the challenge becomes understanding these differences functionally. And one of the caveats is always going to be your experimental system – for example, although using cells in a dish can give important insights, it is still *in vitro*. So I feel that evolutionary studies benefit a lot from taking multiple orthogonal approaches. Will it be possible to understand human-specific brain development? Maybe not completely, but we can learn a lot and, as a field, we are really starting to make exciting progress.

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What is your ethos for running your lab, and what approach do you take to mentoring your team?

Each person who joins my lab has their own scientific interests and career goals. So I avoid assigning folks a project because I want to help trainees identify topics that they are passionate about. When someone joins my lab, we have lots of conversations to define their interests – for example, are they more interested in the basic science or driven by understanding disease? I meet weekly with the people in my lab, mainly talking about the science (troubleshooting, designing, etc.) but also about their specific career goals – helping them identify and progress along their own personal journey. One of my favorite parts of being a PI is helping trainees develop their interests, progress a project, and increase their confidence. One thing I try to emphasize to trainees is that their career path may not go in a straight line – you sort of bump into things that guide you in one direction or another. And I really value having a team that works together – I encourage collaboration and not competition between lab members.

In terms of mentorship, I like to think that I have integrated pieces from each of the training opportunities I was fortunate to experience before starting my own lab. The transition to becoming a PI is really challenging because we are generally not trained to manage personnel, so I aim to give the folks in my lab opportunities to

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mentor undergraduates or rotation students so they can learn what mentoring style is effective for them.

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You've just joined Development's team of editors. Why were you keen to join us, and what do you hope to achieve in this position?

I am really excited about this opportunity. I have always viewed Development as a consistently great journal for publishing solid and important findings across broad areas of development. There are a few things I love about the journal from the perspective of joining the editorial team. One is having academic editors, and then there is the vision the Company has of embracing Open Access, supporting early career scientists and providing funding for the community. Also, from the experiences I have had as an author – I felt like the review process was fair and reasonable.

In terms of what I hope to achieve, I want to contribute to the mission of bringing in important papers. There are lots of journals out there, but I would like to encourage many in our field to see Development as their go-to journal, and to make the community more aware of the many advantages that publishing in Development has to offer.

What types of papers would you like to see come your way?

Obviously I would like to see papers on cortical development and RNA biology, and I am keen to attract papers asking evo-devo questions in the context of nervous system development. I would also like to see more people considering Development as a home for papers on the later stages of nervous system development – circuit building, synaptic formation and so on. I think there can be a tendency to think of development in terms of what happens in the embryo, but there is so much in the nervous system that happens after birth.

There have been so many technological developments that are now driving our field forwards and it would be great to see papers that are exploiting these technologies. The single cell 'omics revolution is definitely changing our understanding of development, but I am looking forward to seeing how these varied approaches can be applied to understand RNA metabolism, the single cell proteome and so on. And I am excited by new live imaging technologies, including those which directly manipulate proteins and RNAs. I feel like this is one of the best times to be going into developmental biology as we now have the tools to answer so many questions.

Finally, what might Development readers be surprised to find out about you?

I love the underwater world. When I was in college, I spent a semester studying abroad in the Turks and Caicos. It was here that I fell in love with scuba diving, which prompted me to even consider a career in marine biology. In fact, now as a developmental neurobiologist, one of my favorite parts of academia is that we get to travel and explore new worlds.