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INTERVIEW

An interview with Samantha Morris

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Samantha Morris is an Assistant Professor of Genetics and Developmental Biology at Washington University in St Louis, and an Allen Distinguished Investigator. Her lab aims to understand how cell identity can be reprogrammed, focusing on the gene regulatory networks that define cell identity and applying this knowledge to engineer clinically important cell types. Sam has also been a pioneer in developing novel single-cell technologies and, earlier this year, she joined Development as an Associate Editor, where she'll be providing expertise on single-cell approaches in developmental and stem cell biology. We caught up with Sam to ask her more about her career and her role at Development.

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

When I was about 10 years old, I carried out a school project on the weather. It was my first research project – I had to go to the library, read a lot of books and bring everything together in a little booklet. I think that just got me hooked on doing research and gathering ideas. Then, when I was leaving school and going around collecting teacher autographs (which is what we used to do before we left school), my science teacher also wrote a note that said: 'Grasp the nettle – you have the potential to become a very good scientist'. At the time, I didn't think it resonated with me. As a teenager, I became more and more interested in biology, and one of my teachers directed me toward biochemistry, which is what I ended up studying as an undergraduate. But I had kept the note, and it wasn't until I was older – when I became serious about science and research that I looked back at it and thought about it and how it must have encouraged me. It still means a lot to me.

How did you then become interested in developmental biology?

I studied Biochemistry at Imperial College London but it was actually an incredibly broad course; it was like drinking from a fire hose and learning lots about different aspects of science. One of the units was on developmental biology and I was blown away by it! My lecturer on that course, Jane Saffell, could see how interested I was – I was always asking lots of questions – so she invited me to work in her lab for the summer. In her lab, I had the opportunity to study neurite outgrowth, and as a result I became completely hooked on bench research. Jane encouraged me to do a PhD so I searched for labs with openings, specifically in developmental biology, and landed in a *Xenopus* lab in Cambridge. Initially, I was excited at the idea of becoming a developmental biologist, but my PI wanted me to work on a cancer project. For the first year, my project was going nowhere. Everybody else seemed to be focused on interesting embryology questions, but I was stuck in cell culture – I just didn't get much joy out of it at that time. In the end, I adopted some 'side projects', basically doing some developmental biology on the sly, and those experiments really took off.

For your first post-doc, you switched over to working with mice and looking at cell fate decisions. What triggered that switch?

At the time, I was actually pursuing a post-doc position with Jim Smith, to research morphogen gradients in *Xenopus* development; I had become fascinated by live-cell imaging, thanks to a talk by Scott Fraser, and thought that imaging morphogen gradients would be exciting and informative. But while I was waiting for a position to open in Jim's lab, a friend sent me a job advert for a position in Magdalena Zernicka-Goetz's lab, using live imaging to study early mammalian embryo development. I gave it some thought (as I wasn't restricted to studying *Xenopus*) and decided it could be an interesting direction to move into. And then I met Magda – who is a force of nature – and I guess the rest is history. I took that position without even seeing a mouse embryo (because Magda is so convincing), but when I saw my first two cell-stage mouse embryo under the microscope, I thought to myself, 'Oh my god, this is incredible'! Even now, when I see a paper on pre-implantation development, I remember how beautiful it was to watch.

You then moved over to George Daley's lab (Harvard University) to do your second post-doc, where you developed CellNet. Can you tell us more about this work and how/why you developed this tool?

As part of my work in Magda's lab, I had been investigating transcription factors that specify cell fate. I wanted to test some

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hypotheses by overexpressing these transcription factors to convert the identity of, for example, primitive endoderm cells to trophectoderm. One day while I was in the tearoom at the Gurdon Institute, I described these experiments to John Gurdon (who has been an important mentor to me), and he said: 'You know, what you're describing is simply reprogramming, Samantha'. And I guess that's what got me interested in reprogramming. As I dug into it a little more, I realized that it's not so simple to generate reprogrammed cells at high efficiency or to produce the correct target cell type. As a result, I ended up joining George's lab, as it seemed like a great place to study reprogramming. I also wanted to be in the USA in the long term, so it felt exciting to make that move.

This move is how I started work on reprogramming, and these experiments, for me, are just as mesmerizing as watching early mouse development because you can overexpress transcription factors and, within days, you can watch your cells as they morph into a different identity. But, as I mentioned, the lineage conversion process is typically inefficient, so we developed CellNet to tackle this – to understand why reprogramming is inefficient and why it lacks fidelity. CellNet takes bulk expression data (which, back then, was microarray data) and computationally reconstructs gene regulatory networks. It also helps you to identify transcription factors that could help enhance the reprogramming process. Using this approach, we targeted one particular cell type called iHeps. These are mouse fibroblasts that are converted (via transcription factor overexpression) into hepatocytes, or so-called induced hepatocytes. Using CellNet, we could see that these cells weakly resembled hepatocytes, but that they also possessed some intestinal cell identity. This observation led to some further experiments in which we transplanted the reprogrammed cells into damaged mouse intestine and showed that they were capable of functional engraftment. That's still one of the most exciting experimental results that I've experienced over my career.

You then set up your own group at Washington University in St Louis, where you've continued with the theme of reprogramming. What's the main question that your group is trying to address?

We're certainly still focused on the general theme of reprogramming cell identity. We've continued to work on the iHeps because I think they are a valuable reprogramming paradigm, although we renamed them 'induced endoderm progenitors'. We've also adopted other reprogramming systems, though, for example, conversion to cardiomyocytes, macrophages and pluripotent cells; hopefully, you'll slowly see this work coming out over the next year or so. We also develop new technologies that are designed to help us understand general reprogramming mechanisms. As I was setting up my lab in 2015, high-throughput single-cell technologies were emerging. However, one of the limitations of many of these genomic technologies is that you do not retain information on lineage relationships. So I found myself interested in how we could develop new technologies to record lineage information. It was fun as a developmental/stem cell biologist to get into this tech development field. We ended up creating a barcoding system, called CellTagging, that allows us to capture lineage information and cell identity in parallel. We've also recently followed up on the CellNet paper by developing a computational platform (CellOracle) that uses single-cell data to infer gene regulatory networks and to predict the outcome of transcription factor perturbation. We also created a new tool (Capybara) to measure cell identity and fate transitions. Together, these tools have given us mechanistic insight into the reprogramming process and have helped us to identify new factors to improve reprogramming outcome.

It's been especially fun to get involved in tech development but also to have biological questions in mind. Personally, it's also been an exciting journey for me. I've always loved working at the bench, doing experiments, but tech development is not something I anticipated building my lab around. The biological questions are what led me toward it, which in turn helped me build a team of people who are passionate about both the biology and technology. The single-cell biology field has also been fantastic. We've been able to reach out for help with protocols and have established lots of great collaborations.

You've also been involved with the Human Cell Atlas project – how did that come about and how has this project progressed?

A few years ago, the Chan Zuckerberg Initiative put out a call looking for groups to develop experimental tools that could help construct the Human Cell Atlas (HCA). One of the challenges for the HCA is how to assemble an atlas of diverse cell types, collected by different labs using different technologies; ultimately, how do we merge all of these data to create a working atlas? We knew that, even within our lab, we could profile identical cells using the same technology on different days and produce slightly different datasets – technical variations drive the data apart. To address this, our first project aimed to develop a standardization method. Our idea was that labs could 'spike in' a labelled cell type to act as a standard to correct for technical variation, helping preserve interesting biological variation. Funnily enough, the tech development, in this case, didn't take off, but the project resulted in our multiplexing approach that we developed to track cells in competitive transplant assays. We've used this to genetically track reprogrammed cell identity and behaviour following their transplantation into the mouse intestine.

The second project was a computational project that aimed to automate cell annotation. Our goal was to devise a method to measure cell identity in an unbiased way, using single-cell data and existing cell atlases. This brought about the 'Capybara' platform (which is named Capybara because the obvious names were taken, so we picked something completely random!). There are a lot of these cell classifier platforms now – it's a pretty crowded field, but Capybara is slightly different. My student Wenjun, who devised the platform, realized that cells undergoing developmental or reprogramming transitions harbour multiple identities, so she was able to use the classification scores from Capybara to find cells in transition. Whereas a lot of other cell classifiers pigeonhole cell identity as a discrete property, Capybara views cell identity as a continuum and can describe a cell as a blend of cell type A and cell type B, which gives it a unique angle.

The third project is a blend of experimental and computational biology. Experimentally, we're trying to couple our CellTagging lineage tracing approach to single-cell ATAC-seq, so that we can assess lineage and chromatin accessibility simultaneously. For this project, we collaborate with Luca Pinello, who's a computational biologist at Massachusetts General Hospital and Harvard Medical School, to explore how we can synthesise single-cell lineage data into faithful lineage trees.

Earlier this year, you joined Development as one of our Associate Editors. Can you tell us why you decided to get involved and what you will be doing at the journal?

Development has always been one of my favourite journals! It's consistently published exciting, hypothesis-driven research. I've also respected how the journal engaged with the stem cell community a few years ago because development and stem cell biology certainly go hand in hand. Having feet in both camps, I was keen to get involved. I'll be handling submissions directly and guiding papers through the peer-review process.

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I've also been on Development's Editorial Advisory Board for the past year, and this has been an interesting experience. Just being able to discuss where the field is going, how we can engage with different groups of researchers, and how we can advise other editors on papers has been quite eye-opening. I hadn't realised how much goes on behind the scenes in publishing, but it strikes me that, at Development, there's a group of people that genuinely care about the research and want the right outcome for papers. I also feel that Development has been setting the new standard for publishing. So overall, I'm very excited to be getting involved.

And what do you think is exciting in the field right now?

I think that new methods for lineage tracing are particularly exciting right now. The technologies that Alex Schier, Alexander van Oudenaarden and Allon Klein, for example, are developing are particularly elegant. Applying these methods to zebrafish development has already been very fruitful, but they're poised to be deployed in different developmental systems, as well as in stem cell biology. It's going to be an exciting field to watch as the tools are applied to various questions.

The other area that I'm anxious to watch (and dive into) is spatial transcriptomics. With most of the current single-cell technologies, spatial information is lost. However, if we can retain that spatial information, we can create new opportunities for classical fate mapping at high resolution, for example. And with new methods to integrate complementary datasets, a dynamic fate map can be created to support in silico investigation and hypothesis generation. With this, we can return to some classic developmental biology questions and address them using these new technologies.

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It's also been especially satisfying to see many of these technologies being made freely available; it's almost as if there's a competition to see which lab can be the most cooperative! But, overall, there's undoubtedly been a shift towards opening up protocols, sharing reagents and datasets, and making tools more accessible, which is just great for the field.

And what sort of papers would you like to see at Development?

Fundamentally, I'm excited about stem cell and reprogramming papers, but I also wouldn't mind a sprinkle of early mouse development papers, as that's a field that I still follow closely. I'm particularly excited about articles that incorporate some form of technology into them. I think we're now at a point where some of the genomic technologies have matured, and we can learn much from them. We've now seen a lot of cell atlas papers, which of course are tremendously valuable, but I feel we're now moving beyond cell profiling. We can now routinely use these technologies to generate and test exciting new hypotheses. I think we're going to see more people incorporating these technologies in a much more creative way.

You've worked in a few different places and for different people so, based on all of this, what's been your approach to mentoring people in your lab?

I love spending time with my lab. I relish one-on-one meetings and enjoy discussing new ideas. However, with my mentees, I learned rapidly that every person in the lab needs a slightly different mentoring style. That's been fun to develop, to learn about my team and to understand what works for each member. In terms of my mentoring style, I like to lead by example, for instance by getting back to the bench when it comes to revisions for a paper, or helping to train people with single-cell library preparation. I'm determined to keep doing that. I'll also periodically dive back in to assist with data analysis, which I love doing but also helps me to see exactly how people are approaching their projects. Also, as a lab that develops technologies, we can sometimes get blinkered, so every so often it's good to take a step back and reset things based on our core hypotheses, rather than apply the technology without having a clear question in mind.

I also think it's important to reflect on your mentoring style. For example, it took me a while to realize that words can easily be misinterpreted (e.g. when you're sending a quick message in Slack), so you have to be careful how you communicate with people. Setting expectations is also essential. I've seen and experienced some people that use disappointment as a weapon, and I don't think that has any place in a productive mentee-mentor relationship. I'd rather be more transparent and let people know exactly what I'm thinking – it's a healthier approach, and I expect the same in return.

What would be your advice to junior people who are starting out in the field?

From a young age, I was very fortunate to have people around me who recognized that I was passionate about science. These people became unofficial mentors to me. Since then, I've also been lucky to have more senior people who've advised me and acted as mentors. Ultimately, I've always had these 'go-to' people – people I can go to for a chat, or get an opinion on something, or send grants and manuscripts to. People have always been incredibly generous with their time and that's helped me throughout my career. So I'd encourage junior people to reach out beyond their local environment to find mentors and build support networks.

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I recently experienced junior people approaching me for mentorship. That, to me, is not work – it's an absolute honour. So, I wouldn't be shy of finding mentors. Institutions try to build these types of relationships by establishing formal committees for mentoring but I think you need to build relationships with people you trust, naturally over time. It's something that's worked well for me and is something that I keenly recommend.

One last question, which is something that we ask everyone: is there anything that people will be surprised to find out about you?

When I was 19 years old, I waitressed in Yellowstone National Park for a summer. This is when my love affair with the USA began. It was an incredible experience: travelling solo, I flew from London to San Francisco, got a Greyhound over to Bozeman in Montana, and then drove down into Wyoming and Yellowstone. I waitressed at the Canyon Lodge – it was a remarkable experience because I would waitress for 4 days then, for 3 days each week, I got to hike and explore the park. As an employee, you came to know the non-tourist, sometimes dangerous, areas of the park and could get close to the wildlife. So if you passed through Canyon Lodge in the summer of 2000, there's a good chance that a 19-year-old Sam was serving you (possibly very badly)!