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CELL SCIENTISTS TO WATCH

Cell scientist to watch – Pleasantine Mill

Pleasantine Mill graduated in microbiology and immunology from McGill University, Montréal, Canada, and completed her PhD in medical and molecular genetics at the University of Toronto, Canada. There, under the supervision of Chi-chung Hui, she studied Hedgehog signalling pathways in skin development and tumorigenesis. For her postdoctoral research, Pleasantine moved to Ian Jackson's laboratory at the MRC Human Genetics Unit, Edinburgh, UK, with a Natural Sciences and Engineering Research Council of Canada (NSERC) fellowship, followed by a Caledonian Research fellowship. Initially focusing on neural crest development, she identified and studied several mouse mutants that displayed defects in ciliogenesis and cilia structure that went on to be implicated in human disease. Pleasantine established her own research program at the MRC in 2014. Her group investigates the genetic programme for cilia structure and function and the links to human ciliopathies. She is the recipient of the 2019 Women in Cell Biology Early Career Award Medal from the British Society for Cell Biology (BSCB).

Pleasantine Mill

What inspired you to become a scientist?

Both my parents are architects, so I grew up in a very creative and intellectual environment. We drew on the back of napkins at the dinner table, we were always building or creating things, always problem solving with lots of discussions. We travelled lots and visited many museums and galleries. It was a very privileged environment to grow up in. I knew that I didn't want to be an architect – I can't draw a straight line with a ruler! Rather, I wanted to be an astronaut and do space medicine. Then, through phenomenal science teachers at high school and after my first lab experience doing actual research, it really struck me that basic discovery research was what I wanted to do.

A big aspect in architecture is the beauty of form, shape and pattern. Do you think that sparked your interest in developmental and cell biology?

Yes. I'm a very visual person and there is something very aesthetic about the type of research we do – symmetries, pattern formation and so on. Dry datasets don't do much for me. They might have a lot of information in them but it is often lost without understanding the context of cellular time and space. Imaging is my secret passion – well, it's not such a secret, is it!

What questions are your lab trying to answer just now?

We are interested in the cell biology of cilia. Why are cilia different on different cell types? We think it informs on human disease – patients can have similar mutations in the same gene but very different phenotypes. Studying cilia in cell lines only captures an iota of what's really going on in our bodies during development and during homeostasis in adulthood. Thus, we try to understand the differences between the cilia types that we find in our bodies and what they do in terms of physiology. Ultimately, we're also looking at how these mechanisms can inform on new therapeutics, which is exciting. What we do is cross-disciplinary, maybe multi-disciplinary cell biology on an organismal scale, informed by genetics.

What has been the most influential publication or work in your field recently?

What has been most exciting and influential for our field is the movement towards preprint servers like BioRxiv, and the early and interactive discussions amongst the community it has been stirring. It is also immensely empowering for early-career researchers to get DOIs for their work in order to secure funding or get citations while they are in formal review. It makes the system much more dynamic and allows you to adapt some new data or develop new hypotheses early for guiding your own research. A specific example I can think about is a great paper from John Wallingford's and Steven Brody's groups on the discovery of dynein axonemal assembly particles, which are these intriguing phase-separated organelles where dynein subunits dynamically associate with their assembly factors. Genetics had told us that these things were interacting and now there's spatial and temporal information in the cell on how this assembly might occur. A year later when it was published, the paper had improved with peer review, but had not significantly changed and we had been able to use it early to shape what we're doing, what questions we're asking, where we need to move in the space. Our lab reads a lot, and we read broadly; sometimes, to focus is more difficult for us. [laughs]

Are there any new techniques that you're adapting for your research right now?

Cell biology sometimes uses a very heavy-handed sledge hammer approach to look at things; you grossly overexpress proteins and look at their localisation in a cell line. What we've been doing

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Adventure is out there! Pleasantine and the Kunath crew (Tilo, Lachlan, Lennox & Matthias) on Blackford Hill, Edinburgh.

recently is to engineer endogenously tagged reporter mice for key genes of interest, which lets us look at changes in protein composition specifically and dynamically in cilia in an inducible fashion. It allows us to capture a particular snapshot of development or disease process, and to ask what in this population of cilia in this particular region of the brain informs on physiology. It's a very nuanced application of tools that people have developed, but applying it in what we think is an elegant and powerful way to get at disease mechanism with organelle resolution.

Research communities often distinguish curiosity- and hypothesis-driven research. Would you place yourself in the former?

I am definitely curiosity driven. You need to really understand the system to be able to ask the right questions. I struggle a little bit with the concept of hypothesis-driven research because it sometimes seems premature; a hypothesis represents the curiosity at later stages well into some of our projects and can drive us to keep going in a particular direction, but it's not the space that we often start with. Being creative is where science makes the leaps and bounds. The language that goes with a hypothesis-driven question and the structure that comes with it in a research proposal is often easier for people to gauge and may be why funding bodies seem to prefer hypotheses-driven applications. But science needs both types – even though I'm certainly curiosity driven!

What challenges did you face when starting your own lab that you didn't expect?

From my postdoctoral time with Ian onwards, I always had some independence, especially regarding the setup of a cilia-centered research focus. At the same time, I didn't have to move city or country again to start a new group, and that is something that people often struggle with. I also didn't have to re-establish myself as a group leader, which I think was very helpful and I didn't lose momentum. Moving wasn't really an easy option since I had a complicated mouse colony at the institute and also family engagements, including three young kids and a partner who is also a research group leader. The downside of it, which I think may have been held over me, is that people question your independence because you have stayed in the same environment. I feel it's an unfortunate trend that people feel you have to move to prove yourself. I would argue that – particularly for scientists with children or other familial commitments – this view still represents a handicap for some. I don't think moving is necessarily a good measure of how productive you are as a scientist, nor the most efficient way of doing great science.

"Being creative is where science makes the leaps and bounds."

How are the challenges that you're facing now different?

It's always about funding and doing more science. On a personal level, you have always got to be thinking two steps ahead with your research to keep your people on, to hire new people, to get new equipment. It doesn't stop. If anything, it starts to ramp up because you realise your productivity has to be more to meet your growing responsibilities. Also, as part of the research community, I have definitely become much more active in outreach and advisory roles. Now more than ever, we need to keep telling the public and funders how important supporting our basic research is.

How do you go about recruiting group members?

We've had great luck with people. I'm a big believer in developing people being the most valuable part of what we do in research. The training of students is incredibly important – let different skill sets come forward over time. I have a phenomenal team of people and we are lucky that the MRC unit has an excellent rotation-based PhD programme. The students often come through the lab because they are attracted to the projects and are constantly in exchange with the people who are already in place. I think having a healthy happy lab to start off with always brings more of the same spirit in and encourages creative science.

What is the best science-related advice you ever received?

A very helpful piece of advice I got was 'there is no such thing as a dead end in science', which means that there is nothing that you choose that you can't come back from. It came at a time I was slightly frozen in what to do, how to make the right choice between career and balancing the rest of my life. In the end, there is no right answer and nothing that you can't come back from. It helped me to make that decision and continues to help me today – there may be easier ways to do research, but there's never a dead end.

What advice or guidance do you pass on to your students?

It's about the individuals going through the lab. We're not just concerned about getting data for our papers when we have PhD students. When mentoring students, you are building skill sets that are going to allow them to apply this knowledge for whatever they end up doing. I also want to make sure people are happy and grounded to be able to ask the right questions, think critically about their data and where they need to be next. And to be excited about their research! I try to spend time with them trying to make sure it is all coming together somehow and they're not just stalled – that it's not just about the data for a thesis but about a bigger picture and the training too!

"…you need to make sure you are happy with where you are at each moment [in your career]."

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How do you achieve a work–life balance when you're trying to establish yourself as an independent investigator?

The difficult thing with science is that you always think there is going to be a better time – you are going to get that paper and you are going to get that grant, it's all going to be sorted and that will be the time. The thing is: life is short. You do not know what is going to lie ahead tomorrow, next week, a year away, so you need to make sure you are happy with where you are at each moment. Of course, it's never perfectly balanced – I like to say we are always one step ahead of total chaos – but the kids are happy, we're happy and we seem to be doing okay. I'm not sure it is a balance, but it has worked so far.

How do you get the most out of the meetings you attend, particularly in the early stages of your career?

Conferences are absolutely key; by meeting people from your field, you get conference 'buddies' who will follow you throughout your career and that you will become close to, and they will be future reviewers for grants, for papers and everything else. It is about establishing a diverse network of contacts in terms of fields, nationalities and career stages. At the same time, you also meet a lot of people who are in a similar situation of starting their own group, and any exchange of thoughts and experiences provides help. Of course, when you have kids, your ability to travel goes down and it is hard to balance those things, but if you can do it and find ways to do it with childcare, it is definitely worth it.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

I'm Pleasantine the 6th. My mother is Pleasantine, my grandmother is Pleasantine and so on…It is a name that goes via the eldest daughter in a family. Luckily, I have all boys so the onus of tradition wasn't on me! [laughs].

Pleasantine Mill was interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.