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CELL SCIENTISTS TO WATCH

Cell scientist to watch – Laura Greaves

Laura Greaves studied pharmacology at Newcastle University, UK, where she also obtained her PhD in the lab of Douglas Turnbull for her work on the role of mitochondrial DNA (mtDNA) mutations in the ageing human colonic epithelium. During her postdoc with Douglas Turnbull and John Mathers, funded by the Food Standards Agency, UK, she showed that clonal expansion of mtDNA point mutations drives mitochondrial dysfunction during human ageing. With MRC funding for the Lifelong Health and Wellbeing Centre for Ageing and Vitality programme as well as a Newcastle University Research Fellowship, she established her independent research group in 2016 at the Wellcome Trust Centre for Mitochondrial Research, Newcastle. Her lab uses genetic mouse models and intestinal organoids to investigate the functional consequences of mtDNA mutations on cellular metabolism and colorectal cancer development. Laura is the winner of the 2022 Women in Cell Biology Early Career Medal awarded by the British Society for Cell Biology.

Laura Greaves

What inspired you to become a scientist?

I'm not one of those people who always knew they wanted to be a scientist. I liked maths and science at school, and was interested in how things work, so when it came to applying to universities I looked through the various science courses that were available; I ended up choosing pharmacology at Newcastle, because it brought together science with drugs and diseases, which were a bit more tangible to me. Back then, I thought that universities were mainly focussed on teaching; this changed during my third year when I did an undergraduate research project, which I absolutely loved, as it opened my eyes to how much research actually goes on at the university. That project was a turning point and it's then that I decided that research is what I wanted to do.

And how did you end up studying mitochondrial mutations in ageing, a topic you've been working on since your PhD?

I wanted to stay in Newcastle, as it's where I grew up and I have strong family ties here, so coming to the end of my degree I met with numerous supervisors who were accepting PhD students to talk about potential projects. I decided to take on a project, supervised by Professor Doug Turnbull and Professor Tom Kirkwood, which was about studying the role of mitochondrial DNA (mtDNA) mutations in neuronal stem cell aging. However, when I got to the department, they had just received a piece of colon and told me that before I start on my project I should have a look at mitochondrial function in the colonic epithelium. I did that, and it turned out that I never went anywhere near a neuron during my PhD or career! Working on the ageing colon also meant that I had my research niche carved out at that point, as it was quite different to what others in the department were working on. So, I had to learn quite quickly to stand on my own two feet.

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What are the main questions your lab is trying to answer just now?

We're trying to understand how mtDNA mutations in colorectal cancers can change the metabolism of the tumour. We see that a high proportion of colorectal cancers have a wide spectrum of mtDNA mutations, and each of them can have different effects on mitochondrial metabolism. One of the questions we're trying to answer is whether specific defects in mitochondrial oxidative phosphorylation sensitize or cause resistance to particular drugs or therapies. Ultimately, we'd like to be able to find the best treatment for an individual person or tumour, but before we get there, we need to understand at the molecular level what different mutations are actually doing to the tumours and how we might exploit them.

Which technologies have had the biggest impact on your research?

For a long time, one of the biggest stumbling blocks in mitochondrial research was the fact that it was really difficult to manipulate the mitochondrial genome, directly or indirectly. Then in 2004, the mitochondrial mutator mouse was developed, which has a mutation in the proofreading domain of the mitochondrial DNA polymerase – so every time the mtDNA replicates, there is a very high chance of a mutation being introduced. I've used this model in a number of studies, combined with other mouse models, to look at the effect of mtDNA mutations on intestinal tumour development or intestinal stem cell proliferation. More recently, new technologies such as mtDNA base editors have emerged, which allow us to directly and specifically manipulate mtDNA – and I think this will make a huge difference in the field! Then from the

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Laura with her partner Barry and son Toby on the beach in Northumberland.

perspective of studying the intestine, the development of intestinal organoids by the group of Hans Clevers has really revolutionized the field and allowed us to carry out the kind of drug testing we are doing.

Looking back at the time you started your own group, what were the main challenges you faced?

I think a big challenge in the transition from postdoc to PI is going from being responsible for yourself to being responsible for a whole group and having to get those grants to be able to keep people in a job – which is a lot of pressure. Also, it's difficult as a new group leader to suddenly have to do all sorts of things that you haven't necessarily been trained for – be it budget management, people management or sorting out all the paperwork for doing experiments. Having an already well-established network at the institute did help me when starting my group.

Could you elaborate a bit on the main advantages of staying at the same research institute for a long time? And on the flip side, what challenges did that come with?

One massive benefit of having been in the same place is that I know a lot of people on a personal level – including the admin staff, technical staff, animal house staff, catering staff and cleaning staff. This has really been useful if I was struggling with something and needed to ask for help. In general, I feel that The Wellcome Centre for Mitochondrial Research is a massively supportive environment. Everyone has the same core interests in mitochondrial DNA mutations and mitochondrial biology, but each group has their unique focus – whether that's neurodegenerative disease, ageing, cancer or primary mitochondrial diseases – so rather than competing against each other, people are hugely collaborative. It's also brilliant to have world-renowned experts on your doorstep who you can discuss any interesting or weird result with. Conversely, one of the main challenges I faced due to not moving to other places was convincing people that I was independent and that the research ideas were mine. Doug Turnbull, our head of the department, would be the first person to tell anyone 'this is Laura's research', but it was still difficult to assert my independence, and to have that recognised by people outside of the department. Since I've started to work more on ageing and then moved on to the cancer field, this has been less of an issue, at least externally. One of the things I really had to do was find my own collaborators and develop my independent network, both internationally and in the UK. Professor Owen Sansom, who is the Director of the Cancer Research UK Beatson Institute, has been a hugely generous collaborator and a really great mentor with whom I discussed various things about my career.

What advice would you give someone seeking independence?

I think it's key to have a really good project that you deeply care about and are passionate about.

Another important thing, as I mentioned, is to find good mentors and talk to people; if you're someone who wants to move institutions, talk to the PhD students and technicians working there, as that will give you an idea of how the lab or the institute operates on a day-to-day basis.

Tell us one thing you'd like to see change in academia

I feel that one of the things that people can fall in the trap of is not realizing that everyone has an important role and is equally valuable, be that a researcher, clinician, student, technician or professional support staff. No research group is going to run without everybody's contribution, and I think this has often been overlooked in academia. But I'm hoping that with the advent of different incentives to promote a positive research culture, this will change, and emphasizing the value of each person is something I'm trying to really push within my own research group.

> **"No research group is going to run without everybody's contribution, and I think this has often been overlooked in academia."**

Is there any piece of advice that you found particularly helpful during your career?

Something that Doug used to tell me a lot is to focus on myself, do my best and forget what everyone else is doing. A lot of people in science, particularly in academia, really struggle with imposter syndrome, myself included. It's easy to get yourself into a situation where you compare yourself to others, but this can actually be quite destructive.

You are this year's WICB Early Career Medal Winner. What does this prize mean to you?

Obviously, I was delighted and really honoured to receive the prize. And looking at some of the past winners, I was also very surprised about how on earth they selected me – you see, my imposter syndrome really shows! Of course, in science, no prize is really for an individual, and without all the amazing people I work with on a daily basis nothing what I've done would have been possible. So, the prize is not really for me, it's for all of us!

What kind of policies do you think are needed to get more women into leadership positions in science?

Although things are starting to slowly change for the better, when you compare the proportion of female PhD students and postdocs with those in leadership positions, there is still a massive imbalance. And I think part of the solution is giving women support when they're at the postdoc level and promoting flexible working policies and work–life balance. I think we need to allow people to work their own way, because as long as we pull together and are successful, it doesn't matter when people do their job – for example, if they need

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to leave early and then can catch up on work during the evening, that should be totally okay.

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How do you achieve work–life balance as a parent?

Don’t get me wrong, it is tricky. But when you have children, your priorities do change and you also learn to delegate – which I’ve found quite easy because I have fantastic people in my lab who I really trust. I think I’ve also become much more efficient in getting things done at work, so I do try to keep work and home life quite separate.

Finally, could you tell us an interesting fact about yourself that people wouldn’t know by looking at your CV?

I ran the Yorkshire marathon last October – which was the first and probably last time I did a marathon. I trained really hard for it and tried to get a specific time which I then missed by 23 s, so I obviously beat myself up about it for the next 6 months (smiles).

Laura Greaves was interviewed by Máté Pálfy, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.