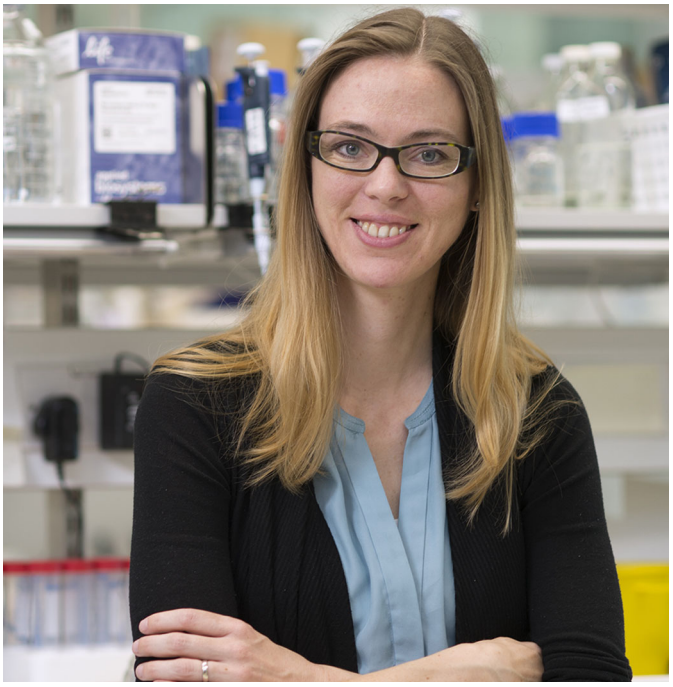
© 2017. Published by The Company of Biologists Ltd | Journal of Cell Science (2017) 130, 11-13 doi:10.1242/jcs.199984

CELL SCIENTISTS TO WATCH

Cell scientist to watch – Madeline Lancaster

Madeline Lancaster received her first degree in biochemistry from the Occidental College in Los Angeles, California, and continued to follow her interests by pursuing a PhD in biomedical sciences in the laboratory of Joseph Gleeson at University of California, San Diego. She then left the USA to train as a postdoctoral fellow with Jürgen Knoblich at the Institute of Molecular Biotechnology of the Austrian Academy of Sciences in Vienna. Madeline was a recipient of the EMBO, Helen Hay Whitney and Marie Curie Incoming Fellowships, and in 2014 her work was recognised when she was awarded the Eppendorf Award for Young Investigators. She started her own lab at the MRC Laboratory for Molecular Biology in Cambridge, UK in 2015 and her group uses brain organoids to unravel the general principles of brain evolution, focusing on human brain development, as well as studying neurological diseases that involve defects in brain size.



What inspired you to become a scientist?

I always had a scientific view of the world, which was supported by the fact that both of my parents were scientifically trained and my father has his own lab. He's in a totally different field, but I was exposed to the scientific lifestyle at a young age when visiting his lab and seeing how it runs. A lot of kids don't get the chance to see what science is actually all about, so I think that played a big role. And then I just really enjoyed it throughout school; I had great teachers and thought it was fun, so I just kept doing it.

And what motivates you now?

I just love what I do. I wake up and I'm excited to go to work. I'm excited about the experiments I might be doing that day, and the idea that you never know on which day you might make a discovery that no one else has ever made. What's great is that whenever you find something out you are the first person in the world to see that, and you get to tell the world about it. It's all the motivation I could ask for.

What questions is your lab trying to answer?

In general, we're interested in biological processes that underlie human brain evolution, but we're not limited to that. We're also interested in general principles of brain evolution, in particular, brain size and expansion, and in that respect, we're also studying neurological diseases that involve defects in brain size, like microcephaly or macrocephaly. Those two sides of the lab intertwine nicely. For example, we look at genes that might be involved in microcephaly and might also have a role in evolution, and then we look at how those genes might be playing a role in our *in vitro* system by comparing different types of mutations and their potential effects in organoids derived from other species. The lab is really focused on using the organoid system as a tool to get at those bigger questions of what makes the human brain different from other brains and general principles of brain evolution. In theory, we can make organoids from any species we want, and use them to address questions that were previously limited to mouse or other typical model organisms. So organoids are the main method that we use, although, as we are also interested in bigger questions, we might come back to *in vivo* studies in mice.

"…whenever you find something out you are the first person in the world to see that…"

How did you come to be working in such an exciting new area of research?

It was a bit of an accident. When I went to Jürgen Knoblich's lab, I was interested in brain development and together we decided that it would be nice to look at some of the regulators of neural stem cells that had been identified in his lab in flies, but using a mouse model. The catch was that there were a lot of genes and it wasn't realistic to make knockouts, so I decided to try an *in vitro* approach first. We decided to use neural rosettes, which is a powerful, widely used 2D system. But when I started to establish it in the lab, I had issues with coating of the dishes. Instead of sitting down on a coated dish, the cells were coming off and forming these big balls. I could have just thrown them away and continued trying to get the rosettes to work, but I also thought that these 3D balls looked interesting. At that time, work came out showing that if you embedded gut stem cells in Matrigel they would make these beautiful 3D organoids. So I took some of these weird balls of neural tissue and embedded them in Matrigel and the transformation was amazing; you could see eyes

Madeline Lancaster works at the MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge CB2 0QH, UK.

E-mail: mlancast@mrc-lmb.cam.ac.uk

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Madeline skiing back home in the US.

and cortical tissue growing out. Once we saw that, we switched to human cells, where we developed the method further, and that is how it became the method that is published.

What recent findings in 3D biology do you find most exciting?

Recently the labs of Melissa Little and Joseph Bonventre independently published work on kidney organoids that look just beautiful. I think this is a really exciting new organoid because it has obvious major therapeutic implications, and also gives us a system to look at kidney diseases and test drug toxicity. It's also very exciting for me, because I studied cystic kidney disease quite extensively during the first part of my PhD. I think that having a kidney organoid is an amazing new tool that could eventually lead to things like kidney transplant alternatives.

What do you think will be the next organoid?

Since 2013, there's been a huge explosion in organoids research. There's been stomach, intestine, liver, pancreas, lung and now kidney. I think we're going to see more organoids in the next year, and maybe better derivatives of the organoids that have already been published. But there are some that still remain to be tackled, like skin, for example. I think for the most part we'll be able to make organoids from epithelial-derived organs, but the mesoderm-derived tissues, like heart or muscle, might be more difficult.

What are the current limitations?

The biggest limitation is vascularisation, which has plagued the tissue engineering field as well. You can see that it's the biggest hurdle, because if you look at the tissue engineering constructs that can have therapeutic implications, you find that the one that is the furthest along is cartilage, and that's because cartilage is not vascularised. Every other tissue is running into the problem of not having enough blood supply and therefore not being able to go beyond a certain size and stage of development. So that's the biggest hurdle we're going to have to try to overcome. I'm not really sure how it's going to be done, because it's something the whole tissue engineering field has been working on for a long time so it will probably require a blending of different fields.

> **"…the transformation was amazing; you could see eyes and cortical tissue growing out."**

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

When I thought about what it would be like to run my own lab, I imagined I would have a lot more time at the bench. I really underestimated the amount of time you have to spend on getting things established. There's a lot of extra stuff behind the scenes in establishing and running a lab that I didn't realise my advisors were doing during my PhD and postdoc. I spend a lot of time emailing, making sure that various approvals are going through, that we've done risk assessments, and also establishing the foundation of the lab, like databases for keeping track of different reagents. I wanted to make sure that I started my lab in an organised fashion so that it could eventually run itself. But that does take a lot of time, so I've spent most of the first six months of my lab getting everything established. But I feel like it was well worth the effort, as with all of these resources up and running now I'm also able to spend more time at the bench.

What is your advice on recruiting the first people into your group?

My view is that it's nice to start with a small lab and not balloon out of proportion too early. But the advice I would give is not to rush into hiring new people, because it takes a bit of time to get the word out that you're starting your lab and the top candidates may not have the exact same timing as you do. It's a good idea to wait until you have a candidate that you really want. You don't want to end up in a situation where you already have a full lab and the perfect person comes along but you can't offer them a position. Don't be concerned about trying to fill the lab – it will get filled.

What elements, inside or outside the lab, have been key to your success?

Enjoying what I do is probably 90% of it. I find that when you like what you do, you can get better at it, and the better you get, the more you enjoy it; that's how it's been for me. I also have a lot of support from my partner, especially as we have a family. With this kind of career you need a lot of support, whether you're a man or a woman.

How do you achieve a work–life balance, especially when you're starting your lab?

Maria Leptin (the director of EMBO) once told me that if you want to have a family, you just have to do it. It's hard and you need support, but you can make it work if you really want to. You obviously have to sacrifice something. I think there are three things you can spend your time doing: work, family and fun, and you can choose two at a given time. I've chosen my work and my family, but

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luckily for me my work is also my fun, so that's fantastic, but you have to realise that you can't always have it all.

What is your advice on collaborations?

Because we have this very nice method, we've been approached by a number of other investigators who are interested in using it. Of course I don't have the manpower to engage in every collaboration that comes my way, so my general rule is that you should get out what you give and vice versa. If it doesn't seem like it's going to be a collaboration that works that way, perhaps it's not worth the effort. That said, sometimes the amount of effort that I need to put in isn't very high, because it's just a matter of providing organoids and I have plenty of these growing. But generating organoids for people is a lot more effort so I think carefully about whether that's worth it, and my advice is to make sure that you think about what both parties get out of the arrangement.

How do you balance going to meetings with being in the lab?

Because I'm just starting the lab and because of my family, I try to limit the number of meetings that I go to and make sure that it's worth it. I do that in a number of different ways. I try to make sure that there are at least six weeks between meetings. I can't get anything done in only a few weeks, so I like to have time in between. The other thing I consider is what I would get out of it, so I look at who else might be presenting, and if I can learn something new. Networking is also very important. I'm just starting out, so I do need to get out there and meet other group leaders. I'm very excited now because I've been chosen to help organise a Company of Biologists Workshop on neural organoids and bioengineering, so that will be a great way to bring several leaders in these diverse fields together.

Could you tell us something about yourself that people wouldn't know from your CV?

I'm an avid skier. I grew up in Salt Lake City, Utah, so I love skiing. I think the first time that I was on skis is when I was 3 years old. I get to go skiing whenever I go home and I go home fairly often. In particular, I really love moguls, though I'm very bad at them. But I like them because I like a challenge, and it's really fun to try to go down a steep mogul run. Takes me a while, but I really enjoy it.

Madeline Lancaster was interviewed by Anna Bobrowska, Editorial Intern at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.