JEM Journal of Experimental Medicine

PEOPLE & IDEAS

Michelle Linterman: We are always learning

Lucie Van Emmenis

Michelle Linterman is a group leader at the Babraham Institute, Cambridge, UK. The research focus of her lab is to understand the fundamental biology of the germinal center response after immunization and infection and how this changes with age. We caught up with Michelle to talk about how her interest in germinal center biology started, the benefits of team science, and her collaboration between the Malaghan Institute of Medical Research, New Zealand, and Churchill College, Cambridge.

Tell us about your background and how you first became interested in studying germinal centers.

I am from Aotearoa New Zealand. I was born in Christchurch but grew up in a small town on the Kāpiti coast called Waikanae. I did a biomedical science degree at the University of Victoria, Wellington, and I just loved it. It was awesome and so interesting! They had designed the degree in a way to capture the genetic revolution which was happening at that time, and that was just fascinating. After doing a 3-yr degree I moved to Canberra for a 3-mo summer studentship in Carola Vinuesa's lab, which was just phenomenal! She's an amazing person, an amazing scientist, and she's just really infectious in every way! I stayed and did a 1-yr honors project working on human genetics, and then I stayed with her to do a PhD. Although I had done human genetics for my major in my undergraduate degree, when I was in Carola's lab I really liked the way that you could use genetically modified mice to do beautiful hypothesis-driven research, and so that's what I decided to do my PhD on. Carola had recently discovered the Roquin gene using sanroque mice, so this was a really exciting time to be in the lab, and one project that I had was trying to understand why these mice had a systemic lupus–like disease. This was also around the time when follicular helper T cell (Tfh) biology was beginning to take off. The sanroque mice had a spontaneous formation of Tfh cells that we were able to show contributed to the lupus-like disease (Linterman et al., 2009), and the fundamental biology of Tfh cells and the germinal center has been the thing that I've been really passionate about ever since!

An inspiring start! What led you to start your lab at Babraham and investigate age-related changes in T cell biology?

When I was in Carola's lab, we also identified a proportion of Tfh cells that also expressed the transcription factor Foxp3, and this was a really exciting discovery, but I had just finished my PhD and wanted to get out into the big, bad world and have some adventures. I went and did a postdoc with Ken Smith in Cambridge working on the fundamental biology of Tfh cells (Linterman et al., 2014), but I couldn't quite let the Foxp3$^+$ Tfh cell project go, so in the end the project was carried out as a collaboration between Carola's lab and Ken's lab, as well as Adrian Liston's lab in Belgium, as he had just finished his postdoc with Sasha Rudensky and had a lot of really nice in vivo tools to allow us to manipulate Foxp3$^+$ cells. It was a really cool opportunity for us all, as we had Tfh expertise coming from Carola's lab, T reg expertise from Adrian's lab, and germinal center work from Ken Smith. We were able to publish a paper on what we called Foxp3$^+$ follicular regulatory T cells (Linterman et al., 2011), and it was a great collaboration for all of us. What was also good about being in Ken's lab was that he does a great job of running human and mouse work in parallel, and that was instructive for me to learn about and was a skill set that I took with me when I set up

Michelle Linterman.

my lab here at the Babraham Institute nearly 10 yr ago. The exciting opportunity at Babraham for me was that they were starting to get more interested in healthy aging, and the reason that I was interested in that was because the germinal center is compromised by the aging process, but it really wasn't clear why. This caught my attention because it seemed like a great opportunity in which the fundamental immunology of the germinal center response could potentially inform how we could stimulate older bodies differently to elicit better responses to vaccines. That's been one of the big things that we've been working on, as well as germinal centers that form non-lymphoid tissues (Denton et al., 2019). At the moment, the heart of the lab is still germinal center biology, and we're trying to be a bit more cell type agnostic rather than having a specifically Tfh focus. Working on aging has really forced us to look at the response

Lucie Van Emmenis: lvanemmenis@rockefeller.edu.

holistically, as conceptually it could be that only one cell type is affected and everything else is fine, or even that everything is affected a small amount. We are really trying to integrate all of these parts together, and I think what's been neat about working on aging is that it forces you to think about things slightly differently and to ask questions that you wouldn't have normally thought of, and I think we have learned more about how the germinal center works because of that.

What are you currently working on, and what projects are you most excited about?

At the moment, there are two things that I'm really excited about. Firstly, our work on aging has revealed that it is probably interactions between immune and non-immune cells that are impaired. In particular, Alyssa Silva-Cayetano showed that Tfh cells are important for the stromal cell response to vaccination (Silva-Cayetano et al., 2023), and this delivery of help to cell types beyond B cells is an axis that has only been hinted at previously. Recently, I was looking at one of Hergen Spits's *JEM* papers from 2021 (Heesters et al., 2021) where they have a data set looking at the transcriptome of human stromal-derived follicular dendritic cells (FDCs) and they show that the FDCs have the potential to talk to T cells, but Alyssa's data actually links the cell types together functionally. Secondly, my lab is really interested in the interface of mouse and human research. During the pandemic, we were working with the Tess Lambe and Jenner Institute team on their COVID-19 vaccine candidate that was ultimately licensed and distributed by AstraZeneca. We ran a pre-clinical study of their vaccine in our aged mice, just ahead of them having results from the human trials. What was really exciting to me about that was how good a model the aged mice were for the human vaccine response (Silva-Cayetano et al., 2021). It might not make sense that a 2-yr-old mouse is the same as a 70-yr-old human, but it's true, at least for their response to vaccination. What we're doing now is figuring out how we can use that information to test new vaccine formulations and approaches in order to elicit a good response in older people. Doing this type of work in aged mice is much faster, and so we've set up some nice collaborations with people who are more on the vaccine development side of things to do this. We are trying to use what we've learned in mice to have an impact in humans. I hope that this all works out, but we'll see!

And outside of your lab, what is some work in your field that you are excited about?

One thing that I am really excited about in the germinal center field, that I think hasn't been explored well enough yet, is stromal cell biology. It's been known for a long time that FDCs are important—if you reread Ian MacLennan's 1994 review on germinal centers (MacLennan, 1994) there's a lot in there about FDCs—and they were originally thought to be the cells that were providing the selection signal for B cells, and then Tfh came along and we got very excited about Tfh. But now the stromal immunology field is really growing and expanding, and there are people like Burkhard Ludewig, Natalia Pikor, Pavel Tolar, and Alice Denton who are doing really beautiful work on the stromal cells that underpin the germinal center. I think that there's a lot to be learned in that space, and we simply don't know enough about it yet. I think that this is going to be an area of real growth.

What are some of the qualities that you learned during your graduate studies or postdoc that you maintain and foster in your own lab?

I think I, like most lab heads, took the things that I liked and left the things that I didn't like. Things that are important for me are regular meetings with my team, and that was something that came out of combined experience of postdoc and PhD. I also want to be available when people have an exciting result; I always want them to come to my office to show me! Carola was great like that; sometimes she'd make a point of keeping track of your experiments and would ask, "What was the result from that experiment?" I remember that for one of the papers I was working on, I was a bit disappointed because the effect size I was seeing wasn't as big as I was hoping for and I was still thinking about it, and when I told her I was disappointed, she had the opposite response and told me it was an awesome result! She helped me to see that even though it maybe wasn't as good as what I was hoping for, it was still biologically meaningful. So I think that that's probably one of the things that I try to do, to make sure my team knows when their work is biologically meaningful. I think we're always learning, though. One of the things that I really enjoy, particularly at this career stage, is speaking to people who set up their labs at around the same time as me. In addition to talking about science, we're always talking about how we do our journal clubs, how we manage our staff, etc. It's a continual learning process, and the best people to learn from are other people who are facing the same challenges as you. For example, in my lab we have changed the format of how we do journal club based on some of these discussions, and it is working so much better! We're now experimenting with changing the format of our lab meetings to try and focus more on experiment planning rather than on data. If we want to be innovative in our experiments, we also need to be innovative in how we do all of the other things as well. We have to be open to new ideas, and it's a continual learning process. I certainly don't think that I've got all the right answers, but I'm willing to experiment.

What do you consider to be the best part of your job?

Absolutely the best part of my job is working with the talented people in my lab. I've been so lucky that I've had such an amazing bunch of people who have come through the lab; they are the ones that drive science forward. I particularly like that when you recruit a postdoc you hire a colleague. Already, three postdocs from my lab have established independent academic trajectories, which to me is one measure of success. Not that I think progression within academia is the only successful path—I've had many people from my lab go into industry, and they really enjoy it. Especially around Cambridge, it's a really vibrant area, although the pay raise they get is terrifying for me because I could never compete with that!

Do you feel positive about the future of science, particularly when thinking about how "brain drain" is affecting academic science?

I do, actually. The current and former members of my lab are a testament to the bright scientific future ahead, both in academia and in industry. My personal feeling is that for anyone who goes through my lab,

if they have a career in science then I consider that to be a success. We're also quite lucky that in the Cambridge area there are lots of really exciting and innovative companies that people can go into, and people are really excited about the work that they're doing there.

This year at *JEM* we are working to amplify and highlight women in science. We've heard from a number of different women about the need for gender parity, how to create healthy working environments, and the importance of mentorship. Are there any aspects of scientific culture that you feel passionately about yourself, or an area in which you have seen improvement in?

One tangible initiative at the Babraham Institute is called a "roving researcher." This is a postdoc position at the Institute whose job it is to cover when other people go on leave; typically this has been postdocs or PhD students going on parental leave, but not exclusively, so it could also be if someone needs cover for other reasons. It's a difficult role, and obviously when you're a highly skilled and highly experienced, highly specialized postdoc, someone else will never be able to fully replace you, but to have that project ticking along while you are on leave I think is a real benefit. My lab benefited from it when I went on parental leave, not because I wanted them to cover my job, but because one of our research assistants got headhunted by a company while I was away and she was working on a massive human vaccination study that we were running, and so the roving researcher was able to step in and fill that gap at short notice. A senior scientist in the lab, Louise Webb, just sorted it out while I was away, and it was able to solve something that could otherwise have been a huge problem very quickly. That's something that I feel really positive about.

I also generally feel very positive about mentoring from the wider immunology community. I've been the recipient of mentoring from so many people, and in particular I think that successful women in immunology do look out for younger women, particularly in the UK. I've felt really supported, and I believe that mentoring doesn't necessarily have to be an ongoing long-term relationship. For example, I remember when I was a postdoc, Gitta Stockinger invited me to give a talk at Mill Hill, and this was just at the cusp of having got my position at Babraham, but I hadn't moved yet. She was on the European Research Council panel and I was asking her for advice on that, and she just looked at me and said, "Oh, just apply for the grant, Michelle!" It was just the kick that I needed, and even though I don't go to Gitta regularly for advice, she's someone who's popped up at key phases in my career and either given me a little push or a little bit of help when I needed it, and I think there is a lot of that in our community. This type of help doesn't get as recognized as it should because it's not necessarily a formal mentoring relationship, but it's really helpful. There are so many other examples that I could give—it's my experience that people do support each other very well.

Having a roving researcher sounds like a great initiative, and it's great that scientists at Babraham can benefit from it. Another initiative that you are involved in is the Te Urungi Churchill College By-Fellowship, which is a collaboration between the Malaghan Institute of Medical Research in Wellington, New Zealand, and Churchill College, Cambridge. You are currently hosting Theresa Pankhurst as a postdoctoral fellow in your lab; what does it mean to you to be able to host a fellow and to participate in this collaboration?

I'm super excited to have Theresa in the lab first and foremost because she's an excellent scientist (Pankhurst et al., 2023). What's particularly exciting about her fellowship is that it is for Māori researchers to build their scientific expertise with a lens on Te Ao Māori. This is important because if you look at health statistics, there's quite frankly a disgusting disparity between Māori and non-Māori, which is just unacceptable in this day and age. This fellowship has been set up both to enhance Theresa's career development, but also to provide an interface between science and the community. It's equal parts about her professional development and strengthening relationships with Māori communities, ensuring that Aotearoa New Zealand has future leaders in science who have an eye on health equity.

Building on Theresa's fellowship, we've also been awarded a grant from the Biotechnology and Biological Sciences Research Council to formalize this collaboration and to facilitate research exchange between the Babraham and Malaghan Institutes. I'm looking forward to this collaboration because in addition to research exchange happening for postdocs like Theresa, we've also organized an exchange between the technical staff from the core facilities. I'm really pleased that we're going to be involving people from different job roles across the two institutes to build a successful and productive working relationship.

And finally, when not in the lab, how do you enjoy spending your spare time?

I have an 18 mo old, so I spend a lot of time reading books with my son! I also play for one of the local netball clubs, the Cherry Hinton Cherries. It's a bit intense at the moment because it's the end of the season and so a lot of the team have injuries, but we won the county Premier League, which means that we're going to the regional playoffs!

References

Denton, A.E., et al. 2019. *J. Exp. Med.* https://doi.org/10.1084/jem.20181216

Heesters, B.A., et al. 2021. *J. Exp. Med.* https://doi.org/10.1084/jem.20210790

Linterman, M.A., et al. 2009. *J. Exp. Med.* https://doi.org/10.1084/jem.20081886

Linterman, M.A., et al. 2011. *Nat. Med.* https://doi.org/10.1038/nm.2425

Linterman, M.A., et al. 2014. *Elife.* https://doi.org/10.7554/eLife.03180

MacLennan, I.C. 1994. *Annu. Rev. Immunol.* https://doi.org/10.1146/annurev.iy.12.040194.001001

Pankhurst, T.E., et al. 2023. *Cell Rep.* https://doi.org/10.1016/j.celrep.2023.112310

Silva-Cayetano, A., et al. 2021. *Med.* https://doi.org/10.1016/j.medj.2020.12.006

Silva-Cayetano, A., et al. 2023. *Nat. Immunol.* https://doi.org/10.1038/s41590-023-01519-9