Transcript

Emily Thornton- I'm Emily Thornton, Junior Group Leader at the HIU at the WIMM and am a mucosal immunologist. A mucosal immunologist is somebody who studies immunology, how the immune system is working at barrier sites. In particular I'm interested in the lung and the guts. So if you think about it, your lungs and your guts are each about a tennis court worth of of surface area and so your immune system has to figure out how to interact with everything that you're breathing in everything that your eating, without overreacting, so those sorts of questions of how does that work, how is everything kept under control, and how is the immune system seeing it all, are really what I'm excited about. So I started my PhD at the University of California, San Francisco, and that is sort of an umbrella programme, so you can sort of do different rotations in different labs and figure out what you like and what you're interested in. And my first one was in Max Krummel's Lab and he got me interested in doing lung immunology, which he hadn't actually done before, but we sort of took on the adventure together and so that's what I did for my PhD. I was interested in how things that are breathed in are taken up by immune cells and then presented to other immune cells and where those interactions are happening in the lung. And then for my postdoc, I wanted to move to the gut because there are lots of other challenges in the gut, including interactions with the whole microbial community, that's there, and so that's why I came to the University of Oxford to join Fiona Powrie's lab.

Catherine Seed- When did you start at the HIU?

Emily Thornton- So I started in the HIU in July of 2020.

Catherine Seed- Which is an interesting time to start.

Emily Thornton- Not the best time to start an independent research group, but I mean, then obviously the global pandemic was in its throes and obviously that's a huge mucosal immunology project, so I picked up some work looking at the immune response to SARS-COV-2 in the intestine. Lots of people are studying how the immune system is interacting with the pathogen in the lungs, but it can also infect the intestine and so that's one of the questions that we're still studying.

Catherine Seed- So you talked about two main mucosal sites of the lung and the gut. What are the different environmental challenges that those two, in some ways similar, organ systems have when it comes to the immune system?

Emily Thornton- So the lung and the gut have sort of common origins in development, right? But they have completely different interactions with the outside world. So your lung is a is a gas exchange organ, so you can't have too much inflammation in your lungs or you'll die, right. You can't just have a bunch of inflammation. Whereas the gut is the opposite, where you so you need to have interactions with everything from the outside. You're always taking up food. You're always interacting with microbes and so, whereas the lungs were are sort of considered "sterile", we know that they're not now, the gut is a teeming you know community and so, so the challenge of the two organs are actually almost diametrically opposed. You want your immune system to be able to recognise things at both sites, and the responses have to be controlled, but the sort of breadth of response will be very different in the lung or ideally should be very different in the lung than it is in the gut.

Catherine Seed- Most people have come across the idea of your gut microbiome of all these kinds of bacteria that can have either positive or negative effects on your health or your digestion. How does that then interact with the immune system?

Emily Thornton- Yeah, so in the in the gut your immune system isn't naive to what's going on in the microbiome, so there are cells called antigen-presenting cells that are sort of constantly sampling from the microbiome so they're actively taking up bits from the microbial communities and sort of sampling them, sensing what's there, and then presenting them to adaptive immune cells, which is what I'm interested in are T cells. And so that interaction is sort of controlled by the antigen presenting cells and then what I like to think of is that they're sort of interpreted by the T cells, so they're sort of the brains of the operation and the antigen presenting cells are sort of just you know, going along and picking up - it's more complicated than obviously because the antigen presenting cells can also, you know, interpret all of these signals from the milieu as well, but that's sort of where what my interest was in is understanding how T cells that are specific for microbes, how they're behaving in the gut because we know that there are a lot of them there, but whether they can be helpful or harmful, and so that's sort of where my scientific curiosity has taken me. I guess. And there are lots of different flavours of T cells and that's something that a lot of work has gone into, especially here at the WIM and how antigen presentation works and all of those pathways is really sort of like in the in the in the walls here in the WIMM.

Catherine Seed- What's the variety of things that are going on in our own guts to create that balanced system, is it a simple on and off switch? Are there are we just starting to know? What's the picture so far?

Emily Thornton- So understanding how the immune system is interacting with the with the microbiome, and everything that it that counters in the gut is just absolutely mind-blowing to me. Even after working on it for years and years and years, so it if I think about it too hard, I'm shocked that not everyone has colitis, right? We have a huge amount of bacteria. Literally inside of us and we are fine. So there are loads of processes that are in place. One is probably this tonic sampling to, you know, keep the immune system aware of what's going on. Keeping the microbial community sort of under control, so you're always making lots of antibodies to the microbiome that are being secreted and allowing things to be sloughed away from the surface so that you don't see them so much anymore that you don't get huge amounts of immune activation. As I mentioned, there are regulatory T cells, so another flavour of immune cell that seems like their job is to, you know, come in and keep everything under wraps and. And that it and then it all works I think is surprising and there are probably pathways that we don't understand yet that are involved in (it). I mean, even just having the barrier intact is important. So you have an epithelial barrier that's separating you from the microbes that are within, and so I mean, that's obviously playing an important role in separating the immune system from the microbes as well.

Catherine Seed- And you've recently had a new publication. How did that project come about?

Emily Thornton- Yeah, so we were interested in, as I was sort of discussing, how T cells that are specific for microbes, how they behave in the intestine, whether they can be good or bad. I mean, obviously it's 1,000,000 shades of grey in between. One of the tools that's used in the manuscripts, the CBir TCR transgenics- this is a mouse that has T cells specific for commensal microbes. So a great tool to study how immune regulation is happening, but if you look in this mouse they aren't becoming T regs. They're becoming this weird phenotype that then this paper is about, but. Obviously, at the time I I was like “I want to be studying T regs”. Anyway and then had a baby as one does and so had to put it to the side for a while. Went on maternity leave, came back, picked up the

project again. These weird cells were still there, so I then dug in to see OK, is this just a weird observation of these cells, opr is this in other mouse models? Yes, could find them in other mice and then teamed up with Phillip Hackstein who is in Paul Klenerman's lab because he was finding a similar population in humans. So it actually dovetailed really well. Had another baby, took some time and then we came back together, we were like oh this is great, we'll put a manuscript together. We can find them in the humans and the mouse, and everything fits perfectly. Enter global pandemic, so put all of the human samples on hold.

Catherine Seed- I'm just gonna say from a from a lab based perspective. What does that mean for a project that's not only in process but underway? How does shutdowns you know? A lot of people's research, especially in the HIU, been redirected to COVID. How does that then affect the project?

Emily Thornton- Yeah, I mean it meant that we couldn't go into the animal facility for a long time. They couldn't collect patient samples because it wasn't clear whether SARS-COV-2 was infecting the gut. Everything was sort of put on hold so we couldn't get any more samples, we could put the manuscript together as well as we could and wait for things to open back up, but it really put things on hold. We were hoping to get everything submitted right at around July of 2020 but you know, perseverance is important in science, and that's what we've done. And so I'm really happy that now it's out and people can see it. But it has been a labour of love and has taken. Terms that we weren't expecting along the way I thought I would be studying regulatory T cells and we've got a new population of innate like T cells. So you know, that's that's how science goes I guess.

Catherine Seed- And what would you like - for any immunologists, we will include a link to the paper in the details below wherever you've accessed the podcast, but for people reading the paper, what do you hope their main takeaway is, or what or how it might influence people's thinking?

Emily Thornton- It takes the sort of what you would think AT cell is going to be exquisitely specific for one antigen and really sort of makes you open your mind to the possibility that these cells are there and able to respond to the microbes but then they're also there to sort of interpret the signals of of the rest of the milieu and the rest of the immune cells around them, so if you have one bad actor in the microbiome, that might be enough to kick everything off course and that's where I think these cells are interesting, but also in the context of immune regulation and how that would be happening in the gut versus in the lung, so I didn't really discuss it, but actually the other place where you can find a lot of these unconventional looking CD4T cells is in the lung. So why is that? So there's going to be a. Lot a lot more work to be done to figure out what they're doing.

I think that I would like I would like immunologists not to put weird looking cells to the side or in the bin that actually these sort of innate like cells are probably going to be really important in how immune responses are developing, especially at barrier organs but also you know throughout the whole body, and so I think looking at those phenotypes as well is going to be really important going forward, and so I think that's the main takeaway like for them, for immunologist to have and I guess everyone else. Just to just think about how your your immune system and your microbes are interacting. Not that we know exactly how you can intervene on that front yet. Anyway, just think about it for a while.

Catherine Seed- A little focus on this cool thing that's happening that we don't even think about. One more question, what's next?

Emily Thornton- Yeah, I mean in terms of the T-megs, the MHC 2 restricted innate like commensal reactive T cells...I think Philip is going to pick them up and keep working on them hopefully in his independent career, and I'm focusing more on the regulatory T cell side. And we have a pre print out

for that at the minute if anyone wants to check it out with Gu and Bartolomew Cassado as the first authors. And so I think more focus on these antigen specific T cells and mucosal sites and really digging into how the two mucosal sites are interacting with each other, the lung and the gut is really what I want to be doing next.

Catherine Seed- Thank you so much for your time and for talking through. It's a really exciting area and. I'm sure a lot of the listeners are excited to see the next steps too.

Emily Thornton- Oh thanks so much for the opportunity to discuss it.

Catherine Seed- Yeah, this has been inside where if you. Like the course please. Subscribe, live or review. Thank you.