Provox - **Professor Emma Slack**

Transcript

Paul Johnson

Hello and welcome to Provox, a podcast from the Queen's College Oxford. I'm delighted today to be joined by Professor Emma Slack, who is not only a fellow of Queen's College, but also the Barclay Williams Professor of Molecular Mucosal Immunology. Have I got that right? Yes, I have. at the University of Oxford. So Emma, welcome. It's fantastic to have you here. And I want to spend most of the next half hour or so talking about your incredibly interesting research. And you can probably explain what molecular mucosal immunology is. at some point through this. But perhaps you could just start by, and you've had an amazing career, I mean you've worked in all sorts of places and you continue actually to split your time between Oxford and Zurich in a way that I find mind-boggling and getting to and fro London once a week is pretty difficult. But living in two places, two countries and flying in between all the time must be pretty hard work. But let's come on to that. in a minute. All scientists started somewhere. How did you start? Where did the desire to do what you're doing come from?

Emma Slack

So I was one of those kids who from the age of about sort of seven had decided I wanted to be a scientist. So I was sort of one of these, I'd always took my toys apart and, you know, some irritating childhood behaviour. And I was the daughter of a country GP growing up, long enough ago that we used to get taken round, particularly for the palliative care visits by my dad. He'd take his two little daughters to go and cheer people up, which you wouldn't be allowed to do these days for very good infection control reasons. But it was always, from very early in you, I knew you had this thing called the immune system, and I was being taken to visit these terminally ill people.

Paul Johnson

Primary school age. Wow.

Emma Slack

And it was always very surprising to me that your immune system didn't know what to do. that you had this system that was there that was meant to be protecting you against things, and yet people were still dying of cancer or of infection.

Paul Johnson

You were thinking about this at primary school.

Emma Slack

So I'd started thinking about this very, very early on. And then I got into nuclear physics, as many kids, the really exciting stuff, of course, is physics, right? I like this. Like many kids do, I go into nuclear physics. Absolutely true. And actually up till about some GCSEs, I was thinking I was going to go into physics. And I had a wonderful, wonderful science teacher at school, Mrs. Chisholm, who managed to make everything very exciting and very relevant. And you had this real feeling of being involved in and the edges of reality, which was fantastic. And then for A-levels, I had a different physics teacher, who I won't name. He wasn't so good. Who had a teaching method involved repeating things a lot, at which point I decided I was going to be a biologist. So here we are, and I got back into the immune system question sort of right towards the end of school, talking to colleagues of my parents who were doctors.

Paul Johnson

You didn't think of doing medicine as the children of many, many doctors do.

Emma Slack

No, So I definitely didn't want to do medicine. I'd seen a lot of it. Also, there's a lot of patients showing up at the house. And I was very much interested in the sort of global interaction of what could we do to improve health at a sort of worldwide kind of level. I was definitely less interested in the sort of individual, really hard work, day-to-day, sometimes a bit thankless work that doctors, you know, it's a really hard job being a doctor. I was very keen to be a scientist.

Paul Johnson

Excellent. And so you went, you did natural sciences at Cambridge and was that immediate, were you immediately sort of, I mean, it's amazing, you started off wanting to work on the immune system. Was that something you could do as part of the undergraduate degree?

Emma Slack

So not until the third year. So I kept interested in it. You can always read. I think the good thing for me for the Cambridge degree was that it was very broad. So I did a lot of maths and chemistry in the first year, which at the time you think, you know, I'm never going to use maths and chemistry. I want to be a biologist. And definitely now that's the part of my degree I use most. That's interesting. You know, there's the bits and pieces that I still use undergraduate level chemistry and maths because There's a lot of that in biology. Whereas a lot of the biology I learned has since been renewed and reinterpreted and has moved on, right?

Paul Johnson

Maths and chemistry has moved on less than biology.

Emma Slack

Well, I mean, that level of maths and chemistry has.

Paul Johnson

And how are you using maths because you're modelling things.

Emma Slack

We do quite a lot of modelling, yep. So we work in the intestine. It's a very dynamic system. It's very difficult to approach from a pure logic point of view because everything is happening at the same time.

Paul Johnson

Tell us a bit about what you're doing. I mean, I'm going to read it out again. Molecular mucosal immunology. I mean, what is that?

Emma Slack

Right. So mucosal immunology is really studying the immune system body surfaces. So the way that your immune system works in your blood and in your spleen and in your heart is fundamentally different from the problems your immune system has to deal with where you're coming into direct contact with the outside world. So you can sort of think of it as, sort of deeply in your spleens, a bit like trying to police Buckingham Pallets, right? So generally speaking, there should only be the royal family there. And if anybody else gets in, it's, you know, it's quite easy to recognise them and it's very clear they could leave. Similar thing, you know, microbes in your spleen, there shouldn't be any microbes in your spleen. If the microbes show up in your spleen, you've got to get rid of them as quickly as possible. So there's a bit of collateral damage. That's acceptable because you've got to get rid of microbes or growing in your heart tissue, for example. Whereas your body surfaces are most profoundly in the gut, which is where we work, you actually have more microbes than you have human cells in your entire body. It's a roughly 50% microbe in terms of composition, every human is. And some of those microbes are genuinely beneficial. They do things like they make vitamin K, for example. So without your gut microbes, your blood wouldn't clot, which is why we give vitamin K to neonatal babies, because they don't have the right bacteria yet to make sufficient vitamin K. They also help you digest your food. But at the same time, both of us sitting here in this room are probably carrying some bacteria in our intestine that if they got into our bloodstream, they would kill us.

Paul Johnson

Okay.

Emma Slack

And yet they don't, right? We're blissfully unaware of this. And the reason they don't is because you have a pretty active immune response going on continuously at all your body surfaces that makes all these things stay in the right place. And they don't grow too abundant and they don't invade elsewhere. And of course, as soon as you have a defect with the immune system or are in hospital for some sort of procedure that results in immunosuppression, those things can overgrow, they can spread. And that's where we see things like E. coli-driven sepsis in adults. Those bacteria can also spread during...

Paul Johnson

So E. coli-driven sepsis, how does that relate to what we're talking about in the gut?

Emma Slack

In the gut. So these would be bacteria that you have in your intestine. They're fine. Not a problem as long as you're healthy, right? But then something else happens they spread from your intestine into the deep tissues, sometimes via the urogenital tract into the blood and then cause systemic infections.

Paul Johnson

So you're studying specifically the relationship between the sort of microbiome in the gut and people's immune systems, is that right?

Emma Slack

Exactly. And what we're trying to work on is how much your immune system can actually control what is colonizing in that environment. So your.

Paul Johnson

Body's immune system is having some control over what's actually in the gut.

Emma Slack

It has some control. It's of course, your gut content is topologically outside of you. So most of your immune system is in the tissues, is in the blood, is in the cells. So we have only very few mechanisms that really get secreted out into that environment.

Paul Johnson

So just to be clear, you're looking at the relationship with sort of immune to gut rather than the effect of the gut biome on the immune system.

Emma Slack

Much more in the other direction. We have to consider it a little bit the other way because it's all part of the same system. But what we're really interested in is how you can activate the immune system via the intestine in order, for example, if you know somebody's going for a bone marrow transplant, you could give them a type of vaccination that would get rid of the particular colonising species that we know cause invasive infections post-transplant, for example. So, because if the bacteria aren't there in the 1st place, then you have to worry, right, they're not going to cause anything else.

Paul Johnson

And it's fair to say, is it that, I mean, it's not just in what you're doing. Actually, I mean, one of your colleagues at Queen's, Jane Mellor, is also working on sort of gut biome, but in a different kind of way. Is it broadly true that people are seeing this the sort of the creepy crawlies in the gut are increasingly seen as really, really important to our overall health.

Emma Slack

Yeah. So this is, they're seen as important, but we still have a pretty poor understanding of the mechanisms by which that's true. So what we're good at these days is mapping which microbes are present, where and when. We have next generation sequencing, it's very high throughput techniques that gives us lots of data. And that's great, but it's a little bit like getting the names of everybody who lives in London. And trying to go from that to working out what's good and what's bad and what's problem is actually very difficult. And some of it is definitely that these microbes have an enormously higher metabolic capacity than we do. Which means you have around 30,000 unique genes in your human genome. The bacteria in your intestine have millions and millions and millions of unique genes. And that means if you take, for example, a drug, we can pretty quickly, in vitro, very well work out what your human metabolism is going to do to that compound. But we have a very poor handle on what the microbes do with that compound. There's a lot of research going on now in pharmacology to try and build gut microbiome into pharmacological models because it probably seems to explain quite a lot of variation in responses between people for different drugs because they have a bacteria that metabolizes a compound in a particular way or not.

Paul Johnson

So how much variation is there between us in what's going on in our guts?

Emma Slack

It depends how closely you look. So if you look at the phyla level and just to kind of explain how zoomed out that is, right? Our human phylum is vertebrates.

Paul Johnson

Okay, so it's quite high level.

Emma Slack

So we're quite high level. If we look at the phylum level, roughly all most warm-blooded normal mammals have a similar distribution of phyla.

Paul Johnson

So phyla is a sort of very high level classification of different bacteria.

Emma Slack

Families of bacteria. Yeah. So that's quite similar.

Paul Johnson

How many phyla of bacteria are there?

Emma Slack

Oh my goodness. I mean, in total. Huge, huge numbers. They're very, very hard to define because within.

Paul Johnson

Each phylum, there's also huge numbers within each phylum and huge numbers of phylums, phyla.

Emma Slack

Yeah, and the bacterial phyla differ from each other more than you differ from a mushroom, right? Because those things are... Evolutionarily, this is these are things that diverge much, much longer, longer ago than anything with anything eukaryotic.

Paul Johnson

So we, I mean, to us. to an ignorant person like me, they're all sort of the same, they're all tiny, they're all unicellular, aren't they?

Emma Slack

All bacteria, well, pretty much all bacteria behave as unicellular organisms, yeah.

Paul Johnson

And there are billions of different kinds by the sound of it.

Emma Slack

There are, and they are very diverse despite being very small. Yes. This is sometimes surprising how different these things can be, but that means they also make very different relationships with us. Hence, this whole range from beneficial.

Paul Johnson

So, with the filer level, we've all got fairly similar.

Emma Slack

If you start to get down to looking at what species I have and what species you have, there's possibly no overlap at all.

Paul Johnson

Golly.

Emma Slack

So at the species level, we're pretty diverse.

Paul Johnson

Does that change over your lifetime or are you pretty much, you know, you've got what you've got?

Emma Slack

And it depends on the species. So there are some groups of species that you seem to pick up very early and you keep for the whole pretty much as long as we've tracked it. Next generation sequencing came in 2009, so I can't say whole lifetimes yet, right? We haven't had that much. But from what we see, you see some of them extremely stable over decades. Some others, so E. coli being one of the prime examples, you seem to exchange your E. coli every six months or so on average. So it's very common, for example, if you were to travel to Southeast Asia, the majority of people travelling to Southeast Asia come home colonised by extended spectrum beta-lactamase resistant E. coli, because these are very prevalent in that region of the world. And if we track that over time, within about three months, most of those people have spontaneously got rid of that strain again. So some of it turns over very quickly, some of it turns over very slowly. Do we know why? No.

Paul Johnson

And how much difference does it make to my health as against your health? I've got a different set of bacteria in my stomach.

Emma Slack

Million dollar question. We would love to know that. What we have some information on is what is a really unhealthy microbiome. So at that end of the spectrum, the example I mentioned earlier of people who've gone through bone marrow transplants sometimes end up with a microbiome that's dominated by effectively one species of bacteria. It's often a vancomycin resistant Enterococcus which can cause disease. So that's clearly an unhealthy microbiome. At the other end of what makes this a particular healthy microbiome, if you've got a 100 metre sprinter who's particularly good is their gut microbiome, a particularly good microbiome for making you faster at running, we don't know that.

Paul Johnson

But does it have an effect on my propensity to put on weight, for example?

Emma Slack

So weight gain is a really interesting one. So there was a lot of data, it was one of the early hypes in the microbiome field that that microbiome composition was linked to obesity. And the data looked pretty convincing at the time. It was reanalysed later, which was all done on individuals in the US. And of course, many people with severe obesity also have type 2 diabetes and are taking a drug called metformin. And actually, the entire signature that was linking microbiome composition to obesity was being driven by a metformin-driven change in microbiome composition. So at the moment, the data is not clear that there is really a link between your microbiome composition and putting on weight. We do think there are links between the microbiome composition and activity and appetite control. So there's clearly, there's good data in animal models that the amount of energy released from dietary fibre by your gut microbiome is compensated into your food intake. So an animal knows that it's got 1000 extra calories from fermentation from its gut and therefore it doesn't need to eat the rest of those calories. Again, we don't have a very good idea of how that works. So I think there's still a lot more to do in that field. It might be treat. More research needed. something interesting, but it's not as simple as that the bacteria extract more energy and therefore you get fat. It's something much more subtle to do with that related to how your brain actually regulates your food or doesn't regulate your food intake.

Paul Johnson

So tell us a little bit more about your current research on the relationship between that microbiome and the immune system.

Emma Slack

So what we've What we're really currently working on is these interventions that allow you to engineer a specific species out, or a specific strain of a specific species out of the microbiome without needing to use anything like antibiotics. We particularly are

trying to find alternatives to antibiotics for getting rid of bacterial infections. And the way that we've been doing that is by combining vaccines that you swallow. So nothing you need to inject. These are based actually just on dead bacteria. So interestingly, the sort of concentration of bacteria in these things is not very different to what you would find in sort of sourdough bread. So they're very, very safe, very, very straightforward to administer. And swallowing those vaccines induces a very specific type of antibody response in the intestine that can very selectively bind to the strain you want to target. And when it does that, it generates big clumps out of these bacteria because antibodies have...

Paul Johnson

No, I didn't even know I had antibodies in my intestines. I thought they were all in my blood.

Emma Slack

So it's very true, most of them are in your blood, but there is a very specific type of antibody, it's referred to as IgA in humans, that is actively secreted across all immucosal surfaces. And it's only this one very specific type of antibodies. Your immune system really controls what goes out. Most of the antibodies, as you say, stay in your blood. They're interesting. These have always been very interesting to me because we secrete effectively grams of these things into the gut every day. And that's actually quite a lot of these secretory antibodies. And they're big proteins. So you lose a lot of protein just secreting the things. It's quite an expensive thing to do. I've seen in the modern world, modern world irrelevant because we have enough food, but in places where protein would have been actually one of the challenges. So it must be important, right? One would think. And actually, the other, the other, you know, the other evidence that's important is that if you look at the evolution of these antibodies in bony fish, teliost fish, and also in amphibians, they have secretory antibodies, but they evolved independently. of our IgA antibodies. So animals have seemed to decide if this is a useful system to have. They're functionally very similar, but they have a different evolutionary strategy.

Paul Johnson

So we haven't evolved, ours hasn't evolved because they were in our ancestors, the amphibians.

Emma Slack

So no, exactly. So they diverged earlier than that, but we've all got secretory antibodies. And there's an intriguing thing about them is that these antibodies you have in your blood, connect to all sorts of useful looking killing machinery. So you have cells called macrophages that are very good at eating bacteria and viruses and protozoa. And what

these antibodies really do is label bacteria and viruses and protozoa so they get eaten up and disposed of. And that's sort of obviously useful. Whereas the antibodies that you secrete into your gut don't do any of that. They don't seem to link to anything that kills anything. And so for a very long time we sort of hand waved and said, okay, they can neutralise viruses. We know that works because all we have to be able to do for that is stick to the virus receptor and you block it interacting with the cell. You don't get virus infection. That's great. And you can neutralise toxins, same deal. But a lot of bacteria cause disease without secreting toxins. And yet we know these antibodies were protective. And so The real trick with these turned out to be that if you have an antibody that can stick things together, it can stick bacteria together into big clumps. And in a sort of test tube-like system, it's not obvious what that's good for. Bacteria swimming around, you have the same number of bacteria in clumps. They're still there. It's nothing very interesting. But of course, your gut content flows quite rapidly. So you handle about 9 litres of fluid through your intestine on an average day. It's about 2 litres from what you eat and drink and seven litres of secretions that go out and get reabsorbed. So you have a pretty dramatic flow rate, particularly in the small intestine. And if you aggregate things together, they're actually removed much more efficiently in the flow.

Paul Johnson

Right.

Emma Slack

So just sticking things together, it turns out.

Paul Johnson

By remove, this is not going above.

Emma Slack

Flushed out into the toilet. Flushed out into the toilet, yeah. And so you don't need to kill them, right? You simply eliminate them by flushing them through in these big aggregates. And we can use that in order to eliminate, you know, these ESPL. E. coli, so these nasty drug-resistant E. coli and replace them with a bacterium that is not drug-resistant, is not invasive, is not a pathogen.

Paul Johnson

Oh, I see. So it's about replacing.

Emma Slack

So it's really about replacing things within this sort of ecosystem.

Paul Johnson

I mean, more broadly, I mean, when you talk about trying to, so this is killing something without using antibiotics. What happens to my, sorry, this is probably a very basic question, but when I go to the doctor and they prescribe me antibiotics because I've got an infection of some kind, what does that do to all the bugs in my belly?

Emma Slack

Kills them.

Paul Johnson

The whole lot.

Emma Slack

So the vast majority, yeah, I mean, it depends a bit on the antibiotic and the dose, but definitely the vast majority of antibiotics will cause 100 to 1000 fold loss of abundance of gut microbes. And I mean, obviously, the reason you've been given the antibiotics is that otherwise you'd die of a horrible infection.

Speaker 3

Well, possible.

Paul Johnson

Or I've been, I've got antibiotics, you know, which I didn't really need.

Emma Slack

Oh, yeah, if you had them and you didn't need them, that sense. But so, antibiotics are great drugs and very important, and if your doctor tells you to take them, you should take them. But the side effect is clearly that you do destroy the gut microbiome with this. And some antibiotics are definitely these sort of third, 4th generation cephalosporins are associated with Clostridium difficile infection is the typical example. So post-antibiotic diarrheal disease and really severe, unpleasant post-antibiotic diarrhoeal disease, because the microbes themselves normally inhibit that bacteria from growing too much and secreting toxins and making you sick. So that's one of the most obvious consequences that we see, and that's not so unusual.

Paul Johnson

Where does the microbiome come back from? I mean, if you've killed it all, how does it? just regrows, does it.

Emma Slack

I mean, so when I say you killed it, you killed it all. Oh, this is a perfect question. So there's a numerical aspect to this, that you have 10 to the 13 bacteria in your gut. So if

you reduce those by 1000 fold, you've still got 10 to the 10. Okay, so there's still quite a lot to grow back from. But some of it, so we've, quite a lot of people have done experiments where they've tracked what happens to your microbiome after an antibiotic treatment, how long it takes to recover. And you see some individuals recover fully within a few weeks. Some individuals, they never recover the same composition afterwards. So you're obviously always exposed to microbes from low levels via food, via water, via everything you breathe in. You would expect some of the things not to come back, some things to be replaced.

Paul Johnson

And I mean, is all of this related to, I mean, a whole series of diseases, like I mean, whether we're looking at cancer or heart disease or anything like that, I mean, is that all related to what's going on?

Emma Slack

So for cancer and heart disease, I'm not sure how convincing the evidence is for the immune-related diseases, so allergies, autoimmune diseases.

Paul Johnson

So what do we mean by autoimmune diseases?

Emma Slack

Things like multiple sclerosis, rheumatoid arthritis.

Paul Johnson

The immune system is attacking you.

Emma Slack

It was doing something that it shouldn't be doing. Yep. And there is, so for allergies, there's some quite interesting data coming out about microbiome composition in very small children. So during the first two to three years of life. If you look at the microbiome of children who go on to develop severe allergies, so allergies that we diagnose very early, you see that they have less of particular pathways that produce a compound called butyrate. And we know that this compound butyrate is important for a part of your immune system that generates tolerance. So that allows, you know, your immune system sees a lot of things that it shouldn't react to. It does actually have to learn to not react to them. And we know that there's a microbiome-derived component that really supports that. And if there's not enough of it during early life, it seems that that's one of the things that may predispose to developing allergies later. Not A one-to-one link, right? It's still correlative data.

Paul Johnson

And is there a sense that we think this has changed through generate because it seems that more children have these problems now, as long as the kids in the past, and we think that's related to diet, presumably.

Emma Slack

So this microbiome diet exposure are impossible to pull apart in that equation at the moment, because they all relate to each other. If you have a poor diet, I grew up in 1980s, we thought sliced bread was amazing.

Paul Johnson

I remember my dinners throughout childhood were sort of, chips and sausages. I mean, that's so, but my mother just put chips in front of me every single day. That's just what I remember having lunch at school. When we went to the canteen, I had baked beans on fried bread. That was my lunch. I think I might be in trouble.

Emma Slack

I seem to know not only was it our lunch, but we were in a lot of trouble if we didn't eat it. So actually beans at least have some fibre in them. So beans, beans, baked beans, thank goodness. But the British diet in the 80s definitely was not supporting your microbiome and not supporting your immune system development for sure. And there is data in animals that there's compounds over generations because as fewer and fewer people have a diverse microbiome, there's less and less transmission.

Paul Johnson

So we transfer between ourselves.

Emma Slack

We transfer between ourselves.

Paul Johnson

We're transferring here. We're sitting about a couple of, you know. Probably not much.

Emma Slack

No, I mean, so if we look at sort of sharing of microbiome species, you see this between people who really live together. Okay.

Paul Johnson

Yeah.

Emma Slack

So, and actually you also see this between people who live together and their pets.

Paul Johnson

Who?

Emma Slack

So there is. There is also an element of actually keeping pets is one of the things that can diversify your microbiome to some extent.

Paul Johnson

Diversifying is good.

Emma Slack

And we, roughly speaking, think that diversifying is good at the moment. It's clearly a proxy for... something else that we haven't understood. I think diversity per se is not the driver of health in this, but maybe you're more likely to have something.

Paul Johnson

I'm eating probiotic yogurts and all these things that people try to sell to me.

Emma Slack

Gosh, yeah, so probiotics is a tricky field, right? A lot of the probiotic yogurts are only allowed to claim health benefits because they also add vitamin A and vitamin D to the product. So, you know, there is no proven benefit of a lot of the probiotic yogurts. Definitely the ones that say support your immune system, they're only allowed to write that because they've also vitamin fortified the product.

Paul Johnson

Okay, well, I don't eat probiotic yogurts.

Emma Slack

What definitely does, there's good data that, you know, if you want to support your microbiome, particularly some post-antibiotic treatment, is actually fermented foods.

Paul Johnson

Why?

Emma Slack

If you ate a sediment at the bottom of the barrel, potentially. But definitely things like kefir, so more diverse fermented products, fermented vegetables, sauerkraut, kimchi. In parts of the world where they eat those things in large, particularly places like Japan, and they eat a lot of fermented products, you see that has a sort of obvious beneficial effect on microbiome composition.

Paul Johnson

Okay. I was joking. I presume that drinking alcohol just kills it rather than helps it.

Emma Slack

I don't think there's any good evidence that drinking alcohol is of any benefit to your microbiome. No, I'm not sure anyone's done any studies. You'd have to drink a lot of alcohol for this to really kill.

Speaker 3

Well, I mean, yeah, it's always worth a try.

Emma Slack

I mean, there is incidental evidence from, so lots of N equals one studies from doctors that alcoholics do rather well on enterohemorrhagic E. coli infection.

Paul Johnson

What does that mean?

Emma Slack

Potentially because there's so much alcohol that they kill the E. coli. So you'd expect these people to do very badly because they tend to have liver failure, but actually they do surprisingly well, presumably just because they manage to maintain an ethanol level that is actually toxic to the E. coli. But I don't think that's not to be encouraged.

Paul Johnson

Your research is probably going to do a small good.

Emma Slack

I think, yeah, not the way to go.

Paul Johnson

I mean, we've talked a lot about the sort of the sciences. How do you do this? I don't quite imagine. I mean, you run a lab here, you run one in Zurich as well. And what does this look like? I mean, what are people actually doing day-to-day in order to do the research that you're describing.

Emma Slack

Good question. So we have, we're quite a big team. So across the two sites, we're about 30 people. And we have a range, one of the real joys of my work is we're a range of different expertise. So everybody from doing sort of synthetic biology to design these types of vaccines, which we're actually giving orally. And there's also an interesting

logic behind that because fits your digestive system. So if everything you swallow, the risk is it just gets digested. And we want it to get into your immune system. So there's some quite interesting design principles behind this of making vaccines that get to the immune system via the gut. Then we have, we work also in mouse models. So it's still impossible So we do as much as possible with in vitro experiments, but you cannot at the moment, either in a computer or in a test tube, model the complexity of having a functional gut with a functional microbiome and a functional immune system. So to really understand this, we're still reliant on being able to use animal models. And then we also do some clinical studies. So we have also some parts of the group interested in collecting samples, sequencing the microbes that are there, looking at the distribution of, you know, are the E. coli that cause infections in Switzerland different to the ones in Oxford, different to the ones in India, different to the ones in Thailand. Because if you're going to make these vaccines effective, you need to be targeting the right thing. And All of these people come together and work as a team. So it's really exciting to be part of it and a real privilege to lead these people. And generally, it works well. You know, it's always complicated. There's a lot of paperwork. That's what I do mainly these days.

Paul Johnson

And the output, as it were, the outcome, have you got to the point with anything where you've done human trials, for example?

Emma Slack

So we've just grounded a spin-out company actually from the Swiss end of the lab who are moving one vaccine product towards the first in-human clinical trial. It's still a huge amount of work to get from the lab really into a human.

Paul Johnson

So, but it's a huge amount of work because you need really strong evidence this is going to be safe and effective before you even start.

Emma Slack

Definitely. I mean, the evidence we're actually, that's fine. We're quite good at that. It's what gets really challenging are the things that are beyond your skill set. So manufacturing is a big thing. What are you going to package it in? How are you going to, you know, can you store it on a shelf for six months, a year, two years, 10 years. And all of the safety and regulatory paperwork that needs to be done to go with that. Any injected vaccine, it's still a requirement that this needs to be tested in a non-human primate before it goes to humans. So setting up collaborations to be able to actually do that in a way that we think is ethically tenable. So all of these things are still challenging. So what is the?

Paul Johnson

Specific thing that you're moving forward with there?

Emma Slack

And the specific thing we're moving forward there is a, it's a so-called glycoconjugate vaccine. So similar to the vaccine you get for pneumonia, right? The Streptococcus pneumonia vaccine is also a glycoconjugate. That's not an oral vaccine. It's just an injected intramuscular vaccine. This one will also be an injected intramuscular vaccine. aimed at targeting invasive E. coli infections, so pyelonephritis and sepsis.

Paul Johnson

So this is something you give people?

Emma Slack

People who are at high risk of developing invasive infections.

Paul Johnson

And so how, I mean, I've heard from other people that this, you know, this is then a really long and expensive process to get from where you've got, you're just sort of, you know, got this in the lab, you think it might really be quite effective. But it's going to be a lot of time and a lot of money, even if this is super successful.

Emma Slack

Yeah, this is very true. And it's a difficult time also for biotech right now because a lot of the support for this sort of thing was coming from the US. And that's not coming from the US at the moment.

Paul Johnson

From US private companies.

Emma Slack

Also from things like NSAID. because a lot of these things are targeted at low and middle income countries.

Paul Johnson

I see a lot of this was funded by USAID.

Emma Slack

So vaccine development. So we never had funding because we were too late for that. But the vaccine development actually has been has been affected by this.

Paul Johnson

And also your E. coli vaccine will be most relevant in those low income countries.

Emma Slack

Would be most relevant in those types of environments. So That's a challenge. And of course, then you have to make a vaccine that not only works, but is considered value for money and that people are actually interested in having. And these days, that's become also a massive communication challenge because a lot of people have been shouting very loudly that they think vaccines are not safe.

Paul Johnson

Indeed.

Emma Slack

Which, you know, I can have an hour-long conversation about. That's probably a separate podcast, but where that where the basis of, as with all things, there's a tiny bit of information that has probably sat at the bottom of some of those fears, most of which is really completely unfounded, right? It's a game of sort of broken telephone.

Paul Johnson

Yeah.

Emma Slack

So there's still a lot of work to do there outside of the lab, right? Really, we can make the most perfect vaccine we want But if nobody wants to take it, then that's pointless.

Paul Johnson

So you give us a sense of time and money from, getting out of the lab to getting into someone's arm. So beyond the trials.

Emma Slack

So beyond the trials. Okay. So it's easier to estimate to get to the first in human trial. So a first in human trial is really done purely to assess safety. And that we're aiming to do within the next two to three years.

Paul Johnson

Right.

Emma Slack

If that goes through, then.

Paul Johnson

So these two, three years after you've essentially done the basic scientific research, yeah.

Emma Slack

If that all goes through, and that the spin out has support from an organisation called CARBEX that is developing alternatives to antibiotic treatment and will, assuming all the milestones are met, support the company through to these phase one clinical trials. It's probably another 10 years. beyond that point for a normal vaccine to actually get into the clinic. So during the pandemic, they showed you can do this faster. But a lot of that delay is really administrative time because there's many things that these clinical safety boards need to evaluate.

Paul Johnson

And is your hunch that this is over-regulated or is this stuff that actually needs to happen that actually needs to take 10 years?

Emma Slack

I think it needs, I mean, I think the regulation is good, it needs to be safe, right? We need public confidence in these things. If we put a few more people on the, you know, set up a few more committees, you could go twice as fast, right? It's so it's a little bit of a cost trade-off, speed, speed-cost trade-off there.

Paul Johnson

Was there a particular reason you chose Switzerland for the spin out rather than the UK?

Emma Slack

So it's simply that started before we were, that was work developed in Switzerland and before we were moving to Oxford. I actually think the spin out environment from Oxford is very attractive and there's very good support here. And the company is considering having a UK subsidiary because also the support for clinical translation in the UK. is very, very good. It's actually one of the reasons for moving to Oxford.

Paul Johnson

And clinical translation means.

Emma Slack

To be actually able to run the clinical trials. So the UK has very good clinical trial centres. We have the Innovate Fund. We have good support, good collaboration

between industry and scientists. So positive, really a positive story here. And the NHS, which is...

Paul Johnson

Big.

Emma Slack

Is big is across the whole country, whereas in Switzerland we actually have effectively A privatised medical system.

Paul Johnson

Yeah. And I mean, what does that mean? I mean, one hears lots of horror stories about how difficult the NHS is to work with, even if it is in principle, you know, the world's best customer because it is so big.

Emma Slack

I mean, so far, you know, ask me again in three years' time. So far, so good. So far, so positive, I would say. I think the scale of things you can achieve with the NHS is what makes the investment worth it.

Paul Johnson

So, I mean, to what extent is the projects you're working on at the moment, are they going to be essentially occupy the rest of your life? Are you moving on to new things? I mean, where do you go from here?

Emma Slack

So I'm relatively convinced probably we'll still be working on getting these E. coli vaccines working up to the end of my research career. That doesn't mean we're not starting other things. So, and we always have all sorts of projects going on the side in the lab. So our hope is what we've done for E. coli, which is one of the bacteria we understand the most about, right, of all bacteria, that we can expand that then to relatively closely related bacteria. So Klebsiella cause a similar range of diseases, less famous. I've never heard of Klebsiella exactly. But then also Klebsiella is a relatively close relative of E. coli, which causes a very similar disease spectra. But then also to, one of the other things one consider doing, this is as many people around the world work out what it is that makes a healthy microbiome, this is also a tool you can use to very rationally engineer that you want to bring in this one specific species, because this is going to make Paul much healthier than he is now. And we could do this then for the very diverse bacteria that you have in your gut in a very targeted way.

Paul Johnson

So finally, you've relatively recently moved partly to Oxford. I mean, what drew, what brought you here? And I mean, to live this, as I said right at the beginning, this incredibly difficult life, it seems to me, of doing work in Oxford and in Europe. And I suppose I should also ask, where does Queen's College fit into all of that?

Emma Slack

So I mean, it's also a massive privilege to be able to live across two countries. And the real benefit is that we get to access all of the expertise in both places. And science is really an international activity. We're not siloed. We always have worked across borders. And the more brains, the better. The reason I applied, there were many reasons that I applied for the job in Oxford. One was simply that, an Oxford senior professorship in molecular immunology came up and I read the advert and thought, I could do that first. That sounds like the sort of thing we do.

Paul Johnson

Yeah.

Emma Slack

And, in many ways I applied sort of on the off chance thinking, they'll never give me an Oxford professorship. This is surely not. I was then very flattered when they offered it to me. The other thing that was a big drive here is actually was really this clinical translation aspect, that the infrastructure, the support, the types of things you can do in the UK system are orders of magnitude bigger and better than what can be achieved in the Swiss medical systems. And we're sort of just getting ourselves set up to really take advantage of that. And Queen's is great. I didn't really understand, I think, what I was letting myself in for with a professorial fellowship. Nobody had explained really what a professorial fellowship was, I think. I assumed it would be all sorts of teaching and it turned out when I arrived, there's anyway, we really just expect you to eat dinner. It is a central part of it. It took me a long time to work out what this is. I don't know what the role is, but actually it's particularly because I'm often alone travelling to Oxford. It's a real family from home and also an incredibly inspiring environment. So I interact with colleagues. I've made friends who are experts in Egyptology, in philosophy, in all sorts of material scientists. Some of whom we have actually useful discussions about that have become incorporated into my research. And I've also started also to work with the students since discovering that there were things that things I can't. So I do a lot of college advisee work, which I enjoy. And so I feel like I'm doing slightly more than just eating dinner, which is a good.

Paul Johnson

That's wonderful. I sometimes wonder whether I'm doing much more than eating dinner, I have to say. But I think we probably need to draw that to a close. I mean, I

could honestly do this for hours because it's so fascinating. So Emma Slack, just brilliant, just really interesting, really inspiring. I think anyone who's listening to this will agree. And I hope anyone who's thinking of careers in science who really thinks about that very seriously, particularly if they were thinking about it from the age of 6. It's fine to start later. Thank you so much.

Emma Slack

You're very welcome. Thank you.