Ep10 Transcript

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Andrew Pollard: Hello, my name is Andrew Pollard. I'm director of the Oxford Vaccine Group at the University of Oxford. Welcome to our podcast series, The Oxford Colloquy: Trust in Science, bringing you the stories, facts, and people behind the science.

In this episode, I'm speaking with Professor Ian Frazer, whose work led to the discoveries that allowed us to develop a human papillomavirus vaccine to prevent cervical cancer.

Andrew Pollard: Professor Ian Frazer, fellow of the Royal Society, founding CEO and Director of the Translational Research Institute in Brisbane, welcome to our podcast.

Ian Frazer: Thank you for having me along.

Andrew Pollard: Thank you for coming. You have over the last few decades won numerous prizes for your work on human papillomavirus. Queenslander of the Year in 2006 and the Prime Minister's Prize for science, and then the Companion of the Order of Australia in 2012.

So lots of both national in Australia and international accolades; but actually your career didn't start in Australia, you grew up in Scotland. So tell us a little bit about what got you into science in the first place?

Ian Frazer: Yes, I was always as a kid interested in science, probably not the science I'm interested in now. I was interested in astronomy, but had thought to go to university to study astrophysics. And then looked around at the job prospects and decided maybe it would be better if I did medicine. So I have spent the first five years of my academic life, if you like, becoming a doctor. But even then I was interested in the science and I took a year out and did an honours year in pathology where I spent quite a lot of time learning about immunology, which was actually a relatively new science at that time.

Andrew Pollard: And so did you then bring that into what you were doing in medicine? Because after you qualified, you worked as a junior doctor at least for a while.

Ian Frazer: Yes. When I graduated in Edinburgh, I was torn between going off and doing more science and naturally practicing medicine, and I decided that if I'd got a medical degree, I should be using it. So I went into renal medicine because of all the areas in medicine at that time, renal medicine was the one where there was indubitably a role for the immune system, because we had to deal with transplant patients who had basically organs which weren't quite theirs and the immune system would do its best to try and reject those. And we had to try and understand what we could do to control that.

But we also realised at that time with a lot of disease, especially chronic disease, the immune system seemed to be not working quite right. That's been justified in spades over the course of the last 30 years, but in those days, it was quite exciting because people didn't know what was going on. We couldn't measure half of the things that we can now measure. I mean, lymphocytes were small round cells that went around in the blood, and we had absolutely no idea what they did.

Andrew Pollard: And so, with that sort of work in renal medicine, which is the treatment of kidney diseases, how did you get from that to being interested in viruses and the immune system's role against viruses?

Ian Frazer: Look, that was luck, I guess... When I was a medical student, one of the things that we had to do was to do a three month sabbatical somewhere during the course of the medical course. And I wanted to do something in immunology even then, and was fortunate enough to get an opportunity to come out to Australia for three months. And I worked with a group of immunologists in Melbourne who were interested in autoimmune disease for three months, and then went back to my medical studies and did my five years working in renal medicine.

But halfway through that I got a telegram from the then head of the medical renal unit, offering me a place, you know saying "Why haven't you come back to see us?" And after having discussed that with my wife, we decided, yes, it would be nice to go to Australia for a couple of years and I could get a better education in immunology at the Walter and Eliza Hall Institute in Melbourne, which at that time was worldwide recognised as the best place to study immunology.

Andrew Pollard: So did you start right from the beginning when you got to Melbourne working on human papillomavirus, which we'll talk in detail about in a moment, or did you start with other areas following on from what you were doing with kidney diseases?

Ian Frazer: My boss, Ian Mackay, he was interested in liver disease and whether the immune system was responsible for a particular disease called chronic hepatitis, where the liver was inflamed. And so that was what I worked on for the first couple of years that I was in Melbourne and he sent me to see a guy called Karl-Hermann Meyer zum Büschenfelde in Germany because he was the professor who was probably the world expert at that time on autoimmune liver disease. And he was kind enough to introduce me to Harald zur Hausen. Now, Professor Harald zur Hausen was the head of the institute and he said, "You know, I've been doing this stuff on viruses and particularly on papillomavirus, which I think" - I being him - he thought might be responsible for cervical cancer. And that would have been a little bit unusual in those days, there wasn't really a great thought that cancer was caused by viral infections.

Anyway, he talked about that with me, and when I went back to Melbourne, as well as doing the work I was supposed to be doing on liver disease, I also decided I would start up a programme looking at evidence for papillomaviruses responsible for cancers. And, at that time, of course, the disease of the month was HIS/AIDS, which had just hit Melbourne.

Andrew Pollard: So this is the early 1980s that this is all happening?

Ian Frazer: Yeah, at that time, there was a considerable interest, obviously in HIS/AIDS because Melbourne was second after New-York to have the problem with serious rate of infection of HIS/AIDS. And I had a study group, which I was looking at, with men who had sex with men, and many of them had many of the symptoms of HIS/AIDS. But one of the things that I also realised was that they were having real problems with papillomavirus. They had warts, but they also had precancer lesions.

That, basically, was something which hadn't been really recognised at that time. I decided because of that, that when I finished my spell in Melbourne and had to look around for another job, I would look for somewhere where I could take on the study of papillomavirus and how the body defends itself against it, and whether it was indeed responsible for more cancers than just the occasional one.

Andrew Pollard: So the initial idea about that link was from your colleagues in Germany, but then critically it was the observation that in individuals whose immune systems are not working well, which is those patients with HIV at the time, that they then had worse papilloma disease and cancers associated with it.

Ian Frazer: Yes, it was the thought that this was a virus infection, which the immune system controlled, but if it didn't control it, not only did you get persistent viral infection, but the persistent viral infection could lead to cancer. And Harald zur Hausen obviously should take the most part of the credit for that observation, although he never actually proved that the immune system was an important part of controlling it.

But it gave me a start in that area and I decided that I would continue to study that. The cohort that I'd set up in Melbourne proved, first of all, that the connection between persisting papillomavirus was really only in the patients who had immune suppression, and that the immune system was obviously really important in controlling this. And secondly, that the virus type, which caused cervical cancer in Harald zur Hausen's work turned out to be causing anal cancers in the men who had sex with men. So this is another cancer that was obviously associated with the same virus.

We weren't very good at typing the viruses in those days, but it was clearly the same HPV-16 that we now know is one of the more common ones causing cancer.

Andrew Pollard: So obviously today, we know a number of viruses are associated with cancers. Hepatitis B virus, which is an infection of the liver, that can eventually damage the liver and lead on to cancers. Epstein–Barr virus which causes glandular fever, and certainly is associated with a reasonable number of the global cancers, and more recently shown to be associated with multiple sclerosis, which is a really interesting observation that could in the future be a game changer.

So this idea today is pretty mainstream, but did you have a lot of resistance at the time when you were discussing this area and thinking about getting research funding?

Ian Frazer: Certainly, when we started in that area, it was really quite hard to get funding. I mean, we were very interested in whether it would be possible to get the immune system to wake up and cure these cancers, which seemed a logical thing to do given that the virus was already there. I mean, it took us a little while to think about, well, maybe it'd be better if we never got the virus in the first place...

And so for a couple of years, my colleagues worked on the natural immune response to papillomavirus, and we worked out that there are certain little bits of the virus, which hung around in the precancers and that they also generated an immune response, but the immune response wasn't good enough to get rid of the virus. Indeed, I spent about 25 years trying to work out why that was, it became one part from the research work that I did when I came up to Brisbane.

Andrew Pollard: So this virus, human papillomavirus, it actually causes a range of diseases. What are the diseases that human papillomavirus causes?

Ian Frazer: Well, we're absolutely sure they cause warts, and we're also equally sure that they cause a range of cancers. Probably cervical cancer is the major burden of disease, but oropharyngeal cancers, quite a large percentage of them turn out to be due to the same HPV-16 and some types that are HPV-18, which is fairly similar to -16, and then a number of other ones...

Andrew Pollard: So oropharyngeal is the throat and the upper part of the airway.

Ian Frazer: Yes it's sometimes called "head and neck cancer", which is a rather bad term for it, but it's basically the throat. And those cancers used to be almost entirely in people who smoked, smoked cigarettes or chewed tobacco. Nowadays, they're almost entirely due to papillomavirus. The burden of tobacco-related disease has dropped off considerably, but papillomavirus has taken over, unfortunately.

Andrew Pollard: And so having got that information, and starting to understand some of the immunity and as you say the challenges of trying to work out why the immune system can't clear the virus. What was it then that made you think, well actually, you know, we could do something about this and make a vaccine?

Ian Frazer: Well, we didn't really set out to make a vaccine. I went on sabbatical to Cambridge, and worked with Margaret Stanley and she was interested in the immune system and how papillomavirus interacted with the immune system.

But I was fortunate enough to meet Dr. Jian Zhou when I was there in Cambridge. He was also on sabbatical there from China. We talked a lot about papillomavirus and decided that maybe it would be a good idea if we could actually make a papillomavirus, so that we could work with it in the lab. Because papillomavirus is a really annoying virus - because unlike most viruses, you simply can't grow them in the lab. You've got flu virus, you put it on the right sort of cells, you get millions of flu viruses out. But if you wanted to make up lots of papillomaviruses, you couldn't. You could only extract the virus from tissue. But we thought that maybe we could perhaps make a synthetic virus in the lab, Jian and I.

And when he had finished his sabbatical in Cambridge and I'd finished mine, he came back to work with me in Australia, and we spent quite a bit of time basically using the then relatively new techniques for expressing genes *in vitro*, in the test tube. And we'd expressed the viral genes, including the genes that made up the coat of the virus. And much to our surprise, when we did this the right way, then you ended up with the building blocks of the outside of the virus, but more importantly, the building blocks assembled themselves into the shell of the virus in the lab.

And when we saw that immediately, at least I, and I think Jian as well, thought "vaccine" because now we had something that looked like the virus and it could be made in the lab, and therefore there was a serious possibility of getting the vaccine.

Andrew Pollard: So these are known as "virus-like particles" because they actually on the outside look like the virus, and they're all assembled in the same way, but they actually can't cause an infection. They don't have the genetic material, the machinery to be a virus. They just have some of the proteins that make up the virus.

And so, when you saw this in the laboratory, I suppose this was something you saw using electron microscopy, was it, actually looking at what you'd made?

Ian Frazer: Yes, that was exactly how it was.

I mean, basically what you did was you expressed the genes that code for the coat of the virus in a suitable expression system, and genetic engineering was able to provide that. Critically, we used the right sort of cells to do it, because if you did it in quite a lot of cells, it just didn't work.

And particularly, we also had reasonably good means of purifying anything that might potentially be a coat of the virus. And with the technologies that were available, we were able then to harvest material, which we sent off to our favourite electron microscopist, who ought to get quite a bit of credit for that work because she did a really good job too. And we

did this for over a period of time and got nothing, got nothing, got nothing... It was getting rather boring in fact. But then we realised, going back to the drawing board, that probably we weren't using just quite the right bit of the major capsid protein when we were expressing it using genetic engineering. And when we changed to what actually was the right starting point for getting the virus protein made, suddenly we started getting virus-like particles.

And that was, I mean, that was really quite exciting. I mean it was negative, negative, negative results over a whole year. And then we got the positive result.

And we realised pretty much straight away that if there was going to be a vaccine against this virus, we weren't even sure that there was going to be any interest in a vaccine at that point, but we thought if there was going to be a vaccine against this virus, then that would be the way to do it.

Andrew Pollard: So when you saw the electron microscope pictures of this virus-like particle, did you immediately think, "Aha, this is a vaccine", or was that something that dawned on you over a number of days?

Ian Frazer: No, it was straight away. I mean, we knew what we were looking for. We basically said, right okay, we'll go write a paper for Nature. We did, it didn't get accepted by Nature, but we wrote it for Nature.

And at the same time, we sent a copy of that to our patent attorney and said, "Mmh, this looks like it might be something of interest commercially, let's not miss the boat on this one."

Andrew Pollard: So an absolute key part of this was the patent, which then means that developers for vaccines are actually becoming interested because there's a market potential for them.

Ian Frazer: Yeah, there wasn't really a clear market, as I say at that time, and the concept of actually vaccinating to prevent papillomavirus infection seemed a bit bizarre, because we really didn't know how strong the connection between papillomavirus and cervical cancer was and how many people got the virus infection, how many of them went on to get cancer. We just weren't hundred percent sure that stopping the infection would be enough.

We worked on that basis and got in touch with a number of pharmaceutical companies. I had a tour around America and went to most of the big ones and some of the smaller ones. There was quite a significant interest at that time because the companies themselves had begun to start thinking about - could we get a vaccine? They hadn't actually got to the stage of getting something, and we were fortunate by about three months, I think, in getting in there early enough to be able to claim that we had found a method of doing it that would be reproducible on scale.

Andrew Pollard: So once you persuaded the companies to take on this concept, as you say, there's then a huge amount of work to do, to take the concept of those virus-like particles through clinical development.

So first of all, you have to be able to work out that you can manufacture it, to meet the regulatory requirements to go into people and then the clinical trials. How long did that process take from your observation on the particles to actually having a product that was going through trials?

Ian Frazer: Well, the provisional patent was filed in 1991 and the first clinical trials - well, there were some animal studies done in the mid 1990s, and the first clinical trials started in the late 1990s. I mean the actual, the big studies really started in the late 1990s and went on

'till 2005, 2006, when the results from the first really big study came out and showed pretty clearly that there was a good chance that the vaccine was protecting against the infection that was known to cause cervical cancer.

Andrew Pollard: And I suppose over that period, it became very well established that the infection was a prerequisite to then the abnormalities in the cervix, which eventually led on to cancer, becoming one of the most important cancers for women. So that, by the time you actually had the results of those pivotal trials, it wasn't so difficult to persuade people that this was gonna be a game changer.

Ian Frazer: Yeah, look, in the mid 1990s, it was pretty clear that cervical cancer was pretty much a hundred percent associated with HPV-16 and HPV-18 infections. Most of the people that got those infections did not go on to get cancer though. It was a relatively rare event, for probably what turned out to be an extremely common infection rather than a consequence of what was thought to be a rare infection in the 1990s.

So that was the ideal situation for developing a vaccine: a very common infection which caused a nasty disease.

Andrew Pollard: So, at the time, back in 2006, when the final trials were reported, were they able to show then that the vaccine could prevent cancer? Or was that more just about prevention of infection?

Ian Frazer: It was about prevention of infection and precancer. It was well recognised by then that there were stages towards cancer, which are called Cervical Intraepithelial Neoplasia, or CIN. And CIN-1 was just the actual viral infection. But CIN-2 and -3 were seen in cells that were well on the way towards becoming cancer, so that CIN-3 fairly regularly would progress to cancer if nothing was done about it.

So it was a sort of merger of a whole range of different bits of information that enabled speedier thought about the need for a vaccine and the utility of a vaccine for preventing cervical cancer.

Andrew Pollard: And so those early results suggesting that that precancerous form could be prevented, gave a lot of confidence that this huge global burden of a terrible cancer. And I said affecting women, because obviously cervical cancer does, but actually this is a virus that can, as you mentioned earlier, cause other types of infection as well, including in the upper airway and in the throat, and also in men who have sex with men around the anus.

So was the vaccine also able to prevent those types of lesions, those types of cancers in people?

Ian Frazer: Well we hope so. The studies have all been done and shown that people who are not yet infected with human papillomavirus can be prevented from getting human papillomavirus infection, and also you can prevent the development of this pre-cancer lesion, CIN-2, CIN-3. That was the critical evidence that this would be a useful vaccine.

I mean, nobody wanted to do a study obviously, where you waited until somebody went on to get cancer. You know, you couldn't do that. But now we can reasonably assume that if we go out and vaccinate, we'll stop CIN-2, -3 and cancer.

As for the other cancers, it's just an open question as to whether we're going to stop them at the moment. It seems very likely that oropharyngeal cancer should become less common, but that's a 50 year study. So it will all be done on the public health data that's gathered, and

the epidemiologist will be able to tell us whether the vaccine also prevents oropharyngeal cancer to some extent or completely.

Andrew Pollard: Although, as you say, it seems extremely likely that it will, given the mechanisms of the development of those cancers probably being very similar to cervical cancer.

Ian Frazer: Yes it seems very plausible. Of course, there is another co-factor for the oropharyngeal cancers, which is tobacco smoking.

But now I think it's probably accepted that the majority of the oropharyngeal cancers we're seeing these days are actually HPV related. And hopefully with universal vaccination as is now done in the United-Kingdom and in Australia, and gradually in other parts of the world, we should see the disappearance of these oropharyngeal cancers as well.

Andrew Pollard: You mentioned the two types of human papillomavirus, type 16 and 18, which obviously account for the vast majority of cancers, but there are others as well that can cause cancer. So have we made any progress with them?

Ian Frazer: Well, we incorporate other virus types into the vaccines, the ones that are - it's a numbers game: 31, 35, 52... So the vaccines that are widely used at the moment have HPV-16 and -18, HPV-31, HPV-35 and HPV-52.

There is some thought of adding other types then as well. But with those five types, you cover 96% of cervical cancers - not a hundred percent because there are a few cancers that at least seem to be associated with other HPV types. But, the vast majority, it's 16 and the vast majority of the rest is 18. And then the other ones each contribute a little bit of the burden of cancer.

Andrew Pollard: So you've been very involved over the years in trying to communicate about science - and it's a difficult world to be in with lots of challenges to trust in science at the moment. What have your personal experiences been of that in Australia?

Ian Frazer: Look, people are always nervous when you come along with something new, it's understandable. Scientists don't always get it right. There are examples, plenty of examples where we've got it wrong. So it is our responsibility to do the very best we can to make sure that we've got it right, and particularly that, above all else, that whatever we're planning to do is safe. So it is a big responsibility.

Unfortunately, the only real way to establish that something is safe is to do clinical trials. I mean, even if you've done any number of animal trial studies, once you put something into humans - we are animals, but we're a little different. You may not get exactly the same outcome.

But what has changed over time is that the business of making vaccines has moved from being a relatively amateurish process, which it was back in the 1940s, 1950s, when people were starting to think about vaccines - to now a very polished, professional approach to things with a whole range of new technologies which have come along.

Some of them are there because we need to make vaccines quickly. COVID, for example, would be a really good example of that, where we turned to a completely new system for making vaccines because we needed to do something quickly.

Some of them we just wanted to get better immune responses and longer immune responses, so we changed the way that we make the vaccines from one way of doing it to

another way of doing it, which turns out to be better. And I think that there's still quite a lot of room for improvement in vaccine development and we need to be ready for anything that's coming along.

Andrew Pollard: So with all the experiences you've had in your career in immunology and discovery and vaccine development, what excites you about the future? What's coming next?

Ian Frazer: Oh look, I'm an immunologist and immunology will continue to help to control diseases. We recognise that immunology plays an important part in a number of chronic diseases.

Me at the moment, I'm kind of interested in how the gut microbiome impacts on the immune system. It's the burden of disease we carry around with us, inside us. We have all these millions of different bacteria that live in our guts and are very important for keeping us healthy. They help us digest our food. They help to boost our immune system responses against things that might cause problems, but also sometimes they cause immune responses, which lead to chronic disease. And we need to understand how that happens and what we can do to prevent it. So learning how we interact with the bugs that grow in our gut. And my interest now is more of the ones that grow in our skin and how they might be contributing to diseases like skin cancer.

So there's a lot of work that needs to be done, and that's really what the whole thing is about. I mean, it's not about speculating about what might happen. It's about doing the clinical and the preclinical work so we know what's going on.

Science has to be right.

Andrew Pollard: Ian, thank you so much for joining us on this podcast, and for all of your contributions, which will have, over the decades ahead, such a huge impact on prevention of cancer on the planet.

Andrew Pollard: That was the Oxford Colloquy: Trust in Science, bringing you the stories, people, and facts behind the science. So you might be wondering, what is a colloquy? A colloquy is a discourse or conversation, and I hope you'll agree that's what we've been having.