

Transcript of interview with Professor Ian Frazer

Voice-over: Welcome to the National Health and Medical Research Council podcast. Our podcasts aim to keep you in touch with major health and medical research issues, and the people who shape them.

Introduction: Former Australian of the Year, Professor Ian Frazer spent more than a quarter of a century labouring over the human immune system, searching for a way it might be used to fight cancer. As a result, young women around the world now have, for the very first time, protection against the second biggest cause of female death – cervical cancer – thanks to Professor Frazer's medical breakthrough, Gardasil. Now director of the Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Professor Frazer tells Dr Mark Bradley about the extraordinary twists and turns in his journey of discovery.

Interviewer: Ian, I thought we might begin right at the very beginning, defining the initial problem you were looking at in those early days of cervical cancer and the causative agent behind that and how it led you on a journey to ultimately develop this now commercial product which is Gardasil.

Prof. Frazer: Funnily enough the problem started with hepatitis B virus and the research work that I was doing in Melbourne when I first came out to Australia in 1981, where we were looking at the causes of chronic liver disease. And the group of men that I was studying at that time were men who had sex with men and this was before the HIV-AIDS epidemic, indeed, before there was even a knowledge that there was a virus which we now call HIV-AIDS. But one of the things that became clear was that the significant immune problems that these young men had led to them having a great deal of difficulty getting rid of infection with papilloma viruses that were causing genital warts, and a colleague of mine, Gabrielle Medley, in Melbourne, suggested that I should also be interested in whether they were having problems with any cancer as a result of the papilloma infections that they couldn't get rid of, because at that time, or shortly before that time, Professor Harald zur Hausen in Germany had for the first time hypothesised that in fact human papilloma viruses might be responsible for cervical cancer.

It had been known for a very long time that cervical cancer had an epidemiology which suggested a sexually transmitted infection. Indeed the first observation on that was made by a pathologist in Verona, Rigoni-Stern, in about 1840. He made a very simple observation from an epidemiological point of view that nuns never got cervical cancer and prostitutes very frequently did and quite correctly assumed that there was something transmitted sexually which caused the disease. But it was really only with zur Hausen's work that it was finally pinned down that it was papilloma virus. Indeed, it was about 10 years after he first hypothesised that before it became generally accepted that that was the case. And here we were sitting in 1984 with evidence of another cancer, anal cancer, now being caused by the same virus.

Interviewer: So then the next sort of evolution in this particular defining of the problem, that was men, but we're talking now about women?

Prof. Frazer: Well, obviously when we saw that there was this connection between the immune system and the ability to protect against one cancer caused by this virus, we became much more interested in the other cancer, which at that time was also thought to be caused by the virus, cervical cancer. And when I came from Melbourne to Brisbane in 1985, I took with me a little bit

of my past interest in chronic liver disease, but a very much stronger interest in working out how you could use the immune system to do something about cervical cancer.

Initially the thought was that we would try to develop vaccines to treat existing infection with the viruses which were responsible for the cancer, because at that time we didn't really know the epidemiology of the disease all that well. And what we were postulating was that the virus that caused cervical cancer was a rare infection, which commonly went on to cause the cancer. We now of course know it's the other way around. It's a very common infection which rarely goes on to cause cancer, but in those days we didn't have the tools that we now have, and the epidemiology wasn't that well mapped out.

Interviewer: Okay, so take us on the journey then about the development of this vaccine.

Prof. Frazer: Well, again it started by us going in a different direction to the one we ended up going in. The original aim was to develop a vaccine to treat the existing infection, so we set out to make vaccines based on two viral non-structural proteins, E6 and E7, which are together always preserved in the cancers and are clearly responsible for transforming the skin cells into precancer and probably into the cancer lesions.

Interviewer: Can I ask you how they do that?

Prof. Frazer: It's fairly well understood. The purpose of those proteins as far as the virus is concerned, of course, is not to cause cancer. I mean shall that's a failure as far as the virus is concerned, but rather to prevent the epithelium from differentiating, so the virus gets more time to copy itself. So, anyway, these two proteins are necessary and sufficient to transform an epithelial cell and, indeed, they're always present in the cervical cancers. So we thought, right, we'll target these two proteins and we'll make a therapeutic, and we did quite a bit of work on that. Indeed, we're still doing work on that 20 years later. But we recognised very quickly that one of the problems we had was that we couldn't really measure the immune responses that we were generating, because the standard tricks of making virus-infected cells and using them as targets couldn't work, because we couldn't grow the virus, so we couldn't get the virus.

So when I went on sabbatical in 1989 to Cambridge, I met the late Dr Jian Zhou, who became my colleague and partner in the process of developing the vaccine. And he and I agreed that we both wanted to make infectious virus - you know, that was what we'd sort of decided we needed to do. Rather than making cells expression with our proteins, we would build an infectious virus which we could use to infect cells and then they would become the targets for our assays and that was the general and rather simplistic idea that we had. Again, eventually we went on and did that. In 1993 we made a complete synthetic papilloma virus, an infectious virus.

But along the way towards that, we realised we would have to build the coat of the virus, the shell of the virus, by expressing the viral capsid proteins, and that's where Jian's skills came into the picture, because he was a very good molecular virologist who had skills in gene cloning, and he cloned by polymerase chain reaction the major capsid proteins, L1 and L2, of the virus at a time when cloning 1600 base pair genes by PCR was really quite an achievement. And it was good that he did it that way, because basically he cloned from clinical material the genes that were responsible, and then we worked out expression systems using vaccinia virus to express those. The aim, as I say, was to build the shell of the virus. Now that kind of failed for about a year. He came back to Brisbane with me after we'd been on sabbatical, and we really did the work when he came back to Brisbane. And it wasn't working.

At the same time we learned that colleagues overseas had tried the same thing and failed. So we locked out in one way in that we did of what in those days would have been regarded as very primitive comparative genomics and wrote out the sequences of the papilloma virus capsid proteins on bits of paper and shuffled them around and realised that it was quite likely that to get the correct authentic L1 protein we would need to express the gene not from the first initiation code on but rather from the second one in the gene. And, indeed, we'd been trying from the first and it hadn't worked. We subsequently found out that our colleagues who had failed had tried from the first and it hadn't worked. But when we tried to from the second, it eventually worked.

The second thing that was pretty critical was that we chose the right cell type - we chose an epithelial cell, and vaccinia virus worked much better in epithelial cells than in any other cells that we subsequently tried.

The third thing that we were lucky with, of course, is that we actually had a human clinical isolate, because if we had worked with the then circulating gene that Harald zur Hausen's lab had originally cloned back in 1983 or '84, it actually had a mutation in it. It wasn't known at that time there was a mutation. It actually hadn't been completely sequenced, I think, at that point. But it had a mutation in it, and the mutation was a critical non-conservative one, which resulted in a protein that couldn't assemble - you could express it, but it wouldn't assemble into the particle shape. So that we got the right sequence in the right cell and without the mutation. And when we got all of those bits right, then much to our great surprise not only did we get a reasonable amount of the L1 protein, the major capsid protein, but also it assembled itself into these virus-like particles, which was really not something that we had expected. But because we had actually set out to look for it - we'd been running gradients to see if there was anything to see if there was anything that was appearing of particle density rather than protein density - we were able to see that a significant amount of the protein was assembling as particles.

Interviewer: Tell us what the significance of that is.

Prof. Frazer: Well, from the point of view of building the virus, we would have had to achieve it by one means or another, but from the point of view of making a vaccine, it was critical, because if the protein had not self-assembled into the virus-like particles, we would have had to make it do that somehow, because to get a vaccine to work, it's got to look to the immune system physically like the virus, and shape is everything when it comes to the immune system making antibody, so what we made had to have exactly the right shape. There's nothing infectious about it, it just has the protein there. But to the immune system it looks pretty much the same as the virus itself.

Interviewer: So this was sort of the first significant step in this vaccine pathway. What did you have to do next?

Prof. Frazer: Well, the next thing that we did was practically to check out and see if these virus-like particles induced an immune response, which, when we put them into mice they did. When we saw the virus-like particles, our thinking switched from thinking therapeutic vaccine to thinking prophylactic vaccine literally overnight, because as soon as we saw on the electron micrographs that they were virus like particles, we could conceive of a vaccine to prevent infection. So by that time we were thinking since all vaccines that prevent infection work through antibody, antibody is what we need to look for.

Interviewer: Okay, so how did you progress this work to the next step?

Prof. Frazer: Basically we said, 'This is going to be the basis of a vaccine, let's go and tell everybody.' So that's what we did. We went off to a meeting in Vancouver in the northern hemisphere autumn of 1991 and the international papilloma virus workshop and said, 'Look, if you do this, you get virus-like particles.'

Interviewer: But you've got to be able to prove that this thing's going to work, be protective, so take us on the next step.

Prof. Frazer: Well, from our point of view the next step was to go and talk to CSL, because we'd already been talking with them about the therapeutic vaccine, indeed for the two years prior to that, and they kind of knew what we were doing and we knew that they were interested in papilloma virus and vaccines in that area. So we went and talked to them about it. But also at the same time virtually every pharmaceutical company worth a mention that was working in the vaccine field came to talk to us, because once we'd talked about it at the meeting in Seattle and once we had published the paper in the *Journal of Virology* that was published in 1991, we kind of laid out the road map, and the last paragraph of the paper said, 'This will be the potential for a vaccine against cervical cancer.' So it wasn't exactly difficult to work out that we'd get a lot of visits, and indeed we did, from every company from Merck through to MedImmune and a whole range of other companies in between. So there was a lot of interest in the area.

Interviewer: It must be immensely satisfying to see this rolled out?

Prof. Frazer: I think it's a great testimony to the power of biomedical research, let's face it. Look, it's great fun - I was able to give the very first vaccine, first licensed vaccine, if you like, in Australia to the first girl to receive it, and being involved in it right through from back at the beginning when we were just talking about papilloma viruses in 1982, right the way through to getting a vaccine delivered to women, that's really exciting. But it's also really exciting to see that if you put your mind collectively to a problem, a whole group of scientists working together on something, then you can come up with the answers.

Interviewer: On that great note, thanks very much.

Prof Frazer: Thank you.

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