

MATTHEW RIMMER

Edited by Simon Grose - "Local Hero in a Credit Squeeze", The Canberra Times, 5 June 2006, p. 6.

AS 2006 Australian of the Year, Professor Ian Frazer has become a household name. A recent survey commissioned by Reader's Digest ranked him as the second-most-trusted person in Australia, beaten only by Dr Fiona Wood, who was Australian of the Year in 2005. Many know Frazer as the inventor of the cervical-cancer vaccine which is to become commercially available in Australia later this year. Yet there is some unrest in the international scientific community as to how much credit Frazer should be receiving, a disquiet that has been highlighted recently in patent decisions around the world. "To say that the vaccine was developed in Ian's laboratory is a stretch in the papilloma- virus research community," says Robert Rose, an associate professor of medicine at the University of Rochester in New York.

"We certainly don't want to take away from the sense of pride that Australia has in Ian's work, but it's not really correct in our view to see the vaccine as something he invented." The University of Rochester is one of four research institutions claiming to be responsible for original work leading to a cervical- cancer vaccine. The other three are the US National Cancer Institute, Georgetown University in Washington, DC, and Frazer at the University of Queensland. According to Frazer, he and Dr Jian Zhou were equal co-inventors of the vaccine in 1991. Zhou died in 1999.

"People like to know who did things first," says Frazer. "I'm not quite sure why. But if it makes people feel happy, I think we probably taught people significantly how to do things." Frazer and Zhou filed a provisional patent covering their human papillomavirus (HPV) research in June 1991 and presented their findings at a scientific meeting in the US in September 1991. "When Ian made this breakthrough in early 1991, we were aware of what he was doing and immediately indicated our desire to be involved and to support him," says intellectual property consultant John Cox, who works for the Australian biotechnology company CSL. Merck negotiated a deal with CSL to exclusively license Frazer's discovery and non- exclusively licensed the NCI's patents from the US National Institutes of Health. GlaxoSmithKline, on the other hand, exclusively licensed patents held by the University of Rochester and Georgetown University, and also non- exclusively licensed the NCI patents.

According to Matthew Rimmer, a senior lecturer at the Australian National University, who specialises in intellectual property, what resulted was a "three-way battle between the University of Queensland and CSL Ltd, the University of Rochester, and the National Institutes of Health." With similar patents lodged in many countries around the world, patent cases have been heard in Australia, the US and Europe, with vastly different outcomes. In Australia, despite Frazer's patent being lodged first, a recent decision handed down by the Australian Patent Office found that the scientists at the University of Rochester were the first to make virus-like particles (VLPs) from HPV16, a strain of human papillomavirus found in 50 per cent of cervical cancers. the particles contain no viral DNA, so they are non-infectious, but can be used to stimulate the immune system to produce antibodies to the virus. That makes their production a crucial part of creating an effective vaccine. The Australian Patent Office found that Frazer's patent had not disclosed immunologically correct VLPs from HPV16. "Therefore the later patent applications could be considered to be novel and inventive in light of the earlier 1991 Frazer patent," says Rimmer. Frazer's patent still stands. "Our patent was granted in Australia, it is the dominant patent in Australia and covers all virus-like particles," he said. "It is a generic patent, so anyone who wants to sell a vaccine in Australia made with virus- like particles has to get a licence to our patent."

Cox agrees: "Certainly in Australia, regardless, the earliest and dominant patent is that granted to Frazer and that patent was not challenged." In the US, Georgetown University was found to have the dominant patent for its contribution to the "background science". "Ironically, the Georgetown patent specifically said they did not produce VLPs," says Dr John Schiller, from the NCI group that also filed HPV patents in the 1990s. Despite the US patent decision currently undergoing appeal, an agreement in February 2005 between Merck and GSK means that the cervical-cancer vaccines continue to progress to market. "Because of the level of uncertainty, Merck and GSK cross-licensed the important patents that they held in the area so that each had the ability to proceed to commercialise the vaccine," Cox says. "The whole purpose of it was to make sure that the development of the vaccine wasn't held up by patent squabbling and that has absolutely been achieved." Merck and GSK are independently developing nearly identical HPV vaccines, both based on the ability of the L1 protein of HPV to self-assemble into VLPs. Gardasil, the cervical-cancer vaccine being developed by Merck, covers four major HPV strains: 16 and 18, which account for 70 per cent of HPV-related cancer cases, and 6 and 11, which cause 90 per cent of genital wart cases. "Frazer and Zhou did their initial work with HPV16, which is the most important serotype," Cox says. "Subsequently, when they completed their patent a year later, they included further data on HPV6 and HPV11, which are the two dominant causes of genital warts in humans." The provisional patent filed by Frazer and Zhou in 1991 and a subsequent paper

published in Virology described their discovery of how to assemble VLPs using the L1 and L2 proteins of the human papillomavirus. L1 and L2 are capsid proteins that make up the outside coat of HPV particles. They facilitate infection by interacting with surface molecules on human cells to enable invasion by viral DNA. "Frazer actually made an error in his first work," Cox says. "He believed that you needed the L1 and L2 capsid proteins to make VLPs for HPV16. But he subsequently showed that you only needed the major capsid protein to make VLPs." Schiller says, "Frazer and Zhou reached the erroneous conclusion that L1 alone does not assemble into virus-like particles. Both of the vaccines soon to be licensed are based on L1-only VLPs." Also, to clone a gene, you need a start codon and a stop codon. These codons inform the cell how long to make a protein. Cox says, "The reason why Frazer and Zhou succeeded for the first time was that they made a rather interesting breakthrough. They discovered the correct start codon." Three publications followed

Frazer's: Georgetown University, for research which did not make VLPs but showed that L1 was recognised by antibodies, the NCI, which showed that L1 from bovine papillomavirus made VLPs which induced antibodies that prevented virus infection, and Rochester University, showing that L1 from HPV11 self- assembled into VLPs which were later shown to induce antibodies. A fourth publication in the Journal of Virology in 1993 by the group at NCI showed that there were a so-called "wildtype" and a "prototype" strain of HPV16 and that the wildtype was needed to make functional VLPs. "There was this belief in the world that Ian Frazer had used the so called prototype and not the wildtype in making his VLPs," Cox says.

Frazer says, "We actually used a wildtype one, a real one. We subsequently showed that and sequenced it and filed that sequence with Genbank and deposited it in a genetic depository in the United States at the same time we filed the patent. So we actually used the right L1 code"" However, Rose says, "If they did use the wildtype sequence, there's every expectation that their results would have been vastly different." Credit where credit is due.

According to Rimmer, the cervical-cancer patent dispute "is a battle not only in terms of patent priority but also in terms of the apportionment of scientific credit and kudos between different players". "In some ways the second issue is really a question for the scientific community to decide in terms of apportioning who should be given the credit," he says. All groups involved acknowledge that contributions to the original research into HPV were made by various people, but who deserves the most credit may never be resolved. Rose says, "I know that there were a large number of people worldwide that worked towards this and it was disconcerting to me as an individual that there was no effort made by Dr Frazer to make a similar acknowledgment. "He basically allowed the perception to grow that he was the sole inventor of the vaccine and that's not accurate.

Frazer says, "Patents are all to do with licenses and making money and selling vaccines, which is quite a different business to scientific inventorship. "We're going to get a vaccine. The vaccine will be of benefit to women. Who invented it probably doesn't matter very much." He also says, "I've had a fair bit of publicity for it in Australia. "I'll be the first to admit that that has helped the cause of medical research in Australia no end at all. The money will come in large measure to Australia and that's also good, because it helps to argue a case for more funding for medical research in Australia."