

# Ian Frazer

Almost 15 years after Ian Frazer began the work that created the first vaccine to prevent cervical cancer caused by human papilloma virus (HPV), the 54-year-old immunologist is using his newfound prominence to educate others about treating HPV and to pass along the lessons he's learned about drug development.

The commercial approval in June 2006 of the first HPV vaccine, Gardasil (recombinant HPV subtypes 6/11/16/18), marketed by Whitehouse Station, New Jersey-based Merck, has enabled Ian Frazer to raise awareness about the potential to eradicate cervical cancer. But his increased visibility—he was named Australian Man of the Year in 2006—and 20/20 hindsight have also given him the forum and voice to advocate for more effective ways to build public-private partnerships.

Born in Glasgow, UK, Frazer trained as a renal physician and clinical immunologist at Edinburgh University. He emigrated to Australia in 1980, where he joined the Walter and Eliza Hall Institute to conduct research in viral immunology, and in 1985 he moved to the University of Queensland in Brisbane. Today, Frazer is director of the university's Diamantina Institute and head of its immunotherapy group.

Frazer is frank and humble enough to admit that he feels a “bit embarrassed” by all the attention that has come with Gardasil's approval, saying that “while we played what was in retrospect an important part in the development of the vaccine, it was developed as a consequence of a lot of people's work.”

“He's a lab rat, like me,” says Alan Shaw, a prominent member of the Merck development team for Gardasil and now CEO of VaxInnate, a Cranbury, New Jersey-based flu vaccine start-up company. “Frazer's an Australian Scot—that's about as down to earth as you get.”

Frazer first became interested in HPV in the early 1980s while treating gay men infected with HIV; they often had genital warts, which are caused by HPV. He met Jian Zhou, his collaborator on the development of the vaccine, while on sabbatical in Cambridge, UK, in 1989. Jian had cloned and isolated the HPV capsid genes in order to study the immune response to them in cells, “much the same as I was doing with the viral nonstructural genes,” Frazer explains.

After the sabbatical, Frazer enticed Jian to move to Brisbane. The team eventually expressed the correct short version of the L1 coat protein, cloned out of a clinical sample, and purified what turned out to be the whole virus shell, or virus-like particles (VLPs). They knew then that they had the basis for a vaccine.

That was in early 1991. Licensing discussions with Melbourne, Australia-based CSL followed; the company was funding research in Frazer's lab primarily aimed at developing a therapeutic—not protective—vaccine, and thus held a right of first refusal over their work in HPV. A half-dozen other vaccine companies also wanted in, but ultimately CSL took the license and in turn licensed the technology to Merck in 1995. Eleven years later, Merck received approval for a vaccine that now seems likely to be a blockbuster despite the significant local opposition that arose following Merck's hard lobbying for the mandatory use of Gardasil (in February 2007, for example, the governor of Texas passed an executive order to that effect, which ended up being overturned). Sales of the vaccine were \$418 million in the third quarter of 2007 and are projected to easily top \$1 billion annually.

In hindsight, Frazer points to several things he would have done differently from the start: the original CSL agreement was too broad;

the provisional patent claims on VLPs were too narrow; the commercial implications of those claims were not thought through; and more money should have been invested in the program to bolster both the data and the negotiating positions of the university and CSL. Indeed, those issues now form talking points for Frazer when he speaks of the need for increased public—and private—support for research in Australia.

“If you're going to get value out of the intellectual property, you've got to pursue it to the point [where] you can show it works rather than just showcase the technology,” he explains. The trouble for Frazer was that his group lacked the infrastructure and funding—either government or venture capital—to take their vaccine into clinical trials. “With the little bit of money we had, we showed that [VLPs] could be made and were immunogenic and then basically we handed them on,” he says.

Frazer has also happily taken on the role of educator: he spends 20–30% of his time talking about the connection between HPV and cervical cancer, the prevalence of this cancer in specific countries, the amount of screening actually occurring, how women are treated and at what age they start having sexual intercourse. “That's what I've found my role to be,” he says.

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Kathrin Jansen, another key member of the Gardasil development team at Merck and currently at Wyeth in Collegeville, Pennsylvania, applauds Frazer's efforts. “He's doing a fantastic job. It's important that people who know what vaccines can and cannot do go out and educate the public.” Gardasil was not the first example of a higher-priced, hard-to-manufacture vaccine proving its medical and commercial worth: Jansen points to Prevnar (diphtheria CRM197 protein), Wyeth's vaccine against *Streptococcus pneumoniae*, which protects infants and children against meningitis and infections of the blood, as the trailblazer. But the fact that Gardasil is given to teenagers—and is closely linked to sexual behavior—makes for a different medical dynamic.

The availability of the HPV vaccine gets young people into the doctor's office, where they can broadly discuss the ramifications of sexual activity, suggests Shaw. Because Gardasil includes the HPV subtypes 6 and 11, thus offering protection against genital warts, teenage boys should also be interested in the vaccine. (London-based GlaxoSmithKline's Cervarix, which is in development, also contains HPV subtypes 16 and 18, but not 6 or 11.)

Indeed, Frazer purchased Gardasil as a holiday gift for his two boys last year, putting a personal exclamation point on his generation-long odyssey through vaccine R&D.

*Mark Ratner, Cambridge, Massachusetts*