

HPV Vaccine: Global Effort Defeats Cancer-Causing Virus

Georgetown University

German Cancer Research Ctr (DKFZ)

National Institutes of Health (NIH)

University of Queensland, Australia

University of Rochester Medical Center



The world's first vaccine against human papilloma viruses (HPV) is also the world's first vaccine developed to specifically combat cancer. Distributed under the brand names Gardasil and Cervarix, by Merck & Co. and GlaxoSmithKline, respectively, the vaccine is widely known for its effectiveness against precursors of cervical cancer in women. The breakthrough medical advancement, recently approved for use in males, stands to benefit men too.

According to the World Health Organization (WHO), some 500,000 women a year worldwide develop cervical cancer, and 274,000 die from the disease. Cervical cancer is caused by HPV and is the most common cancer affecting women in developing countries. The virus, however, does not restrain its attack to women or even to the female reproductive tract; there are more than 100 known types of HPV, and at least 13 are cancer-causing. WHO estimates it also causes

90 percent of anal cancers, 40 percent of cancers of the external genitalia, at least 12 percent of oropharyngeal (throat) cancer cases and at least 3 percent of oral cancer cases. In the United States, HPV is the most common sexually transmitted disease, according to the Centers for Disease Control and Prevention, and will infect at least 50 percent of sexually active people at some point in their lives.

In other words, HPV strikes more humans than it spares and it continues to spread.

The need to confront and prevent this threat is universally recognized. As such, it came as no surprise that scientists, working separately and under different flags, would toil to the same end: Find a way to stop HPV.

Miraculously, an HPV vaccine was created. Science did prevail. But the prophylactic protection followed a long and complicated path of conflict, collaboration and cooperation on its way to your doctor's office.

The Race for Answers

Research groups around the world — funded by government institutions in Germany, Australia and the National Institutes of Health in the United States — worked furiously on solving the puzzle of how HPV infects the human body. There were promising signs in several laboratories in the early 1990s. Leading the pack toward a breakthrough were the German Cancer Research Center (DKFZ); University of Queensland, Australia; and, in the United States, the National Institutes of Health (NIH), the University of Rochester Medical Center and Georgetown University.

The knowledge gained by each was leading to a single conclusive answer.

While their research paths took different routes, the starting point for all of the scientists was the same — the findings of Harald zur Hausen, M.D., D.Sc. (Hon), M.D.s (Hon), professor emeritus. A virologist and former chair and scientific director of the DKFZ, zur Hausen is credited for discovering that HPV causes cervical cancer, in particular HPV 16 and 18. The Nobel Committee awarded zur Hausen the 2008 Nobel Prize in Medicine for discovering the mechanism of HPV-induced carcinogenesis that made vaccine development possible.

“The global public health burden attributable to human papilloma viruses is considerable. More than 5 percent of all cancers are caused by persistent infection with this virus,” the Nobel Committee said in its statement explaining its decision for the award.

The combined achievements of the contributors proved extraordinarily successful. The HPV vaccine was nearly 100 percent effective — a rare result in clinical trials — in preventing precancerous lesions in young women. Gardasil also proved to be 90 percent effective in preventing anogenital warts. In both cases, the extremely high success rates were in women 16 to 18 years old with no previous HPV infections. This rare success rate eventually helped fuel collaboration as competitors readily acknowledged the vaccine's worth to humankind.

The Many Paths to Collaboration

Zur Hausen's co-worker, Lutz Gissmann, Ph.D., a professor and head of the Division of Genome Modifications and Carcinogenesis at DKFZ, contributed significant findings crucial to vaccine development: Chief among them were virus-like particles (VLP) discoveries.

Several researchers concluded that the use of virus-like particles (VLPs) were the most likely answer to the HPV problem. VLPs prevent infection by papillomaviruses by inducing an immune system response, also known as neutralizing antibodies. Early on, Gissmann and team noted that the HPV 16 isolate had to be taken from samples with

active virus production in order to generate VLPs.

Further research showed that VLPs consist of only one protein (L1). Gissmann suggested that the L1 gene worked in VLP generation only if active virus production was present. The L1 protein has the ability to spontaneously assemble into VLPs, hence they can easily be manufactured by standard molecular biology technology.

Scientists at other institutions, including the team led by Ian Frazer, M.D., of the University of Queensland, Australia, and another organized by Gissmann while at Chicago's Loyola University, were rapidly gaining ground on the same or similar solutions to the universal HPV problem. The University of Queensland scientists had narrowed down the virus to L1 and L2 proteins, but had yet to narrow it further to just L1. They were, however, on a significant path and closing in on the solution that others would arrive at as well.

Meanwhile in the United States, principal scientists at NIH, Douglas Lowy, M.D., and John Schiller, Ph.D., were also working on HPV vaccine development. This team examined biochemical and genetic aspects of the papillomavirus oncogenes and their protein products. Once VLPs were discovered to be an effective immunization agent, the NIH team developed techniques for large-scale production. The NIH team also found that little cross immunity exists between different HPV types. This information is important to developing a polyvalent vaccine, which is a vaccine that can simultaneously protect against several HPV types.

Over at the University of Rochester, virologists Richard Reichman, M.D., William Bonnez, M.D., and Robert Rose, Ph.D., had set out 20 years before to discover how the immune system fights HPV infection. They too created VLPs by putting an HPV gene into insect cells using a virus, which then produced particles that mimicked the shape of real HPV particles and incited the immune response.

Still more scientists at Georgetown University, a team led by Richard Schlegel, M.D., Ph.D., chair and professor of pathology, looked at how the mechanism of papillomavirus-mediated cell transformation can eventually lead to the design of viral-specific therapeutics. Following the development of the first-generation HPV vaccine, his work led to second- and third-generation vaccines that enable rapid purification of the vaccine and stabilization of its protein conformation.

The events of discovery were thus sufficiently entangled as to cause confusion over who should own any resulting patents.

Commercial Interest Sputters

Despite overwhelmingly similar findings in many of the world's leading research institutions, commercial interest in the imminent vaccine was mixed.

"DKFZ had a long cooperation on HPV with the former 'Behringwerke,' a vaccine company in Marburg, Germany," explains Ruth Herzog, Ph.D., head of the Office of Technology Transfer at DKFZ. "So they were aware of HPV, but the company completely underestimated the market potential of a HPV-vaccine, as did others."

In the United States, reception was not so chilly but still a long way from the fanfare many thought the accomplishment deserved.

"NIH did receive interest early on from vaccine companies, but there was initially some doubt as to how effective the approach would be using virus-like particles and the challenging fact that such a vaccine would be used as a preventative against cancer, rather than simply against an infectious agent," explains Steven Ferguson, CLP, deputy

director, licensing and entrepreneurship, Office of Technology Transfer at the NIH.

“There was significant risk and questions in the early days, which provided a small company at the time, Medimmune, to become a significant player in the field in the early 1990s,” he adds. “Medimmune was able to leverage their prior research experience with VLP vaccines — in this case, parvovirus, also licensed from NIH — to form an early belief that the VLP approach could also be commercially developed into a product for HPV.

“Had it not been for U.S.-based Medimmune, the outcome for this breakthrough may have been much bleaker.

“*“Medimmune did what a biotech should do and did at the time very well: Take on early innovative projects, develop them and sell them to big pharma,” says Herzog.*

“Medimmune gambled that the HPV vaccine would be a big winner and made strategic investments into the technology. In addition, Medimmune assembled intellectual property from different sources, including the NIH, and moved the project to the clinic. Eventually they were able to interest a partner in the project, SmithKline, which later on became GlaxoSmithKline.”

In a parallel effort, U.S. pharmaceutical giant Merck & Co. acquired some licensing rights from NIH and the University of Queensland, Australia.

Patent Claims and Clashes

The question of who owned the patent on the technology remained.

The U.S. Patent Office (USPTO) was left to sort which of the many scientific teams was the first to make the pivotal invention.

In the end, the players themselves resolved the problem. In early 2005, Merck & Co. and GlaxoSmithKline entered into a cross license agreement. To facilitate the settlement of the patent cases, the U.S. licensors renegotiated their shares of vaccine sales revenues with licensees. This paved the way for millions of women to benefit from the vaccine’s life-saving benefits.

“That there were so many institutions involved both on the research and commercial development sides represents both the size of the market need for this product as well as the unproven initial difficulty and complexity of the underlying science,” explains Ferguson.

Although the dispute at the USPTO was hard-fought, the resolution itself proved peaceful.

“In the end, an increasing awareness by all parties that the underlying science for the vaccine was in fact sound and that a solution to this very difficult public health problem was actually close at hand, provided a means for an agreement that recognized the contribution of all the parties,” says Ferguson.

While the path to the vaccine was challenging, competitive and even combative, the successes were counted on many fronts.

“The development of the HPV vaccine was a complicated story with many players, but it is a great testimony to the success of academic and federal tech transfer,” says Marjorie Hunter, J.D., associate vice president, Office of Technology Transfer of the University of Rochester Medical Center.

Even so, the best barometer of success is measured in human lives saved. The inventors and investors have not lost

sight of that fact.

“I consider myself extremely lucky,” says Gissmann. “It does not happen often that a researcher — within his own lifetime — participates in the process of discovery of the link between an infection and a disease, is part of the development of a vaccine against it and then lives to see it being successfully used.”

The sentiment is echoed by all who contributed.

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