

## Who Invented the VLP Cervical Cancer Vaccines?

If you ask public relations departments, the answer is simple. Press releases from the University of Rochester in New York, Georgetown University in Washington, D.C., and Queensland University in Brisbane, Australia, have claimed responsibility for original work leading to the Merck or GlaxoSmithKline vaccine. The two vaccines are nearly identical, based on the ability of the L1 protein of the papillomavirus to self-assemble into virus-like particles (VLPs) that elicit neutralizing antibodies.

If you ask patent offices, the answer is anything but simple. The U.S. Patent Office recognized four claimants to the basic technology—the National Cancer Institute, Georgetown, Queensland, and Rochester. After a 10-year “interference” to adjudicate the overlapping claims, Georgetown won the dominant patent for its contribution to the “background science.” Ironically, of the four, Georgetown was the only one not to have developed VLPs.

Other U.S. patents are held by NCI’s parent institution, the National Institutes of Health. Rochester, NIH, and Queensland hold patents in other countries. Merck and GSK have cross-licensed the patents of all parties.

Based on the peer-reviewed literature, the development of the VLP/L1 vaccine was an incremental process with multiple contributors. Here are five key discoveries that underlie both public relations and patent claims:

**1991:** Expression of the human papillomavirus L1 and L2 proteins together, but not L1 alone, resulted in the formation of small VLPs described as “incorrectly assembled arrays” of

subunits (reported by Jian Zhou, Ian Frazer, and colleagues at Queensland; *Virology*).

**1992:** HPV L1 expression in mammalian cells led to an L1 in cells that was recognized by monoclonal antibodies that bind conformational epitopes; no VLPs were produced in this study but it was considered important because the ability of L1 to self-assemble into VLPs and produce neutralizing antibodies depends on the native conformation of L1, which involves conformational epitopes (reported by Shin-Je Ghim, A. Bennet Jensen, and Richard Schlegel of Georgetown; *Virology*).

**1992:** L1 from bovine papillomavirus type 1 self-assembled into morphologically correct VLPs that induced high levels of neutralizing antibodies in immunized animals (reported by Reinhard Kirnbauer, Doug Lowy, and John Schiller at NCI and colleagues; *Proceedings of the National Academy of Sciences*).

**1993:** L1 from HPV 11 self-assembled into VLPs, later shown to induce neutralizing antibodies (reported by Robert Rose at Rochester and colleagues; *Journal of Virology*).

**1993:** L1 from HPV 16, taken from lesions that had not progressed to cancer, self-assembled more efficiently than the HPV 16 L1 that researchers everywhere had been using; the old strain was shown to be a mutant, possibly because it had been isolated from a cancer (reported by Kirnbauer, Lowy, and Schiller at NCI and colleagues; *Journal of Virology*).

—Caroline McNeil

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