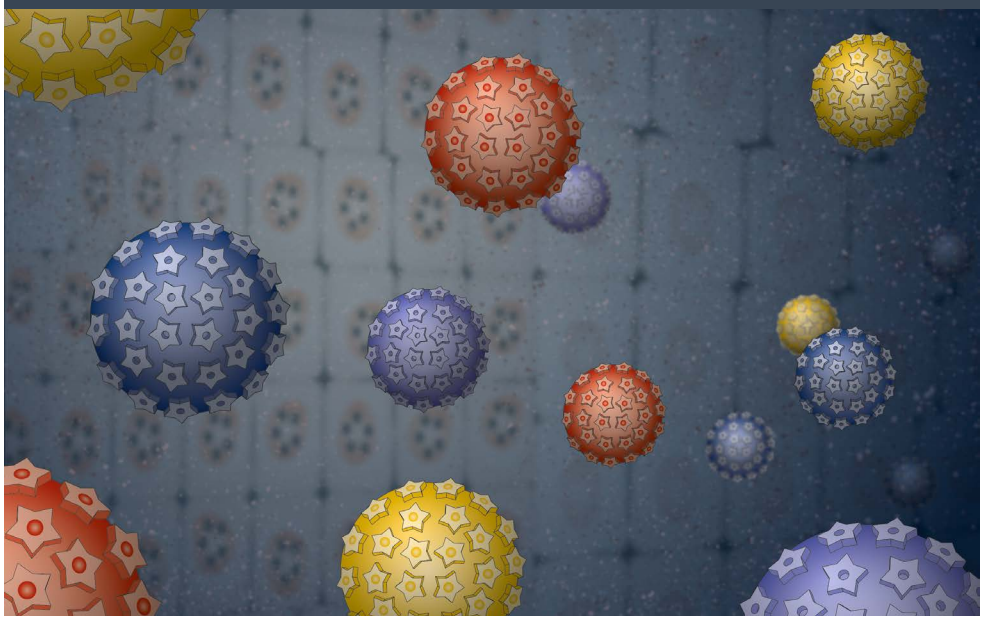
MILESTONE 14

A vaccine to prevent HPV-related cancers



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In 1976, a German virologist, Harald zur Hausen, hypothesized that cervical cancers might be caused by a papillomavirus. Later work by his and other groups around the world demonstrated that human papillomaviruses (HPVs) were present in cervical cancer samples. Confirmation that infection with a 'high-risk' HPV is necessary for the development of cervical cancer raised the intriguing possibility that a cervical cancer-preventing vaccine might be developed.

A major roadblock to creating a cancer-preventing HPV vaccine, however, was that HPV could not be grown in the lab, and thus it was not possible to create a vaccine from attenuated or killed viruses, as was usually done. This changed in 1991, when a crucial technological advance was made by Ian Frazer and colleagues.

Frazer and colleagues used the then relatively new technology of expressing genes in cell culture to create virus-like particles (VLPs) of HPV16, a key cancer-causing high-risk HPV type. These VLPs formed spontaneously when the HPV16 capsid proteins L1 and L2 were expressed together (but not separately) from a vaccinia virus expression vector in monkey kidney epithelial cells. Visualization of the VLPs by electron microscopy indicated that they had a virus-like 3D structure, unlike individually produced viral proteins, and it was hypothesized that VLPs would be more likely to induce an immune response in animals. Reporting their findings in the journal *Virology* in 1991, the authors recognized that VLPs "could provide a safe source of material for the development of a vaccine".

Eventually, these VLPs did just that. Efforts from groups led by John Schiller, Robert Rose and Toshiyuki Sasagawa, combined with ongoing work from the Frazer group, used more efficient gene expression systems in insect cells and yeast to produce larger quantities of HPV VLPs with the correct conformation. These VLPs were shown to induce antibodies in animals that were similar to those induced by infectious virus particles. Similar VLPs derived from non-human animal papillomaviruses were then used as the basis of experimental vaccines that induced antibodies that successfully prevented papillomavirus infection in animal models.

> "[VLPs] could provide a safe source of material for the development of a vaccine"

Clinical trials of HPV VLP vaccines of various HPV types indicated that they were safe and effective at preventing HPV infections. Then in 2006, the first HPV vaccine (Gardasil), containing VLPs of four HPV types — high-risk HPV16 and HPV18 (which cause ~70% of cervical cancers) as well as low-risk HPV6 and HPV11 (which cause genital warts) — was approved for use in the USA in adolescent girls. This was followed shortly after by approval of Gardasil or another VLP-based vaccine against HPV16 and HPV18 (Cervarix) in many other countries. Epidemiological studies in countries where vaccination is now routine and uptake is high have shown clear reductions in infections with the HPV types included in the vaccines, as well as in the development of cervical pre-cancerous lesions.

A newer version of Gardasil, which protects against five additional high-risk HPV types has now been approved. Furthermore, several other cancer types (including oral, head and neck, penile and anal cancers) have been attributed to HPV infections, so in many countries boys as well as girls now receive these vaccines. Although there are still issues in many countries with uptake of vaccination and access to these vaccines, the development of HPV VLPs and the recognition that they could be used to create vaccines has had a substantial public health impact that should only increase further as these vaccines become more widely adopted.

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ORIGINAL ARTICLE Zhou, J. et al. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology* **185**, 251–257 (1991)

FURTHER READING zur Hausen, H. Condylomata acuminata and human genital cancer. *Cancer Res*, **36**, 794 (1976) | Boshart, M. et al. A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. *EMBO J.* **3**, 1151–1157 (1984) | Watts, S. L. et al. Cellular transformation by human papillomavirus DNA in vitro. *Science* **225**, 634–636 (1984) | Munger, K. et al. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. *J. Virol.* **63**, 4417–4421 (1989) | Kirnbauer, R. et al. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. *Proc. Natl Acad. Sci. USA* **89**, 12180–12184 (1992) | Kirnbauer, R. et al. Efficient self-assembly of human papillomavirus type 16 L1 and L1-L2 into virus-like particles. *J. Virol.* **67**, 6929–6936 (1993) | Rose, R. C. et al. Expression of human papillomavirus type 11 L1 protein in insect cells: in vivo and in vitro assembly of viruslike particles. *J. Virol.* **67**, 1936–1944 (1993) | Sasagawa, T. et al. Synthesis and assembly of virus-like particles of human papillomaviruses type 6 and type 16 in fission yeast *Schizosaccharomyces pombe*. *Virology* **206**, 126–135 (1995) | Gertig, D. M. et al. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med.* **11**, 227 (2013) | Roden, R. B. S. and Stern, P. L. Opportunities and challenges for human papillomavirus vaccination in cancer. *Nat. Rev. Cancer* **18**, 240–254 (2018)