National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

HPV Vaccine: An Industry Partnership to Prevent Cervical Cancer

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CCR/TEDCO Technology Showcase
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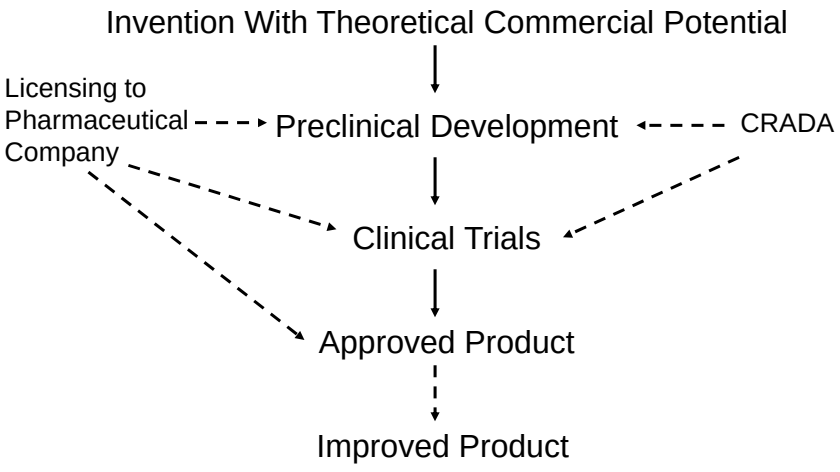
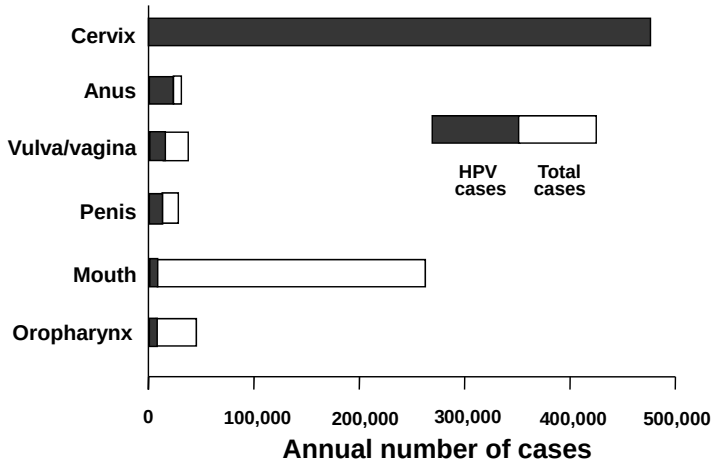
The views expressed are my own and do not necessarily reflect those of NCI/NIH

Technology Transfer & Product Development



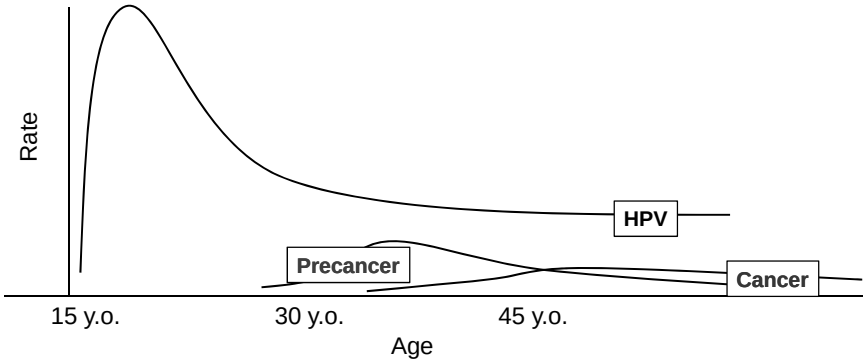
Worldwide Incidence and Distribution of Cancers Attributable to HPV



- ***Cervical cancer represents ~10% of all female cancers worldwide***
- ***~80% of cervical cancer occurs in the developing world***

Adapted from Parkin, Int J Cancer 118:3030, 2006

Time Line of Cervical HPV Infections And Progession to Cervical Cancer



- **Lifetime incidence of genital HPV infection >80% in U.S.**
- **Most infections clear spontaneously, eliminating cancer risk for that infection.**
- **Persistent infection with a high-risk HPV, especially HPV16 or 18, is the single most important risk factor for progression to precancer and cancer.**

Adapted from Schiffman & Castle, New Eng J Med 353:2101-4, 2005

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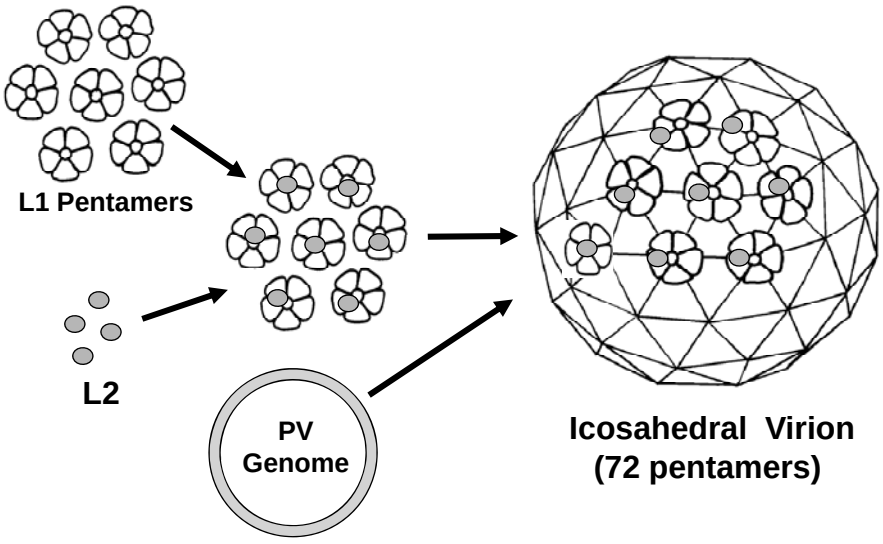
Challenges to development of a preventive HPV vaccine

- Most transmission, and there has been a poor track record for vaccines against local STDs.
- Most preventive vaccines depend on serum (i.e., systemic) neutralizing antibodies, but HPVs spread locally, not systemically.
- No source for preparative amounts of virus.
- HPVs contain viral oncogenes (E5, E6, E7).

A Prophylactic Vaccine

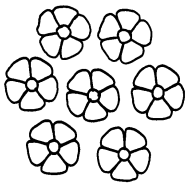
- **To date, successful viral vaccines are primarily prophylactic.**
- **A sub-unit vaccine approach seemed preferable for a prophylactic HPV vaccine (viral oncogenes E5, E6, E7).**

Formation of Papillomavirus Virions



L1 & L2 each contain neutralization epitopes; L1>L2

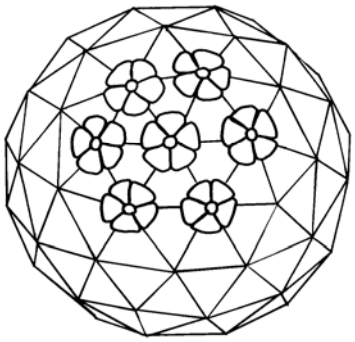
L1 Self-assembles to form Virus-like Particles (VLPs)



L1 Pentamers

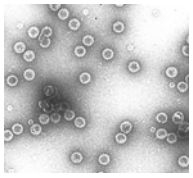
Self-assembly

Into VLPs



L1 Virus-like Particle (VLP)

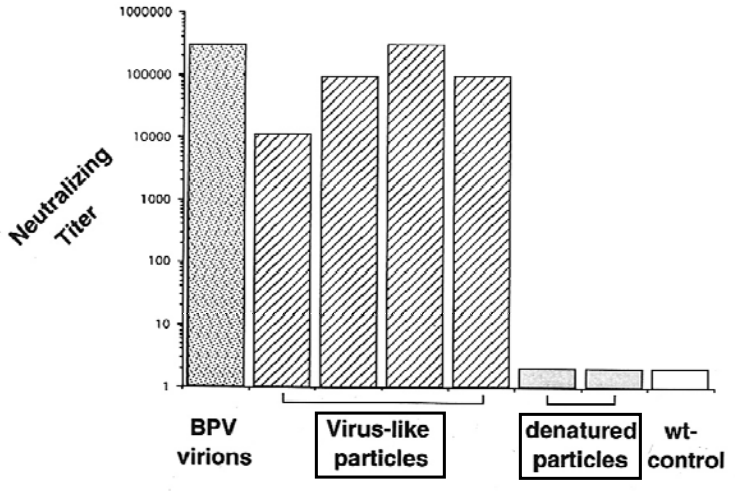
Reinhard Kirnbauer et al, PNAS, 1992



L1 VLPs

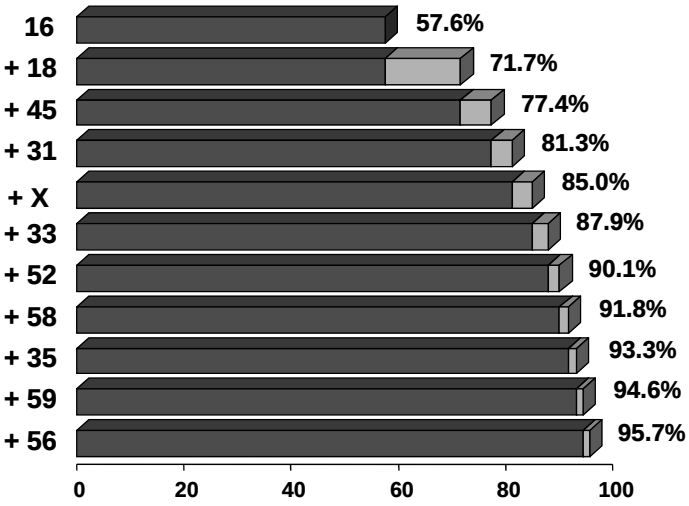
L1 VLP Induction of Neutralizing Antibodies Was First Demonstrated with Bovine Papillomavirus

Reinhard Kirnbauer et al, PNAS, 1992



In vitro neutralization of BPV Virions by Sera from IM Vaccinated Rabbits

Cervical Cancer is Attributable to Multiple HPV Types; HPV16 Predominates



From X. Bosch

Problem: HPV16 L1 VLP Formation was Inefficient

- HPV16 L1 from the reference strain self-assembled very inefficiently into VLPs (less than 1% as efficiently as BPV1).
- Was poor VLP formation inherent to HPV16, or was the HPV16 L1 from the reference strain a mutant? The HPV16 DNA had been cloned from a cervical cancer, and cancer cells are prone to mutation.
- When we tested RhPV L1 (closely related to HPV16), it formed VLPs as efficiently as BPV1.
- ***We therefore hypothesized HPV16 L1 from the reference strain was a mutant.***

JOURNAL OF VIROLOGY, Dec. 1993, p. 6929–6936
0022-538X/93/126929-08$02.00/0

Vol. 67, No. 12

Efficient Self-Assembly of Human Papillomavirus Type 16 L1 and L1-L2 into Virus-Like Particles

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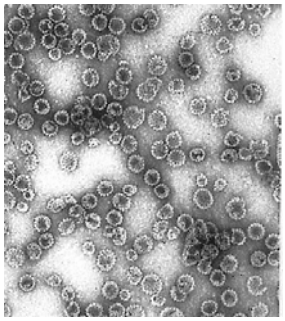
Received 14 June 1993/Accepted 18 August 1993

- HPV16 L1 from the HPV16 reference strain was a mutant. The critical mutation was at Histidine 202, while wild type HPV16 and other HPVs encode Aspartate at this residue.
- Wild type HPV L1, isolated from benign lesions, formed VLPs efficiently, in contrast to the HPV16 reference strain.



HPV16 VLPs

Systemic VLP Vaccination is Protective in 3 Animal Papillomavirus Models: Skin (rabbits) and Oral Mucosa (cows & dogs)

- **Protection:**
  - **prophylactic, not therapeutic**
  - **efficient without adjuvant**
  - ***passively transferred with immune IgG (neutralizing antibodies)***
  - **type-specific (VLPs from a divergent papillomavirus were not protective)**

Conclusions from NCI Early Phase Clinical HPV16 L1 VLP Vaccine Trials

- **Systemic vaccination (3 intramuscular doses) of HPV 16 L1 VLPs even without adjuvant induces consistent and durable serum antibody responses (>40-fold higher than after natural HPV infection), with antibodies present at the cervix.**
- **The antibody titers achieved in people are similar to those that protect animals against experimental viral challenge.**

Disclosure

The NIH has patents on papillomavirus vaccine technology. I am an inventor of this technology. The NIH has licensed the technology to both Merck and GlaxoSmithKline, the two companies developing commercial HPV vaccines.

Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 11553–11557, December 1995
Immunology

Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas

JoAnn A. Suzich*†, Shin-je Ghim†‡, Frances J. Palmer-Hill*, Wendy I. White*, James K. Tamura*§, Judith A. Bell¶, Joseph A. Newsome‡, A. Bennett Jenson‡, and Richard Schlegel‡

*MedImmune, Inc., Gaithersburg, MD 20878; ‡Georgetown University Medical Center, Washington, DC 20007; and ¶Marshall Farms, Rose, NY 14516

Communicated by Lloyd J. Old, Ludwig Institute for Cancer Research, New York, NY, July 24, 1995

BUTTERWORTH HEINEMANN

0264-410X(95)00103-4

Vaccine, Vol. 13, No. 16, pp. 1509–1514, 1995

0264-410X/95 $10+0.00

Vaccination with yeast-expressed cottontail rabbit papillomavirus (CRPV) virus-like particles protects rabbits from CRPV-induced papilloma formation

Kathrin U. Jansen*, Mark Rosolowsky, Loren D. Schultz, Henry Z. Markus, James C. Cook, John J. Donnelly, Douglas Martinez, Ronald W. Ellis and Alan R. Shaw

Department of Virus and Cell Biology, Merck Research Laboratories, West Point, PA 19486, USA. *To whom correspondence should be addressed. (Received 29 March 1995; revised 1 May 1995; accepted 1 May 1995)

Two Distinct HPV VLP Vaccines Are Under Commercial Development

GlaxoSmithKline:
Cervarix

- **HPV16**
- **HPV18**

} **70% of Cervical Ca**

- **ASO4 Adjuvant (Aluminum + MPL)**
- **Made in insect cells**

Merck:
Gardasil

- **HPV16**
- **HPV18**

} **70% of Cervical Ca**

- **HPV6**
- **HPV11**

} **90% of Genital Warts**

- **Aluminum Adjuvant**
- **Made in yeast**

IM Injections at 0, 1 or 2, and 6 months

Three Phase III Trials Are in Progress

Sponsor	VLP Types	Trial Sites	Enrolled
Merck:	HPV16, 18, 6, 11	Multicentric	25,00
GSK:	HPV16, 18	Multicentric	18,000
NCI:	HPV16, 18	Costa Rica	7,500

Women followed for several years

Virologic Endpoints: Persistent cervical HPV DNA

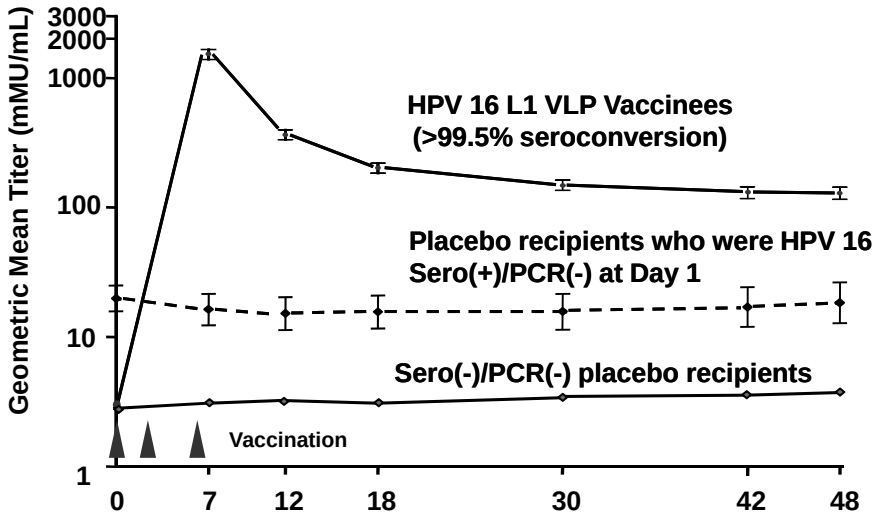
Clinical Endpoints: Intermediate and high grade dysplasias (cervical, vulvar, vaginal) & genital warts (for Merck vaccine)

Merck: Phase III Prophylactic Efficacy Results

	Vaccine		Placebo			
	n	Cases	n	Cases	Efficacy	C.I.
*HPV16 or 18 CIN 2/3 or AIS	8487	0	8460	53	100%	93–100
**HPV16 or 18 VIN2/3 or ValN2/3	8641	0	8667	24	100%	83-100
*HPV6, 11, 16, 18 Genital warts	7897	1	7899	91	99%	94–100

Results in HPV DNA and seronegatives at baseline after three doses (*) or after at least one dose (**), as reported in Gardasil package insert.
Average Duration of Follow-up: 1.5 Years After the Last Vaccination

Protection After Plateau of VLP Antibody Titers Suggests Long Term Protection



Merck data, Mao et al. 2006

Regulatory Approval of HPV VLP Vaccines

Merck's Gardasil was approved in 2006 in the U.S., EU, many other countries

GSK's Cervarix was filed with EU's EMEA in March 2006, with FDA in March 2007, approved in Australia in May, 2007.

Gardasil Approval Specifics

- **US FDA approved for 9-26 yr old females in June '06**

  CDC's ACIP recommended June '06 for:
  - **routine vaccination of 11-12 yr old**
  - **catch up vaccination 13-26 yr old**
  - **9-10 yr old vaccination at physician's discretion**
  - **inclusion in Vaccines for Children program**

- **European Union approved for 9-26 yr old females; 9-15 yr old boys**

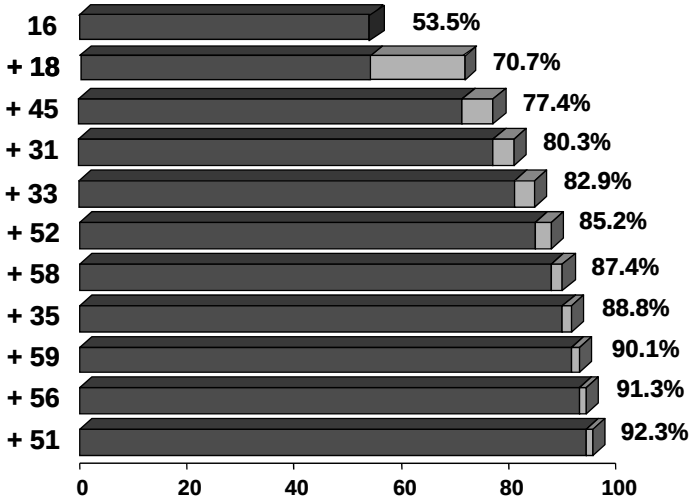
Outstanding Medical Issues

- **Will the vaccine continue to have an excellent safety profile after it has been given to hundreds of thousands of people?**
- **How long will the vaccine remain highly protective? Will there be a need for booster vaccinations?**
- **Will the vaccine be effective in boys/men?**

We can't give up screening

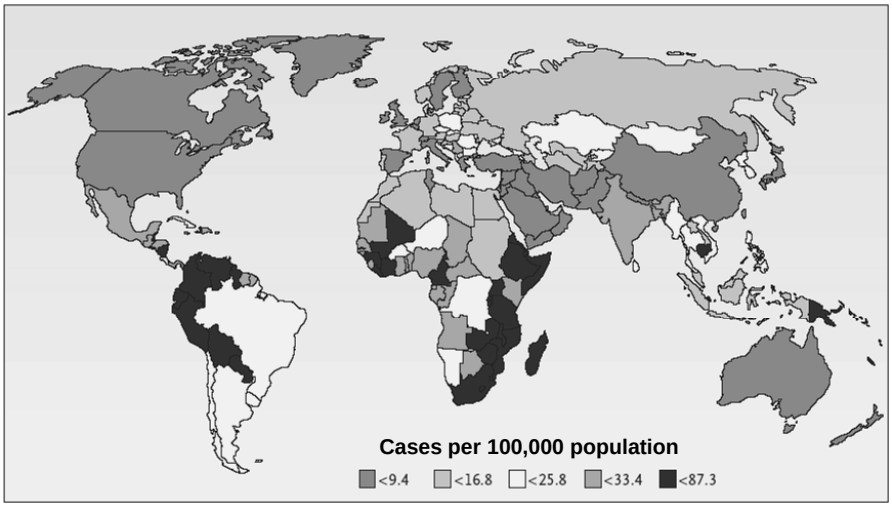
- The vaccines are unlikely to help women with established infections/lesions.
- The current vaccines will not prevent 25-35% of cervical cancers.
- ***Need to convince vaccinated women to follow cervical cancer screening guidelines.***

Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to L1 VLP Vaccine



Adapated from Munoz et al, Int J Cancer 111: 278-85, 2004

80% or cervical cancer occurs in developing nations. How long will it take to implement vaccination there?



From Globocan 2002 Database, www.dep.iarc.fr/globocan/database.htm

Summary and Conclusions

- **Development of commercial HPV vaccines has resulted from pharmaceutical company development of research discoveries made in the public sector.**
- **The current commercial HPV L1 VLP vaccines have the potential to reduce the incidence of benign and malignant genital HPV infections. However, their type-restricted protection means that some serious HPV infections will still occur in vaccinated women.**
- **There is a need for second generation vaccines. One approach will be to increase the valency of the HPV L1 VLP vaccines. Other approaches will need to be compared to this benchmark**
- **It is unclear when the HPV L1 VLP vaccine will be widely implemented in the developing world, where most cases of cervical cancer occur.**