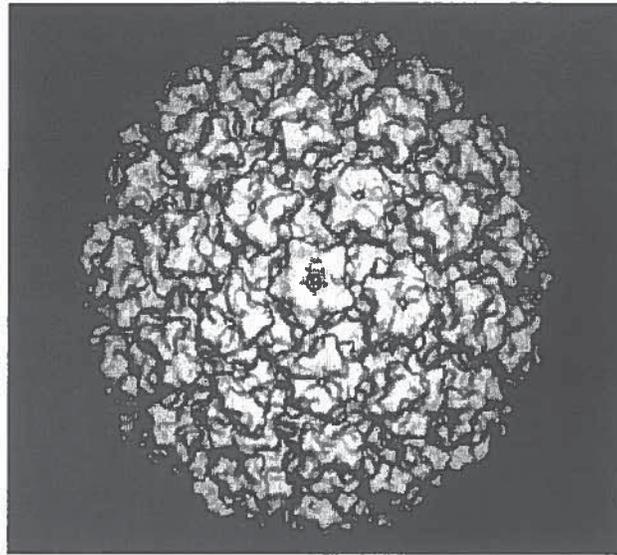


***Papillomavirus Virus-like Particle Vaccines: To
Protect Against HPV Infection and Disease***



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HPV Infection: Implications

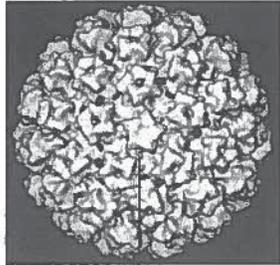
- **Interference with HPV infection should confer protection against the cancers attributable to the infection.**
- **In other infectious diseases, vaccination represents the most cost-effective public health measure to interfere with infection.**
- **Must be safe: sub-unit vaccine preferred because HPV has oncogenes (E6,E7).**

Preventive or Therapeutic

- **A vaccine that could effectively treat established HPV infection in addition to preventing infection would be even better than a purely preventive vaccine.**
- **However, all approved vaccines against other infectious diseases are preventive (neutralizing antibodies), not therapeutic (cellular immunity).**

Papillomaviruses Encode Two Structural Proteins

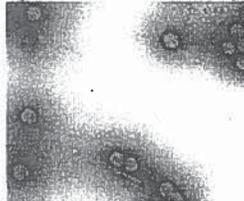
Papillomavirus Particle



- **L1: the major (most abundant) structural protein. Each viral particle has 360 copies.**
- **L2: the minor structural protein. Each particle has 12 copies.**

Major Structural Viral Protein L1 Can Self-Assemble to Form Virus-like Particles (VLPs)

**Infectious Viral Particles
(contain viral DNA)**

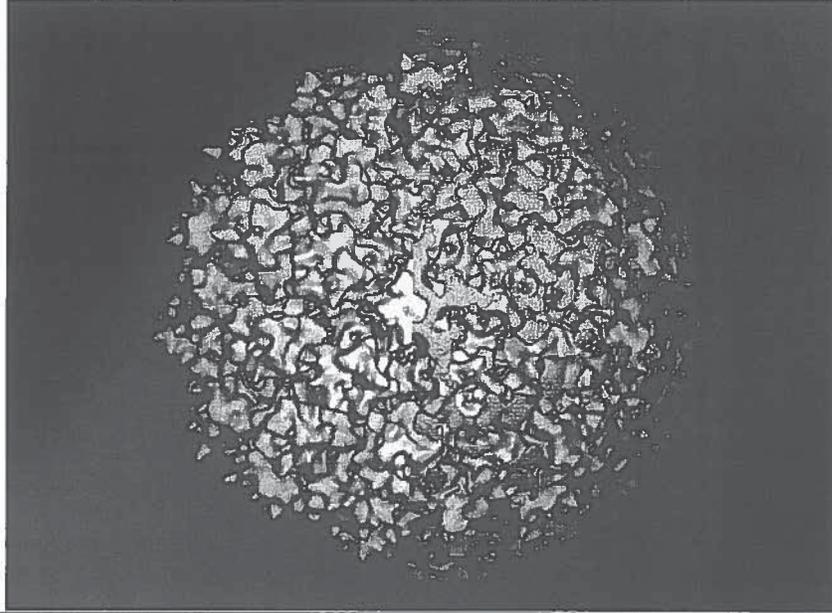


**VLPs made in Insect Cells
(no viral DNA)**

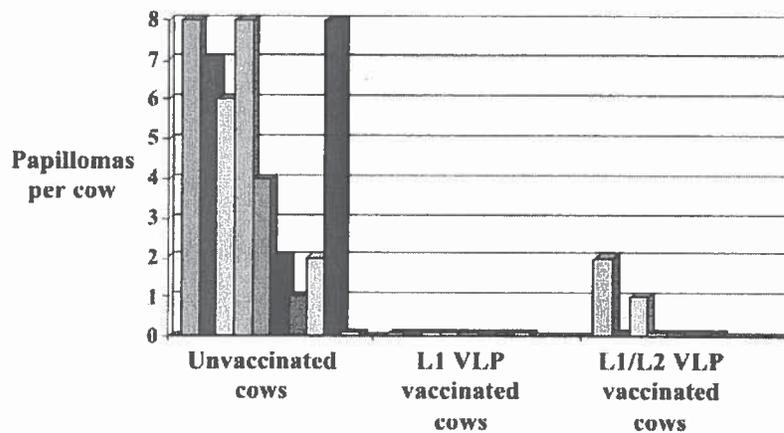


- **L1 VLPs are highly immunogenic because they contain the main neutralization epitopes of the virus.**

Neutralizing L1 Antibodies Bound to Papillomavirus Particle



Oral Papillomas in Cows (BPV-4): Prevention by Systemic Immunization with VLPs



***Systemic Vaccination with L1 VLPs is Protective in 3
Animal Papillomavirus Models:
Cutaneous (rabbits) and oral mucosal (cows & dogs)***

- **Protection:**
 - L1 VLPs are highly effective
 - efficient with or without adjuvant
 - intact (non-denatured) VLPs are required
 - passively transferred with immune IgG (neutralizing antibodies)
 - prophylactic, not therapeutic
 - type-specific (no cross protection)

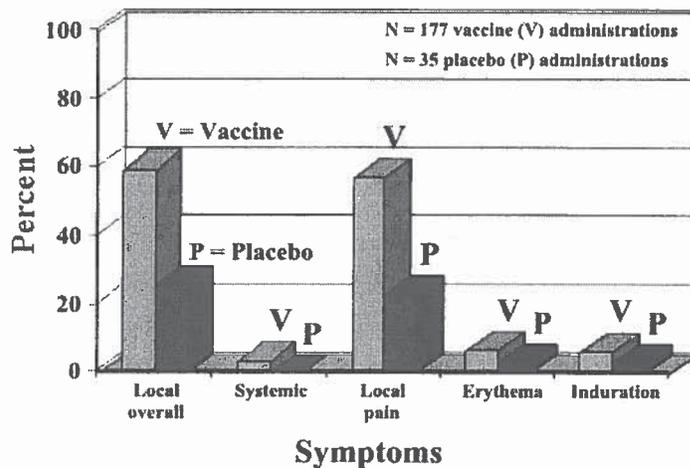
***Key Scientific Questions for
Human Vaccine Trials***

- **Safety?**
- **Immunogenicity?**
- **Efficacy?**
- **Type-specific?**
- **Duration of protection?**
- **Correlates of protection?**
- **Are modified vaccines needed or useful (e.g., polyvalent, therapeutic)?**

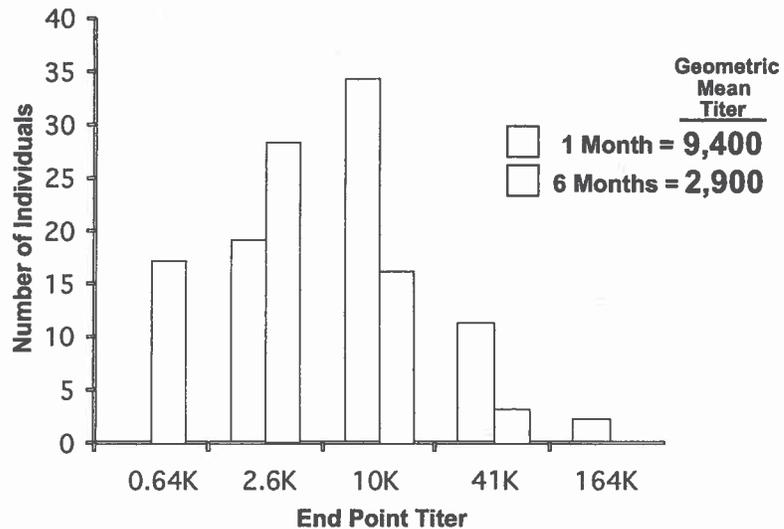
HPV16 L1 VLP Safety and Immunogenicity Trials

- **50 μ g VLP intramuscular without adjuvant x 3 doses in normal volunteers (double blind placebo controlled).**
- **Side effects: minor (similar to saline controls, but about twice as frequent).**
- **Immunogenicity: excellent response even without adjuvant.**

Mean Symptom Incidence for All Vaccine Groups and Placebo Group



Distribution of HPV16 VLP ELISA Titers After 3 VLP Immunizations



Conclusions from Early Phase Clinical HPV Vaccine Trials

- **Systemic vaccination of HPV 16 L1 VLPs without adjuvant induces consistent and durable antibody responses (>40-fold higher than after natural HPV infection).**
- **The antibody titers achieved in people are similar to those that protect animals against experimental viral challenge.**

HPV16 L1 VLP Proof of Principle Efficacy Trial (1)

- **Placebo controlled trial of 2392 16-23 year old women given 3 intramuscular doses of HPV16 L1 VLP vaccine with alum adjuvant.**
- **Analyzed 1533 women who had been fully vaccinated and who were HPV negative throughout vaccination period.**
- **Mean duration of follow-up: 17.4 months.**

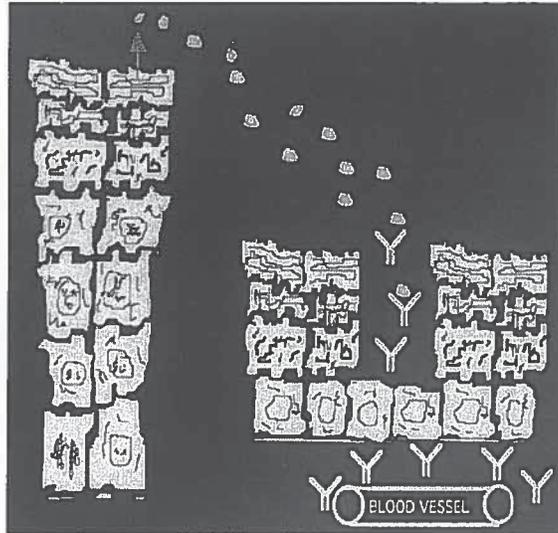
From Koutsky et al., New Eng J Med 347:1645, 2002

HPV16 L1 VLP Proof of Principle Efficacy Trial (2)

- **Transient HPV16 infection: 27 cases in placebos, 6 in vaccinees**
- **Persistent HPV16 infection: 41 cases in placebos, none in vaccinees.**
- **HPV16 associated cytologic abnormalities: 9 in placebo (mild or moderate), none in vaccinees.**

From Koutsky et al., New Eng J Med 347:1645, 2002

How Antibodies May Protect Against HPV Infection

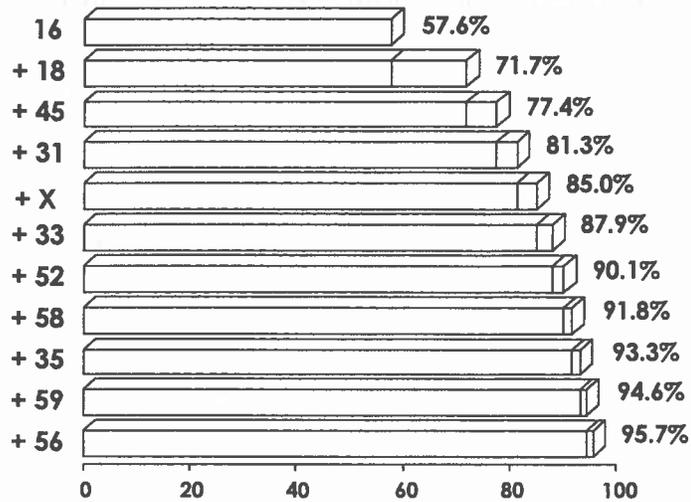


Papilloma
(patient or partner)

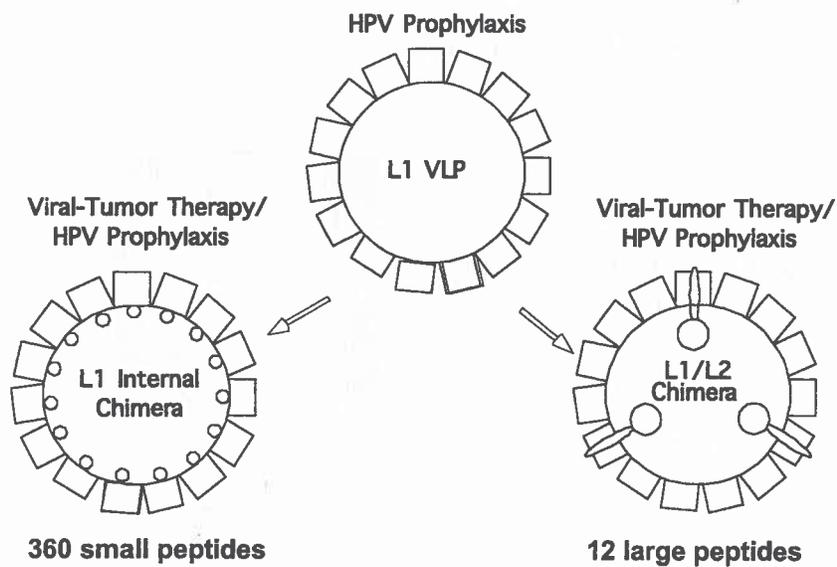
Key Scientific Questions for Human Vaccine Trials

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



Structures of Chimeric VLPs



**Potential Reduction in Cervical Cancer Deaths:
Reduced PAP Coverage after Vaccine Introduction***

<u>% of Current PAP coverage</u>	<u>% Potential Reduction in Cancer Deaths</u>
100	93
90	90
70	84
50	78
30	73
10	67
0	64

*Assumptions: PAP is 80% effective. All women are vaccinated.
Vaccine is 90% effective against 71% of CA HPVs = 64% effective

***Pap screening and 2nd Generation
Vaccines in Industrialized Countries***

- **Education about continuing need for cervical cancer screening**
- **Development of 2nd generation vaccines: to increase coverage against additional high-risk HPV types.**