National Cancer Institute

Current and Future Preventive HPV Vaccines

Douglas R. Lowy
Center for Cancer Research
NCI/NIH

Annual ISBTc Meeting
October 30, 2009

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

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

Disclosure

The National Institutes of Health (NIH) has patents on papillomavirus L1 VLP and L2 vaccine technologies. I am an inventor of these technologies. The NIH has licensed the L1 VLP technology to Merck and GlaxoSmithKline, the two companies with commercial versions of the vaccine. The L2 technology is the subject of a CRADA with Shantha Biotech in India and Johns Hopkins University (Richard Roden).

Outline of presentation

- **HPV, cancer, and the current preventive HPV vaccine**
- **Potential second generation vaccines**
- **HPV has a unique life cycle**
  - **Implications for preventive vaccines**

Laboratory of Cellular Oncology, CCR, NCI, Bethesda

Patricia Day
Rhonda Kines
Cynthia Thompson
Rebecca Cerio

Jeffrey Roberts
Nicolas Cuburu
Susana Pang
Katie Johnson

John Schiller

Chris Buck, Diana Pastrana - ***LCO, CCR, NCI Bethesda***

Peter Choyke, Marcelino Bernardo - ***Molecular Imaging, CCR, NCI, Bethesda***

Mark Schiffman, Allan Hildesheim, Phil Castle, Ligia Pinto - ***DCEG, NCI, Bethesda***

Benes Trus - ***Center for Information Technology, NIH, Bethesda***

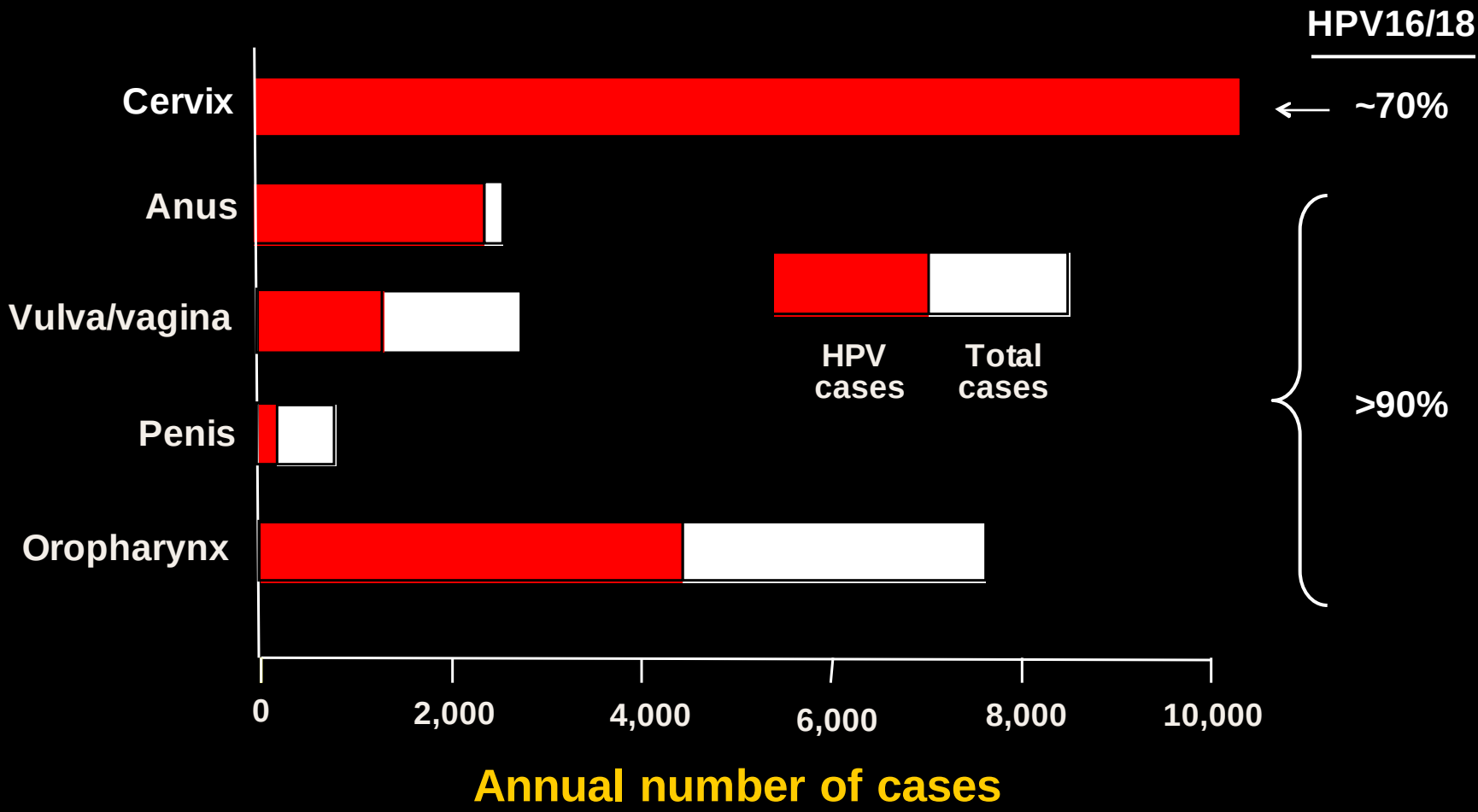
Richard Roden, Subhashini Jagu, Clayton Harro - ***Johns Hopkins, Baltimore***

Reinhard Kirnbauer - ***University of Vienna, Austria***

Implications of Identifying HPV as the Main Cause of Cervical Cancer

- **1983/4: Identification of HPV16/18; zur Hausen and colleagues - Nobel Prize, 2008**
- **Natural history of HPV infection/pathogenesis of cervical cancer**
- **Identification of other HPV-associated cancers**
- **HPV-based cervical cancer screening**
  - **HPV DNA (Hybrid Capture [Digene/Qiagen]; Cervista [Hologic]); ASC-US; adjunctive with cervical cytology in women >30 y.o.**
  - **p16-Ink4a? (E7 inactivates pRb, which increases p16 expression)**
- **HPV-based interventions**
  - ***Preventive vaccine (FDA approved)***
  - **HPV-specific treatment (Karl Munger [approved])**

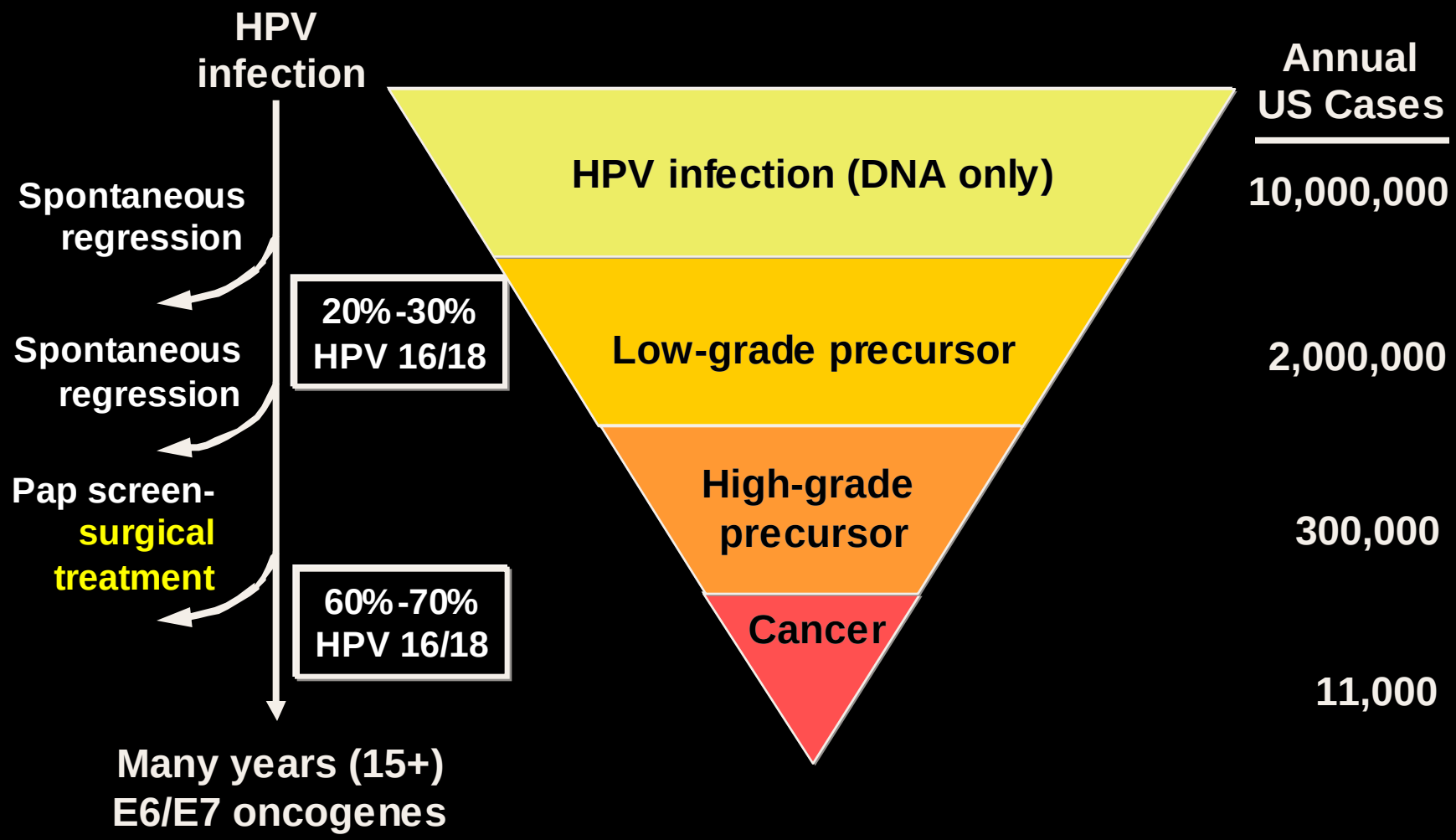
United States: Incidence and Distribution of Cancers Attributable to HPV



- *Pap screening has reduced the incidence of cervical cancer by ~80%*
- *Oropharyngeal cancer data from Fakhry et al, J Natl Cancer Inst 100:26,2008*

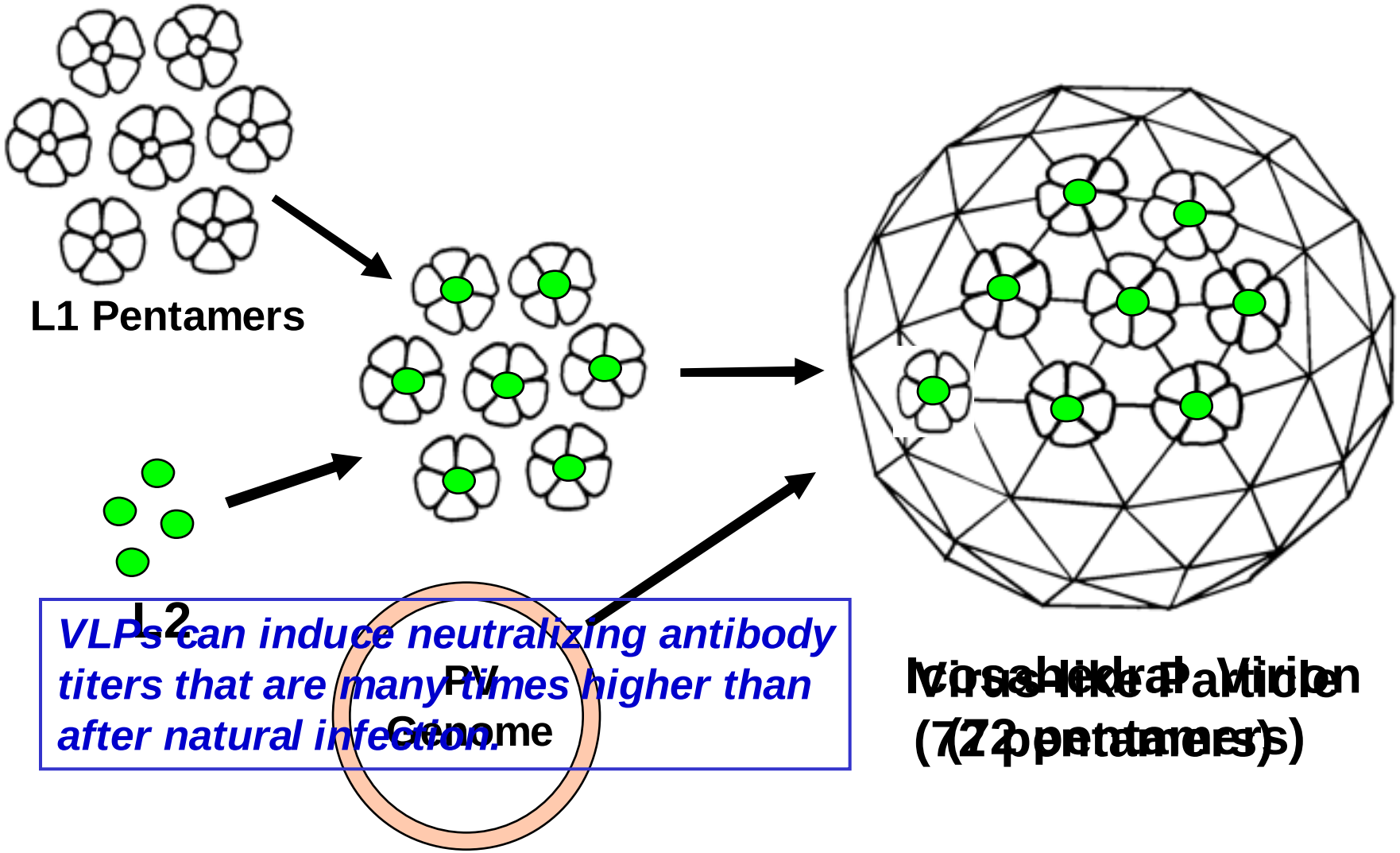
Gillison, Chaturvedi, and Lowy. Cancer 113: S3036-46, 2008

Natural History of Cervical HPV Infection



Persistent infection with a high-risk HPV, especially HPV16/18, is the single most important risk factor for progression to high grade dysplasia.

Formation of Virus-like Particles (VLPs)



VLPs can induce neutralizing antibody titers that are many times higher than after natural infection.

Kirnbauer et al, PNAS 1992

L1 has 2 neutralization epitopes; L1>L2

Two Distinct Commercial HPV L1 VLP Vaccines

GlaxoSmithKline: **Cervarix**

HPV16
HPV18
} **70% of Cervical Cancer**

ASO4 Adjuvant (Aluminum + MPL)

Made in insect cells

Merck: **Gardasil**

HPV16
HPV18
} **70% of Cervical Cancer**

HPV6
HPV11
} **90% of Genital Warts**

Aluminum Adjuvant

Made in yeast

Three intramuscular injections given over 6 months

HPV vaccine efficacy trial outcomes

Efficacy measured as prevention of incident (new) infection and disease caused by the HPV types in each vaccine (fully vaccinated women, 16-26 years old)

Study	Vaccine	Number of subjects		End-points	Vaccine efficacy
		Vaccine	Control		% (confidence limits)
Garland '07	6/11/16/18	2241 2261	2258 2279	CIN2/3 AIS GW VIN VAIN	100 (94-100) 100 (94-100)
Kjaer '09	6/11/16/18	7864 7900	7865 7902	CIN2/3 AIS VIN2/3 VAIN2/3	98 (93-100) 100 (83-100)
Paavonen '09	16/18	7344	7312	CIN2/3	98 (88-100)

HPV6/11/16/18 = Merck vaccine (Gardasil); HPV16/18 = GlaxoSmithKline vaccine (Cervarix)

CIN = Cervical Intraepithelial Neoplasia; 2 = Intermediate, 3 = Severe; AIS = AdenoCa In Situ
VIN = Vulvar Intraepithelial Neoplasia; VAIN = VAginal Intraepithelial Neoplasia
GW = Genital Warts

Vaccine efficacy against non-vaccine HPV types was more limited

Garland et al, New Eng J Med 356:1928-43, 2007 (3 year data);
Kjaer et al, Cancer Prev Res 2:868-78, 2009 (4 year data);
Paavonen et al, Lancet 374:301-14, 2009 (4 year data)

Vaccine Efficacy In Other Groups

- **Women aged 25-45 (GSK & Merck):**
  - **~90% reduction in HPV6/11/16/18 CIN or Genital Warts (Merck vaccine)**
- **Males aged 16-26 (Merck):**
  - **~85% reduction in 6 mo. persistent infection caused by HPV6/11/16/18**
- **Males aged 16-23 (Merck):**
  - **~90% reduction in incident external warts caused by HPV6/11/16/18**

HPV Vaccine Characteristics

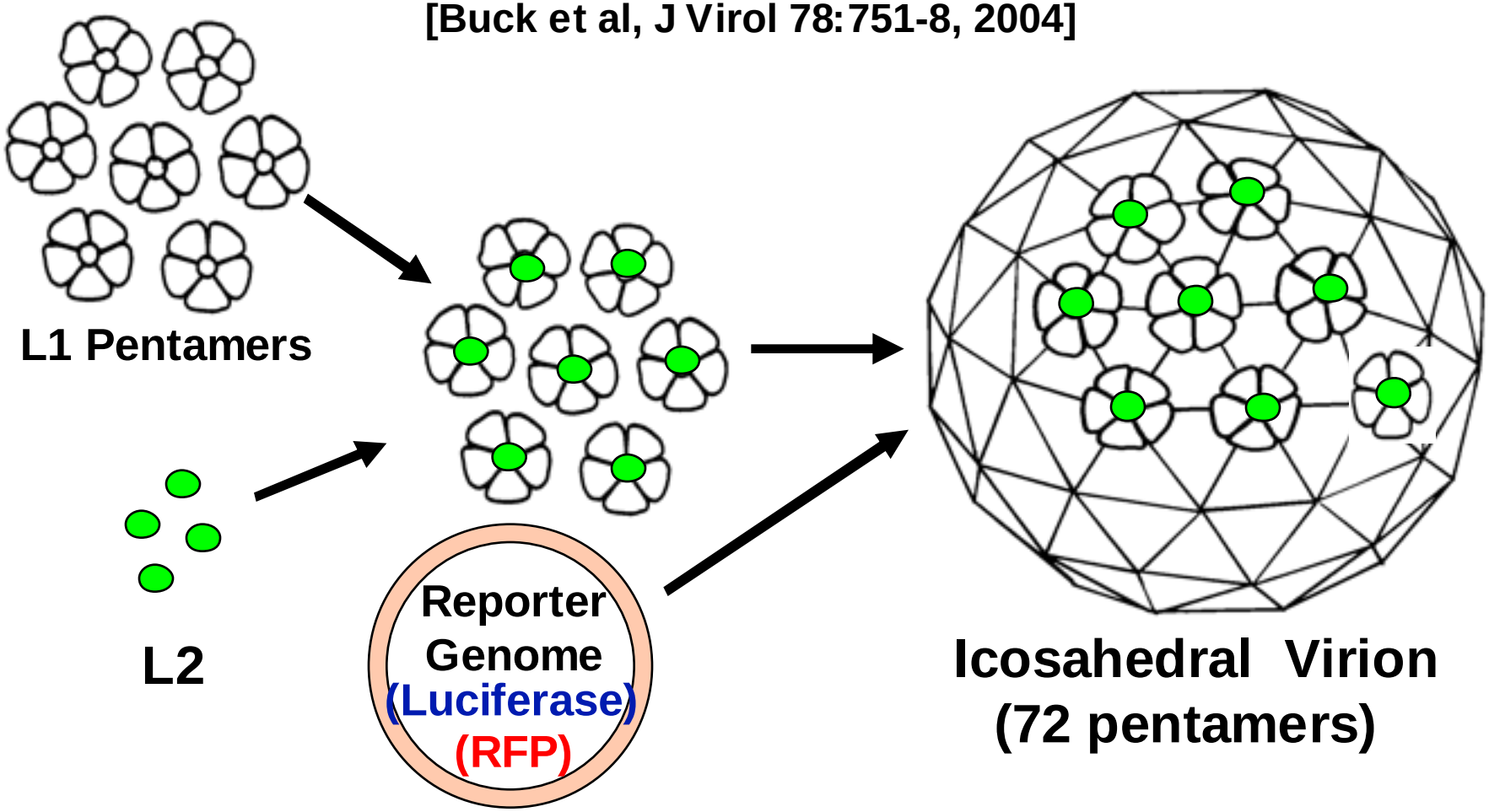
- **Strengths:**
  - **Systemic immunization with a non-infectious HPV vaccine induces high efficacy against mucosal and cutaneous infection caused by HPV types in vaccine**
  - **Can protect against ~70% of cervical cancers and (for Merck vaccine) ~90% of genital warts**
- **Limitations:**
  - **Only protects against new infections, not against established infections**
  - **Protection is type-restricted; current vaccine will not protect against ~30% of serious infections**
  - **Vaccinated women need to continue regular cervical cancer screening**
  - **Expensive (but available in US for eligible populations)**
- **The preclinical models accurately predicted the vaccine would have these clinical characteristics**

How Might the HPV Vaccine Induce Sterilizing Immunity?

- **Hypothesis: a key predisposing event in HPV infection is disruption of epithelial integrity secondary to microtrauma/wounding**
  - ***In vaccinees, microtrauma/wounding would lead to exudation of systemic antibodies at the potential sites of infection***
  - **Rationale: High degree of effectiveness against both cervical infection (mucosa; secretions have antibodies) and genital warts (skin; not bathed in secretions)**
- **Test hypothesis in mouse cervico-vaginal HPV challenge model (Roberts et al, Nature Med 13:857-61, 2007)**

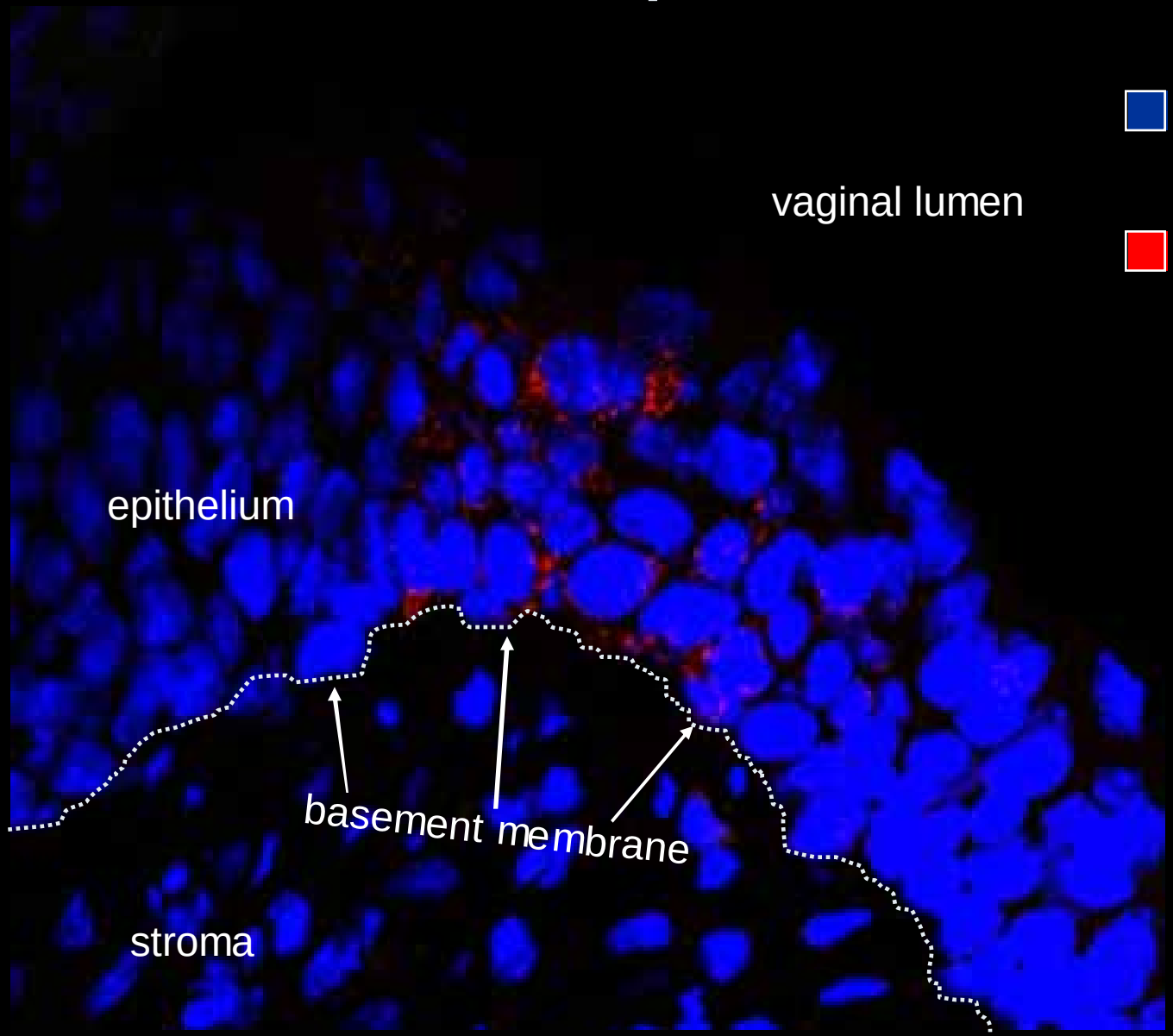
Formation of high titer (>10^9/ml) infectious papillomavirus pseudoviruses

[Buck et al, J Virol 78:751-8, 2004]



- ***Pseudovirus infection mimics the initial steps in HPV infection***
- ***Codon optimization of L1 & L2 is critical to high titer virus (>10^9/ml)***

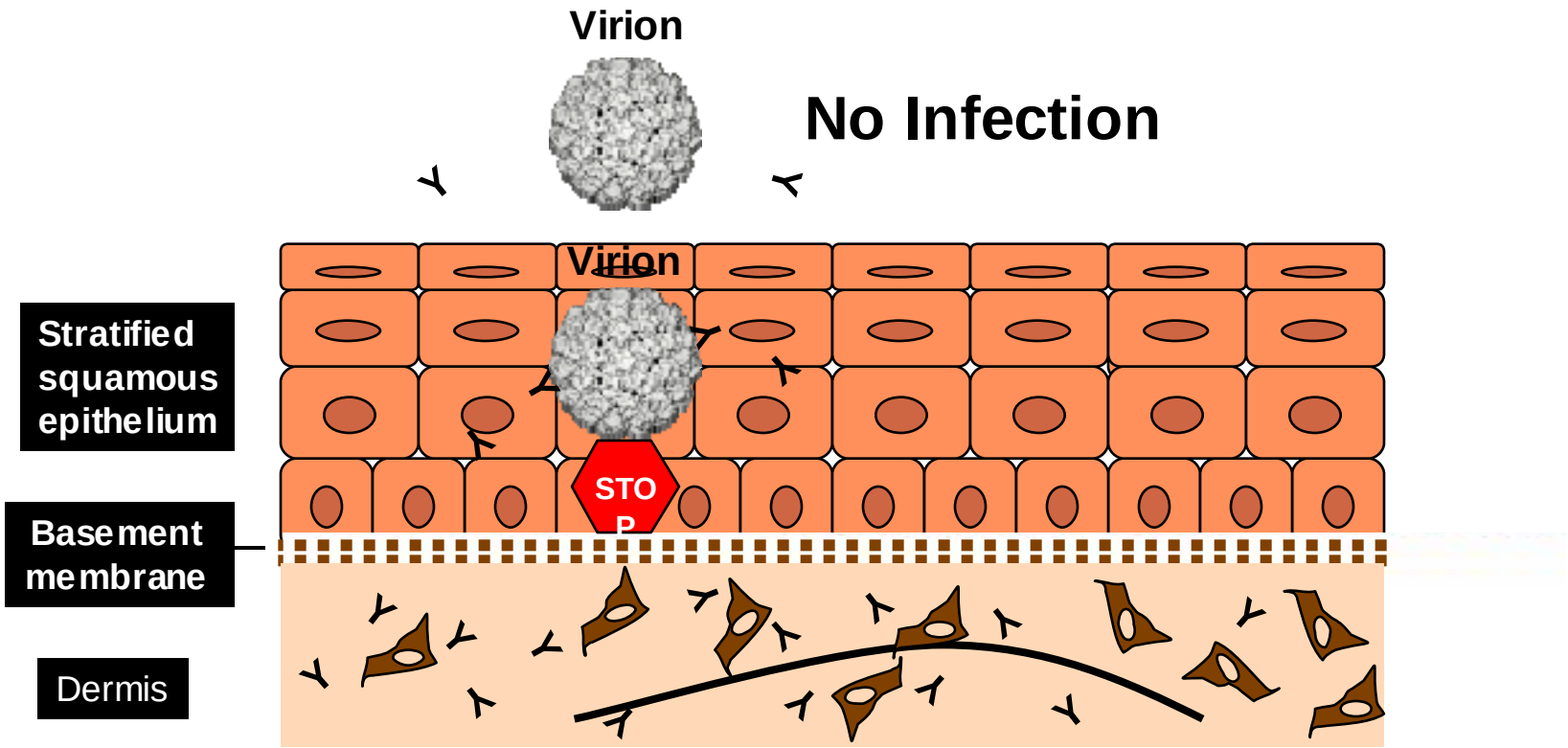
HPV16 PsV infects wounded murine genital epithelium



Blue = DAPI staining of nuclei

Red = RFP expression indicating infection

VLP Vaccination Induces Antibodies that Prevent Basement Membrane Binding



Regulatory status of HPV VLP vaccines

- **Merck's Gardasil approved by FDA in 2006 for females 9-26, for males 9-26 in 2009; EU (females 9-26 + males 9-15); many other countries**
- **GSK's Cervarix approved 2007 in EU (females 10-25), many other countries; approved 2009 by FDA for females**
- ***Main target group in US for either vaccine: 11-12 y.o. girls; prior to becoming sexually active***
- **Catch-up vaccination for 13-26 y.o. girls/women**
- **Included for girls in Federal Vaccines For Children (VFC) program (provides vaccine for girls <19 y.o. from poor families)**

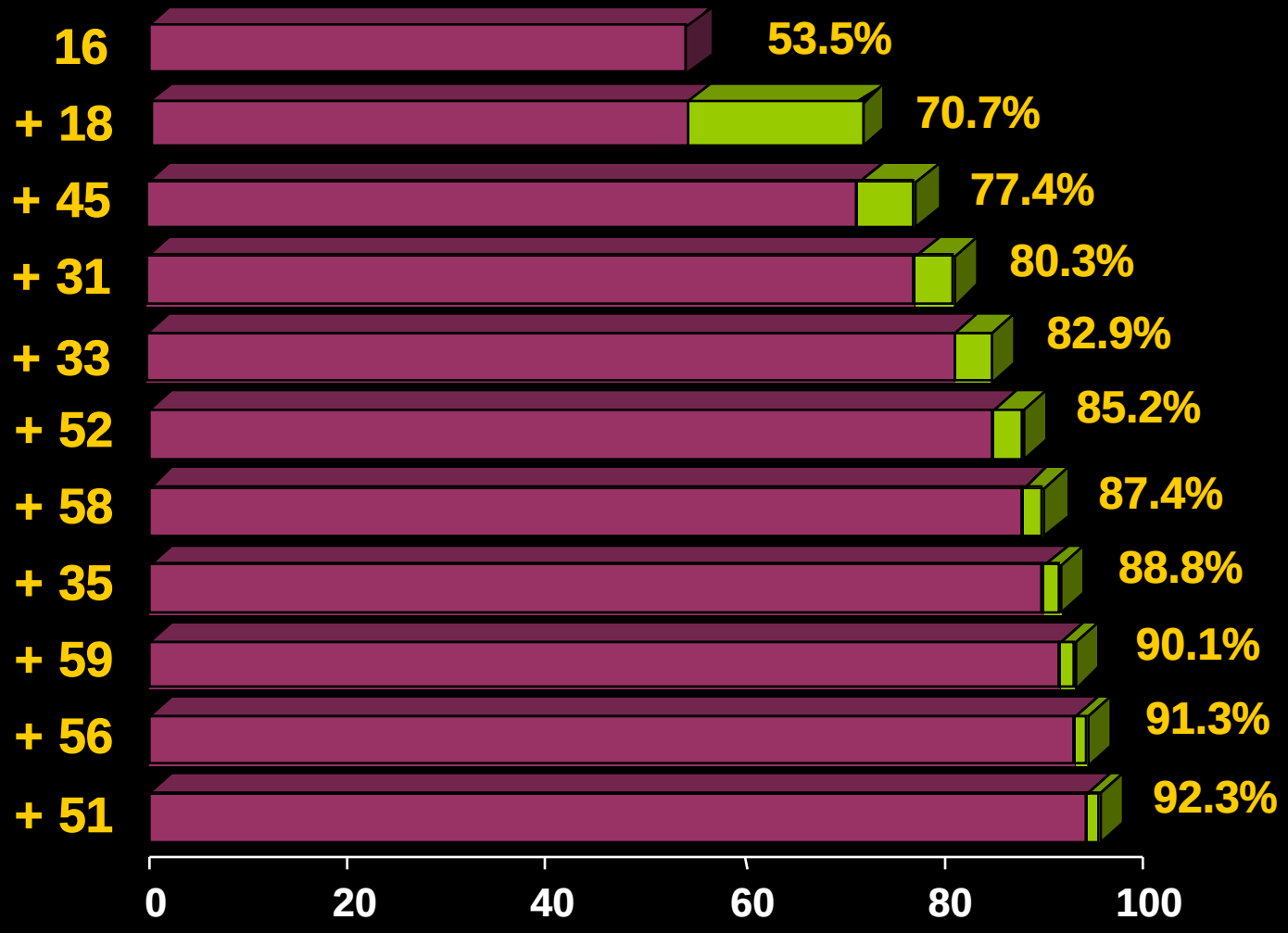
HPV VLP vaccine recommendations: males

- **FDA: indicated for protection against genital warts (HPV6/11)**
- **Federal recommendations for males (CDC ACIP [Advisory Committee on Immunization Practices]):**
  - **permissive (not routine); rationale: vaccination of females more important (cost-effective) for public health than vaccination of males**
  - **However, ACIP has recommended VFC funding for boys; rationale: to make vaccine available to boys from poor families**
  - **Implications unclear for private insurance reimbursement for male vaccination; Merck has stated it will provide partial reimbursement for male vaccination if not reimbursed by insurance (out of pocket expenses no more than $30/dose for costs up to $150/dose)**
- **In 2010, FDA & ACIP may consider prevention in males against anal dysplasia, if (not yet unblinded) ongoing trials show protection**

Possible Goals of Second Generation HPV Vaccines

- To add a therapeutic component to a prophylactic vaccine
- To simplify vaccine production and/or administration
- **To broaden coverage against more HPV types**

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



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

L2 Polypeptides as Candidate Preventive Vaccines

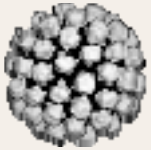
- ***Immunodominant epitopes***, such as those on HPV L1 VLPs, tend to be type-specfic.
  - This feature has evolutionary utility for viruses, so protection against one type does not confer protection against all types.
- Many viruses, including HPV, also contain ***"cryptic" epitopes*** that can induce broad neutralizing activity against a spectrum of types.
  - Crytpic epitopes are only transiently exposed, do not contribute to protection in natural infection, and are therefore not selected against.
  - However, no successful vaccine has ever been developed that targets crytpic cross-neutralization epitopes.

L2 Polypeptides as Candidate Preventive Vaccines

- The L2 minor capsid protein contains cryptic cross-neutralization epitopes.
  - When separated from L1, L2 can induce low levels of broadly cross-neutralizing antibodies (L1/L2 VLPs only induce the type-specific immunodominant L1 antibodies).
- The unusual features of the HPV life cycle ***may*** make it possible to develop an effective L2-based vaccine.
- L2 polypeptides can be produced in bacteria, which should be relatively inexpensive.
- Effective in animal models, but not yet tested in humans: Working with Richard Roden at Johns Hopkins University and Shantha Biotechnics in India towards an early phase trial.

A multi-type L2 fusion peptide induces High titer neutralizing antibodies in rabbits

Immunogen
30 µg x 3



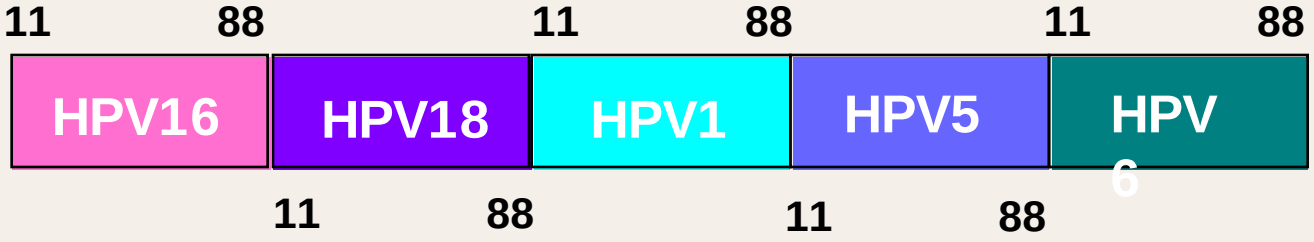
HPV6/11/16/18 (Merck vaccine)

Neutralization Titers

HPV16	HPV31	HPV58	HPV18	HPV45
51,200	25	0	51,200	400

Immunogen
300 µg x 4*

L2 11-88(x5)



Neutralization Titers

HPV16	HPV31	HPV58	HPV18	HPV45
819,200	51,200	409,600	204,800	102,400

***Rabbits vaccinated 4x in Complete and Incomplete Freund's Adjuvant**

Jagu et al, J Nat Cancer Inst 101: 782-92, 2009

Summary and Conclusions

- **Identification of HPV as the infectious cause of cervical cancer has led to:**
  - **an effective preventive vaccine**
  - **improved cervical cancer screening tests**
  - **identifying HPV as a cause for several other cancers**
  - **insight into pathogenesis of HPV-associated cancers**
- **Epithelial microtrauma and basement membrane binding of the virus prior to cell binding appear to be key initial steps in HPV infection.**
  - **Humoral immunity induced by the current L1 VLP vaccine prevents basement membrane binding and/or transfer to epithelial cells**
  - **Exudation of systemic neutralizing antibodies at potential sites of infection probably accounts for the high efficacy of the vaccine**
- **Second generation HPV vaccines with activity against a broader range of HPV types will be required to achieve the greatest reduction in HPV-associated cancers.**