Current and Future Preventive HPV Vaccines

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NCI/NIH

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

Natural History of Cervical HPV Infection

HPV infection

Spontaneous regression

Spontaneous regression

Pap screen-surgical treatment

Many years (15+)
E6/E7 oncogenes

HPV infection (DNA only)

20%-30% HPV 16/18

Low-grade precursor

60%-70% HPV 16/18

High-grade precursor

Cancer

Annual US Cases

10,000,000

2,000,000

300,000

11,000

Persistent infection with a high-risk HPV, especially HPV16/18, is the single most important risk factor for progression to high grade dysplasia.
VLPs can induce neutralizing antibody titers that are many times higher than after natural infection.

Kirnbauer et al., PNAS 1992
Two Distinct Commercial HPV L1 VLP Vaccines

GlaxoSmithKline: HPV16 Cervarix
         HPV18
         ASO4 Adjuvant (Aluminum + MPL)
         Made in insect cells

Merck: Gardasil
         HPV16
         HPV18
         HPV6
         HPV11
         Aluminum Adjuvant
         Made in yeast

70% of Cervical Cancer
90% of Genital Warts

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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine</th>
<th>Number of subjects</th>
<th>End-points</th>
<th>Vaccine efficacy</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vaccine</td>
<td>Control</td>
</tr>
<tr>
<td>Garland ‘07</td>
<td>6/11/16/18</td>
<td>2241 2261 2258 2279</td>
<td>CIN2/3 AIS GW VIN VAIN</td>
<td>100 (94-100) 100 (94-100)</td>
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<tr>
<td>Kjaer ‘09</td>
<td>6/11/16/18</td>
<td>7864 7900 7865 7902</td>
<td>CIN2/3 AIS VIN2/3 VAIN2/3</td>
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<tr>
<td>Paavonen ‘09</td>
<td>16/18</td>
<td>7344 7312</td>
<td>CIN2/3</td>
<td>98 (88-100)</td>
</tr>
</tbody>
</table>

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**

Kjaer *et al*, Cancer Prev Res 2:868-78, 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)

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


• 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

- **Vaginal lumen**
- **Epithelium**
- **Basement membrane**
- **Stroma**
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-specific.
  - 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.
  - Cryptic 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 cryptic 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

**Neutralization Titers**

<table>
<thead>
<tr>
<th>Immunogen</th>
<th>HPV6/11/16/18 (Merck vaccine)</th>
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<td>30 µg x 3</td>
<td>HPV6/11/16/18 (Merck vaccine)</td>
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**Neutralization Titers**

<table>
<thead>
<tr>
<th>HPV16</th>
<th>HPV31</th>
<th>HPV58</th>
<th>HPV18</th>
<th>HPV45</th>
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<tbody>
<tr>
<td>51,200</td>
<td>25</td>
<td>0</td>
<td>51,200</td>
<td>400</td>
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</table>

**Immunogen**

- 300 µg x 4*

**Neutralization Titers**

<table>
<thead>
<tr>
<th>Immunogen</th>
<th>L2 11-88(x5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 µg x 4*</td>
<td>L2 11-88(x5)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>HPV16</th>
<th>HPV18</th>
<th>HPV1</th>
<th>HPV5</th>
<th>HPV6</th>
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<tr>
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<td>51,200</td>
<td>409,600</td>
<td>204,800</td>
<td>102,400</td>
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*Rabbits vaccinated 4x in Complete and Incomplete Freund’s Adjuvant

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.