INTRODUCTION
HUMAN PAPILLOMAVIRUS

Professor Anna-Lise Williamson
Institute of Infectious Disease and Molecular Medicine, University of Cape Town
National Health Laboratory Service, Groote Schuur Hospital
A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions

(human papillomaviruses/low-stringency hybridization/molecular cloning/genital tumors)

MATTHIAS DÜRST, LUTZ GISSMANN, HANS IKENBERG, AND HARALD ZUR HAUSEN*

Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, Federal Republic of Germany

Communicated by Gertrude Henle, March 21, 1983

“In 61.1% (11/18) of cervical cancer samples from German patients sequences were found hybridizing with HPV 16 DNA under conditions of high stringency. In contrast, only 34.8% (8/23) of cancer biopsy samples from Kenya and Brazil revealed this DNA. Vulval and penile cancer biopsy samples hybridized to 28.6% (2/7) or 25% (1/4), respectively.”
Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS)

F Barre-Sinoussi, JC Chermann, F Rey, MT Nugeyre, S Chamaret, J Gruest, C Dauguet, C Axler-Blin, F Vezinet-Brun, C Rouzioux, W Rozenbaum, L Montagnier

ABSTRACT

A retrovirus belonging to the family of recently discovered human T-cell leukemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a Caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS). This virus is a typical type-C RNA tumor virus, buds from the cell membrane, prefers magnesium for reverse transcriptase activity, and has an internal antigen (p25) similar to HTLV p24. Antibodies from serum of this patient react with proteins from viruses of the HTLV-I subgroup, but type-specific antisera to HTLV-I do not precipitate proteins of the new isolate. The virus from this patient has been transmitted into cord blood lymphocytes, and the virus produced by these cells is similar to the original isolate. From these studies it is concluded that this virus as well as the previous HTLV isolates belong to a general family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS.
The Nobel Prize in Medicine (2008)
Harald zur Hausen  for Human Papillomavirus
Françoise Barré-Sinoussi Luc A. Montagnier for HIV
National Institutes of Health Consensus Development Conference Statement: cervical cancer

April 1-3, 1996
J Natl Cancer Inst Monograph 21 1996

“Carcinoma of the cervix is causally related to infection with human papillomavirus. Reducing the rate of HPV infection by changes in sexual behaviors in young people and/or through the development of an effective HPV vaccine would reduce the incidence of this disease …….”
• Host specific
• HPV found only in epithelium
• **>100 HPV types**
• Site specific [mucosal vs cutaneous]
• Latent infections common [normal cytology]
• Can cause benign or malignant lesions
• No serological diagnostic tests
  – test for HPV DNA
THREE MAJOR GROUPS

1. CUTANEOUS WARTS

2. EPIDERMODYSPLASIA VERRUCIFORMIS

3. MUCOSAL HPVs
   - divided into high and low risk types depending on their association with disease
“The presence of HPV in virtually all cervical cancers implies the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer.”

Prof. Jan M. Walboomers
Department of Pathology
The Free University of Amsterdam
The majority of sexually active individuals will be infected with HPV at some point and most will clear the infection.

- Persistent infection with oncogenic HPV types increases the risk of developing cancer.

- Estimated:
  - 5% Human Cancer
  - 10% cancer in women
  - 15% of cancer of women in developing countries

www.who.int/hpvcentre
Estimated Cervical Cancer Incidence Worldwide
Only Oncogenic HPV Types are Associated with Cancer

• **Oncogenic or high-risk types** - **15 HPV types classified as oncogenic** – 16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, 68, 73, 82
  - Cervical cancers
  - Anal cancers
  - Vulvar/vaginal cancers
  - Penile cancers
  - Oropharyngeal cancers
  - Low/high grade intraepithelial neoplasia

• **Nononcogenic or low-risk types** (includes HPV 6, 11)
  - Anogenital warts
  - Recurrent respiratory papillomatosis (RRP)
  - Low grade intraepithelial neoplasia

• Both vaccines (Gardasil and Cervarix) provide protection against HPV-16, HPV-18 and related types – the dominant types found in cervical cancer.

• One vaccine (Gardasil) also provides protection against HPV 6 and 11 which cause anogenital warts and recurrent respiratory papillomatosis.
Cervical specimens from 659 women collected and 570 histologically confirmed as ICC-squamous cell carcinoma observed in 476/570 (83.5%) cases- 167 in Ghana, 192 in Nigeria, 300 in South Africa

The HPV-positivity rate in ICC cases was 90.4% (515/570). In ICC cases with single HPV infection (447/515 [86.8%])

- HPV16 (51.2%),
- HPV18 (17.2%),
- HPV35 (8.7%),
- HPV45 (7.4%),
- HPV33 (4.0%)
- HPV52 (2.2%).

8/50 (16%) HIV positive women and 13/140 (9%) HIV negative women had multiple HPV types
AGE-SPECIFIC HPV PREVALENCE IN WOMEN WITH NORMAL CYTOLOGY FROM FIVE WORLD REGIONS.

Bosch FX, et al. Vaccine. 2008;26
HPV PREVALENCE ACCORDING TO AGE AND HIV STATUS

HIV Positive Women

HIV Negative Women

HIV Positive Men

HIV Negative Men

any HPV
HR-HP V
LR-HP V

any HPV
HR-HP V
LR-HP V

any HPV
HR-HP V
LR-HP V

any HPV
HR-HP V
LR-HP V
• HPV infection increases the risk of HIV infection

• HIV seroconversion influences HPV-related diseases at the early stage of HIV infection

• HIV increases risk of disease caused by HPV
Human Papillomavirus Vaccines
Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas


*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

• Virus like particles (VLPs) of canine oral papillomavirus (COPV) protected from COPV challenge

• Disrupted VLPs did not protect indicating conformation important

• Passively transferred serum immunoglobulins protected from COPV challenge
Prophylactic HPV vaccines - L1 proteins which self-assemble into conformationally correct VLPs which induce high levels of neutralizing antibodies

Monomer → Capsomer → Capsid*

Made in yeast (MSD) or baculovirus (GlaxoSmithKline) expression systems
## Human Papillomavirus Vaccines

<table>
<thead>
<tr>
<th></th>
<th><strong>Gardasil Quadrivalent</strong></th>
<th><strong>Cervarix Bivalent</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Merck Sharp and Dohme - MSD</td>
<td>GlaxoSmithKline - GSK</td>
</tr>
<tr>
<td><strong>Virus like particles from HPV types</strong></td>
<td>6, 11, 16, 18</td>
<td>16,18</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>AAHS: aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate)</td>
<td>AS04: 500 μg aluminum hydroxide 50 μg 3-O-desacyl-4’-monophosphoryl lipid A</td>
</tr>
<tr>
<td><strong>Date of US licensure</strong></td>
<td>2006 - female 2009 - males</td>
<td>2009 - females</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>3 doses</td>
<td>3 doses</td>
</tr>
</tbody>
</table>
HPV Vaccine Efficacy

- HPV vaccines are highly effective at protection against HPV type specific infection, cervical and vulval precancers – neither vaccine is therapeutic.

- Gardasil is also highly protective against genital warts in women and men.

- Vaccines induce high titres of neutralizing antibody which persist for extended times.

- Although duration of protection is unknown.
Decline in in-patient treatments of genital warts among young Australians following the national HPV vaccination program

Hammad Ali¹*, Rebecca J Guy¹, Handan Wand¹, Tim RH Read², David G Regan¹, Andrew E Grulich¹, Christopher K Fairley²,³ and Basil Donovan¹,⁴

Figure 1 Numbers of in-patient treatments for vulval/vaginal warts in women by age-group, 2000–2011.

Figure 2 Numbers of in-patient treatments for penile warts in men by age-group, 2000–2011.
Human Mucosal and Cutaneous Species 7 type species is HPV 18 closely related to HPV-45

Human Mucosal and Cutaneous Species 9 type species is HPV 16 closely related to HPV-31 and 33

Family Papillomavirus Based on L1 Phylogenetic Tree
de Villiers et al. 2004
• Cross-protection against HPV 31, 33 and 45 better for Bivalent than Quadrivalent vaccines

• Reduction in cross-protection efficacy with increased follow-up

• Care needed with interpretation because increased coverage of the Bivalent vaccine may not impact if protection wanes significantly
STEPS IN DEVELOPMENT OF CERVICAL CANCER AND PREVENTION STRATEGIES

NORMAL CERVIX

HPV INFECTION

CERVICAL NEOPLASIA

CERVICAL CANCER

VACCINATION FOR HPV-16 / 18

PAP SMEARS - CERVICAL SCREENING BY CYTOLOGY

HPV DNA DETECTION
THANK YOU

Acknowledgement to Malangatana for the art