

## Mechanisms of Viral Oncogenesis

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## Human Cancers Associated with a Viral Etiology

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### Carcinomas

Anogenital	HPV
Hepatocellular	HBV, HCV
Nasopharynx	EBV
Oropharynx	HPV
Stomach	EBV
Merkel Cell	MCPyV

### Lymphomas

Post-transplant	EBV
Burkitt	EBV
Hodgkin	EBV
Adult T-cell	HTLV-1

### Sarcoma

Kaposi	HHV8
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The global health burden of infection-associated  
cancers in the year 2002

**Int. J. Cancer:** 118, 3030–3044 (2006)  
2006 Wiley-Liss, Inc.

### Total Infection-Attributable Cancers Worldwide

Agent	Cancer	# cases	% all Ca.	
H. Pylori	Stomach	592,000		5.5
	Lymphoma	11,500		
HPV	Cervix	492,800		5.2
	Anogenital	53,880		
	Oropharynx	14,500		
HBV, HCV	Liver	535,000		4.9
EBV	Nasopharynx	78,100	1.0	
	Hodgkin L.	28,600		
	Burkitt L.	6,700		
HIV/HHV8	Kaposi sarcoma	66,200		0.9
	Non-Hod. L.	36,100		
Schistosomes	Bladder	10,600	0.1	
HTLV-1	ATL	3,300		0.03
Liver flukes	Bile duct	2,500		0.02
<b>Total</b>		<b>1,932,800</b>		<b>17.8</b>

### I-A Ca in Developing and Developed Countries

Site	Agent	Developed Countries		Developing Countries	
		# cases	% all Ca	# cases	% all Ca.
Liver	HBV,HCV	48,000	1.0	475,000	8.2
	Flukes	0		2,500	
Cervix	HPV	83,400	1.7	409,400	7.0
Stomach	H. pylori	192,000	3.8	400,000	6.9
Kaposi	HHV8	3,700	0.1	62,500	1.1
NHL	HIV/EBV	9,300	0.2	26,800	0.7
	EBV (BL)	100		6,600	
	H.pylori	5,600		5,900	
	HTLV-1	550		2,790	
Anogenital	HPV	22,450	0.4	31,430	0.5
Nasopharynx	EBV	6,500	0.1	71,600	1.2
Oropharynx	HPV	5,600	0.1	8,800	0.2
Hodgkin L.	EBV	11,500	0.2	17,100	0.3
Bladder	Schistos	0	0.0	10,600	0.2
<b>Total</b>		<b>389,000</b>	<b>7.7</b>	<b>1,527,000</b>	<b>26.3</b>

### Why Study Infection Associated Cancers?

- Prevention - vaccines, eliminate agent
- Diagnosis - identify precursors expressing agent
- Treatment - anti-virals, antibiotics
- Provides insights into mechanism
- Important problem- large world wide burden of cancer

## Principles of Viral Oncology

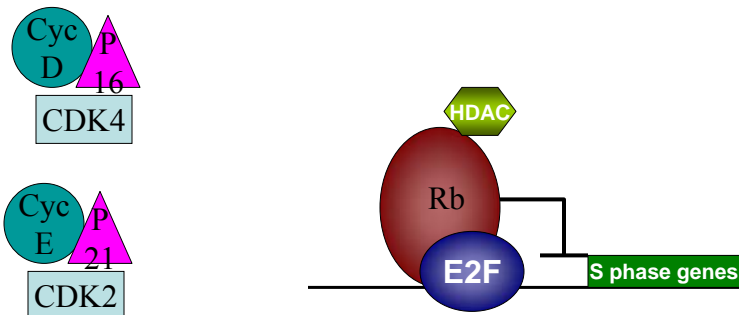
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- Viruses have evolved to replicate and be transmitted to new hosts, and to establish latency/persistence, NOT TO CAUSE CANCER.
- Most viral infections are mildly pathogenic and are controlled by the host immune response.
- Viruses contribute to the etiology of human cancers in diverse ways; by direct and indirect means.

## Principles of Oncology

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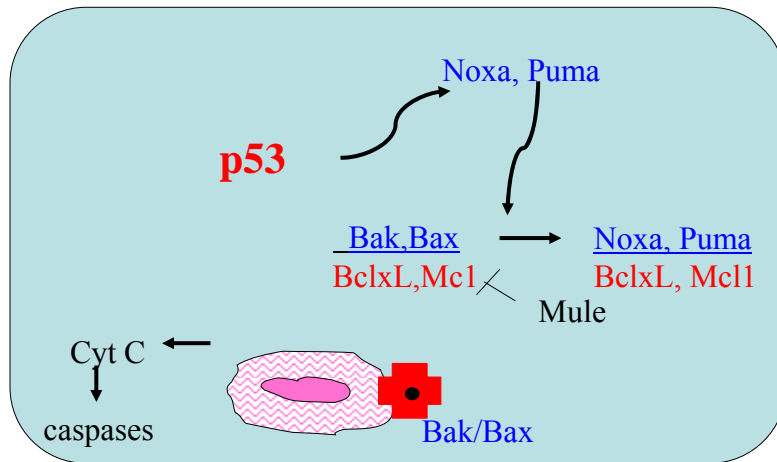
- The induction of proliferation involves exit from G<sub>0</sub> or G<sub>1</sub> into S phase.



## Principles of Oncology

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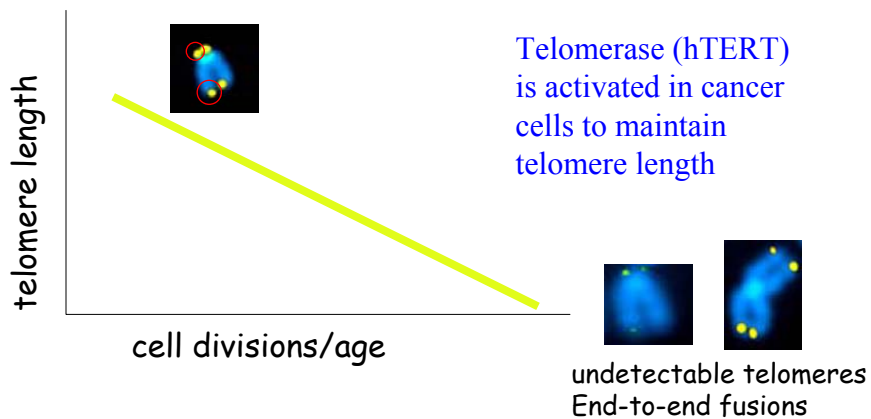
- Uncontrolled proliferation induces apoptosis



## Principles of Oncology

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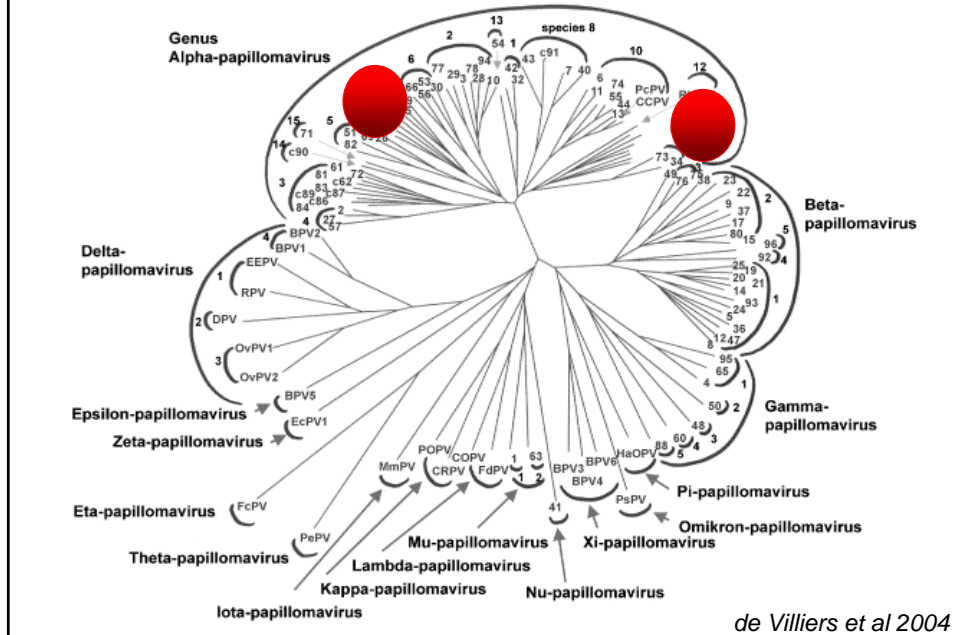
- Uncontrolled proliferation induces senescence through telomere shortening (or S phase DNA damage).



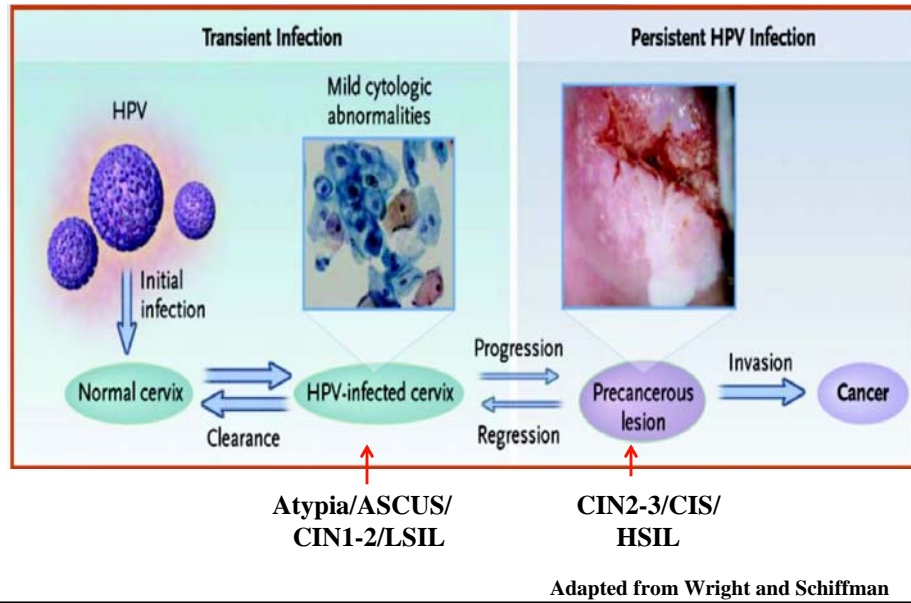
How do HPVs cause cancer ?

Why do only some HPVs cause cancer ?

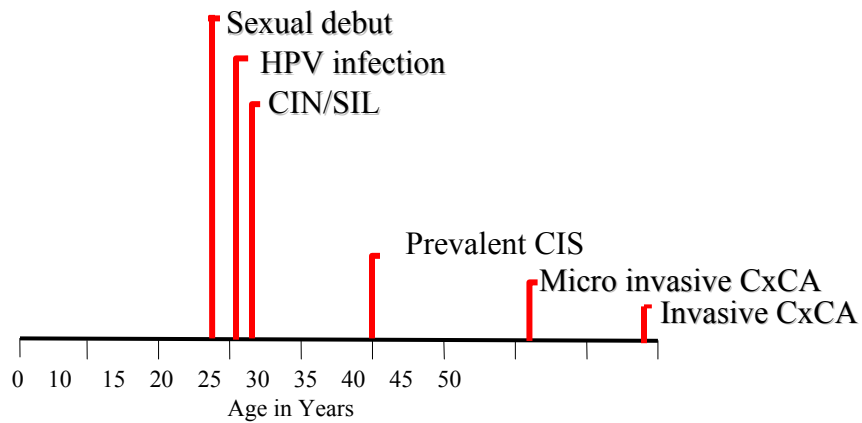
## Papillomaviruses are a Large Family



## Natural History of Cervical HPV Infections



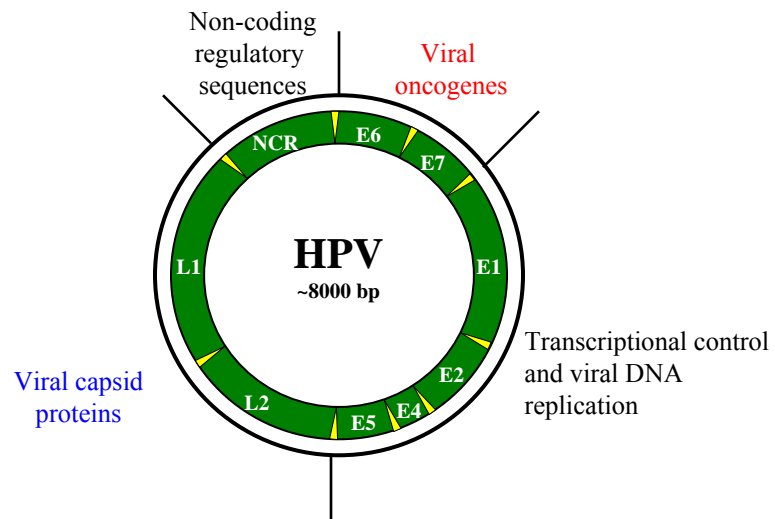
## Natural History of Cervical Neoplasia: Median Age of Events



Koutsky, Kiviat, Winer and others

## Human papillomavirus (HPV)

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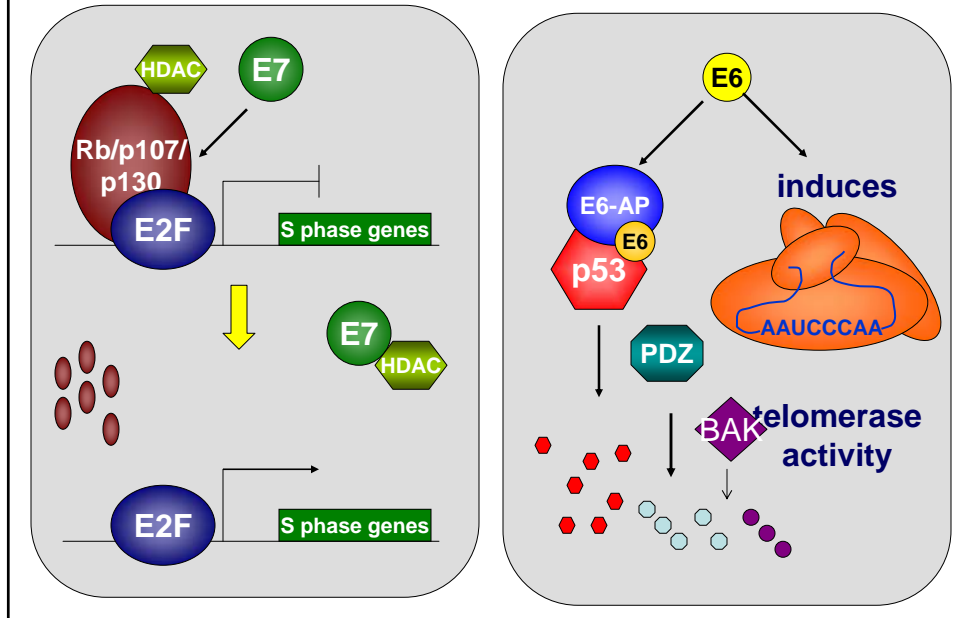
## The HPV Life Cycle

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QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

Doorbar, J.Clin.Vir. 2005

## Targets of the HR □ E6 and E7 oncoproteins

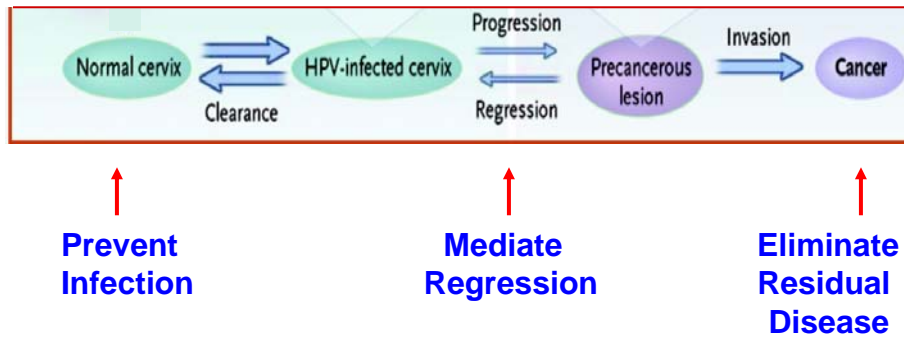


## HPV Expression in Cervical Cancers

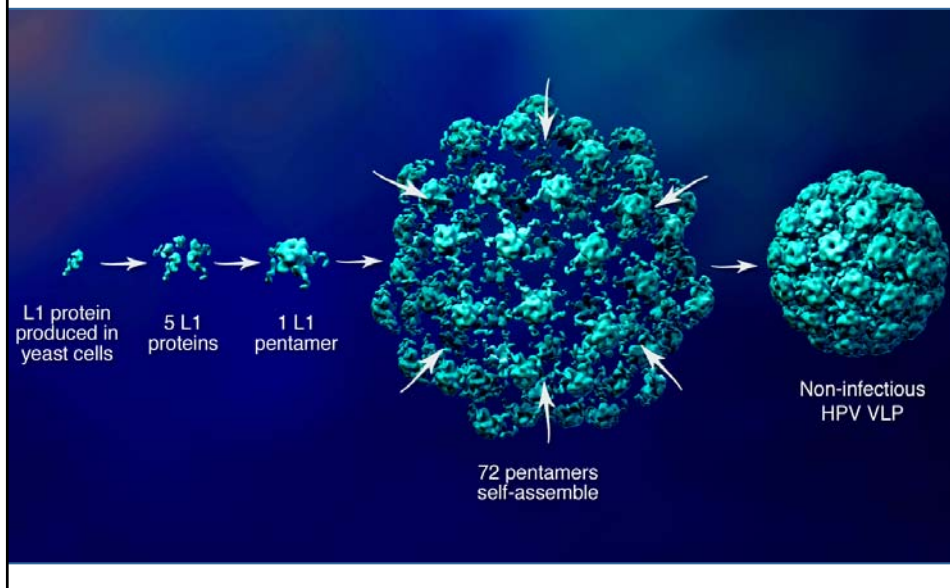
QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

E6/E7 expand the proliferative compartment inactivate cell  
cycle checkpoints, block apoptosis, induce telomerase  
HPV E6/E7 persist; Rb + p53 are wild type

## Strategies for HPV Vaccination

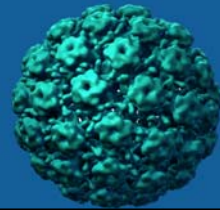


## HPV L1 Assembles into Virus-Like Particles

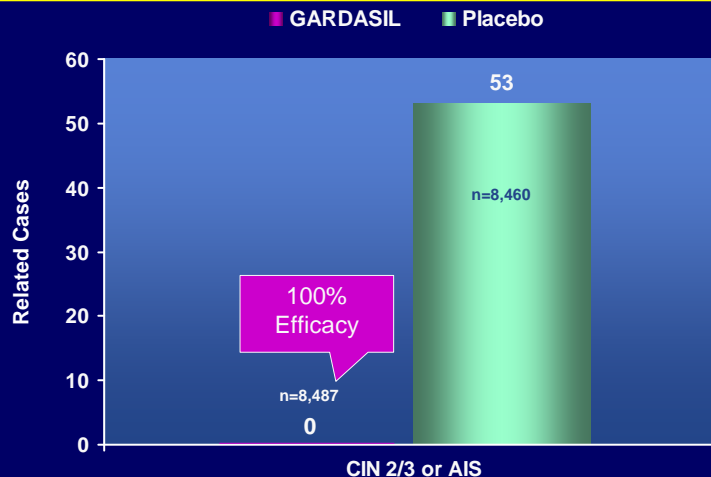


## GARDASIL: A Quadrivalent HPV Vaccine

- Quadrivalent HPV 6/11/16/18 L1 virus-like particle (VLP) vaccine
- VLPs are produced in *Saccharomyces cerevisiae*.
  - The L1 proteins self-assemble into VLPs.
  - Purified VLPs are adsorbed on aluminum-containing adjuvant.
  - The adjuvant is amorphous aluminum hydroxyphosphate sulfate (225  $\mu$ g per dose).
- Each 0.5-mL dose contains HPV Types 6/11/16/18 (20/40/40/20  $\mu$ g L1 protein, respectively).



## GARDASIL Is Efficacious Against HPV 16- and 18-Related CIN 2/3 or AIS



- 16- to 26-year-old females naïve to the relevant vaccine HPV type at enrollment and through 30 days Postdose 3
- Over a period of 2 to 4 years
- Analysis included Protocol 005.

CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma *in situ*.

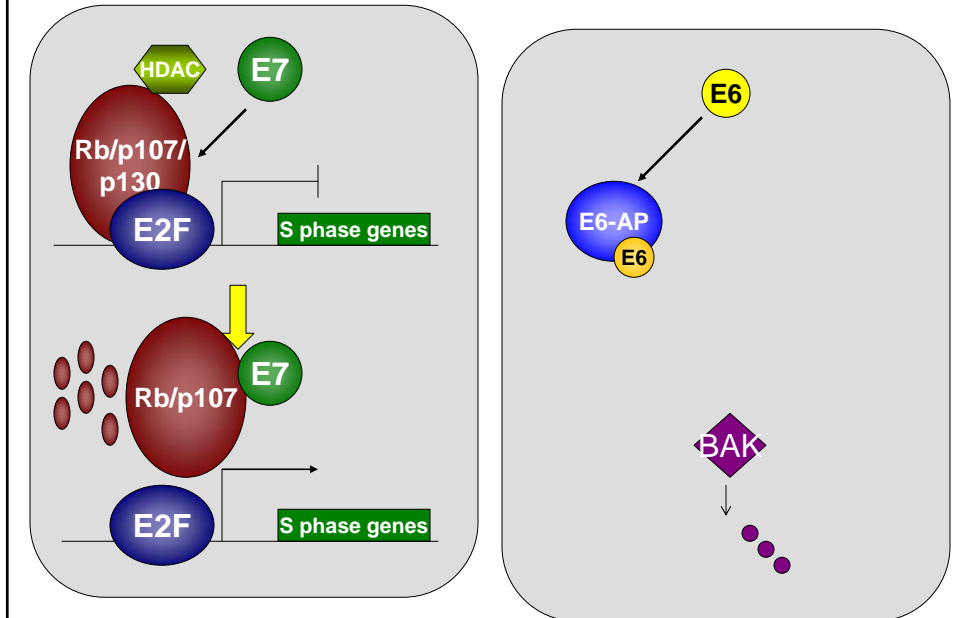
## HPV in other Anogenital and Oropharyngeal Cancers

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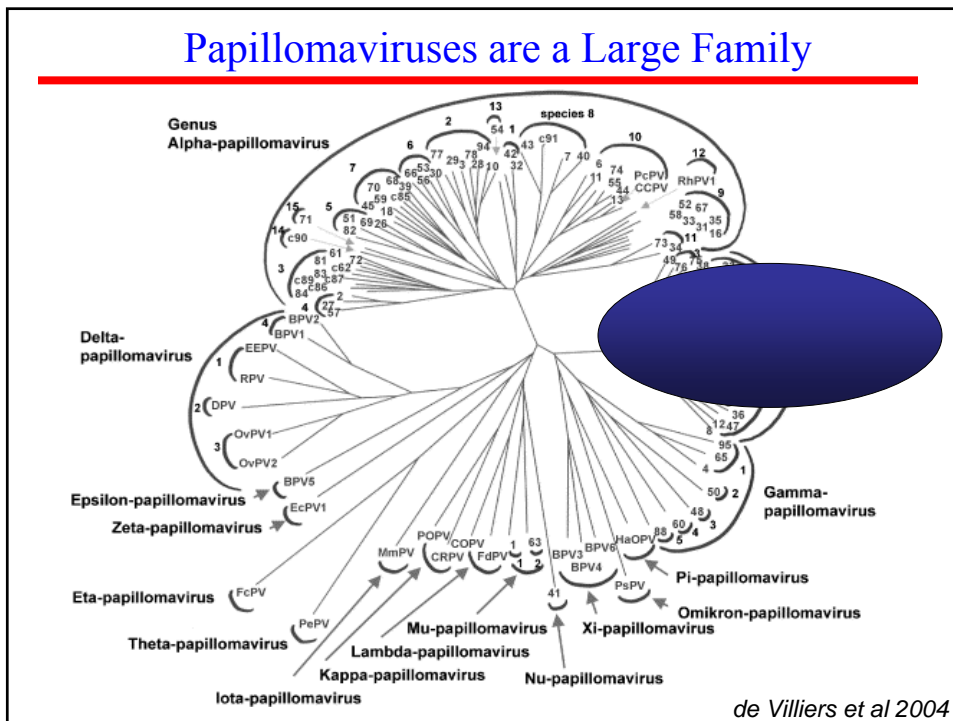
- Same HPV types; predominantly HPV 16
- Viral genome persists and E6/E7 expressed
- Wild type Rb and p53

Why don't low risk HPVs that infect the genital tract cause cancer?

## Targets of the LR □ E6 and E7 oncoproteins



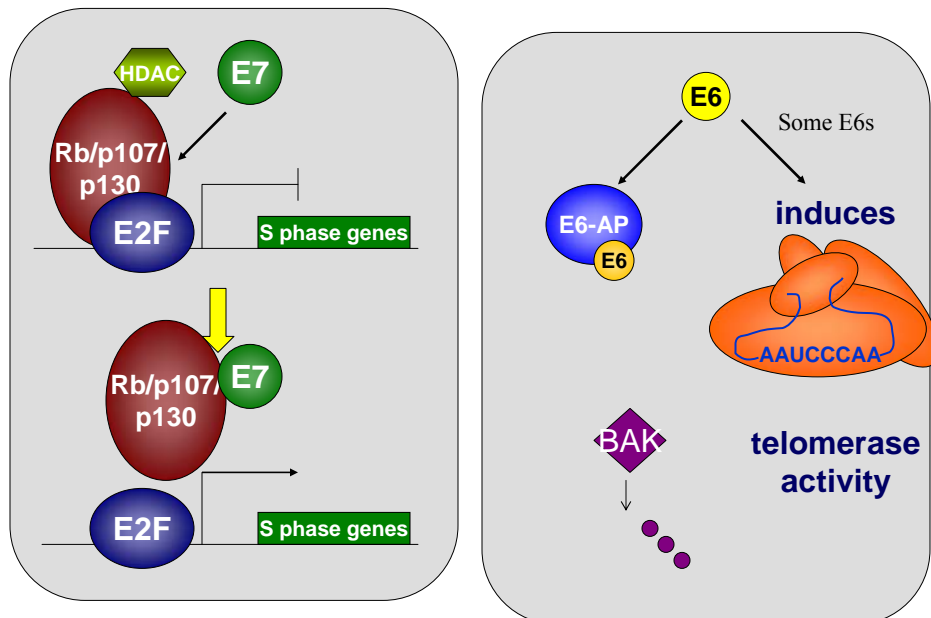
## Papillomaviruses are a Large Family



## Genus Beta HPVs and Squamous cell Skin Cancer

- HPVs first found with Epidermodysplasia verruciformis then in other SCSCs.
- Beta HPVs are prevalent on normal skin.
- Viral genome is not present in most cells of the tumor.
- UV exposure is the major risk factor for SCSC, also Immunosuppression.
- p53 mutation and p16/ARF loss are very frequent

## Targets of the $\beta$ E6 and E7 oncoproteins



## Beta HPVs and Skin Cancer

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QuickTime™  
TIFF (Uncompressed)  
are needed to see tl

- E6/E7 may expand the proliferative compartment
- E6 blocks the apoptotic response to UV
- Carcinogenesis is driven by mutation
- Persistent HPV is not required and may be Selected against

## HBV and HCV in the etiology of Hepatocellular Carcinoma

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- Prevalence of HCC is correlated with endemic chronic infection with HBV and HCV
- Chronic HBV and HCV infections result in cirrhosis in ~ 15% of subjects in 25-30 years, with HCC arising in ~1% of subjects with cirrhosis.
- Non-viral cirrhosis is also a risk factor for HCC.

HCC only arises in the context of cirrhosis.

## Hepatitis viruses are very diverse

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- HBV is a hepadna virus - a DNA, gapped double-stranded genome

Infection induces inflammation, cytokine signalling

HBV DNA is integrated into some, but not all HCCs. Integration to activate hTERT has been documented.

HBV X is frequently expressed  
transactivates promoters indirectly  
regulates proteasome function  
regulates mitochondrial function  
modulates calcium function

## Hepatitis viruses are very diverse

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- Hepatitis C virus (HCV) is a positive strand RNA Flavivirus.

HCV core induces signalling pathways

E2 interferes with interferon signalling

## Do HBV and HCV induce Cancer?

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- HBV and HCV induce unique gene expression profiles indicating that the virus has an effect on the phenotype of the cancer.
- The HBV vaccine has reduced the incidence of HCC.

## EBV is associated with multiple cancers

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- Burkitt's lymphoma
- Post transplant lymphomas
- Hodgkin's lymphoma
- Nasopharyngeal carcinoma
- Gastric cancer

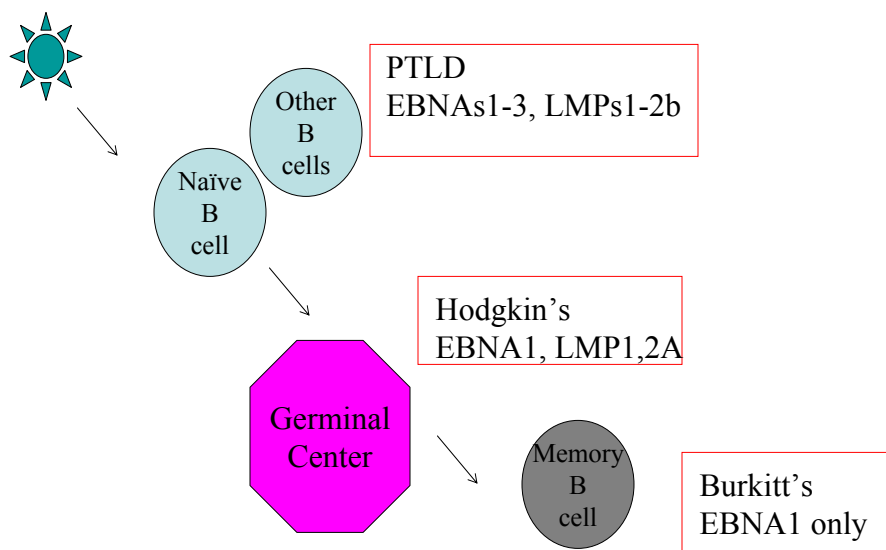
## EBV is associated with multiple cancers

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- EBV infection occurs in > 90% of the population; cancer is very rare.
- Most EBV associated cancers are associated with immunosuppression - transplantation (drugs); HIV; malaria;
- EBV causes cancer in both B cells, where the virus is latent and productive, and in epithelial cells that do not support viral latency.

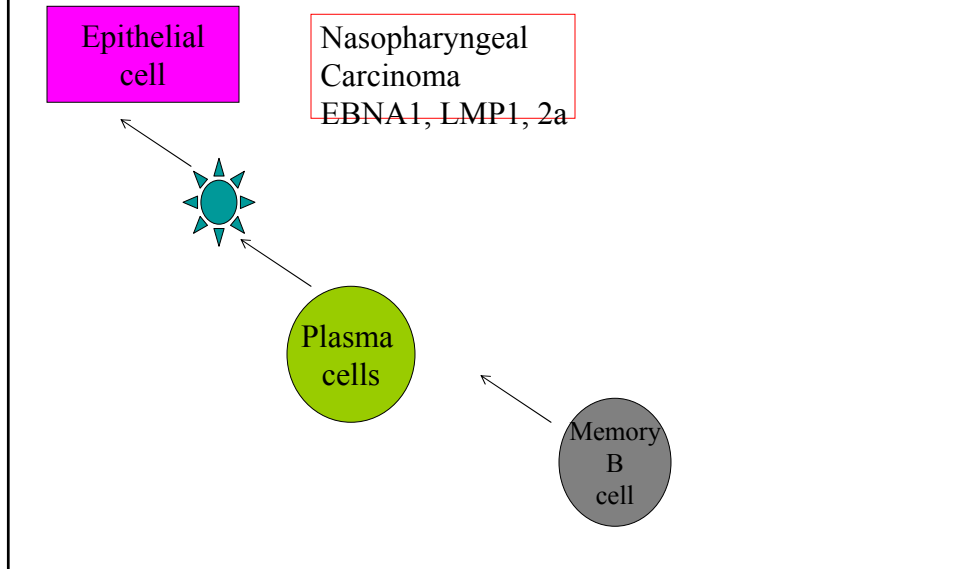
## EBV associated cancers

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## EBV associated cancers

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## HHV-8 (KSHV) and Cancer

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- Kaposi's sarcoma - spindle cell (endothelial origin)
- Pulmonary Effusion Lymphoma
- Multicentric Castleman's Disease - B cell (non-cancer)

Viral genome encodes homologues for cellular genes that block innate and adaptive immunity, block apoptosis, induce proliferation.

## Are there other Cancers with a Viral Etiology ?

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Cancers that increase disproportionately with  
Immunosuppression

non EBV+ lymphomas

skin cancers  
Merkel cell cancer

lung cancer

*Before I came here I was confused about this subject.  
Having listened to your lecture, I am still confused  
– but at a higher level.*

**Enrico Fermi**