Viruses and Human Cancer

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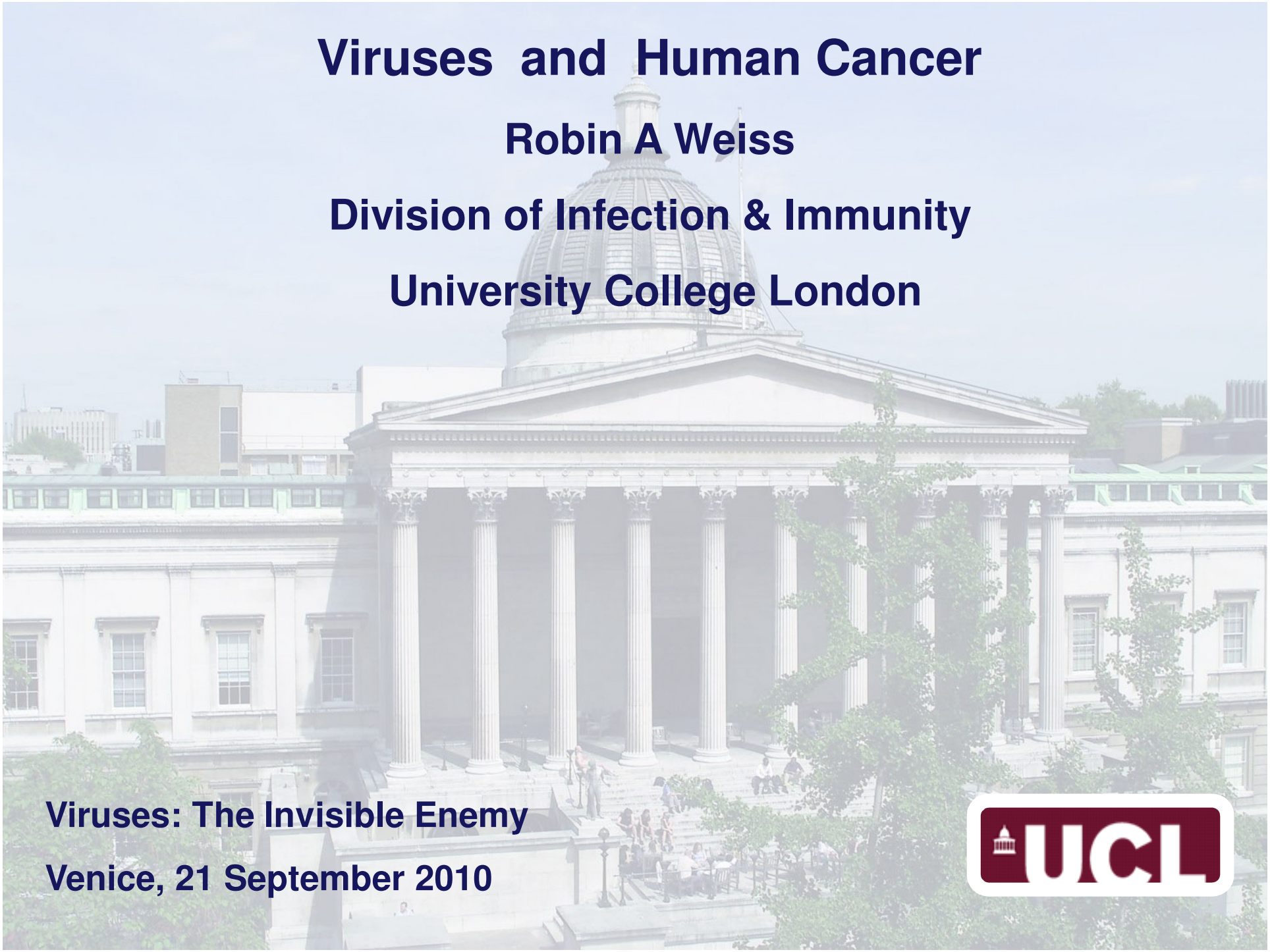


Viruses: The Invisible Enemy

Venice, 21 September 2010

Overview

1842: Domenico Rigoni-Stern, Verona: no cervical cancer in nuns

Oncogenic viruses in animals were discovered 100 years ago

The first oncogenic human virus (EBV) was discovered in 1964

Oncogenic viruses have taught us much about cancer:

- **Tumor suppressor p53 first discovered in association with PyV**
- **Oncogenes were first defined in retroviruses**

Approximately 15% of human cancer worldwide has a viral etiology

Vaccines against these viruses will significantly reduce the human cancer burden

Human cancers attributable to infection

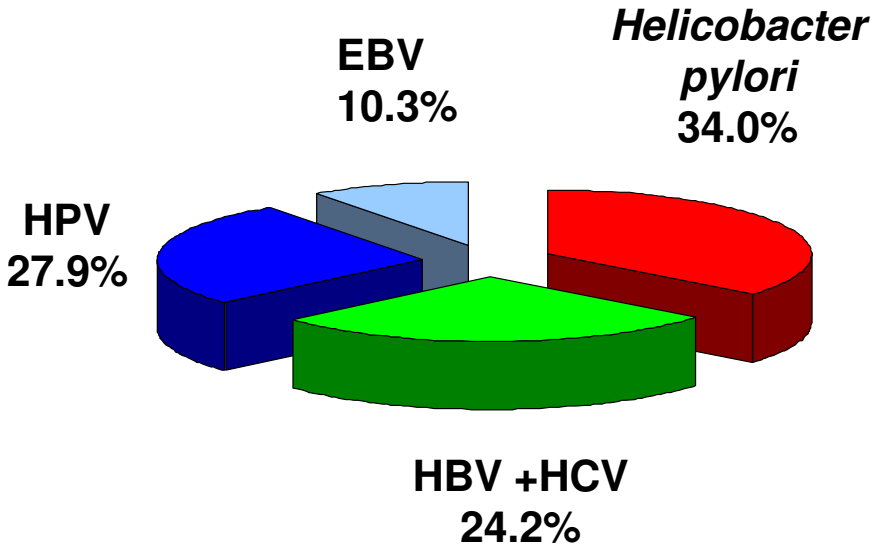
Agent	Cancer	% lifetime risk in carriers	Annual cases	% all cancers	Main trans-mission route
H. pylori	Stomach	~10.0	592,000	5.8	Oral
	Lymphoma (MALT)		11,500		
HPV	Cervix (HPV-16, 18)	~3.0	492,800	5.1	Sexual
	Ano-genital		53,880	0.5	
	Mouth, pharynx		14,500	0.1	
	Skin (HPV-5)	<0.01	~1,000	<0.01	Contact
HBV and HCV	Liver	~15.0	535,000	5.5	Parenteral
EBV	Nasopharynx	<1.0	78,100	1.0	Oral
	Hodgkin lymphoma		28,600	0.3	
	Burkitt lymphoma		6,700	0.06	
KSHV (HHV-8)	Kaposi sarcoma	<1.0	66,200	0.9	Oral
	NHL		16,100		
Schistosome	Bladder	<1.0	10,600	0.1	Water, snails
HTLV-1	ATL	~1.2	3,300	0.03	Milk
Opisthorchis	Gall bladder	~5.6	2,500	0.02	Water, raw fish
Merkel PyV	Skin	<0.01	~1,500	<0.01	Contact

(Adapted from Parkin, 2006)

Annual global cancer burden due to infections

2,216,920 new cases = 20.6% of total cancer incidence

(adapted from Parkin et al. 2002, 2006)



This pie chart excludes the remaining 3.6%:

- Anal and perianal cancers (HPV)
- Vulvar, vaginal and penile cancers (HPV)
- Adult T cell leukemia (HTLV-1)
- Kaposi sarcoma and KSHV lymphomas
- Merkel cell carcinoma (MCPyV)
- MALT tumours (*H. pylori)*
- Cancers linked to helminth infections

>99% cancer of the cervix (HPV)

25% cancers of the oral cavity (HPV)

80% hepatocellular carcinoma (HBV 50%, HCV 30%)

80% gastric cancer (*H. pylori*)

10% gastric cancer (EBV)

>99% undifferentiated nasopharyngeal carcinoma (EBV)

10% non-Hodgkin lymphoma (EBV)

30% Hodgkin lymphoma (EBV)

Paradox: oncogenic viruses that don't cause human cancer

Adenoviruses: AdV 2, 5 & 12

Highly oncogenic in new born rats due to E1A, E1B, E4 & E5

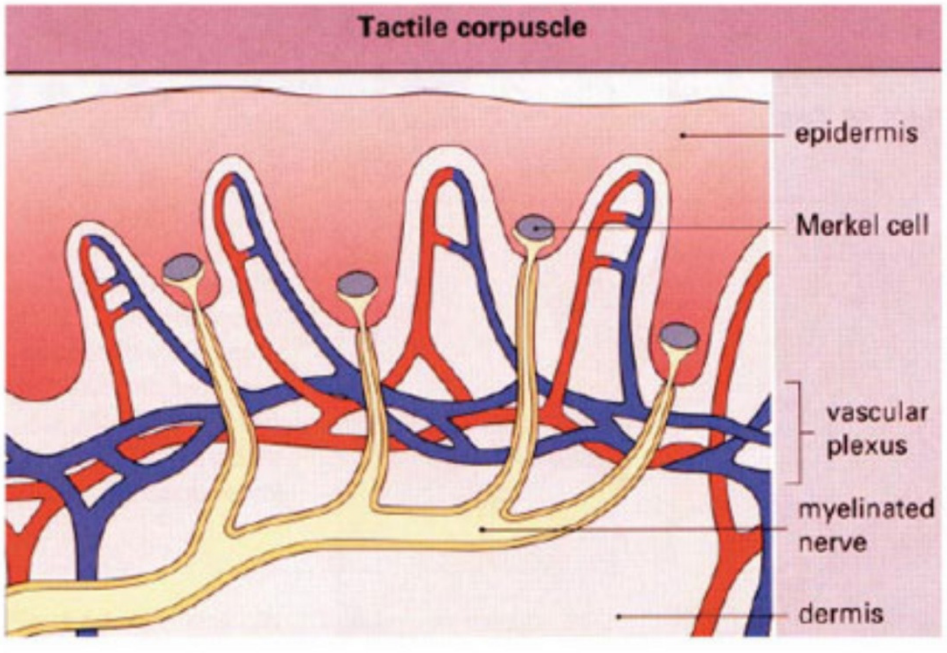
Polyomaviruses: BKV, JCV

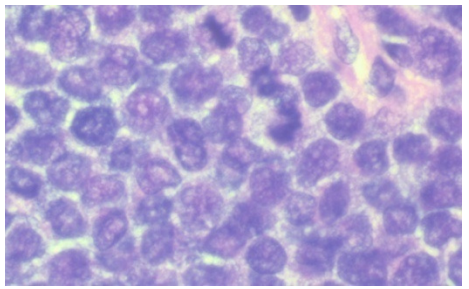
Highly oncogenic in baby hamsters due to large T and small t antigen transformation

HTLV-2: Immortalizes T-cells in culture

Merkel Cell Carcinoma

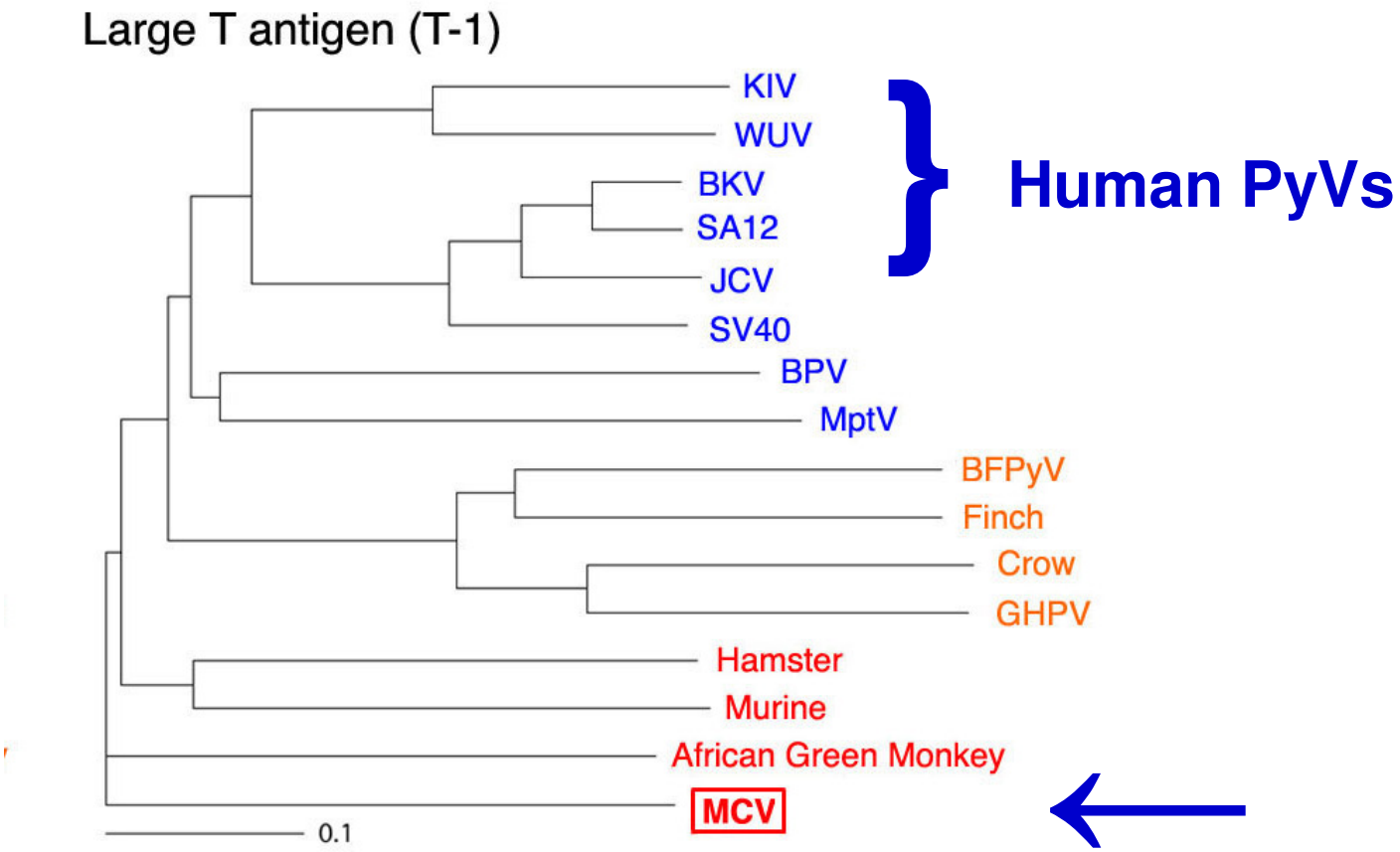
- Rare, aggressive skin cancer
- Occurs in the elderly
- Transplant recipients and AIDS
- New polyoma virus discovered 2008





Feng, Shuda, Chang & Moore (2008) Clonal integration of a PyV in human Merkel cell carcinoma. *Science* 319: 1096–1100.

Merkel cell carcinoma virus is phylogenetically distant from other human polyoma viruses



Distinguishing tumor viruses from rumor viruses

1972-1974	RD114	Pediatric sarcoma	Feline gamma-retrovirus
1972-present	MMTV	Breast cancer	Murine beta-retrovirus
1992-2004	SV40	Various	Simian polyomavirus
2006-2010	XMRV	Prostate cancer	Murine gamma-retrovirus

Rnase L mutation?

XMRV in stroma, carcinoma or neither?

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Rumors about genuine tumor viruses: KSHV (HHV-8)

1994	Kaposi sarcoma	True
1995	Primary effusion lymphoma	True
1996	Multicentric Castleman's disease	True
	(PCR, Southern blot, Ag, isolation, serology)	
1996	Multiple myeloma (PCR)	False
1997	Sarcoidosis (PCR)	False

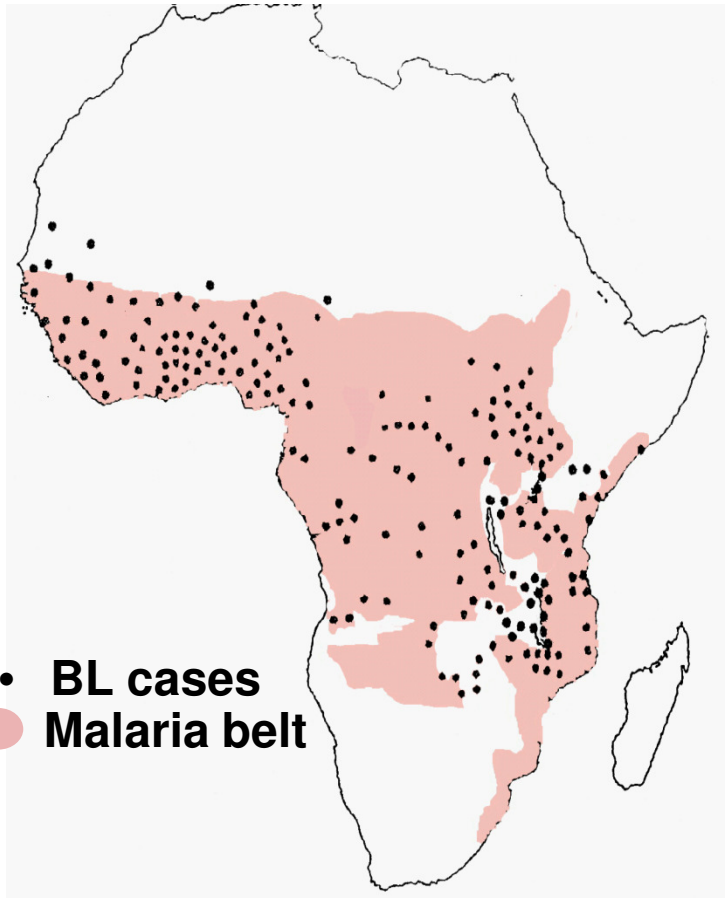
Multifactorial causes of cancer
(virus is necessary but not sufficient to cause cancer)

1. **Liver cancer (HCC)**
   - **HBV alone: medium frequency of HCC**
   - **Aflatoxin in diet: HCC rare**
   - **HBV + aflatoxin: ~5-fold relative risk in HCC**
     (Wild & Montesano 2009)

2. **Skin cancer in EV**
   - **HPV-5, HPV-8 (ubiquitous)**
   - **Ultraviolet light exposure (on face)**
   - **Epidermodysplasia verruciformis gene (rare)**

Multifactorial causes of cancer

3. Burkitt's Lymphoma in children



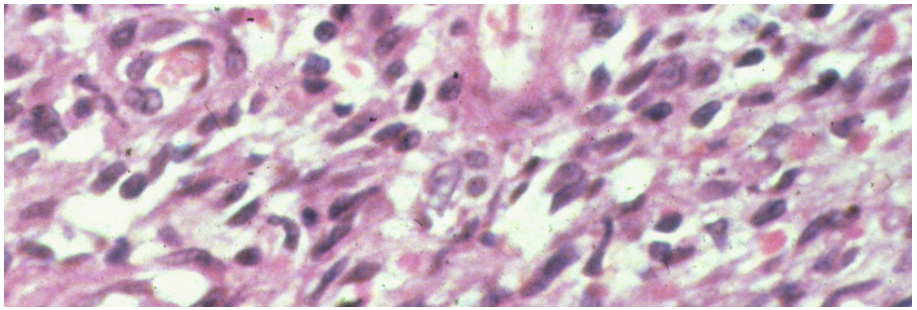
Epstein-Barr Virus (EBV)

Holoendemic malaria

C-*myc* translocation to Ig heavy or light chains 8;14, 8;2 or 8;22

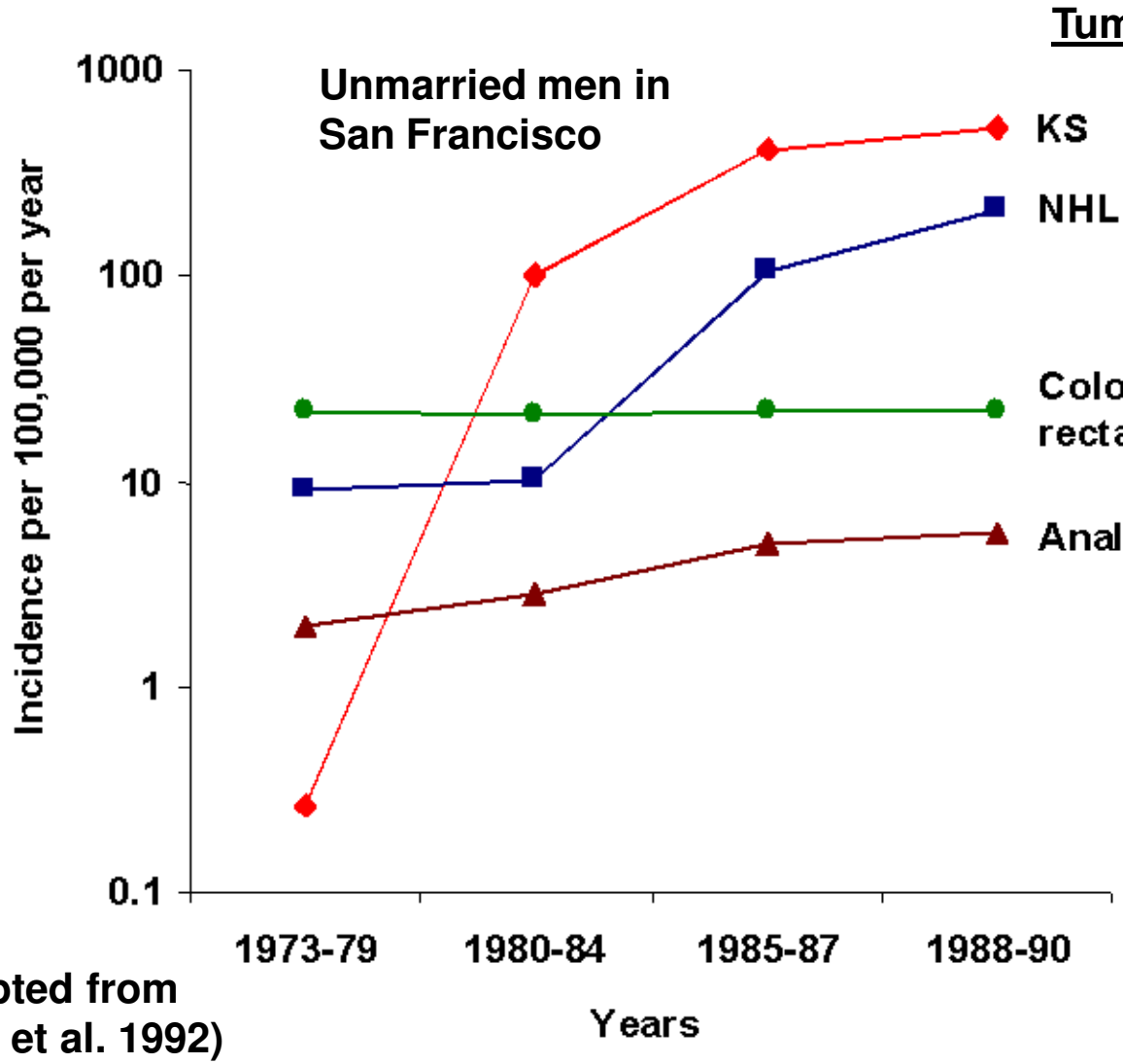
Multifactorial causes of cancer

4. Kaposi's sarcoma (KS)

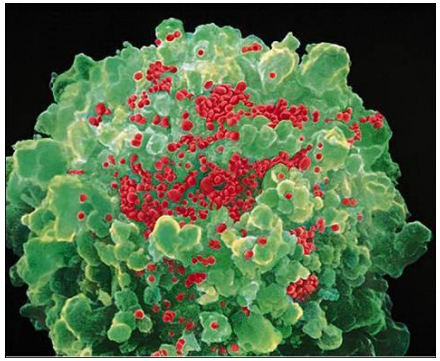


- 1º cause: KSHV (HHV-8)
- Classical:
  rare, in elderly men
- Iatrogenic: commoner in immunosuppressed transplant patients
- AIDS-KS, role of HIV:
  immunosuppression + Tat?

Oncogenic viruses and changes in cancer incidence when AIDS appeared



(Adapted from Rabkin et al. 1992)




(Lucas Cranach, Courtauld Institute of Art)

Humankind's Collection of Viruses

Family Heirlooms (co-evolved with host)

- Endogenous Retroviruses
- Herpesviruses
- Papilloma & polyoma viruses
- Hepatitis B virus

Temporary Exhibits (zoonoses, outbreaks)

- Rabies
- West Nile
- Nipah
- Ebola
- SARS

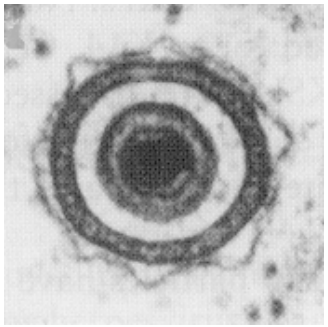
'New' Acquisitions (<12,000 years ago)

- Measles
- Smallpox
- Influenza
- HIV

(Weiss RA & McMichael AJ, Social and environmental risk factors in the emergence of infectious diseases. *Nature Med* 10, S70, 2004)

KSHV is a Maternal Heirloom

- **In Africa, 98% KSHV-infected children have KSHV+ mothers but there is no correlation with infection status of fathers**
  (Bourboulia *et al,* 1998; Dedicoat *et al*, 2004; Plancoulaine *et al*, 2004)



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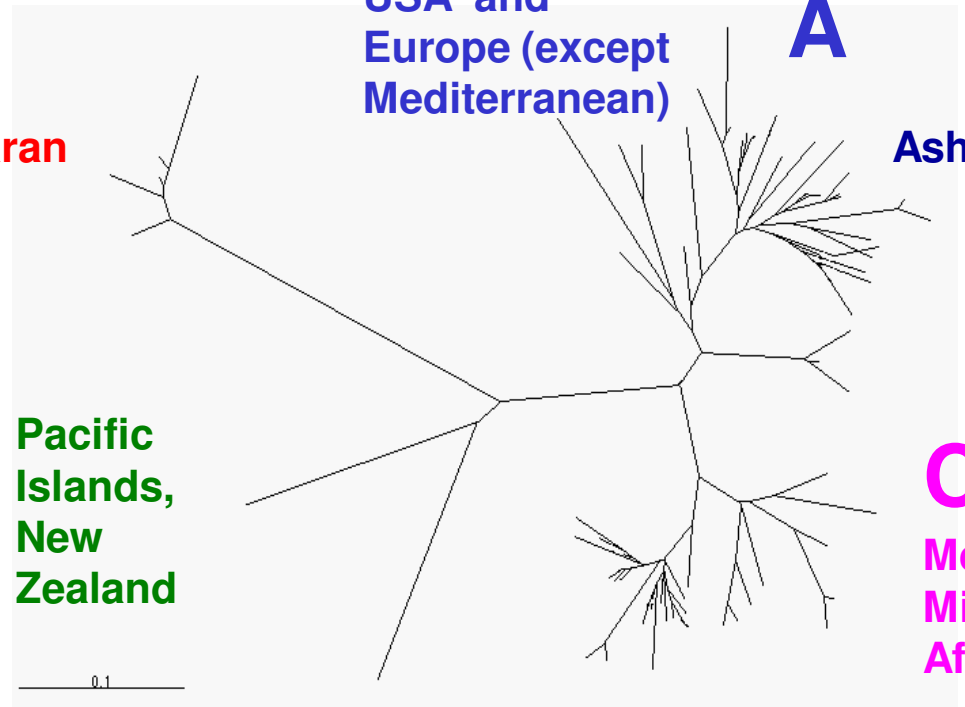
- In Ashkenazi Jews, KSHV genomes co-diversify with mtDNA, but not with Y-DNA
(Wilder, Weiss & Boshoff, unpublished)



Genetic variation in the K1 gene

How long has KSHV been present in the Veneto and the Po valley?

Marcello Fogolino

Madonna with San Gottardo and San Giobbe

1508
Mantova

Virus: the invisible enemy or the invisible friend

Could viruses be useful to their hosts?

Non-pathogenic:

TTV
GBV-C co-infection delays progression to AIDS
HERV-W in the placental syncytiotrophoblast

Low pathogenic:

γ-Herpesviruses	**KSHV & EBV?**
Retrovirus	**HTLV-1 & HTLV-2?**

KSHV: Loss of fitness to host is a rare side effect usually occurring after reproductive age

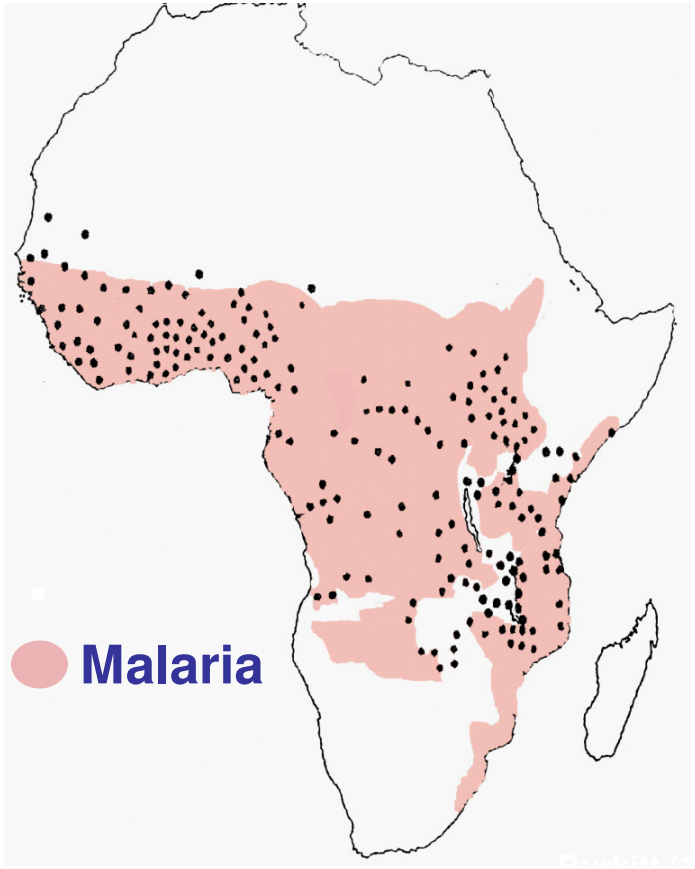
Its minor cost in fitness might be offset by a broad advantage to the host in a certain environment

Analogous to the cost of homozygous lethal genes being outweighed by heterozygous fitness

Interactions between infections: Malaria

Burkitt's Lymphoma

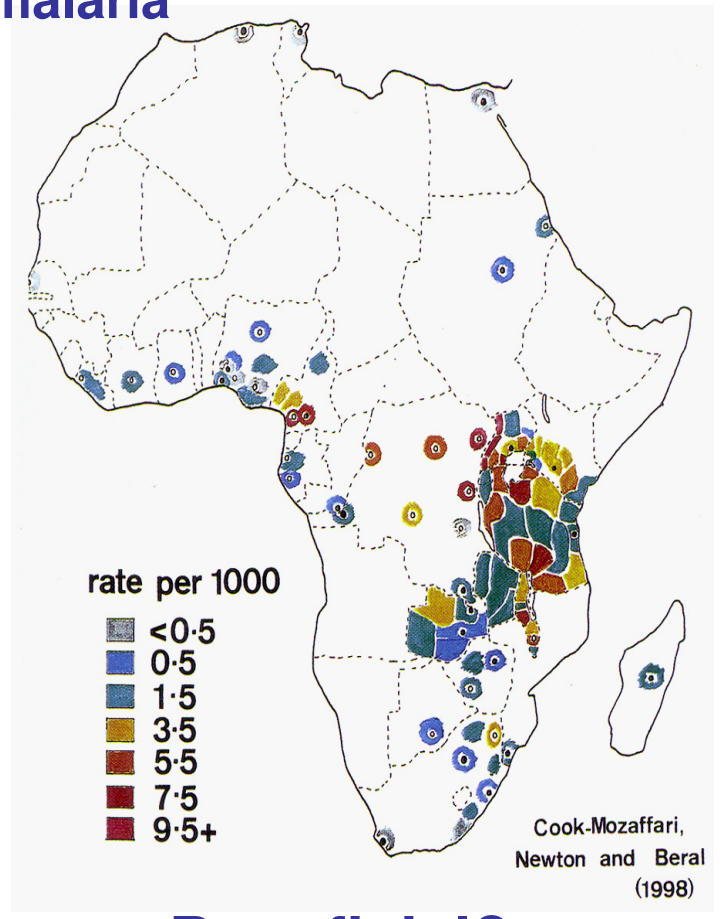
EBV is ubiquitous but BL only occurs where there is malaria



Detrimental

Kaposi's Sarcoma

KSHV prevalence (before AIDS) broadly correlates with malaria



Beneficial?

KSHV and Malaria: Hypotheses

KSHV transmission is enhanced by mosquitos (Ascoli and Coluzzi, 2004)

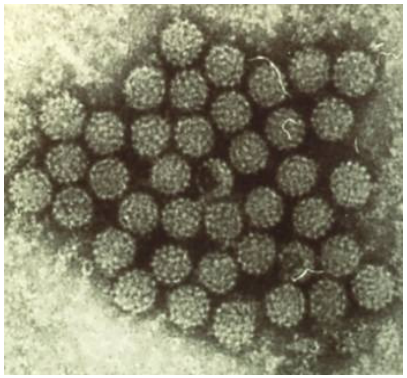
KSHV might protect against cerebral malaria through secretion of v-MIPs that bind to CCR3 at the blood brain barrier

KSHV is not an 'emerging infection' but has been maintained in the human population by positive selection analogous to genetic hemoglobinopathies

>10% KSHV Ab+ **β-thalassemia** **merged**

Vaccination against tumor virus infection

- **HBV SAg recombinant subunit vaccine since 1986: Protects against hepatitis and against liver cancer**
- **HPV virus-like particle capsid vaccine: Two successful vaccines licensed 2006**
- **EBV Gp340 envelope glycoprotein: Not taken up by Pharma Cos**
- **HTLV-1 envelope glycoprotein protects macaques and rabbits from challenge: Not seen by Pharma Cos as a market**
- **HCV and HIV: Huge markets but no really efficacious vaccines yet**



Conclusions

- Oncogenic viruses have given us deep insight into cancer
  eg, oncogenes, tumour suppressor genes
- Cancer is a 'side effect' of persistent virus infections that promote cell proliferation
- Low penetrance of viral oncogenesis: requires cofactors
- Immune deficiencies increase incidence of virus-linked cancers
- ~ 15% of global human cancer burden has a viral etiology, ~1.6 million cases annually
- Vaccines hold great promise to reduce that burden

MRC Medical Research Council

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