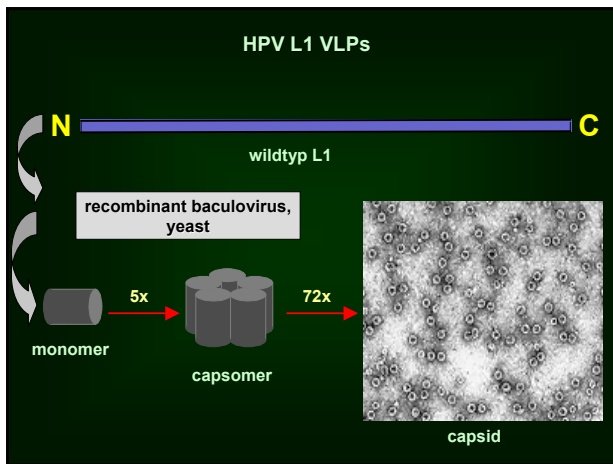


Cellular and humoral immunity apparently are able to clear persisting HPV infections and to prevent re-infections by the same type



First results from phase II clinical trials indicate:

- VLP vaccines induce **high antibody titers**, even in the absence of adjuvants;
- the titers were commonly **at least 10 times higher than in natural infections**;
- the **antibodies persisted** for prolonged periods of time;
- no significant adverse effects** have been noted;
- there exist **first indications of a protective effect in humans** (prevention of infection, prevention of early precancerous lesions);
- a high protective effect has been noted with VLPs of animal papillomaviruses in animal experiments.

Koutsky et al. A controlled trial of a human papillomavirus Type 16 vaccine. New Engl. J. Med. 347: 1645-51, 2002

768 women without signs of HPV infection (age 16-23) were vaccinated with VLP preparations of HPV 16

765 women received placebo vaccinations

Both groups were followed for a median of 17.4 months.

	Transient HPV16 infection	Persistent HPV 16 infection	CIN 1	CIN II
HPV 16 vaccinated group	6 (0.6%)	0	0	0
Placebo group	68 (6.3%)	41	5	4

Two additional large scale studies came essentially to the same conclusions

Harper, D.M., Franco, E.L., Wheeler, C.M., Ferris, D.G., Jenkins, D., Schuid, A., Zahaf, T., Innis, B., Naud, P., de Carvalho, N.S., Roteli-Martins, C.M., Teixeira, J., Blatter, M.M., Korn, A.P., Quint, W., and Dubin, G. and GlaxoSmithKline HPV Vaccine Study Group. **Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial.** Lancet 364: 1757-1765, 2004.

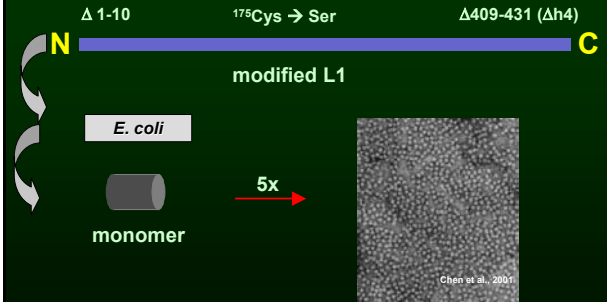
Villa, L.L., Costa, R.L., Petta, C.A., Andrade, R.P., Ault, K.A., Giuliano, A.R., Wheeler, C.M., Koutsky, L.A., Malm, C., Lehtinen, M., Skjeldestad, F.E., Olsson, S.E., Steinwall, M., Brown, D.R., Kurman, R.J., Ronnett, B.M., Stoler, M.H., Ferenczy, A., Harper, D.M., Tamms, G.M., Yu, J., Lupinacci, L., Raikar, R., Taddeo, F.J., Jansen, K.U., Esser, M.T., Sings, H.L., Saah, A.J., and Barr, E. **Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial.** Lancet Oncol. 6: 271-278, 2005.

Cervical cancer represents the most frequent cancer of females in large parts of the developing world.

Effective vaccination will require

- > the production of cheap vaccines
- > heat-stable vaccines
- > optimally non-invasive application of vaccines

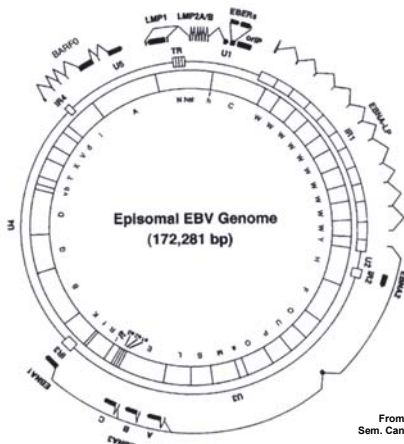
HPV 16 L1 Capsomeres



Epstein-Barr virus is associated with ~ 10% of cancers linked to infections.

The spectrum of these cancers is broad (B-cell immunoblastomas, nasopharyngeal cancer, endemic Burkitt's lymphomas, 30-40% of Hodgkin's disease, ~ 10% of gastric cancers).

The virus is the primary cause of infectious mononucleosis.



From: Osato and Imai
Sem. Cancer Biol. 7: 175, 1996

In EBV-positive Burkitt's lymphomas EBV contributes to the malignant phenotype of the tumor cells.

- > loss of EBV genomes results in continuation of cell proliferation, but in loss of oncogenicity.

In EBV-negative Burkitt's lymphomas other factors driving the oncogenic process, besides c-myc activation, remain unknown.

Epstein-Barr Virus in Hodgkin's Disease

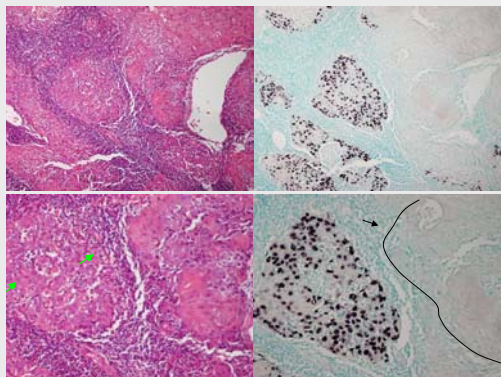
In Western Societies 20-25% EBV-positive
(mainly nodular sclerosis type in young adults)

In Developing Countries ~ 80% EBV-positive
(mainly mixed cellularity type in early childhood)

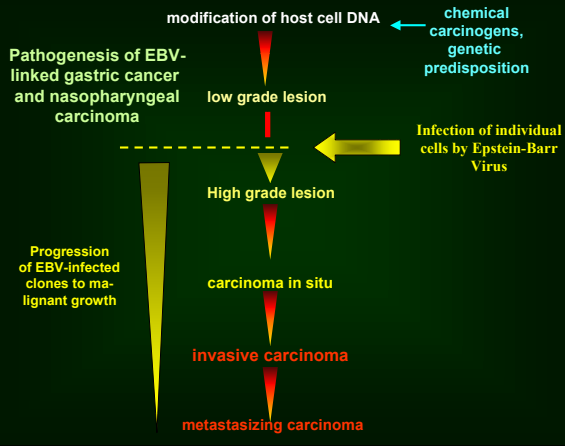
Cheng et al., Blood, 81: 496, 1993
Armstrong et al., Am. J. Pathol. 142: 1683, 1993

Reasons to assume a causal role of EBV in EBV-positive Hodgkin's disease

- Viral DNA persists within the malignant Reed-Sternberg cells and represents not a contaminant of the surrounding lymphoid stroma.
- The clonality of viral DNA indicates its uptake prior to the onset of malignant growth.
- Viral antigens expressed (in particular LMP1 and LMP2) should promote a proliferative and transformed phenotype.
- EBV-induced infectious mononucleosis in young adults significantly increases the risk for the subsequent development of EBV-positive Hodgkin's disease.



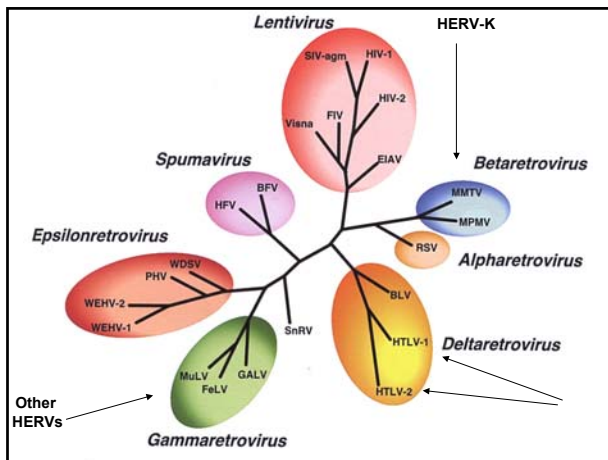
Courtesy of Dr. Kwok Wai Lo, Hong Kong



EBV vaccines have been developed against glycoproteins of the viral envelope.

Their efficacy has not yet been adequately tested. The interest of pharmaceutical companies in producing such vaccines is low.

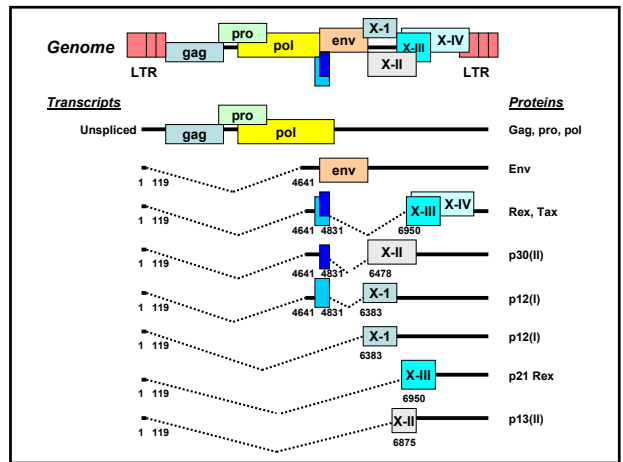
The main interest for vaccination exists in the high endemic regions for nasopharyngeal cancer in Southern China.



HTLV-1 causes the adult T-cell leukemia, predominantly found in coastal regions of Southern Japan.

Transmission of the virus occurs mainly in the early postnatal period (breastfeeding as risk factor), intravenous drug abuse but also more ineffectively by sexual contacts.

The viral genome codes for an active oncogene (TAX), thus, HTLV-1 acts as a direct carcinogen.



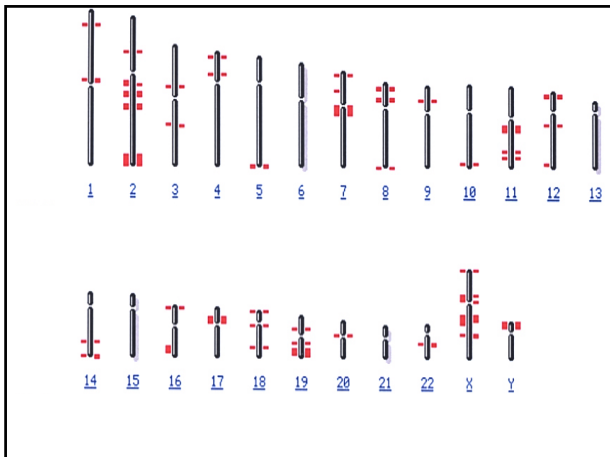
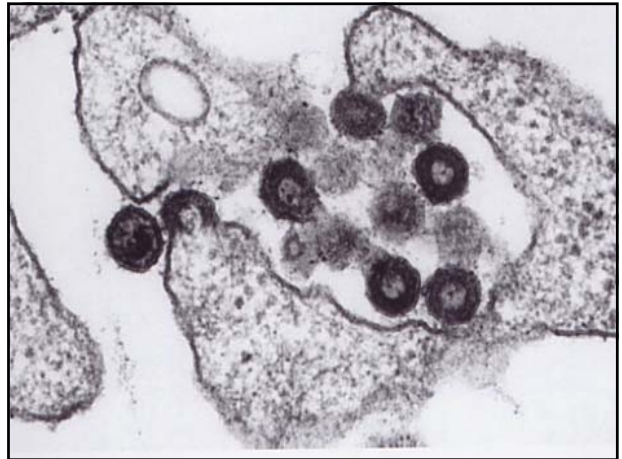
Human endogenous retroviruses (HERVs) comprise approximately 8% of our genomes.

They entered the human germ line in part prior, in part after the separation of the human species from non-human primates.

Most of the genomes became highly defective.

A few copies of two groups (HERV-K) and a newly discovered subfamily contain the information for complete infectious viral particles and may be activated under specific conditions.

Their potential role in human malignancies remains to be defined.



SV40 represents a rhesus monkey polyoma virus which is highly oncogenic when inoculated into newborn rodents.

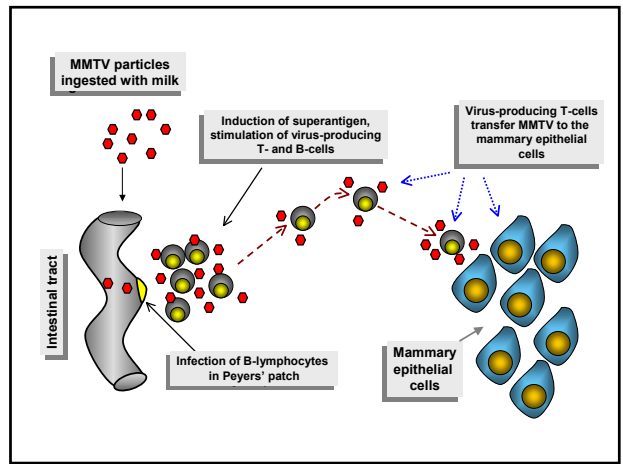
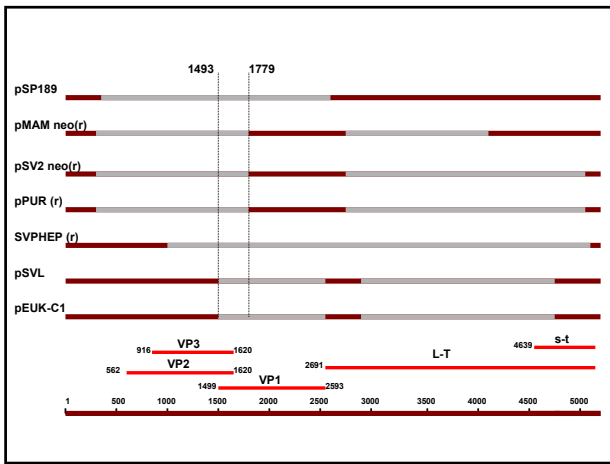
SV40 inadvertently contaminated poliomyelitis vaccines between 1955 and 1961.

Several million people received the contaminated vaccine.

Neither seroepidemiology nor retrospective epidemiological analyses provided evidence for increased tumor incidence among these vaccinated persons or for long-time virus persistence in the human population.

In recent years, however, several claims have been made that SV40 DNA is present in mesotheliomas, B-cell lymphomas and brain tumors.

Obvious problems: Risk of contaminations, high degree of homology of SV40 T-antigen with the one of a human polyomavirus, JC; extensive Homology between part of the SV40 T-antigen with human cellular DNA.



Preventive Vaccines are available against

- Hepatitis B virus infection
- High and low risk human papillomavirus infections (HPV 16 and 18, and HPV 6 and 11)

Preventive vaccines in development

- Hepatitis C
- (Epstein-Barr virus)
- (Helicobacter pylori)

No vaccines available for

- Human T-lymphotropic retrovirus (HTLV-1 and -2)
- Schistosoma and liver flukes

The identification of specific infectious agents as causative factors for human cancers permitted for the first time preventive vaccinations against very common specific types of human malignancies (hepatocellular carcinomas linked to hepatitis B infections and cervical cancer).

This results in the expectation that there will be a drastic reduction of these cancers within the foreseeable future.

Global vaccination programs against specific infections (Human Papillomaviruses and Hepatitis B) and eradication of Helicobacter pylori infections should theoretically prevent about 1.560.000 annual new cancer cases out of a total of 2.017.000 estimated cases linked to infections