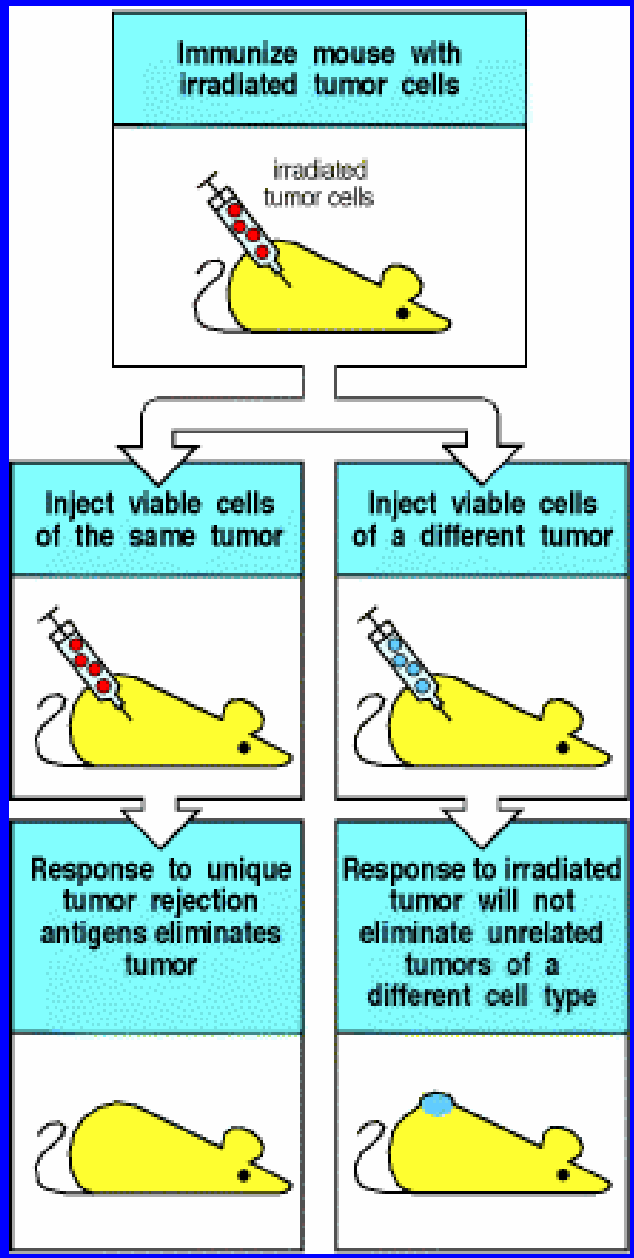
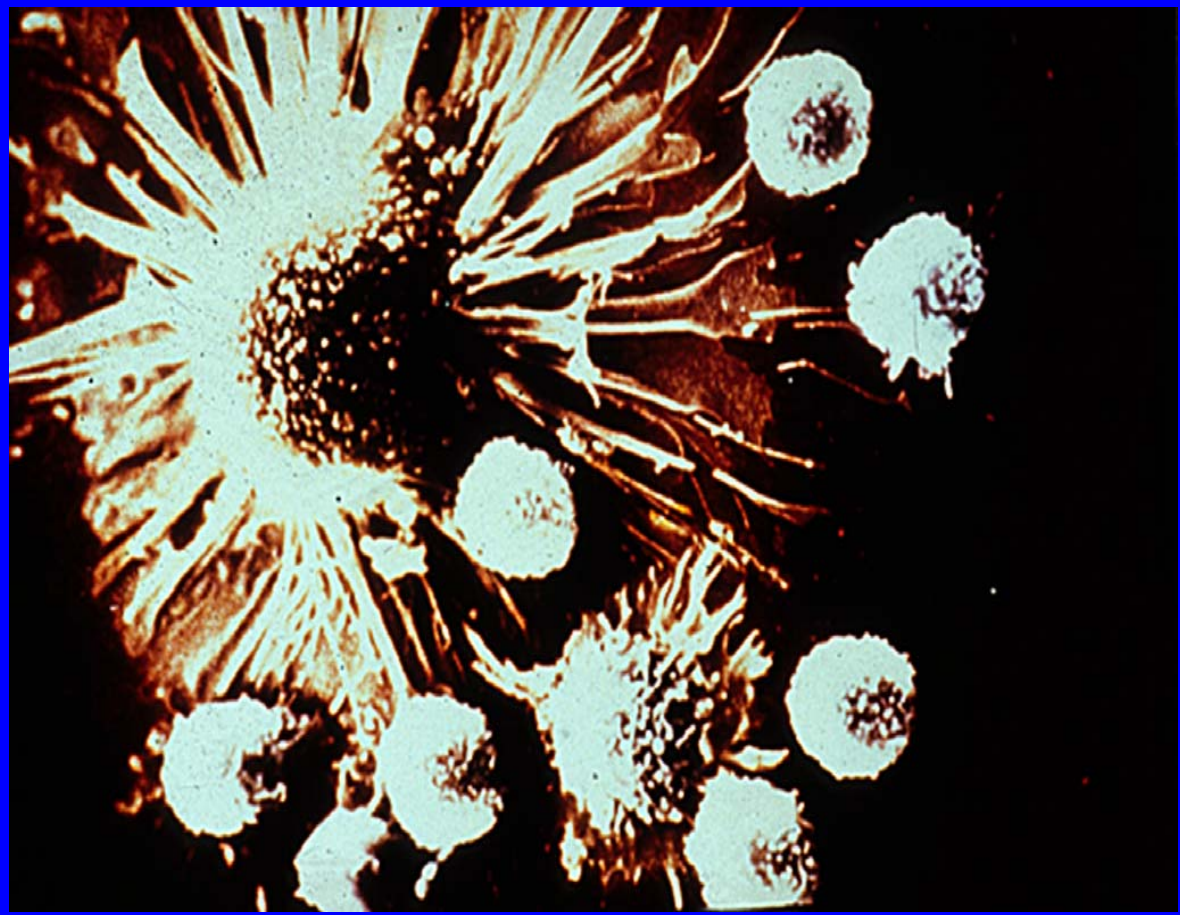
Prophylactic and Therapeutic Vaccines for Cervical Cancer

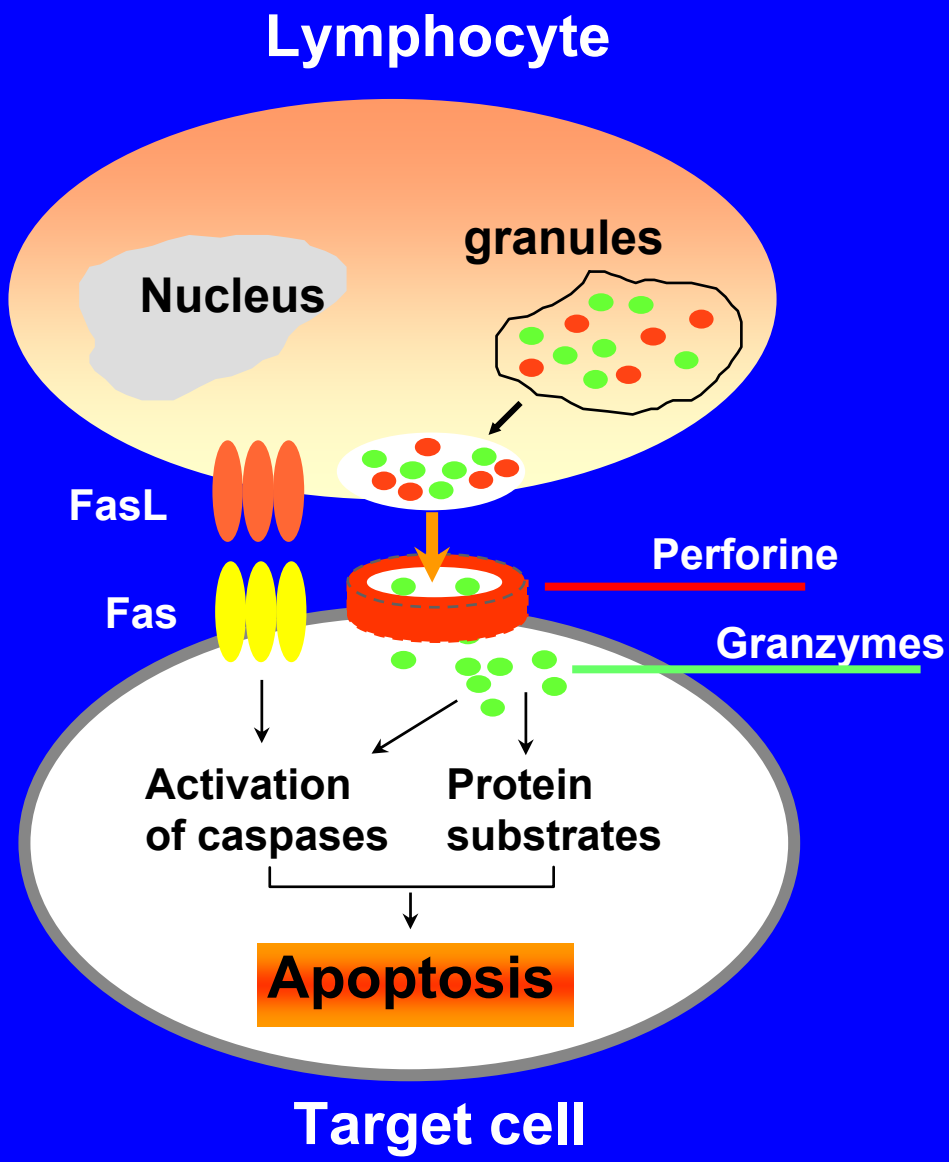
Geneva, March 2003

Immune response against cancer?

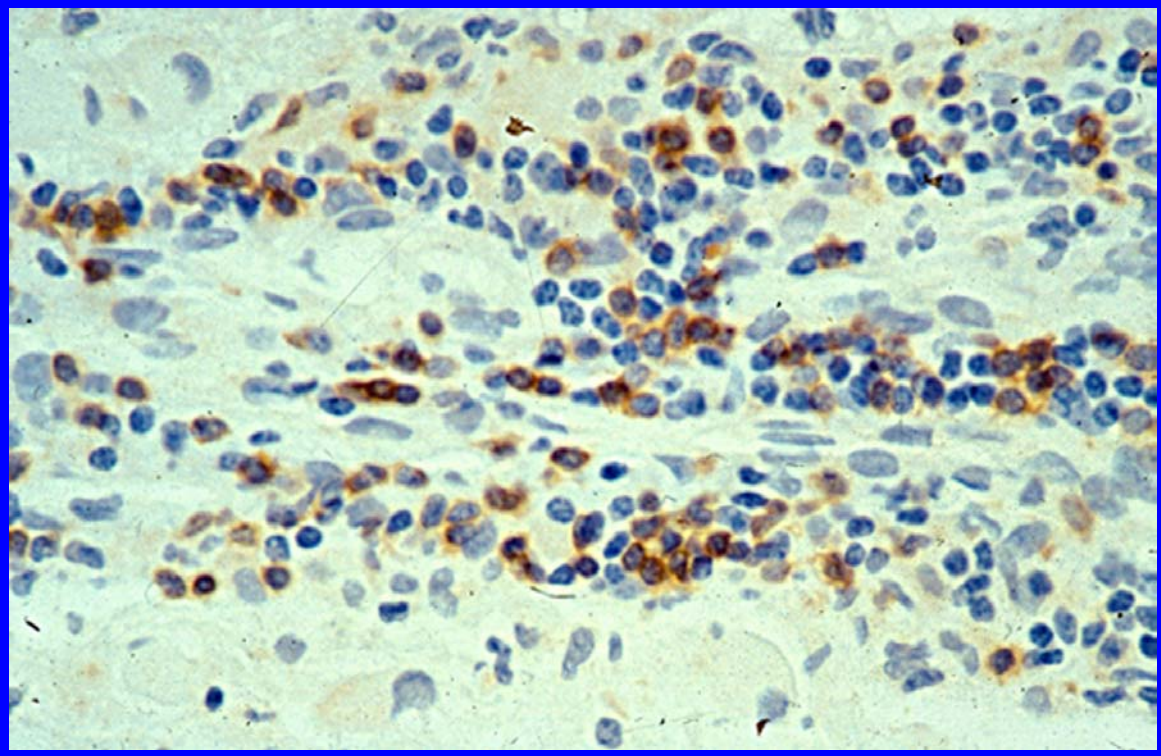

Immunize mouse with irradiated tumor cells
irradiated tumor cells
Inject viable cells of the same tumor
Inject viable cells of a different tumor
Response to unique tumor rejection antigens eliminates tumor
Response to irradiated tumor will not eliminate unrelated tumors of a different cell type

Lymphocytes as killers

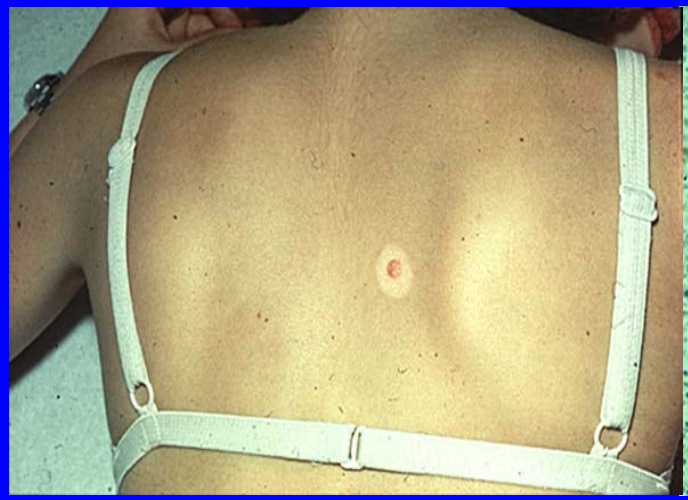


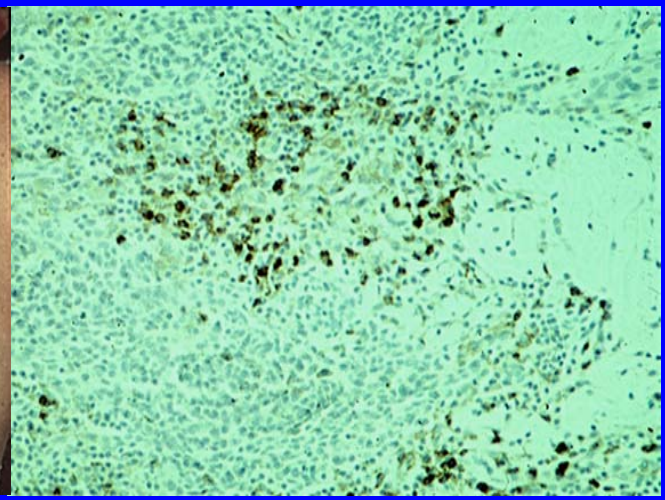

Lymphocyte
granules
Nucleus
FasL
Fas
Perforine
Granzymes
Activation
of caspases
Protein
substrates
Apoptosis
Target cell

Lymphocytes infiltrate tumors



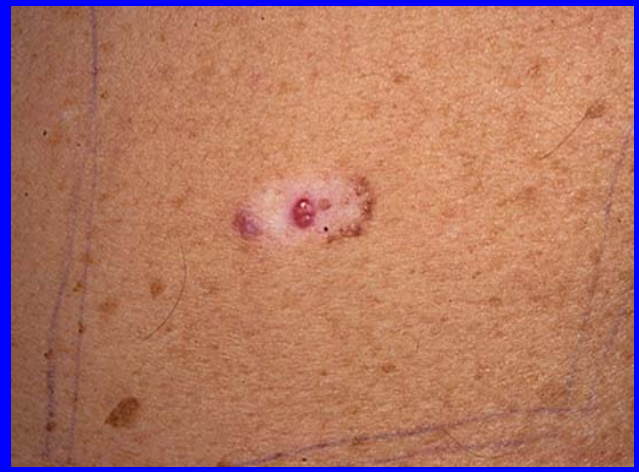
Spontaneous regression



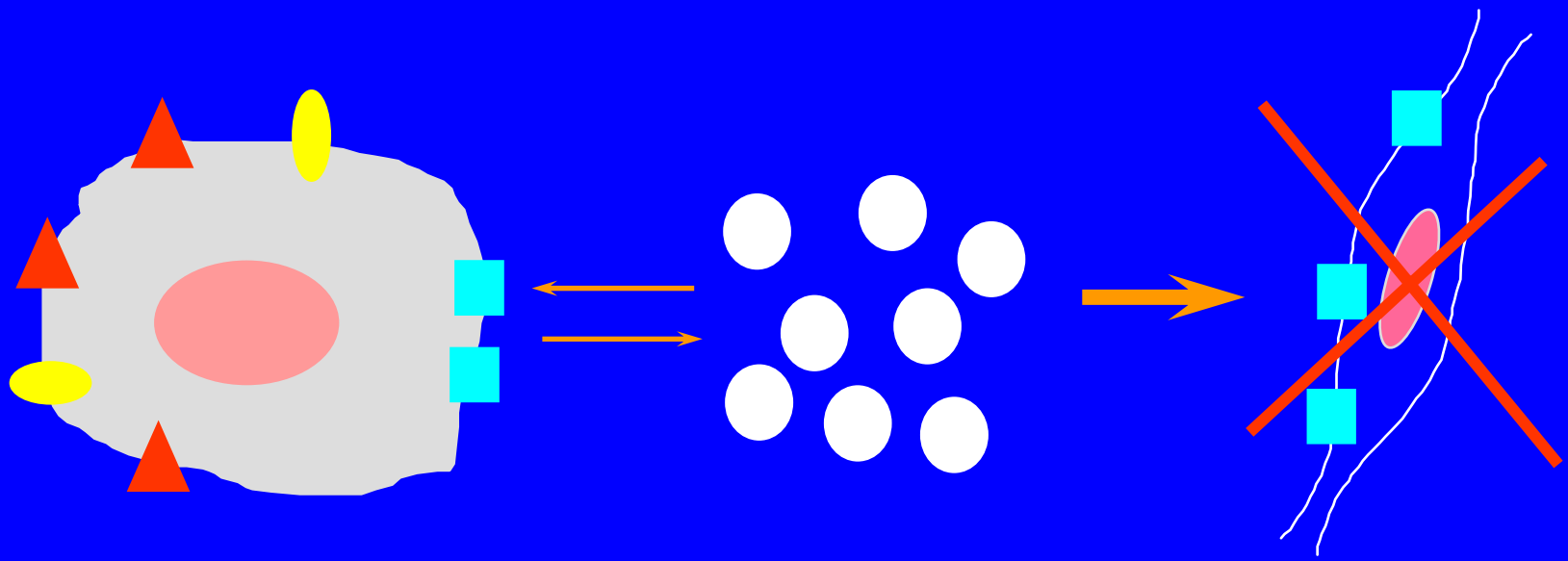


Halo naevus

Melanoma



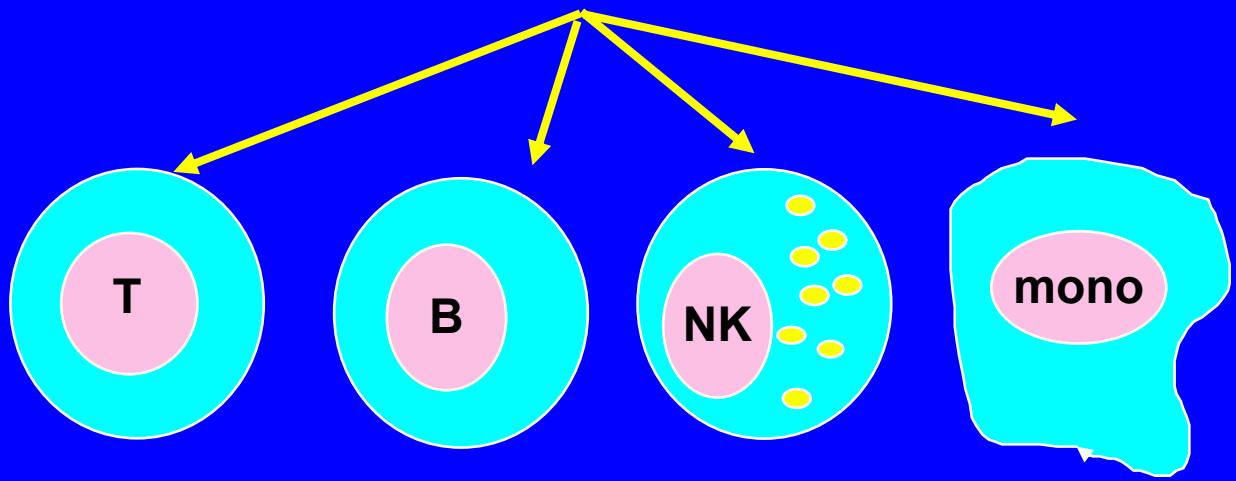
Paraneoplastic neurological disorders



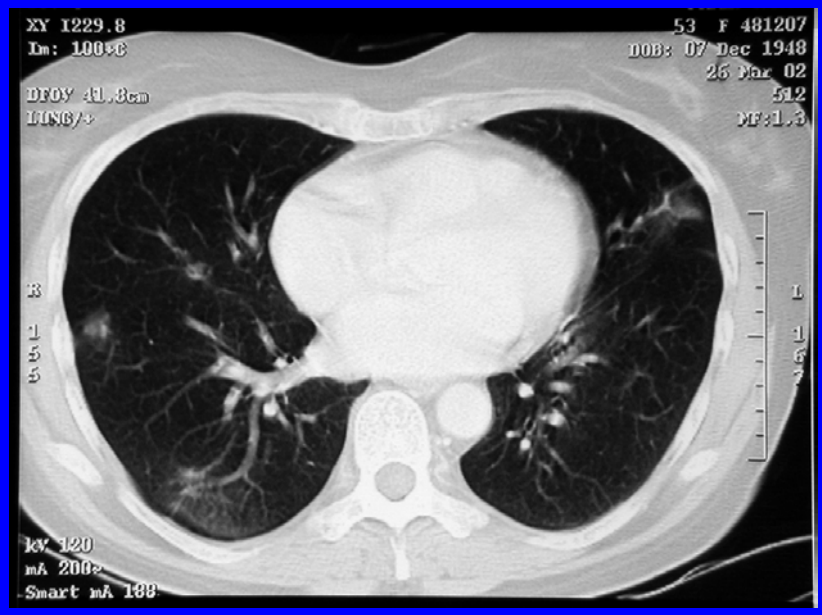
Death by neuronal damage
Tumor growth controlled by the immune response

Interleukin-2

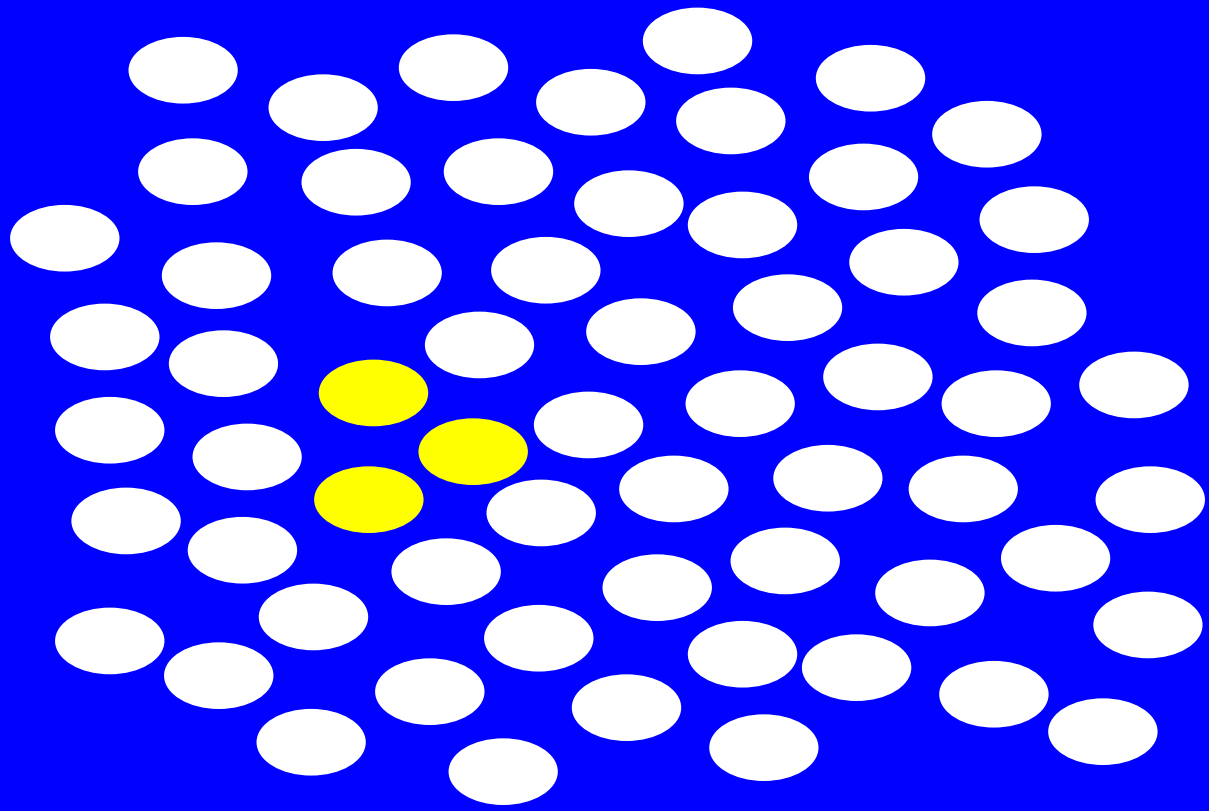
- Identified in 1976
- pleitropic cytokine : amplifies immune responses



Renal cell carcinoma : PR after Il-2/IFN treatment

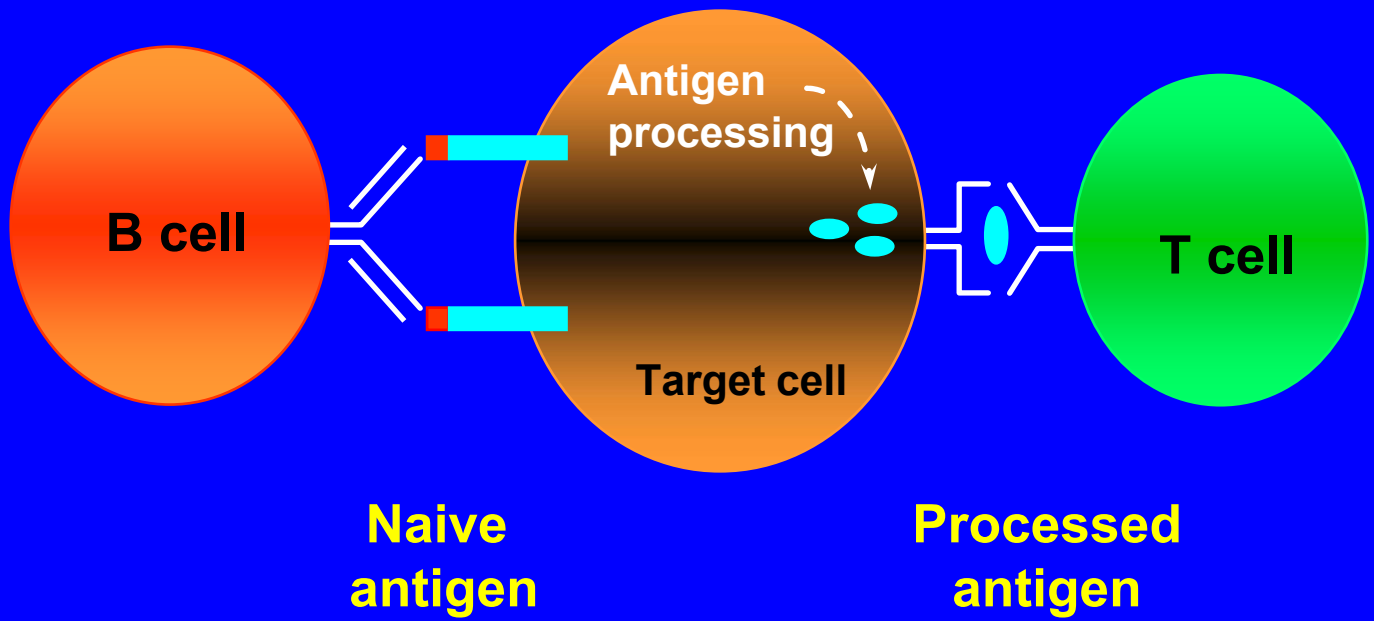


Towards selective immunotherapy?

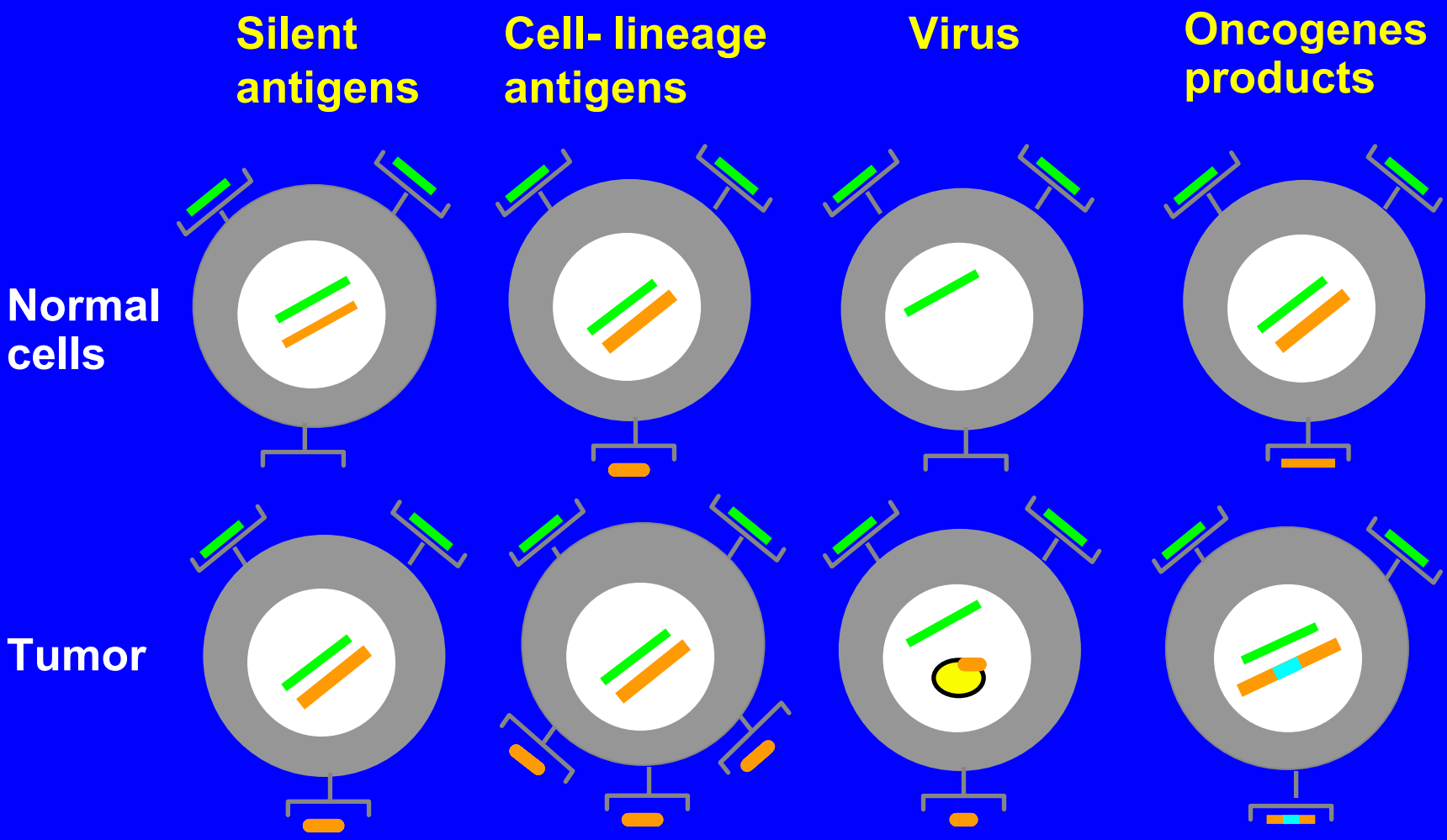


Antigen-specific response

How B cells and T cells recognise antigens

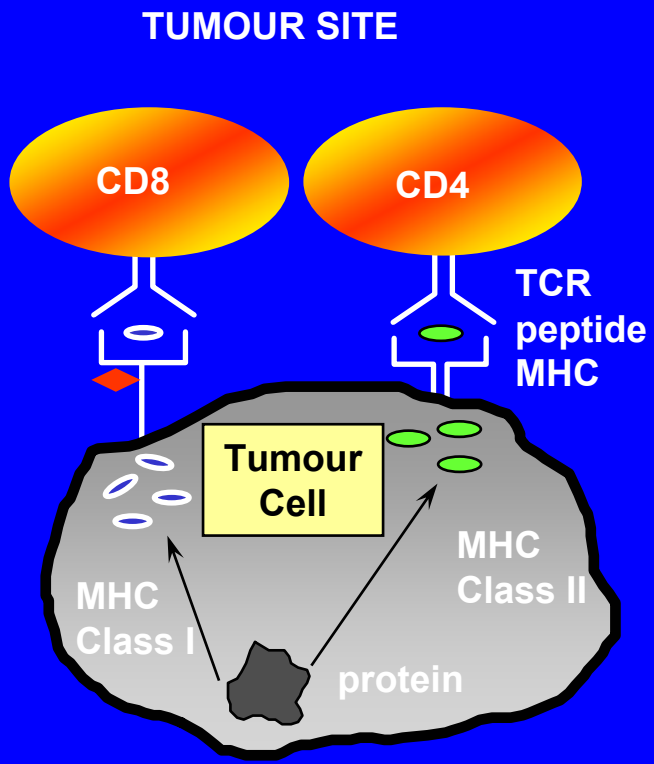


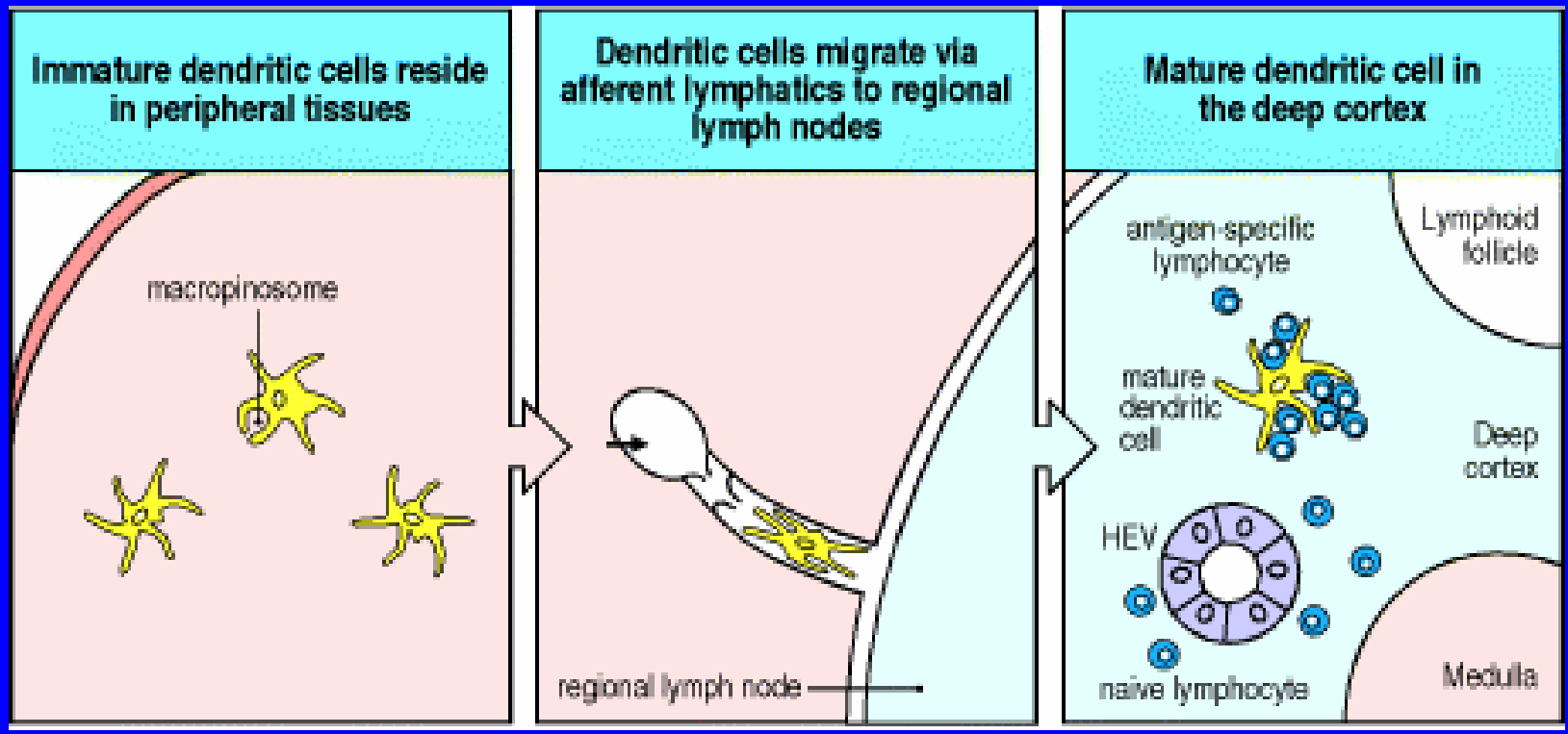
T cells recognize not only surface,
but also cytoplasmic and nuclear proteins



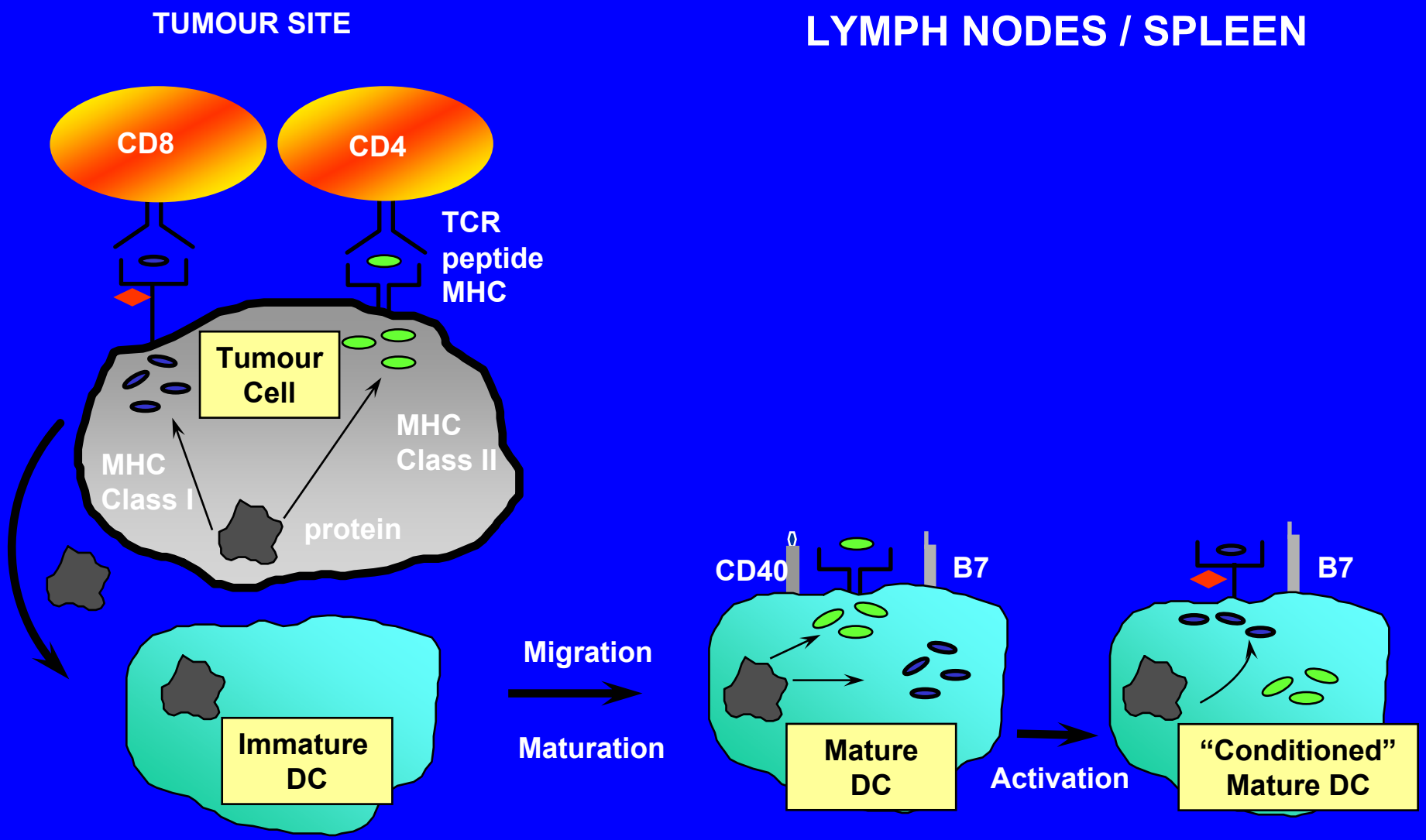
Ex:	MAGE	Tyrosinase	HPV16	p53, ras
	BAGE	Melan-A		bcr-abl
	GAGE	PSA		

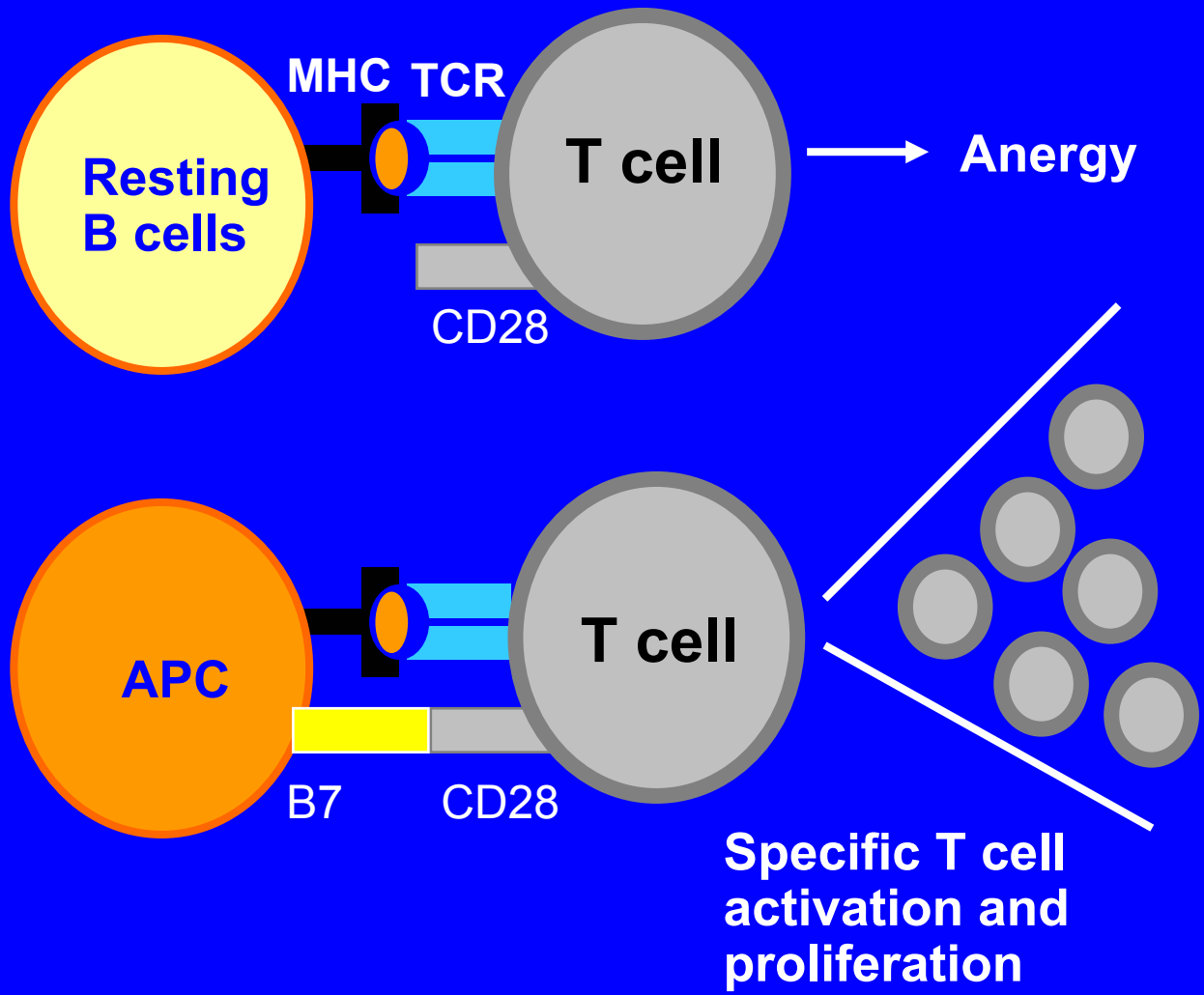
Generation of T cell-mediated immune responses to tumours



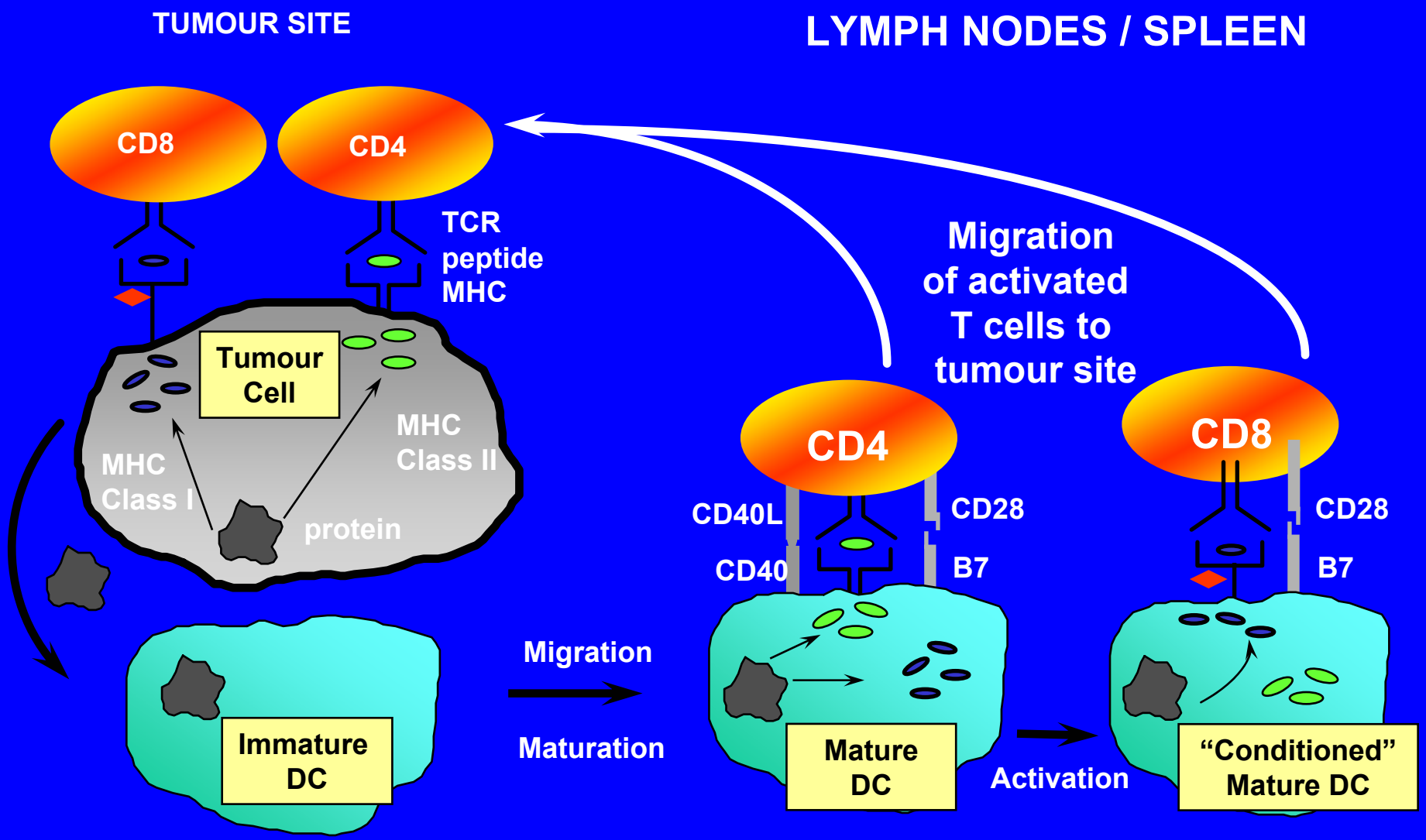

Immature dendritic cells reside in peripheral tissues
Dendritic cells migrate via afferent lymphatics to regional lymph nodes
Mature dendritic cell in the deep cortex
macropinosome
regional lymph node
antigen-specific lymphocyte
Lymphoid follicle
mature dendritic cell
Deep cortex
HEV
naive lymphocyte
Medulla

Generation of T cell-mediated immune responses to tumours

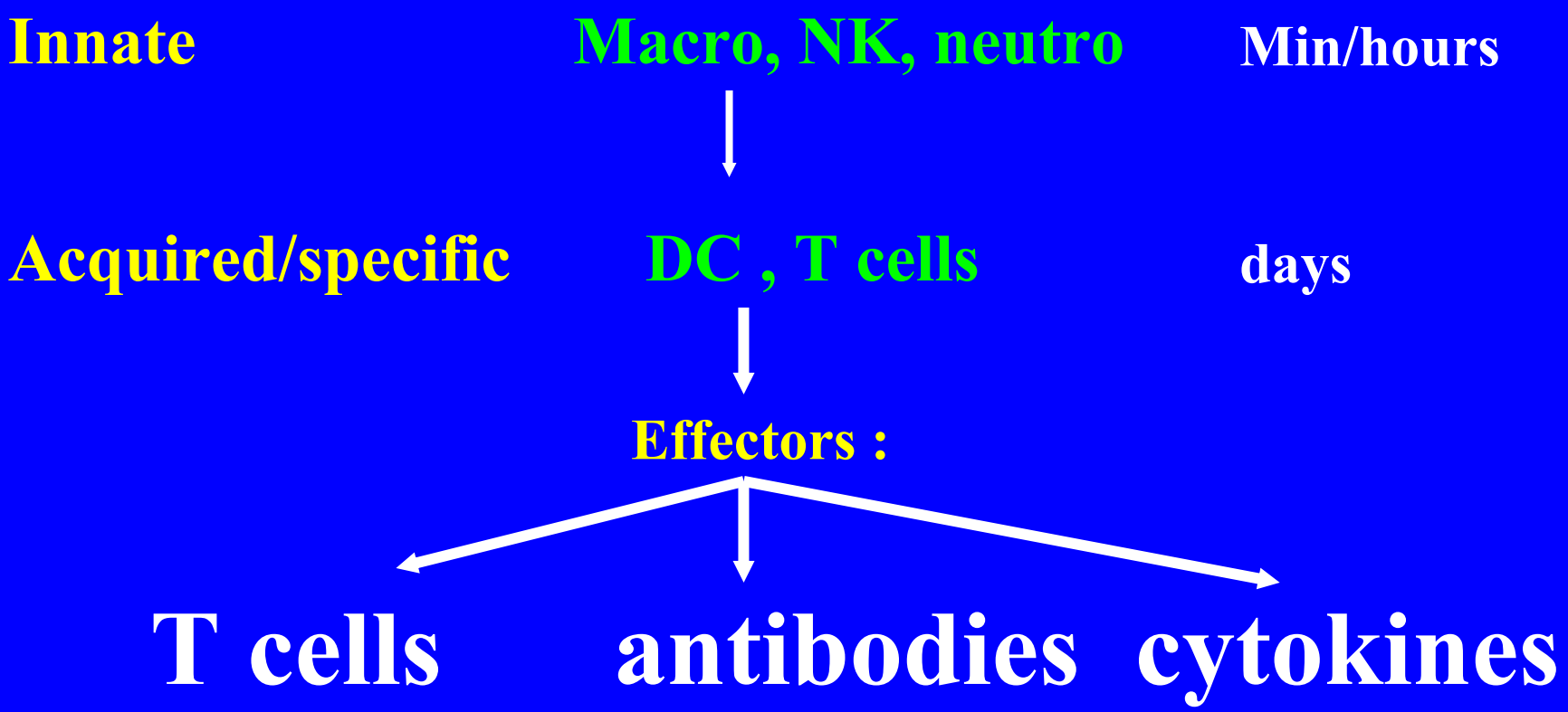



MHC
TCR
Resting
B cells
T cell
Anergy
CD28
APC
T cell
B7
CD28
Specific T cell
activation and
proliferation

Generation of T cell-mediated immune responses to tumours

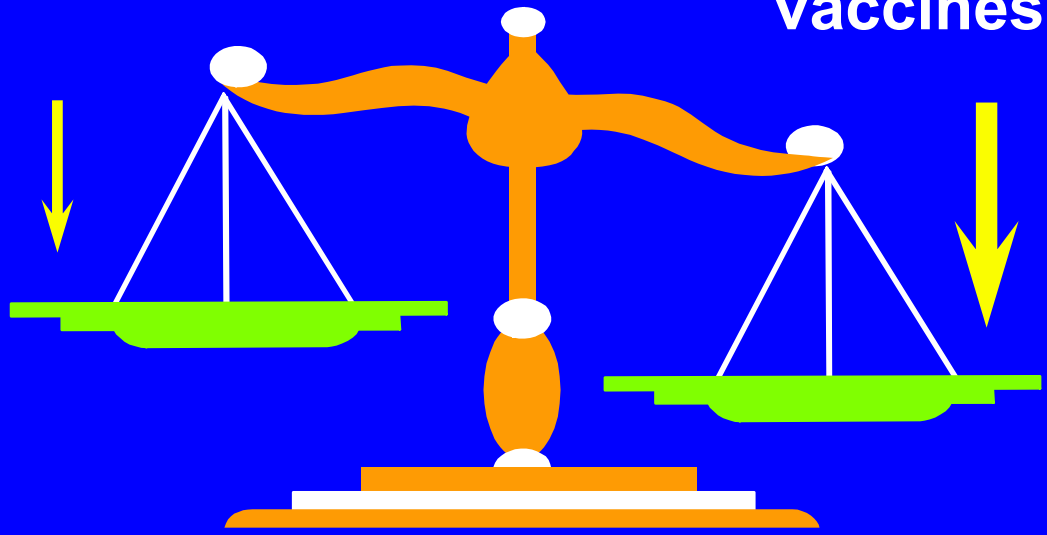


Immune responses : innate and acquired

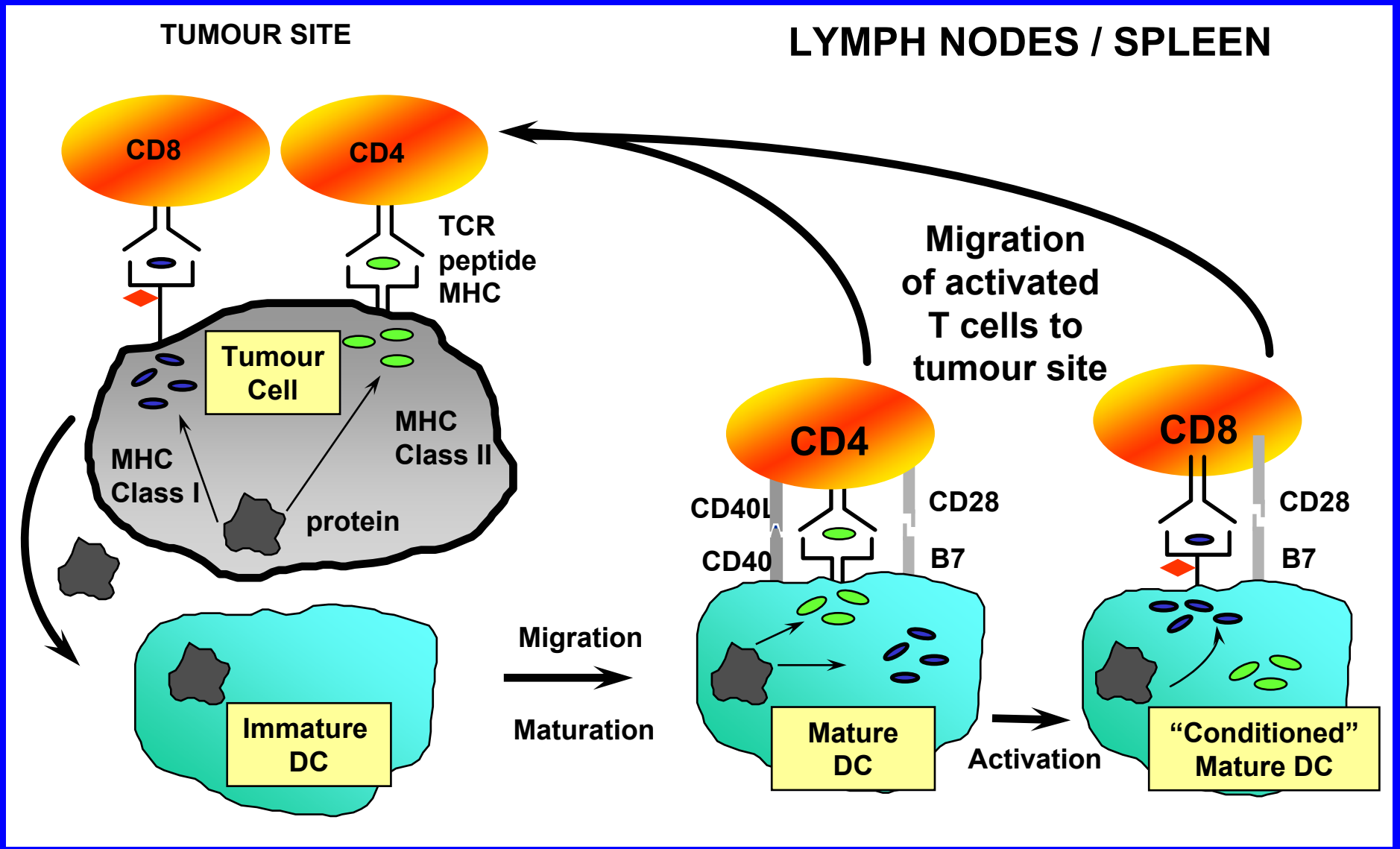


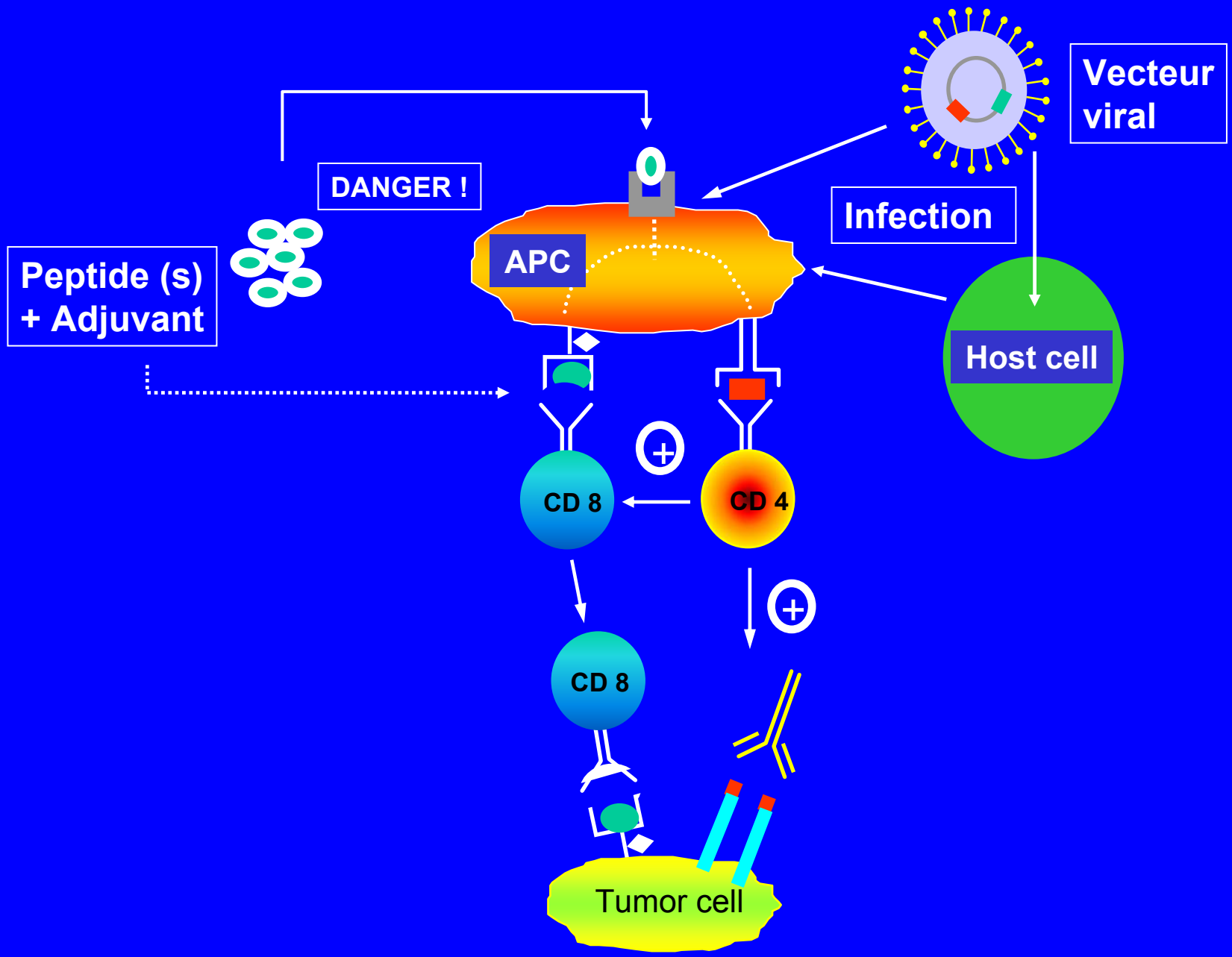
Immune escape

Immune response vaccines



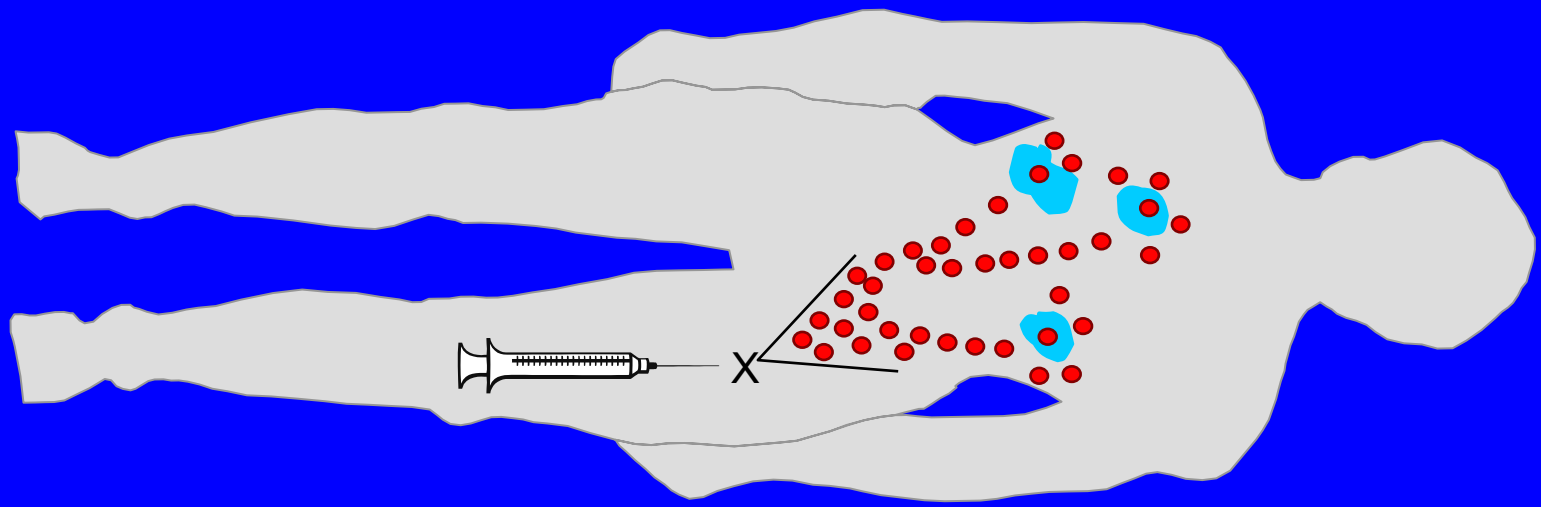
Generation of T cell-mediated immune responses to tumours



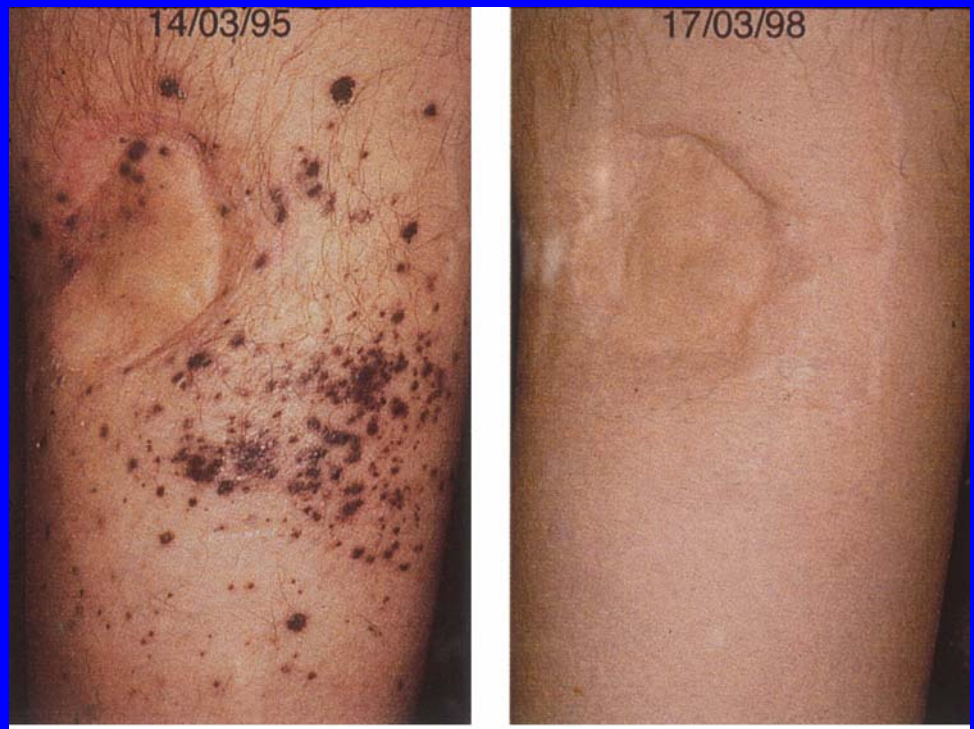

Vecteur viral
DANGER !
Infection
Peptide (s) + Adjuvant
APC
Host cell
CD 8
CD 4
CD 8
Tumor cell

Active Immunotherapy :

Inducing a selective immune response in vivo (antigen-specific)



Experimental Treatment: immunisation with MAGE-3 peptide



M. Marchand, et al. Int. J. Cancer 1999 ; 80 : 219-230

Responses

- skin
- lymph nodes
- lungs

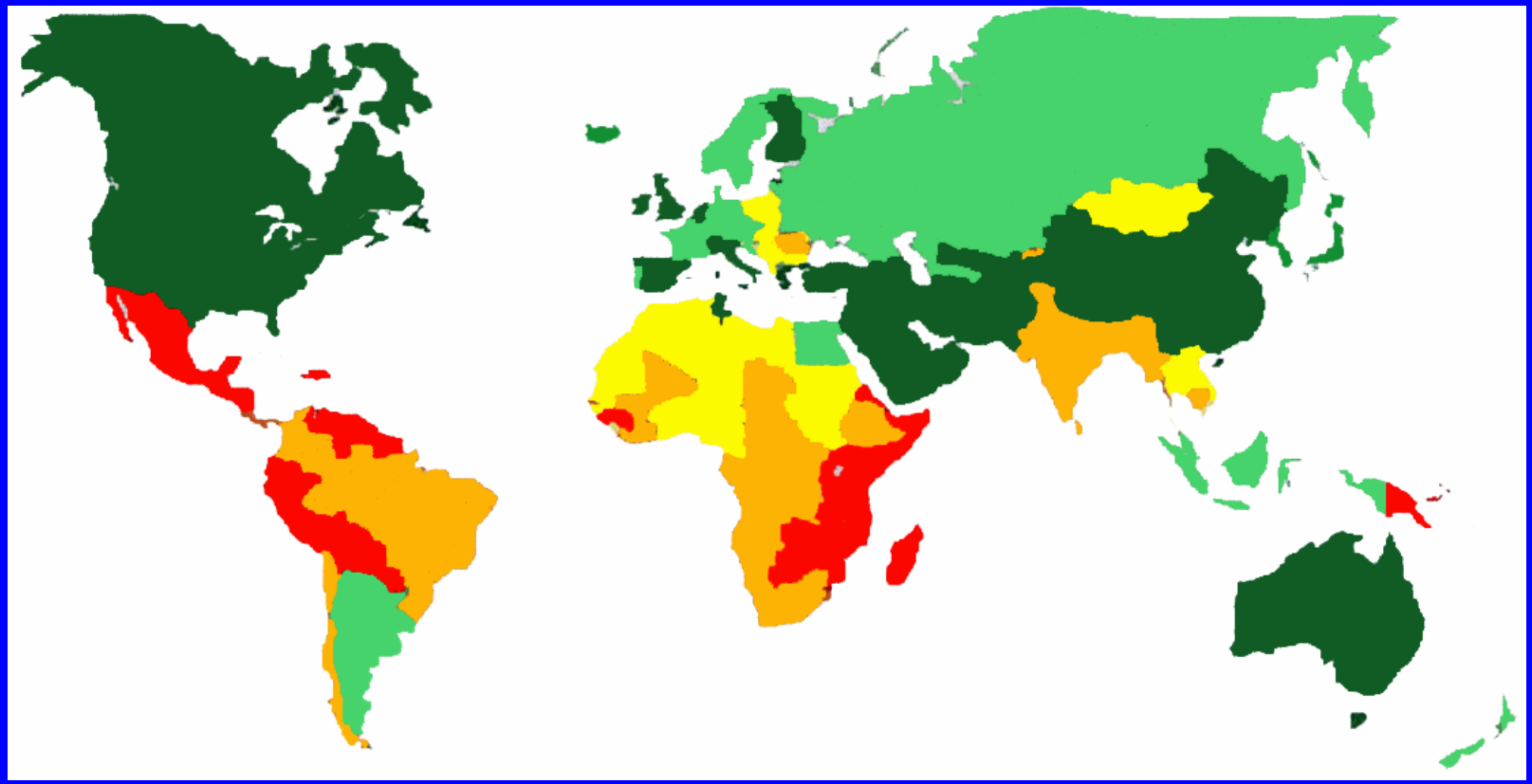
The case of cervical cancer:

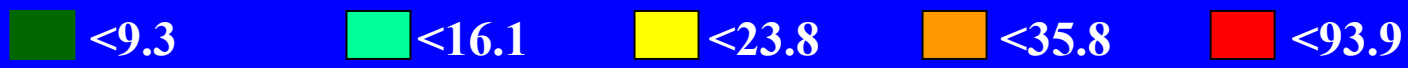
Therapeutic vaccines?

Prophylactic vaccines?

Incidence of cervix cancer in the world

The Lancet Oncology 2001, 2(9), 533-543

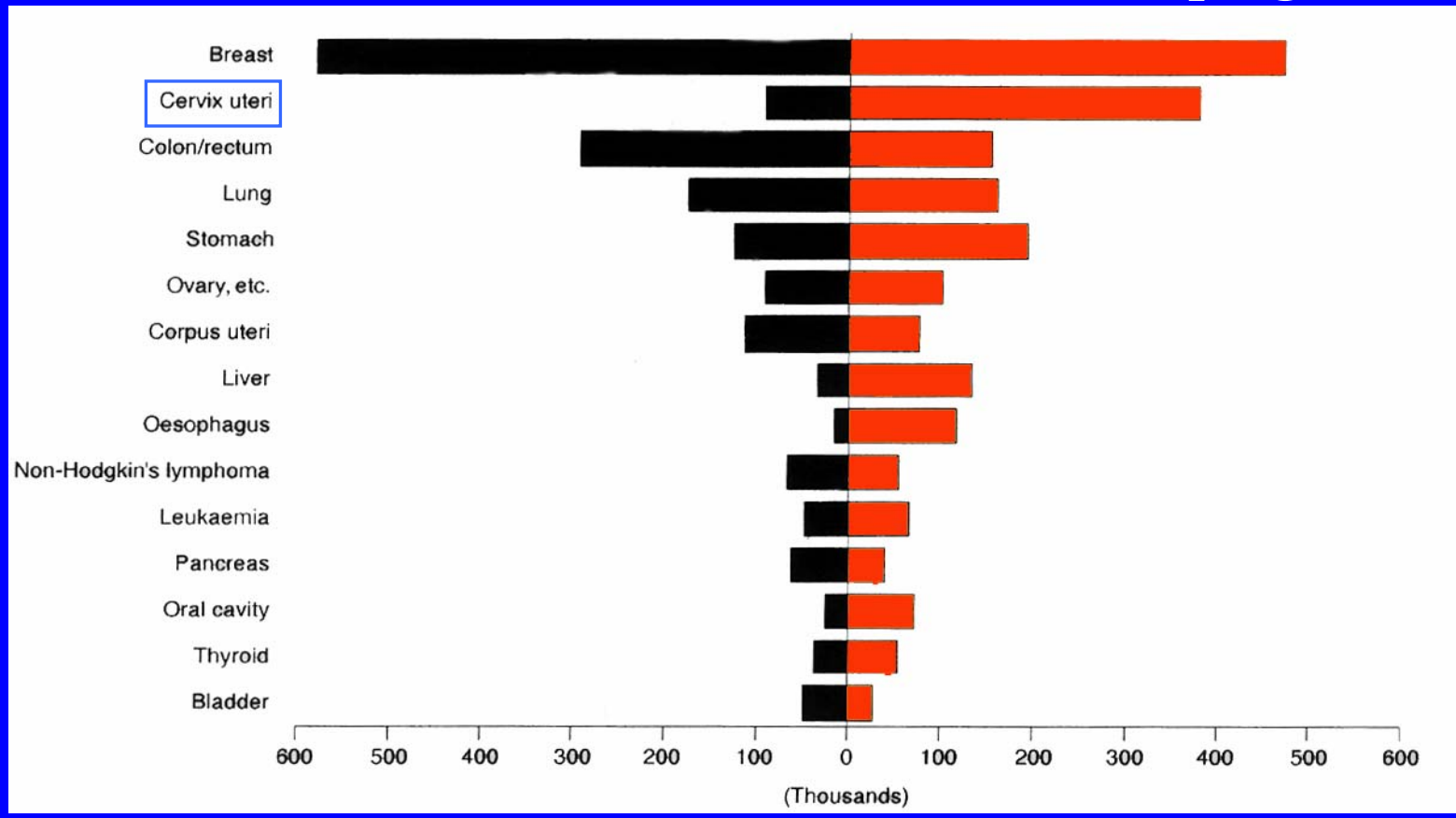




Cancers in females, 2000.

Eur J Cancer 2001, S4-S66

Developed **Developing**



500.000 new cases/year **250.000 deaths/year**

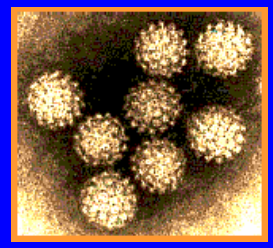
Causes of cervical cancer

- **Epidemiological studies :**
  - **number sexual partners,**
  - **age at first sexual intercourse,**
  - **sexual behaviors of the woman's male partner**

sexual transmission of an infectious agent → **HPV**

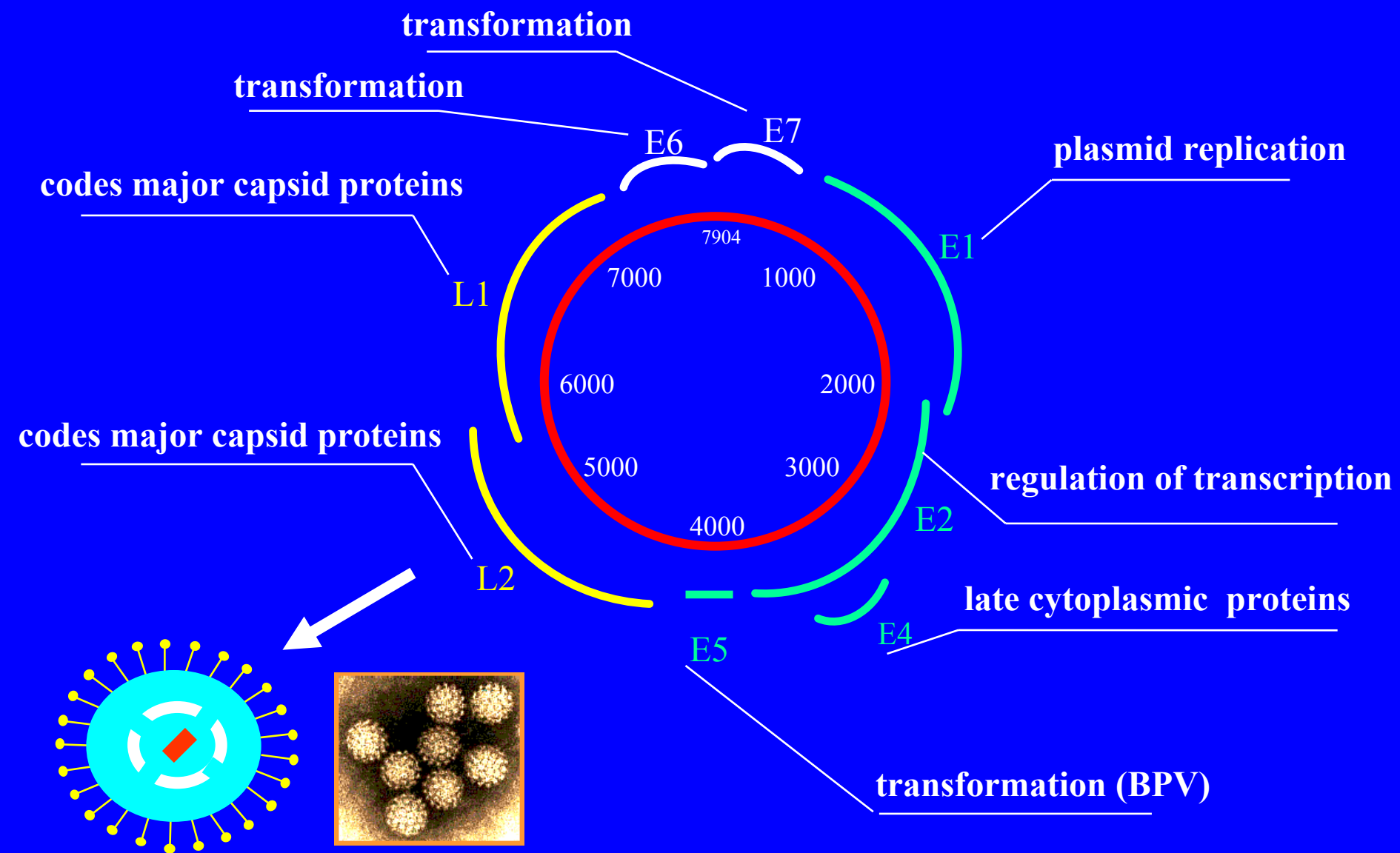
HPVs present in > 95 % of cervical cancers
= a necessary event

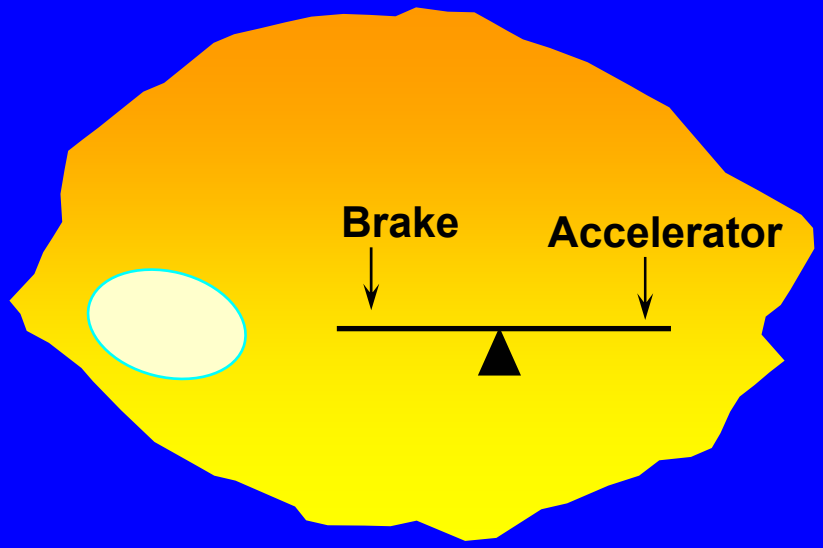
HPVs



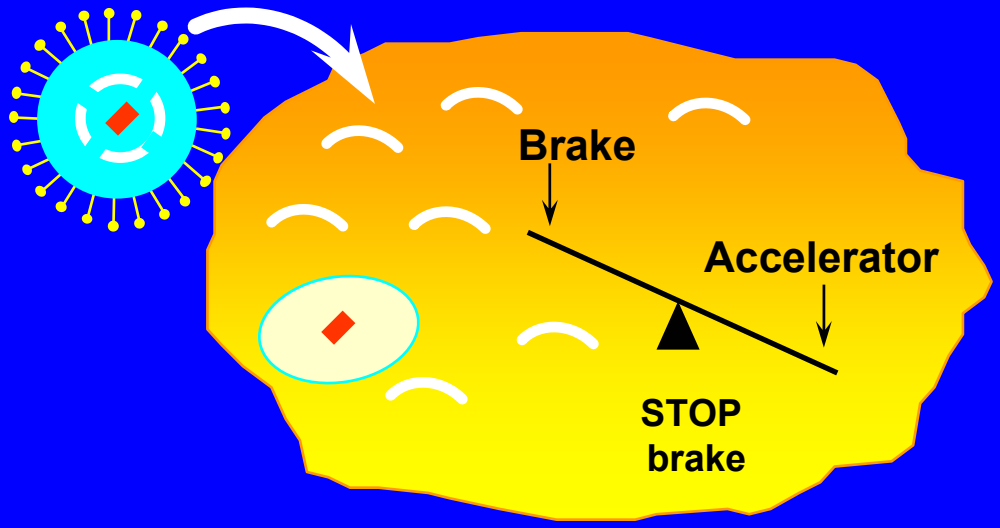
- **HPV = double strand DNA viruses (8000 bp)**
- **> 100 HPV types**
- **>40 can infect the anogenital tract**
- **High risk : HPV type 16, 18, 33, 45**
- **Low risk : HPV 6, 11**

HPV-16

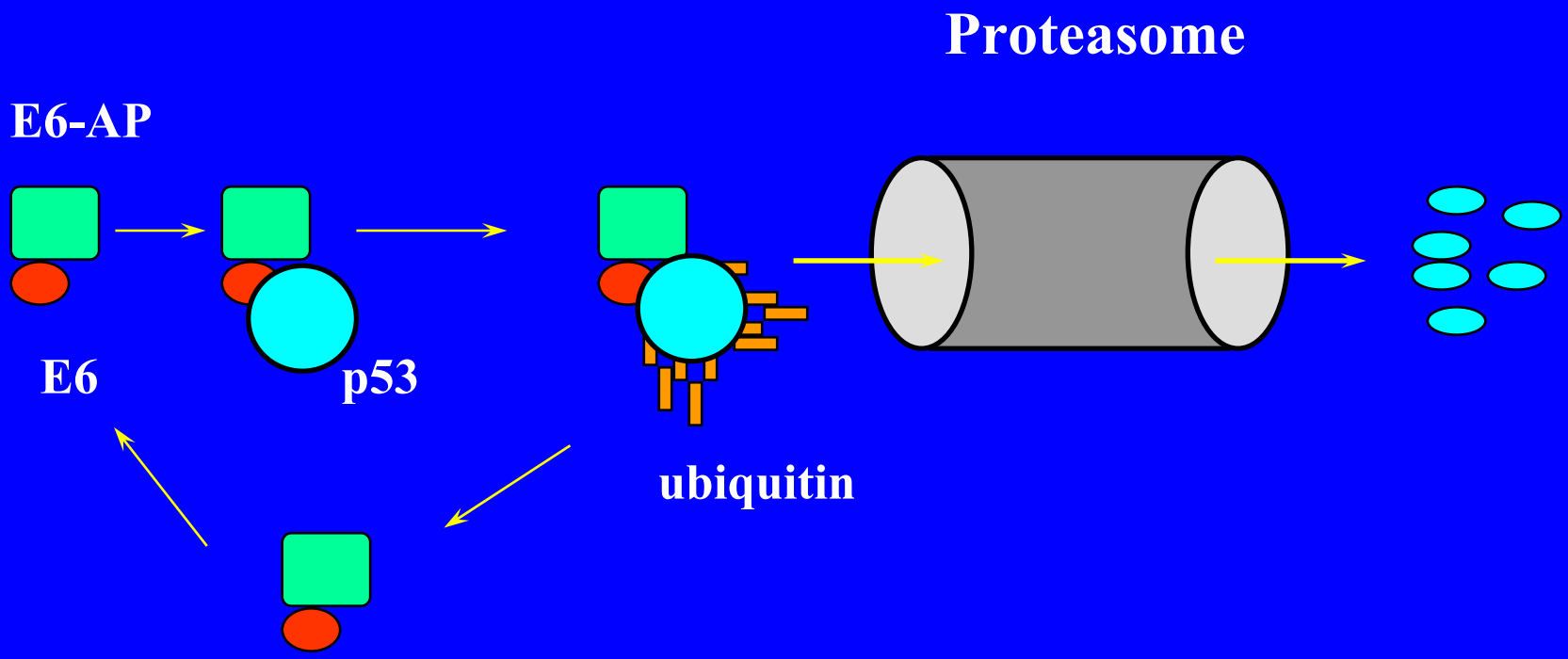

transformation
transformation
E6
E7
plasmid replication
codes major capsid proteins
L1
E1
7904
7000
1000
6000
2000
codes major capsid proteins
5000
3000
regulation of transcription
4000
E2
L2
late cytoplasmic proteins
E4
E5
transformation (BPV)



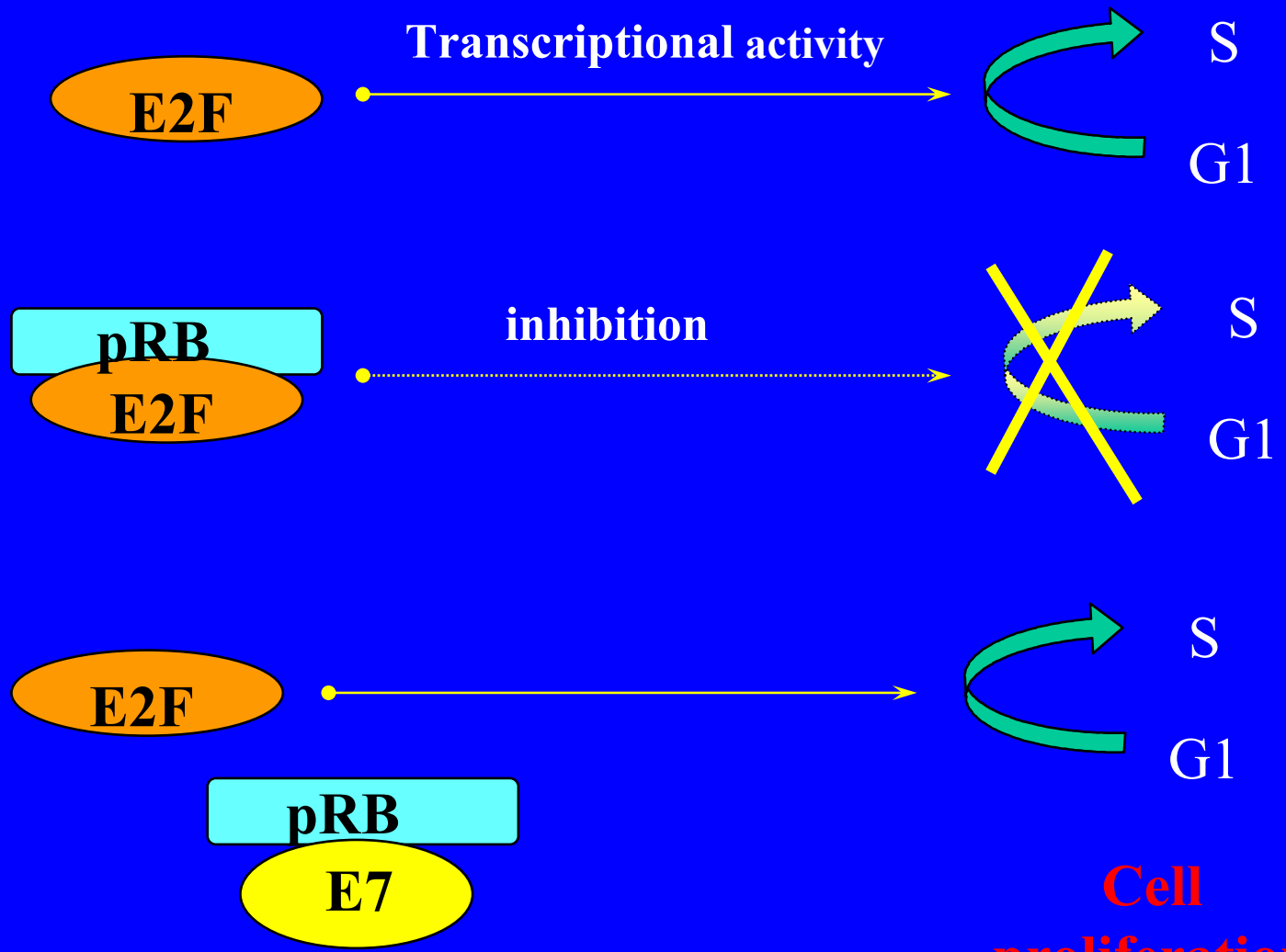
Epithelial cell



E6-dependent degradation of p53



Oncogenicity of HPV-16 E7



Immune responses against HPV

- Clinical evidence (natural history)
- Experimental evidence

Clinical evidence of an immune response against HPV

- Spontaneous regressions (> 90%) of most HPV infections (Franco EL, J Infect Dis 1999; 180: 1415)

- Immunodeficiency is associated with higher risk of HPV infection, CIN and cancer (AIDS and transplants) (Palefsky JM, JNCI 1999;91:226; M Frisch JNCI 2000; 92: 1500)

Clinical evidence of an immune response against HPV

- HIV + women (n=220) , compared to HIV- women (n=231), have a higher rate of persistent HPV infections (high-risk)

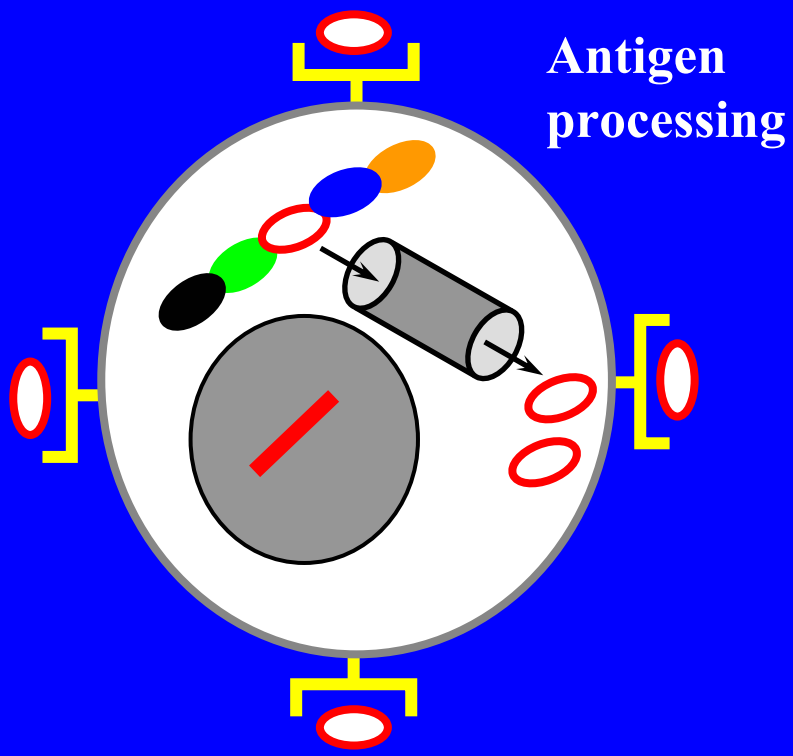
  N Engl J Med 1997; 337: 1343

- Persistent infection is a risk factor for dysplasia and cancer

  JNCI 1999;87:1365

Experimental evidence

1) Identification
of immunogenic peptides
derived from
E6, E7, and others



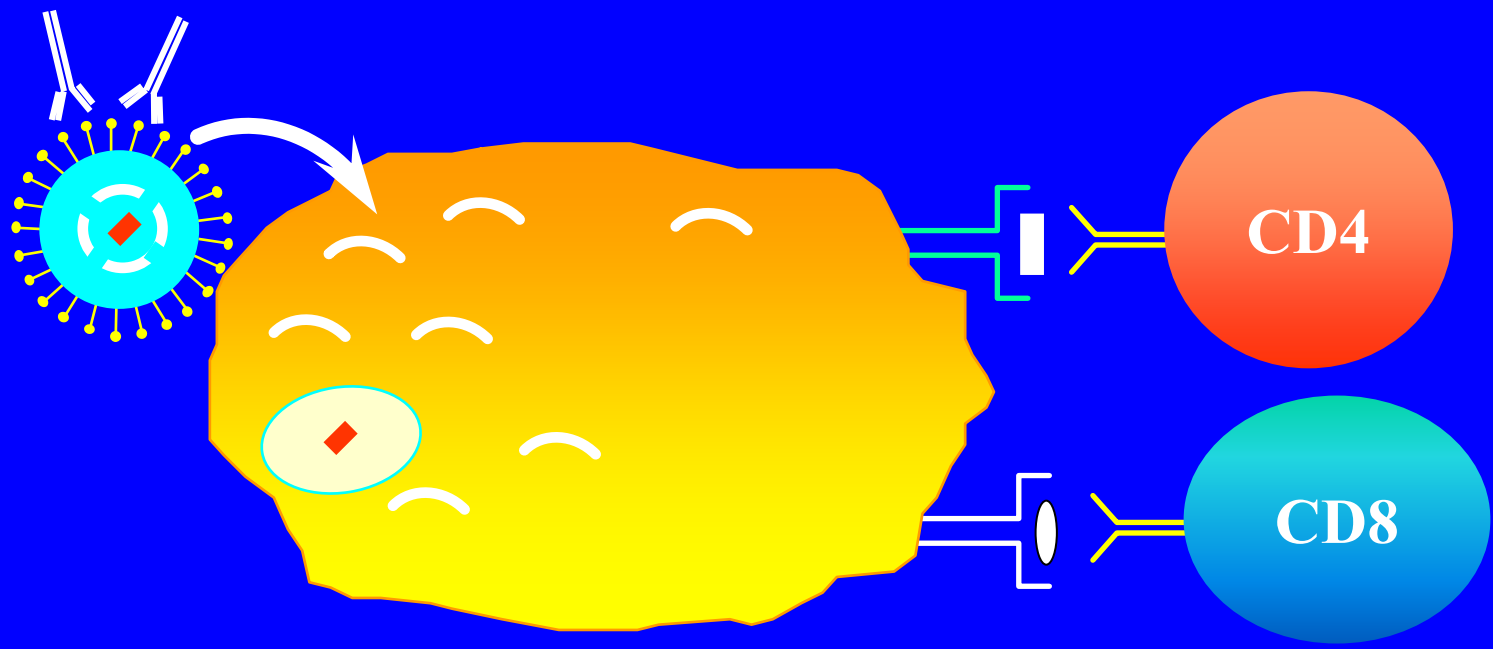
2) validated in animal models
and by analysis of spontaneous
and vaccine induced responses
in humans

PROPHYLACTIC

THERAPEUTIC

Before virus entry

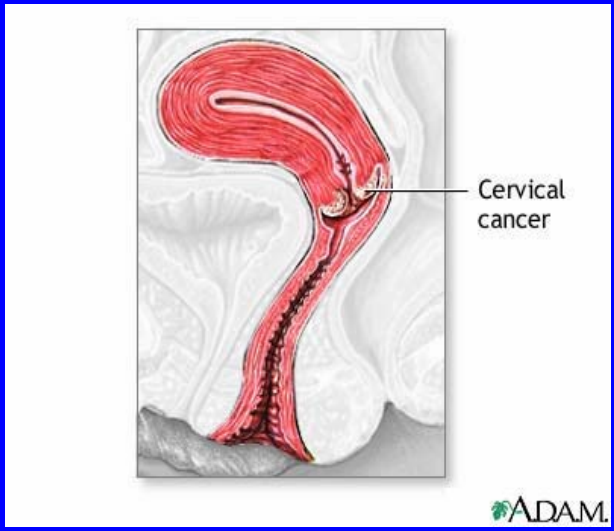
After

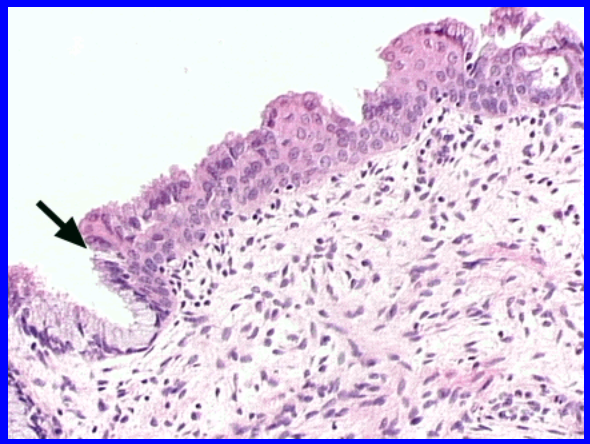


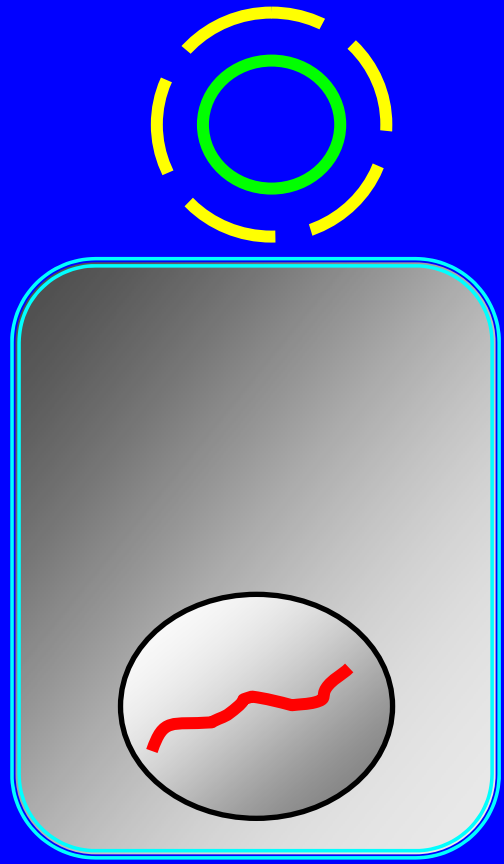
Antibodies

T Lymphocytes

Infection, CIN and cancer: where is the virus ?

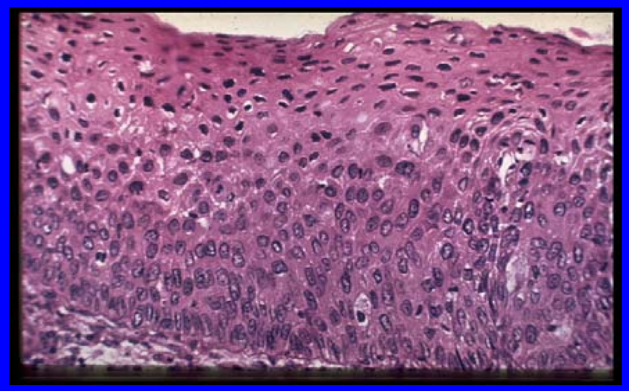




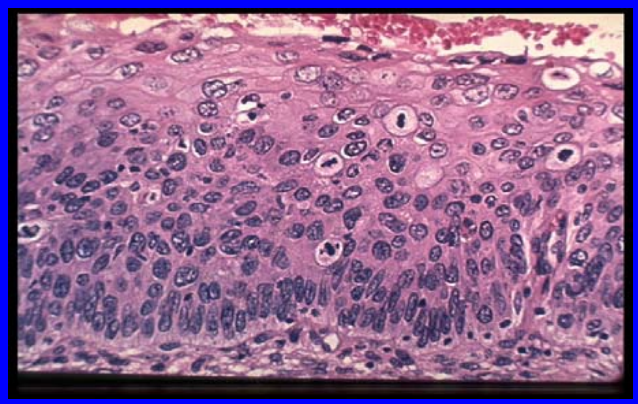


Infection, CIN and cancer: where is the virus?

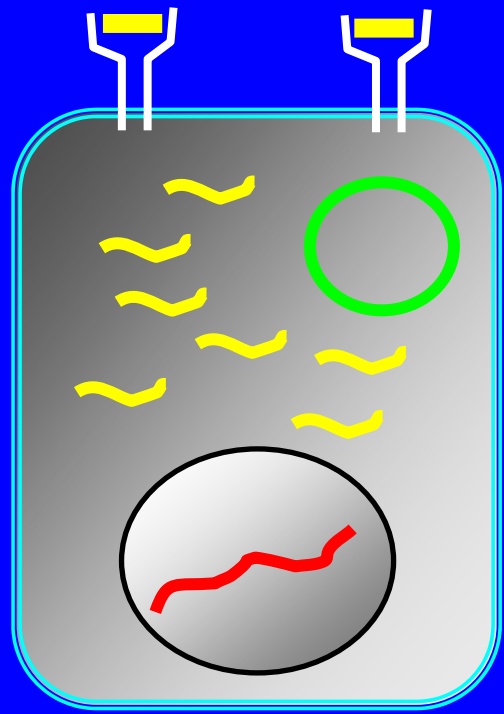
CIN 2



CIN3

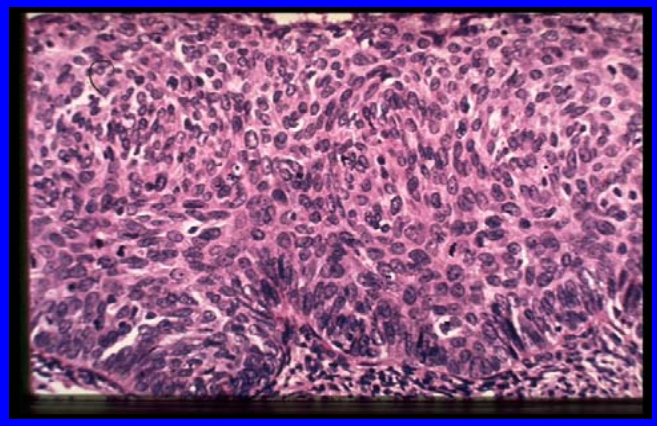


episomal

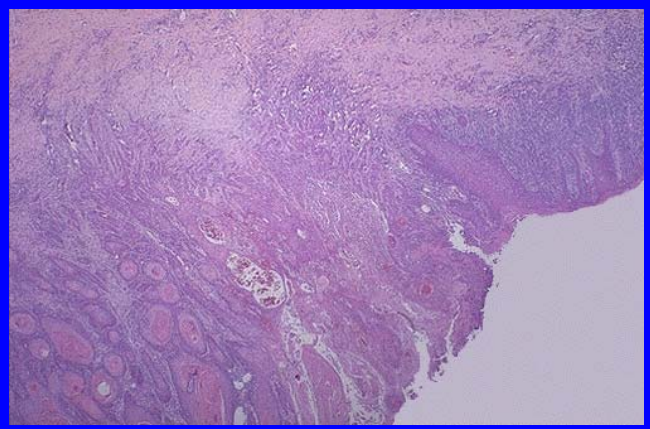


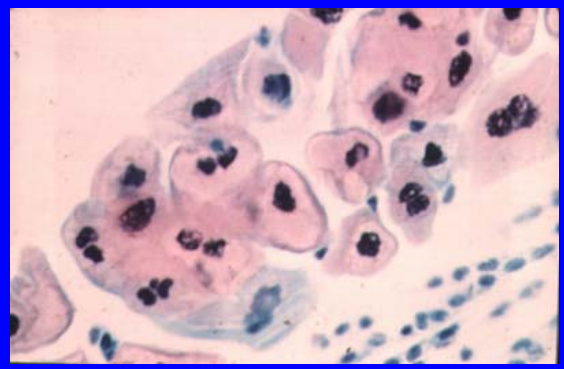
Infection, CIN and cancer: where is the virus?

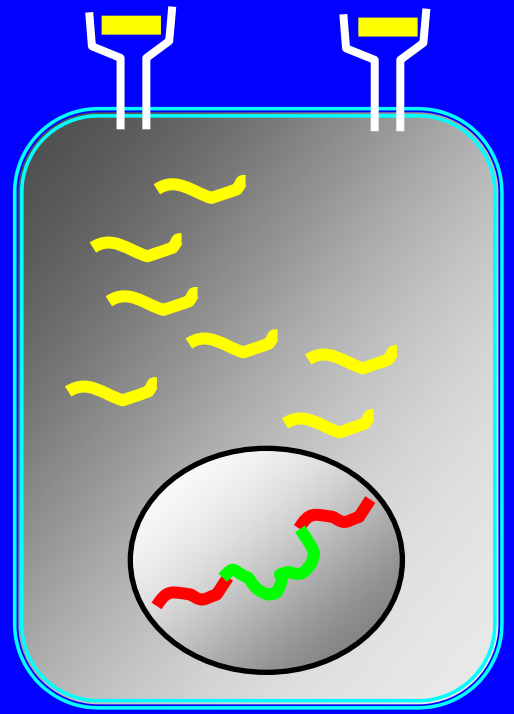
In situ carcinoma



Invasive cancer







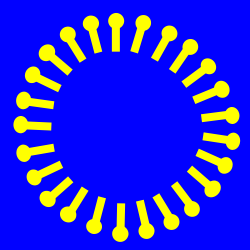
N Engl J Medicine 2002; 347: 1645

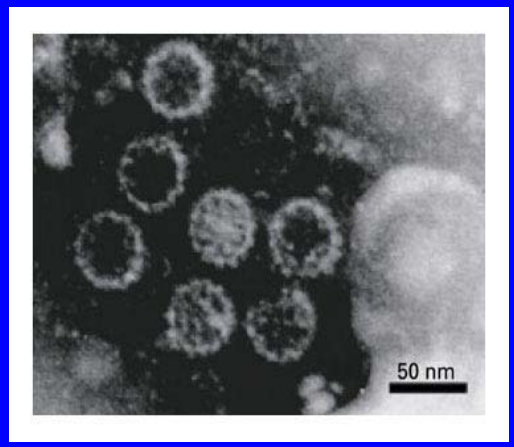
A controlled trial of a human papillomavirus type 16 vaccine

Laura A Koutzy et al ; Seattle

Prophylactic vaccine using VLP

- VLP = Virus like particules
  - No DNA ==> non-infectious
  - mimic natural structure : immunogenic
  - "empty virus"



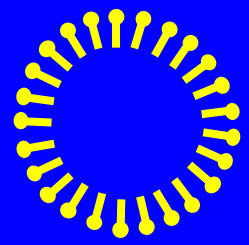


N Engl J Med 2002; 347: 1703, CP Crum

Mat Meth (1)

- Oct 1998-Nov 99,
  - 2392 young women from 16 centers
- 16-23 years of age,
- no prior abnormal Papanicolaou smear
- ≤ 5 male sex partners

Mat Meth (2)



- HPV-16 L1 VLP = highly purified

(> 97 %) VLP of the L1 capsid of HPV 16

- expressed in yeast (saccharomyces cerevisiae)
- Vaccine (dose) :

40 µg HPV16-VLP + 225 µg aluminium = 0.5 ml

- Placebo : 225 µg aluminium = 0.5 ml
- 3 injections i-m J0, Month 2, month 6

Immunogenicity

Month 7 : Titer of HPV-16 antibodies

- Placebo < 6 mMU/ml (all values < 6)
- Vaccine 1519 mMU/ml (1370-1660)

Day 0 for positive individuals : 25.7 (22-29)

Primary end-point :

reduction of
persistent HPV-16 infection

Natural History HPV infection and cervical carcinogenesis

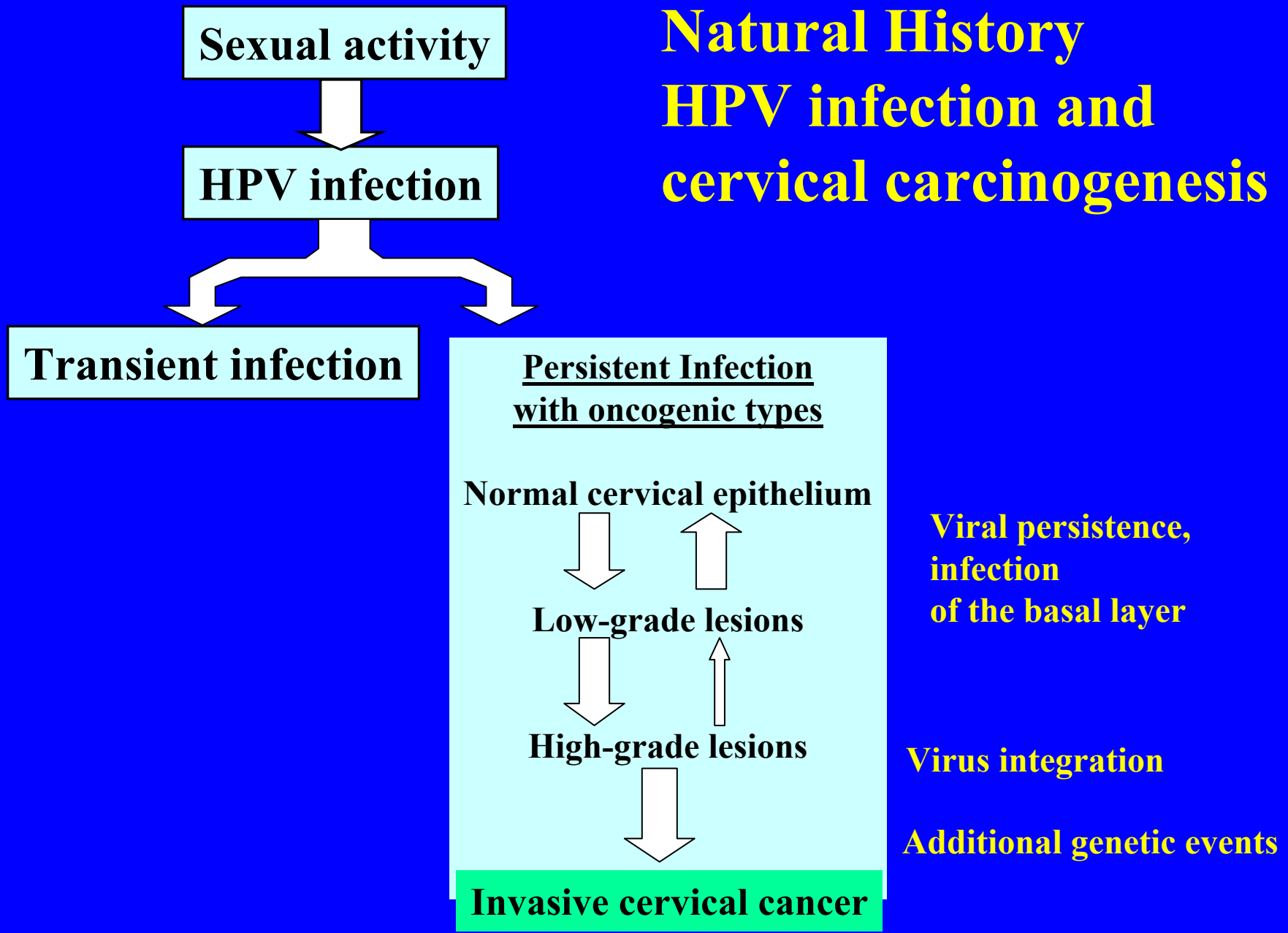


TABLE 3. EFFICACY ANALYSES OF A HUMAN PAPILLOMAVIRUS TYPE 16 (HPV-16) L1 VIRUS-LIKE–PARTICLE VACCINE.

TYPE OF ANALYSIS	END POINT	HPV-16 VACCINE				PLACEBO				OBSERVED EFFICACY (95% CI)*	P VALUE
		NO. OF WOMEN	CASES OF INFECTION	WOMAN-YR AT RISK	INFECTION RATE PER 100 WOMAN-YR AT RISK	NO. OF WOMEN	CASES OF INFECTION	WOMAN-YR AT RISK	INFECTION RATE PER 100 WOMAN-YR AT RISK		
					%				%	%	
Primary per-protocol efficacy analysis†	Persistent HPV-16 infection	768	0	1084.0	0	765	41	1076.9	3.8	100 (90–100)	<0.001
Efficacy analysis including women with general protocol violations‡	Persistent HPV-16 infection	800	0	1128.0	0	793	42	1109.7	3.8	100 (90–100)	—§
Secondary per-protocol efficacy analysis†	Transient or persistent HPV-16 infection	768	6	1084.0	0.6	765	68	1076.9	6.3	91.2 (80–97)	—§

*CI denotes confidence interval.

†The per-protocol population included women who received the full regimen of study vaccine and who were seronegative for HPV-16 and negative for HPV-16 DNA on day 0 and negative for HPV-16 DNA at month 7 and in any biopsy specimens obtained between day 0 and month 7; who did not engage in sexual intercourse within 48 hours before the day 0 or month 7 visit; who did not receive any nonstudy vaccine within specified time limits relative to vaccination; who did not receive courses of certain oral or parenteral immunosuppressive agents, immune globulin, or blood products; who were not enrolled in another study of an investigational agent; and who had a month 7 visit within the range considered acceptable for determining the month 7 HPV-16 status.

‡The population includes women who received the full regimen of study vaccine and who were seronegative for HPV-16 and negative for HPV-16 DNA on day 0 and negative for HPV-16 DNA at month 7 and in any biopsy specimens obtained between day 0 and month 7.

§P values were calculated only for the analysis addressing the primary hypothesis.

Placebo group : 41 events!

31 persistent HPV-16 infections

5 HPV16 CIN-1

4 HPV16 CIN-2

1 HPV16 DNA on the last visit before lost to follow-up

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No CIN for the 33 transient HPV16 positive individuals

Conclusion (1)

First prophylactic vaccine with high efficacy; protects from

- HPV16-related pre-invasive disease (100%)
- persistent HPV16 infection (100%)
- transient HPV16 infection (91%)

- Prevents HPV16 from residing in the genital tract ==> prevents infection of sexual partners

Conclusion (2) Unresolved issues

- **Duration of protection**

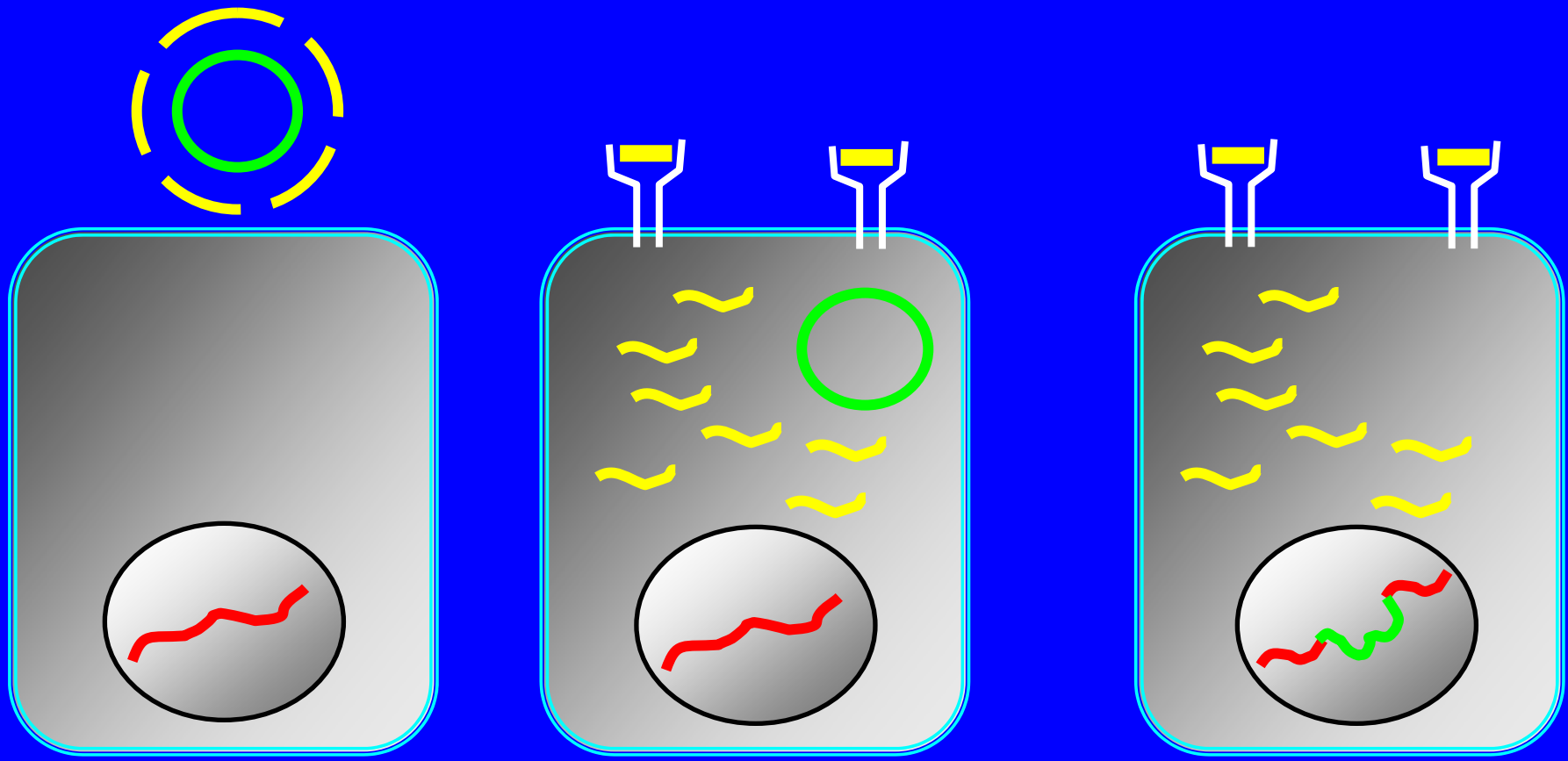
median follow-up 17 months

Conclusion (3) Unresolved issues

- **Are L1 VPL enough?**

- **Do we need a "therapeutic" component in the vaccine ?**

In other words a T cell response against E6/E7



Rapid entry of the virus

Conclusion (4) Unresolved issues

HPV 16 is not enough

- **Highly specific protection was achieved with HPV16 L1 VLP**

CIN not associated with HPV-16 infection:

Placebo 22 vaccine 22

Conclusion (5) Unresolved issues

Prevention against several HPV types is warranted (16, 18, 31, 33, 45)

- **Projection :**
  - **reduction of 85-90% of cervical cancer**
  - **reduction of > 50% of abnormal smears**

BUT

Conclusion (6) Unresolved issues

- **Is it possible to achieve such an efficacy against 5 HPV types ?**
- **Efficient vaccines may induce the emergence of other high risk HPV types?**

Conclusion (7) Unresolved issues

What is the target population?

- **young women before sexual activity ?**
  - **> 10 years to see a reduction in cancer incidence**
- **any women?**
- **Women and men before sexual activity?**
- **Any women and men?**

Difficult issues : feasibility, cost...

Hepatitis B and liver cancer

Taiwan :
20% are HBsAg+
1984: vaccination of children if HBsAg + mothers

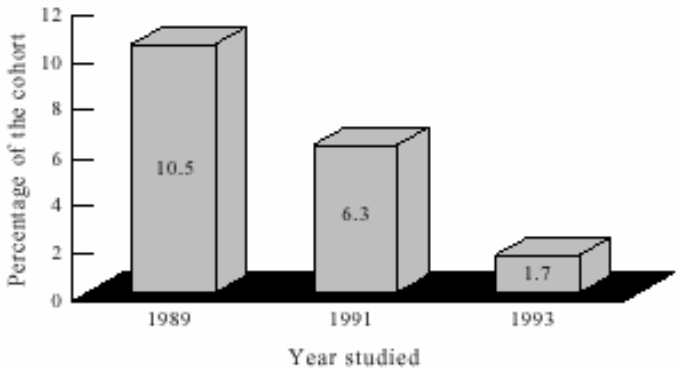


Fig. 1. Prevalence of HBsAg among three cohorts of children aged 6 years during the early years of the HBV vaccination programme. Reproduced from Ref. [14] with permission of University of Chicago Press.

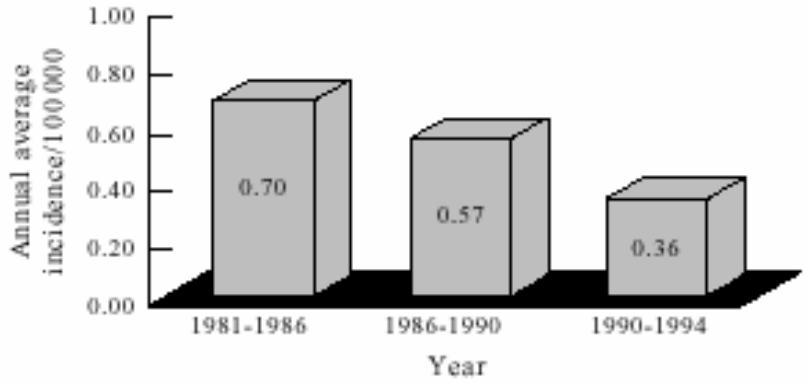
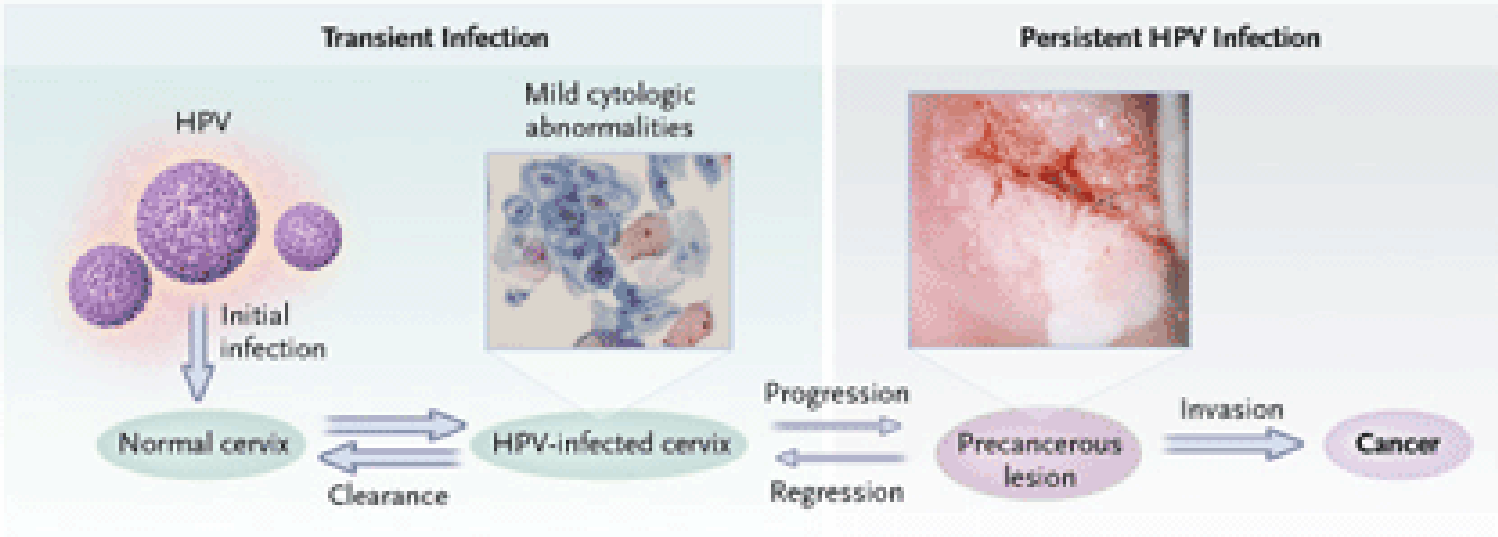


Fig. 3. Average annual incidence of hepatocellular carcinoma in children aged 6–14 years before and after the start of the HBV vaccination programme. Adapted from Ref. [16].

Prevalence of HBsAg children

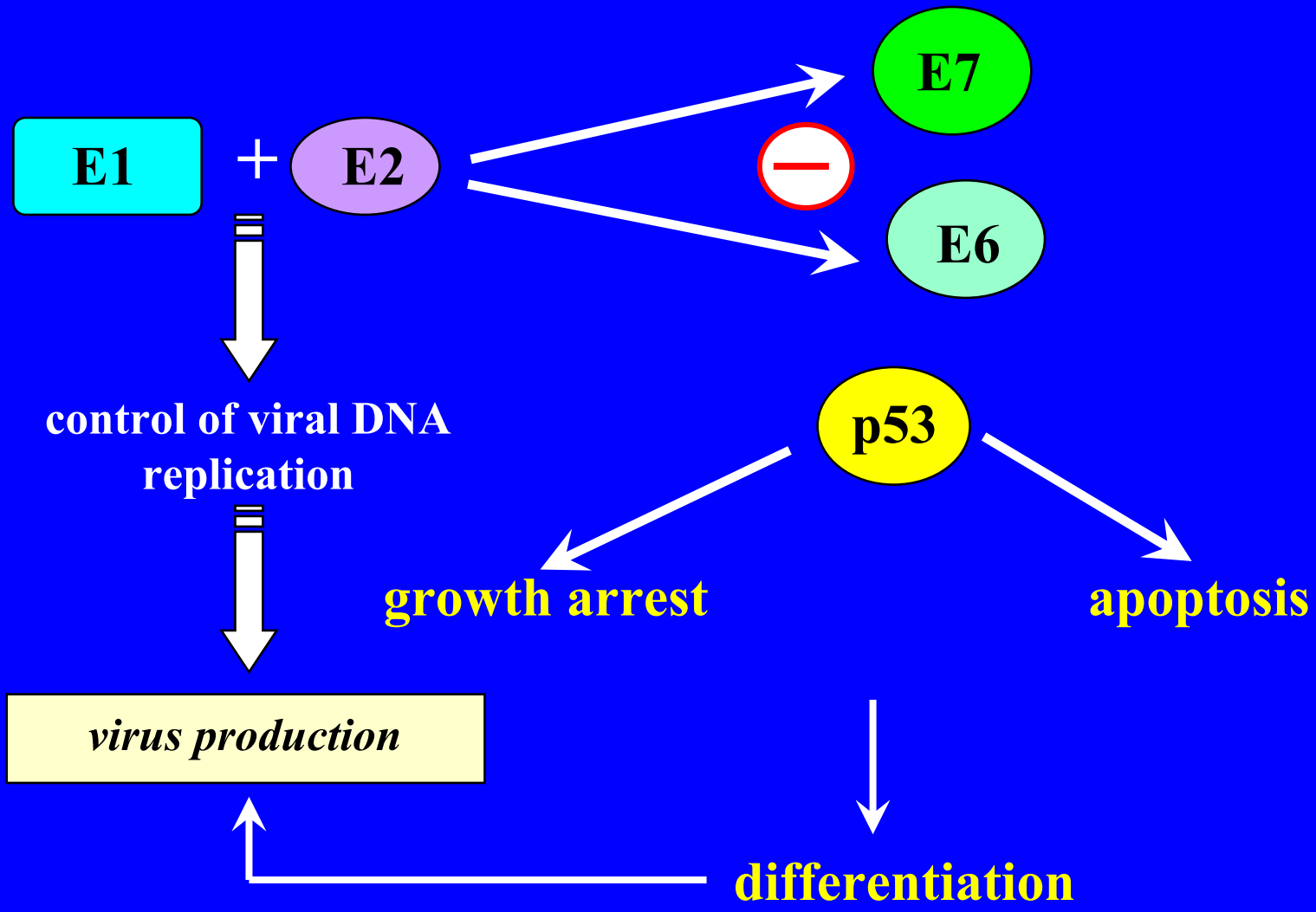
Liver cancer incidence children < 14 year-old

Natural History of HPV infection and cervical carcinogenesis

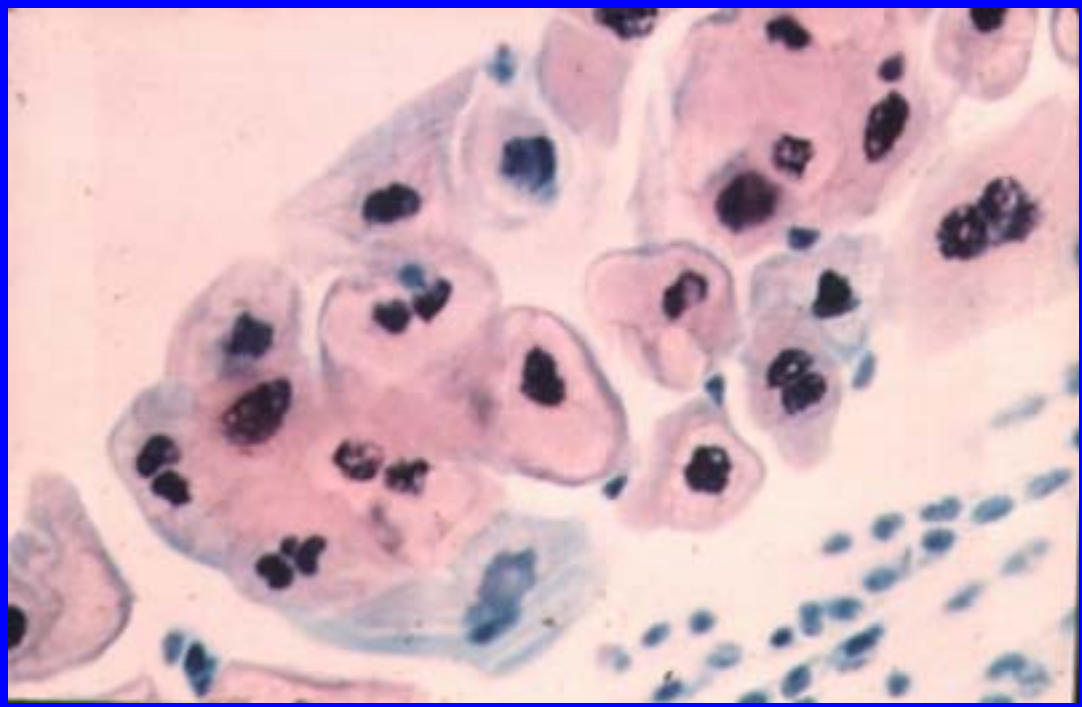


N Engl J Med 2003; 348: 489 TC Wright and M Schiffman

Condyloma : no viral integration



HPV 16: in situ hybridisation



Carcinoma=Integration of viral DNA