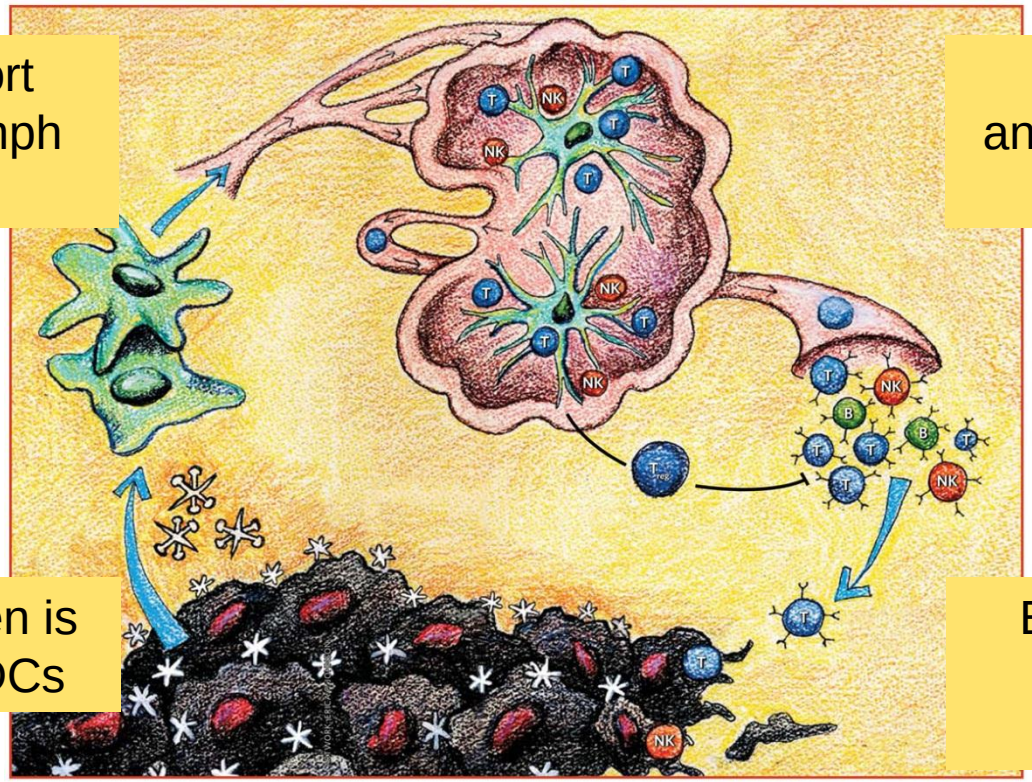
Cancer Immunotherapy

Henning Walczak

Basic features of a 'spontaneous' anti-tumour T-cell response

DCs transport antigen to lymph nodes



DCs activate antigen-specific T-cells

Tumour antigen is captured by DCs

Effector T-cells migrate to the tumour

Mellman 2006

Case History:

Previously healthy woman, 53 years old

03-03-97: awoke dizzy

- severe vertigo
- unintelligible speech
- truncal and appendicular ataxia

07-03-97: unable to sit, stand, use hands

Correct diagnosis:

Breast Cancer

Paraneoplastic cerebellar degeneration (PCD)

Case History:

Previously healthy woman, 53 years old

03-03-97: awoke dizzy

- severe vertigo
- unintelligible speech
- truncal and appendicular ataxia

07-03-97: unable to sit, stand, use hands

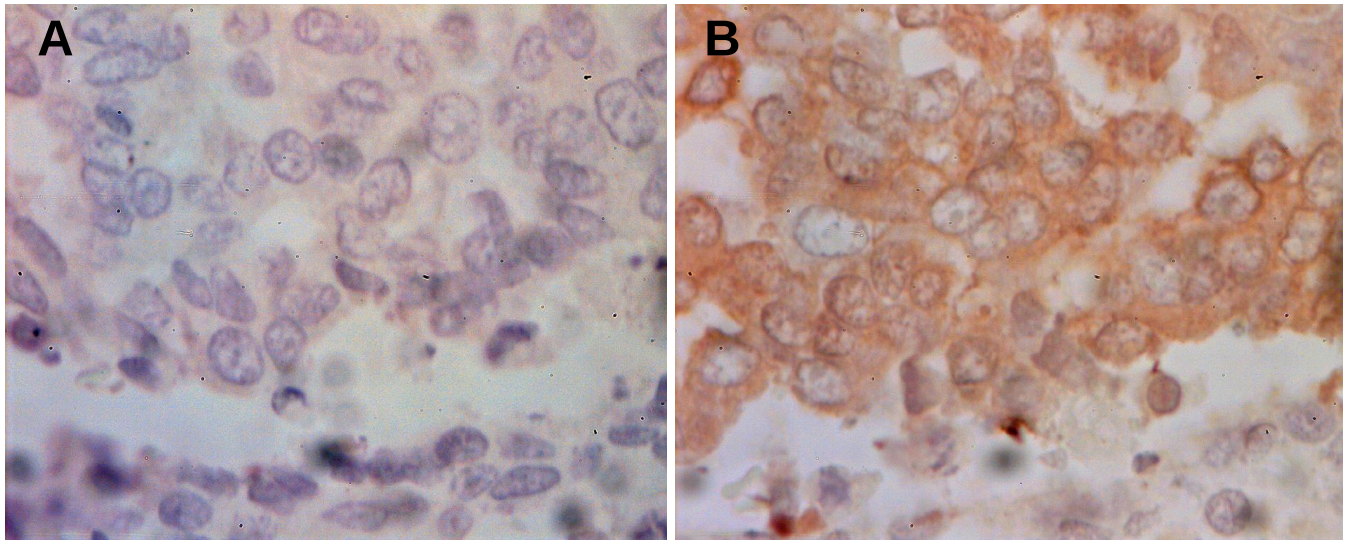
21-03-97: detection of anti-CDR2 antibody in the serum

27-03-97: detection of occult breast cancer

CDR2 = cerebellum degeneration-related antigen 2

PCD patient serum reacts with CDR2 protein in tumour tissue

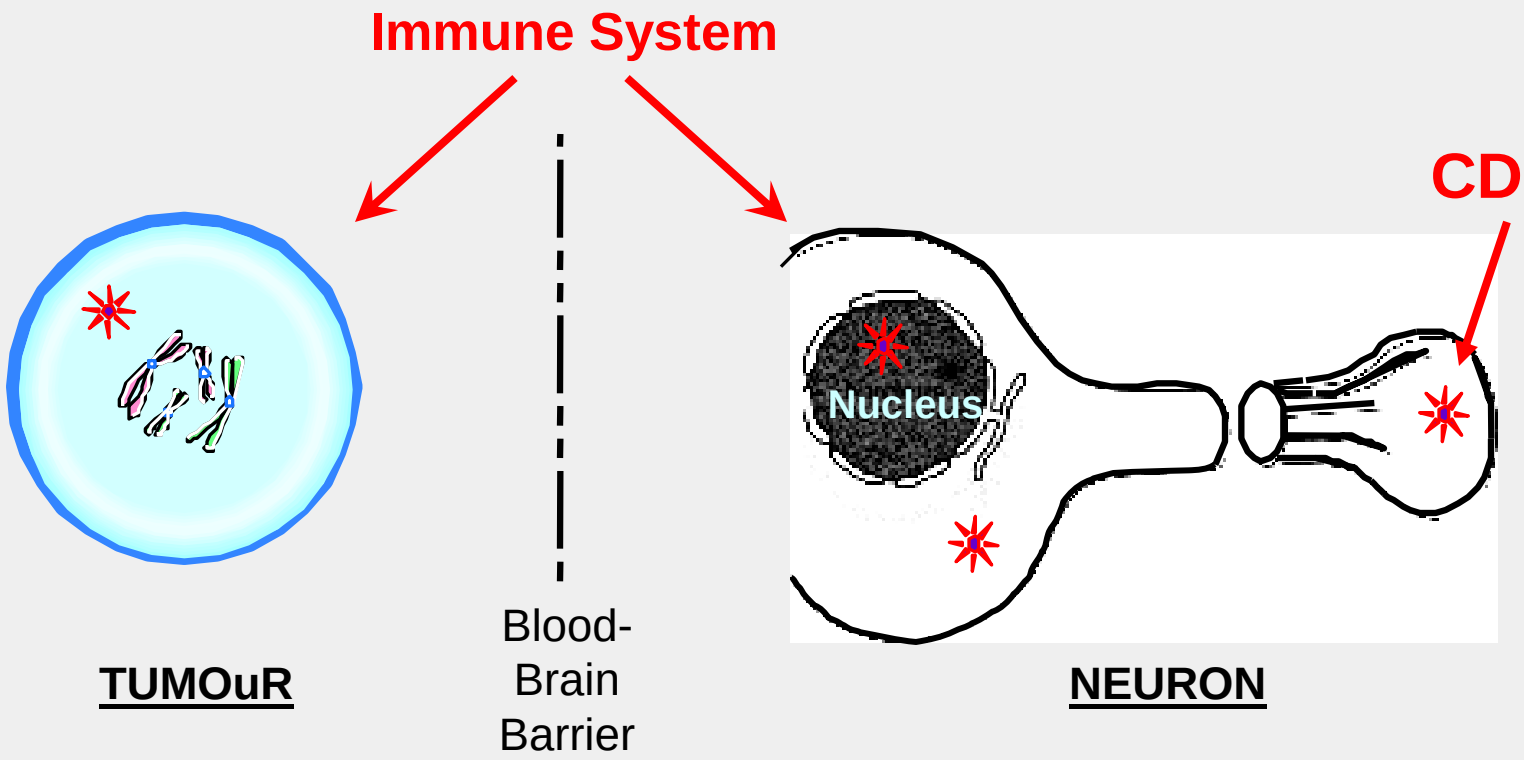
Sections of breast tumour



Control serum

PCD patient serum

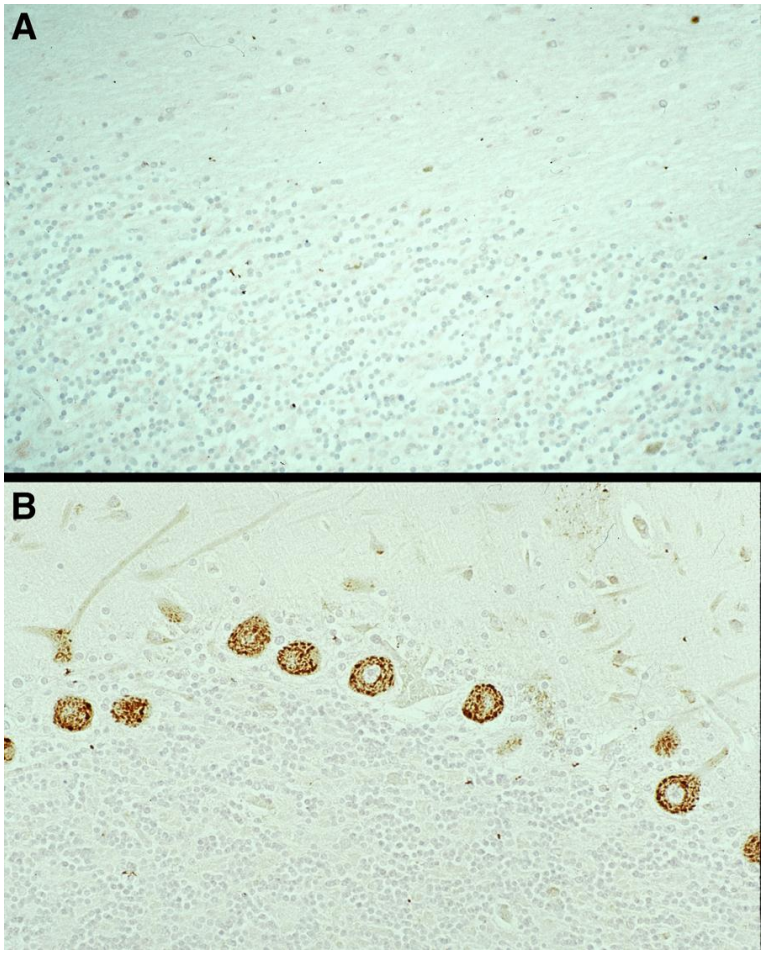
Spontaneous immunity against tumour-expressed antigen results in auto-immune disease

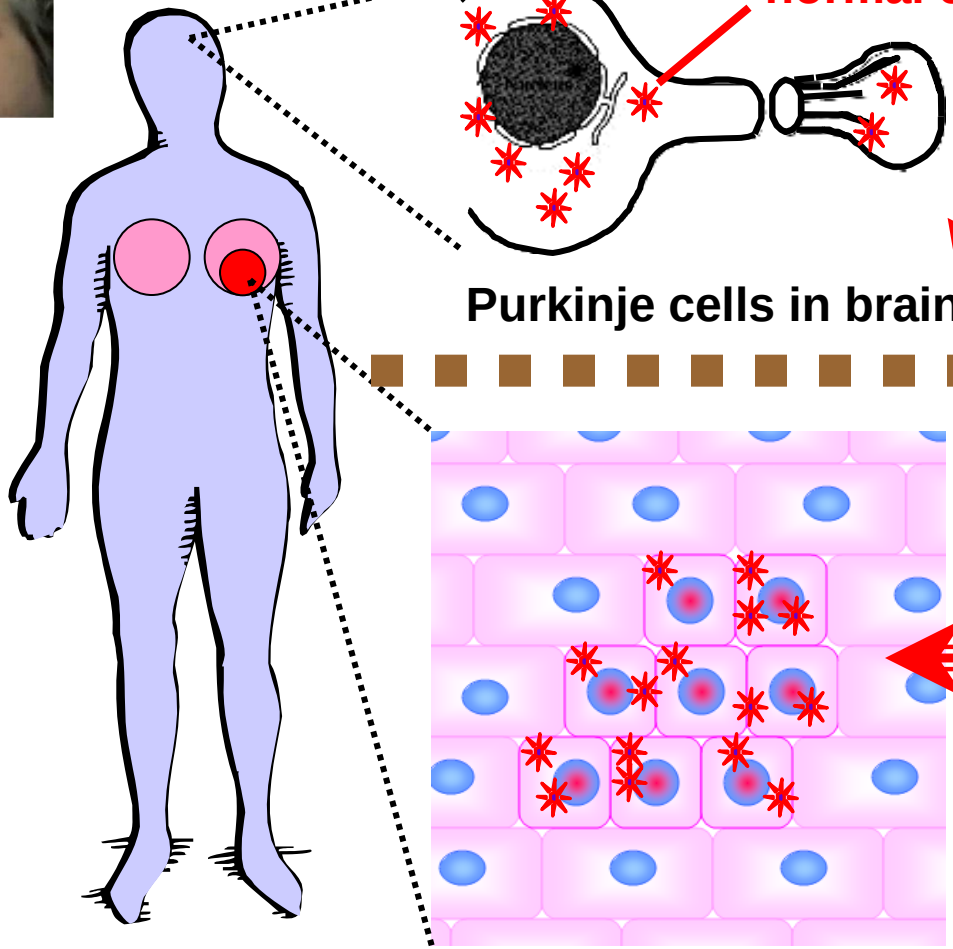


Elimination of Purkinje cells by tumour-induced auto-immune response causes PCD

PCD Brain

Control Brain




normal expression of the antigen
Purkinje cells in brain
Destruction of purkinje cells !
Immune response against tumor antigen
Breast tumour cells

What does this example teach us?

1. **At least certain tumours can express antigens that are absent from corresponding normal tissues**

2. **The immune system can, in principle, detect such abnormally expressed antigens and, as a result, launch an effective attack against the tumour**

3. **In certain cases, this may result in auto-immune destruction of normal somatic tissues**

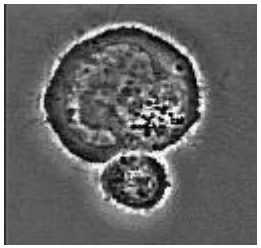
Tumour Immunology

1

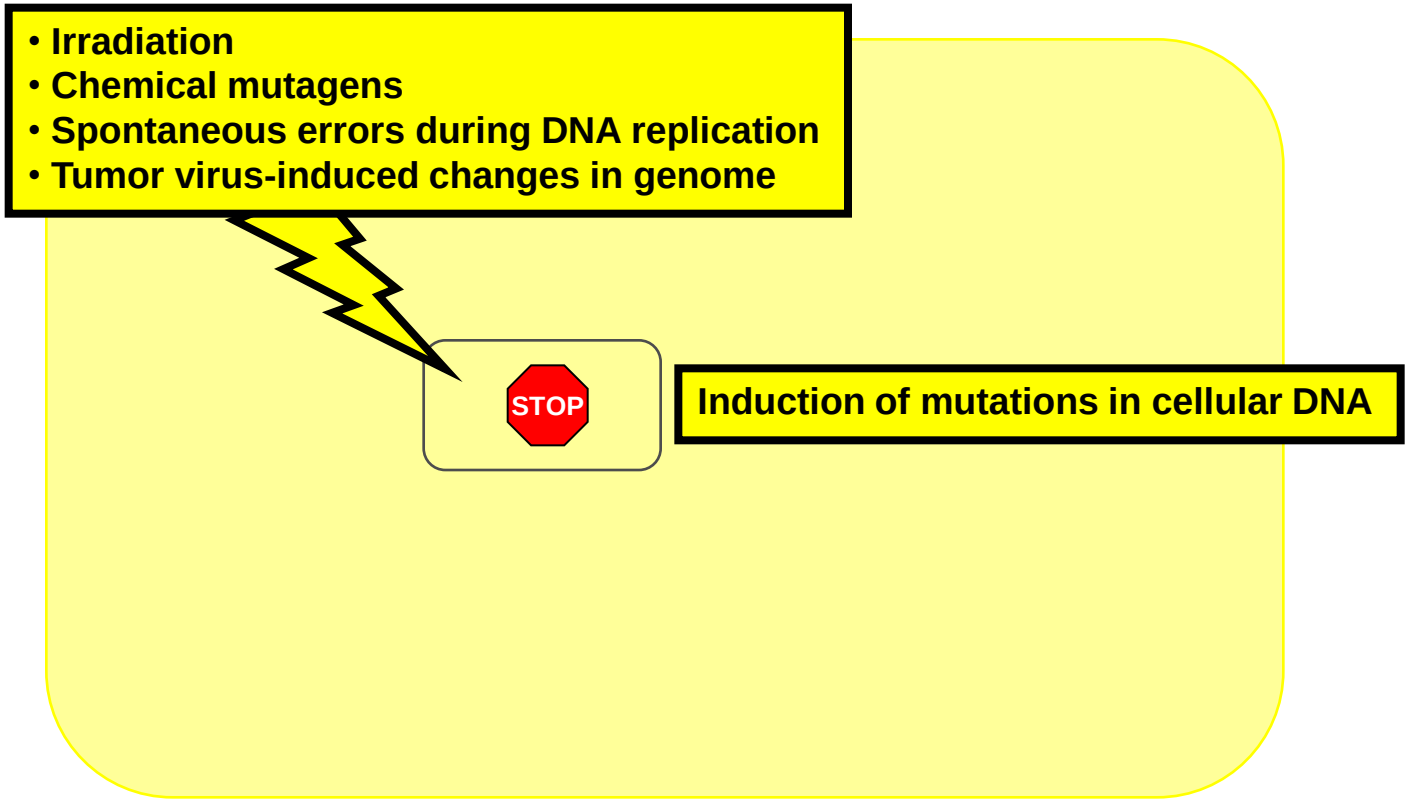
Study of the interaction between tumour and immune system

2

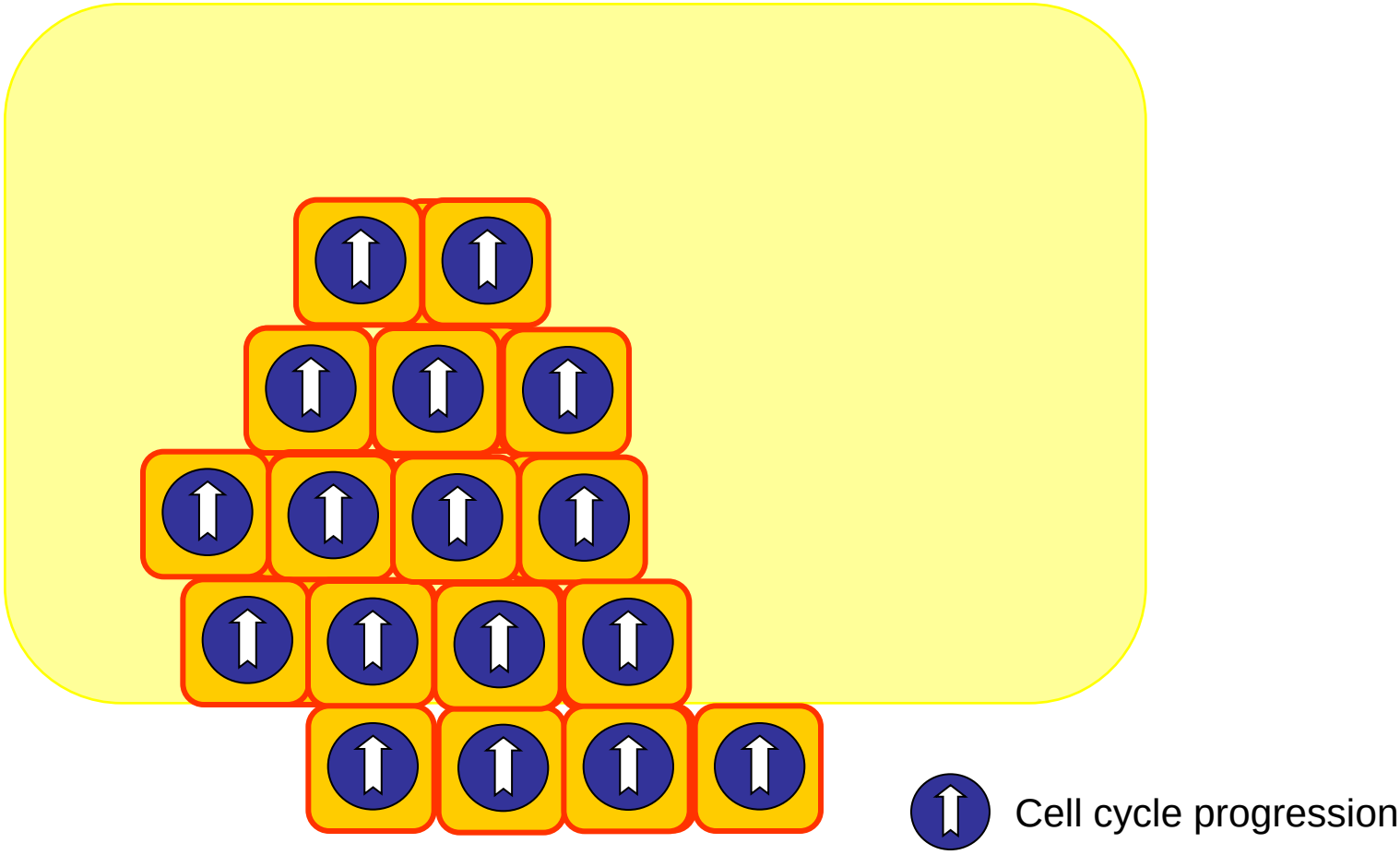
Development of safe immunotherapeutic strategies against cancer



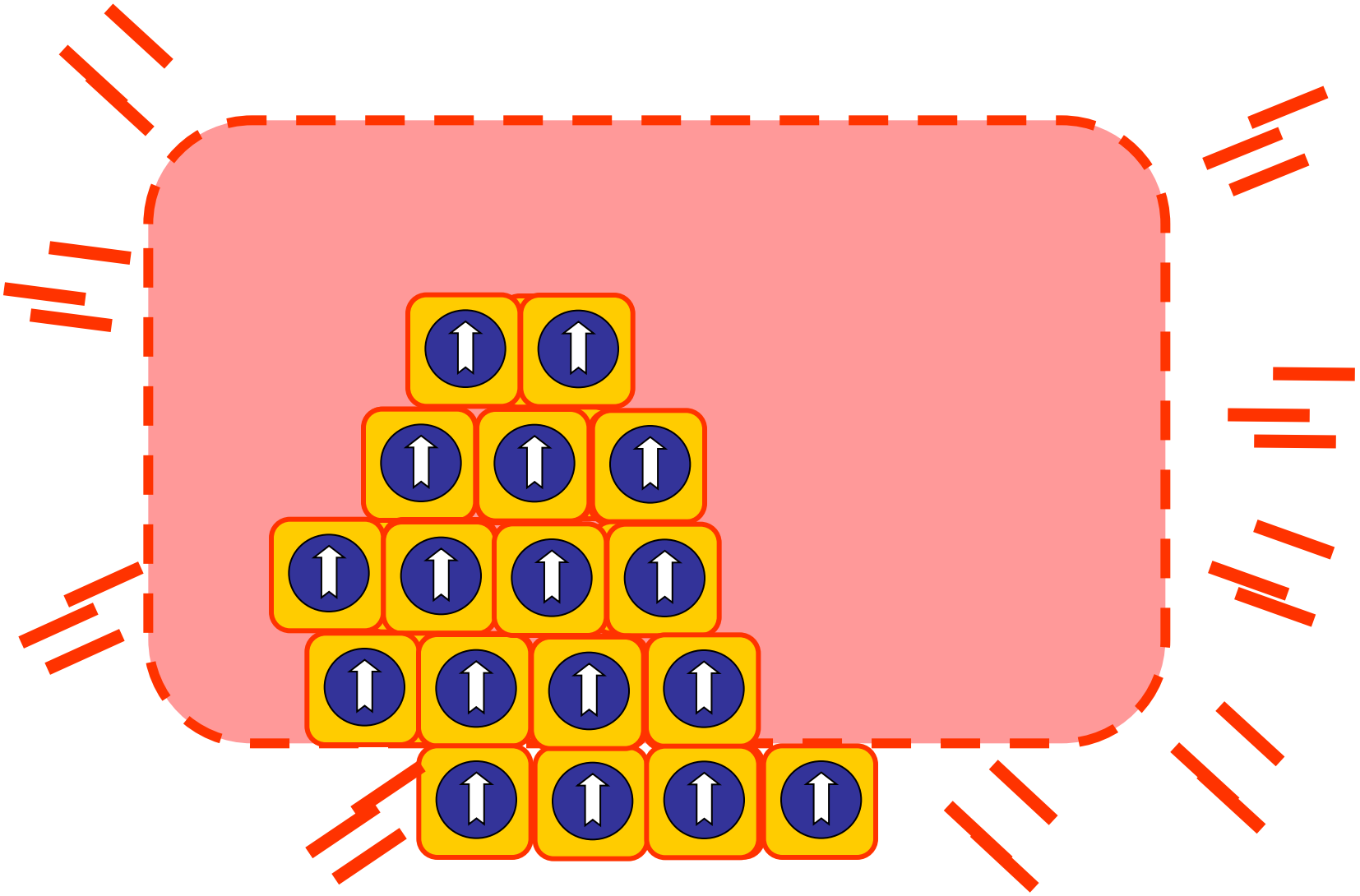
Initiation of cancer usually results from (a) sporadic event(s)



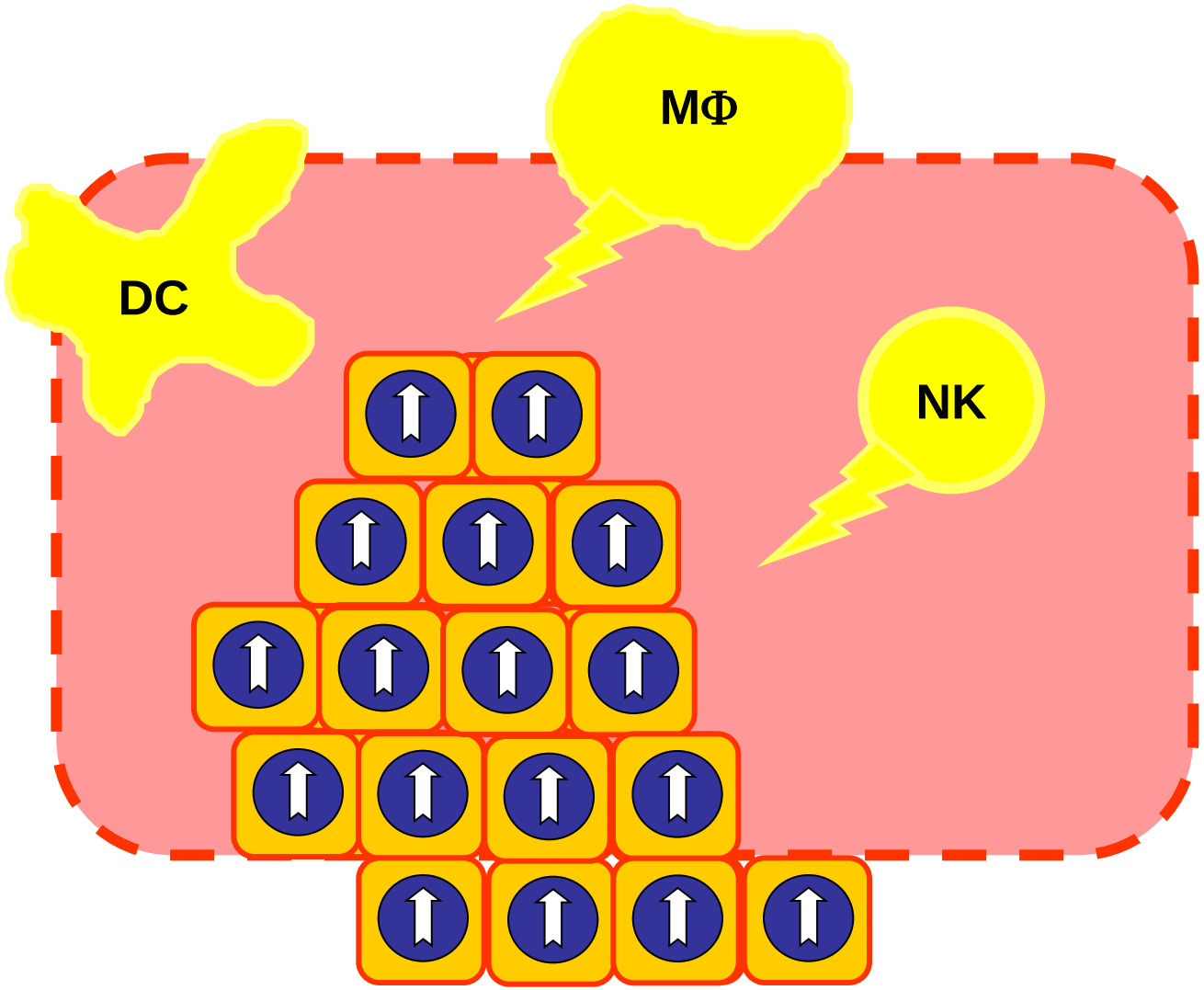
Absence of apoptosis and of cell cycle regulation results in tumour growth



Tumor growth (eventually) results in inflammatory signals

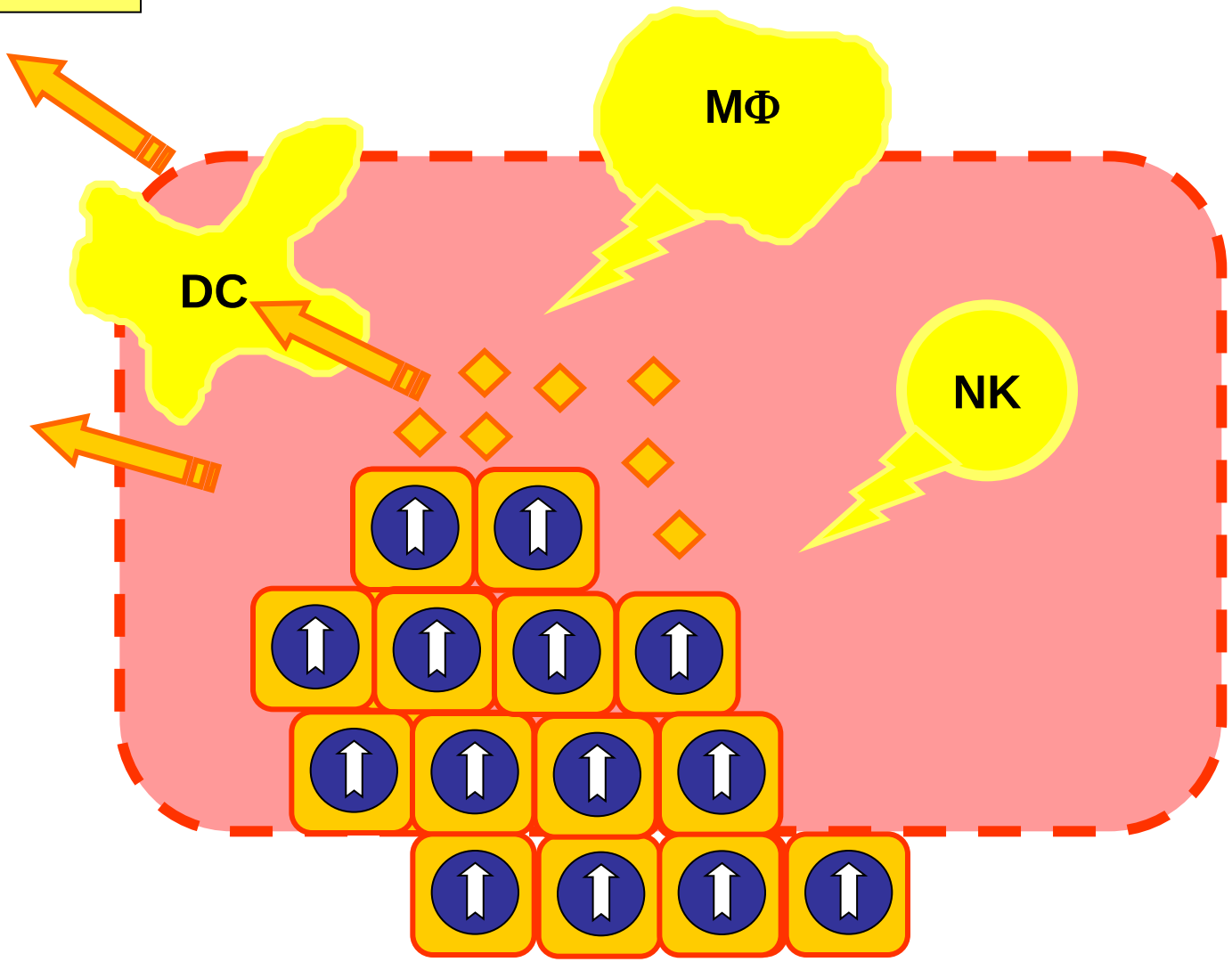


Recruitment of innate immunity

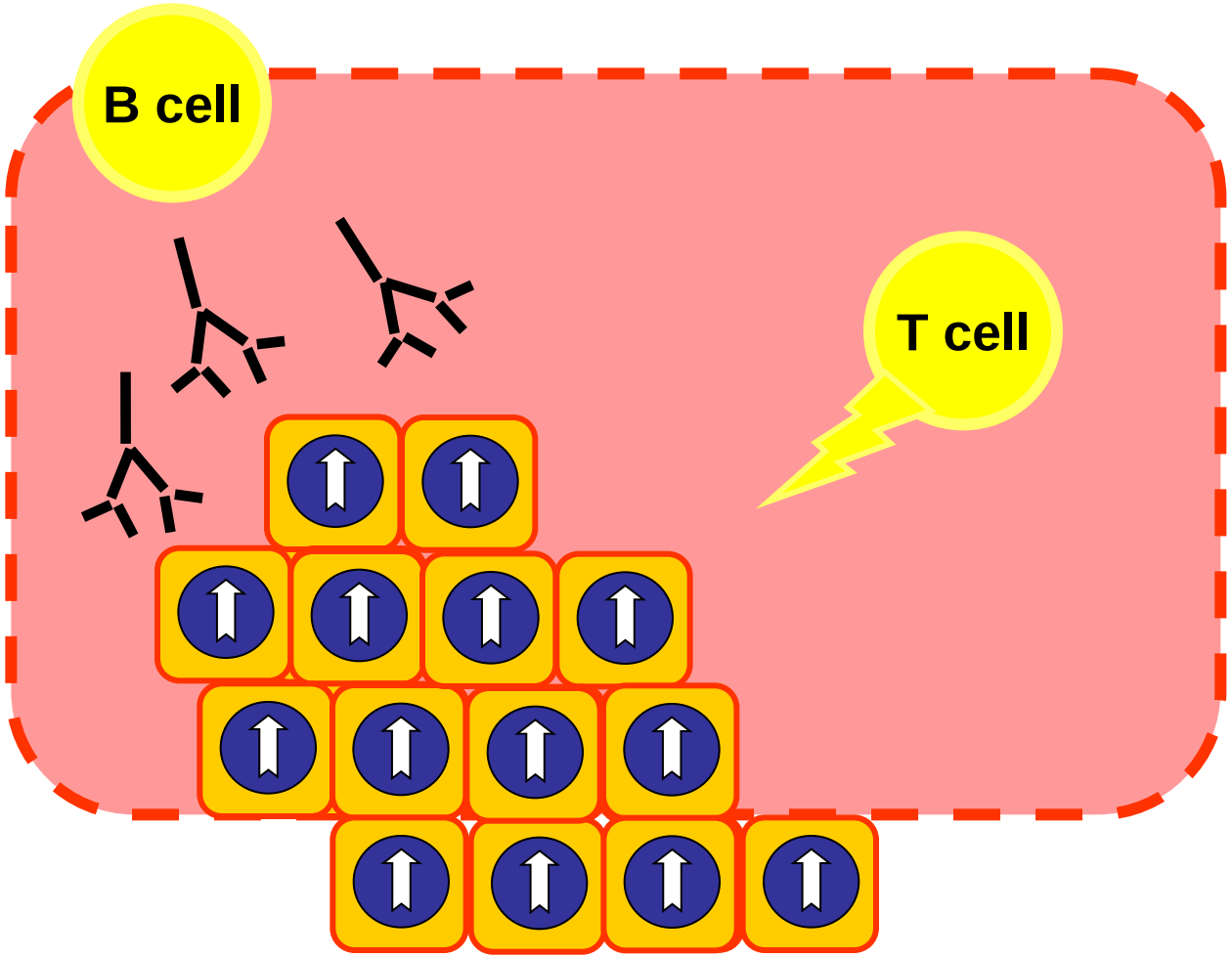


Draining lymphnode

Recruitment of innate immunity



Recruitment of adaptive, antigen-specific immunity

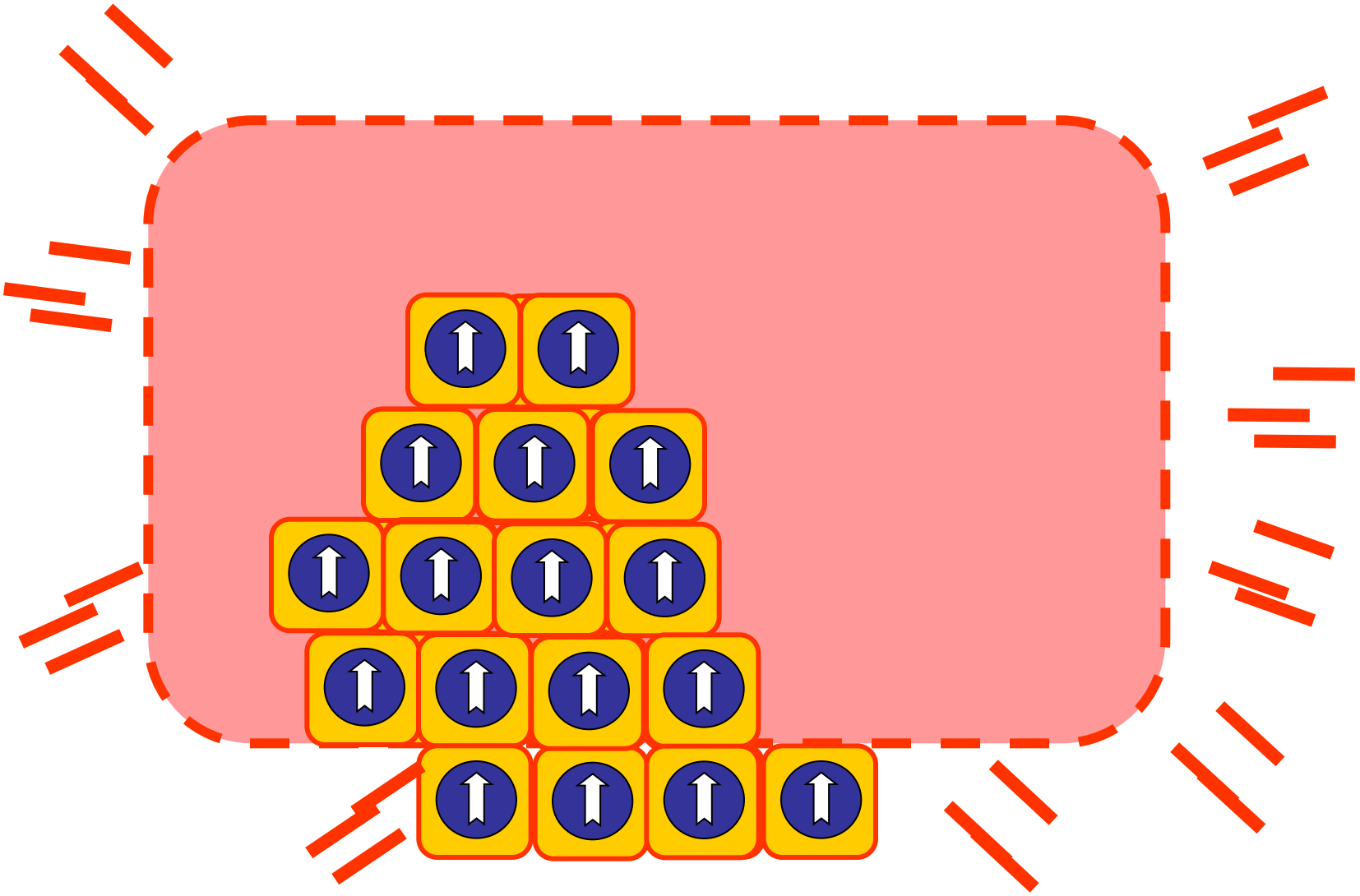


Requirements for activation of an adaptive anti-tumour immune response

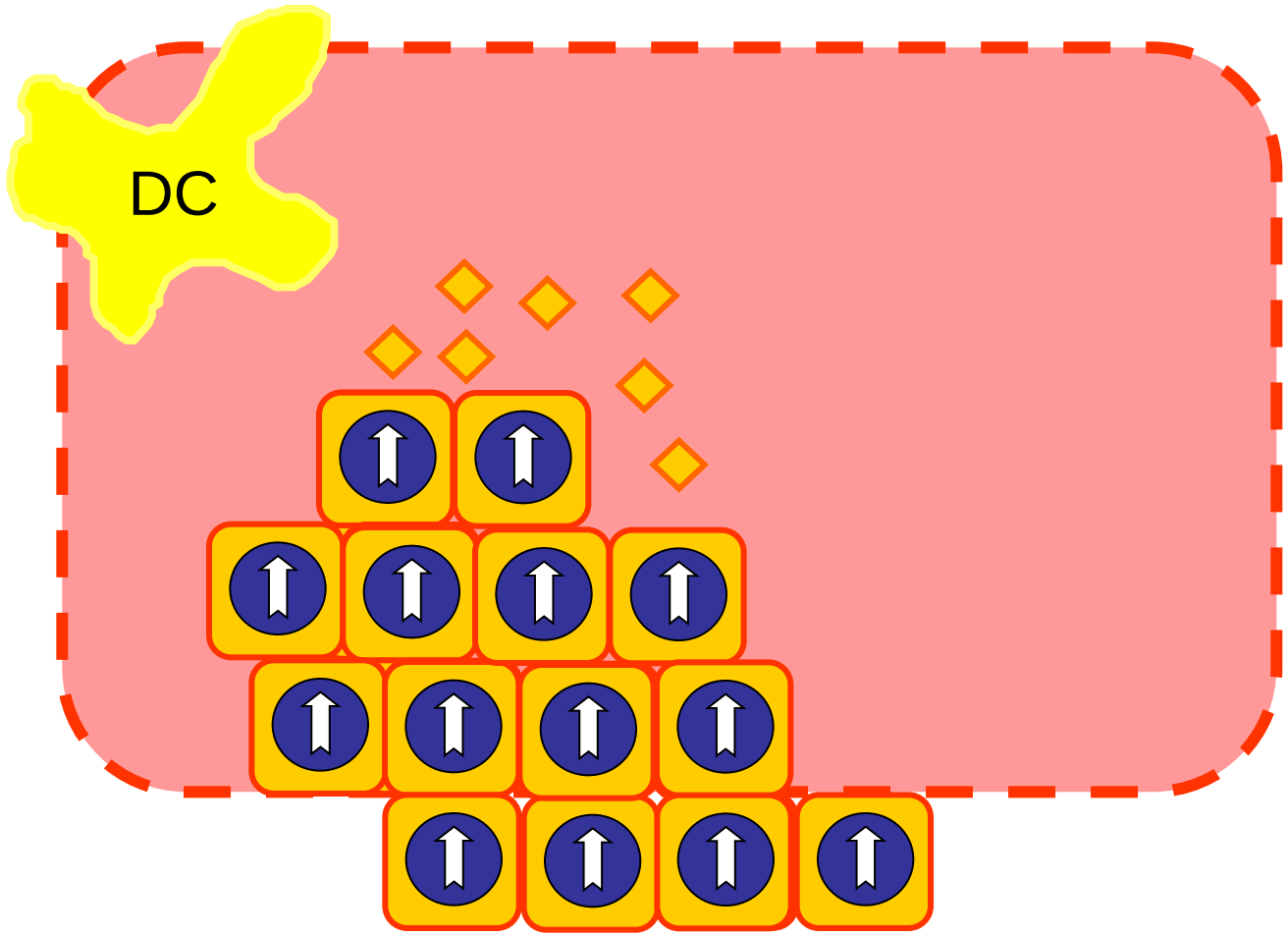
1. **Local inflammation in the tumour**

2. **Expression and recognition of tumour antigens**

Problems in immune surveillance of cancer: #1
It takes the tumour a while to cause local inflammation



Problems in immune surveillance of cancer: #2
Antigenic differences between normal and tumour cells can be very subtle



If requirements for ‘spontaneous’ activation of the adaptive anti-tumour immune response were not met, could we teach the immune system to selectively detect and destroy tumour cells?

Cancer Immunotherapy

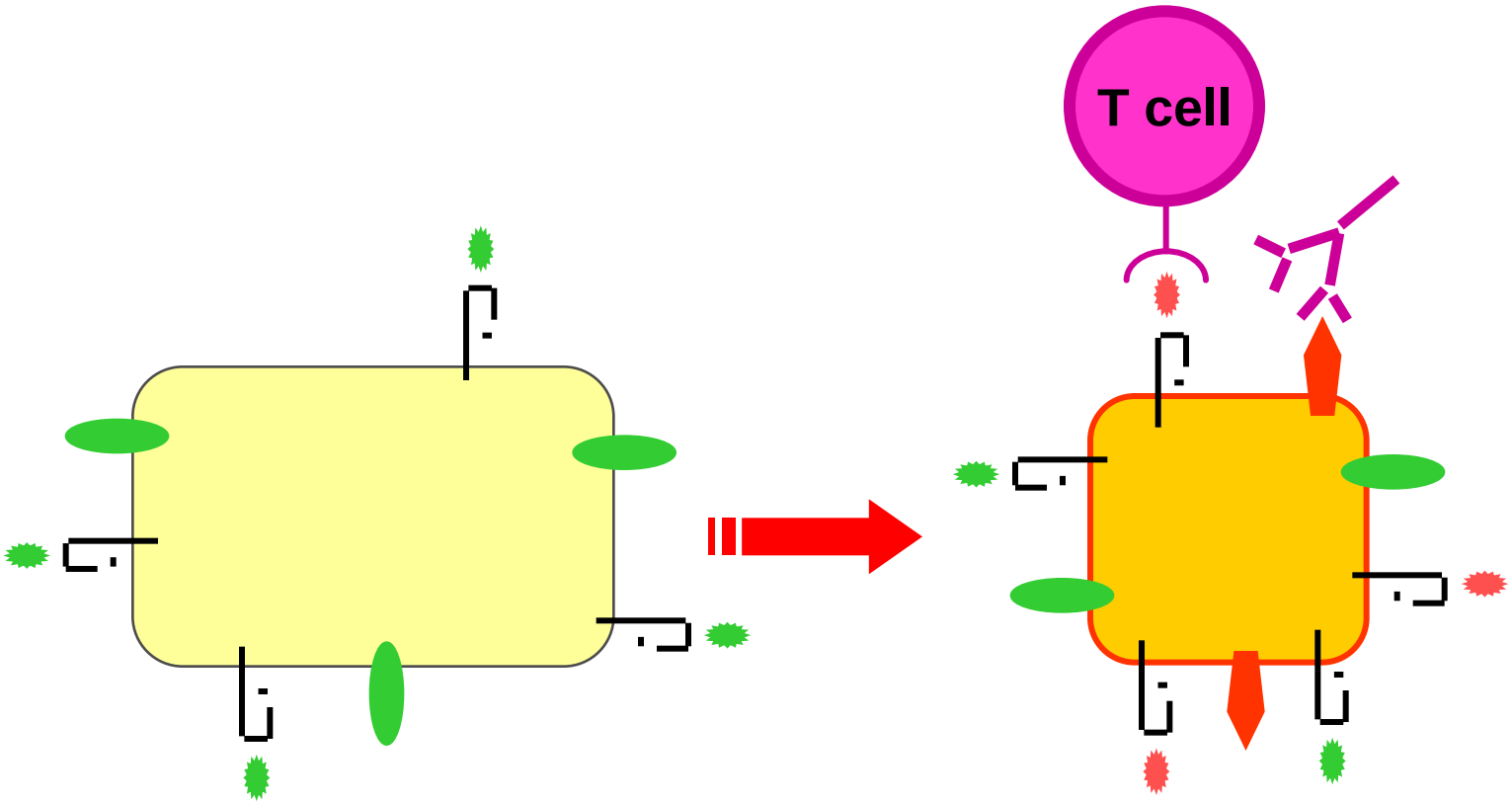
(A possible alternative to conventional therapies)

!

Which antigens should be targeted?

1

Tumour-specific antigens

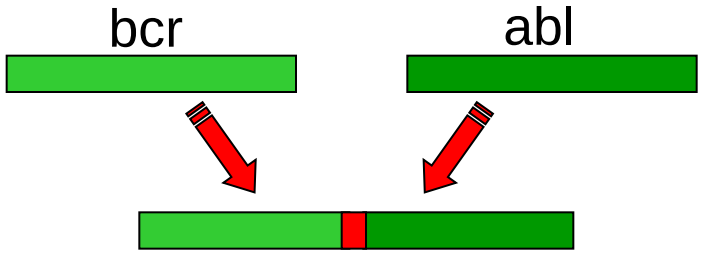


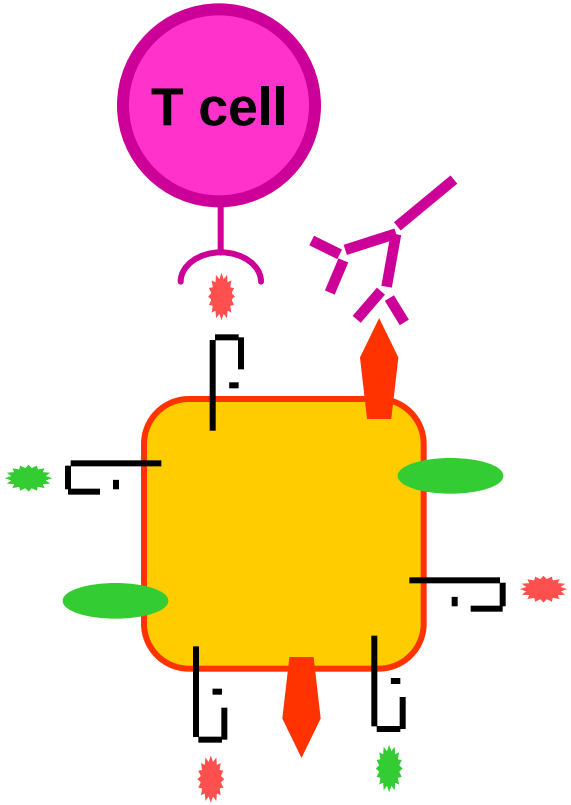
1

Tumour-specific antigens

- Viral proteins
  - Epstein Barr Virus (EBV)
  - Human Papillomavirus (HPV)
- Mutated cellular proteins
  - TGF-β receptor III

- Bcr-Abl





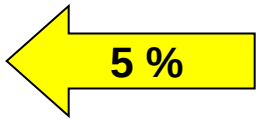
Cancers with viral origin

Opportunistic malignancies:

- EBV-positive lymphoma
- HHV8-positive Kaposi sarcoma

Also in immunocompetent individuals:

- HTLV1-associated lymphoma
- HBV- and HCV-associated hepatocellular carcinoma
- HPV-positive genital cancers

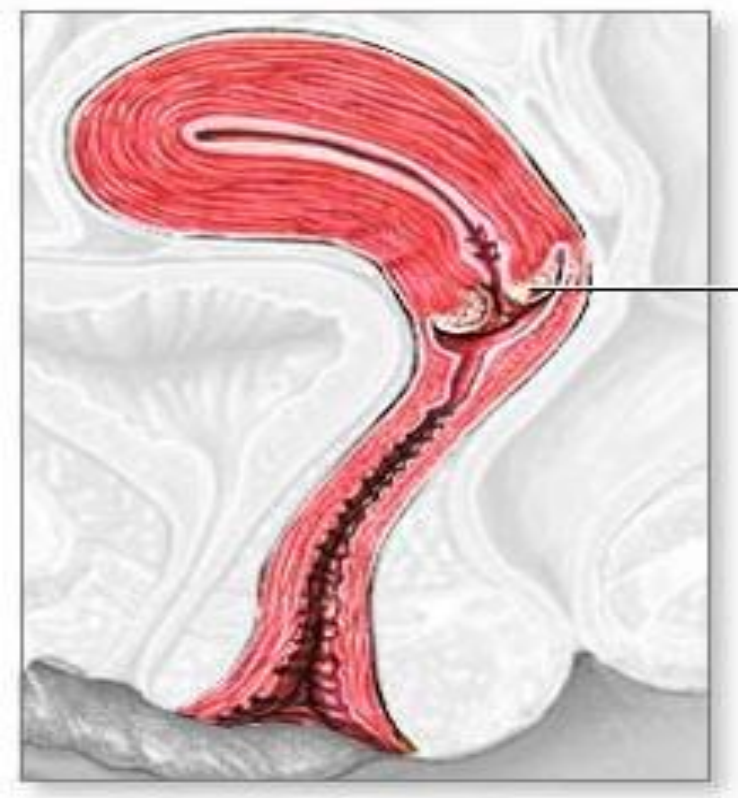


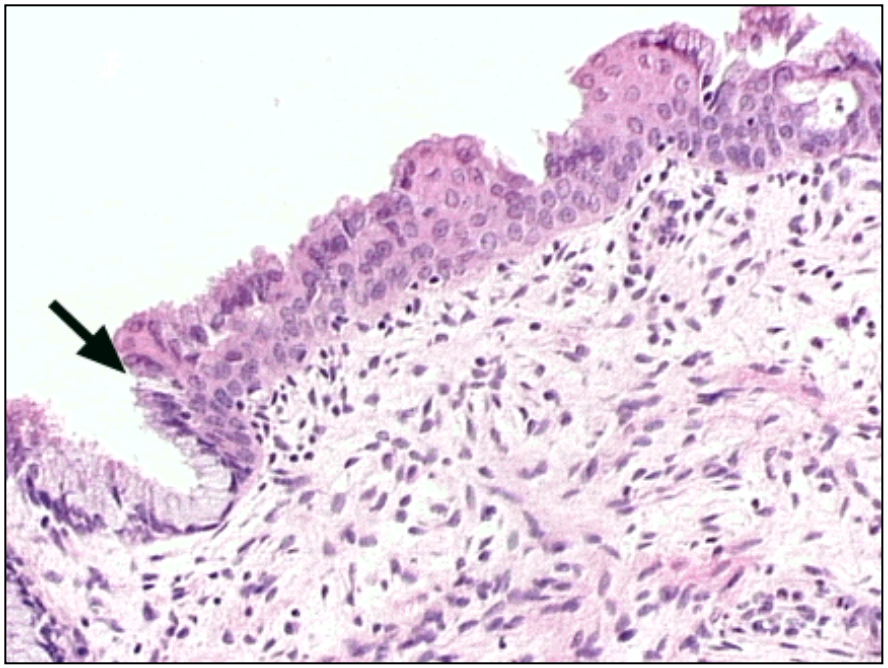
Direct relation between sexual behaviour and risk for HPV infection (study in college women)

Ho et al. (1998) N Engl J Med 338, 423

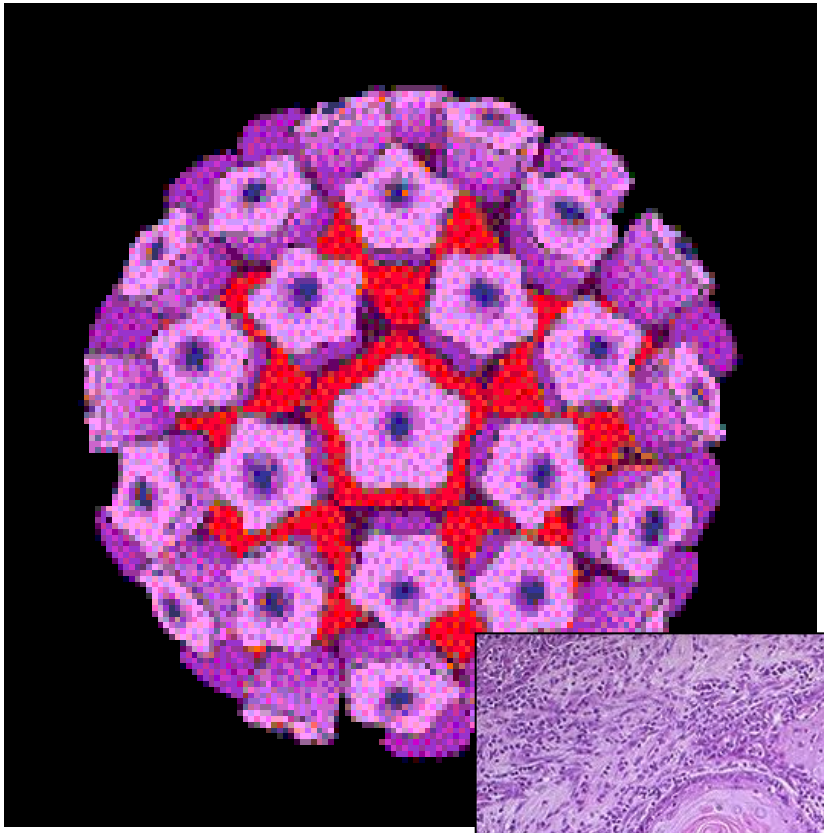
No. of male vaginal sex partners in previous 6 months	Adjusted relative risk	P value
0-3	1.0	< 0.001
4	3.6	
No. of male vaginal sex partners in previous 7-12 months		
0	1.0	
1	1.7	
2-3	3.0	< 0.001
≥ 4	4.2	
No. of lifetime sex partners of regular partners		
1	1.0	
2-5	5.8	< 0.001
≥ 6	10.1	

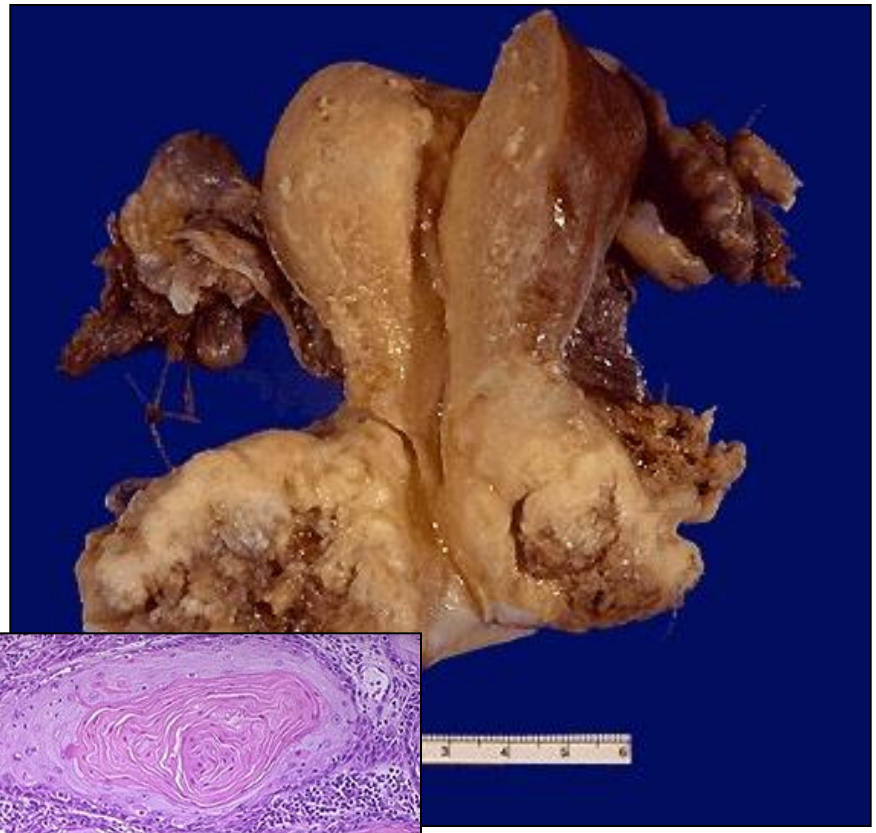
Cervical neoplasia starts with genital HPV infection

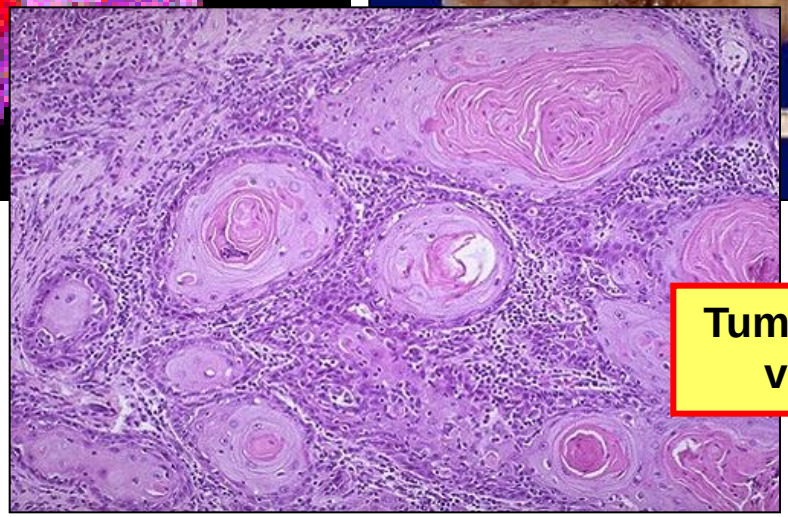




Human Papillomavirus (HPV) Cervical Cancer

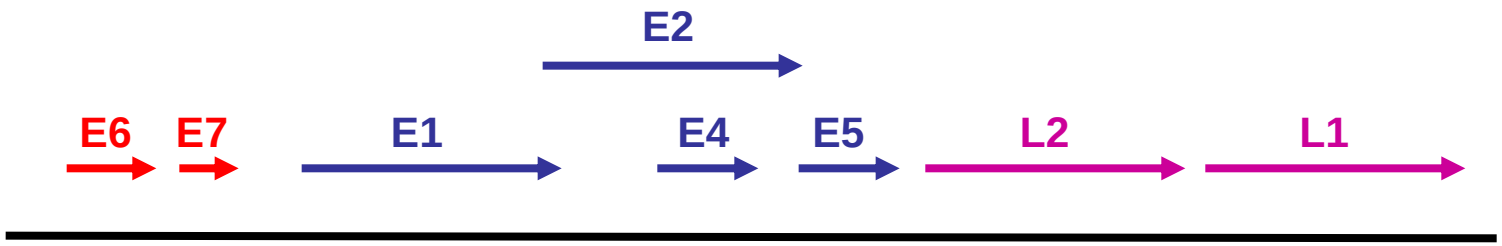




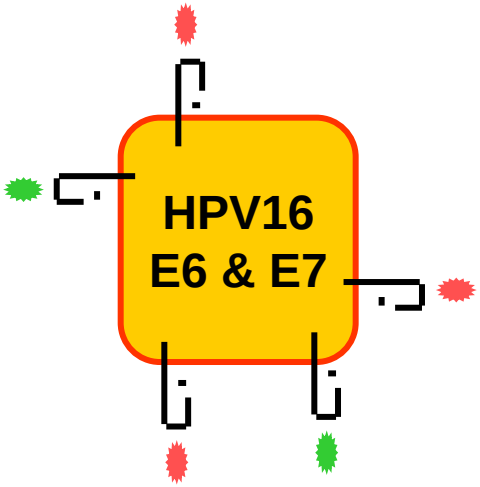


Tumor cells express viral antigens!

Cervical cancer is induced and maintained by the E6 and E7 oncoproteins of HPV

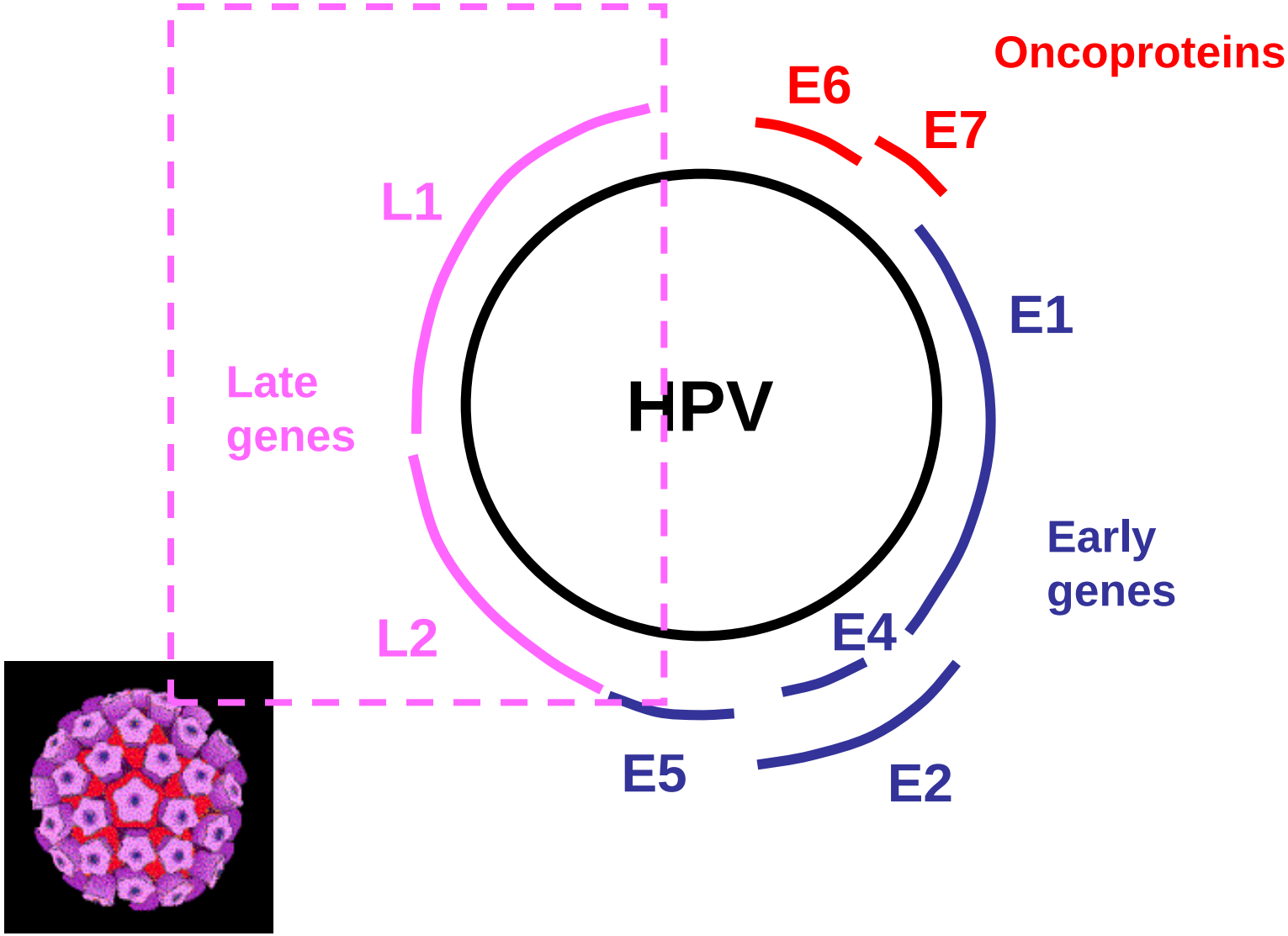


E6 and E7 are intracellular antigens



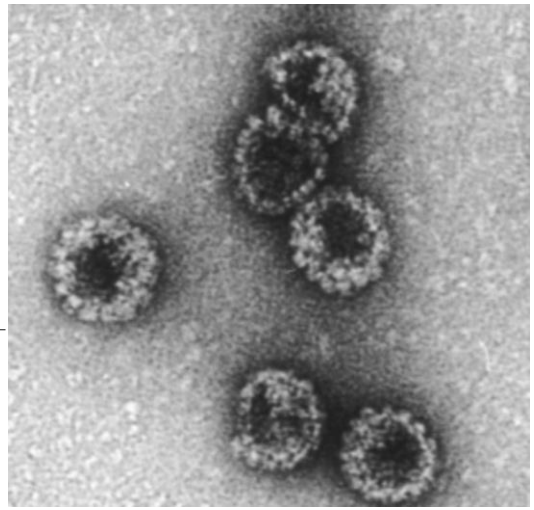
Nobel Prize for Physiology and Medicine 2008, Harald Zur Hausen

Target antigens for preventive HPV vaccination



The New England
Journal of Medicine

VOLUME 347 NOVEMBER 21, 2002 NUMBER 21



A CONTROLLED TRIAL OF A HUMAN PAPILLOMAVIRUS TYPE 16 VACCINE

LAURA A. KOUTSKY, PH.D., KEVIN A. AULT, M.D., COSETTE M. WHEELER, PH.D., DARRON R. BROWN, M.D., ELIAV BARR, M.D., FRANCES B. ALVAREZ, R.N., LISA M. CHIACCHIERINI, PH.D., AND KATHRIN U. JANSEN, PH.D., FOR THE PROOF OF PRINCIPLE STUDY INVESTIGATORS

	Impact of vaccination	placebo	VLP vaccine	efficacy
17 mnd	persistent infection	41	0	100%
	transient infection	68	6	91%
	total	*765*	*768*	
48 mnd*	persistent infection	92	0	100%
	CIN lesions	24	0	100%
	total	*750*	*755*	

(* Mao et al 2006 Obst Gynecol)

GARDASIL–the only cervical cancer vaccine

For girls and young women ages 9 to 26 years

YOU COULD BECOME
1 LESS LIFE AFFECTED
BY CERVICAL CANCER.

GARDASIL is the only vaccine that may help guard against diseases that are caused by human papillomavirus (HPV) Types 6, 11, 16, and 18:

- Cervical cancer
- Cervical abnormalities that can sometimes lead to cervical cancer
- Genital warts

HPV Types 16 and 18 cause 70% of cervical cancer cases, and HPV Types 6 and 11 cause 90% of genital warts cases.

IMPORTANT INFORMATION ABOUT GARDASIL

GARDASIL may not fully protect everyone and does not prevent all types of cervical cancer, so it is important to continue regular cervical cancer screenings.

Anyone who is allergic to the ingredients of GARDASIL should not receive the vaccine. GARDASIL is not for women who are pregnant.

GARDASIL will not treat these diseases and will not protect against diseases caused by other types of HPV.

GARDASIL is given as 3 injections over 6 months and can cause pain, swelling, itching, and redness at the injection site, fever, nausea, and dizziness. Only a doctor or healthcare professional can decide if GARDASIL is right for you or your daughter. Ask about GARDASIL today.

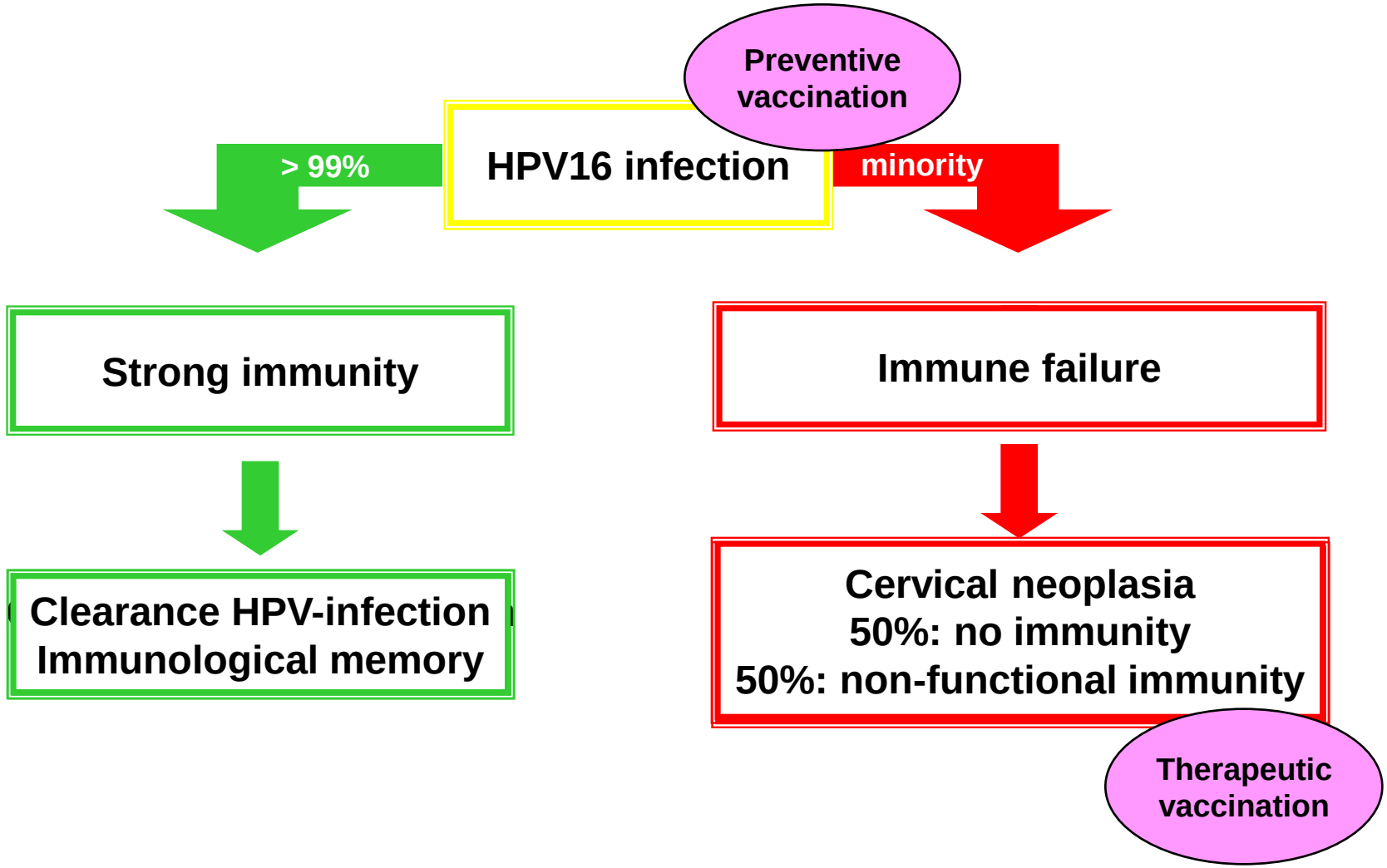
Now you can
DO SOMETHING

» Prepare to visit your doctor
» Make sure you are covered
» Request more information

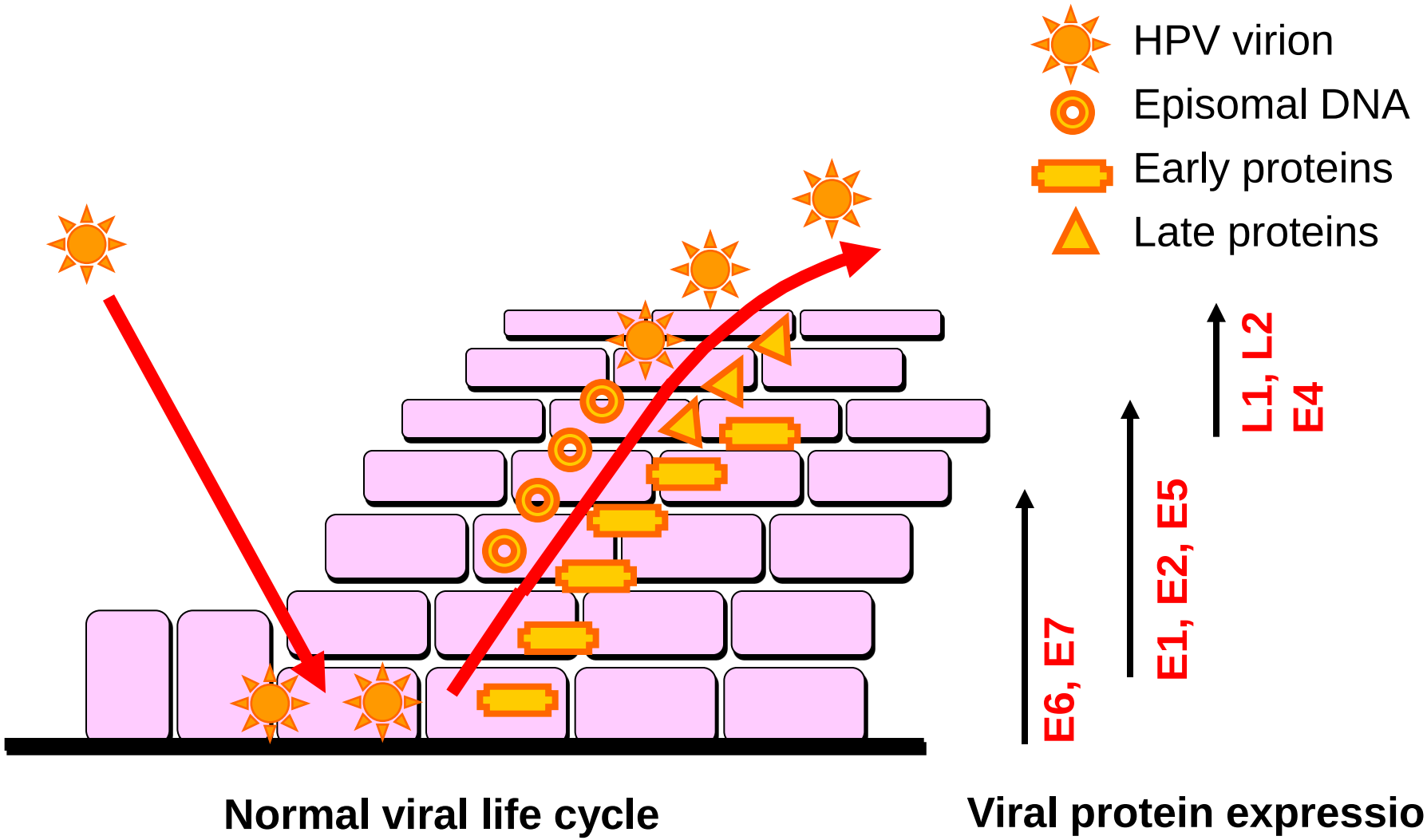
» See our TV ad

www.gardasil.com

Relation between consequences of cervical HPV infection and HPV-specific T cel immunity



The infection cycle of HPV is linked to the keratinocyte differentiation programme



Requirements for activation of an effective anti-viral immune response

1. **Local inflammation**
2. **Target antigens**

Question:
Which of these requirements is <u>not</u> met during cervical HPV infection?

Requirements for activation of an effective anti-viral immune response

1. **Local inflammation**
2. **Target antigens**

Largely lacking in genital HPV infection

Consequences:

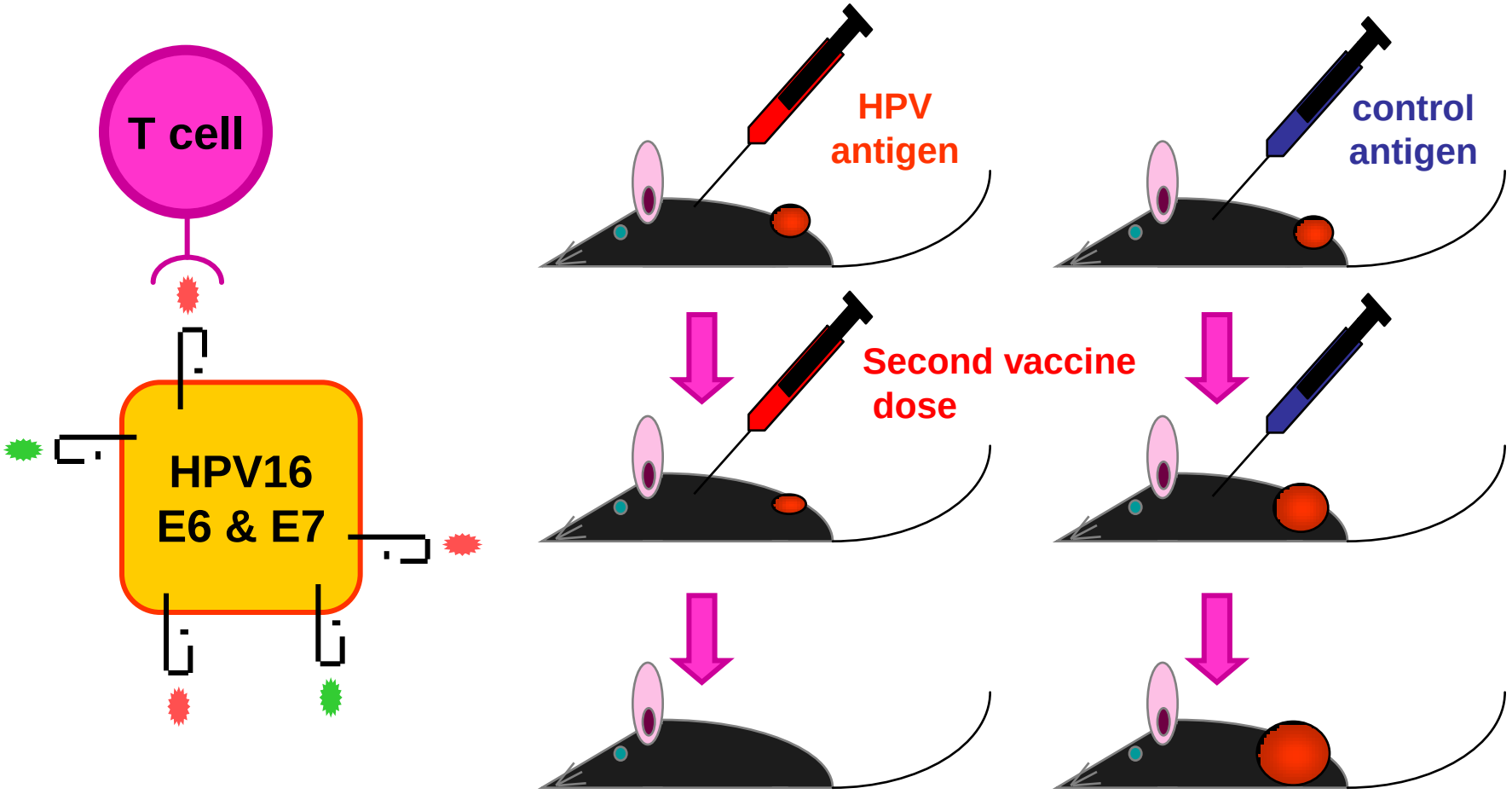
- **Viral persistence for periods well over 1 year**
- **Neoplasia**

What is needed to trigger an effective HPV-specific immune response by vaccination?

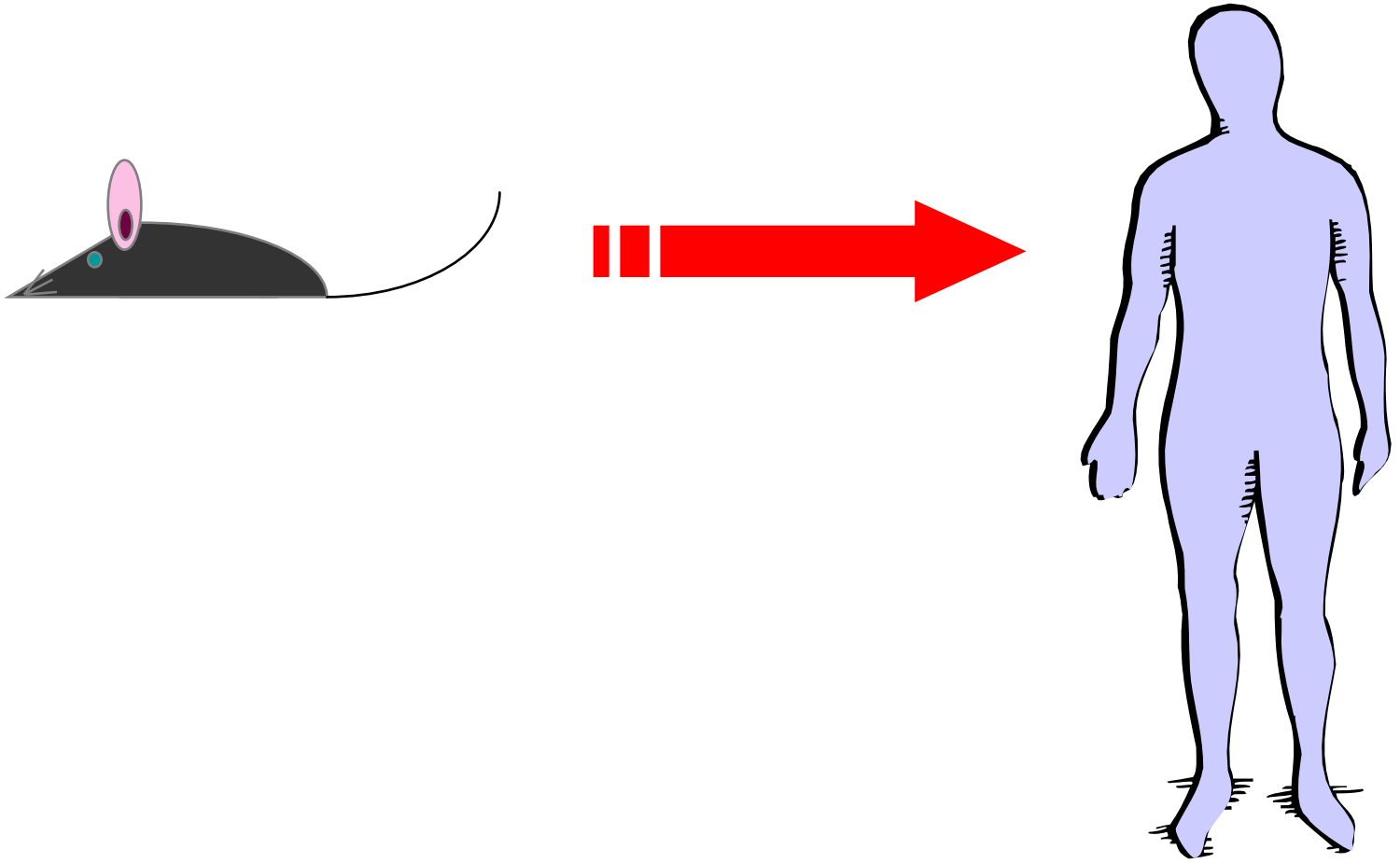
1. **Local inflammation (adjuvant)**
2. **Tumour antigen expression and recognition**

Therapeutic anti-tumour treatment in mice by peptide vaccination

tumour antigen + adjuvants



Clinical testing of therapeutic peptide vaccine in patients with cervical cancer



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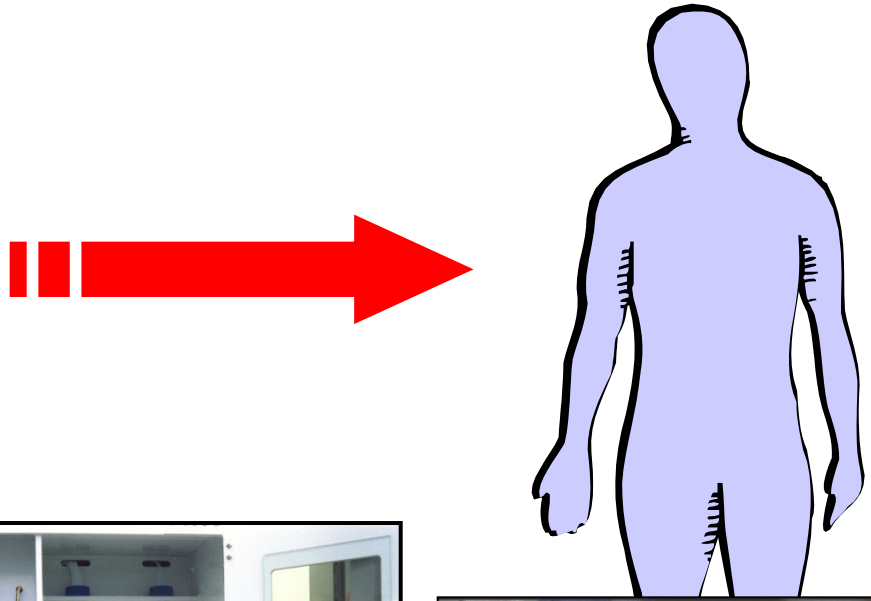
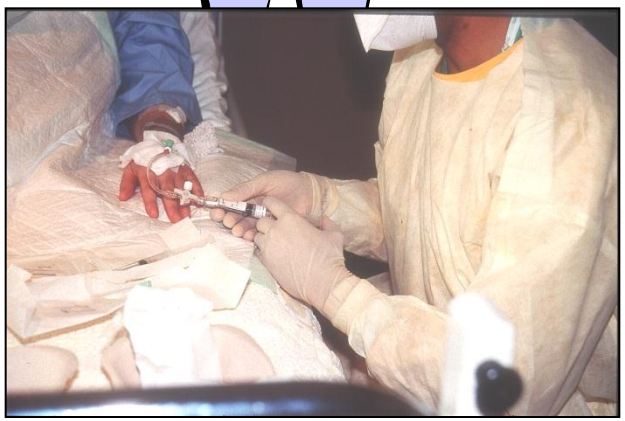




Restoration of HPV16-specific T-cell immunity through antigen-specific vaccination

pre-vaccination | after 2 vaccinations | after 4 vaccinations

	1	2	3	4	5	6	7	8	9	10	11	12
A												
medium	0	2	1	0	2	0	0	4	1	0	3	2
B												
HPV16 E6.1	1	0	1	2	14	18	8	8	29	20	24	23
C												
HPV16 E6.2	2	2	1	3	27	23	21	16	60	67	43	52
D												
HPV16 E6.3	1	2	2	3	46	35	54	55	106	94	82	97
E												
HPV16 E6.4	1	0	0	0	1	4	0	1	0	3	1	1
F												
HPV16 E7.1	2	1	6	5	3	1	1	3	1	0	2	1
G												
HPV16 E7.2	0	0	1	1	19	13	14	24	114	110	118	89

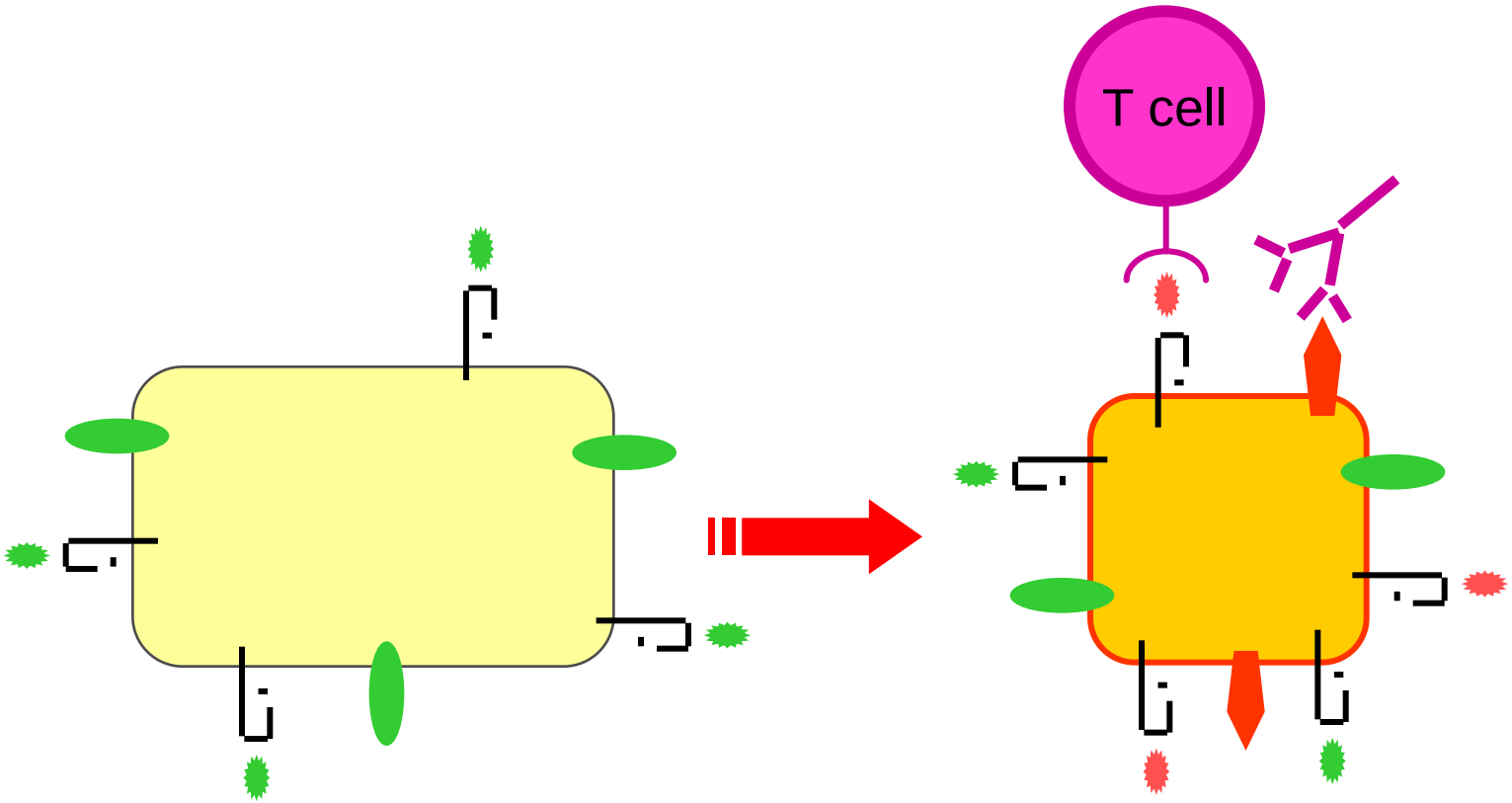
E6

E7

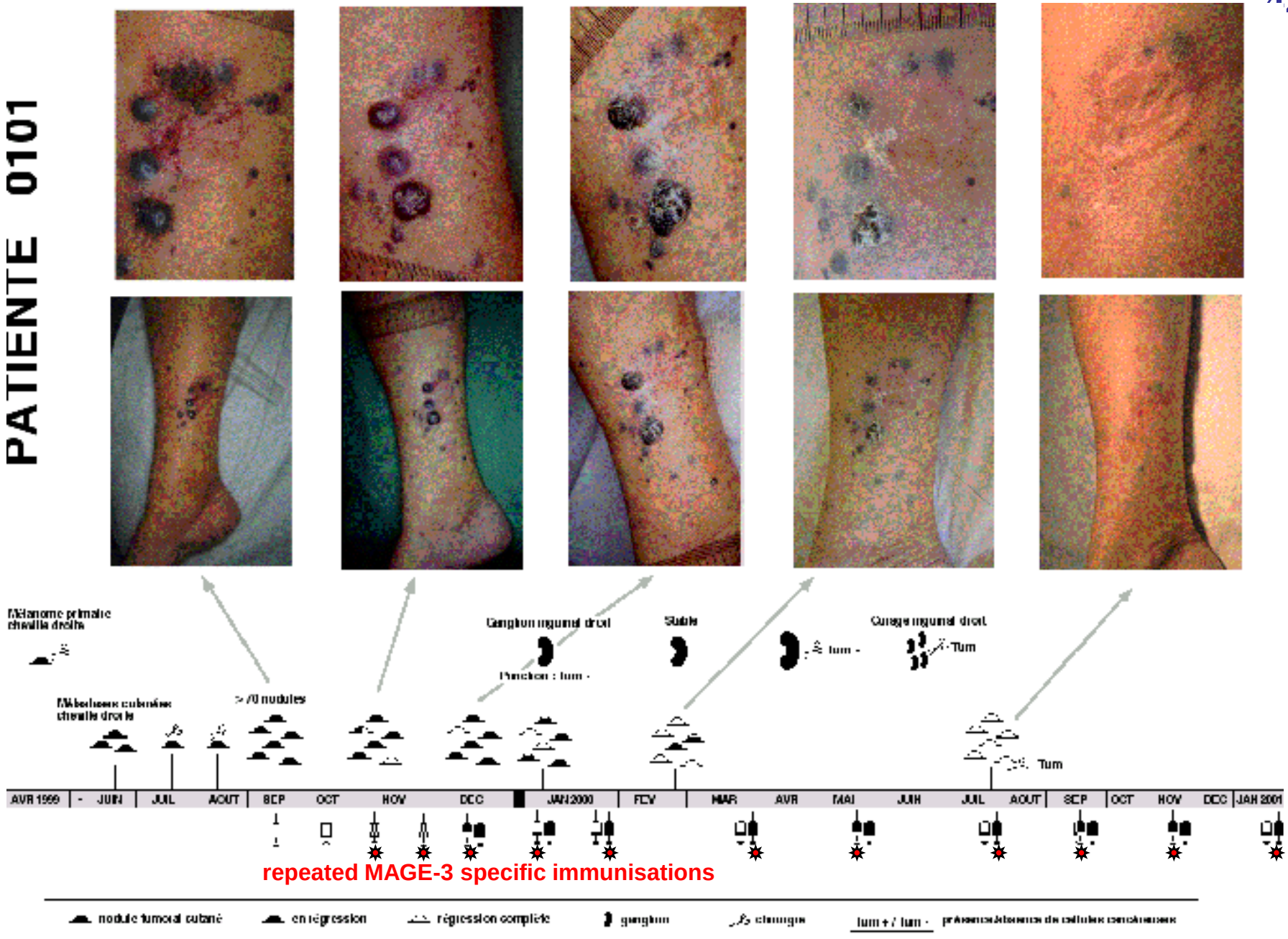
Rienk Offringa, Leiden, The Netherlands

2

Tumour-associated antigens: ectopically expressed auto-antigens

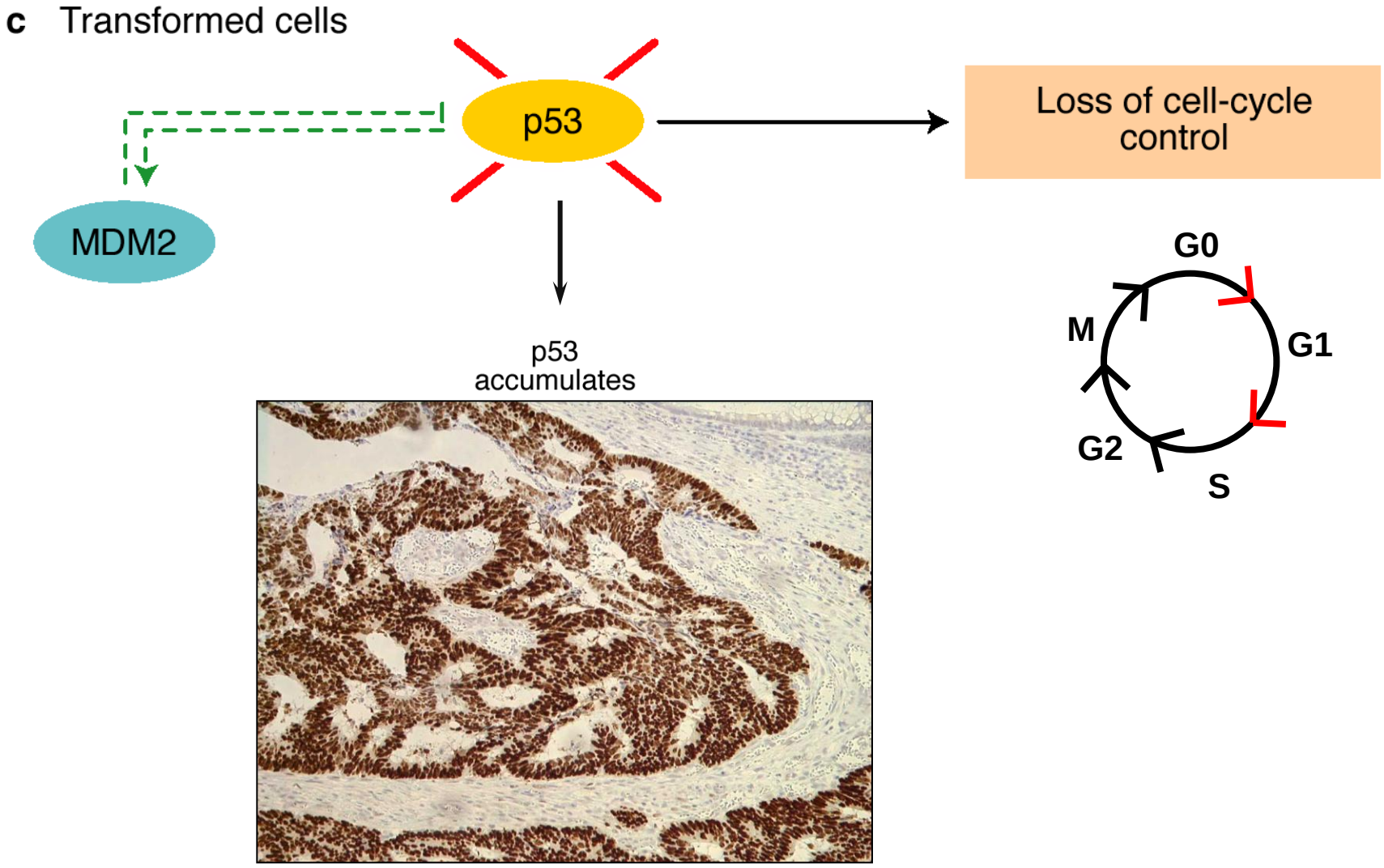


Cancer-testis antigens: **e.g. MAGE-3**



T. Boon and coworkers; Ludwig Institute, Brussels

Other ectopically expressed auto-antigen: p53

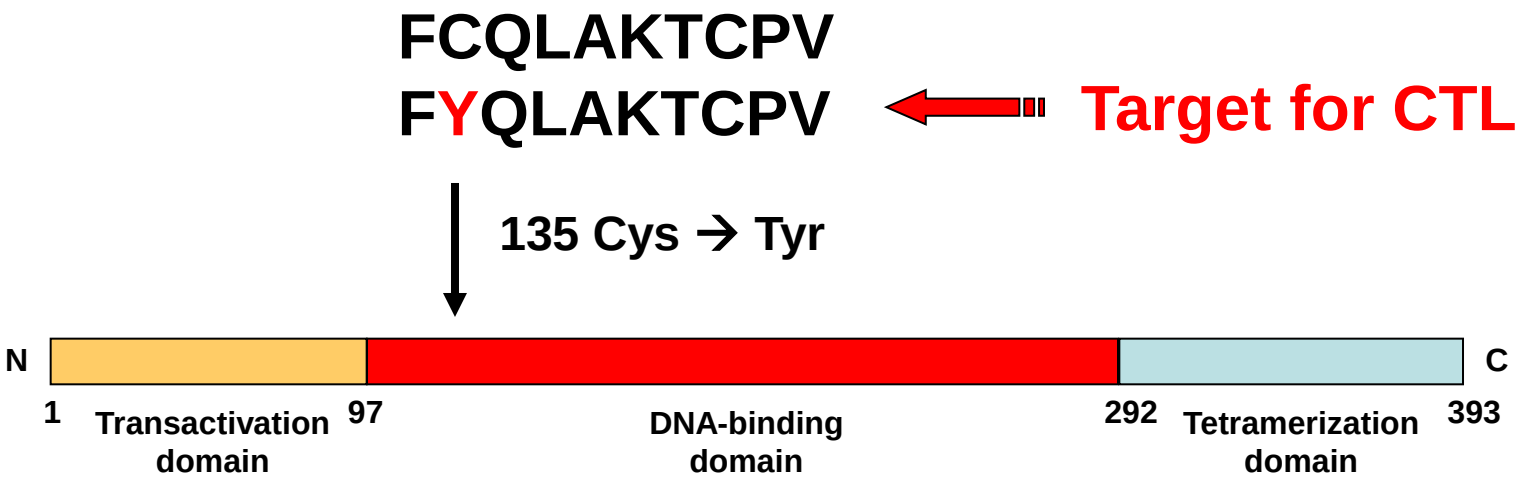


p53 is frequently mutated and overexpressed in human cancer

Cancer type	n	% mut. p53	Cancer type	n	% mut. p53	Cancer type	n	% mut. p53
Lung	897	56	Prostate	87	30	Carcinoid	61	11
Colon	960	50	HCC	716	29	Melanoma	70	9
Esophagus	270	45	Brain	456	25	Parathyr.	13	8
Ovary	386	44	Adrenal	31	23	Cervix	350	7
Pancreas	170	44	Breast	1536	22	Neurobl.	212	1
Skin	220	44	Endometr.	224	22	Wilms'	41	0
Gastric	314	41	Mesothel.	23	22	Testis	40	0
Head/Neck	524	37	Renal	102	19	Pitutary	27	0
Bladder	308	34	Thyroid	299	13	Pheochrom.	47	0
Sarcoma	339	31	Hemathol.	1916	12			

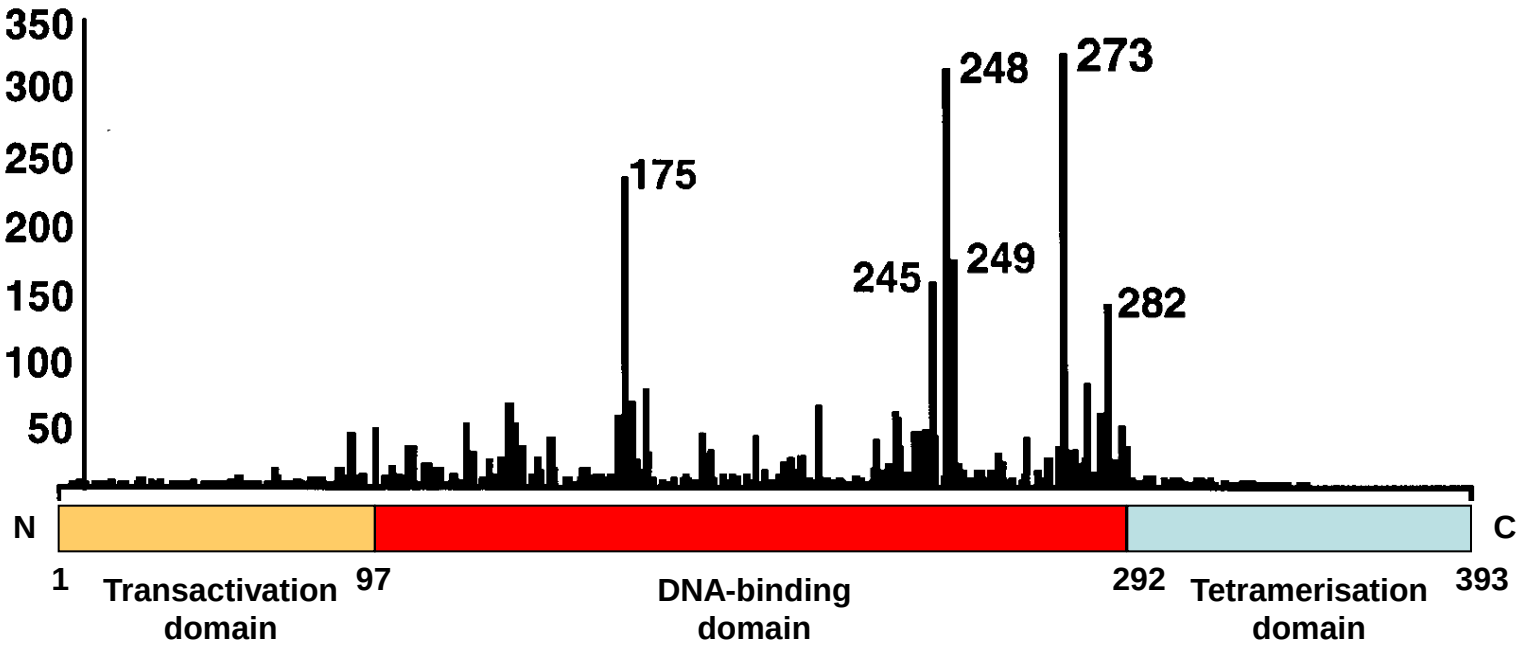
Source: Scientific American, October 1994)

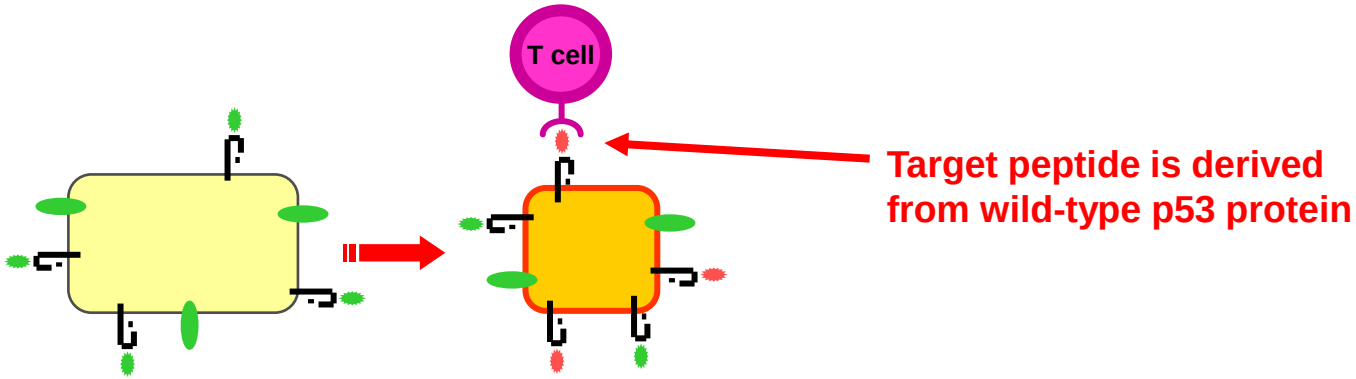
Mutated p53 as a tumour-associated or tumour-specific antigen?



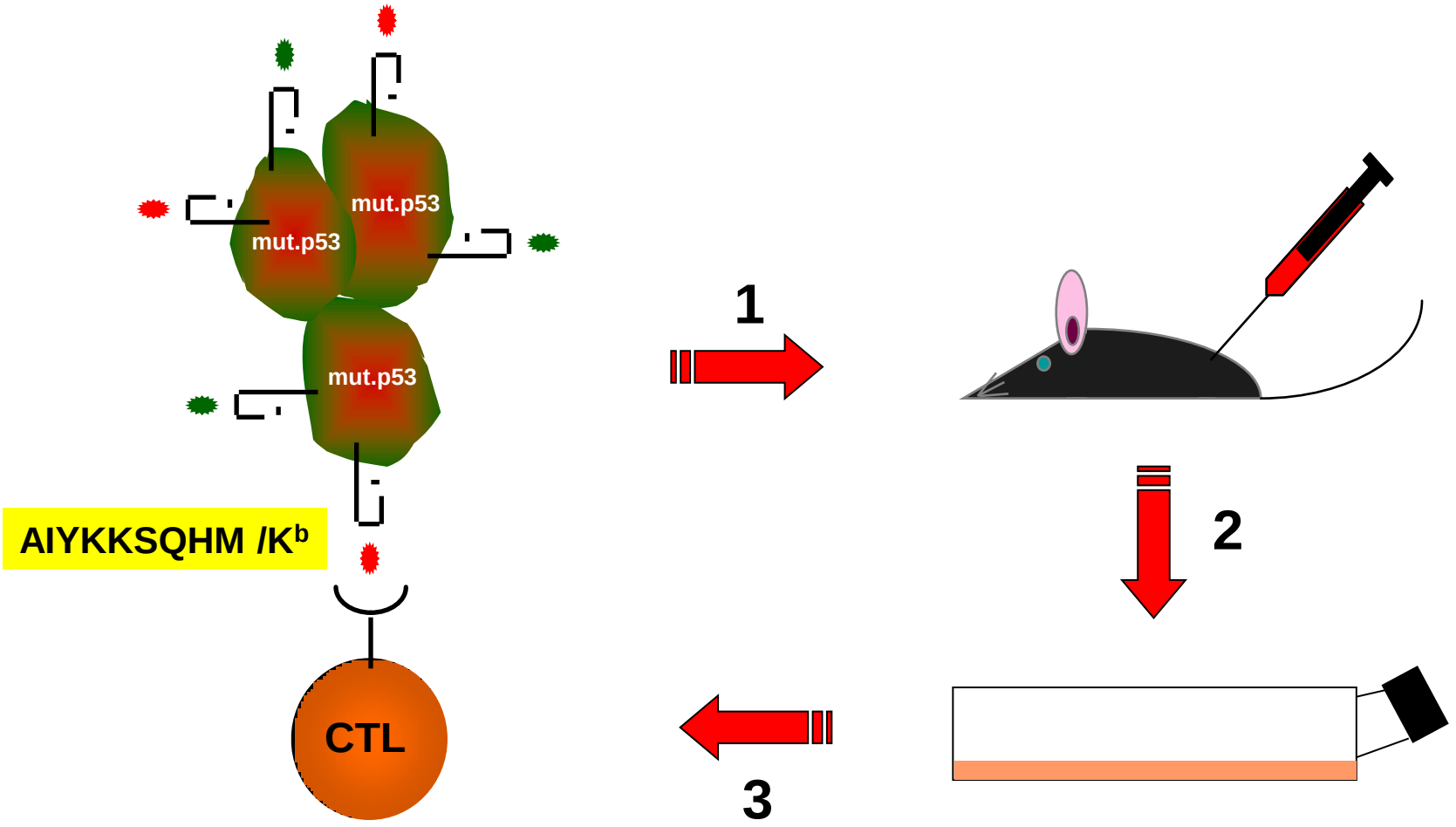
Yanuck et al. (1993) Cancer Res. 53, 3257

Mutations of p53 in human cancer are highly variable

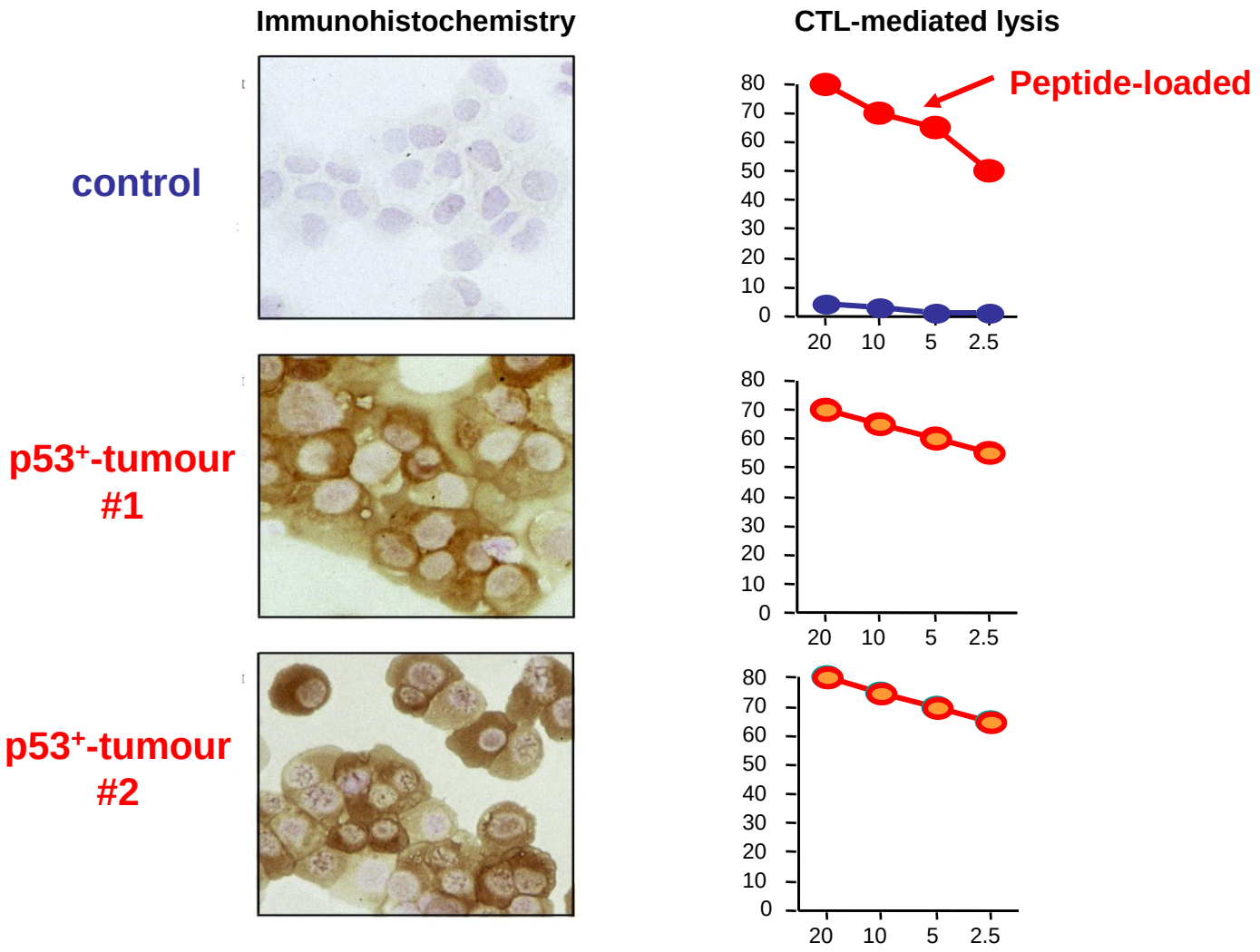




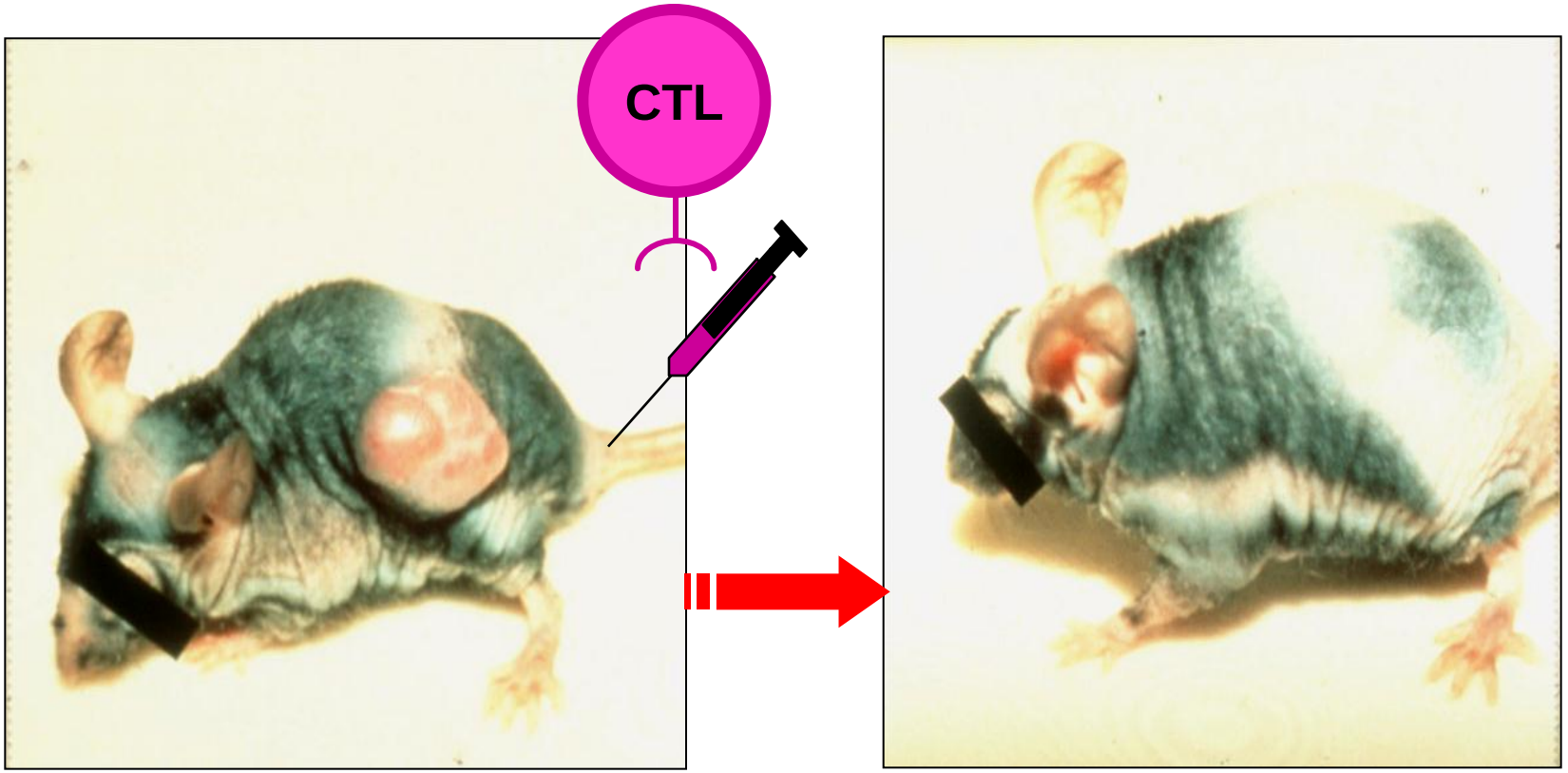
Isolation of p53-specific CTLs from spleens of immunised mice targeting wild-type peptides of p53



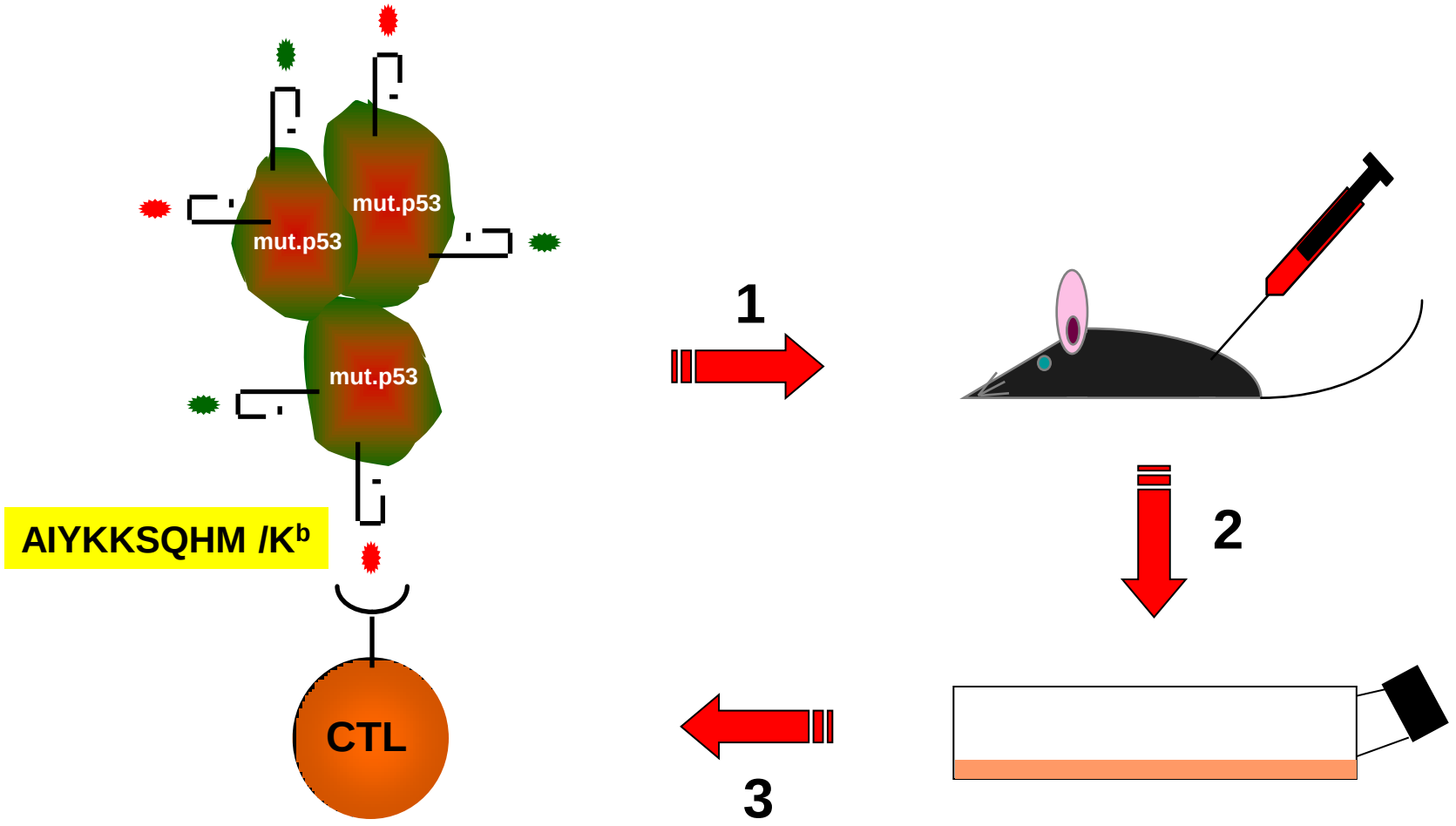
Proof-of-concept: CTLs directed against a wild-type p53 peptide are capable of selectively eliminating tumour cells *in vitro*



Successful cancer immunotherapy by adoptive transfer of *in-vitro*-expanded CTL specific for wild-type p53



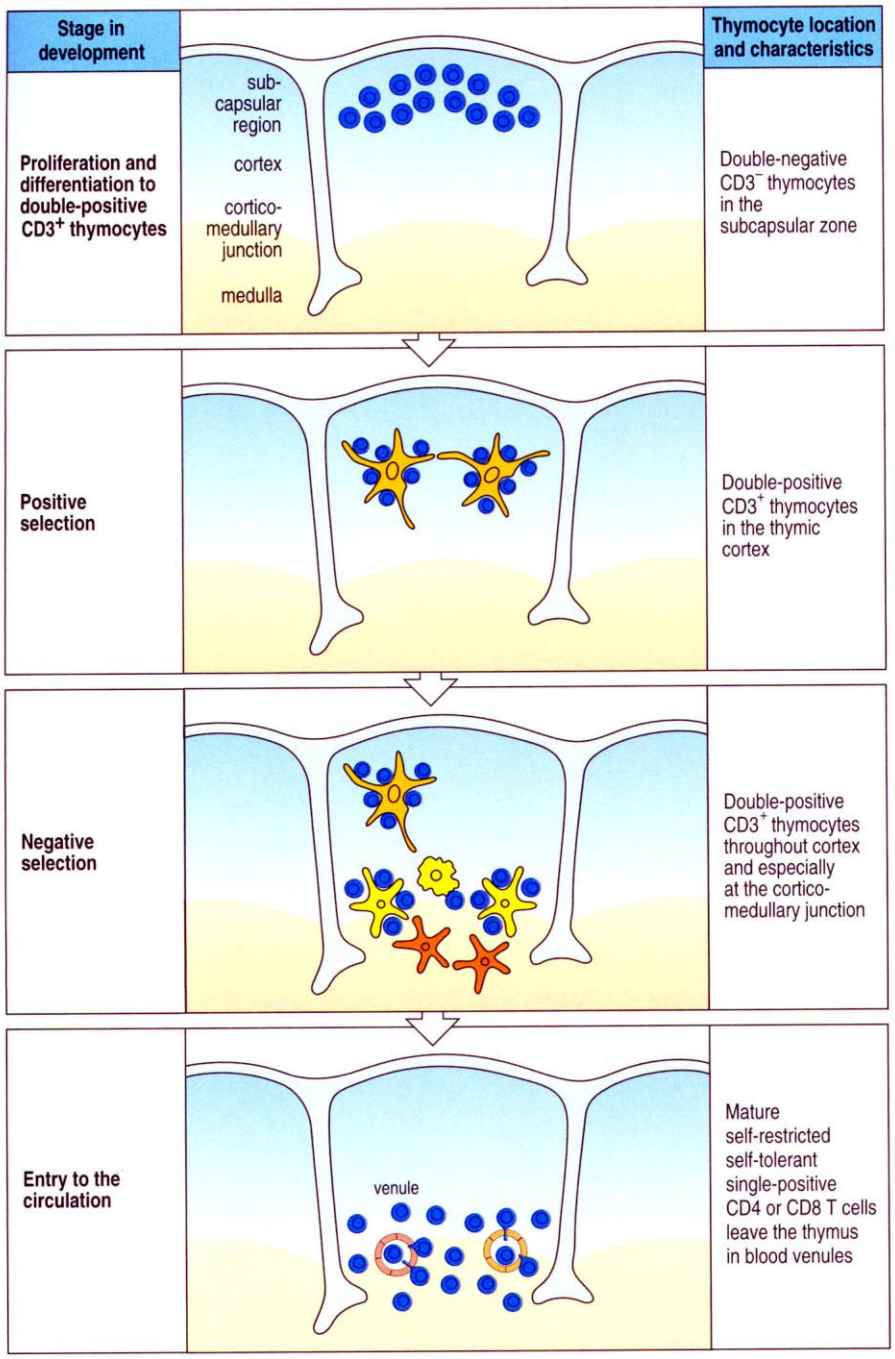
but... p53-specific CTL were isolated from p53-deficient mice



We do not succeed in inducing such CTL in normal p53$^{+/+}$ mice

Question: Why not?

Tolerance induction by negative selection in the thymus

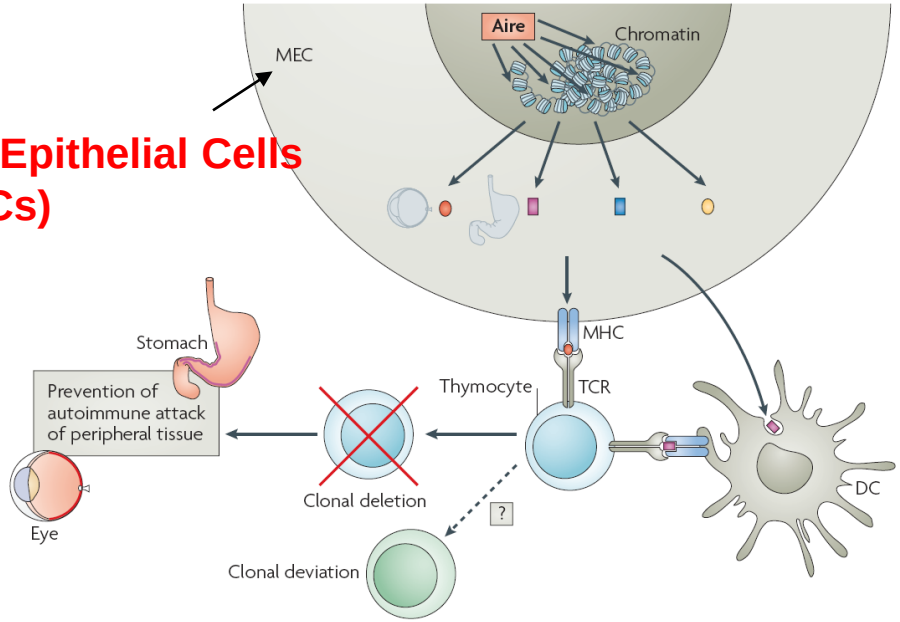


Tolerance induction by thymic negative selection

Central tolerance:

- **Ubiquitously** expressed self antigens (i.e. also in thymus)
- **AIRE-dependent** expression of tissue-specific self antigens* in thymus

medullary Thymic Epithelial Cells (mTECs)

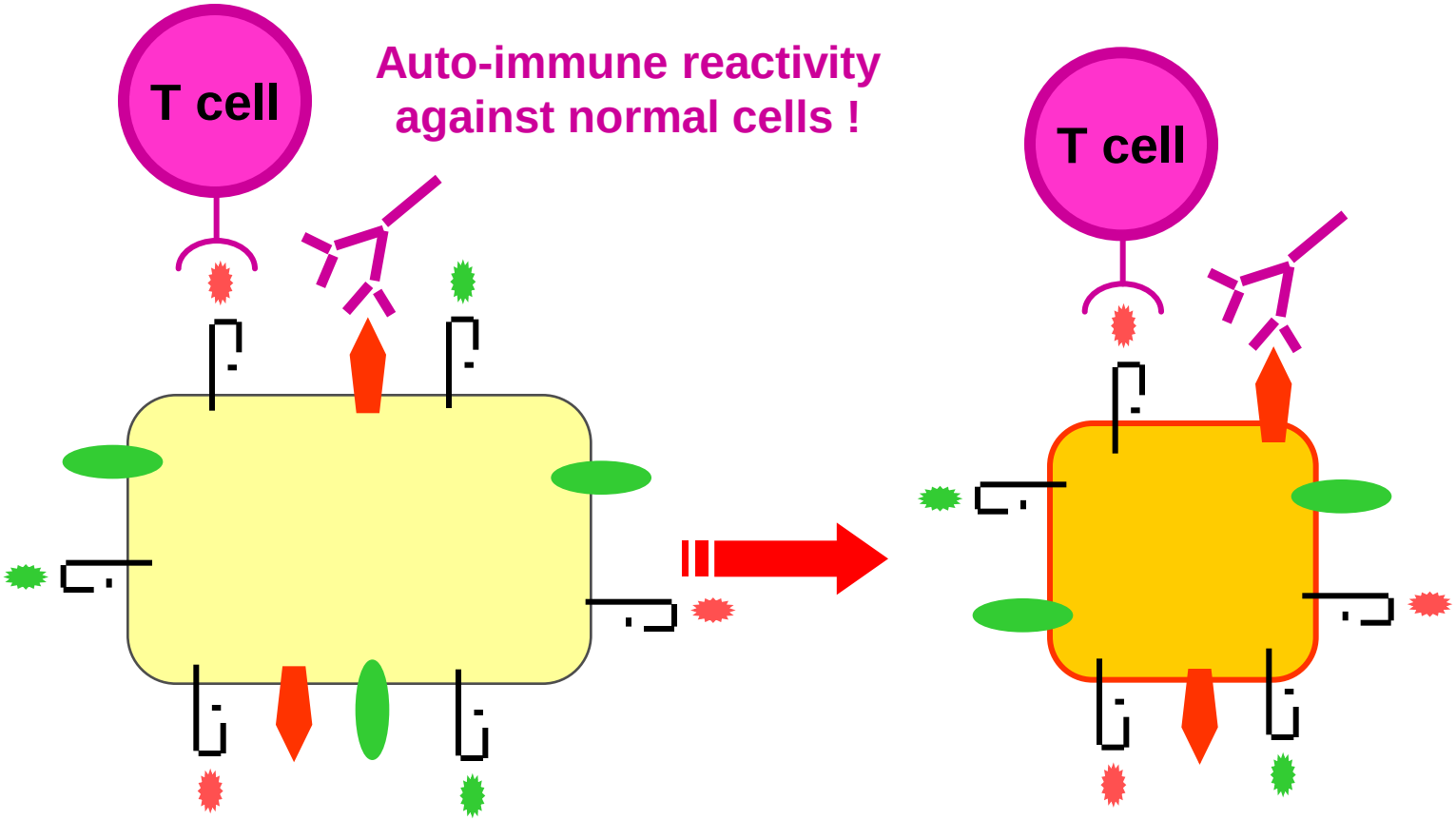


Mathis & Benoist 2007

*** Expressed by mTECs:**
- **MART-1, tyrosinase**
- **MAGE antigens**
- **CEA**

3

Tumour-associated antigens: differentiation (i.e. lineage-specific) auto-antigens



Melanocyte / melanoma – differentiation antigens

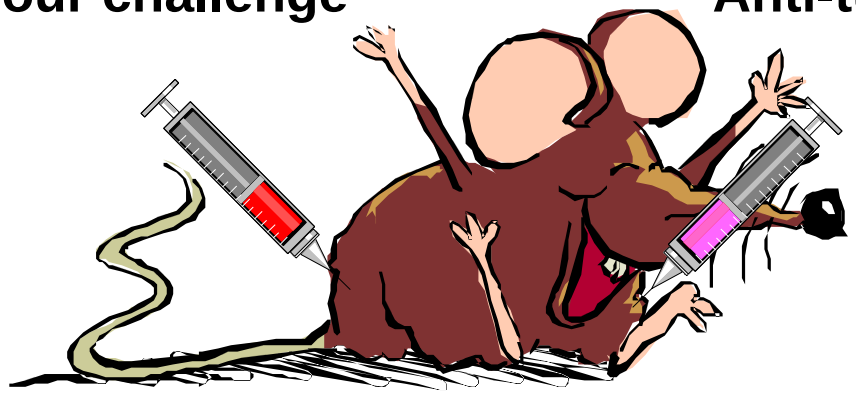
(e.g. tyrosinase)

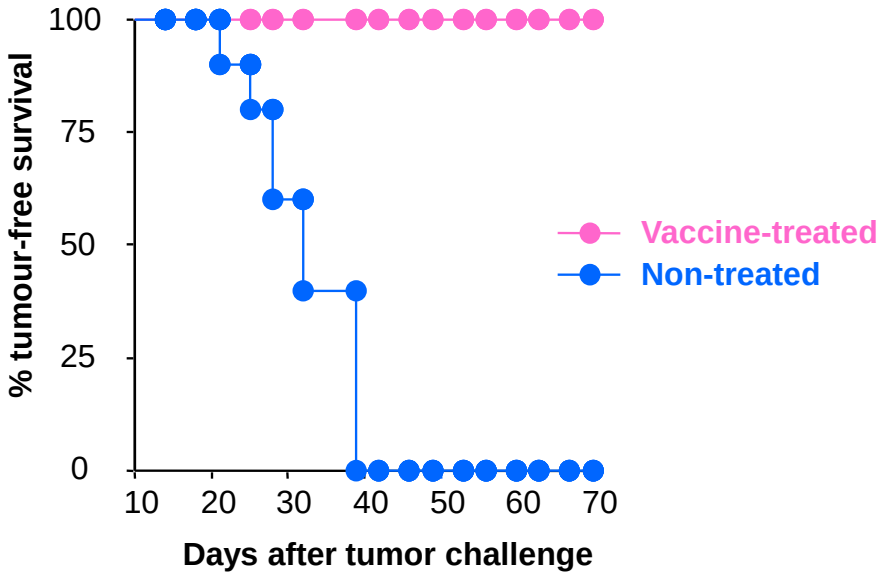
Induction of auto-immune CTLs for therapy of experimental melanoma

Van Elsas et al (1999) J Exp Med 190, 355

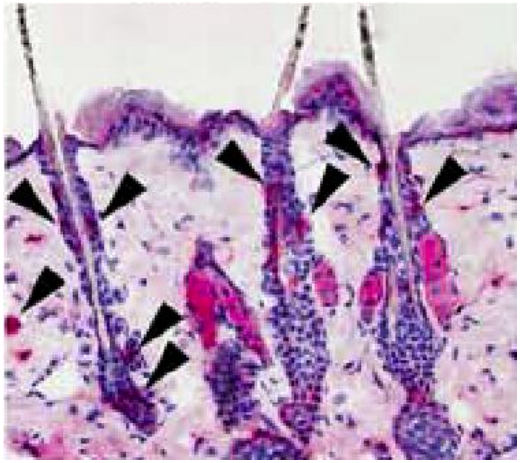
B16 tumour challenge

Anti-tumour vaccination (repeated)



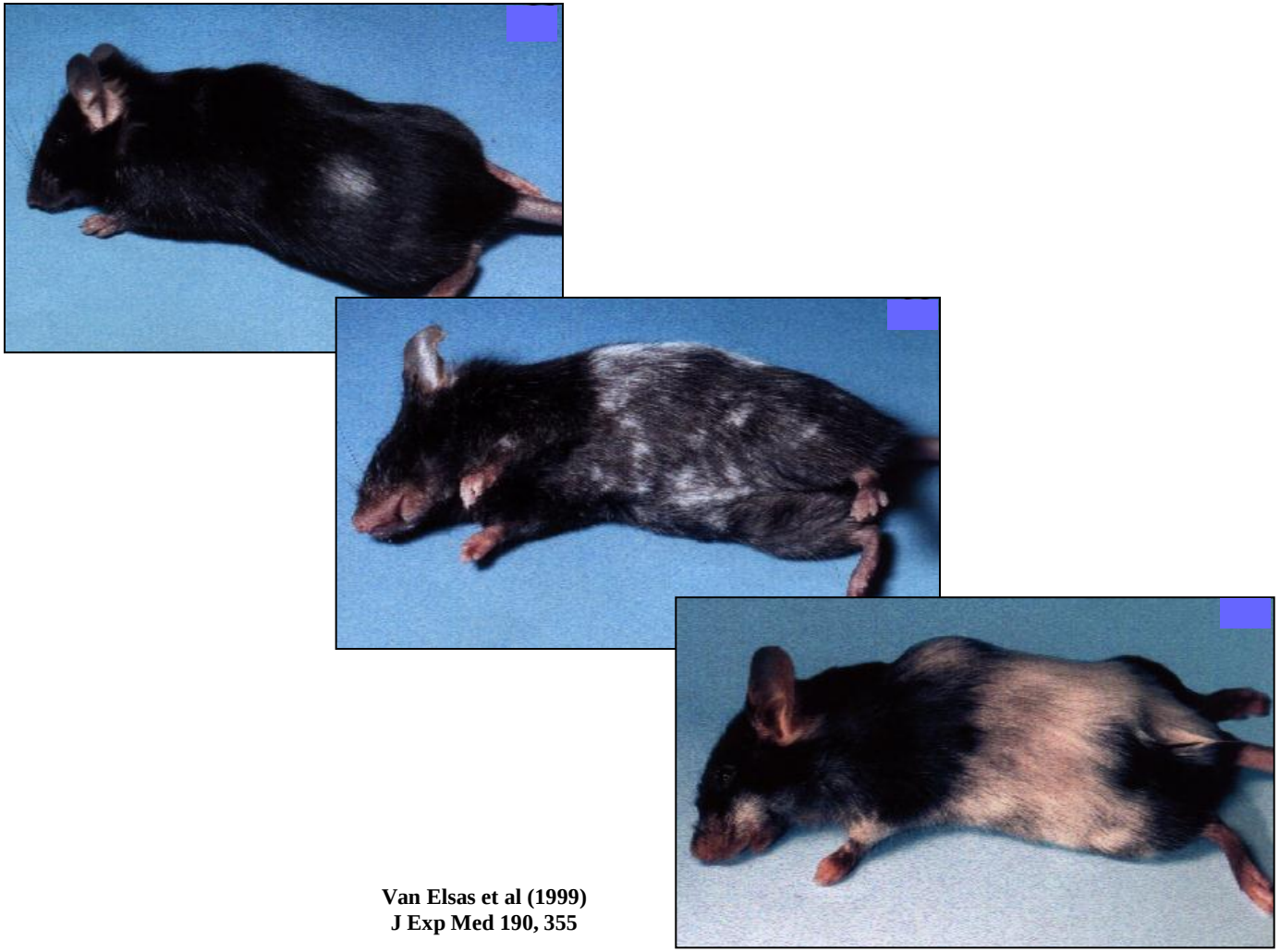


CTLs also attack normal melanocytes



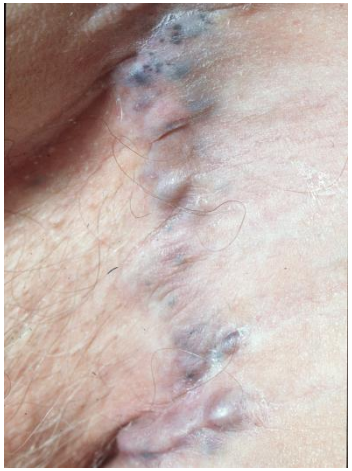
Overwijk et al., unpublished

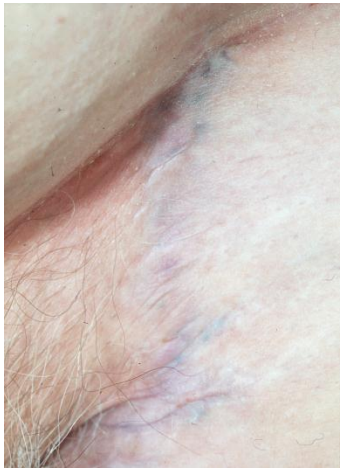
Immunotherapy against melanoma in mice is accompanied by auto-immune skin depigmentation



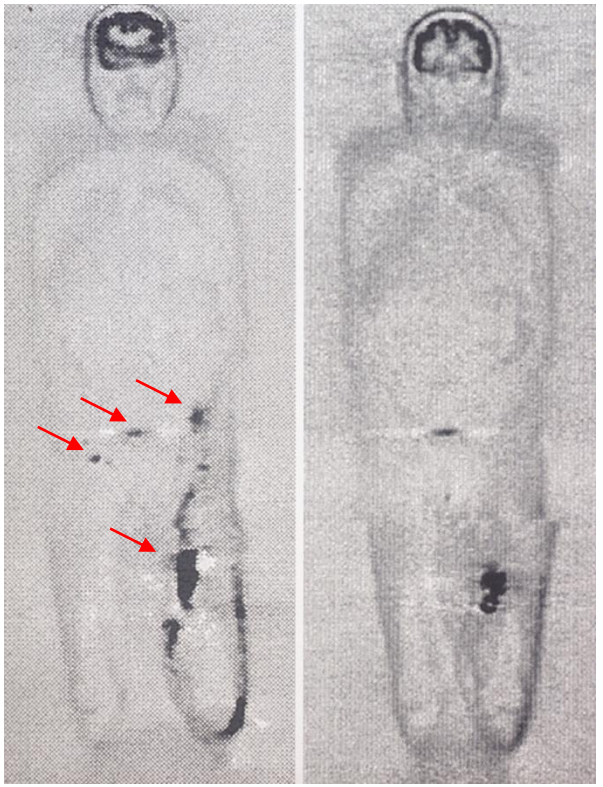
Van Elsas et al (1999)
J Exp Med 190, 355

Immunotherapy of melanoma in cancer patients: dendritic cells pulsed with tumour cell lysate (1)





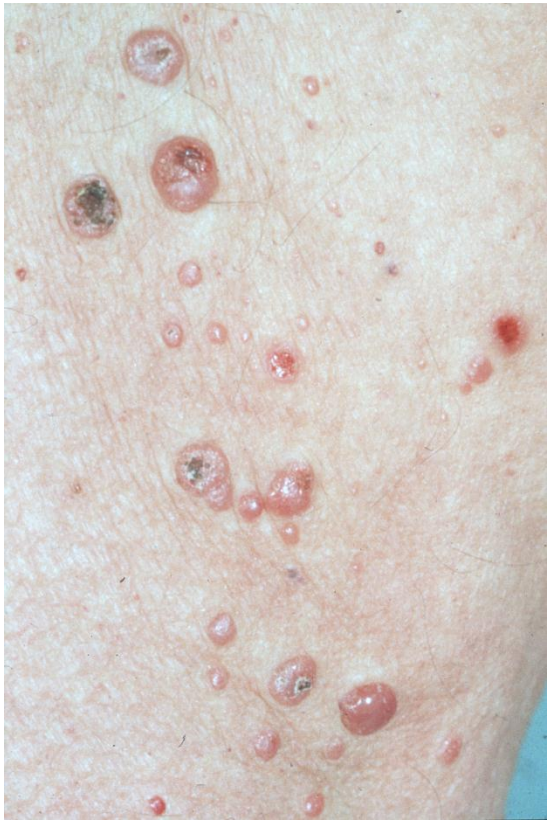
PET scan

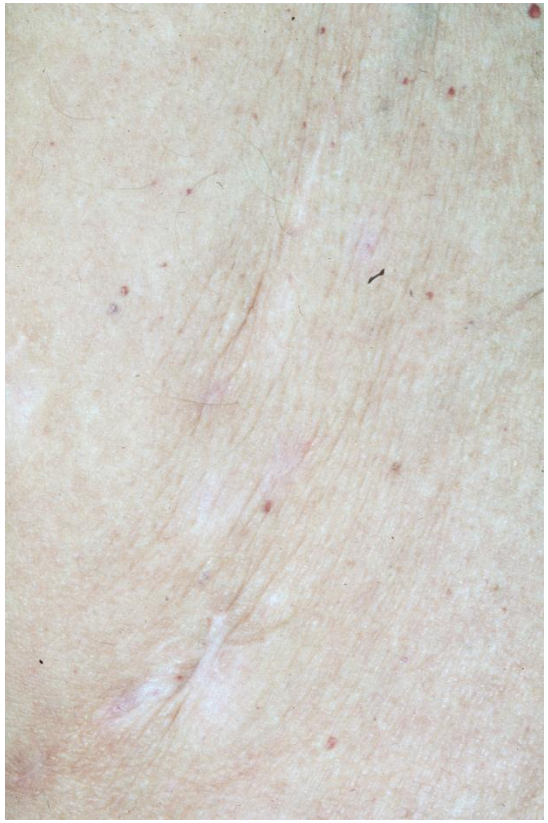


PR → CR

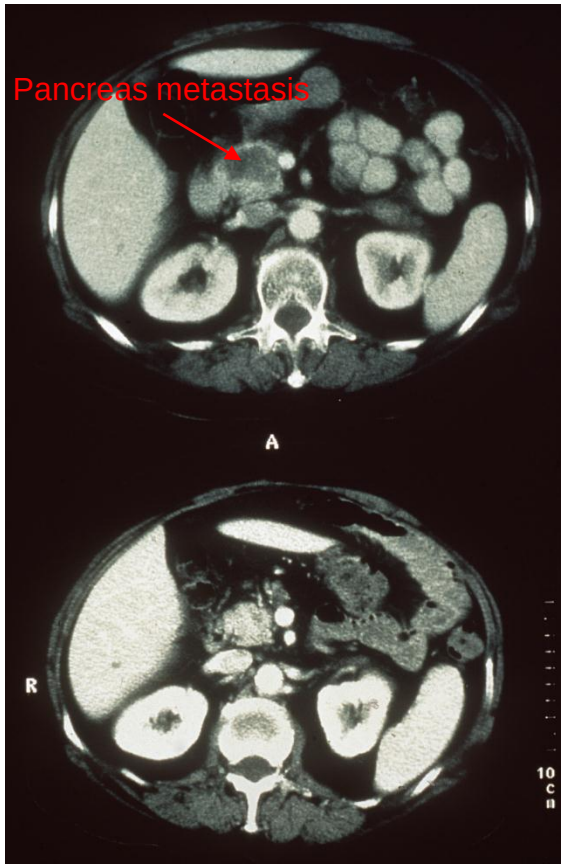
Courtesy of Frank Nestle, Zürich

Immunotherapy of melanoma in cancer patients: dendritic cells pulsed with tumour cell lysate (2)





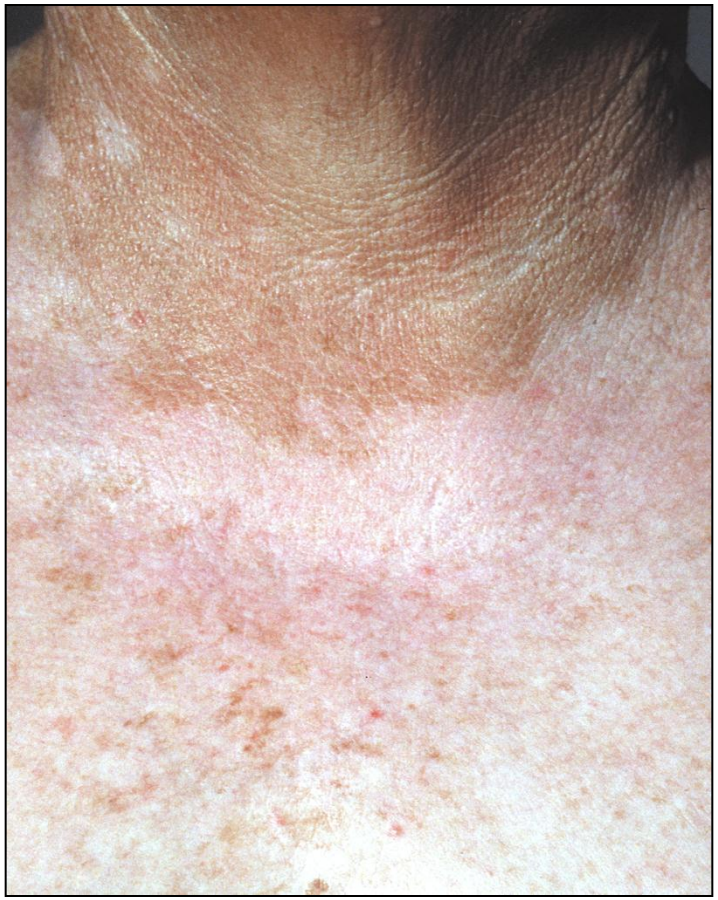
CT scan, cross-section abdomen



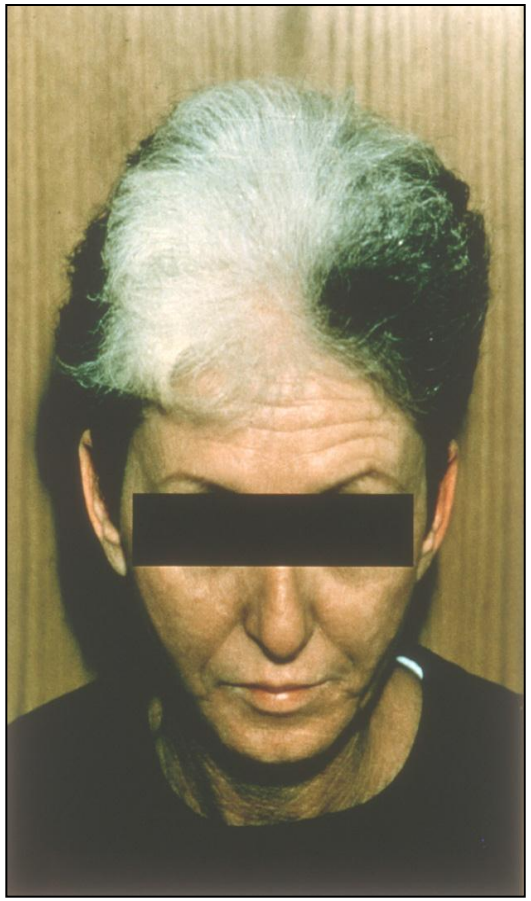
PR

Courtesy of Frank Nestle, Zürich

Auto-immune depigmentation in melanoma patients



Frank Nestle, Zürich
Switzerland



Nick Restifo & Steve Rosenberg
NIH, USA

Targeting of tumour-associated auto-antigens for T cell-mediated immuno-therapy of cancer

Two major obstacles:

1. **Auto-immune responses against normal tissues**

2. **Immunological tolerance**
   - **Normal tolerance to auto-antigens**
   - **Tumour-induced tolerance**

Question:

Thymic tolerance prevents induction of CTL against the auto-antigen p53 in normal mice.

However, such CTL can be induced against other auto-antigens, e.g. Tyrosinase.

What could be the reason for this?

Another question:

Immunotherapy against cancer can be associated with auto-immunity against normal somatic tissues.

In the case of melanoma this is a nuisance, but not dangerous.

In which cases would this be dangerous?

Conclusions

- **Preventive and therapeutic immune intervention against virus-induced cancers comes within reach**

- **Immunotherapy of non-virally induced cancers:**

  - **First promising results in clinical studies have been obtained…**
    however, complete, and hence irreversible, tumour rejection is still rare.

  - **Immunological tolerance, induced by normal tissues or by the tumour itself, still constitutes a major obstacle.**

What you should now be able to do

- Outline evidence for the importance of tumour immune surveillance by the immune system
- understand that immune responses to tumours have some similarities with those to virus-infected cells
- Explain the concept of tumour-associated antigens
- Outline approaches that are being developed for tumour immunotherapy

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