

Basic Immunology

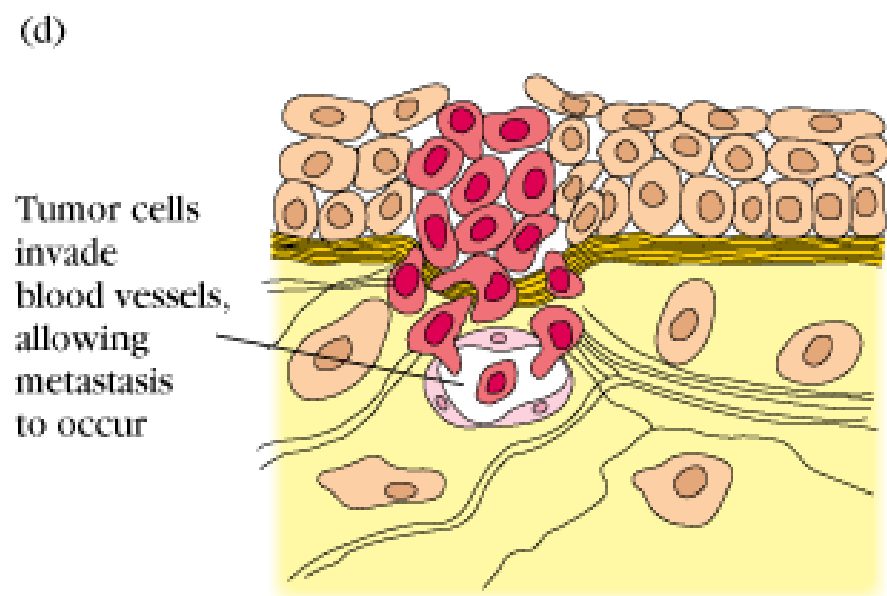
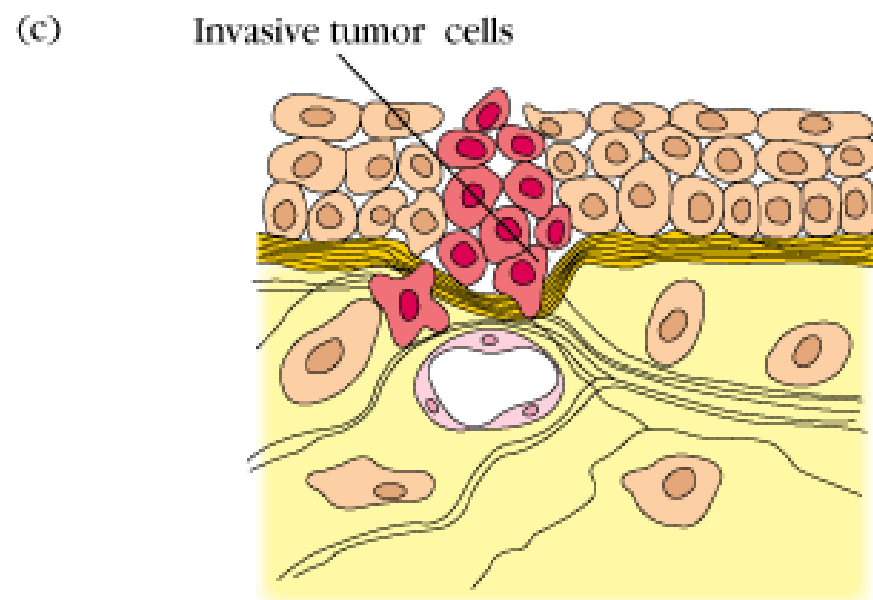
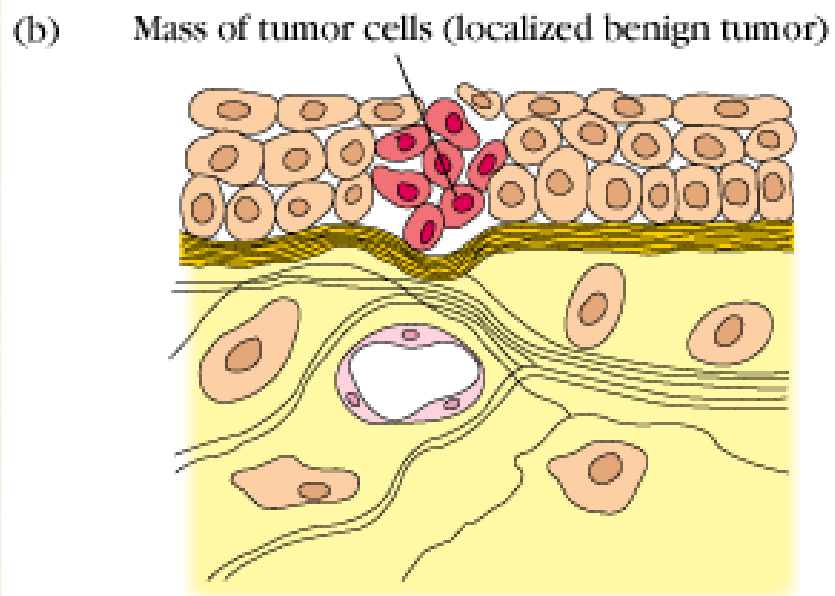
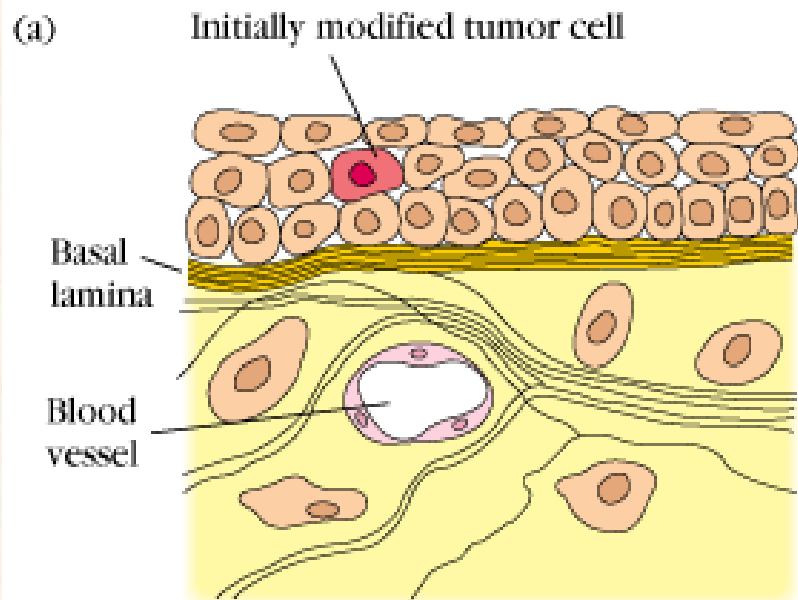
Lecture 27th - 28th

Immunity against tumors

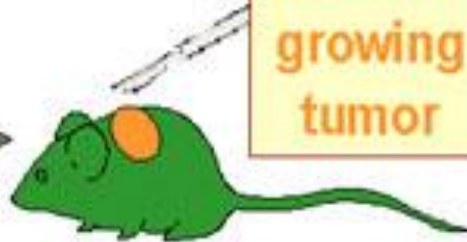
Tumor- and tumor associated antigens. Tumor escape. Trends in immunotherapy against cancer.

Immunological aspects of organ transplantation

Tolerance and graft rejection. Host versus graft and graft versus host reactions. Immunosuppression.



Inject carcinogen



**Remove
growing
tumor**



Isolate tumor cells



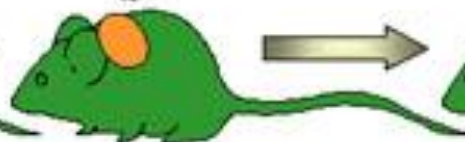
**Tumor cells
injected**



**Remove
growing
tumor**

**Challenge with
same tumor**

No tumor



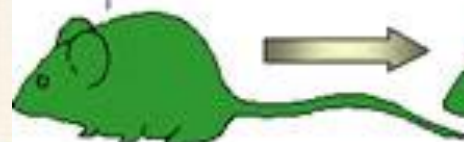
**Tumor cells
injected**



**Remove
growing
tumor**

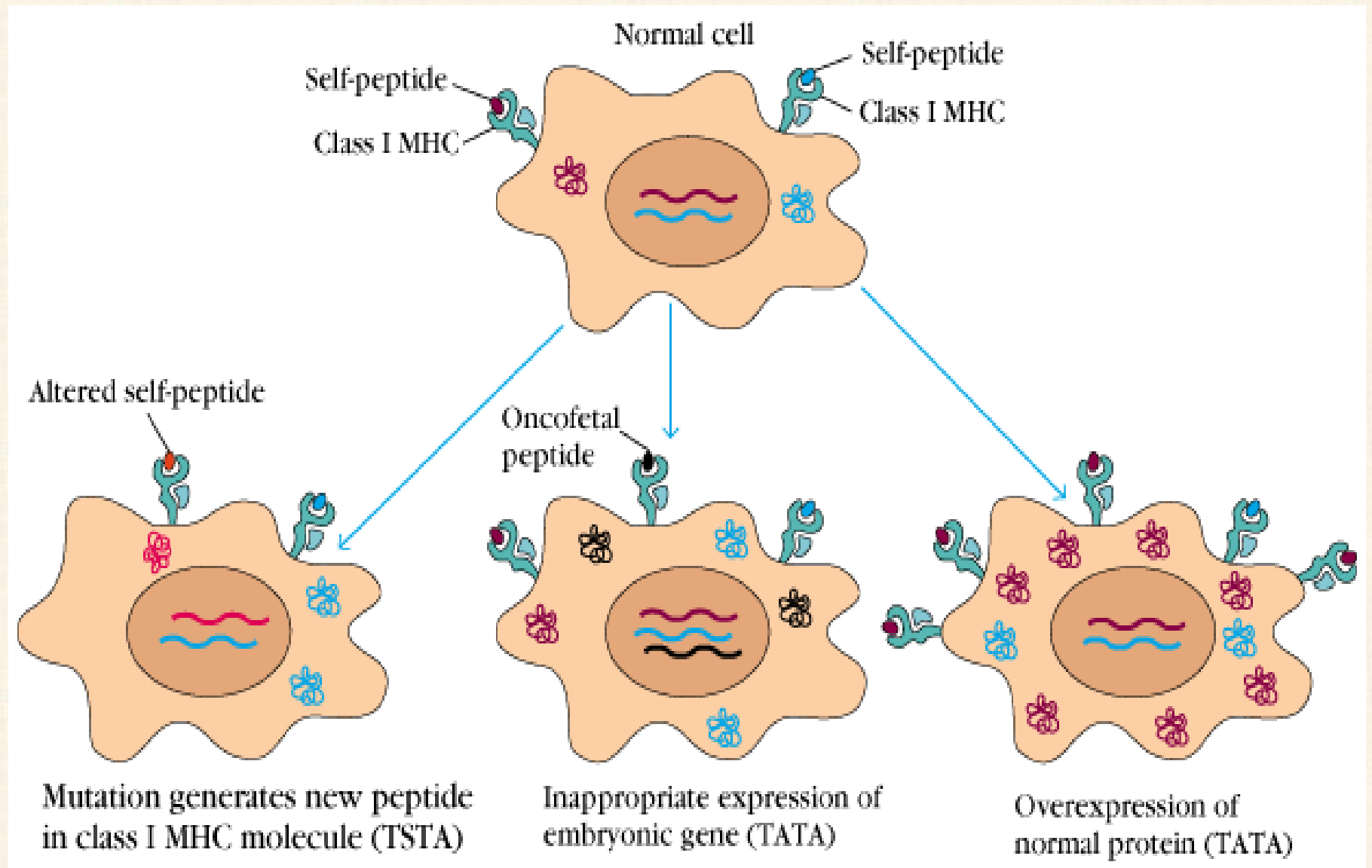
**Challenge with
different tumor**

Tumor



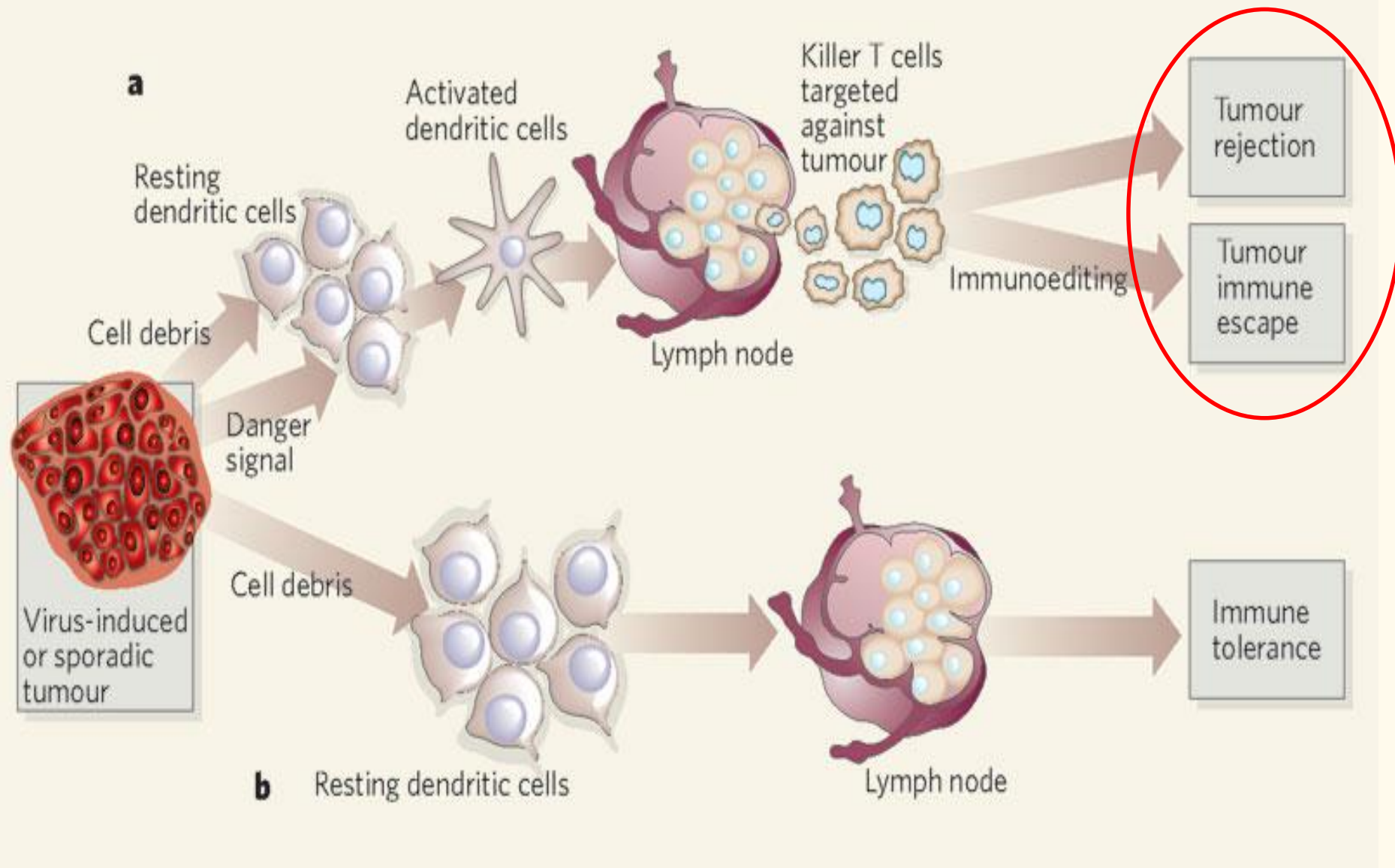
Cell surface antigens expressed on tumor cells

- Normal structures without alterations
- Genetically modified (mutated) structures as *tumor specific antigens*
- Normal structures but expressed in inappropriate differentiation stage as *tumor associated antigens*



Tumor Specific Antigen

- TSA – mutations of somatic cells induced by chemical carcinogenesis, viruses or x-rays
- Each carcinogenic factor induces a unique and specific class of antigens. NO GENERAL TUMOR SPECIFIC ANTIGEN EXISTS!
- TSA is recognized (according to the individual MHC haplotype) by the immune system and induces targeting type immune response or tolerance

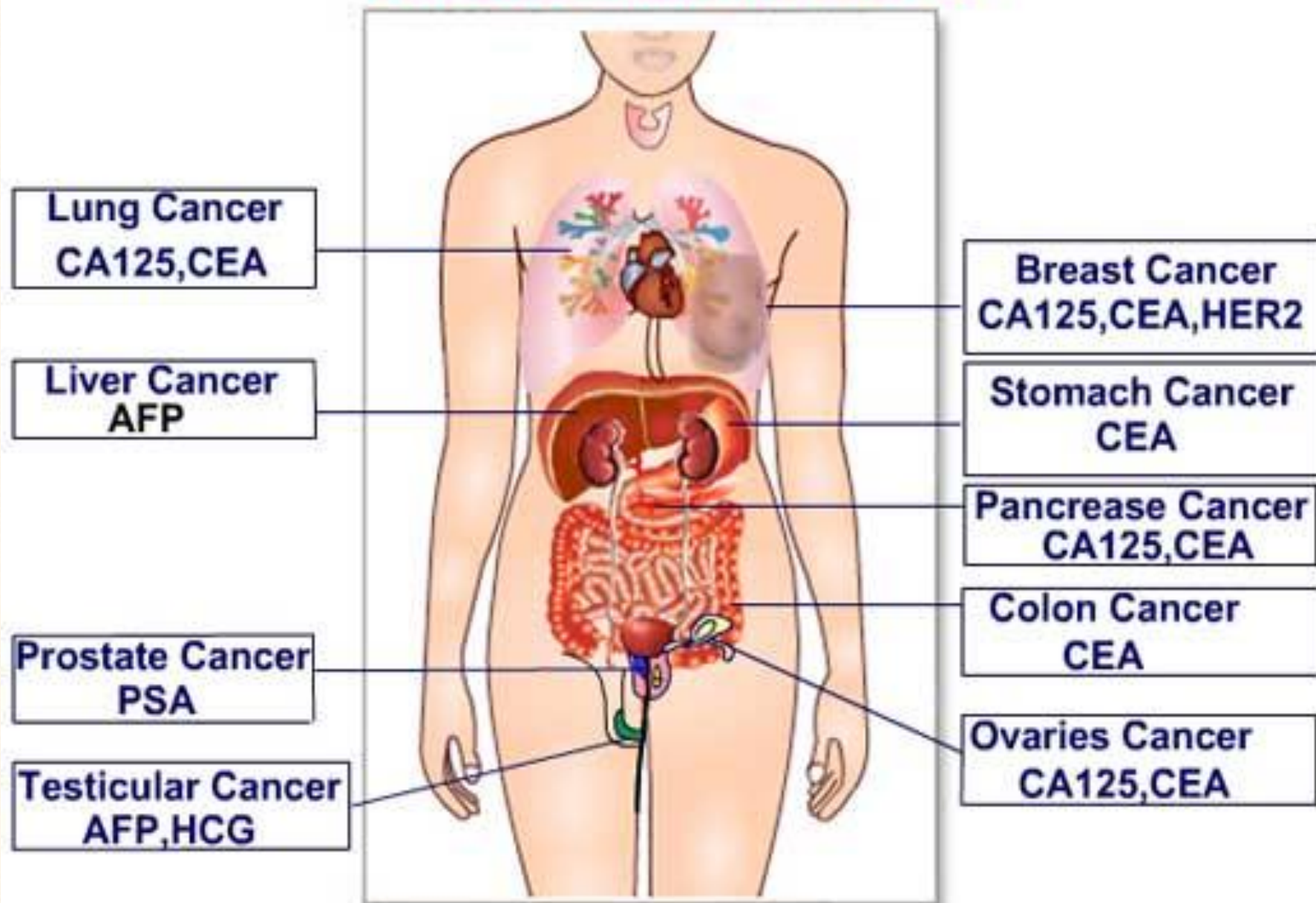


Tumor Associated Antigen

Products (e.g. hormones, growth factors, cell surface receptors, differentiation molecules etc.) of both normal and altered cells during their differentiation.

Production of TAAs is not related with tumorous transformation exclusively, however, expression profile of TAAs could be characteristic in some tumors, and useful as „tumor markers” in differential diagnosis or in the monitoring of therapeutic efficiency.

Clinical Tumor Markers



Often tumor markers

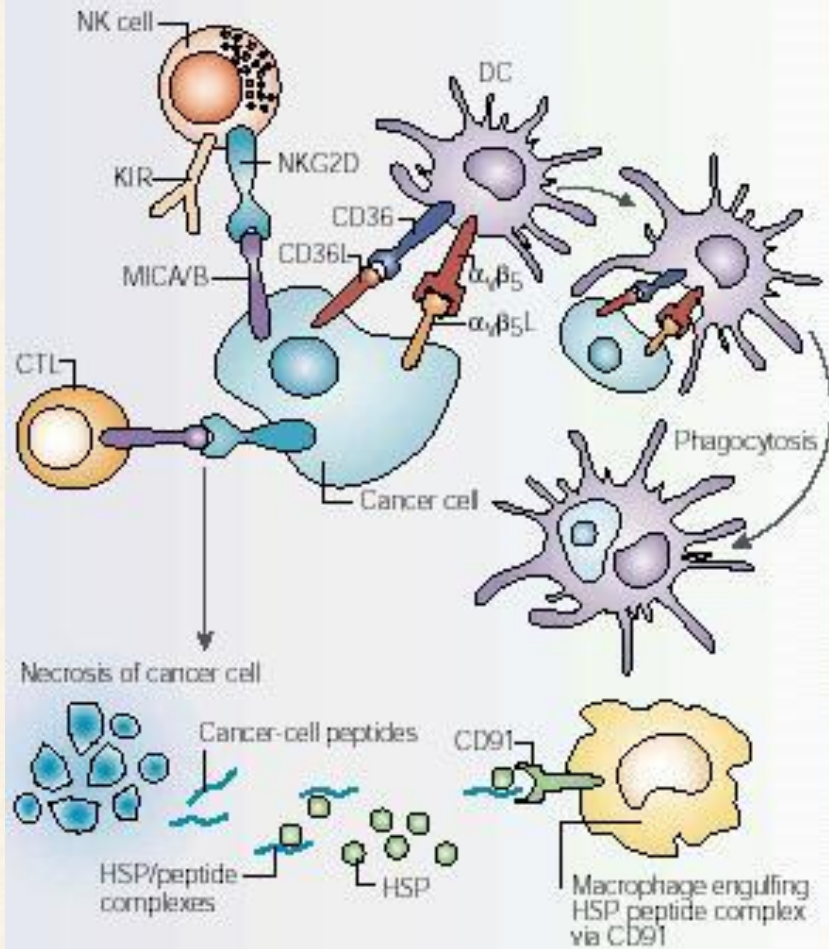
Tumor markers	Abbreviation	Oncological application
Alfa-foetoprotein	AFP	Liver and germ cell tumors
Cancer antigen 125	CA 125	ovarian tumors
Cancer antigen 15,3	CA 15,3	Breast cancer
Cancer antigen 72,4	CA 72,4	Gastric cancer
Cancer antigen 19,9	CA 19,9	Pancreatic cancer
Carcinoembrional antigen	CEA	Gastrointestinal cancers
Neuronspecific enolase	NSE	Small cell lung cancer
Prostate specific antigen	PSA	Prostate cancer
Squamous cell carcinoma antigen	SCC	Planocellular cancers
Tissue polypeptide antigen	TPA	Urinary bladder and lung cancer
Tissue polypeptide-specific antigen	TPS	Metastatic breast cancer

Immune reactions against tumor cells

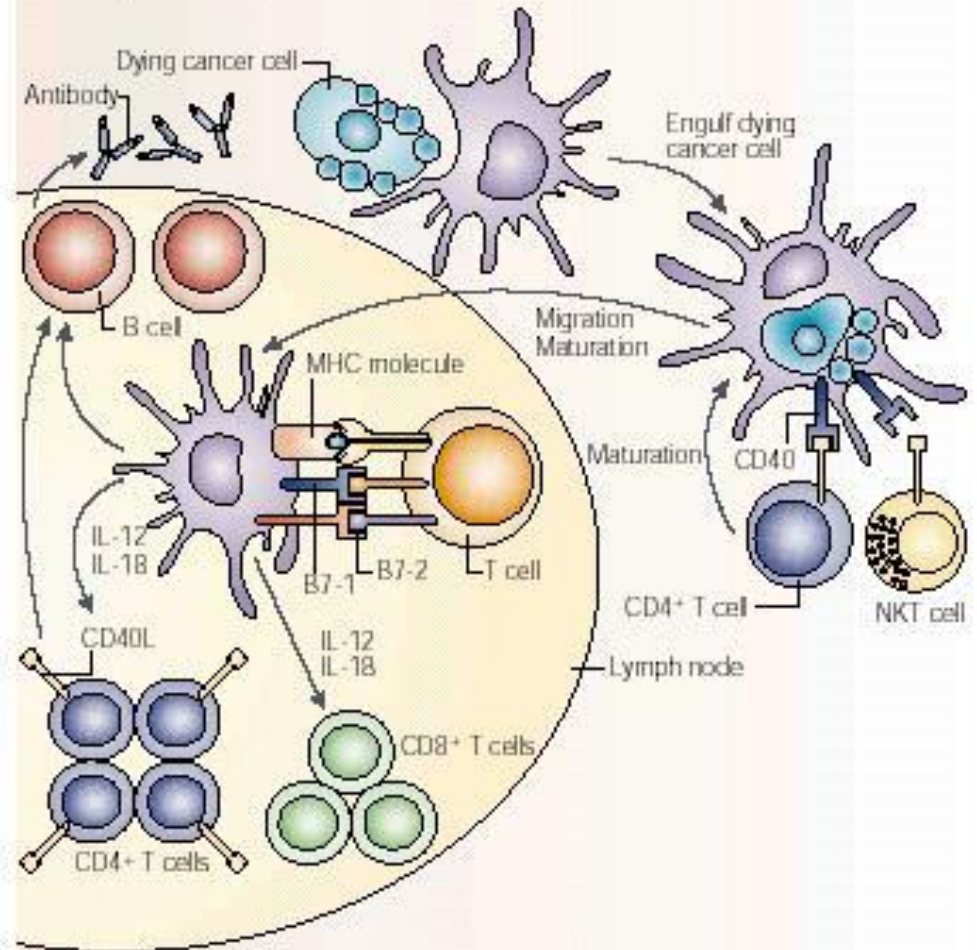
- **T cell mediated (CD8+, CD4+Th1, NK)**
- **macrophage mediated**
- **immunoglobulin mediated (ADCC)**
- **network of cytotoxic cytokines**

Cell mediated immunity against malignant tumors

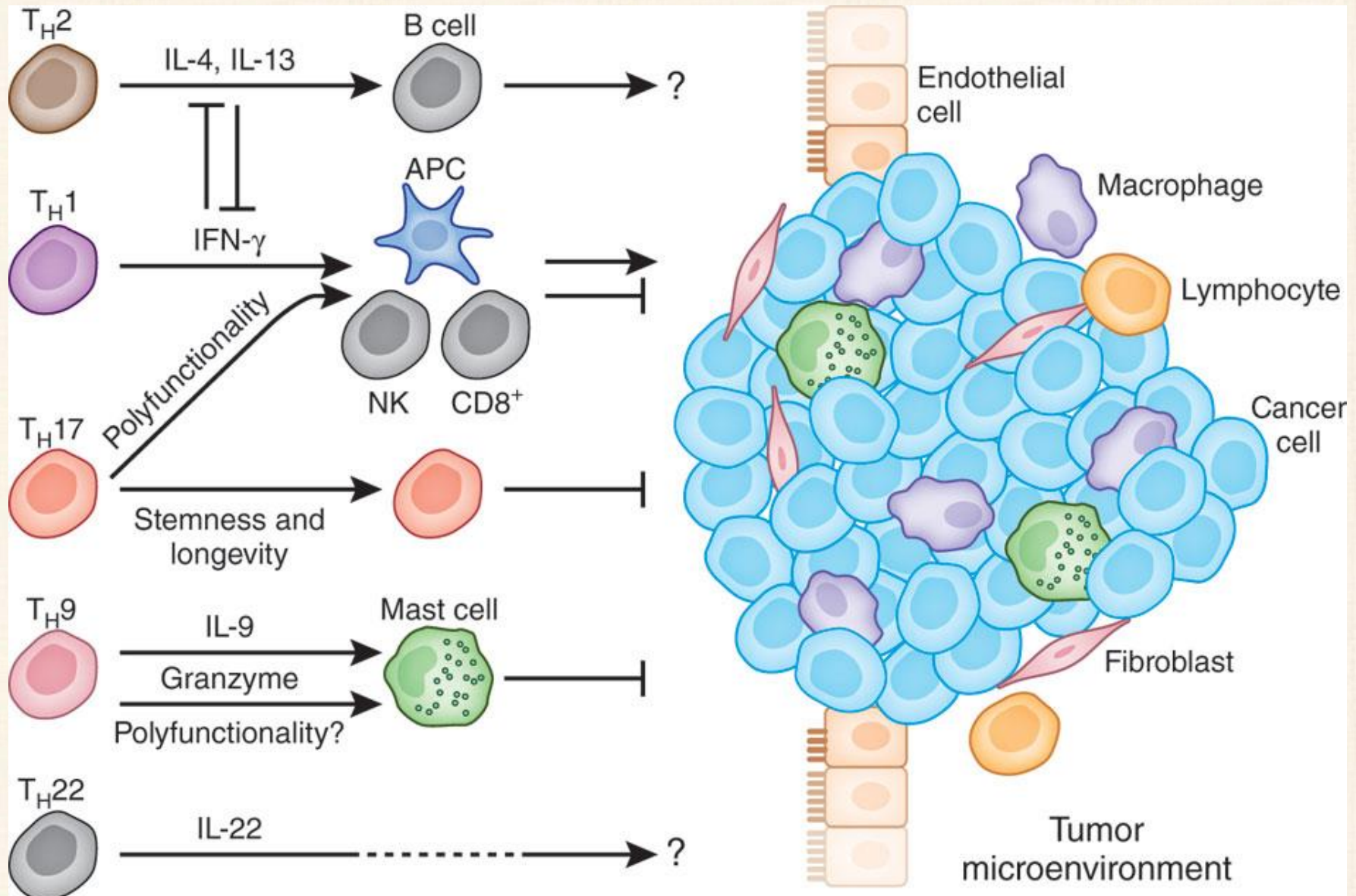
a Innate immunity



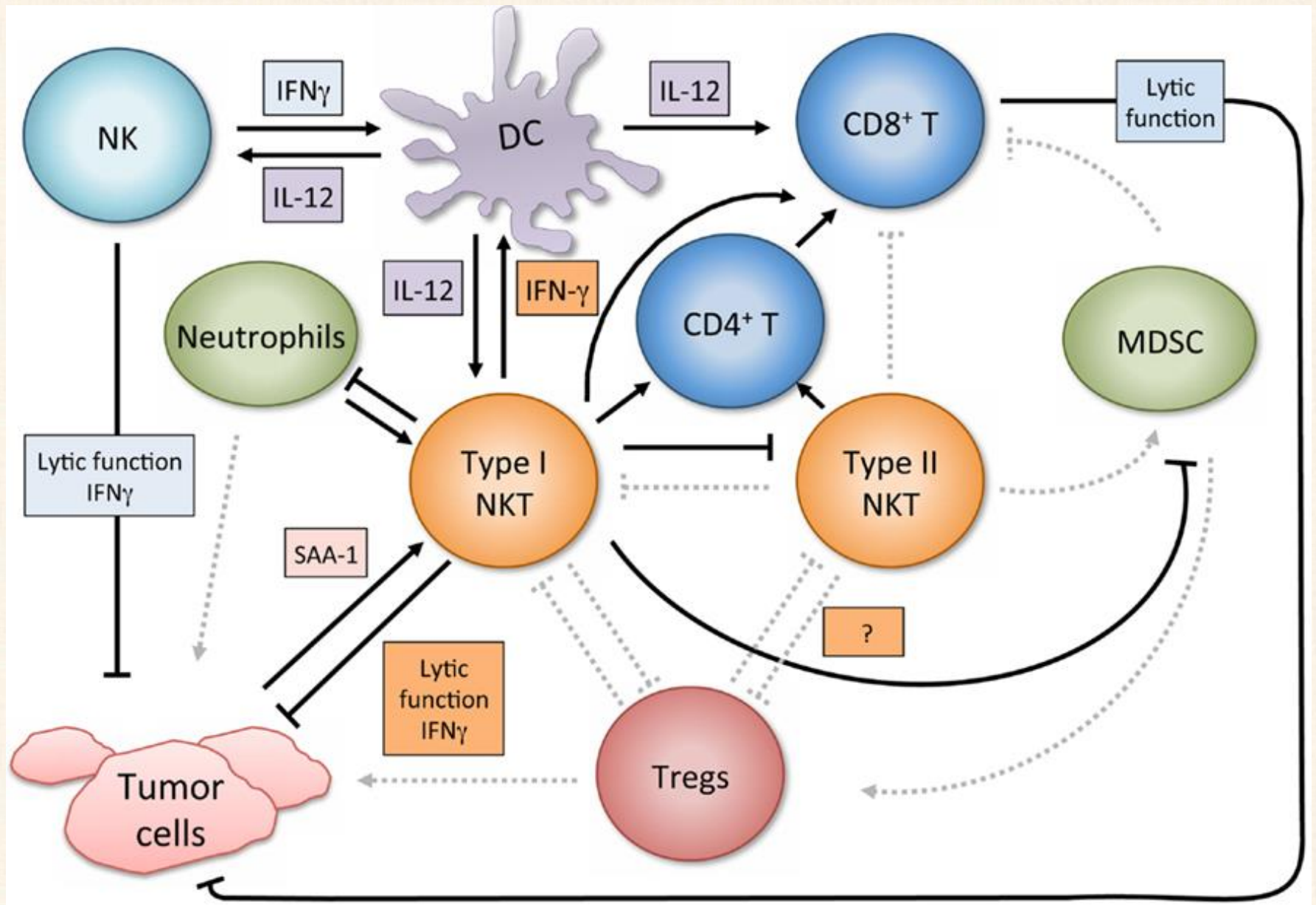
b Adaptive immunity



Anti-tumor activity of CD4 T cell subsets

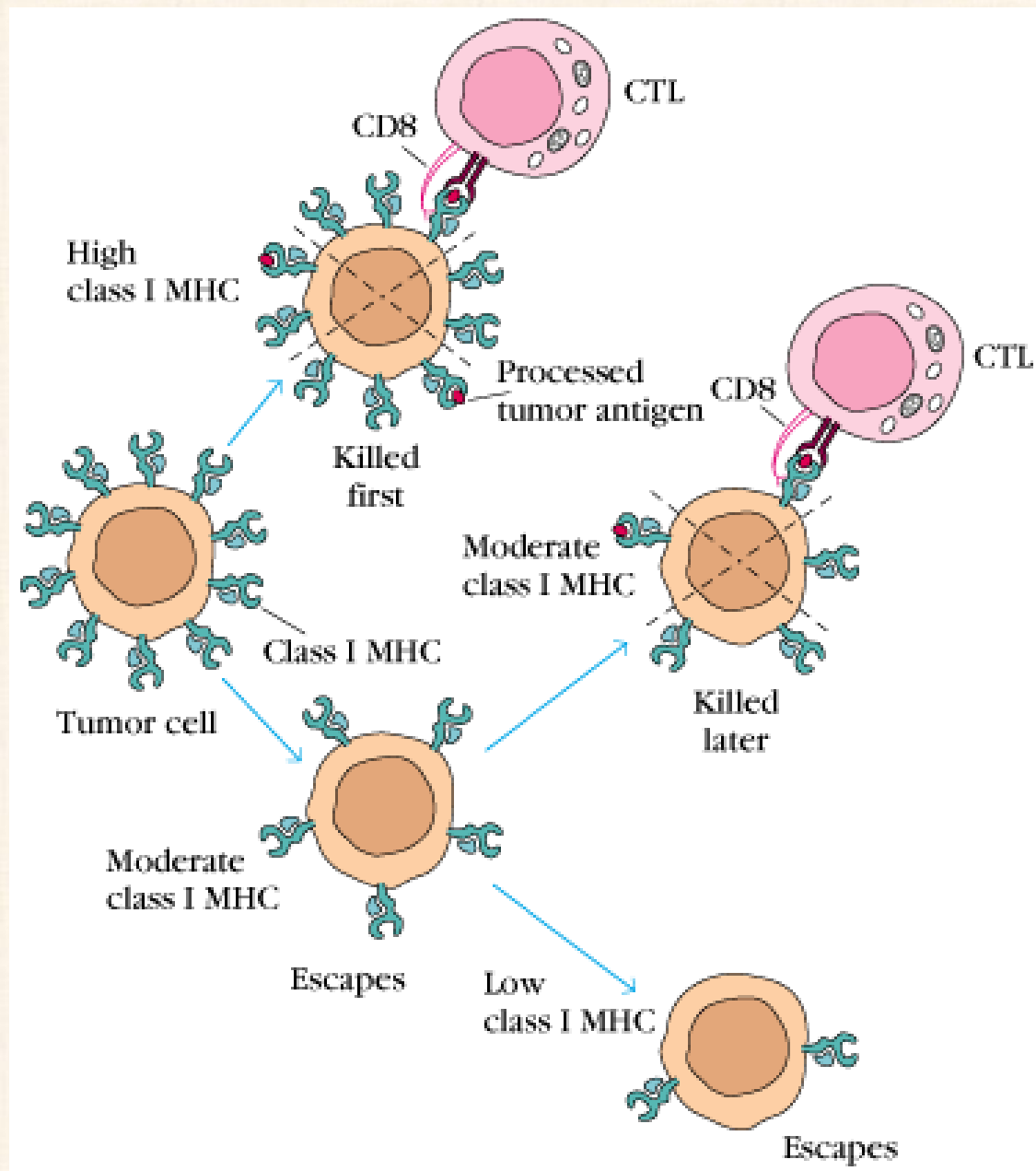


Enhancement of tumor immunity by NKT cells



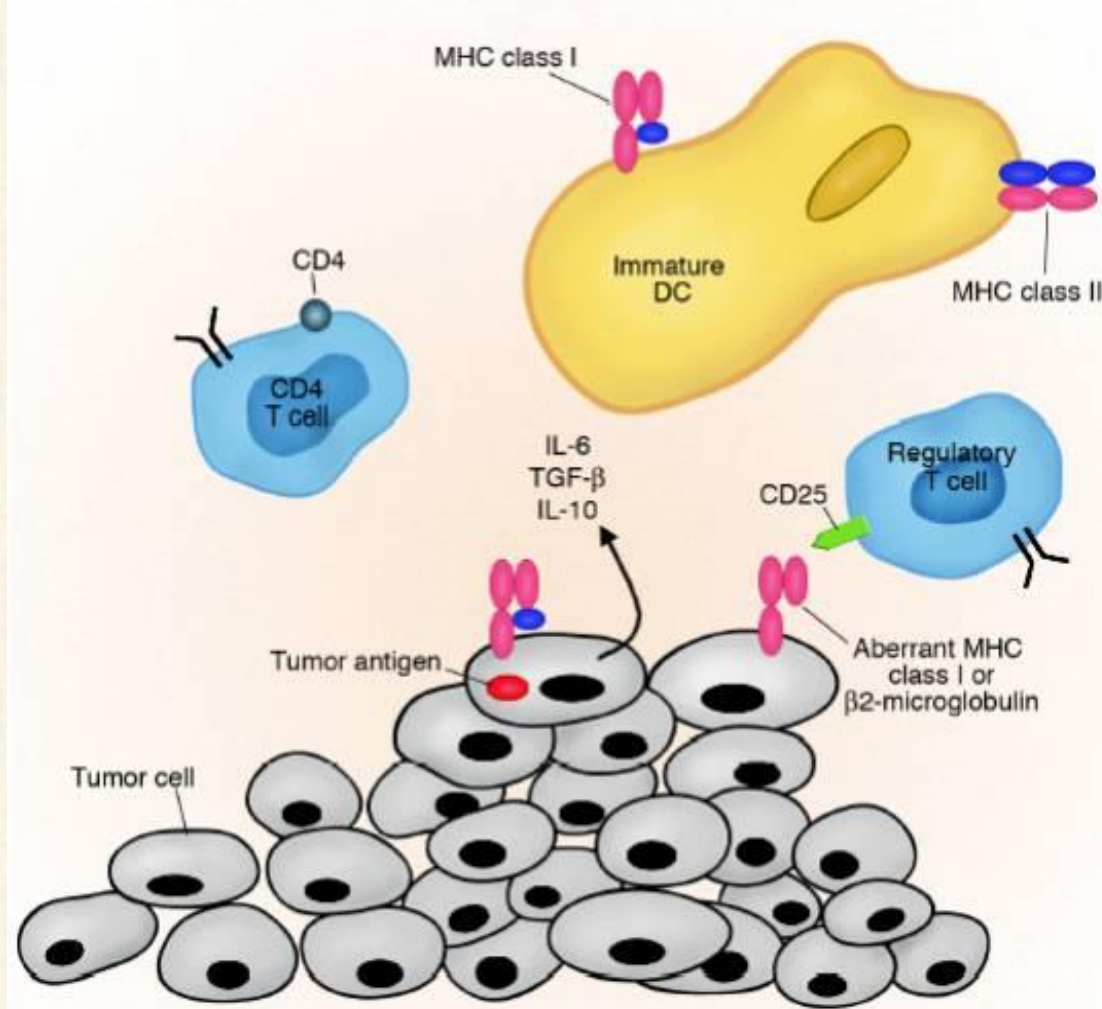
Tumor escape

- **Over expression or down regulation of MHC-I.**
- **over expression of FcR**
- **deficiency of cytotoxic cytokine receptors**
- **production of different glycoproteins with masking effects**

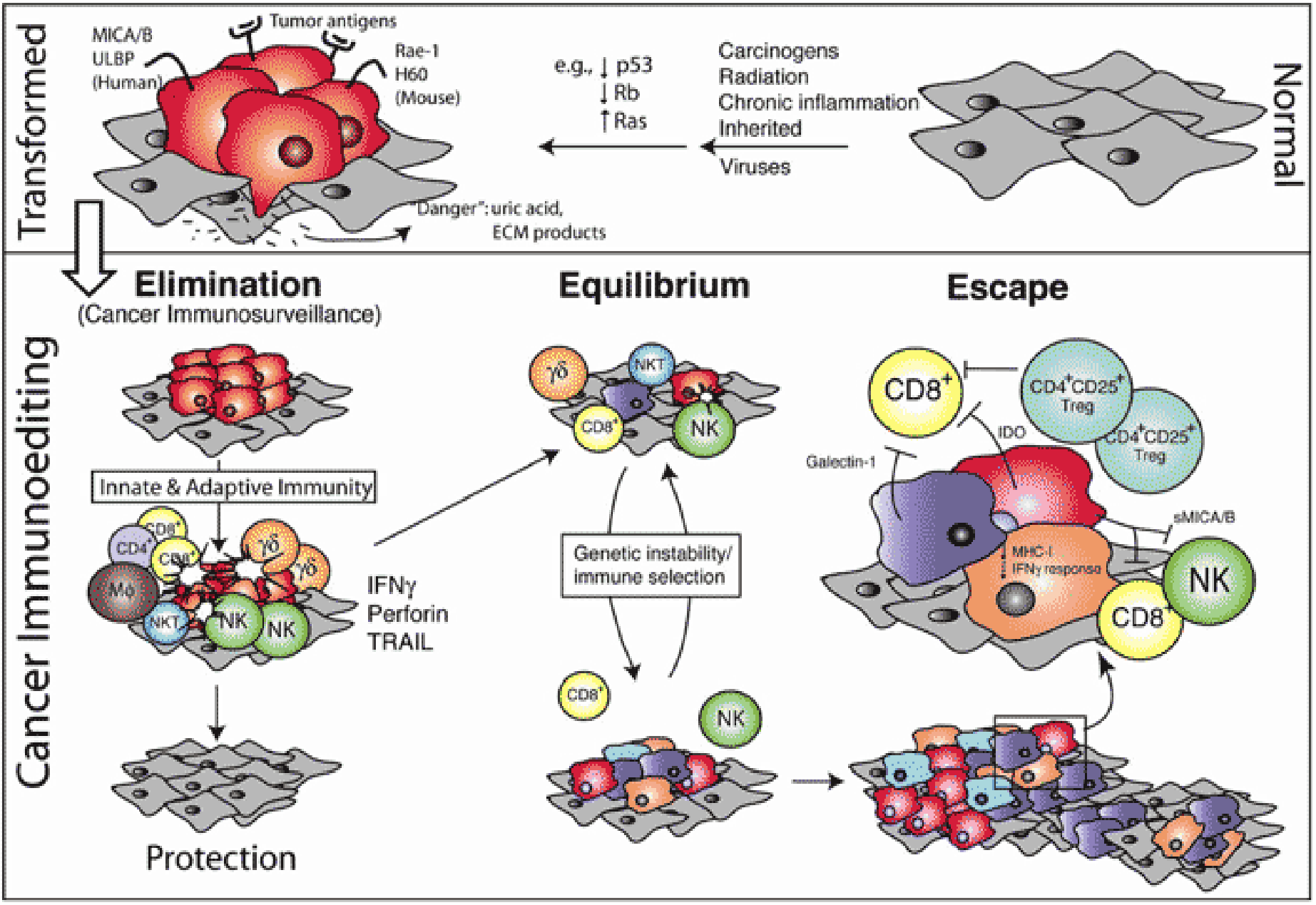




Tumor escape according to the local environment



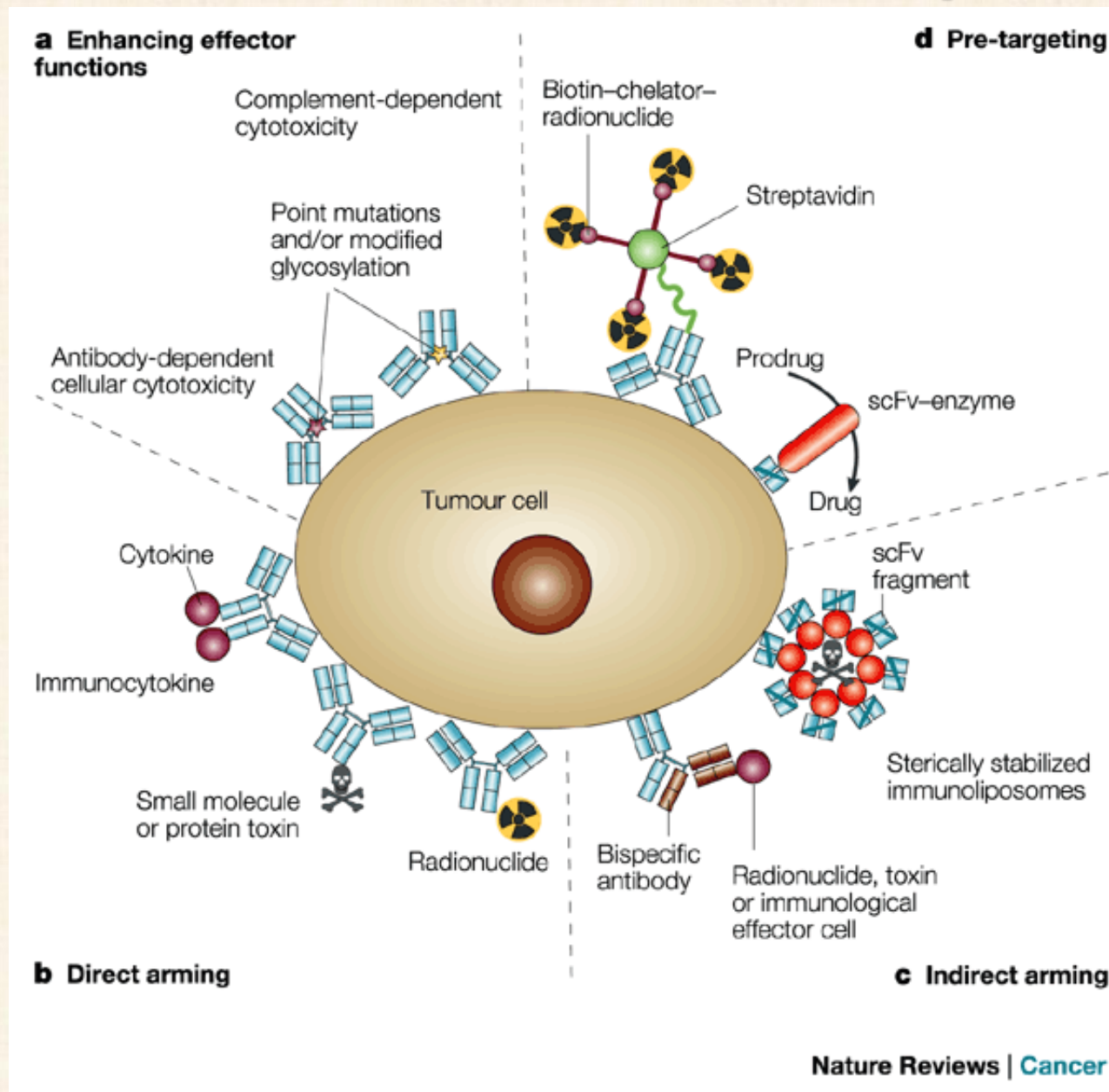
Immature local dendritic cells (unable to take up, process, or present antigens, and may also be inhibited from migrating to regional lymph nodes or may actually induce tolerance). **Regulatory T cells** are able to mediate suppression of antigen-primed T cells. The **Th2 phenotype CD4 T cells** inhibits the initiation of Th1 T cells and effective cellular immunity. The **tumor cells** may express **aberrant MHC class I** molecules or β 2-microglobulin, resulting in inadequate antigen presentation. Tumor cells and the surrounding stroma may release a number of **suppressive cytokines**, such as IL-6, IL-10, and TGF- β .



Possible immuno-therapies

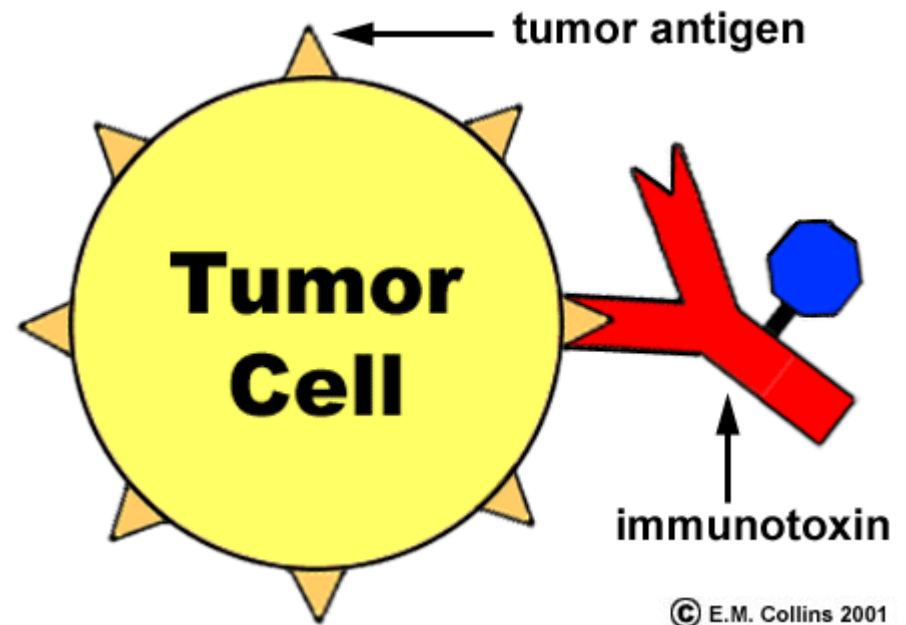
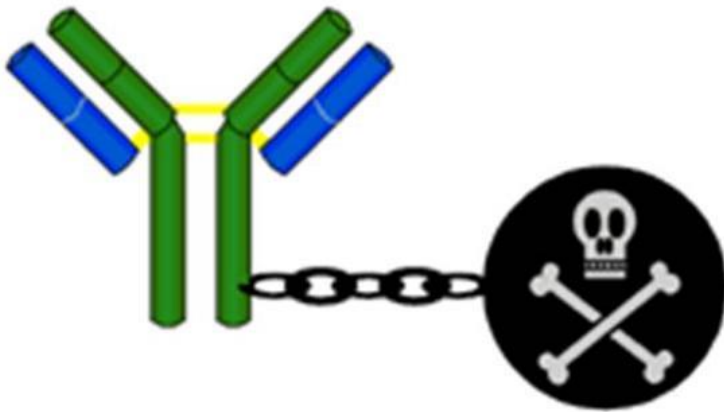
- **Immunotargeting with monoclonal antibodies**
- **Immunomodulation**
- **Tumor vaccines**
- **Oncolytic viruses**

Monoclonal antibodies for therapeutic use



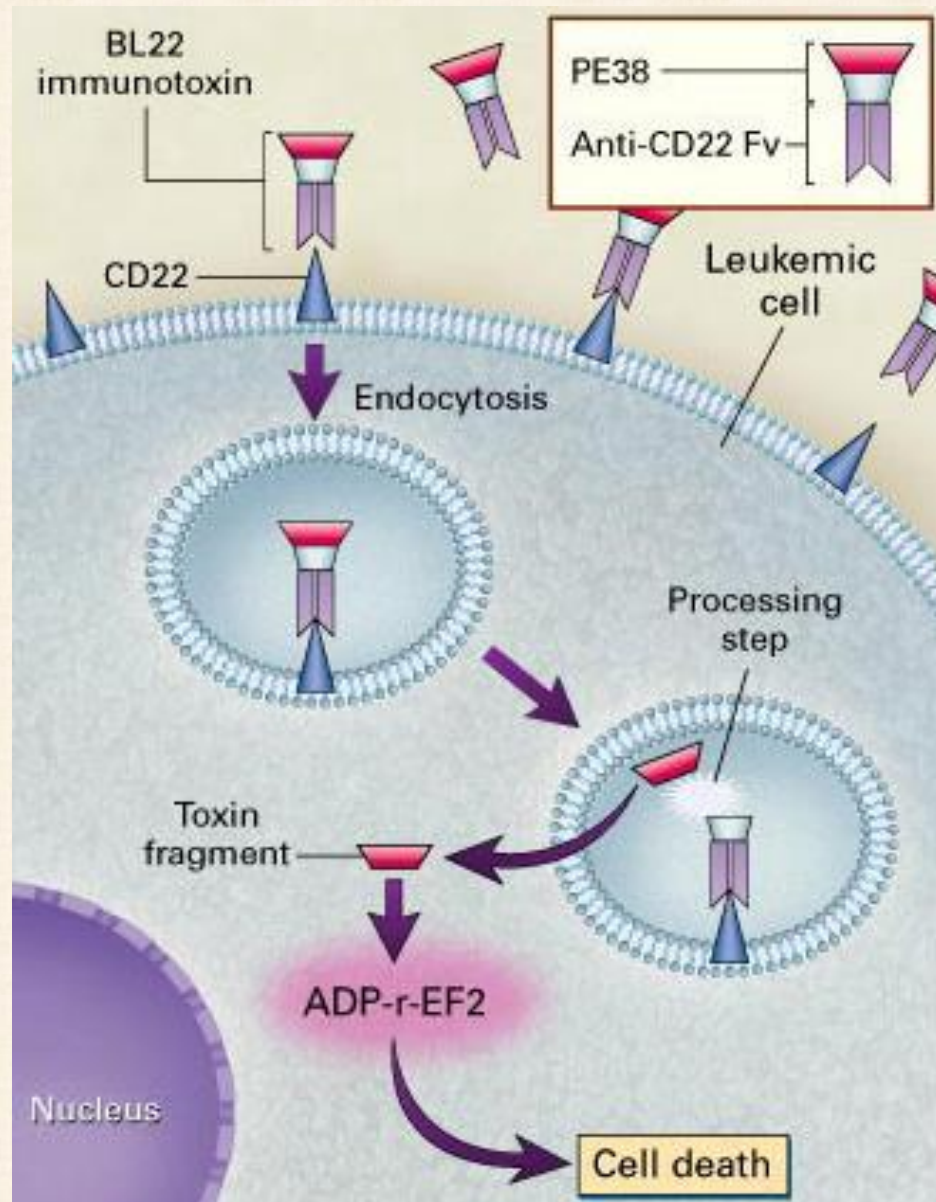
Immunotoxins in cancer therapy

IMMUNOTOXINS



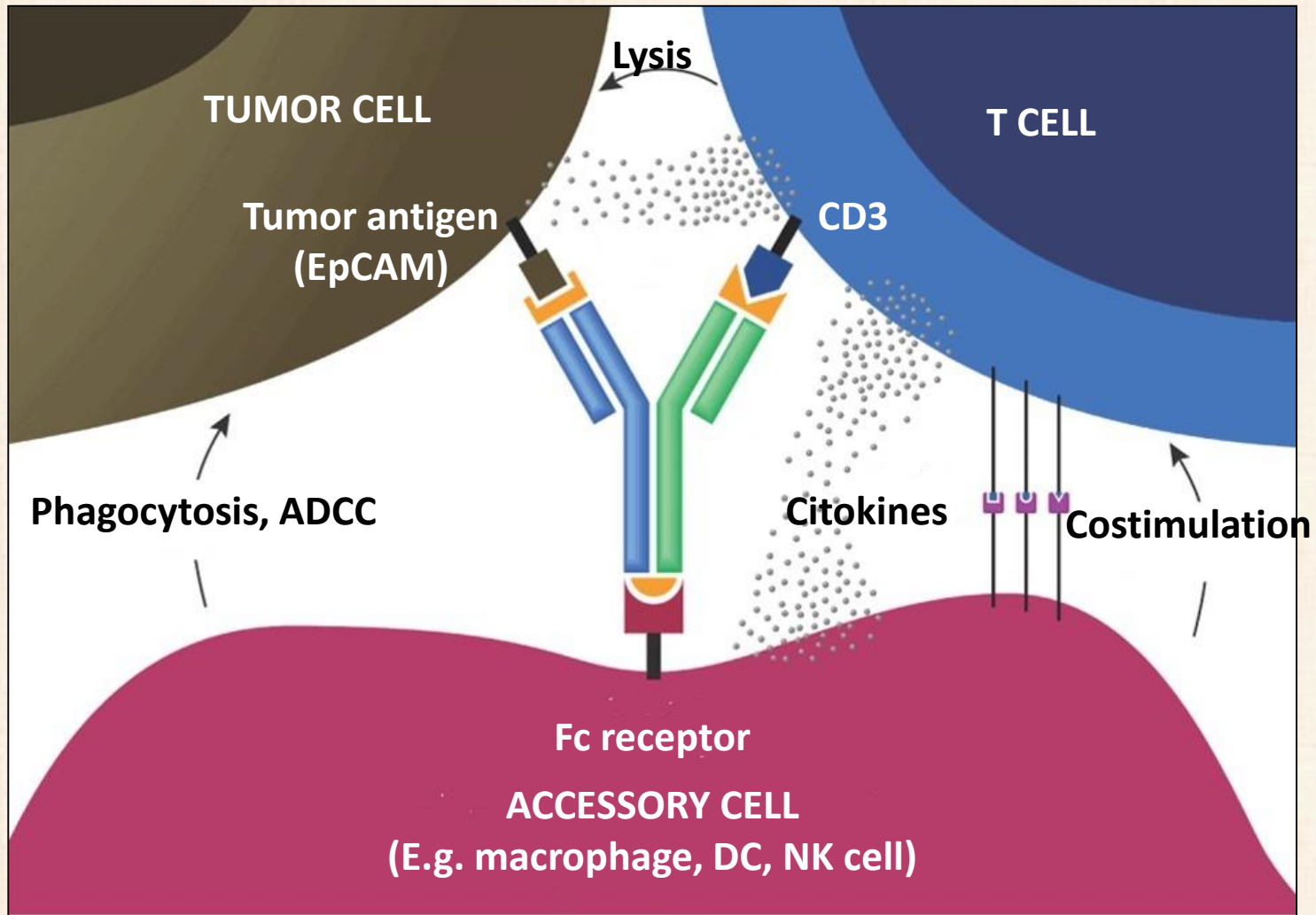
Monoclonal antibodies that bind target cell-surface antigens are themselves non-cytotoxic, but after conjugation with toxins they are able for clinical application in cancer therapy.

Immunotoxin therapy of Hairy Cell Leukemia



Treatment of hairy cell leukemia with recombinant BL22 immunotoxin therapy

Bispecific therapeutic monoclonal antibodies



Mechanism of action of Catumaxomab (the first approved bispecific and trifunctional antibody). (EpCAM: Epithelial cell adhesion molecule)

Immunological aspects of organ transplantation



Cornea

From cadaver
Immunosuppression not required
40,000 transplants per year

Skin

Mostly autologous (burn victims)
Temporary grafts of nonviable tissue
Allogeneic grafts rare, require immunosuppression

Lung

From brain-dead donor
Procedure recently developed;
little data available
845 transplants in 1998
Often heart/lung transplant (45 in 1998)

Blood

Transfused from living donor
ABO and Rh matching required
Complications extremely rare
An estimated 14 million units used each year

Heart

From brain-dead donor
HLA matching useful but often impossible
Risk of coronary artery damage, perhaps mediated by host antibody
2,340 transplants in 1998

Pancreas

From cadaver
Islet cells from organ sufficient
253 transplants in 1998
Increasingly, pancreas/kidney transplant for advanced diabetes (965 in 1998)

Liver

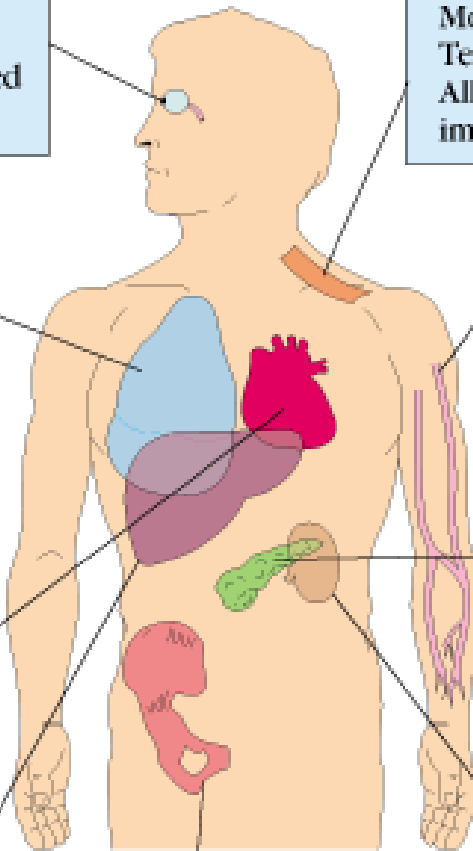
From cadaver
Surgical implantation complex
Resistant to hyperacute rejection
Risk of GVHD
4,450 transplants in 1998

Kidney

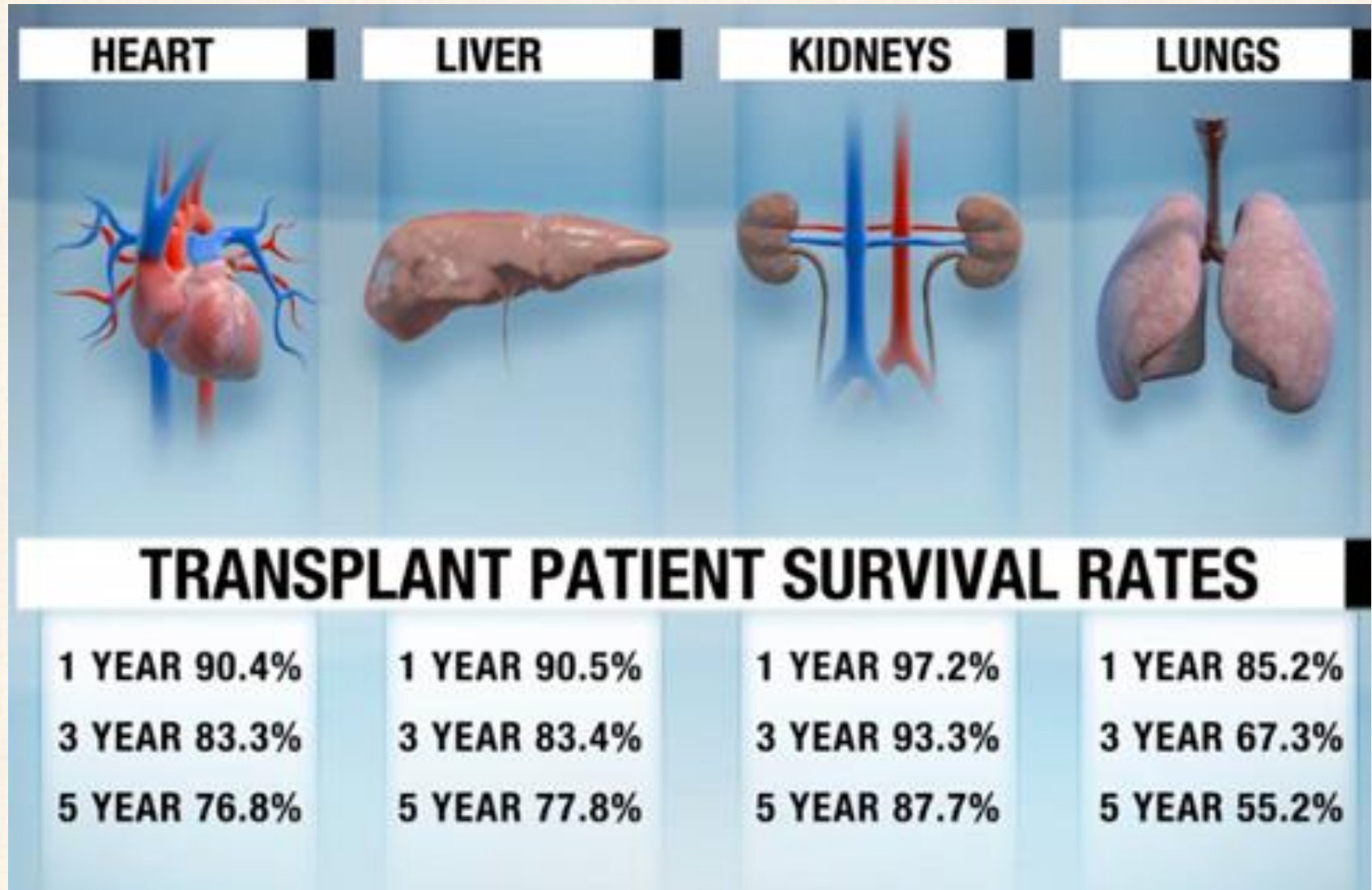
From live donor or cadaver
ABO and HLA matching useful
Immunosuppression usually required
Risk of GVHD very low
11,900 transplants in 1998

Bone marrow

Needle aspiration from living donor
Implanted by IV injection
ABO and HLA matching required
Rejection rare but GVHD a risk



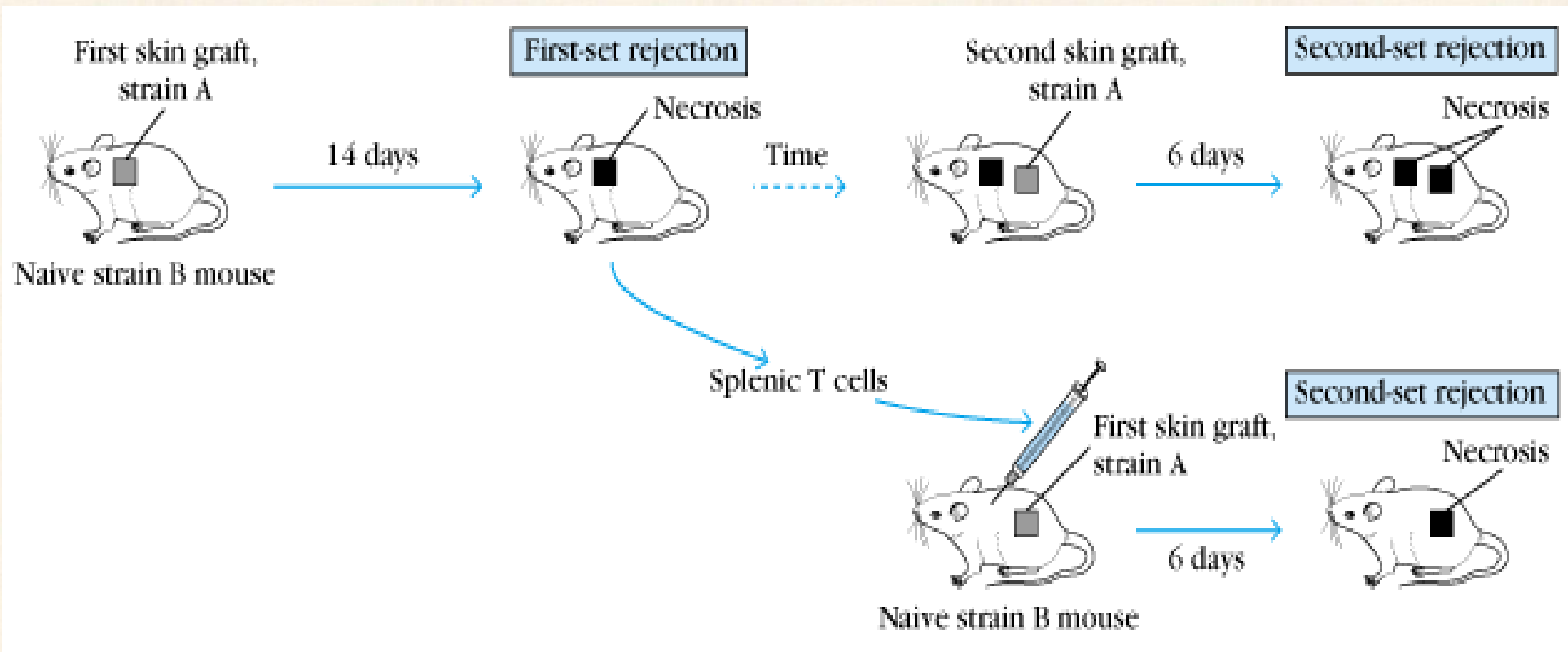
Average survival rate of transplanted patients in US in 2015



Basic terms

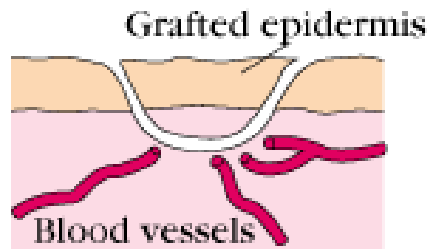
- **autolog, allogeneic, xenogeneic graft**
- **auto-, allo-, xeno-transplantation**

Allograft rejection

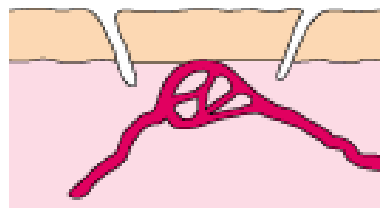


Graft acceptance and rejection

(a) Autograft acceptance



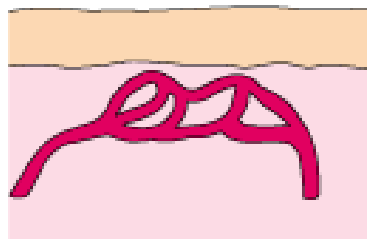
Days 3-7: Revascularization



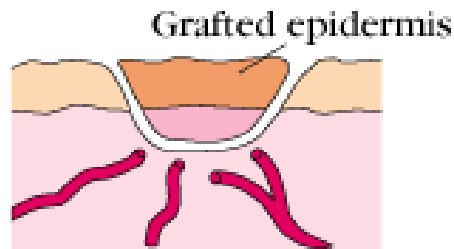
Days 7-10: Healing



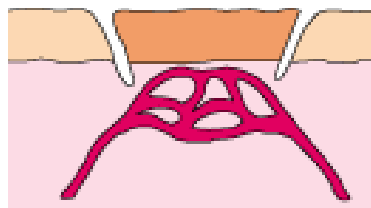
Days 12-14: Resolution



(b) First-set rejection



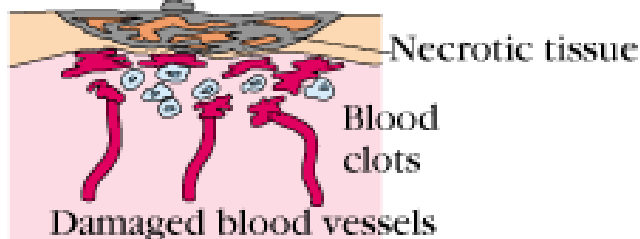
Days 3-7: Revascularization



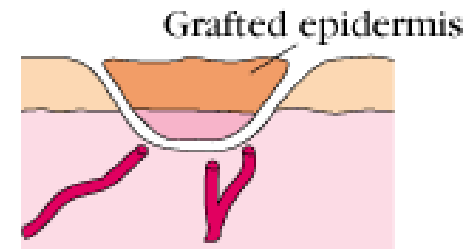
Days 7-10: Cellular infiltration



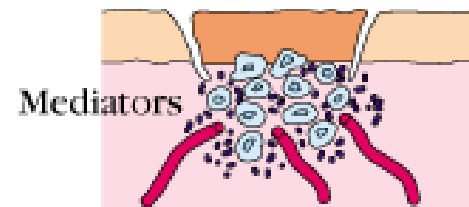
Days 10-14: Thrombosis and necrosis



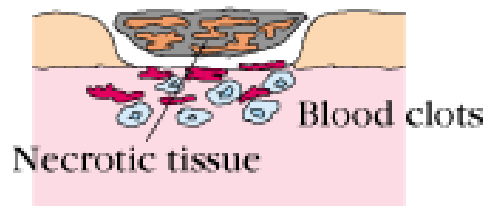
(c) Second-set rejection



Days 3-4: Cellular infiltration



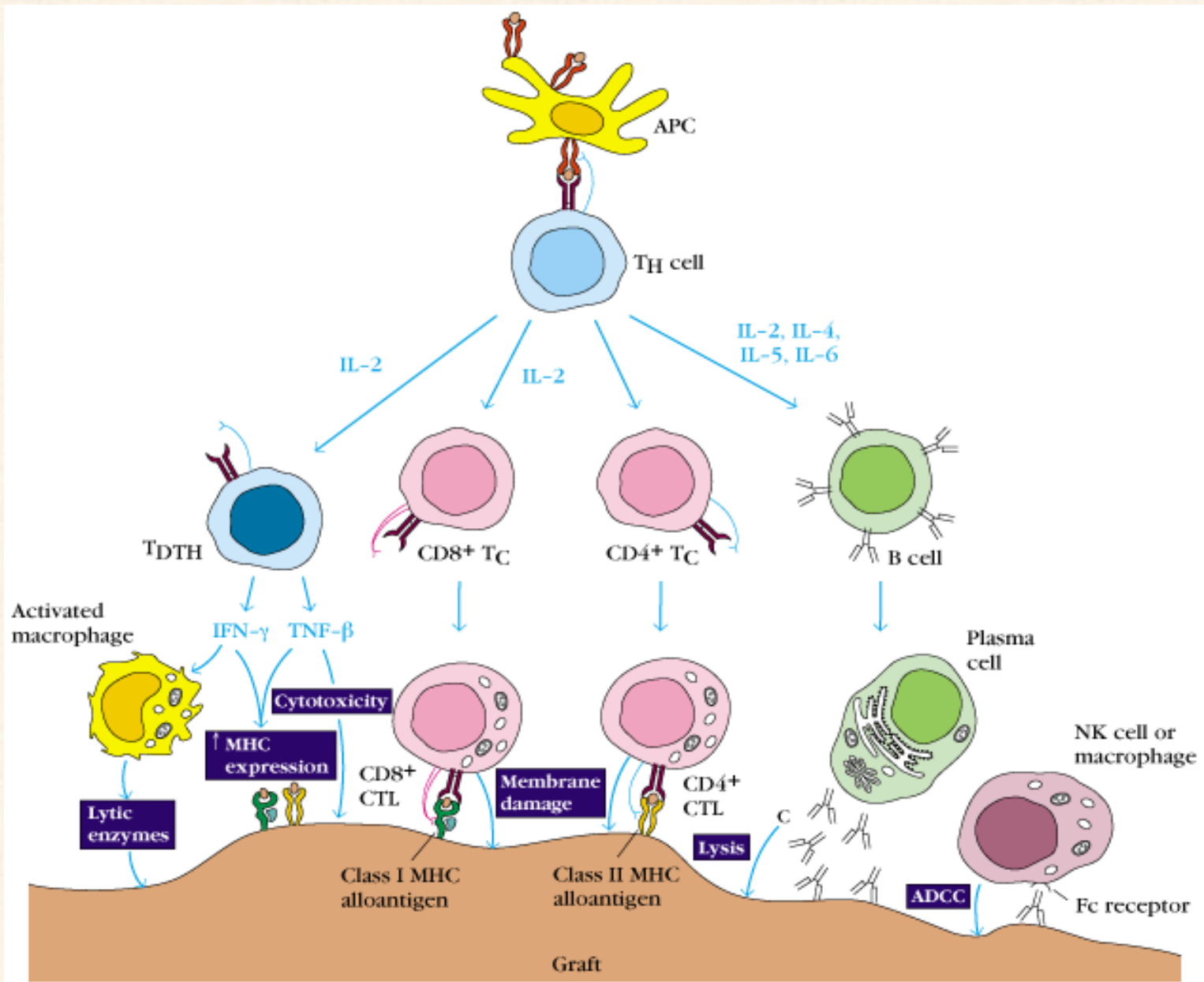
Days 5-6: Thrombosis and necrosis



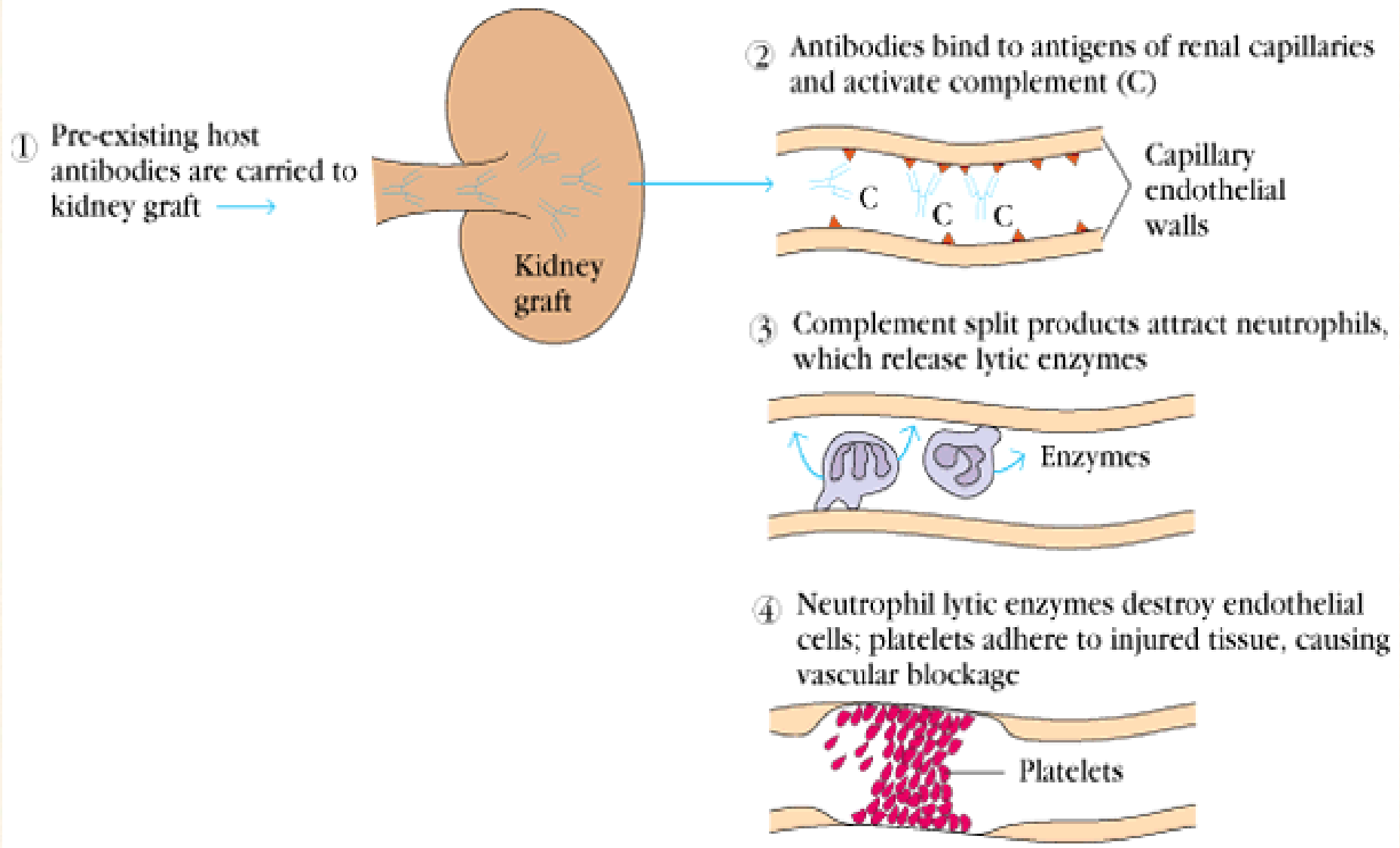
Host versus graft reaction

- hyperacute rejection caused by pre-existing antibodies
- acute rejection managed by T cells, ADCC and DTH
- chronic rejection induced by permanent endothelial injuries and complement activation

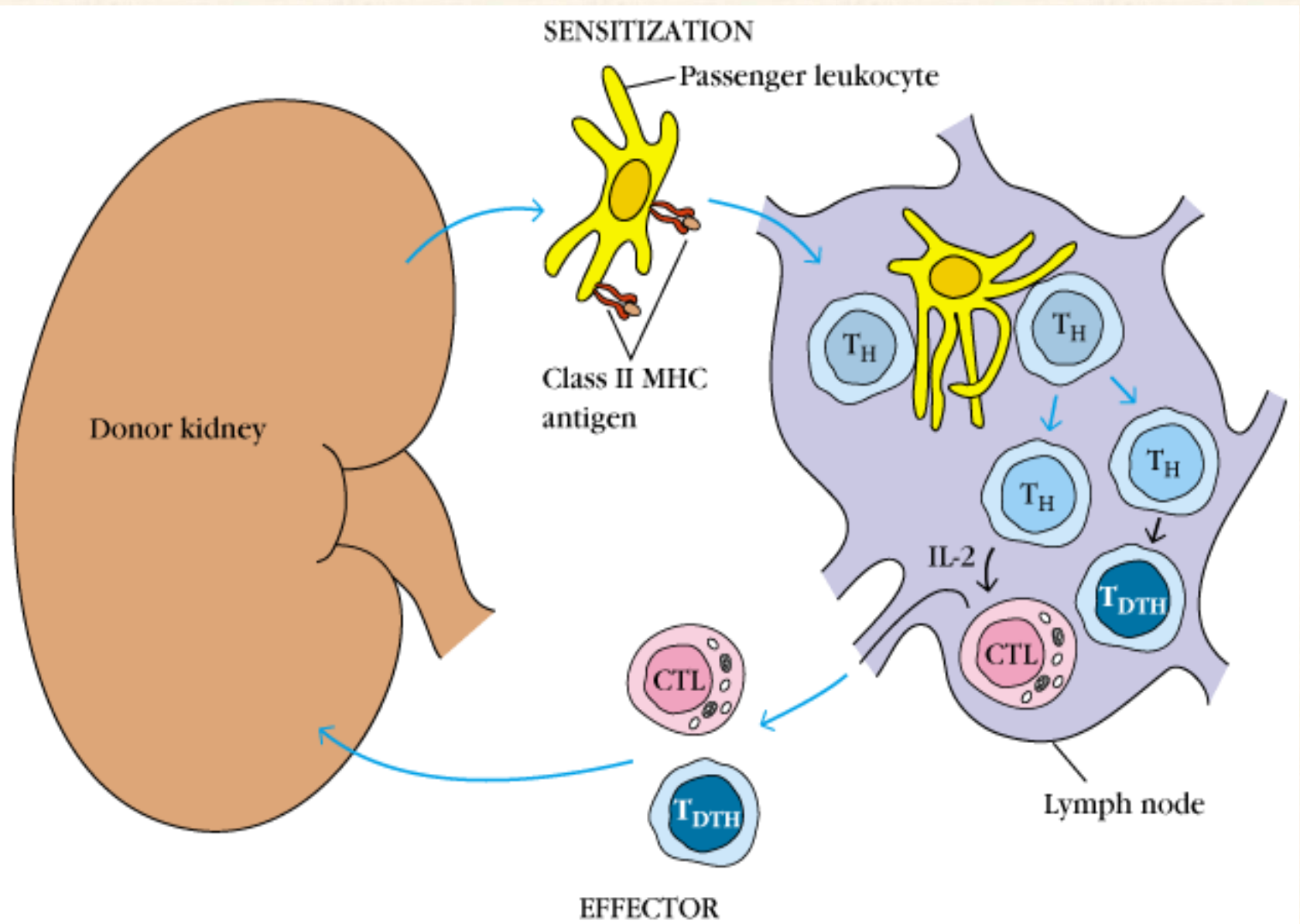
Mechanisms of host versus graft reactions



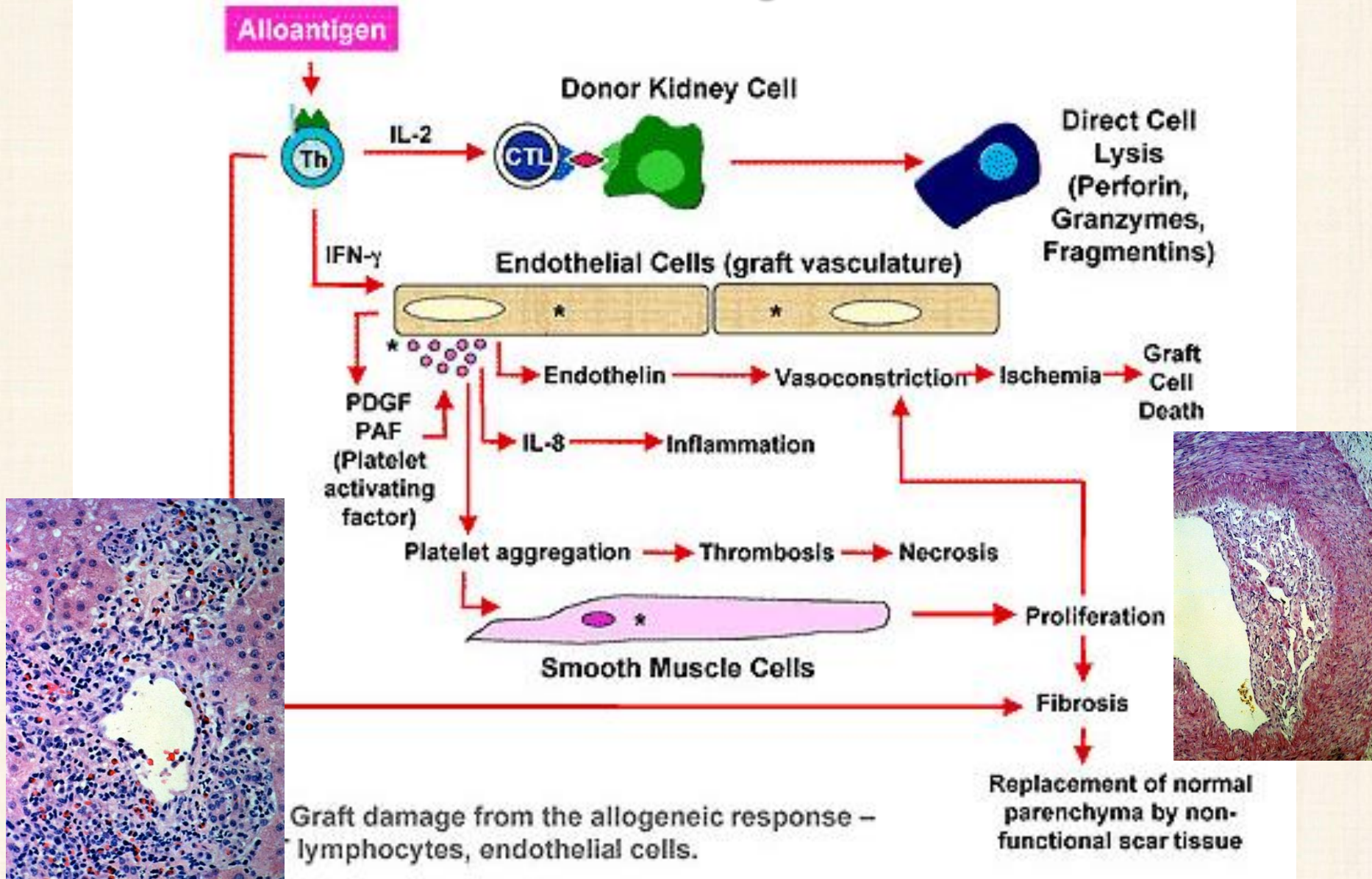
Hyperacute rejection



Acute rejection



Chronic rejection



Graft versus host reaction

- **acute GVHD (acute tissue necrosis of the targeted organs)**

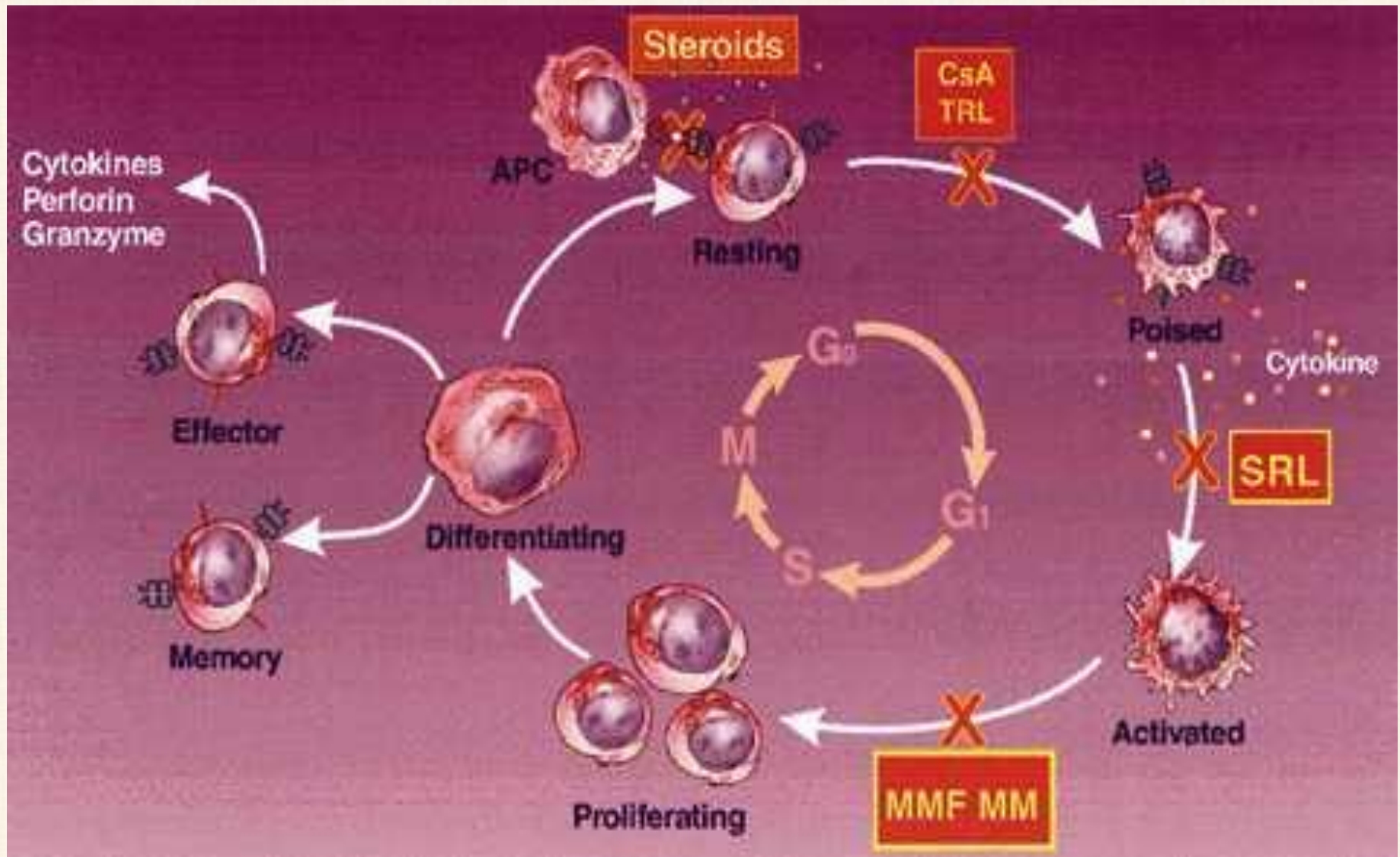


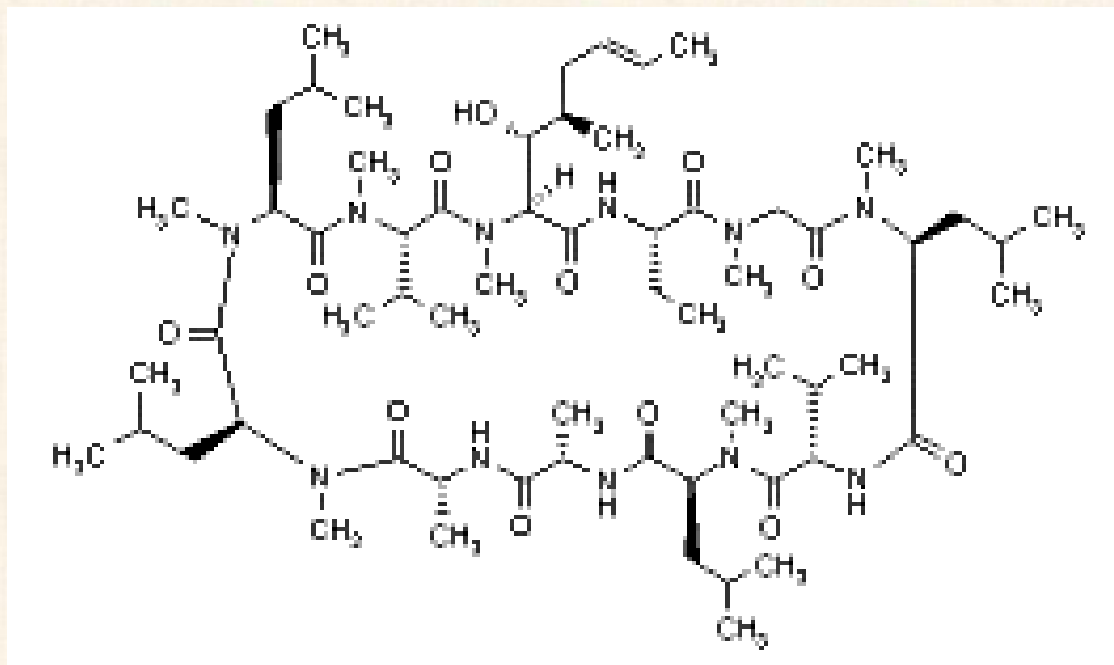
- **chronic GVHD (autoimmune-like phenomenon)**

Bone marrow transplantation

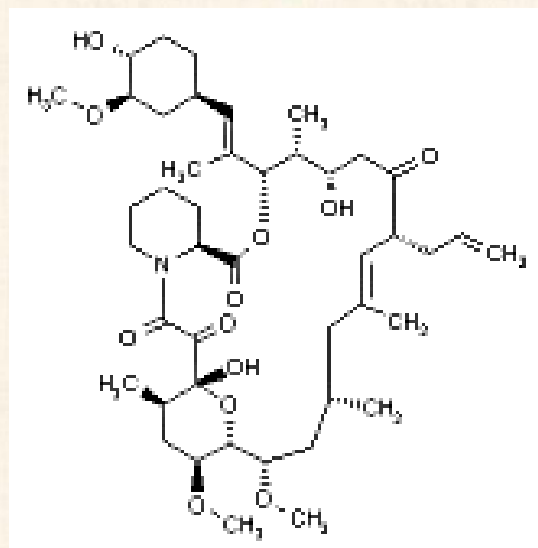
Advantage	Disadvantage
Autologous	Allogeneic
no GVH no rejection no matching needed	GVH rejection need matching tumour in donor cells
Allogeneic	Autologous
no tumour transfer graft vs. tumour myelosuppression avoided	grafting tumour cells (myelosuppression possible)

Immunosuppression



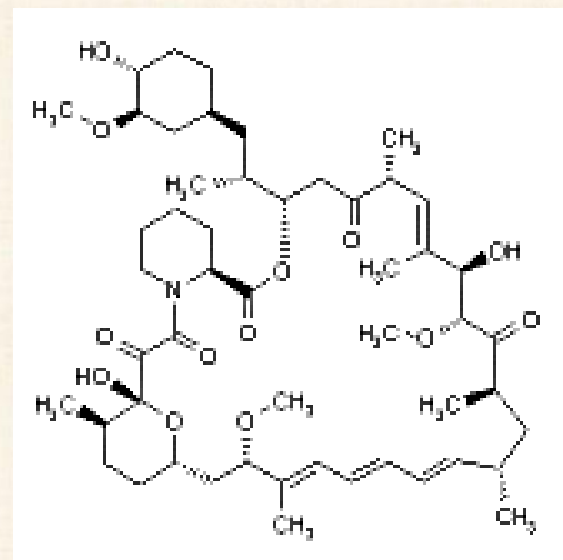


Cyclosporine A

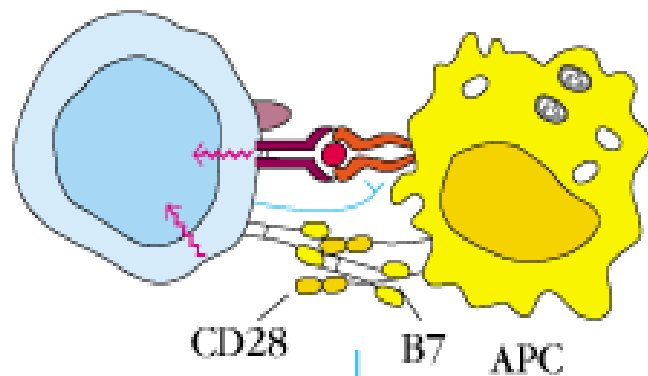


Tacrolimus

Sirolimus

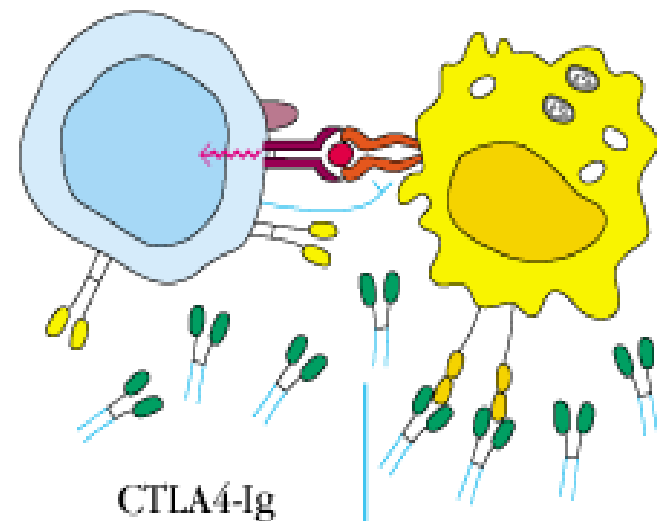


Blocking co-stimulatory signals



T cell

T cells that recognize graft
antigens become activated
Graft rejected



T cells that recognize graft antigens
lack co-stimulation and become anergic
Graft survives

Co-stimulation inhibition by *Abatacept*

