Basic Immunology

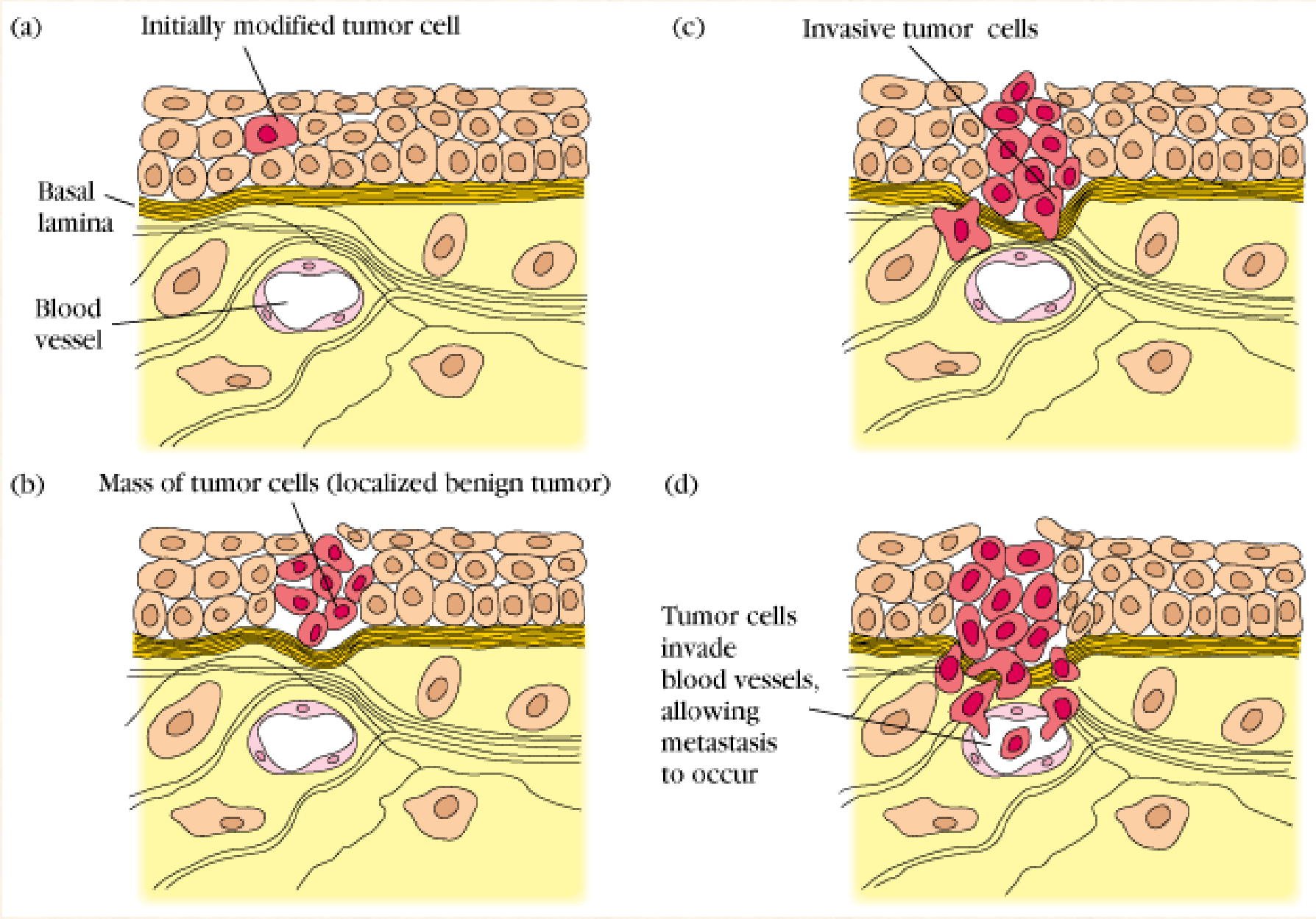
Lecture 25th - 26th

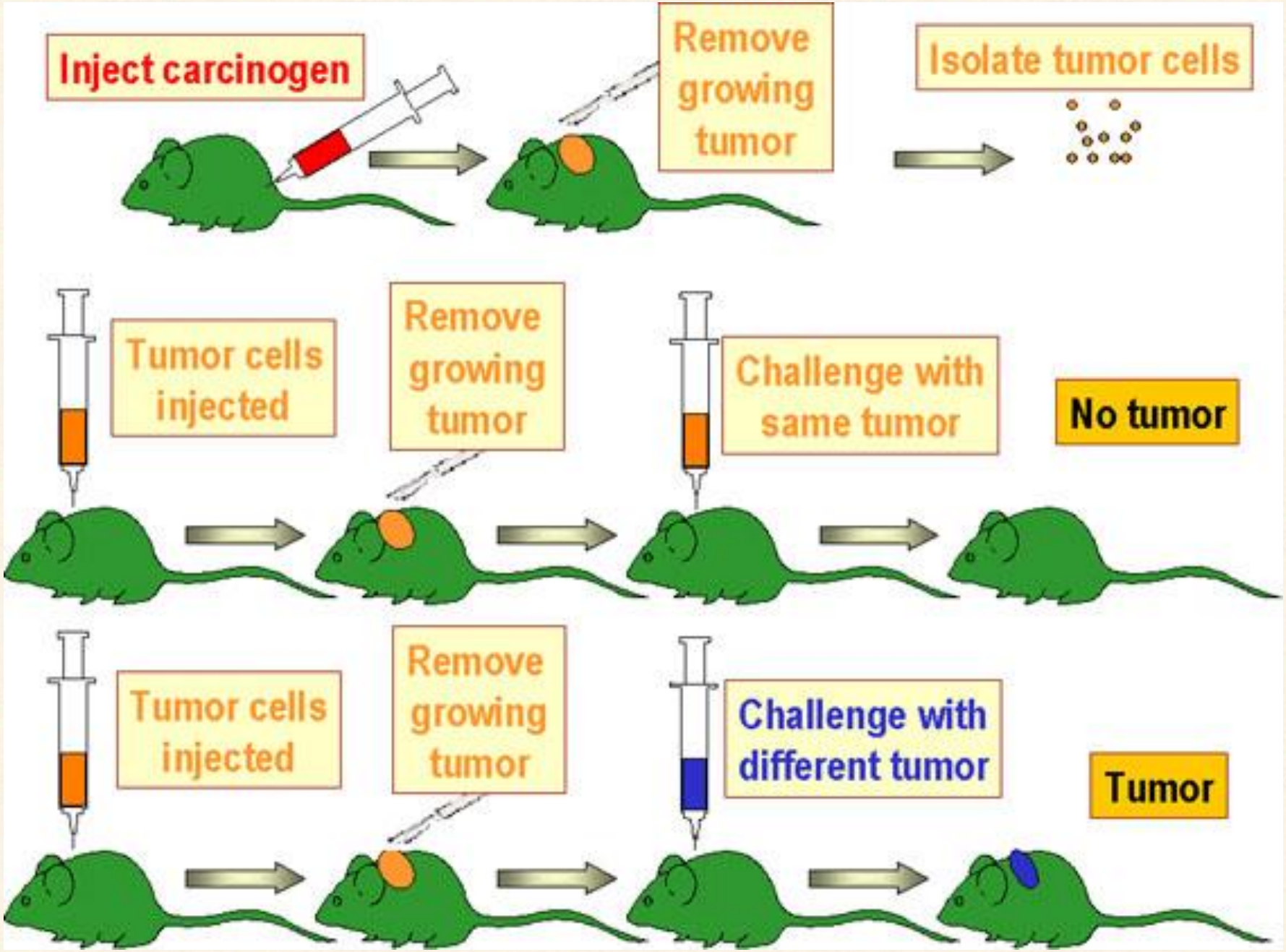
Immunity against tumors

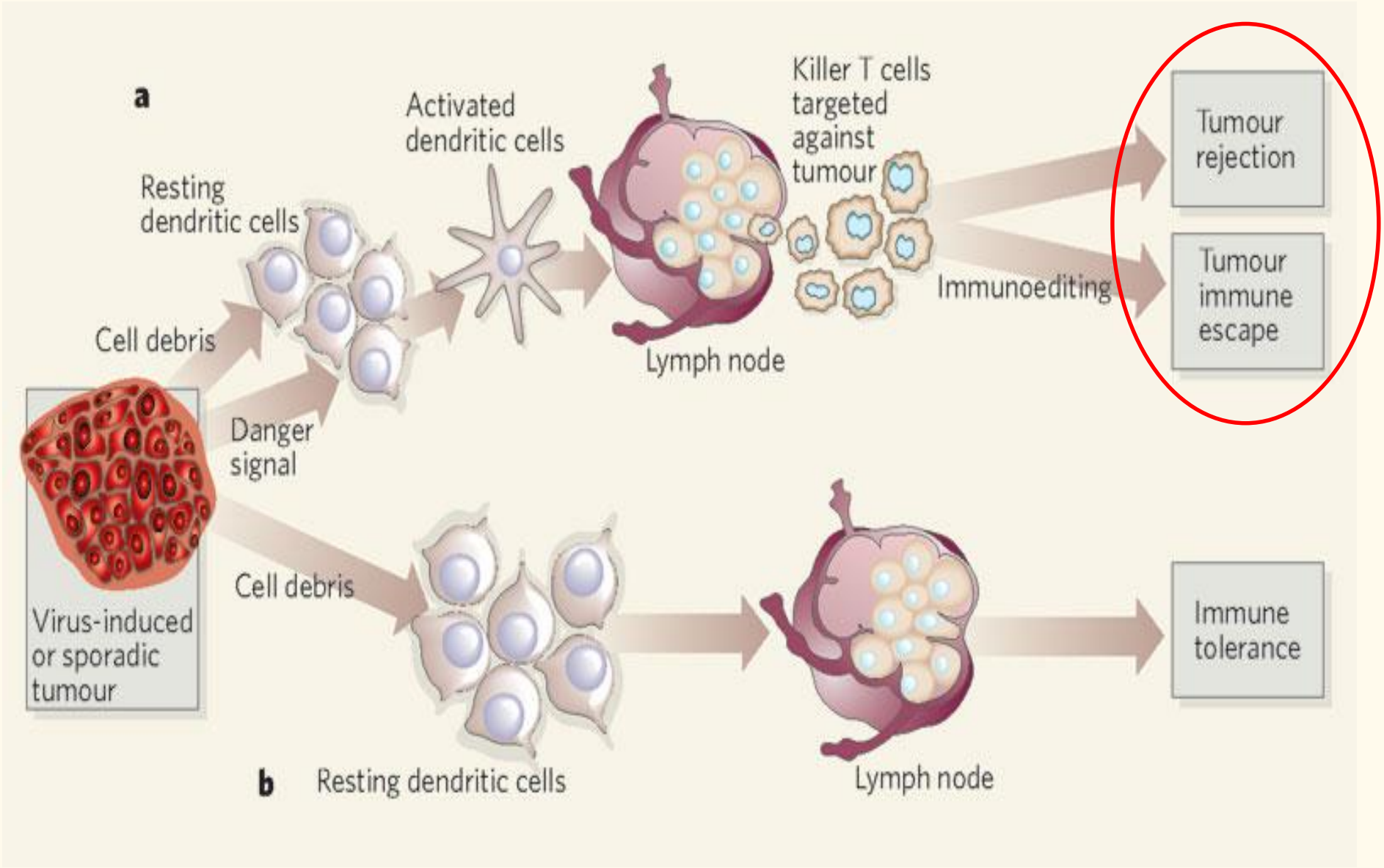
Tumor- and tumor associated antigens. Tumor escape. Trends in immunotherapy against cancer.

Immunological aspects of organ transplantation

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

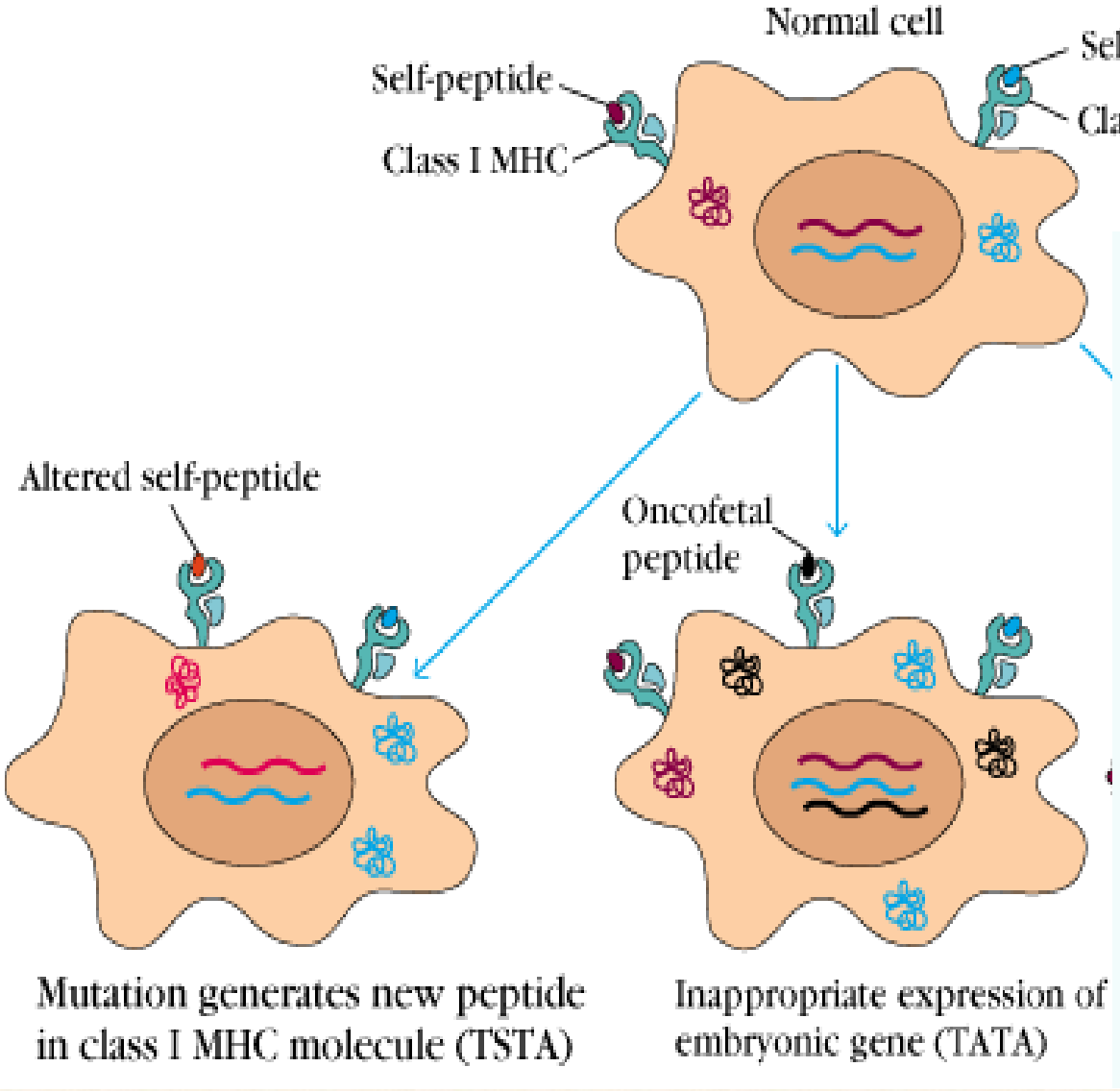

(a)
Initially modified tumor cell
Basal lamina
Blood vessel
(b)
Mass of tumor cells (localized benign tumor)
(c)
Invasive tumor cells
(d)
Tumor cells invade blood vessels, allowing metastasis to occur


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


a
Activated dendritic cells
Killer T cells targeted against tumour
Resting dendritic cells
Tumour rejection
Tumour immune escape
Immunoediting
Cell debris
Lymph node
Danger signal
Virus-induced or sporadic tumour
Cell debris
Immune tolerance
b
Resting dendritic cells
Lymph node

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***



Antigens expressed on the surface of tumor cells

- Normal antigens
- Mutated peptide sequences (Tumor Specific Antigens)
- Normal, but inappropriate sequences (Tumor Associated Antigens)

Tumor associated antigens named as tumor markers.

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 EGSISTS!**

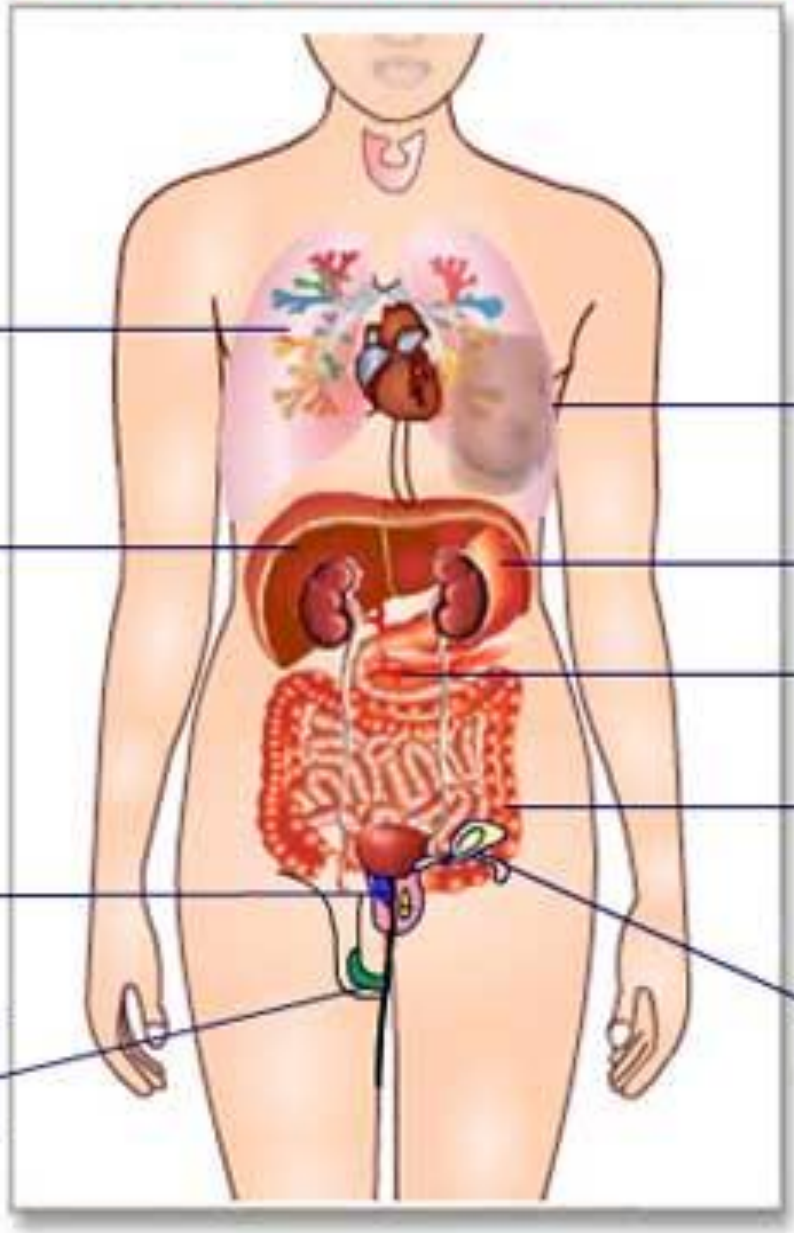
- **TSA is recognized** (according to the individual MHC haplotype) **by the immune system and induces targeting type immune response or tolerance**

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



Lung Cancer
CA125,CEA

Liver Cancer
AFP

Prostate Cancer
PSA

Testicular Cancer
AFP,HCG

Breast Cancer
CA125,CEA,HER2

Stomach Cancer
CEA

Pancrease Cancer
CA125,CEA

Colon Cancer
CEA

Ovaries Cancer
CA125,CEA

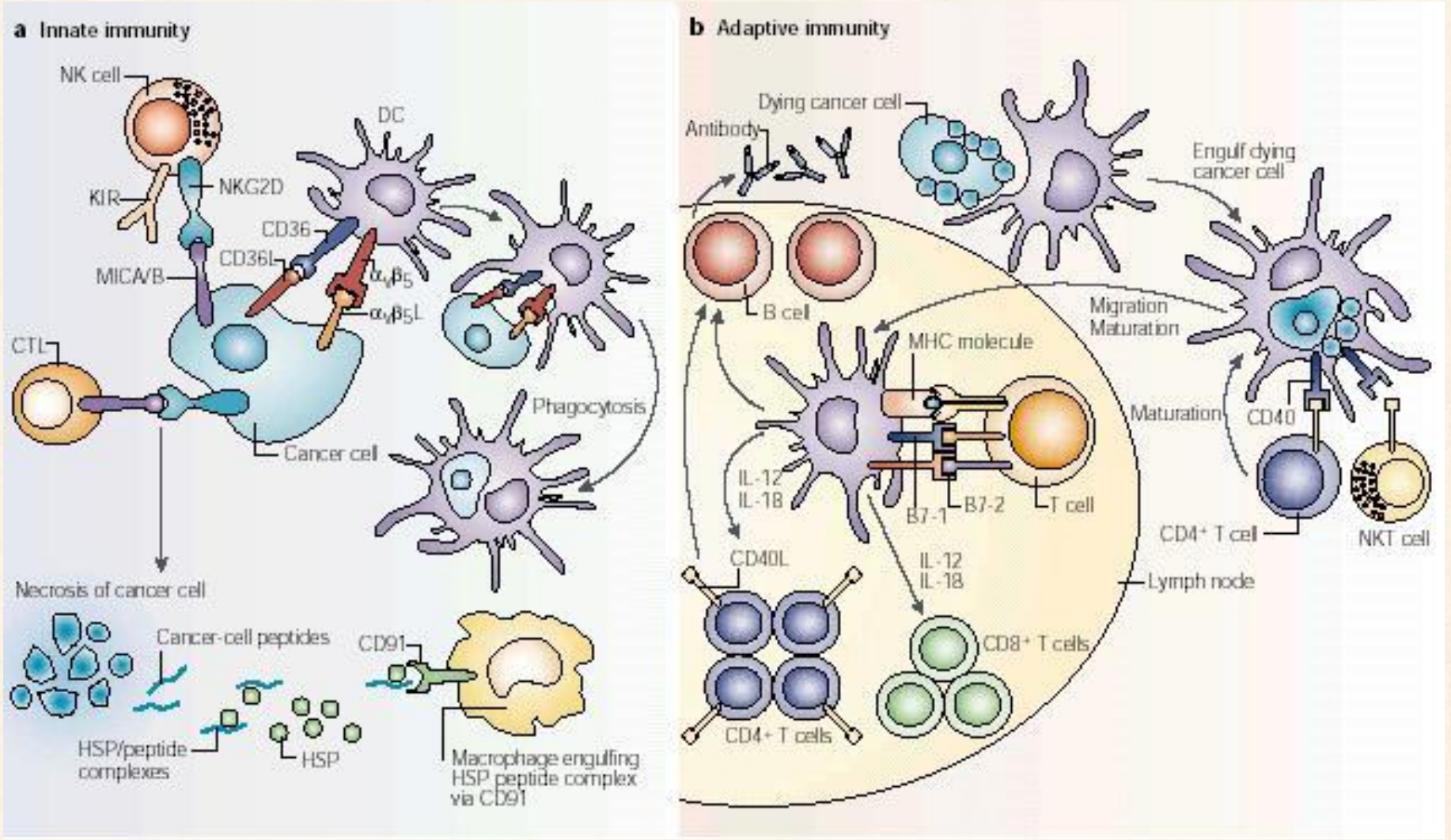
Often tumor markers

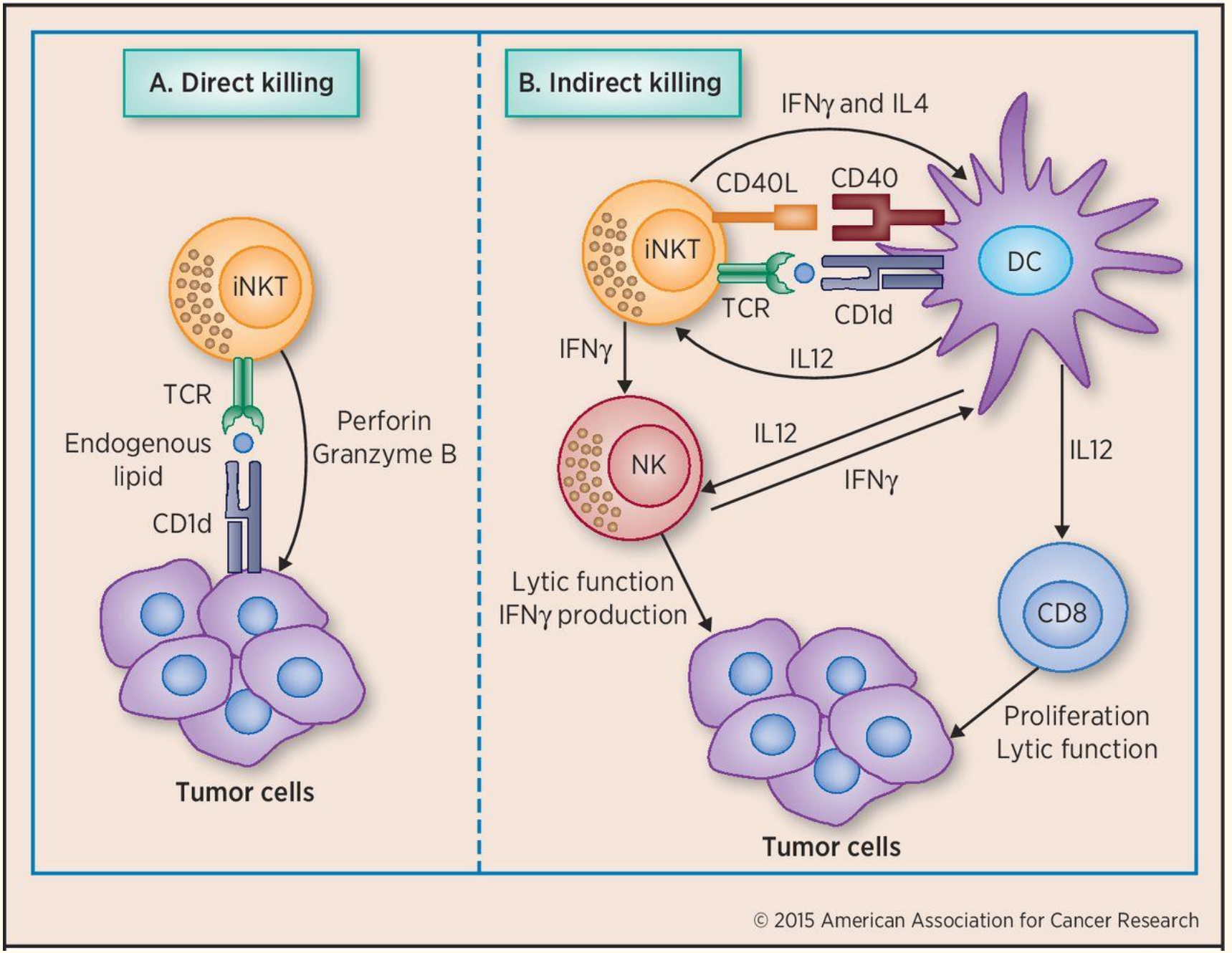
Tumor markers	Abbreviation	Oncological application
Alfa-foetoprotein	AFP	Liver and germ cell tumors
Cancer antigen 125	CA 125	ovarian tumors
Cancer antigen 15,3	CA 15,3	Breast cancer
Cancer antigen 72,4	CA 72,4	Gastric cancer
Cancer antigen 19,9	CA 19,9	Pancreatic cancer
Carcinoembrional antigen	CEA	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

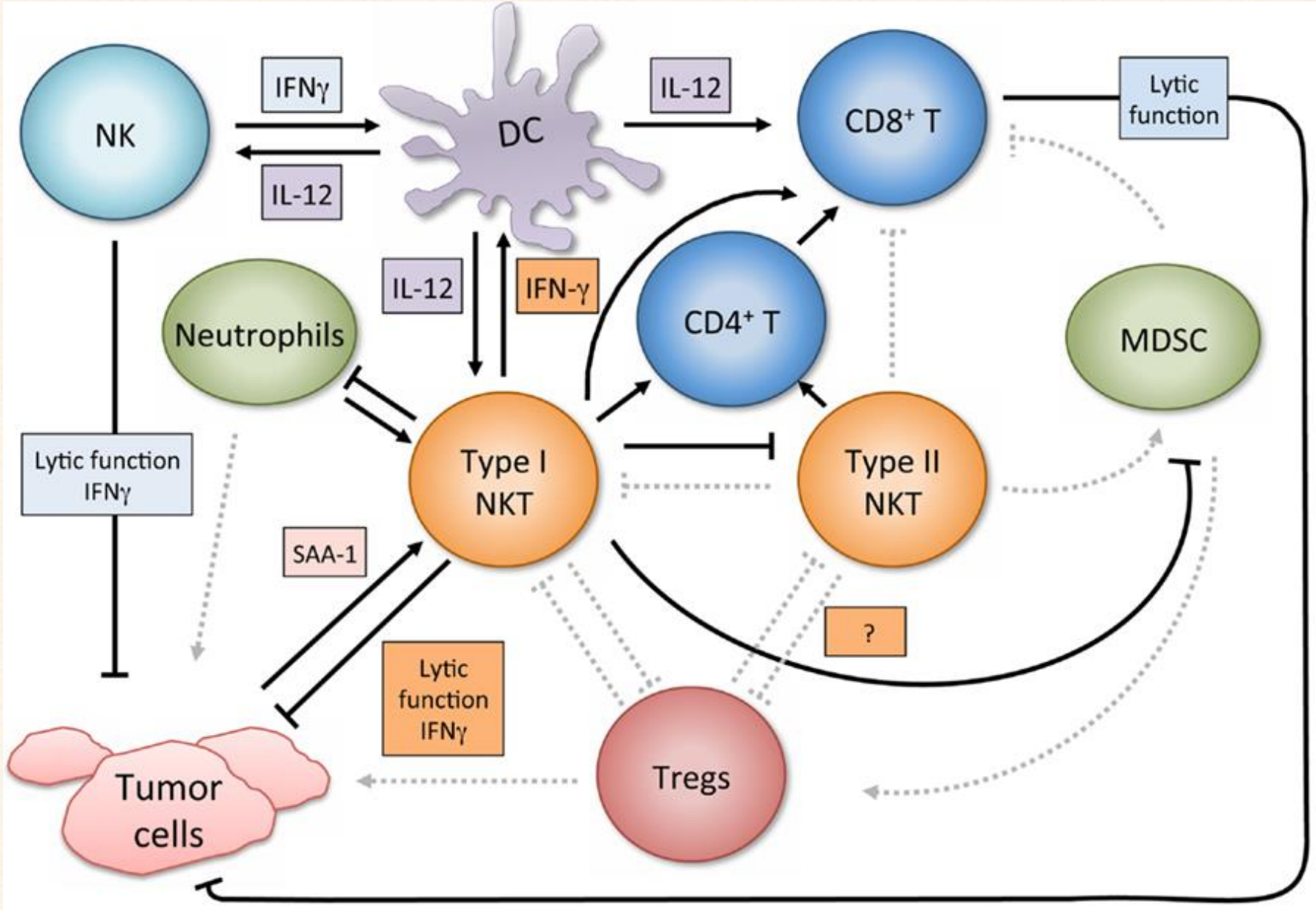
- T cell mediated (CD8+, CD4+Th1, NK)
- macrophage mediated
- immunoglobulin mediated (ADCC)
- network of cytotoxic cytokines

Cell mediated immunity against malignant tumors



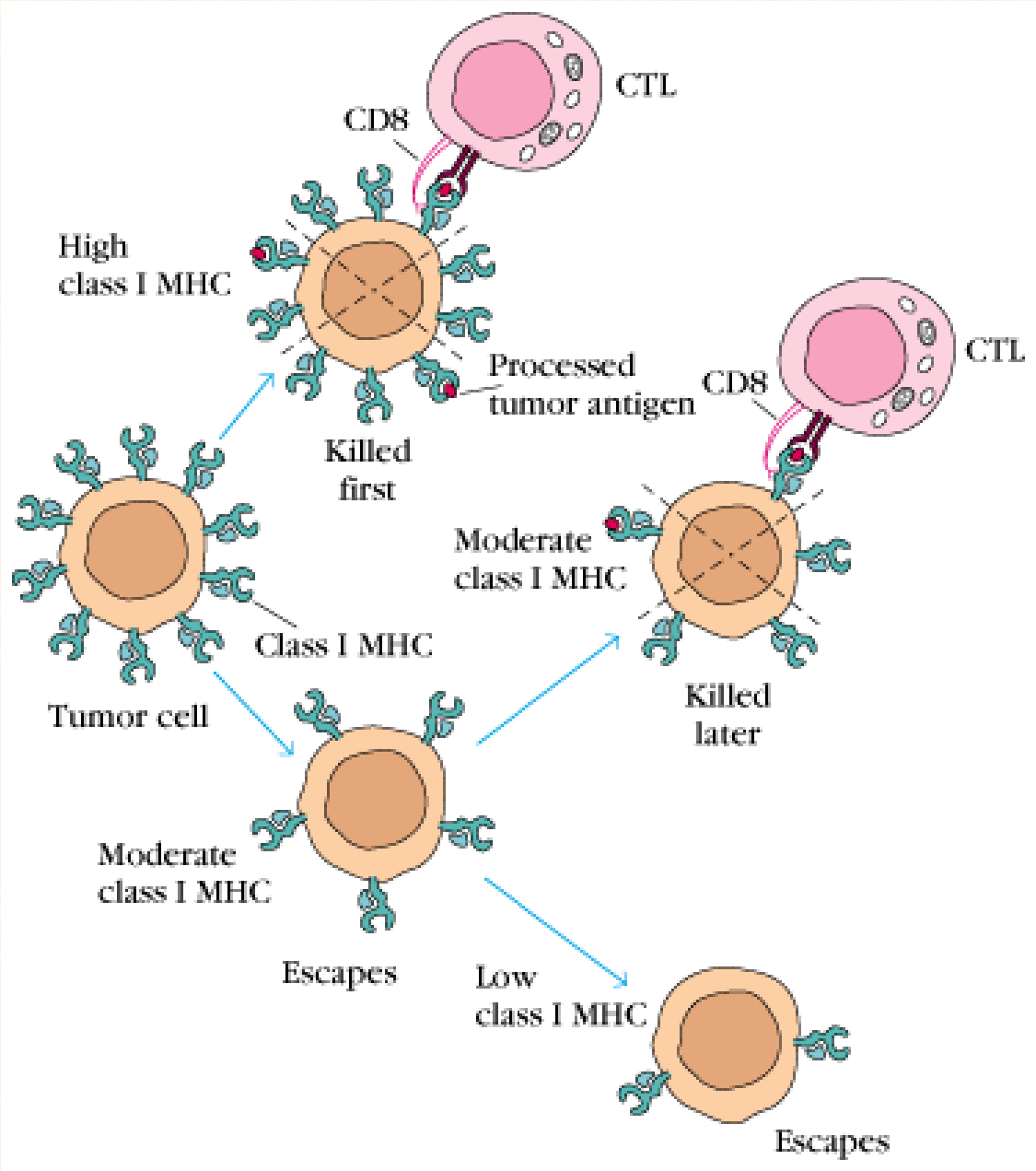


Enhancement of tumor immunity by NKT cells

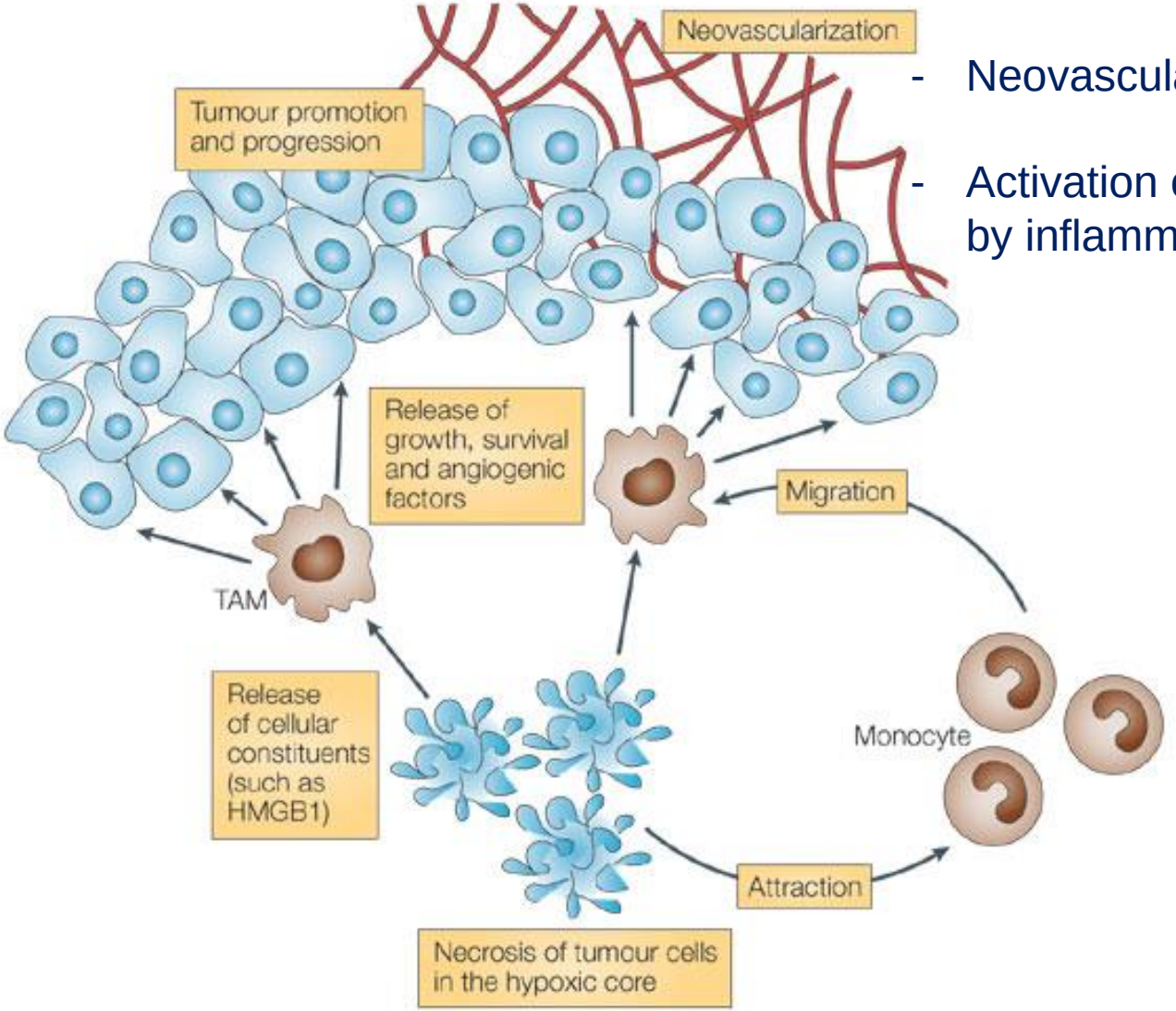


Tumor escape

- Over expression or down regulation of MHC Class I.
- Over expression of FcR
- Deficiency of cytotoxic cytokine receptors
- Production of different glycoproteins with masking effects
- Expression of co-stimulation inhibitors

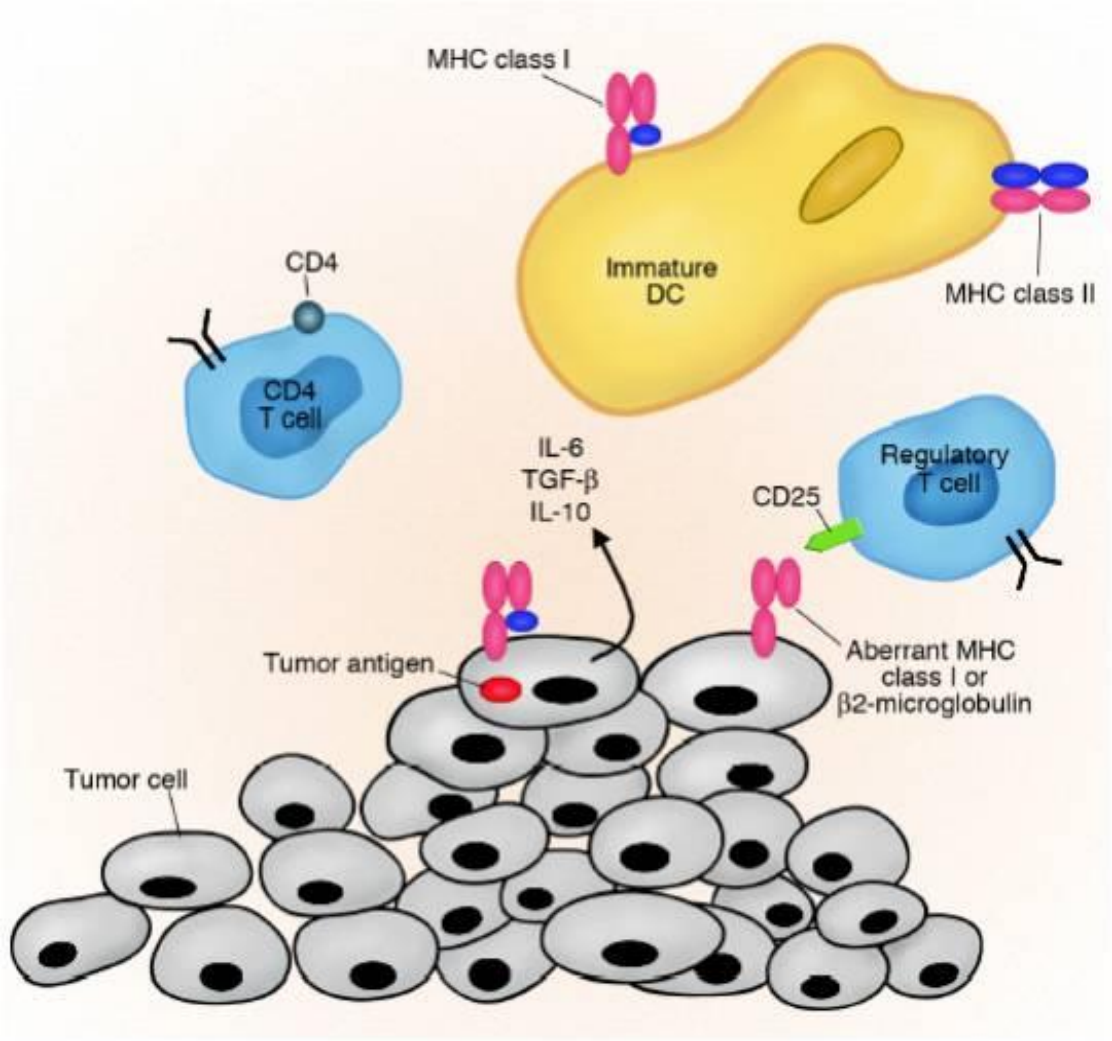

CTL
CD8
High
class I MHC
Processed
tumor antigen
Killed
first
CTL
CD8
Moderate
class I MHC
Class I MHC
Tumor cell
Killed
later
Moderate
class I MHC
Escapes
Low
class I MHC
Escapes

Tumor infiltrating macrophages: double-edged sword

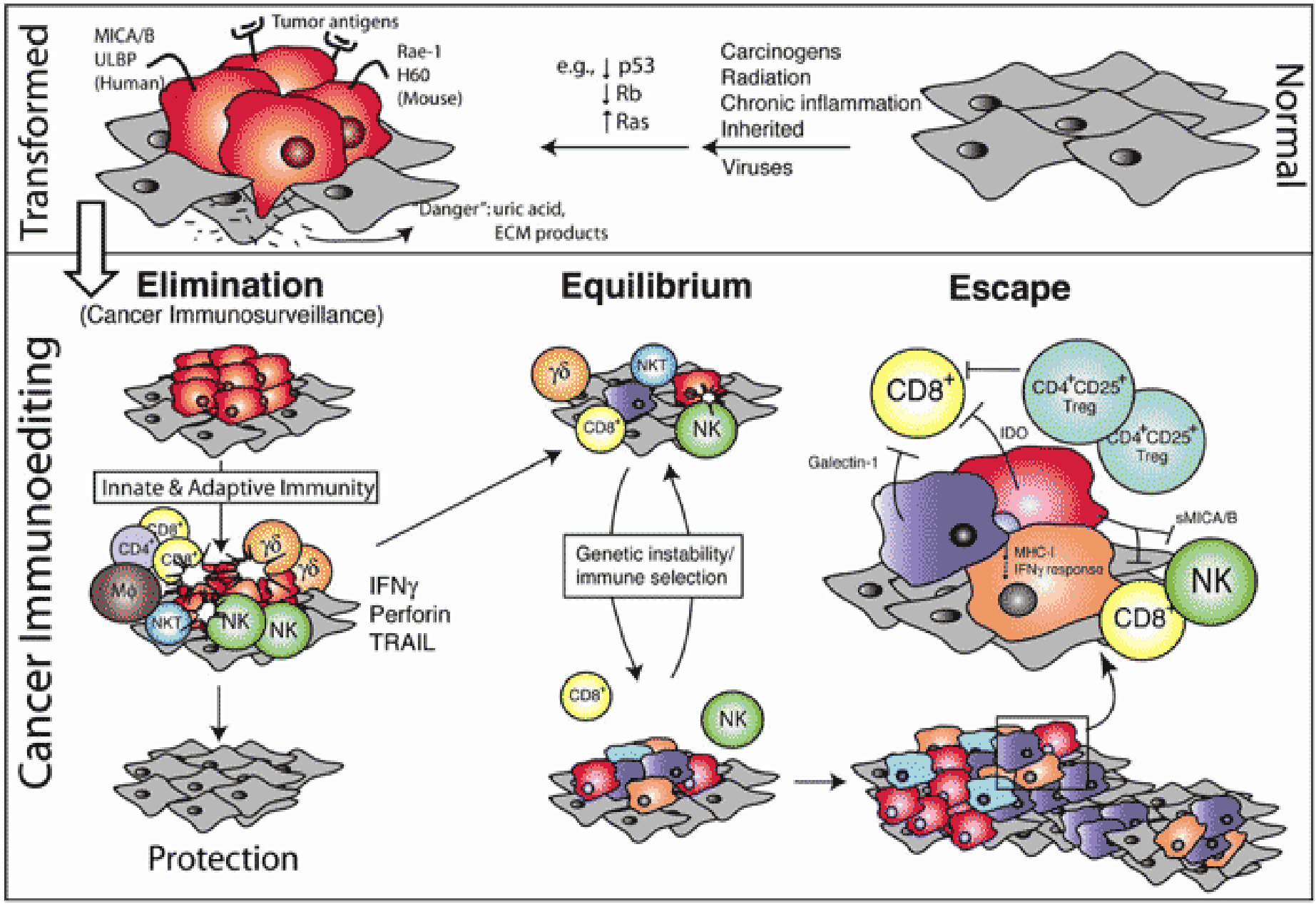


- Neovascularization
- Activation of cancer cells by inflammatory cytokines

Tumor escape according to the local environment



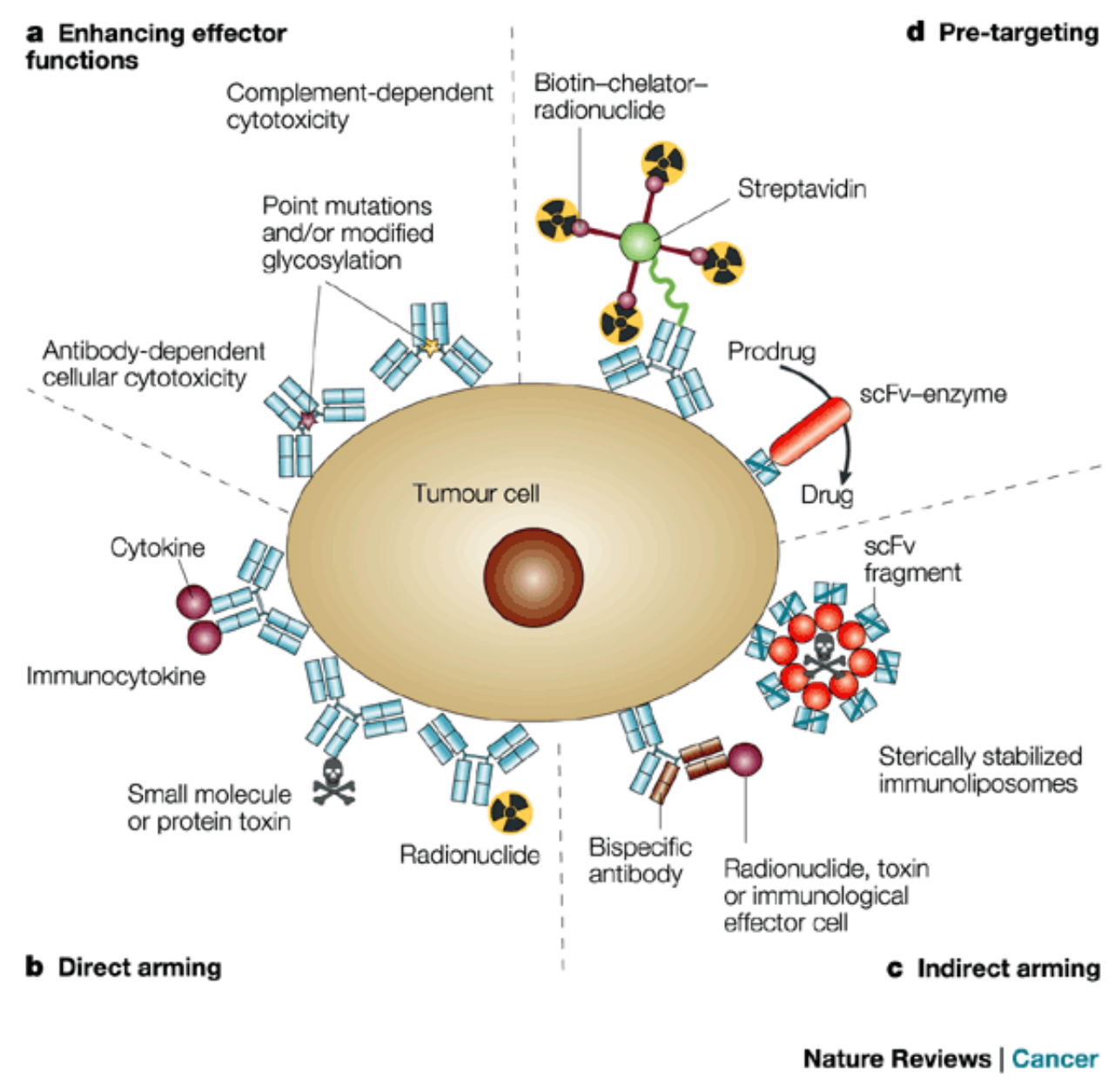
Immature local dendritic cells (unable to take up, process, or present antigens, and may also be inhibited from migrating to regional lymph nodes or may actually induce tolerance). **Regulatory T cells** are able to mediate suppression of antigen-primed T cells. The **Th2 phenotype CD4 T cells** inhibits the initiation of Th1 T cells and effective cellular immunity. The **tumor cells** may express **aberrant MHC class I** molecules or β2-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.


Transformed
MICA/B
ULBP
(Human)
Tumor antigens
Rae-1
H60
(Mouse)
e.g., ↓ p53
↓ Rb
↑ Ras
Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses
Normal
"Danger": uric acid,
ECM products
Cancer Immunoediting
Elimination
(Cancer Immunosurveillance)
Innate & Adaptive Immunity
IFNγ
Perforin
TRAIL
Protection
Equilibrium
Genetic instability/
immune selection
Escape
CD8+
CD4+CD25+
Treg
IDO
Galectin-1
sMICA/B
MHC-I
IFNγ response
NK
NKT
γδ
Mϕ

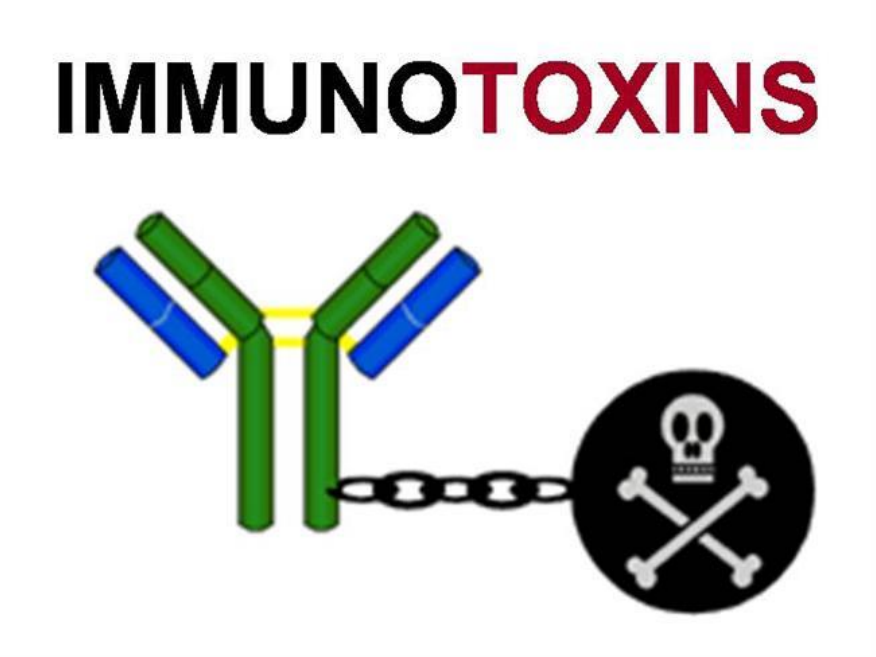
Possible immuno-therapies

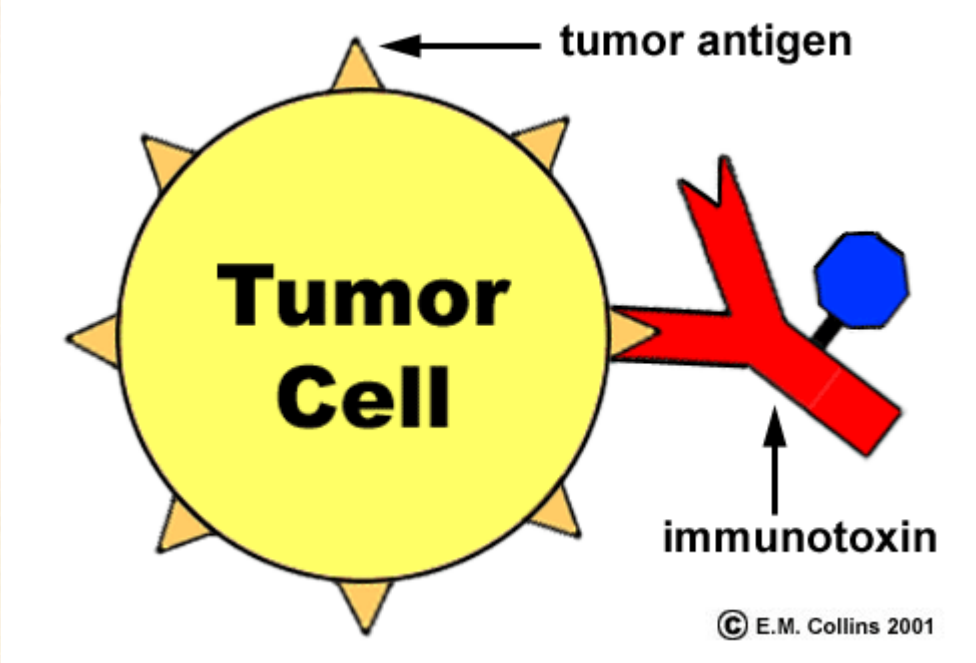
- Immuno-targeting with monoclonal antibodies
- Check point inhibitors
- Immunomodulation
- Tumor vaccines
- Oncolytic viruses

Monoclonal antibodies for therapeutic use



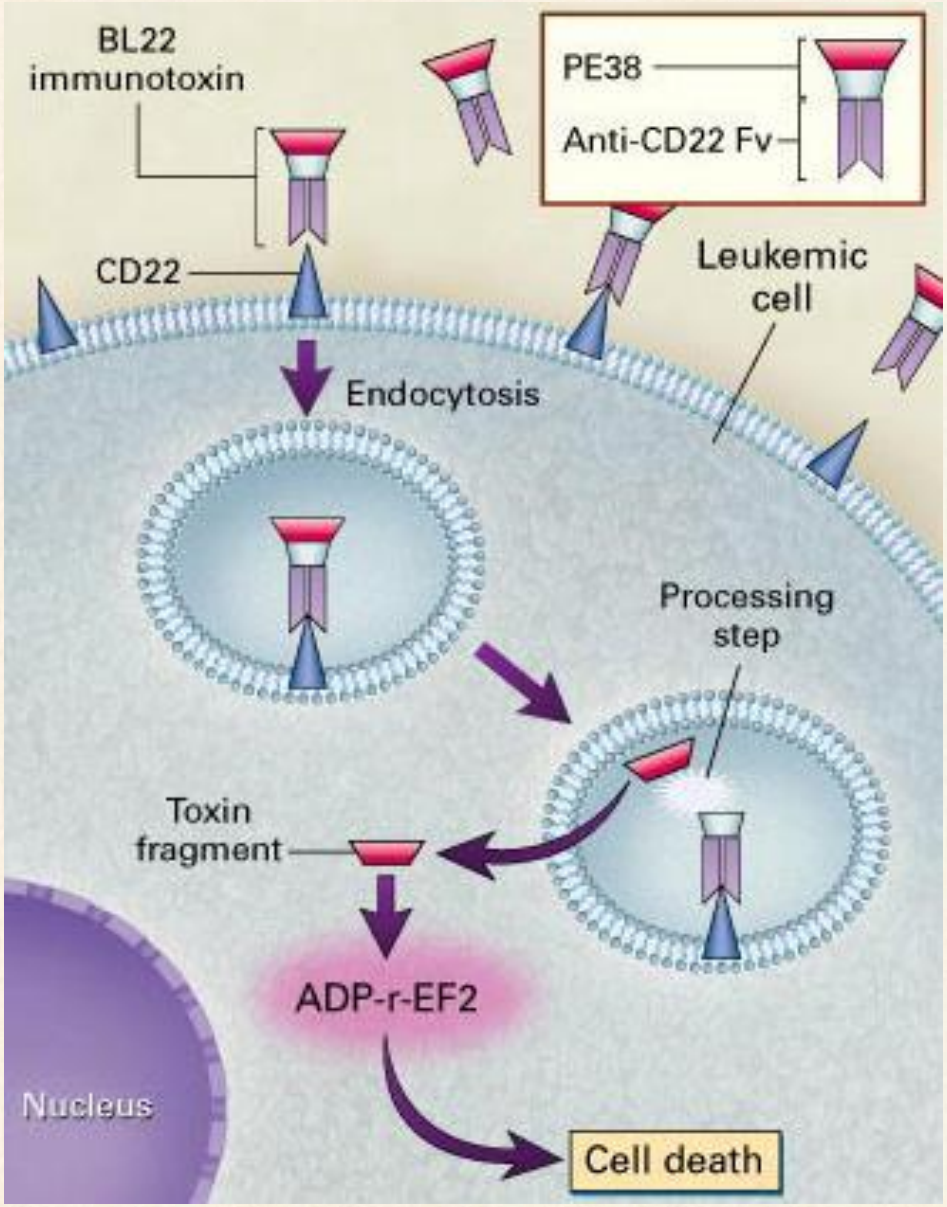
Immunotoxins in cancer therapy





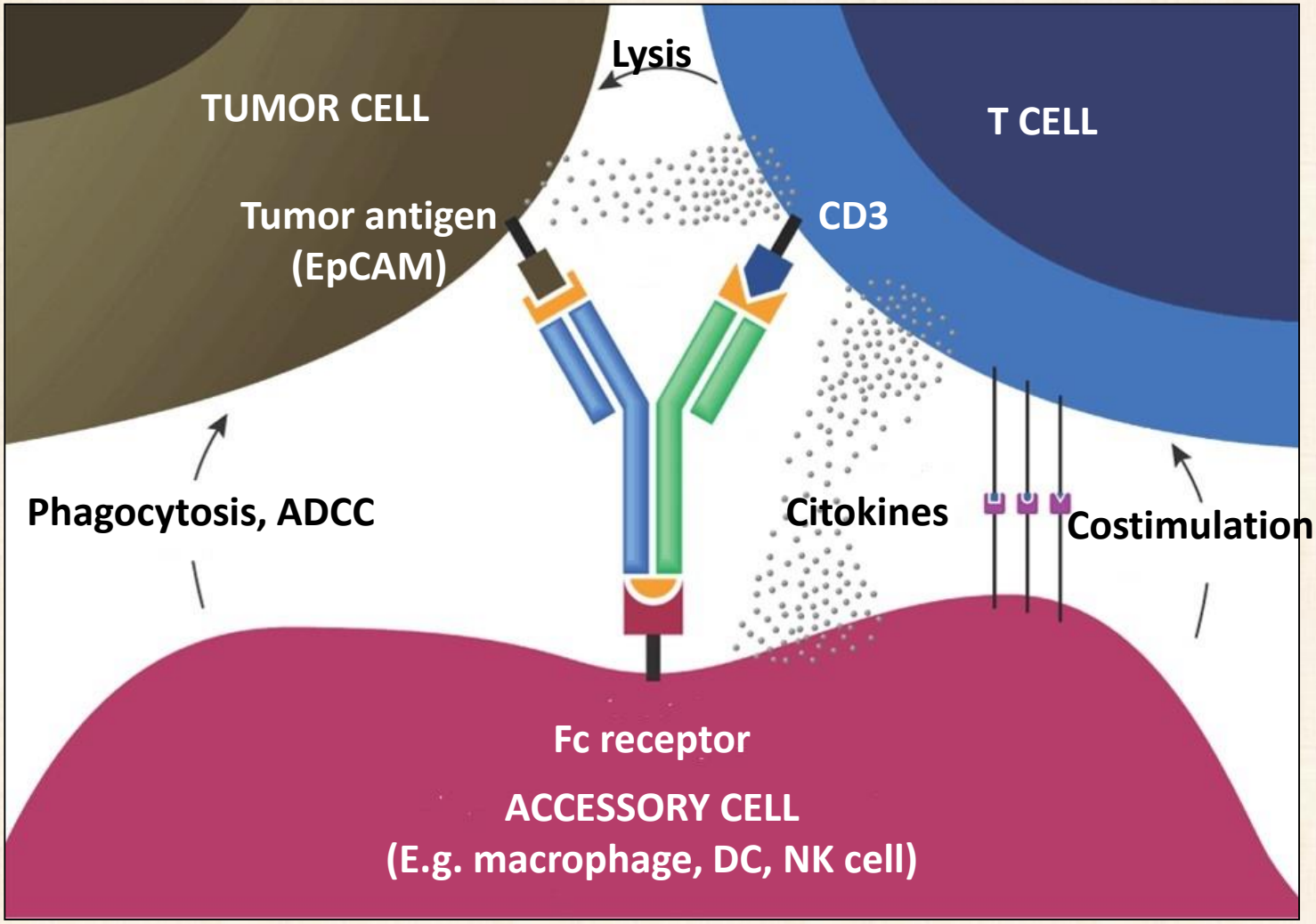
Monoclonal antibodies that bind target cell-surface antigens are themselves non-cytotoxic, but after conjugation with toxins they are able for clinical application in cancer therapy.

Immunotoxin therapy of Hairy Cell Leukemia



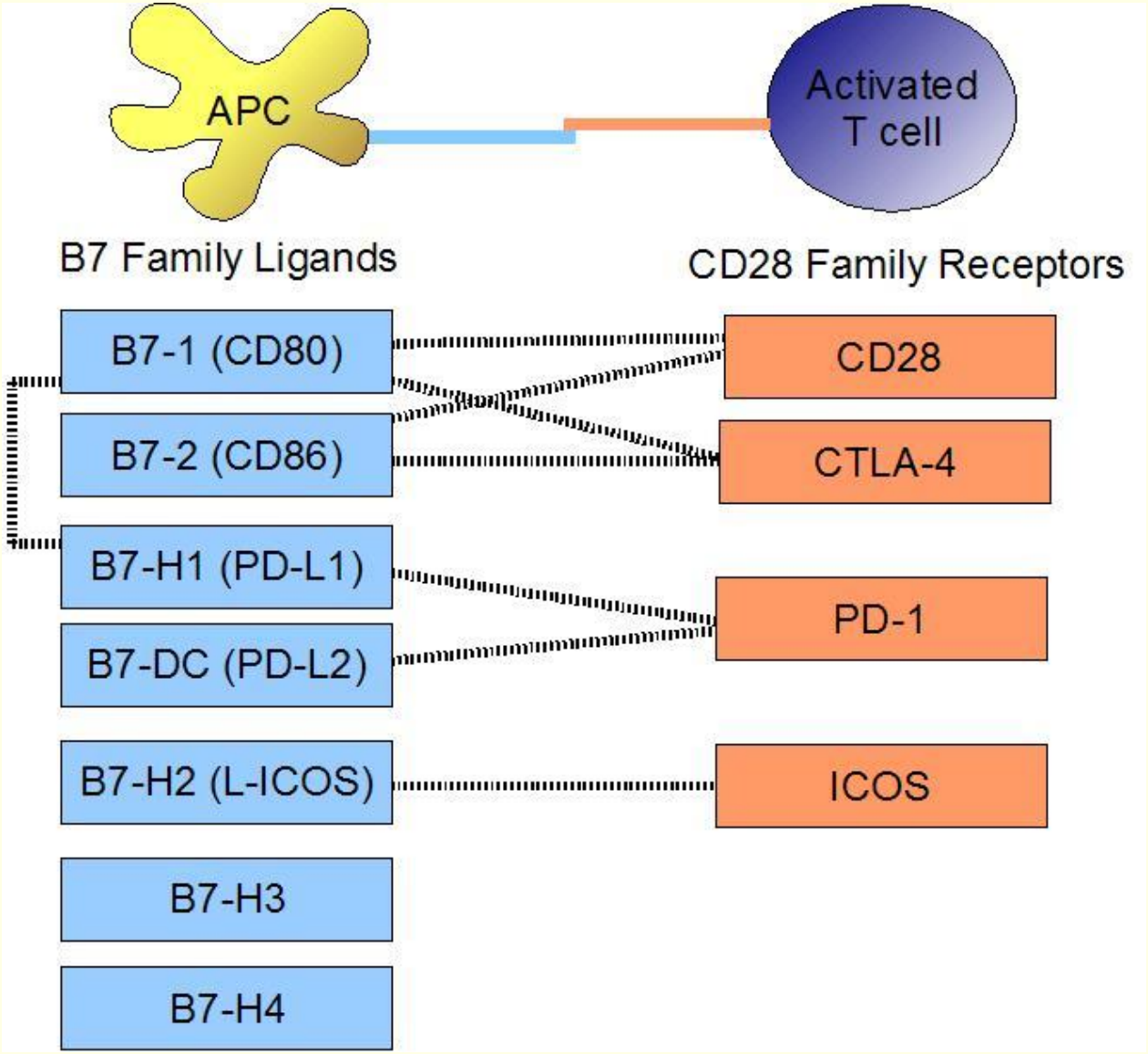
Treatment of hairy cell leukemia with recombinant BL22 immunotoxin therapy

Bispecific therapeutic monoclonal antibodies

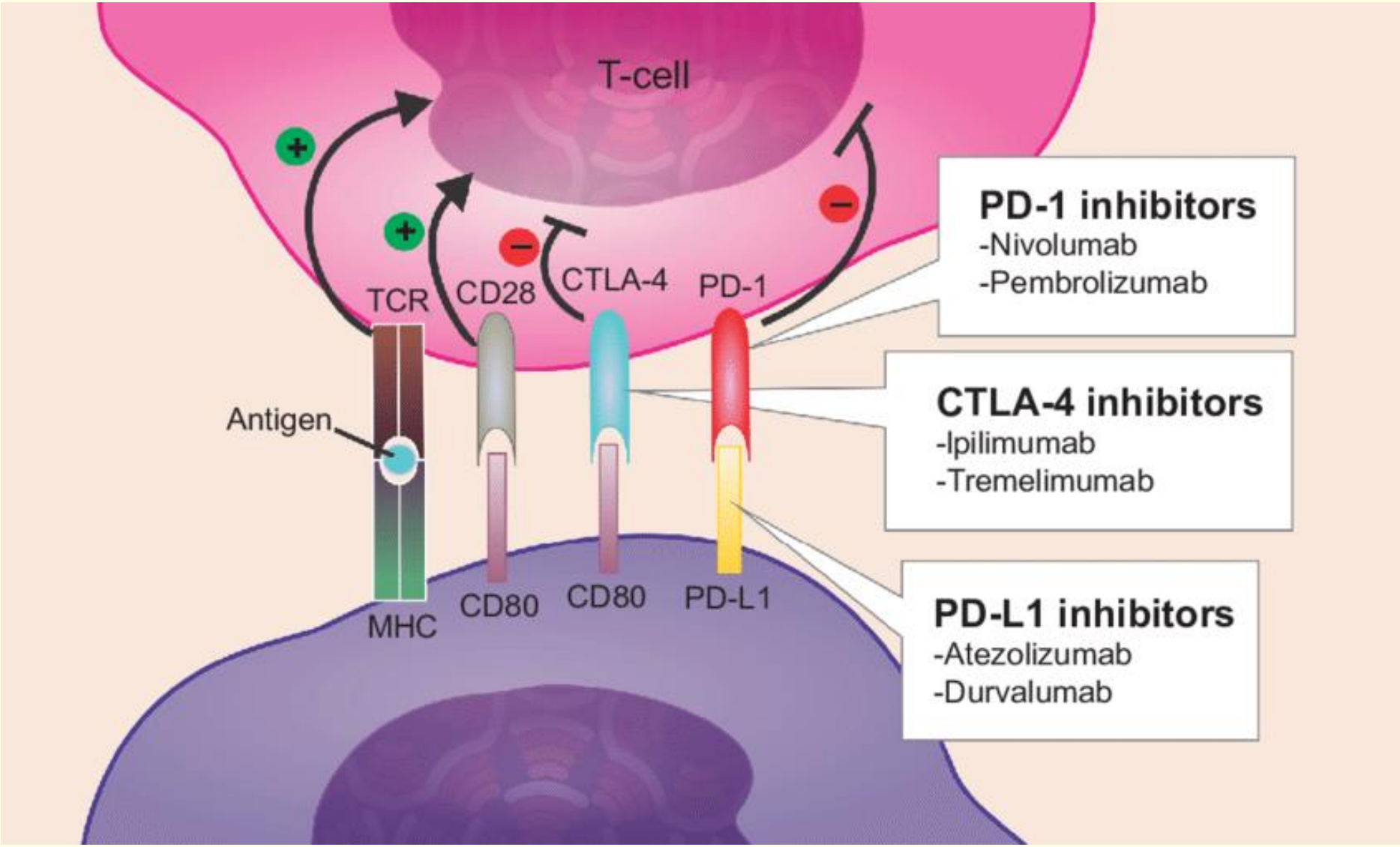


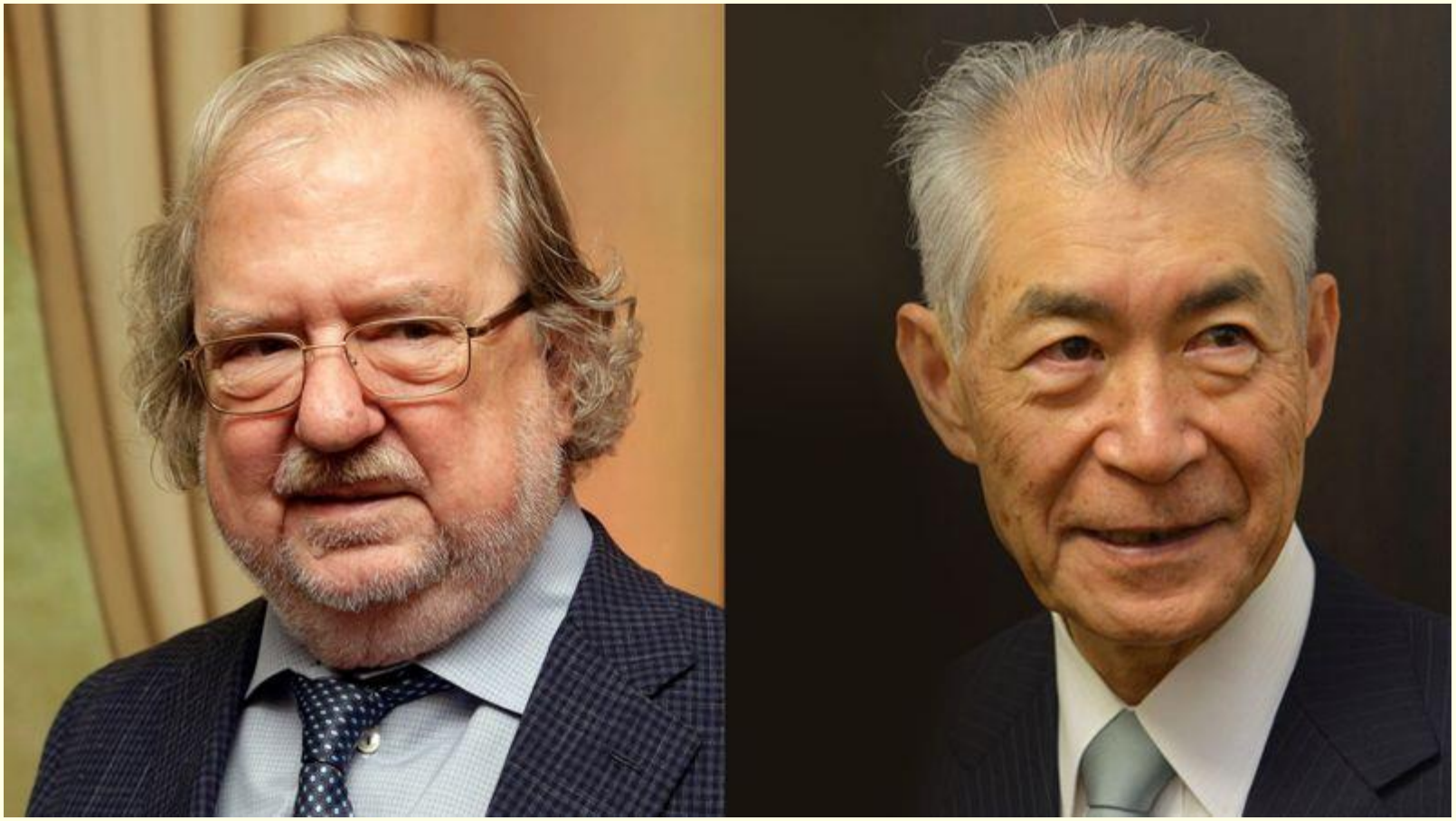
Mechanism of action of Catumaxomab (the first approved bispecific and és trifuntional antibody). (EpCAM: Epithelial cell adhesion molecule)

APC – T cell checkpoints



Immune checkpoint inhibitors



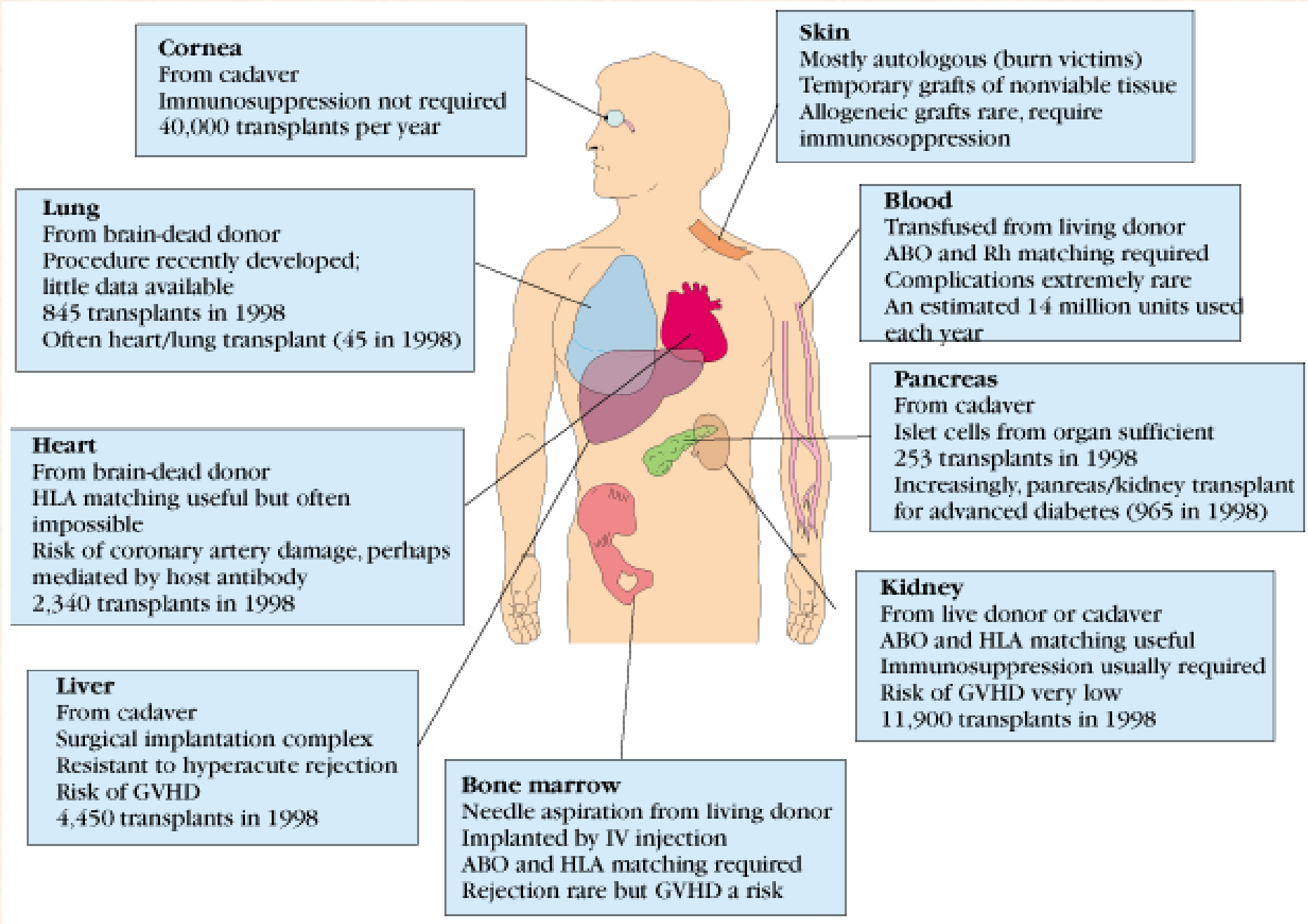


James P. Allison, PhD **Tasuku Honjo**, MD, PhD

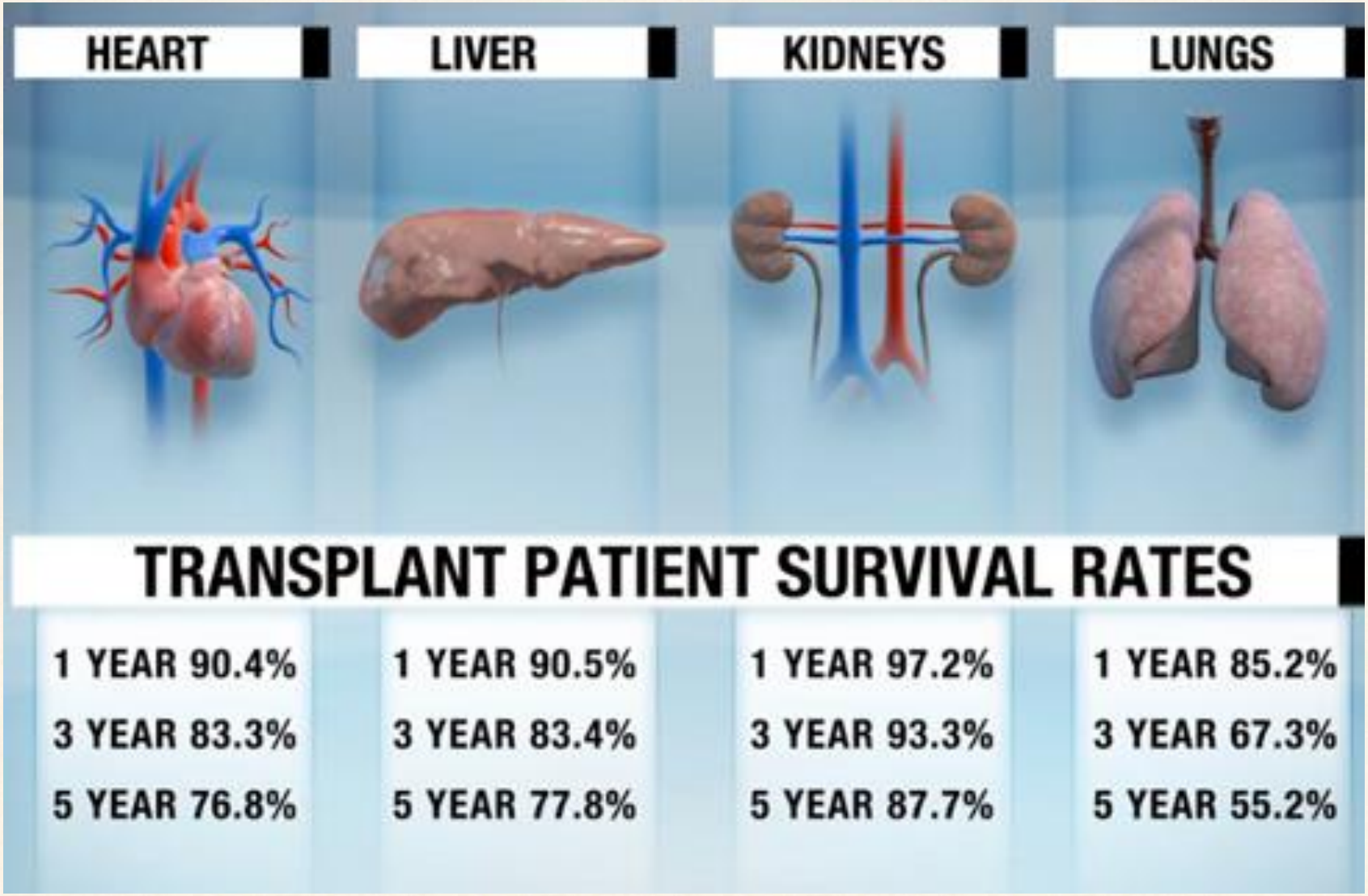
Immunotherapy pioneers have won the ***2018 Nobel Prize*** in Physiology or Medicine for their research that eventually led to the use of immune checkpoint inhibitors to treat cancer.

Immunological aspects of organ transplantation


ΟΙ ΑΝΑΡΓΥΡΟΙ


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 immunosoppression
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
Pancreas
From cadaver
Islet cells from organ sufficient
253 transplants in 1998
Increasingly, panreas/kidney transplant for advanced diabetes (965 in 1998)
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
Kidney
From live donor or cadaver
ABO and HLA matching useful
Immunosuppression usually required
Risk of GVHD very low
11,900 transplants in 1998
Liver
From cadaver
Surgical implantation complex
Resistant to hyperacute rejection
Risk of GVHD
4,450 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

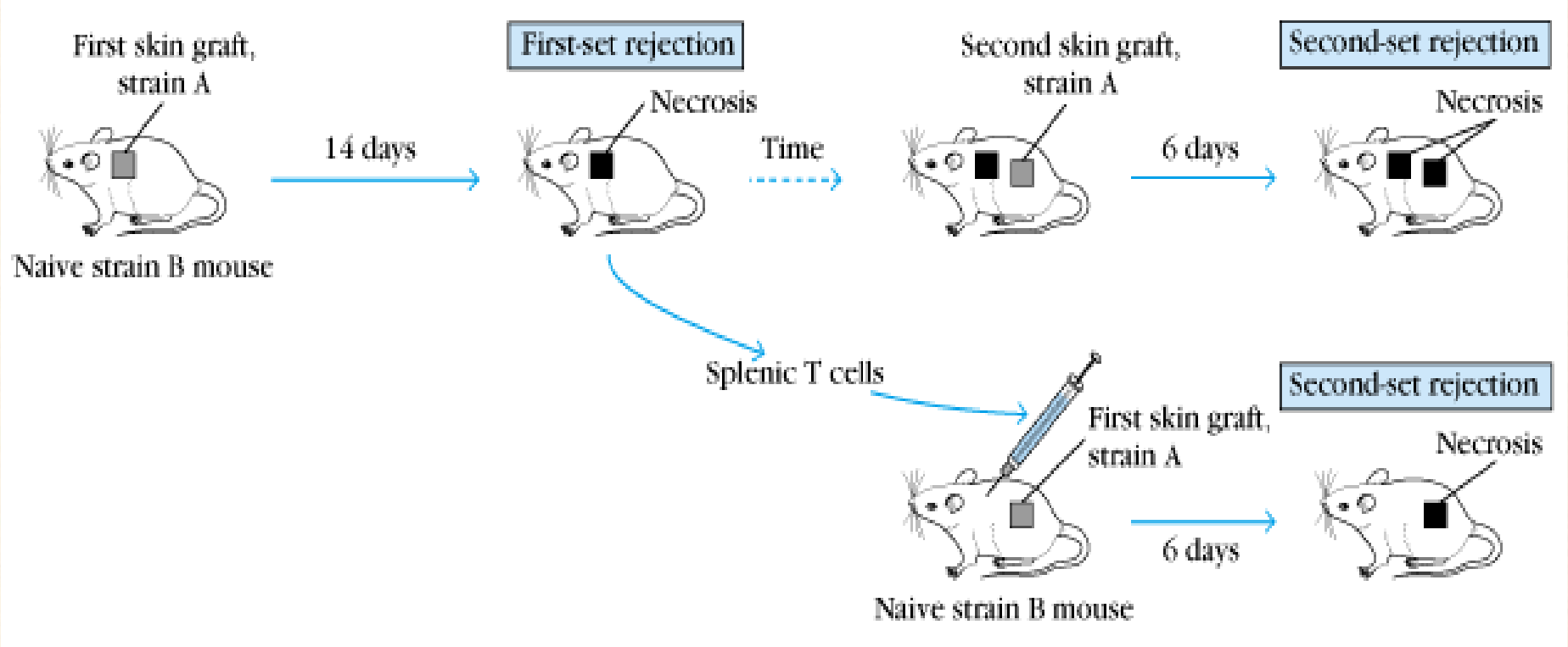
Average survival rate of transplanted patients in US in 2015



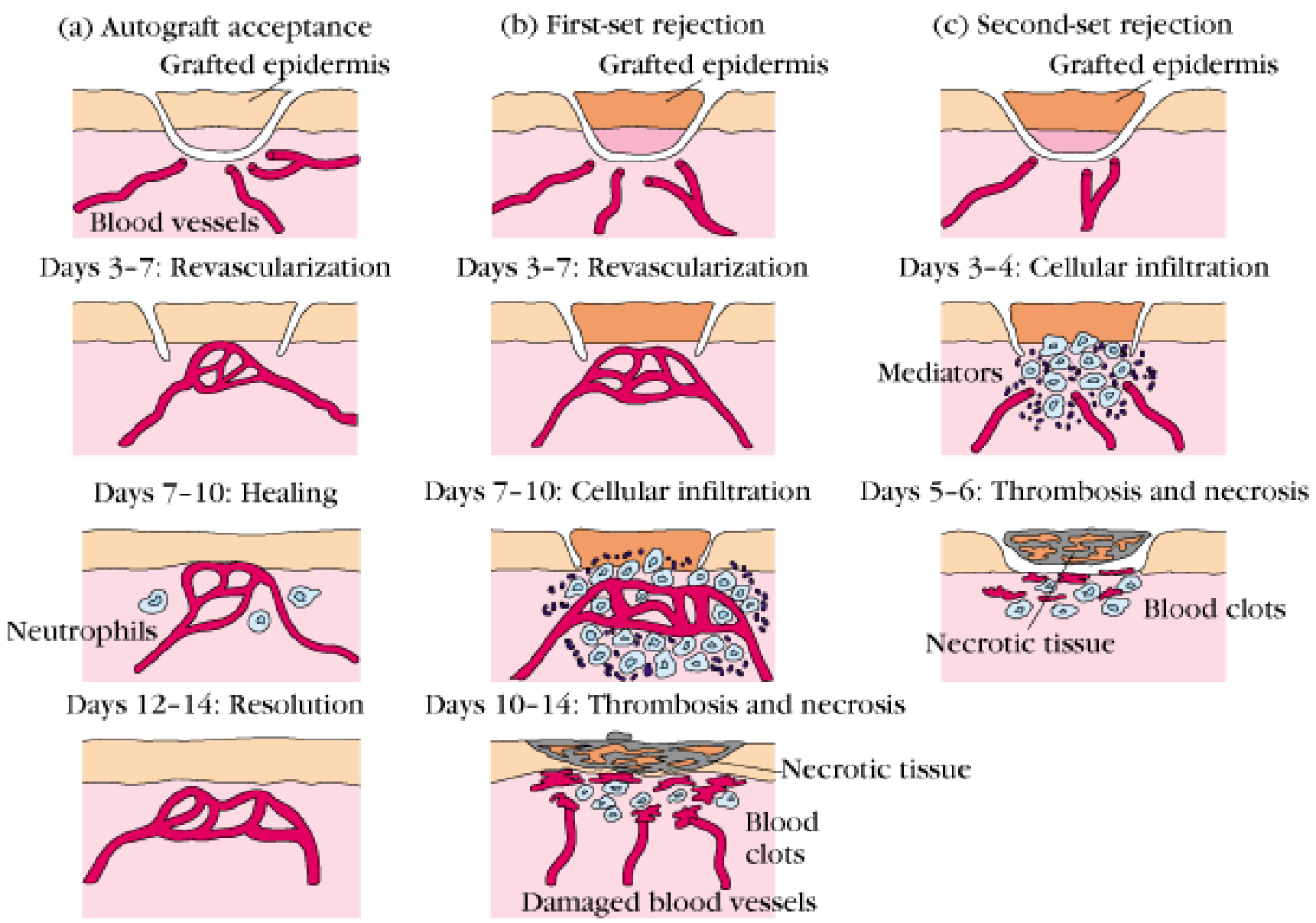
Basic terms

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

Allograft rejection



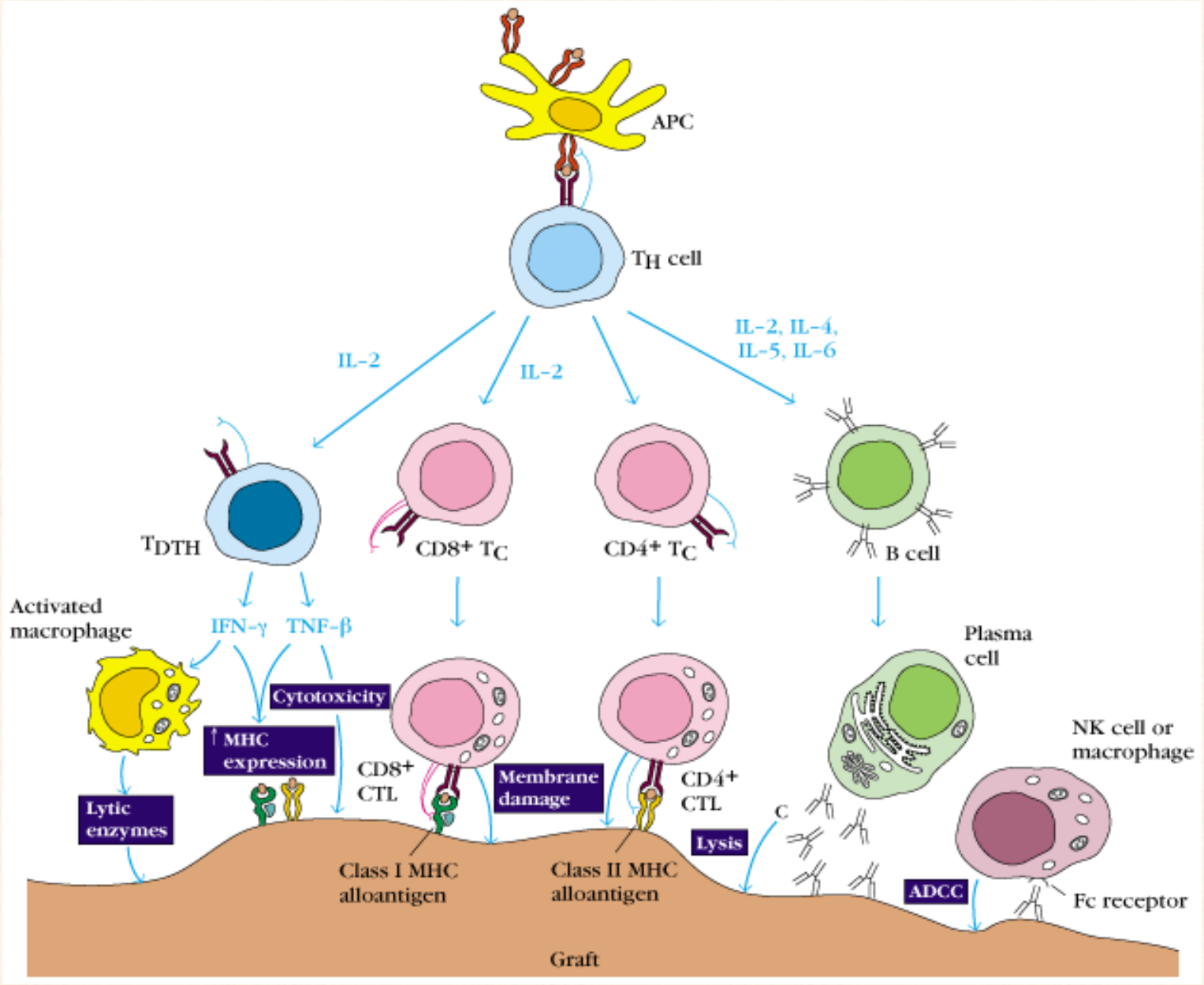
Graft acceptance and rejection



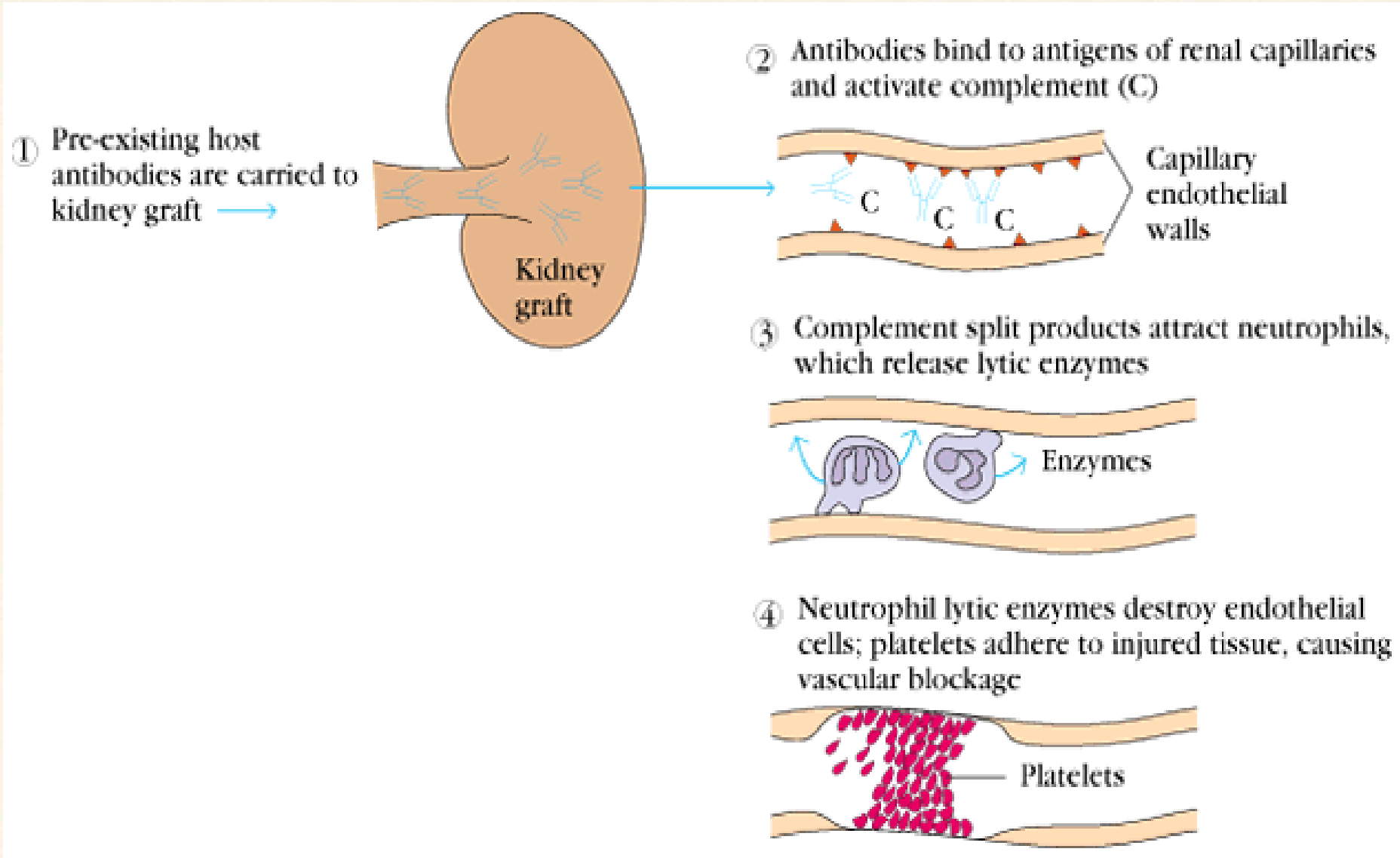
Host versus graft reaction

- 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

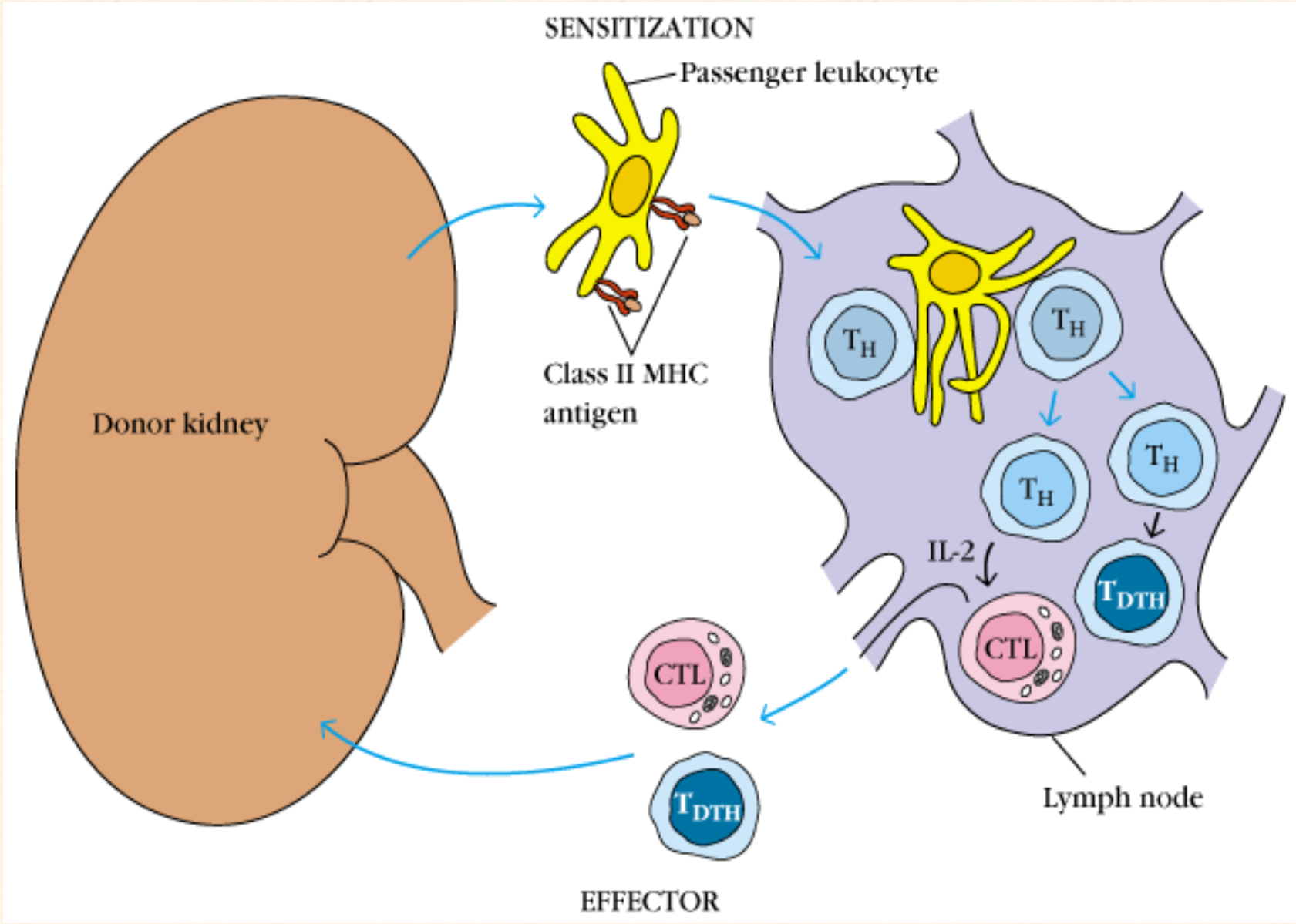
Mechanisms of host versus graft reactions



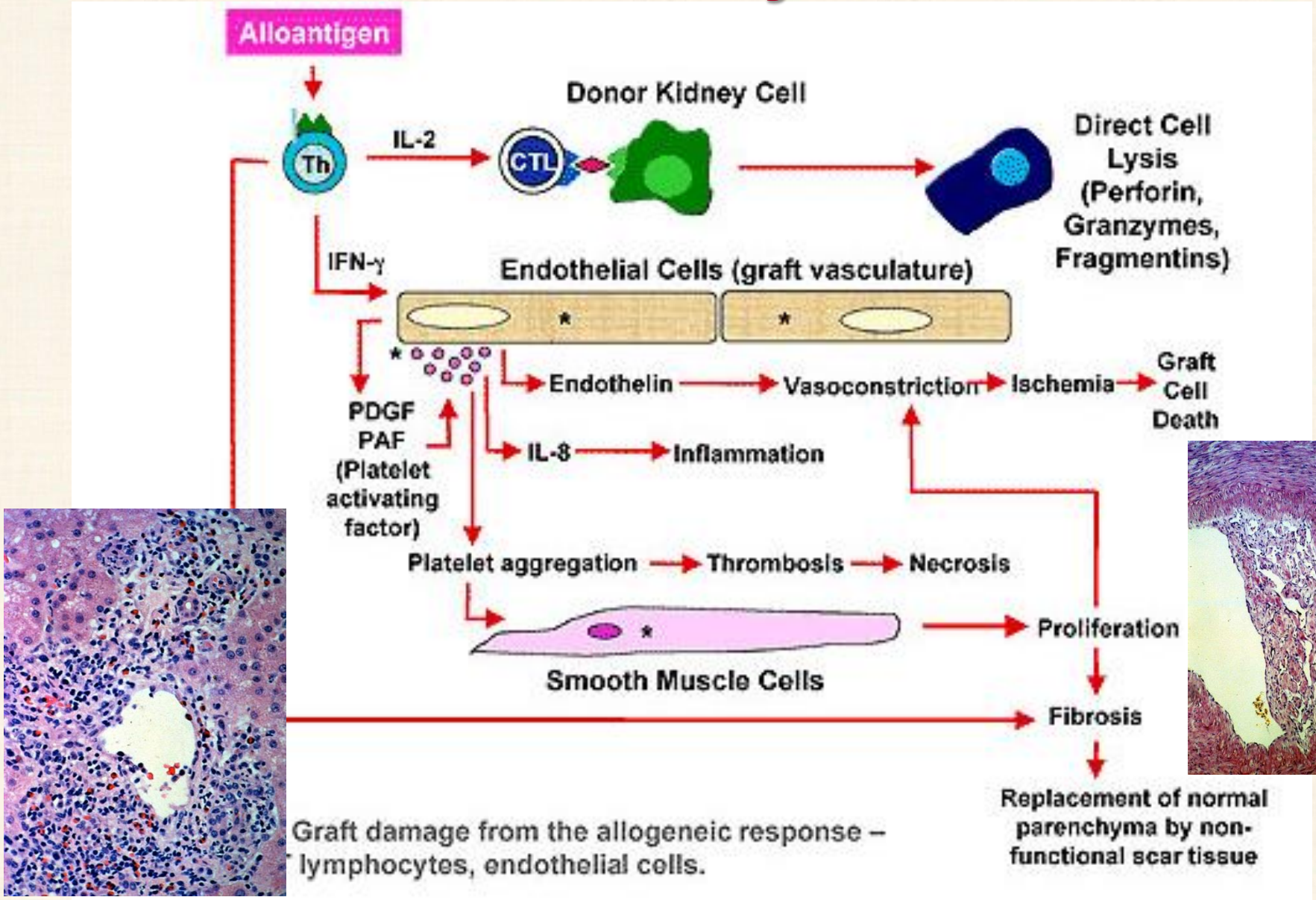
Hyperacute rejection



Acute rejection



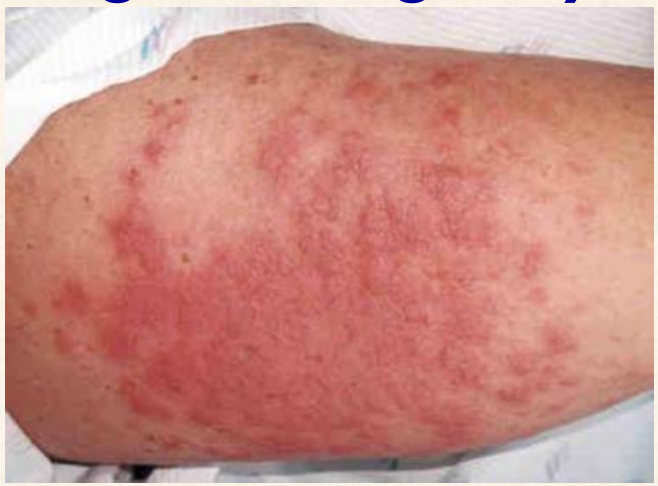
Chronic rejection

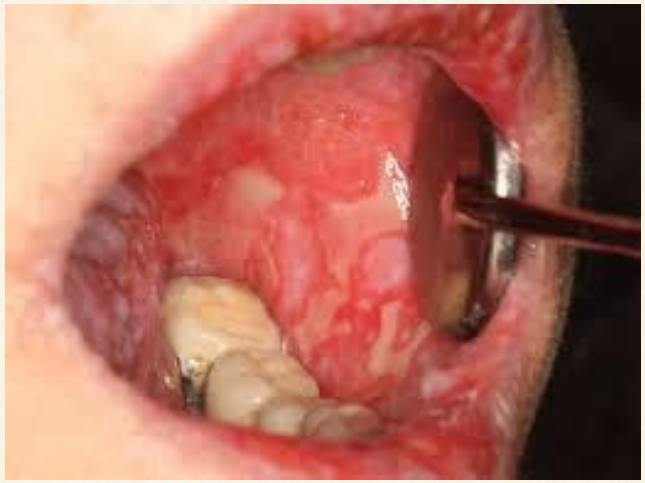


Graft damage from the allogeneic response –
lymphocytes, endothelial cells.

Graft versus host reaction

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



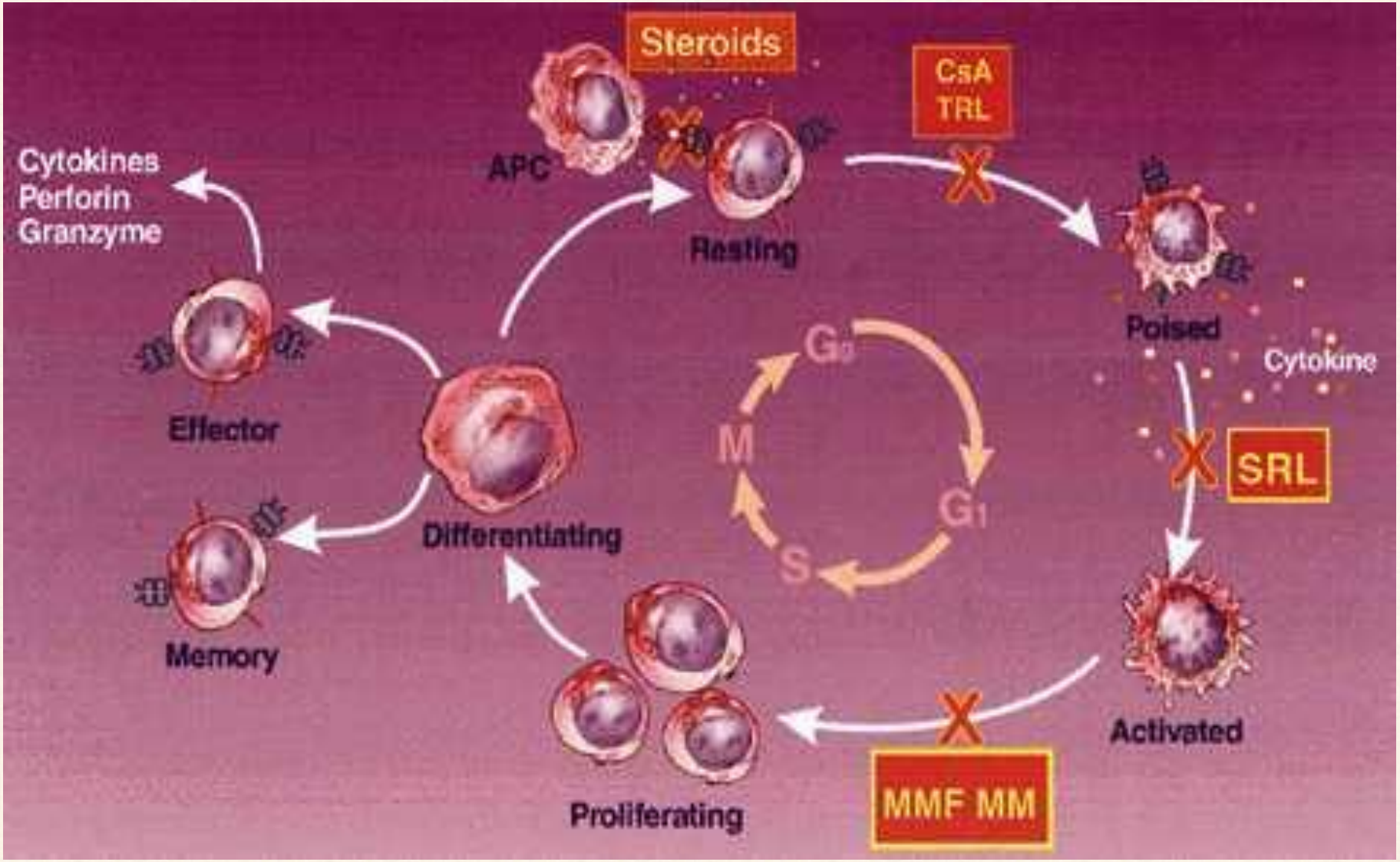


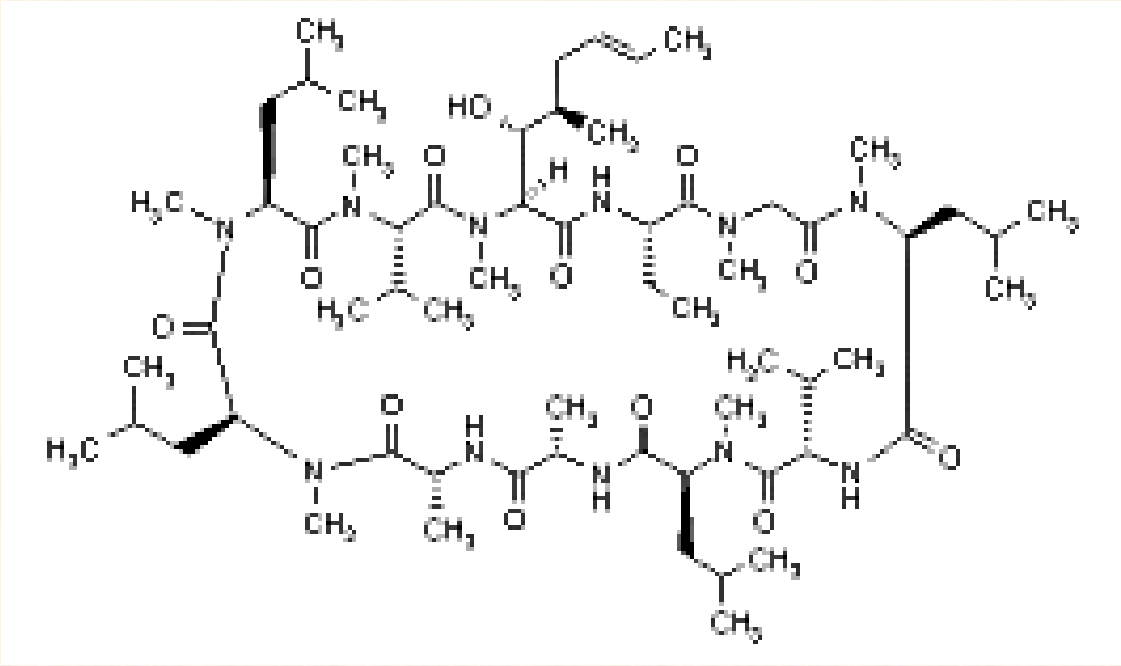
- **chronic GVHD (autoimmune-like phenomenon)**

Bone marrow transplantation

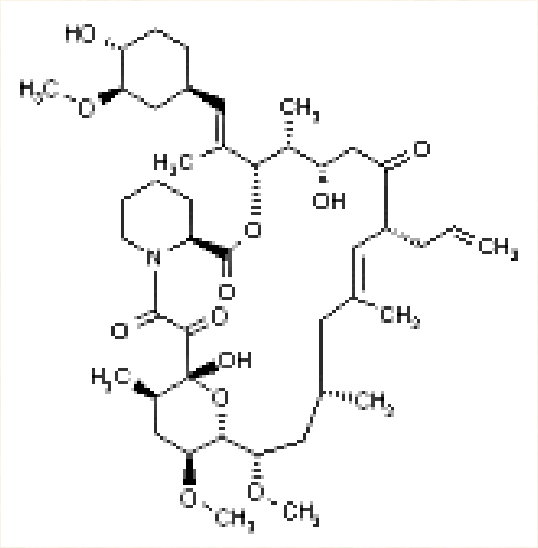
Advantage	Disadvantage
Autologous	**Allogeneic**
no GVH no rejection no matching needed	GVH rejection need matching tumour in donor cells
Allogeneic	**Autologous**
no tumour transfer graft vs. tumour myelosuppression avoided	grafting tumour cells (myelosuppression possible)

Immunosuppression



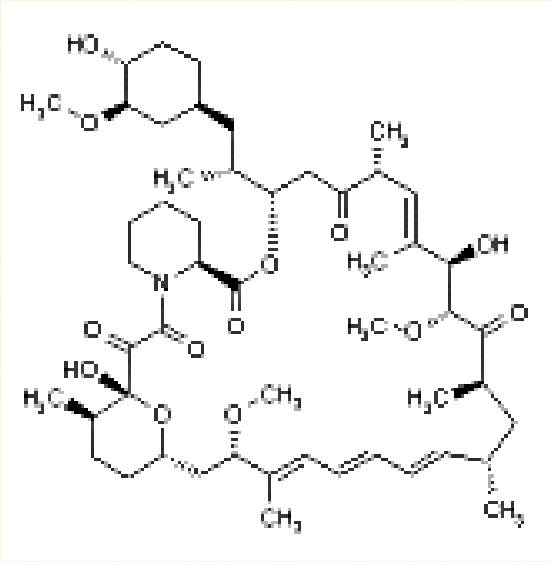


Cyclosporine A

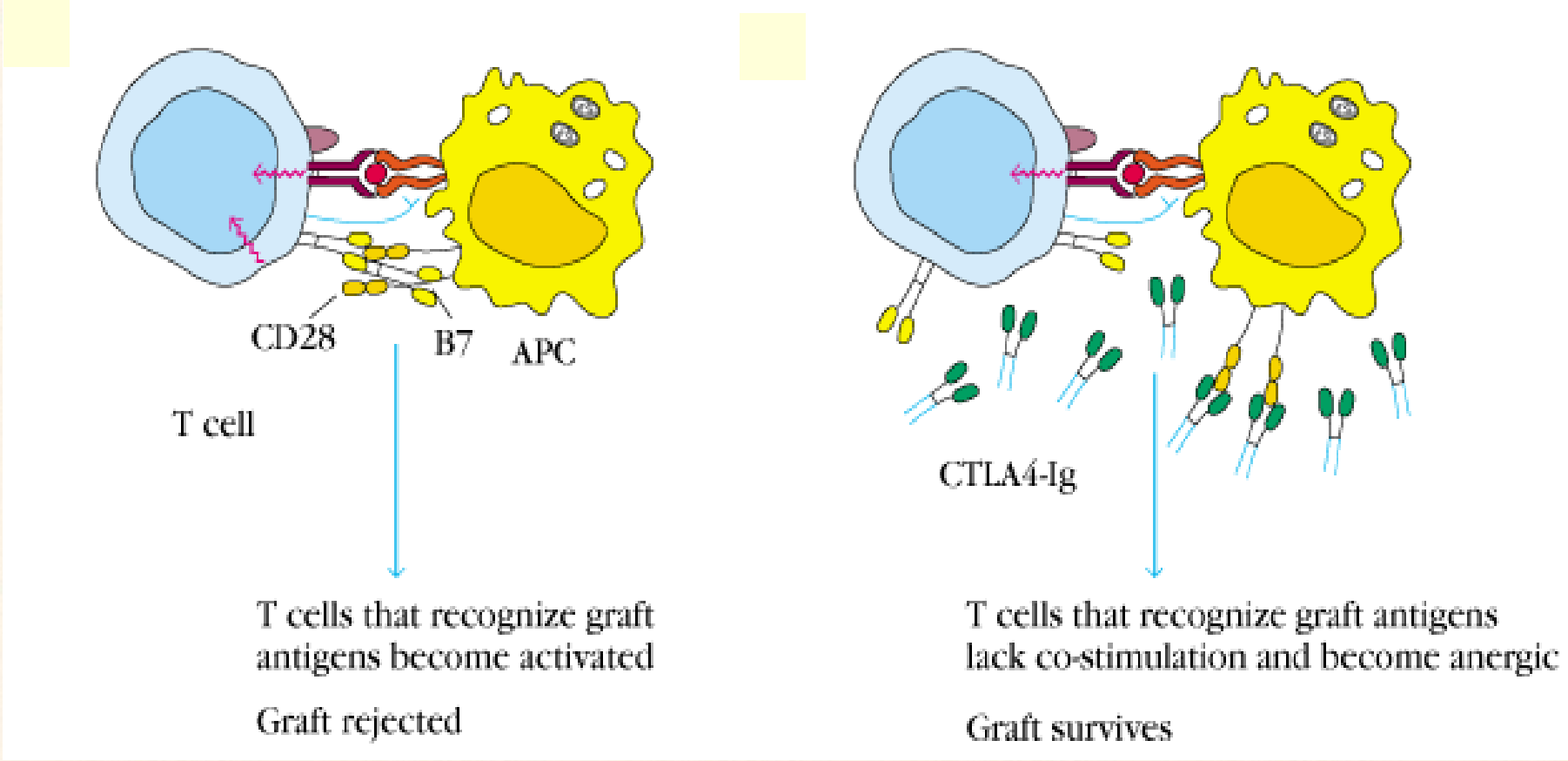


Tacrolimus

Sirolimus



Blocking co-stimulatory signals



Co-stimulation inhibition by *Abatacept*