Basic Immunology

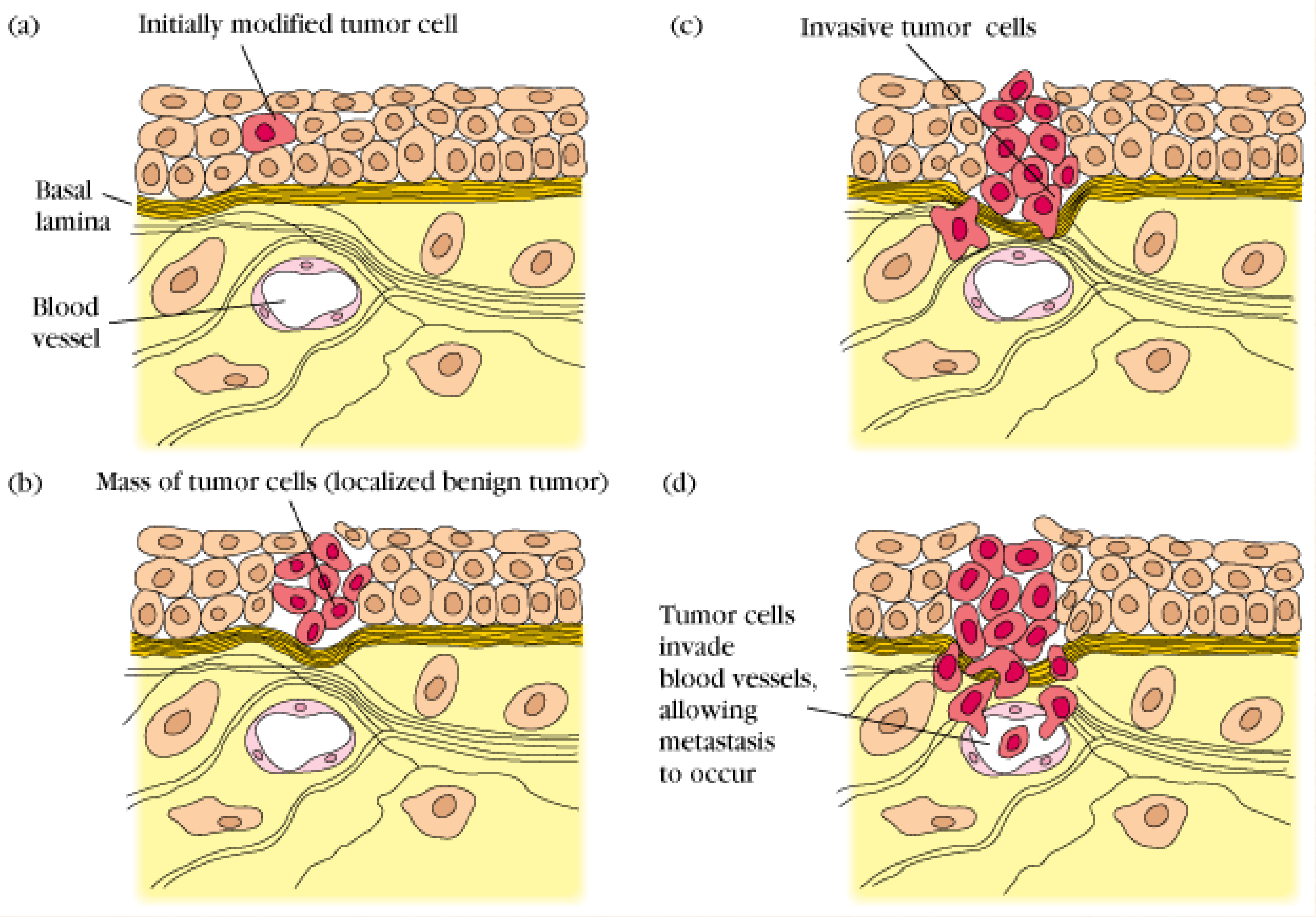
Lecture 25^{th} - 26^{th}

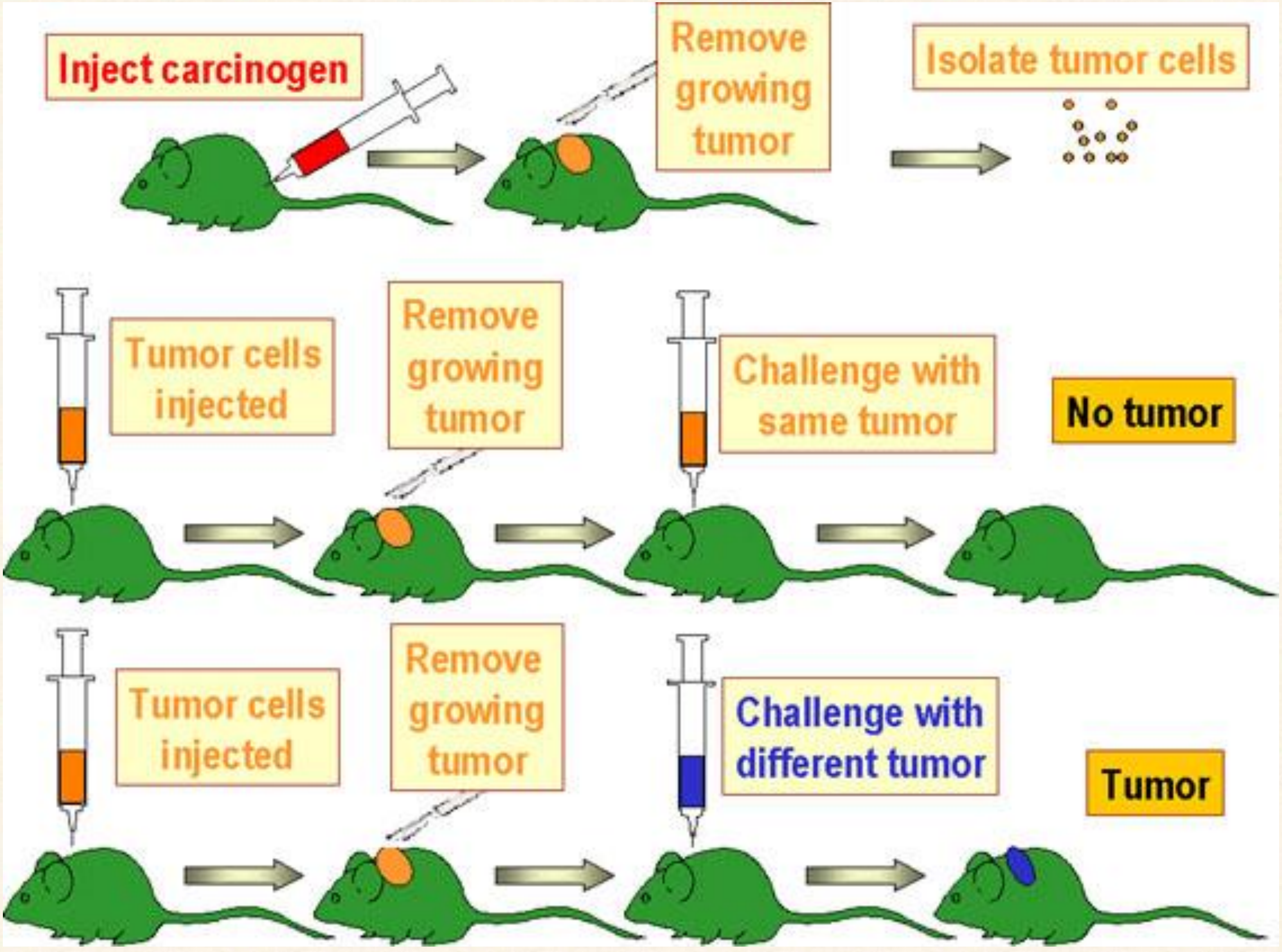
Immunity against tumors

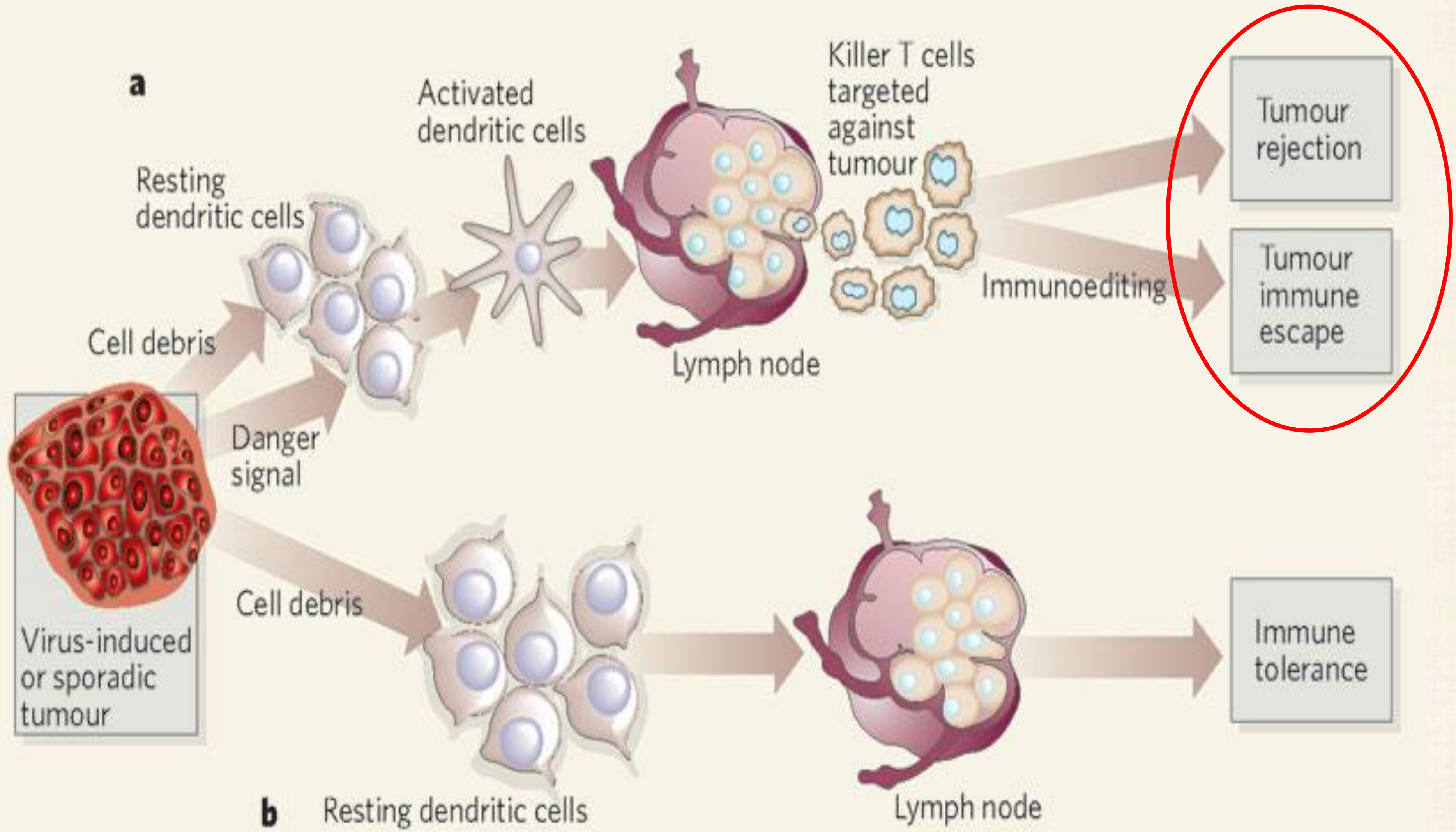
Tumor- and tumor associated antigens. Tumor escape. Trends in immunotherapy against cancer.

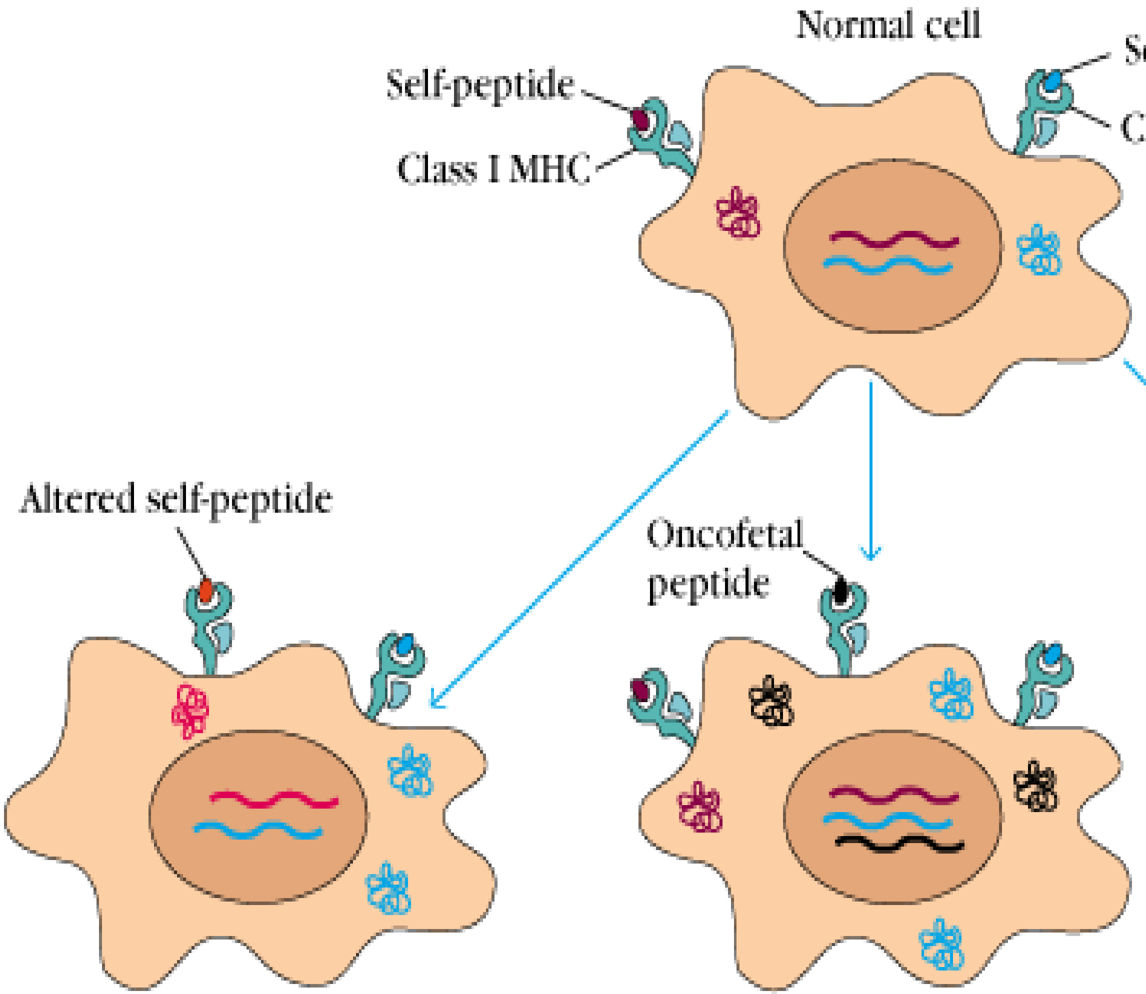
Immunological aspects of organ transplantation

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
Resting
dendritic cells
Activated
dendritic cells
Killer T cells
targeted
against
tumour
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



Mutation generates new peptide in class I MHC molecule (TSTA)

Inappropriate expression of embryonic gene (TATA)

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!**

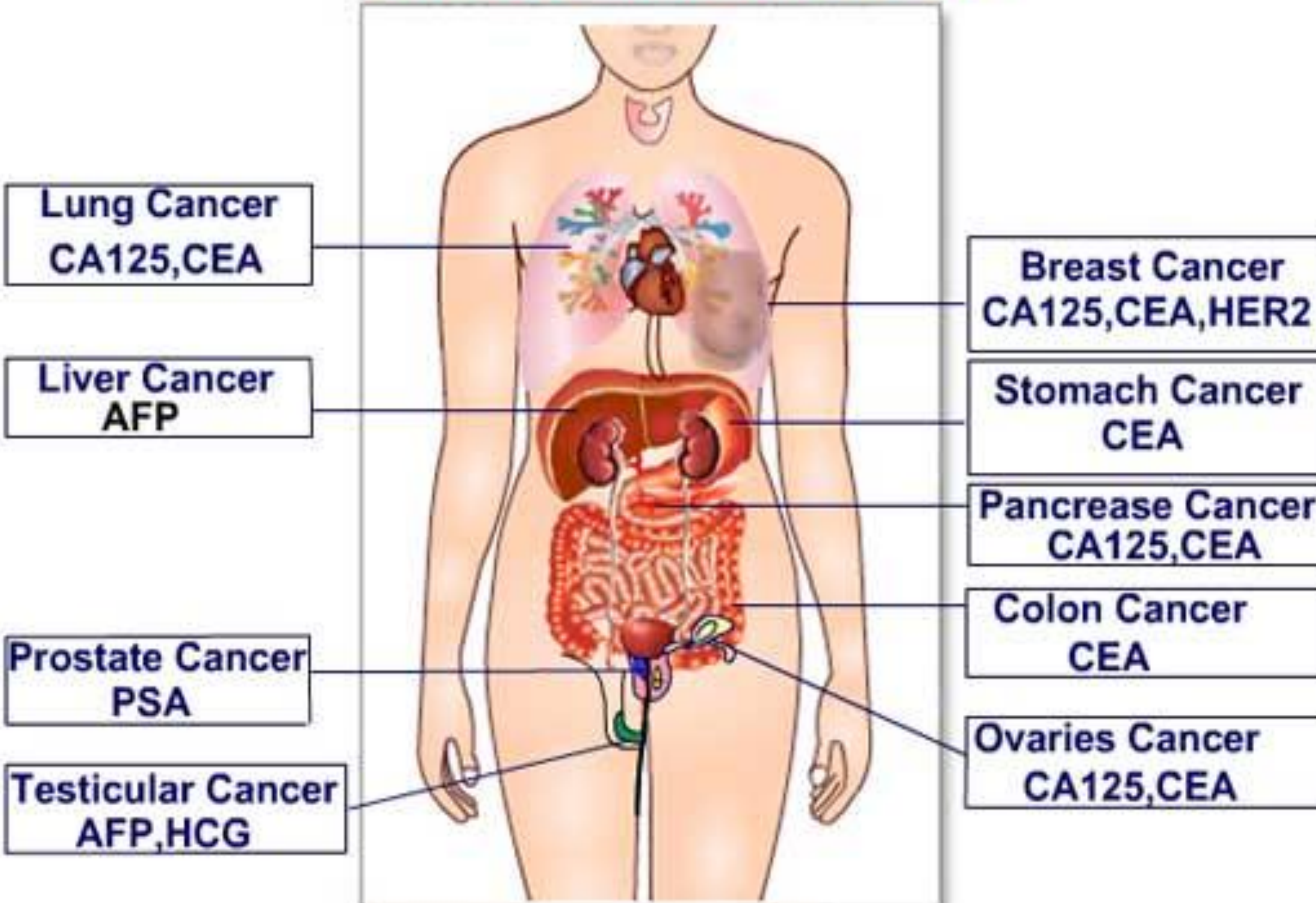
- **TSA is recognized** (according to the individual MHC haplotype) **by the immune system and induces targeting type immune response or tolerance**

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



Often tumor markers

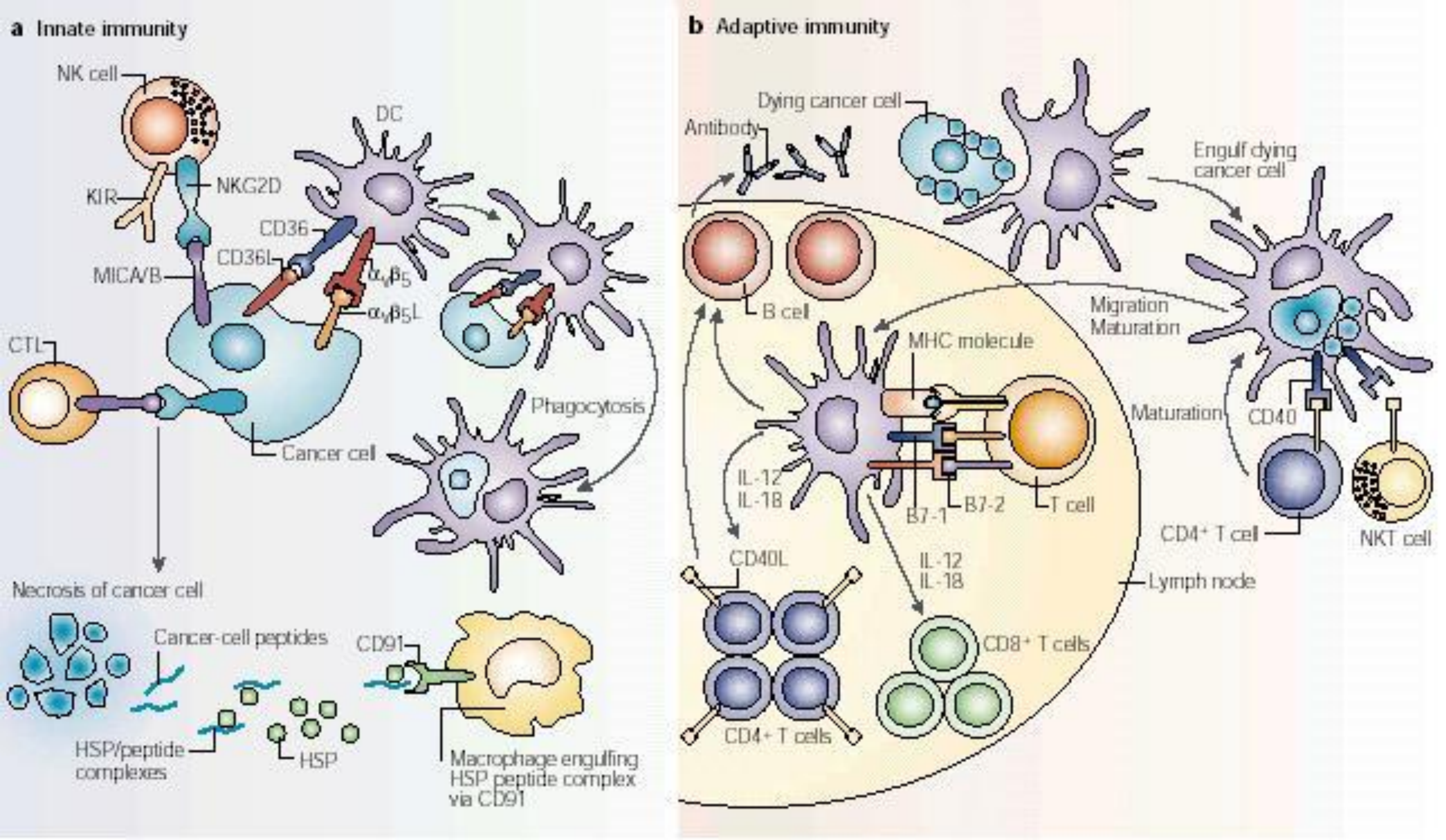
Tumor markers	Abbreviation	Oncological application
Alfa-foetoprotein	AFP	Liver and germ cell tumors
Cancer antigen 125	CA 125	ovarian tumors
Cancer antigen 15,3	CA 15,3	Breast cancer
Cancer antigen 72,4	CA 72,4	Gastric cancer
Cancer antigen 19,9	CA 19,9	Pancreatic cancer
Carcinoembrional antigen	CEA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

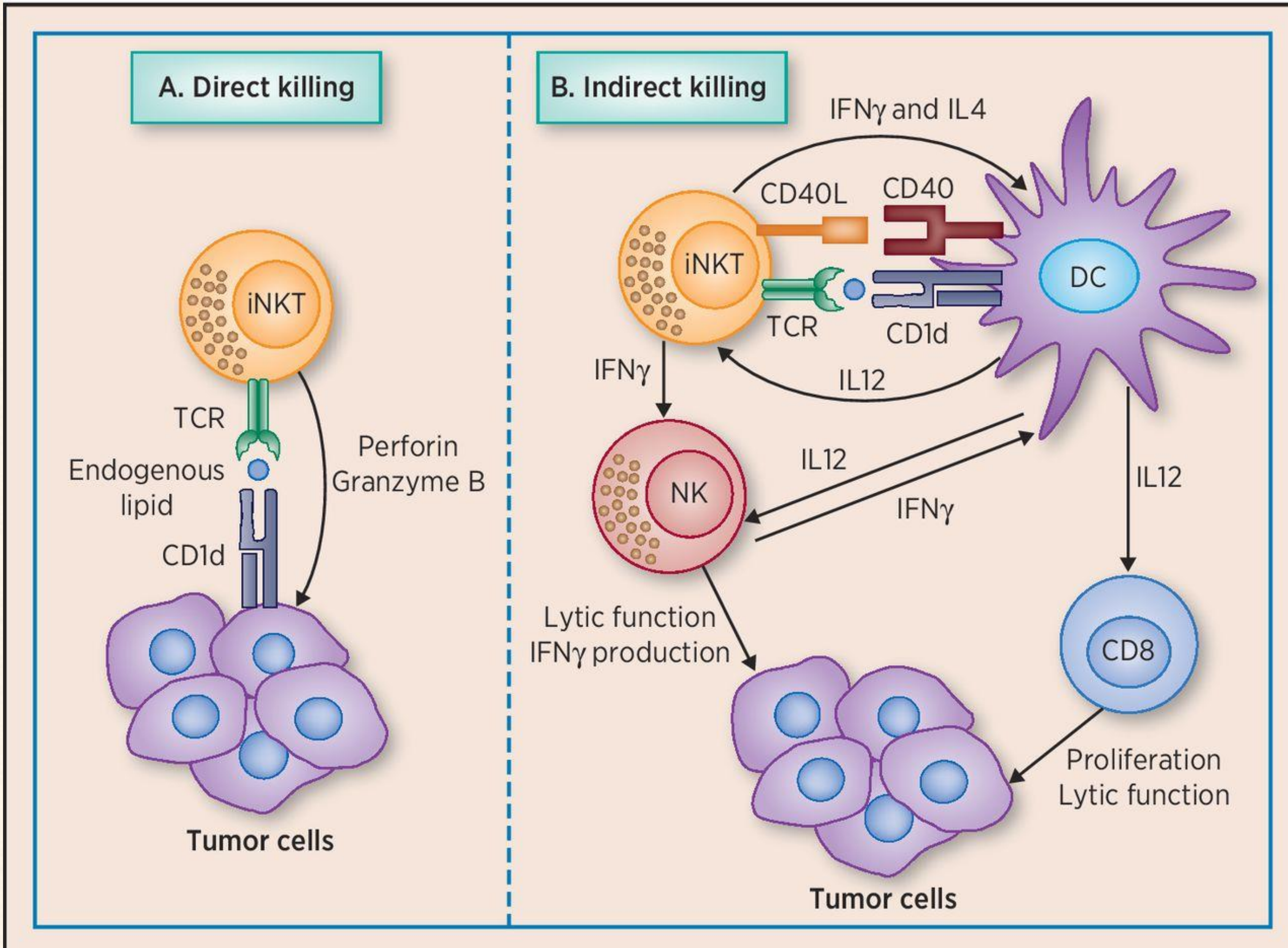
Immune reactions against tumor cells

- T cell mediated (CD8+, CD4+Th1, NK)
- macrophage mediated
- immunoglobulin mediated (ADCC)
- network of cytotoxic cytokines
- all the innate, natural and adaptive immune machineries participate in defense against malignant tumors

N E T W O R K !!!

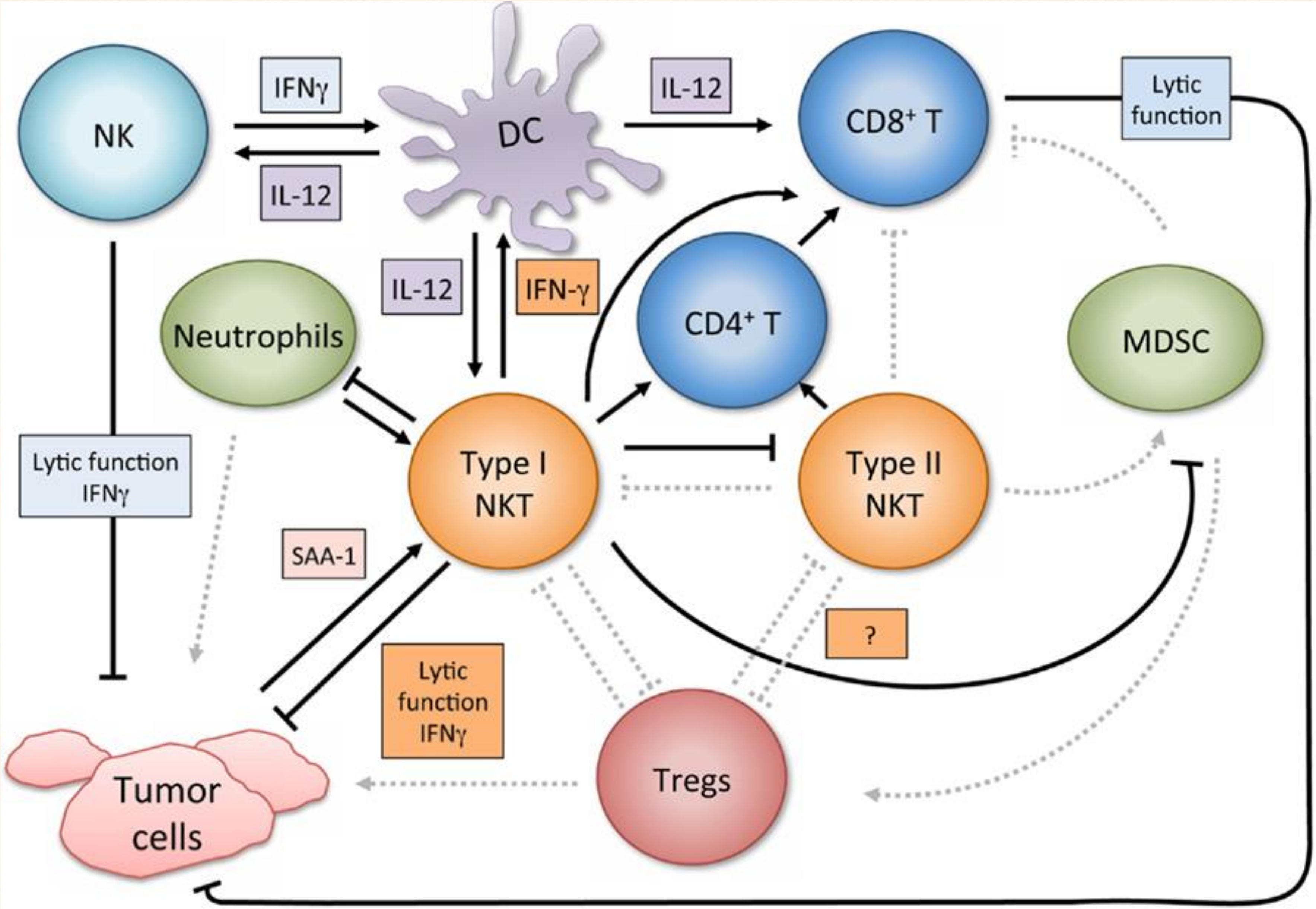
Cell mediated immunity against malignant tumors





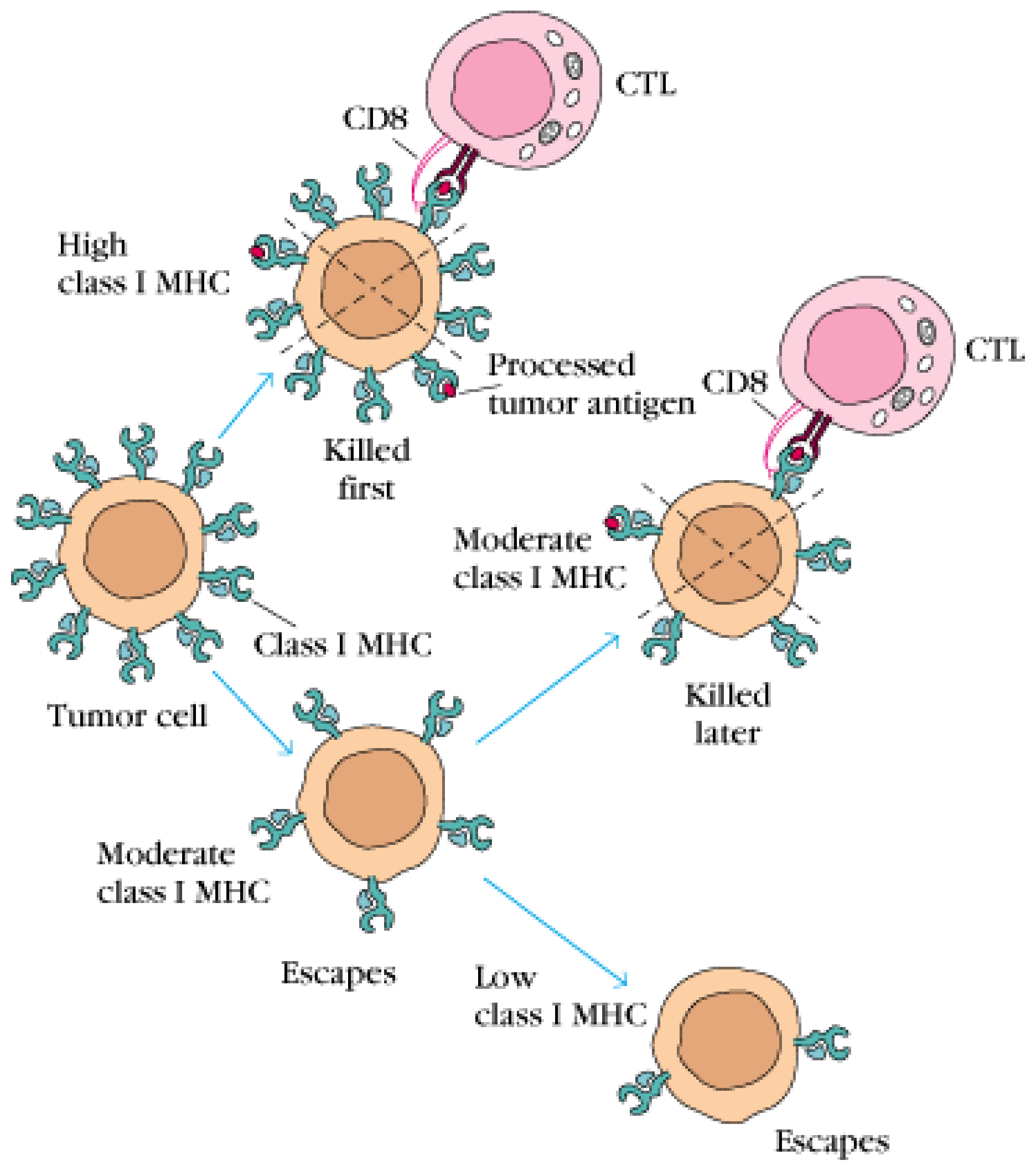
A. Direct killing
iNKT
TCR
Endogenous lipid
CD1d
Perforin
Granzyme B
Tumor cells
B. Indirect killing
IFNγ and IL4
CD40L
CD40
iNKT
DC
TCR
CD1d
IFNγ
IL12
IL12
IFNγ
NK
IL12
Lytic function
IFNγ production
CD8
Proliferation
Lytic function
Tumor cells

Enhancement of tumor immunity by NKT cells

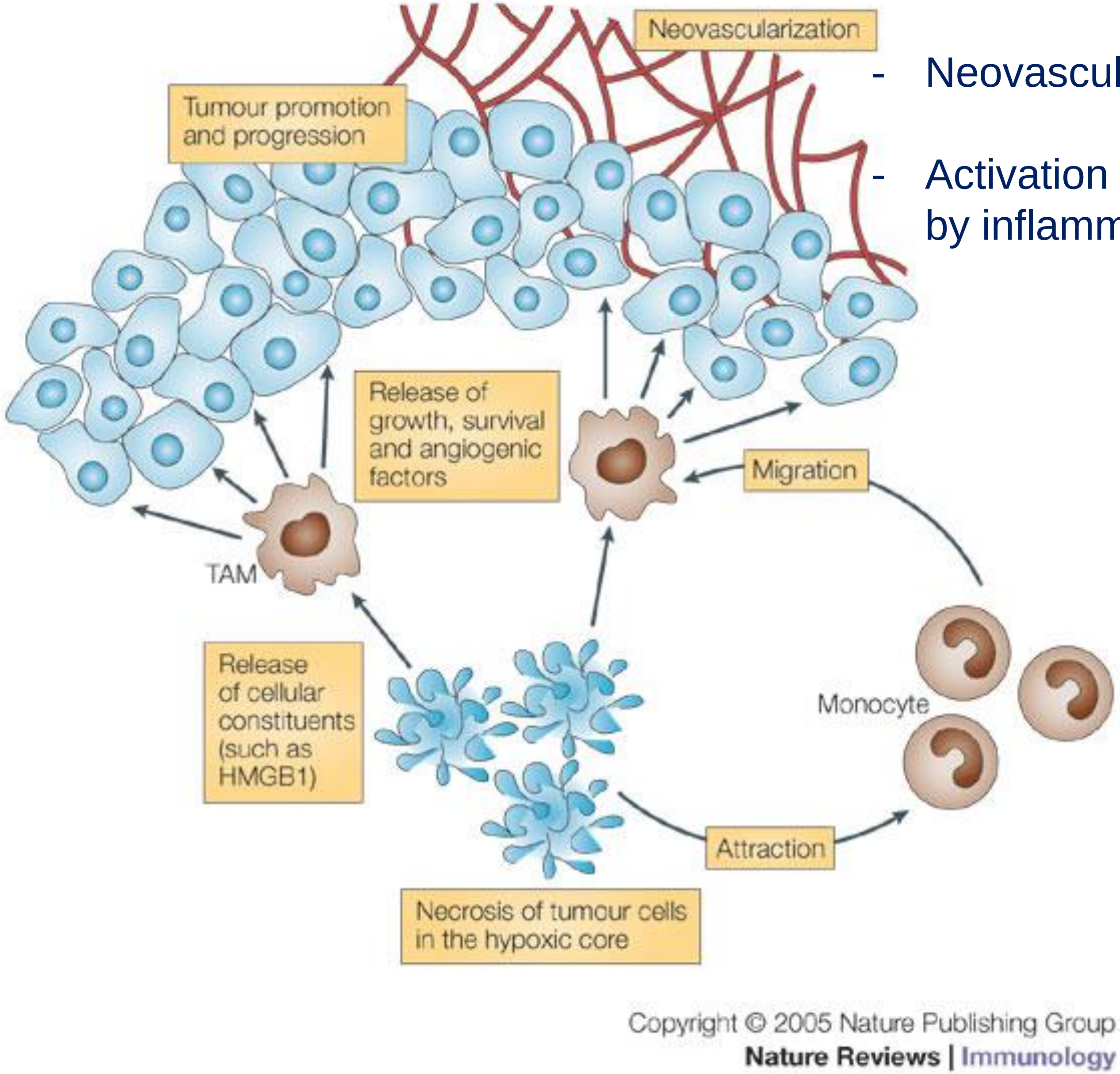


Tumor escape

- 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

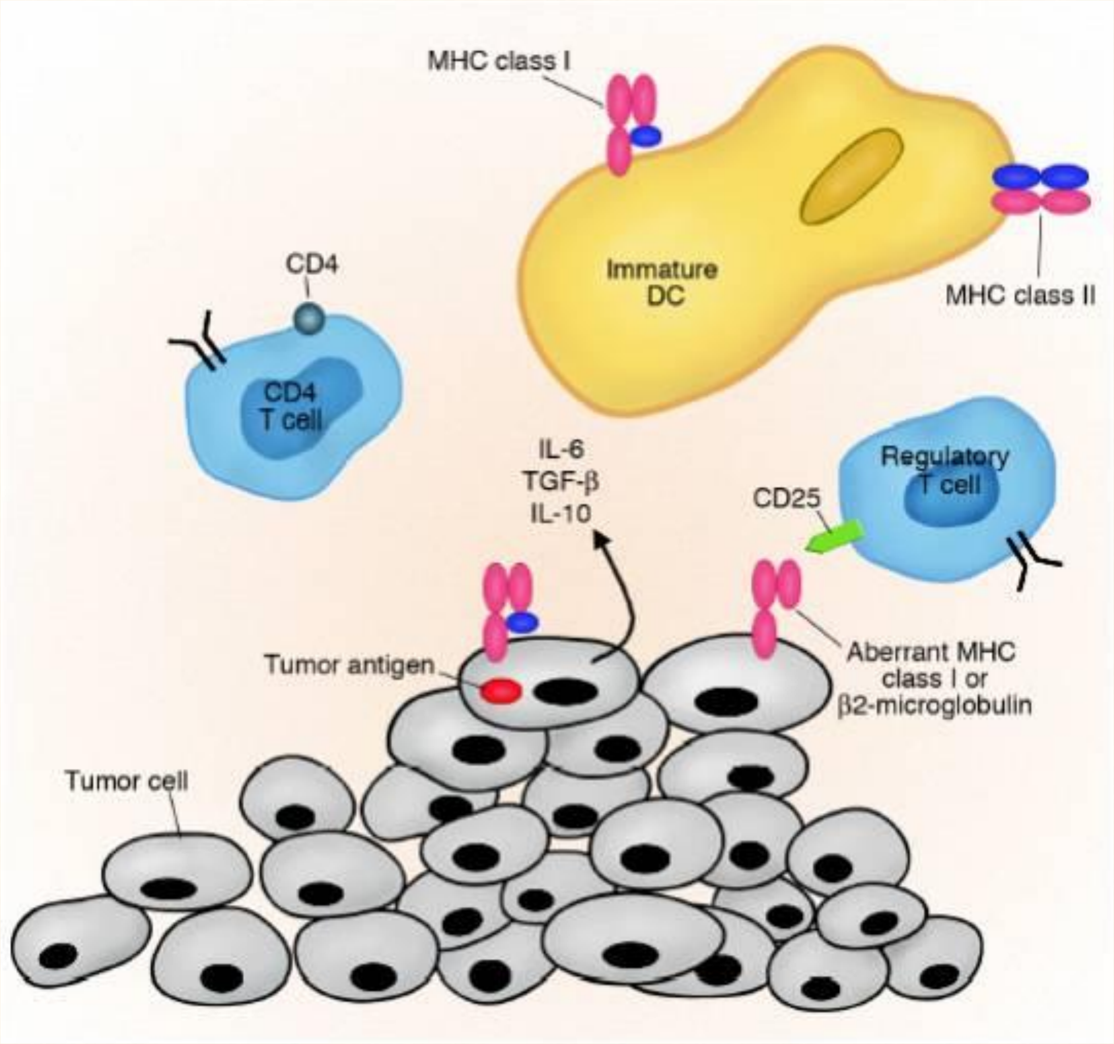

CTL
CD8
High
class I MHC
Processed
tumor antigen
Killed
first
CTL
CD8
Moderate
class I MHC
Class I MHC
Tumor cell
Killed
later
Moderate
class I MHC
Escapes
Low
class I MHC
Escapes

Tumor infiltrating macrophages: double-edged sword

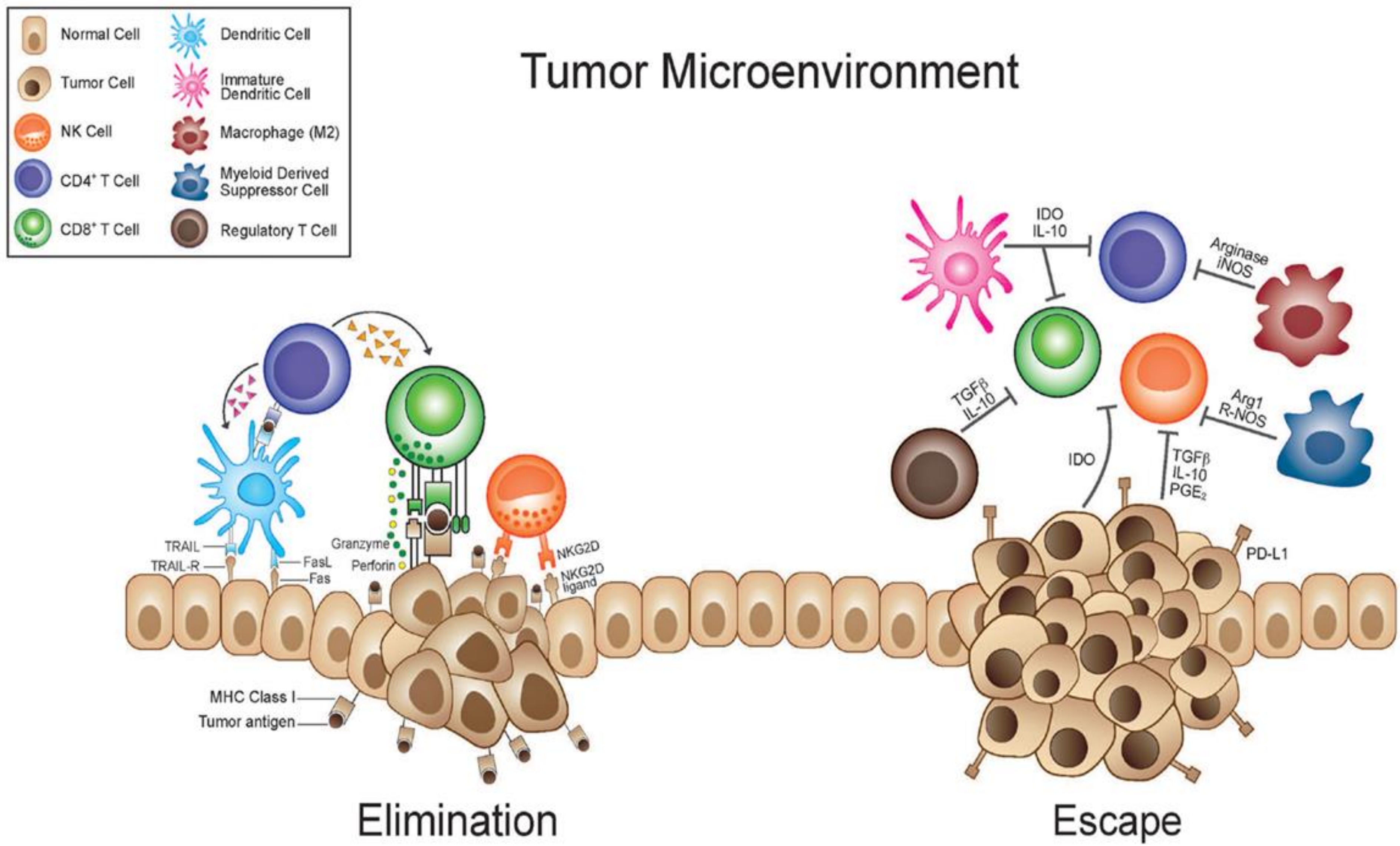


- Neovascularization
- Activation of cancer cells by inflammatory cytokines

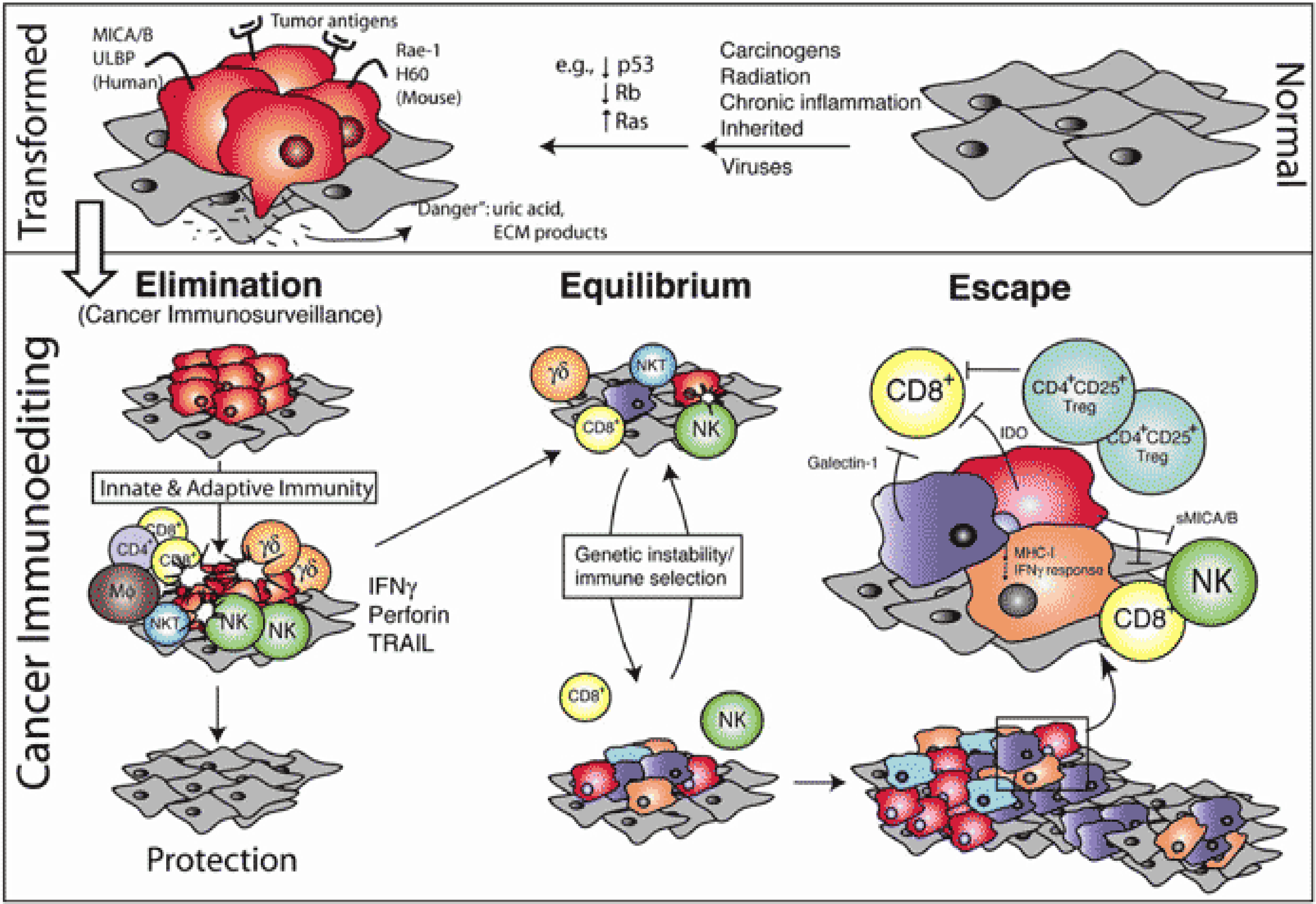
Tumor escape according to the local environment

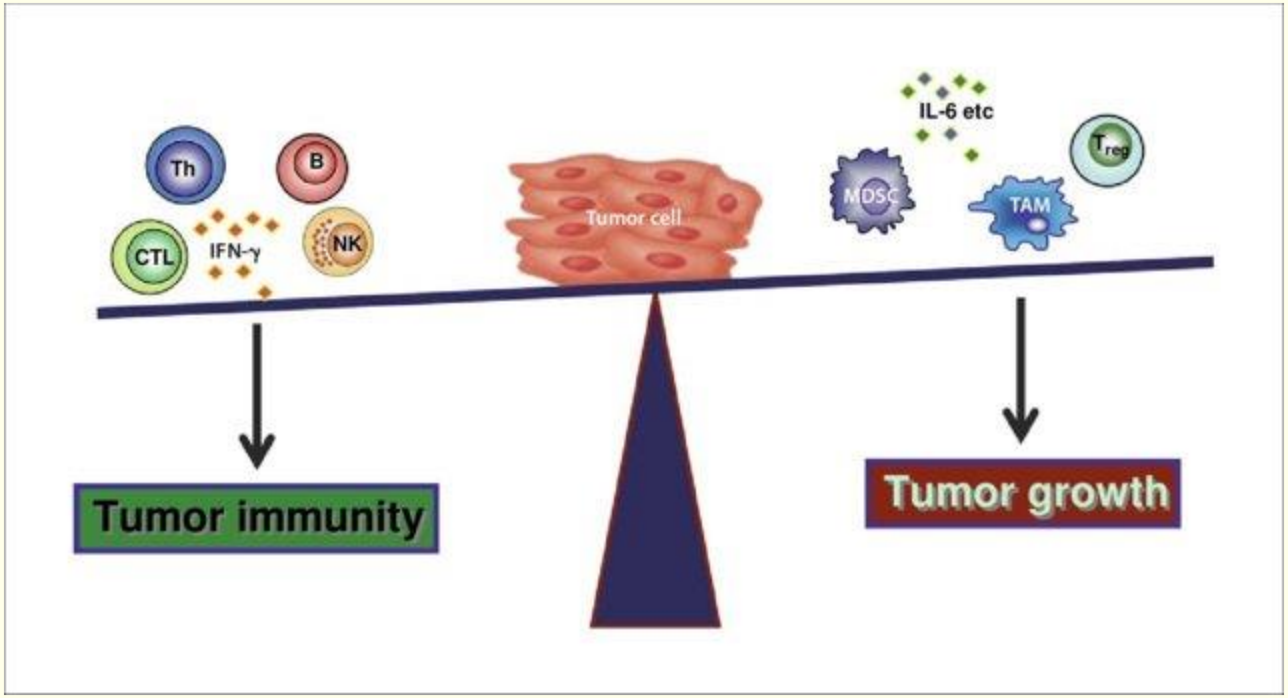


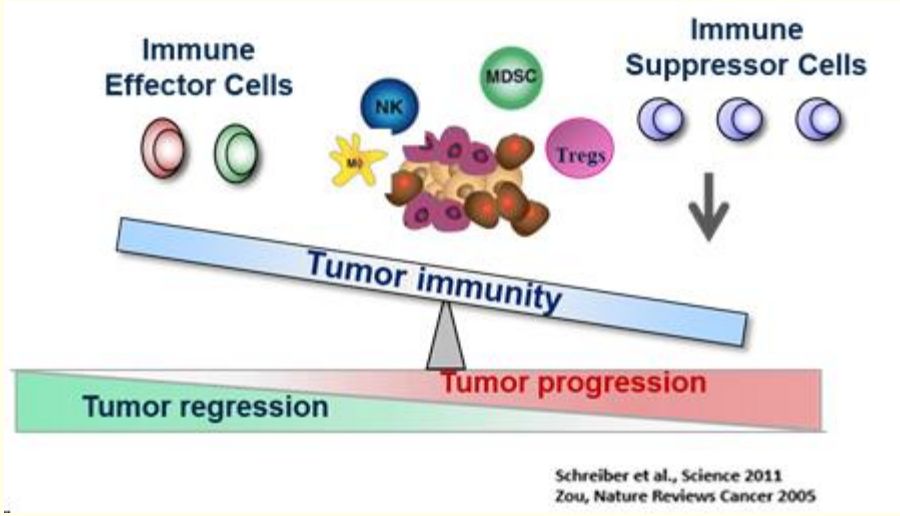
Immature local dendritic cells (unable to take up, process, or present antigens, and may also be inhibited from migrating to regional lymph nodes or may actually induce tolerance). **Regulatory T cells** are able to mediate suppression of antigen-primed T cells. The **Th2 phenotype CD4 T cells** inhibits 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.

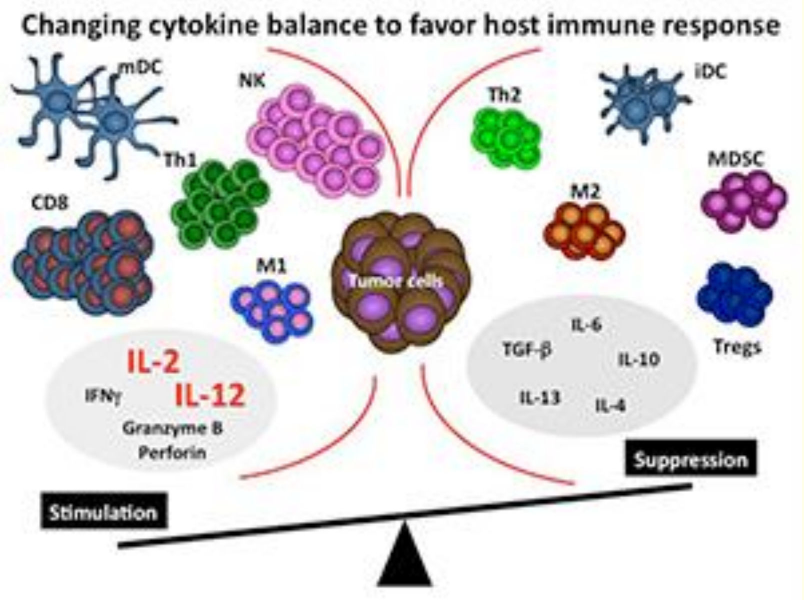


Normal Cell
Dendritic Cell
Tumor Cell
Immature Dendritic Cell
NK Cell
Macrophage (M2)
CD4+ T Cell
Myeloid Derived Suppressor Cell
CD8+ T Cell
Regulatory T Cell
Tumor Microenvironment
IDO
IL-10
Arginase
iNOS
TGFβ
IL-10
Arg1
R-NOS
IDO
TGFβ
IL-10
PGE2
PD-L1
TRAIL
TRAIL-R
FasL
Fas
Granzyme
Perforin
NKG2D
NKG2D ligand
MHC Class I
Tumor antigen
Elimination
Escape


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


IL-6 etc
Th
B
CTL
IFN-γ
NK
Tumor cell
MDSC
TAM
Treg
Tumor immunity
Tumor growth


Immune
Effector Cells
NK
MDSC
Tregs
Immune
Suppressor Cells
Tumor immunity
Tumor progression
Tumor regression
Schreiber et al., Science 2011
Zou, Nature Reviews Cancer 2005

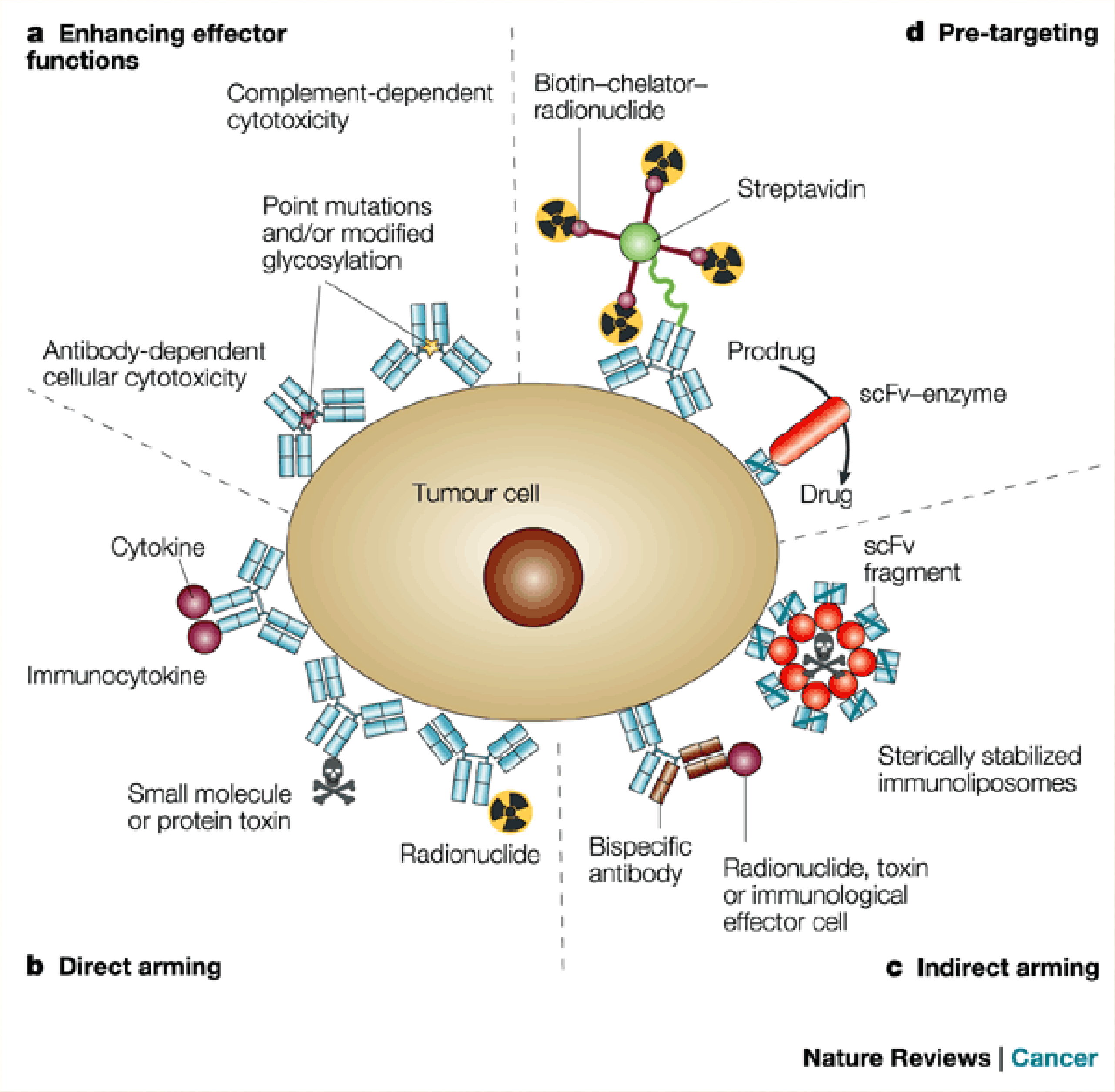

Changing cytokine balance to favor host immune response
mDC
NK
Th2
iDC
Th1
MDSC
CD8
M2
M1
Tumor cells
Tregs
IL-6
TGF-β
IL-10
IL-13
IL-4
IL-2
IFNγ
IL-12
Granzyme B
Perforin
Stimulation
Suppression

Cancer immunotherapy

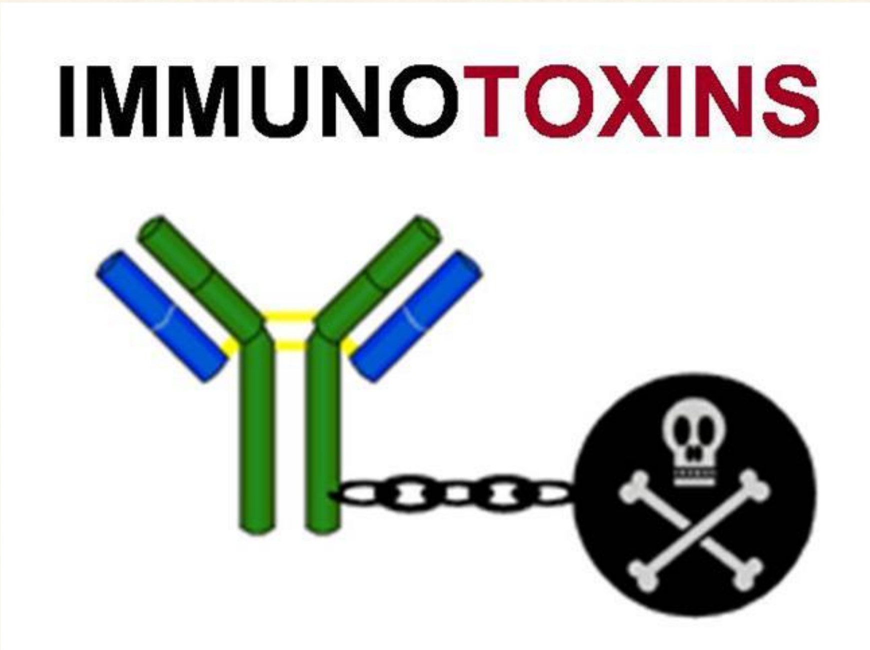
Complementary therapeutic tools after the surgical, chemotherapeutic and/or irradiation treatments:

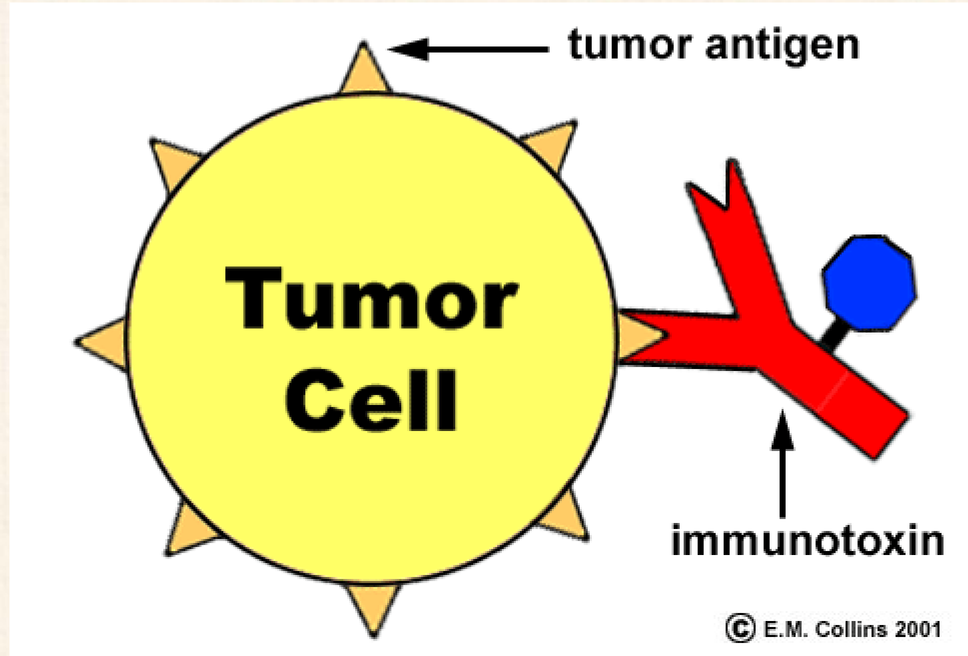
- **Therapeutic monoclonal antibodies**
- **Checkpoint inhibitors (PD-1/PDL-1)**
- **Immuno-modulation**
- **Cancer vaccines**
- **Oncolytic viruses**

Monoclonal antibodies for therapeutic use



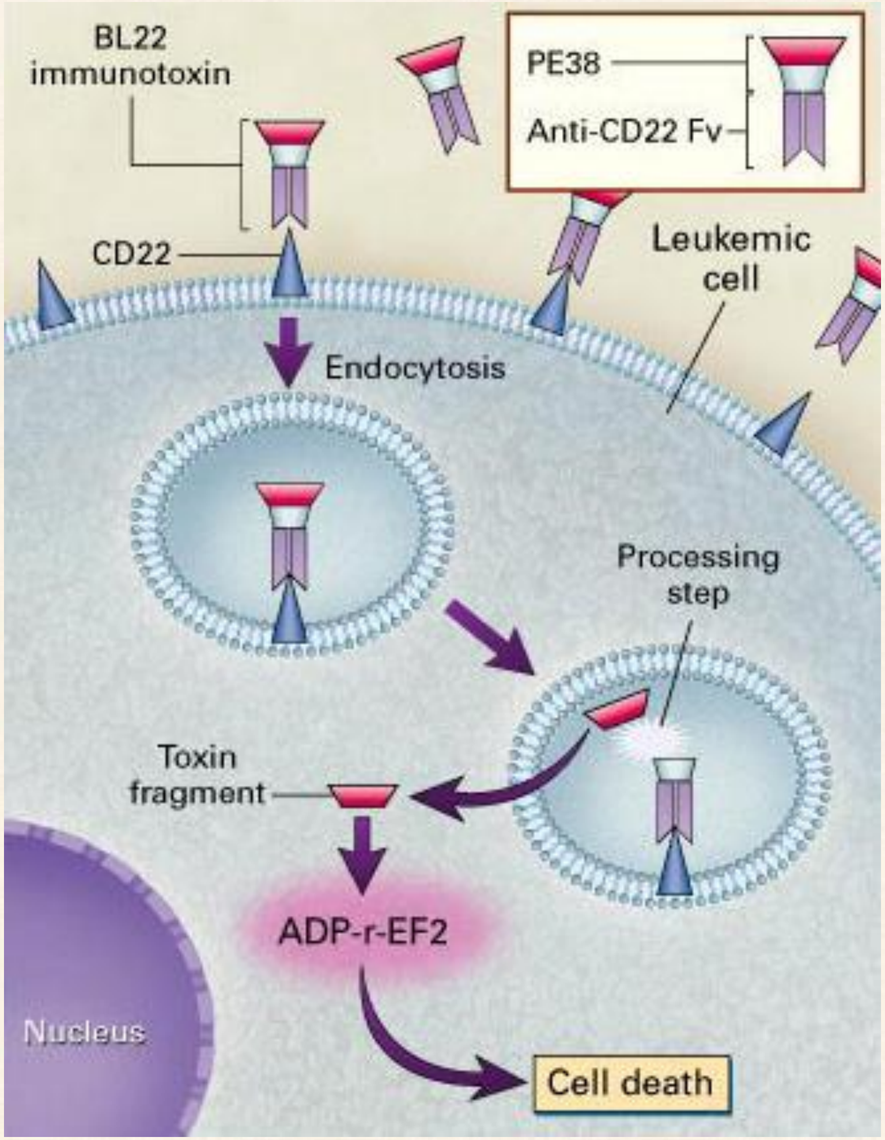
Immunotoxins in cancer therapy



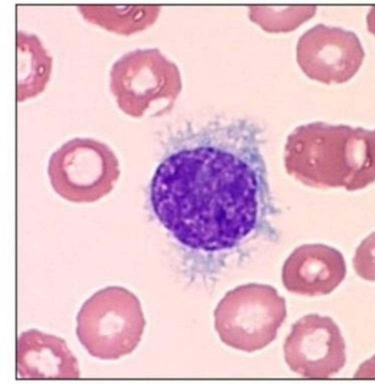


Monoclonal antibodies that bind target cell-surface antigens are themselves non-cytotoxic, but after conjugation with toxins they are able for clinical application in cancer therapy.

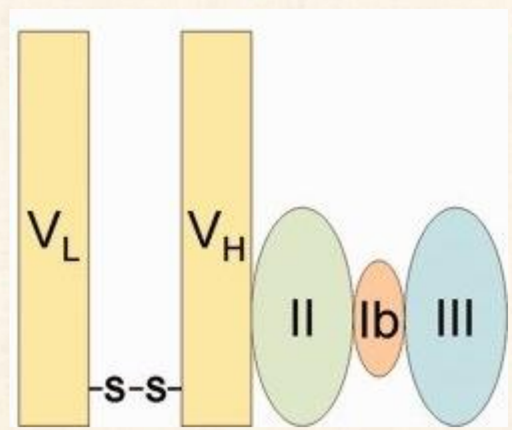
Immunotoxin therapy of „Hairy Cell" leukaemia by BL22



- Rare B-cell leukemia
- Characterized by very high CD22 expression[a]
- Often presents with pancytopenia and splenomegaly[b]
- Identifiable on peripheral blood smear due to characteristic appearance

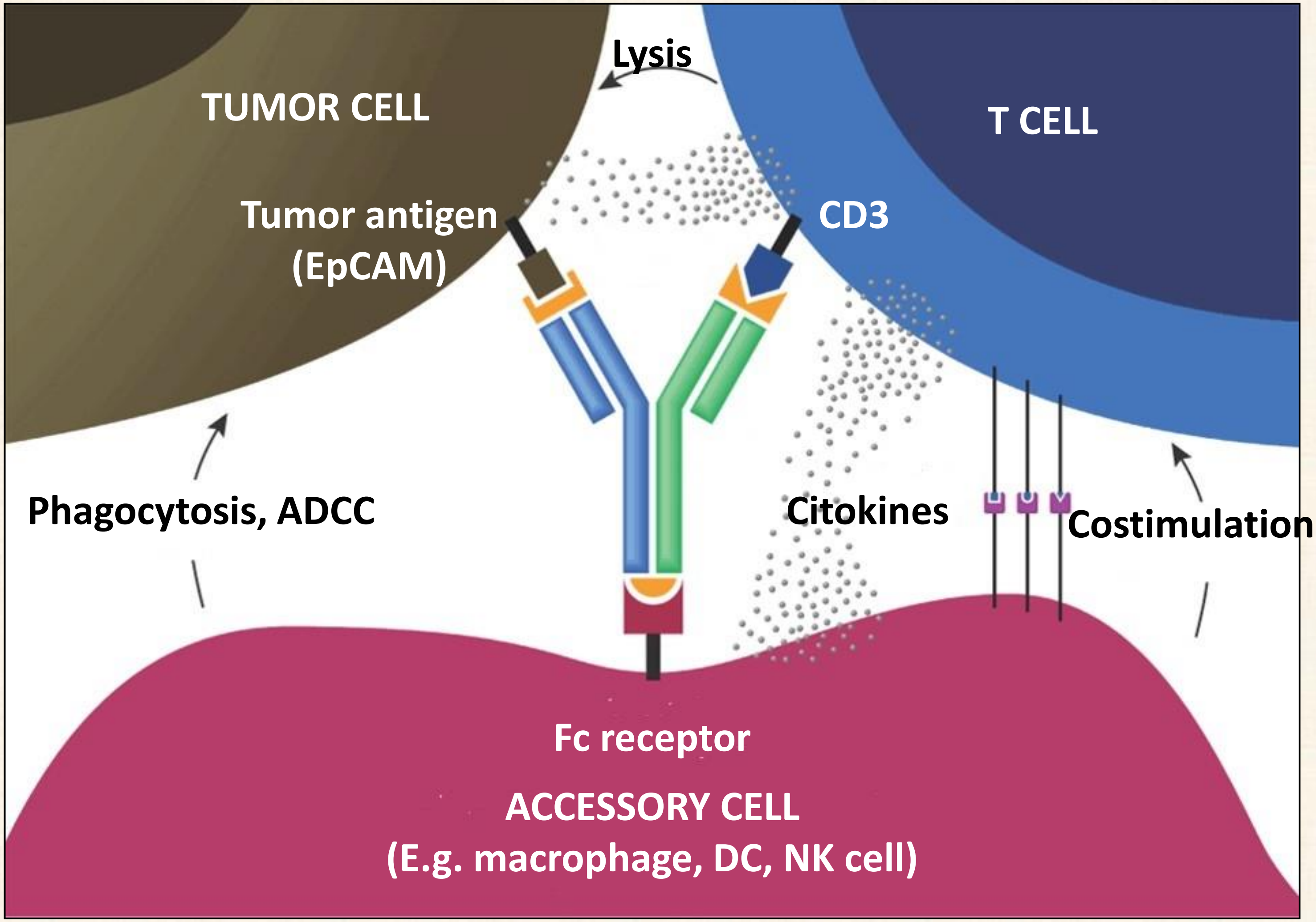


Hair-like projections of cytoplasmic membrane characteristic of hairy cell leukemia[c]

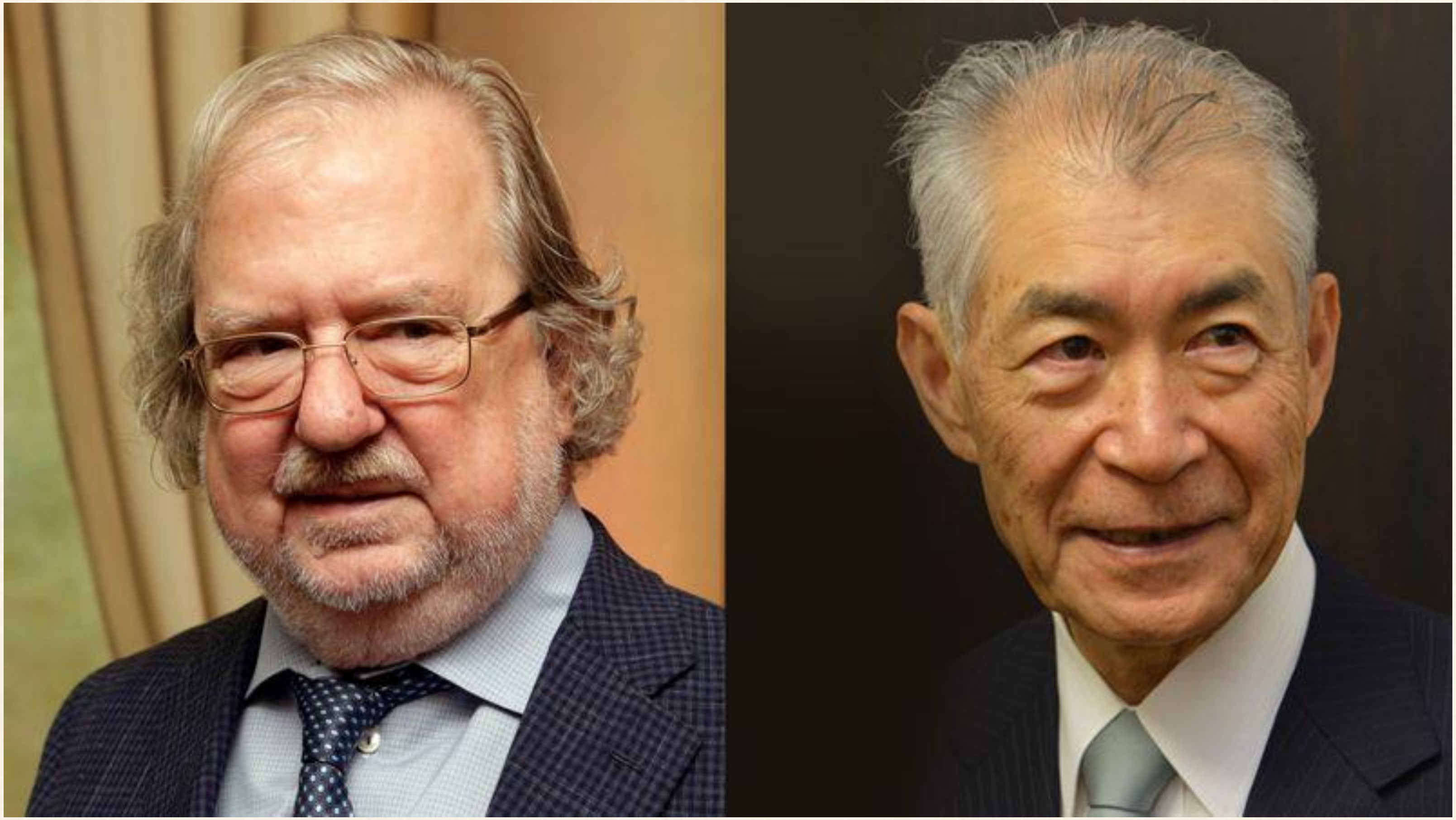


Pseudomonas exotoxin (**pe38**) conjugate to Ig variable H and L chains

Bispecific therapeutic monoclonal antibodies



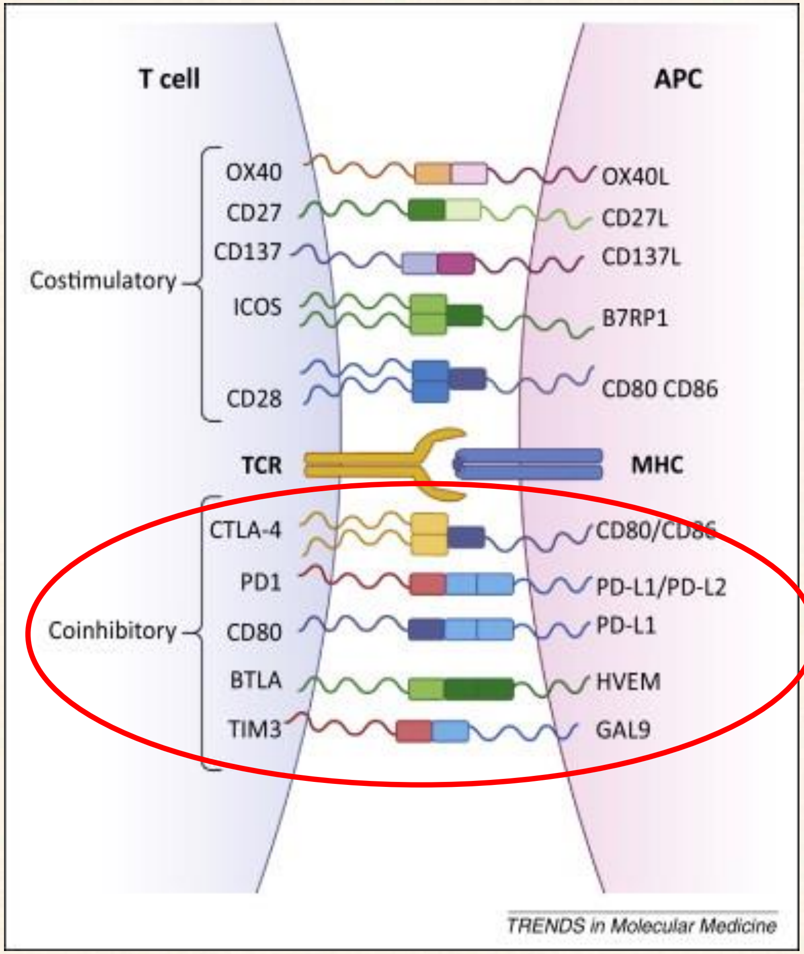
Mechanism of action of Catumaxomab (the first approved bispecific and és trifuntional antibody). (EpCAM: Epithelial cell adhesion molecule)

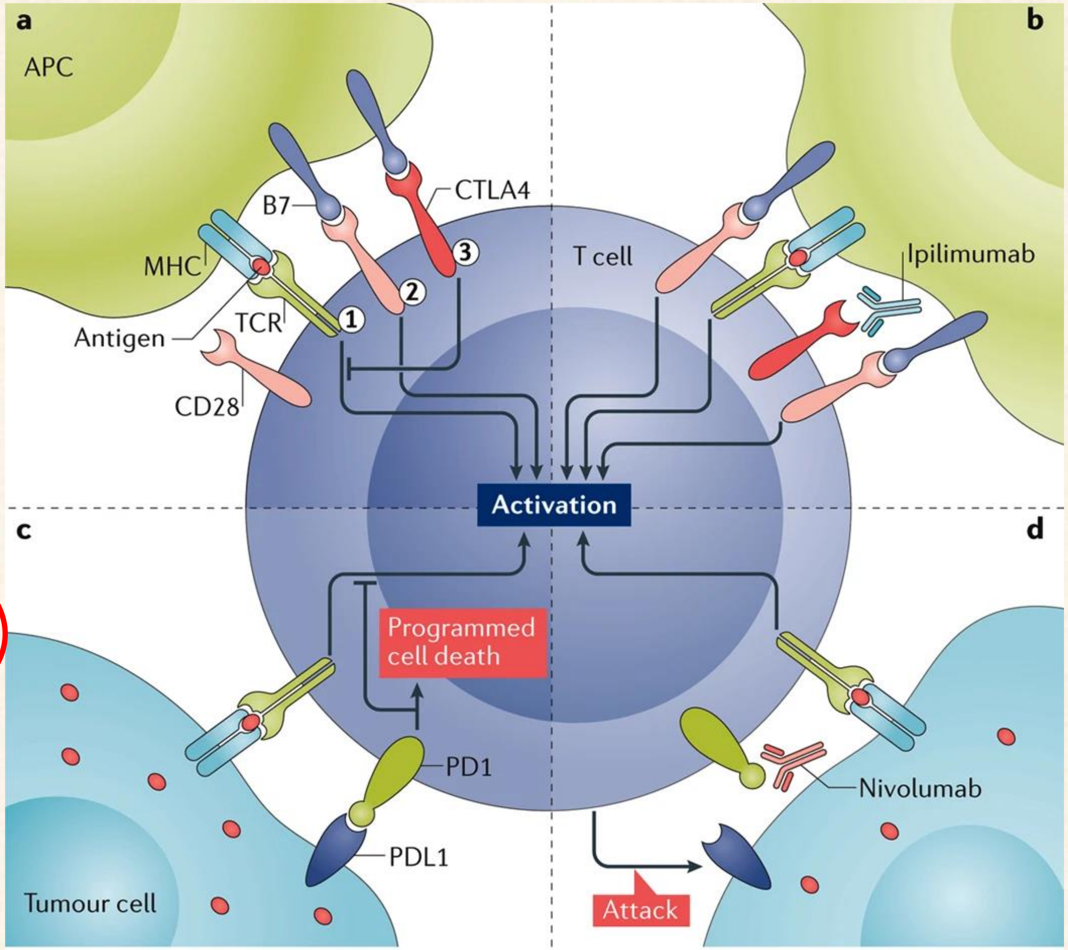


James P. Allison, PhD **Tasuku Honjo**, MD, PhD

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.

Immune checkpoint inhibitors

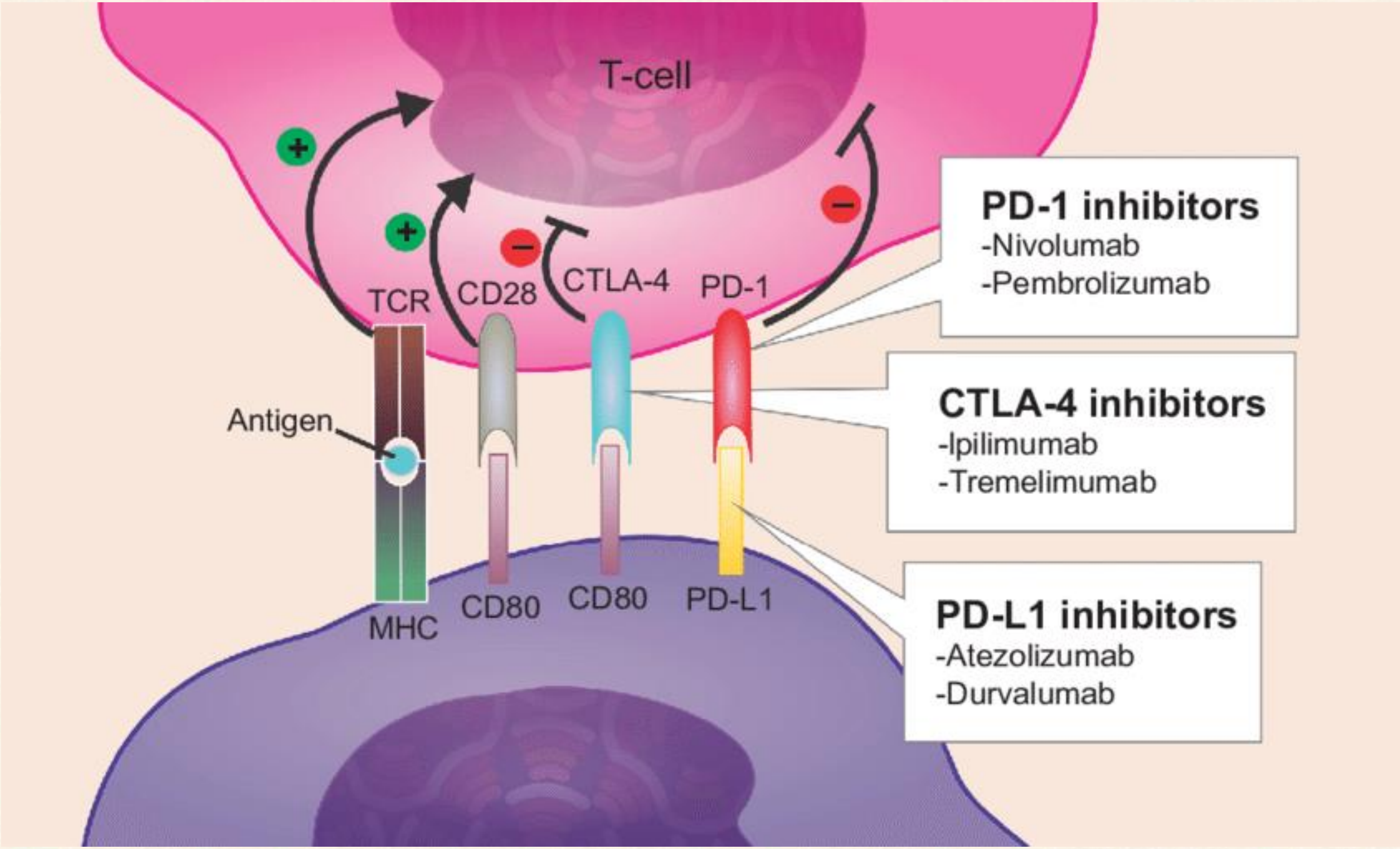




Blocking of CTLA-4, PD-1 and PD-L1 is able to delete the T cell inhibition induced by cancer cells.

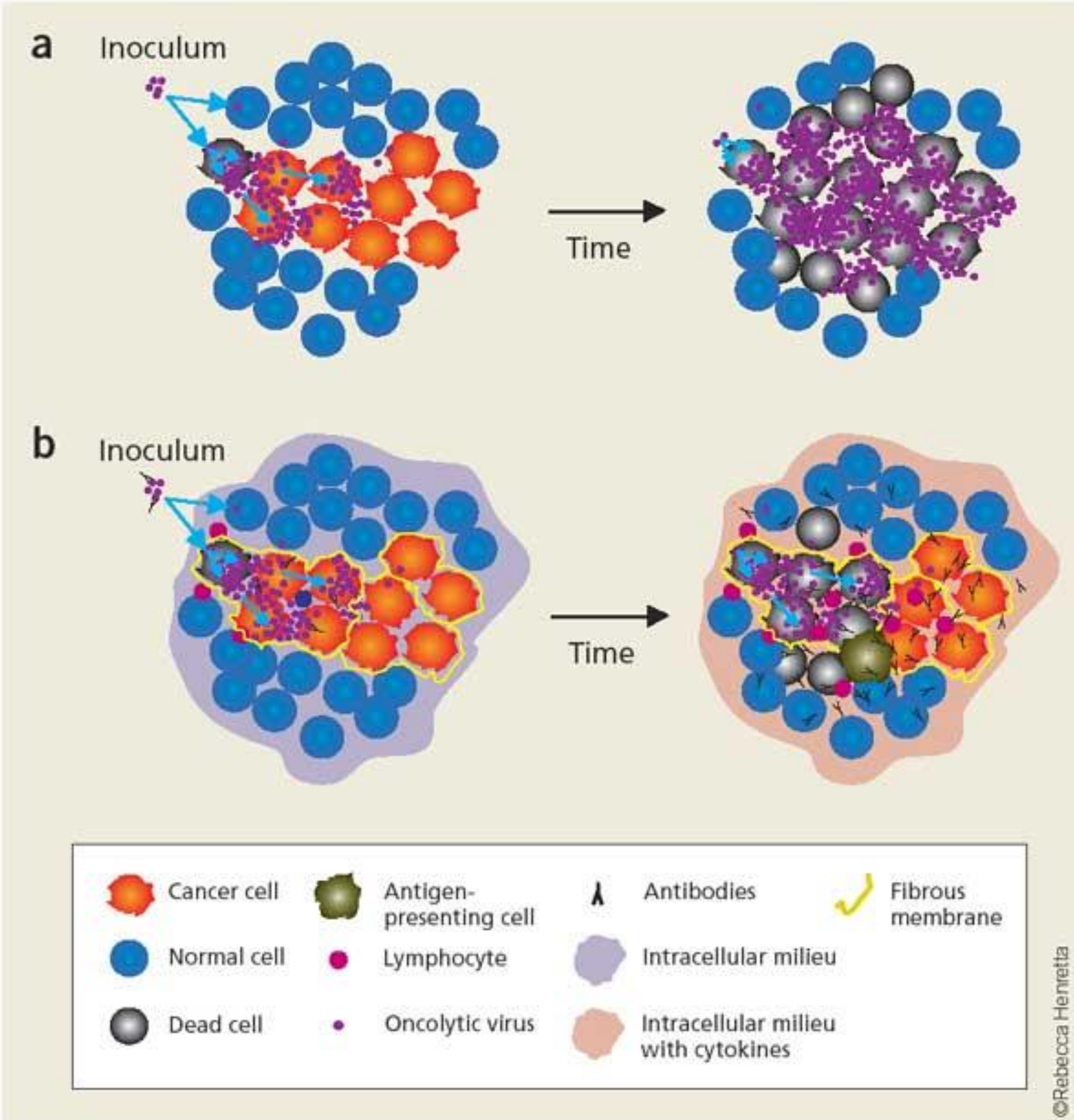
Blocking the T cell blockade = T cell activation

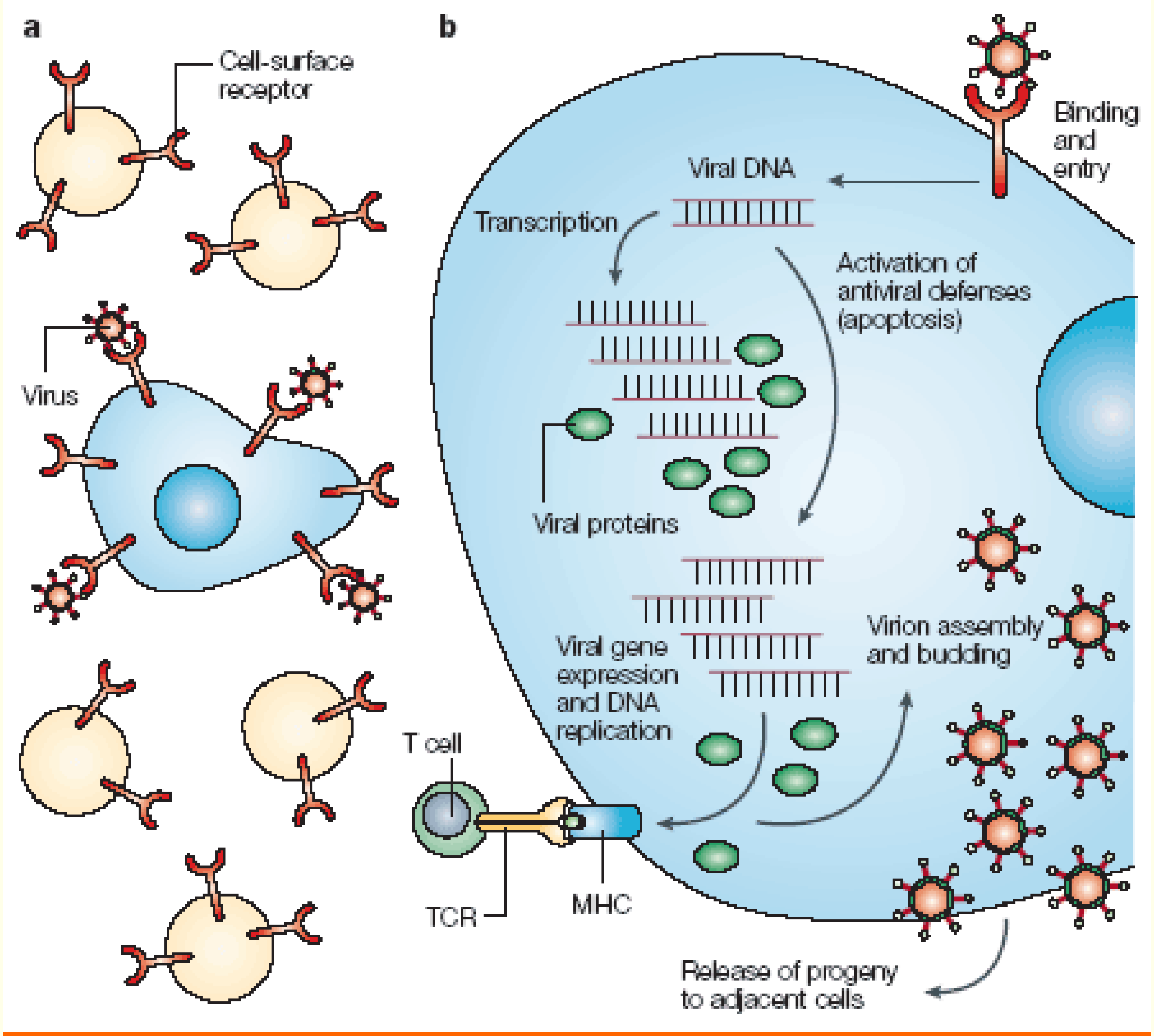
Immune checkpoint inhibitors



Oncolytic virus therapies

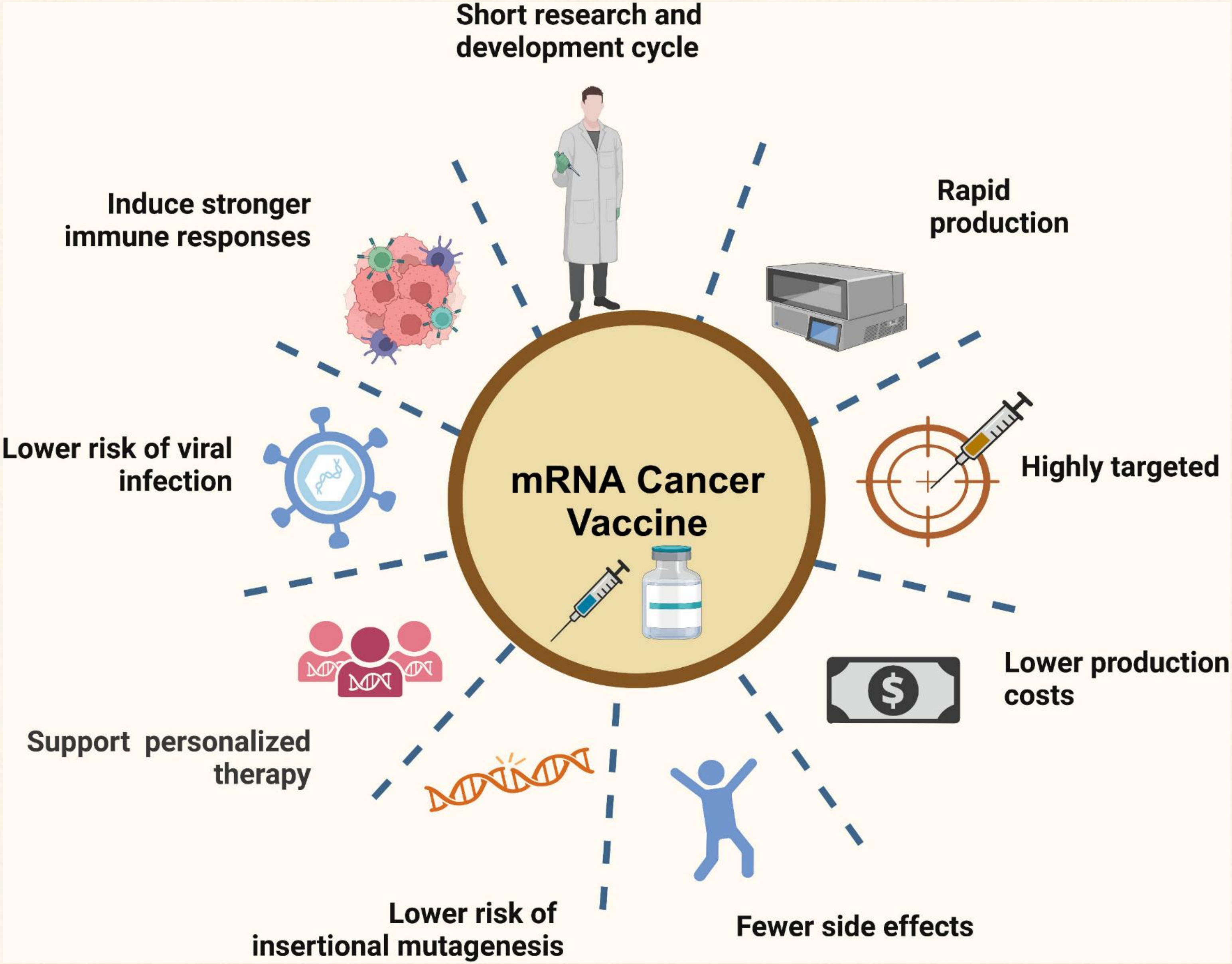
- Oncolytic virus therapy is a promising cancer treatment that uses modified viruses to selectively infect, replicate in, and destroy tumor cells while sparing healthy tissue
- Viral agents administered intarvenously can be particularly effective against metastatic cancers, which are especially difficult to treat conventionally
- However, blood-borne viruses can be deactivated by neutralizing antibodies and cleared from the blood stream quickly e.g. by Kupfer cells in the liver, which are responsible for adenovirus clearance.


a
Inoculum
Time
b
Inoculum
Time
Cancer cell
Antigen-presenting cell
Antibodies
Fibrous membrane
Normal cell
Lymphocyte
Intracellular milieu
Dead cell
Oncolytic virus
Intracellular milieu with cytokines
©Rebecca Henretta

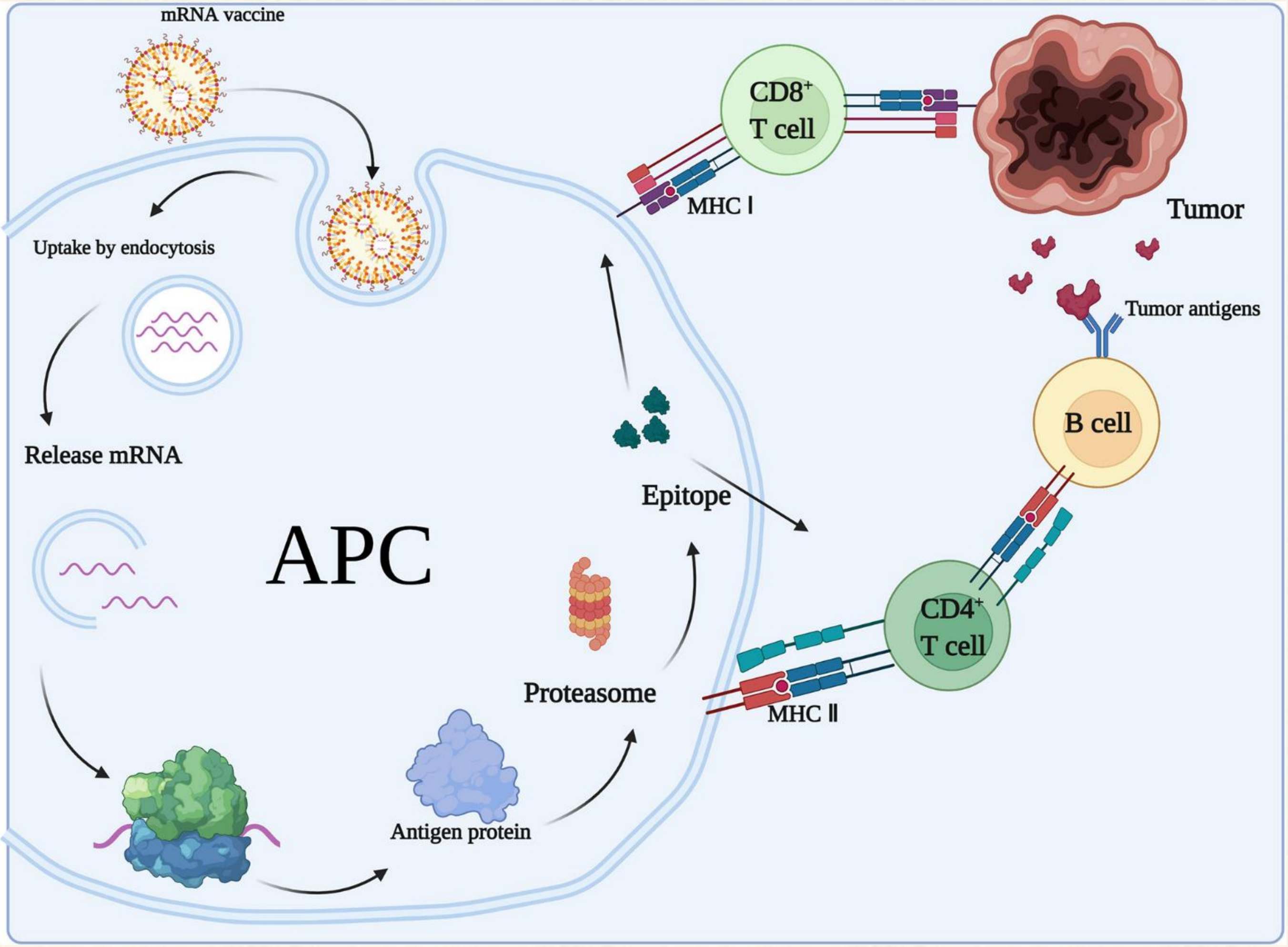

a
Cell-surface receptor
Virus
b
Viral DNA
Binding and entry
Transcription
Activation of antiviral defenses (apoptosis)
Viral proteins
Viral gene expression and DNA replication
Virion assembly and budding
T cell
TCR
MHC
Release of progeny to adjacent cells

Nobel prize 2023' for mRNA technology

The closed future: mRNA-based cancer vaccines

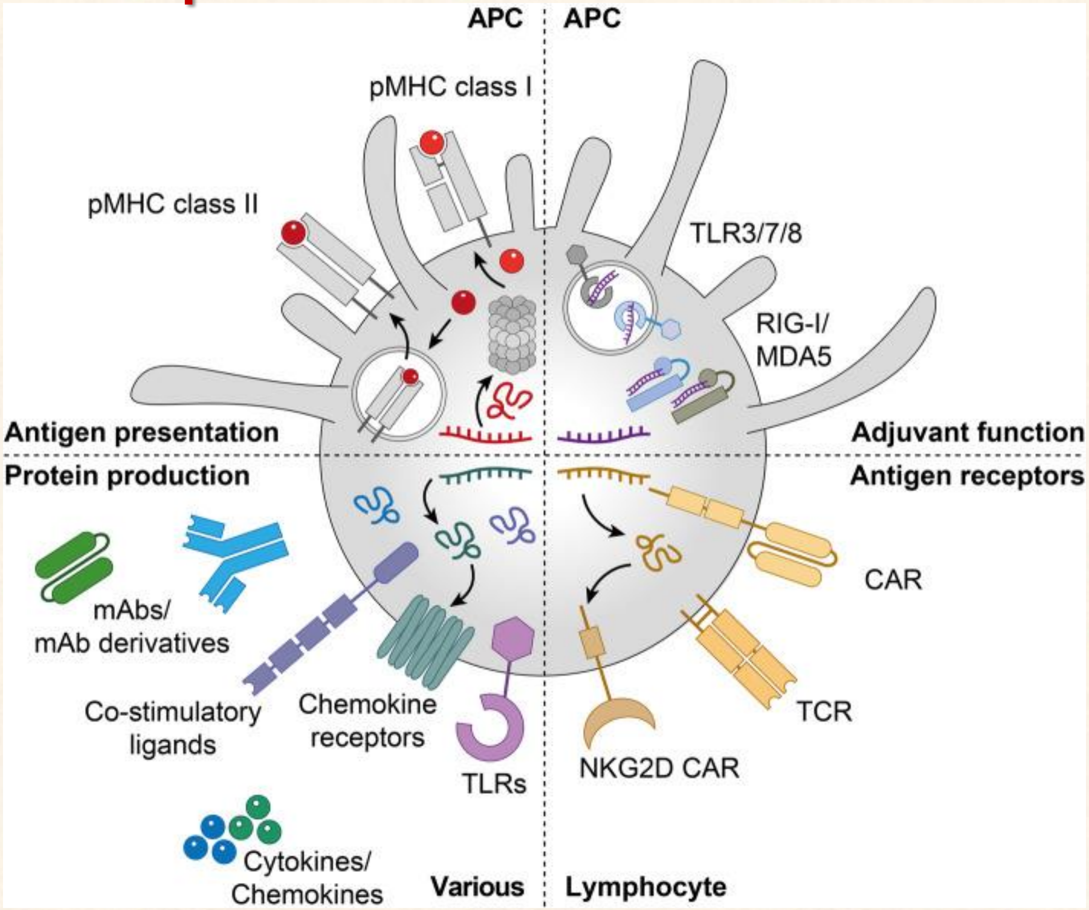


Adaptive immune response to mRNA vaccines



In the case of mRNAs encoding antigens, mRNA vaccines exert immunological effects mainly through adaptive immune responses. After mRNA vaccination, the encoded proteins will be translated and taken up by APCs, which present the antigens to CD4+ T cells via MHC II and cross-present them to MHC I on CD8+ T cells. CD4+ T cells can enhance the antitumor effects of B cells.

mRNA therapeutics in cancer immunotherapy



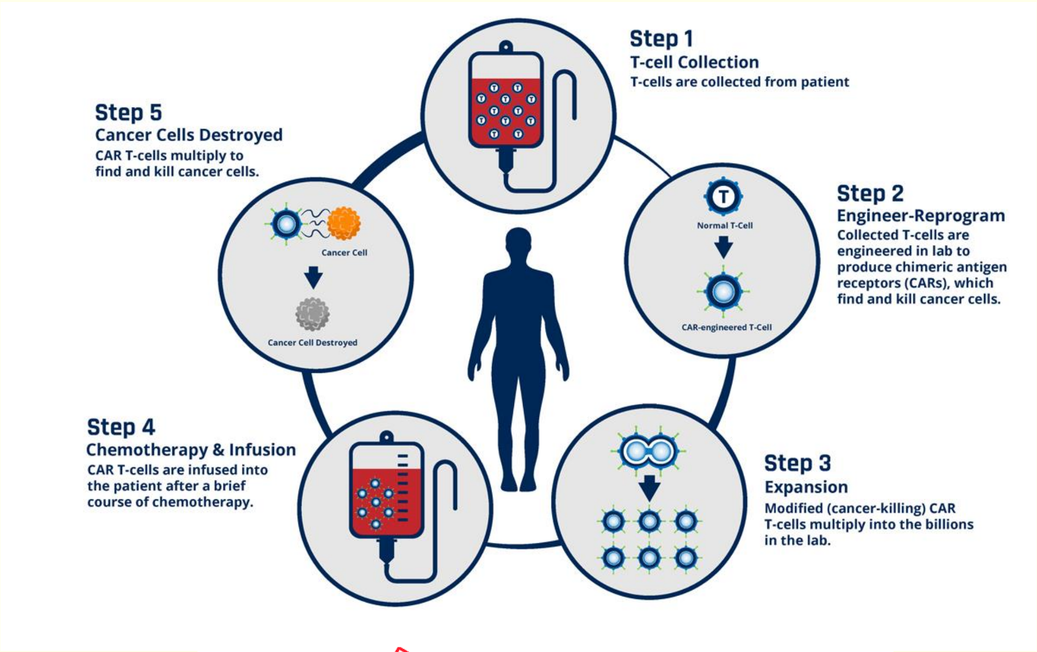
mRNA delivers cancer antigens to APCs for the presentation on MHC class I and II (top left) and stimulates innate immune activation by binding to PRRs expressed by APCs (top right), introduces antigen receptors such as CARs and TCRs into lymphocytes (bottom right), and allows the expression of immunomodulatory proteins including TLRs, chemokine receptors, co-stimulatory ligands, cytokines, chemokines and different mAb formats in various cell subsets (bottom left).

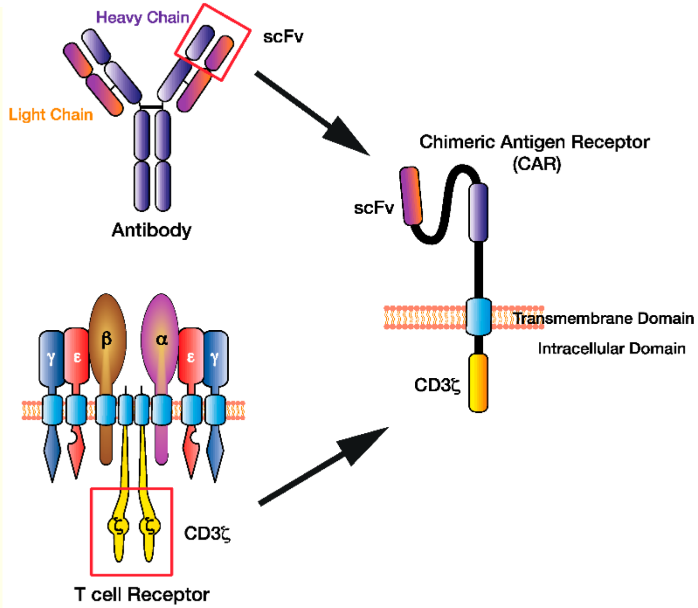
CAR-T cell therapy

- CAR T-cell therapy is a highly personalized immunotherapy that genetically engineers a patient's own T cells to recognize and kill cancer cells, primarily used for advanced blood cancers

- By modifying these immune cells to express Chimeric Antigen Receptors (CARs), they can effectively target tumor antigens. While often leading to high remission rates, it can cause severe side effects like Cytokine Release Syndrome

CAR-T cell therapy

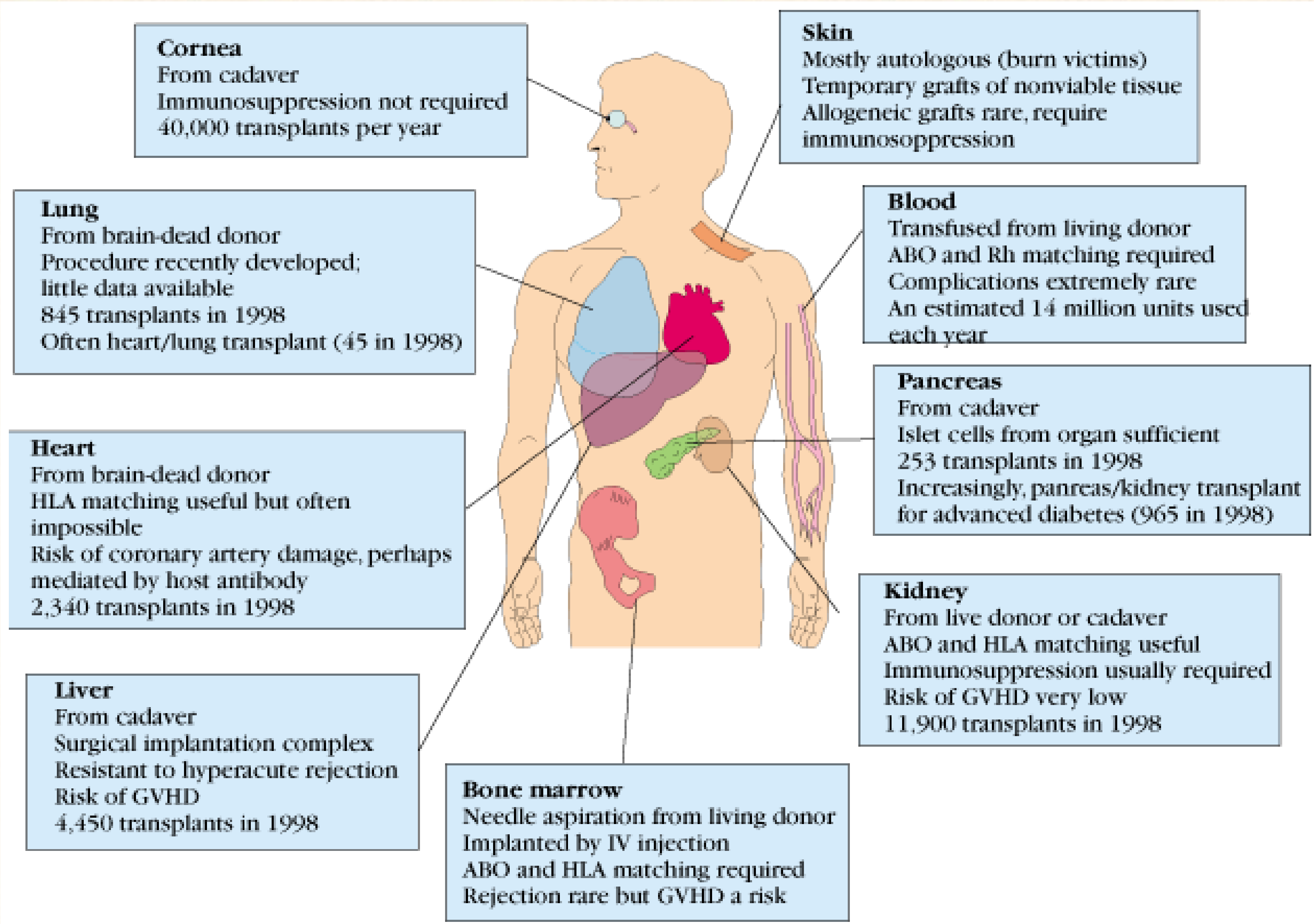




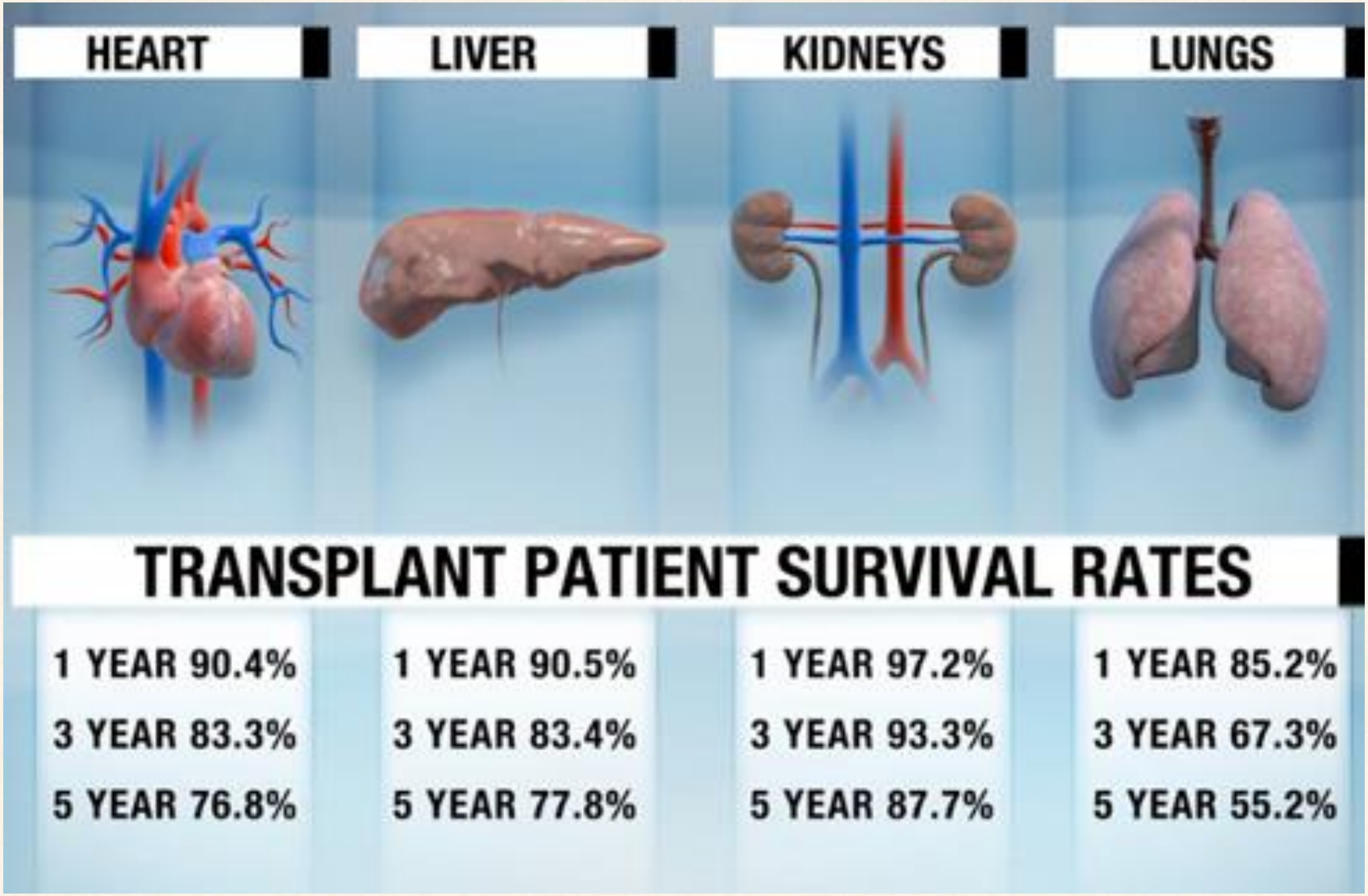
CAR T-cell therapy is a personalized cancer treatment that genetically engineers a patient's own T cells to recognize and attack cancer cells. The process involves collecting T cells, modifying them in a lab to produce chimeric antigen receptors (CARs), expanding the modified cells, and then infusing them back into the patient. This type of immunotherapy is used for certain types of CD19 positive B cell leukemias, lymphomas, and multiple myeloma.

Immunological aspects of organ transplantation


Ο Α
ΚΟΣΜΑ Σ
Ο Α
ΔΑΜΙΑΝΟΣ
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



One-Year Transplant Survival Rates from the January 2024 in US

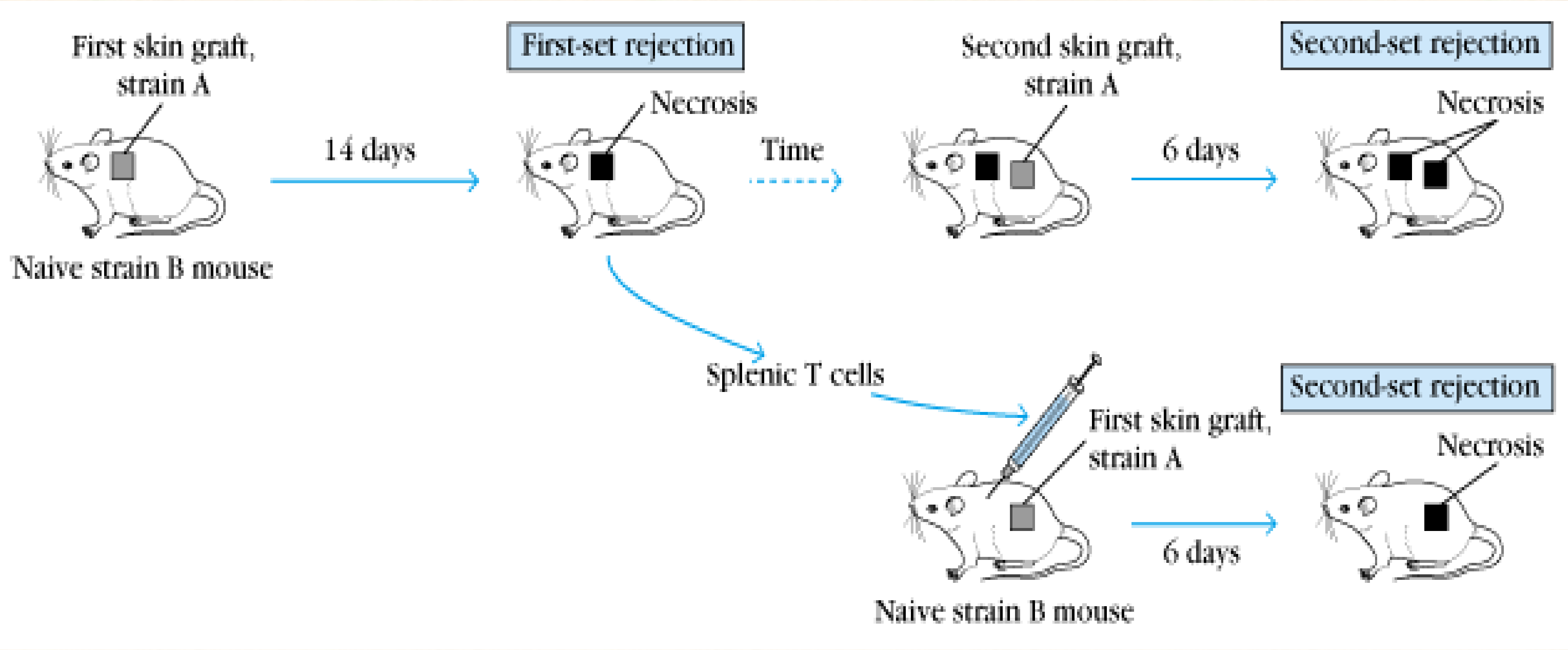
Organ	Patient / Graft Survival*	UC San Diego Health Survival Rate	National Survival Rate
Lung	Patient Survival	91.61%	88.72%
	Graft Survival	91.19%	88.14%
Heart	Patient Survival	96.14%	91.57%
	Graft Survival	94.95%	91.24%
Kidney	Patient Survival	96.39%	96.27%
	Graft Survival	95.41%	94.09%
Liver	Patient Survival	92.91%	93.95%
	Graft Survival	92.40%	92.02%

Basic terms

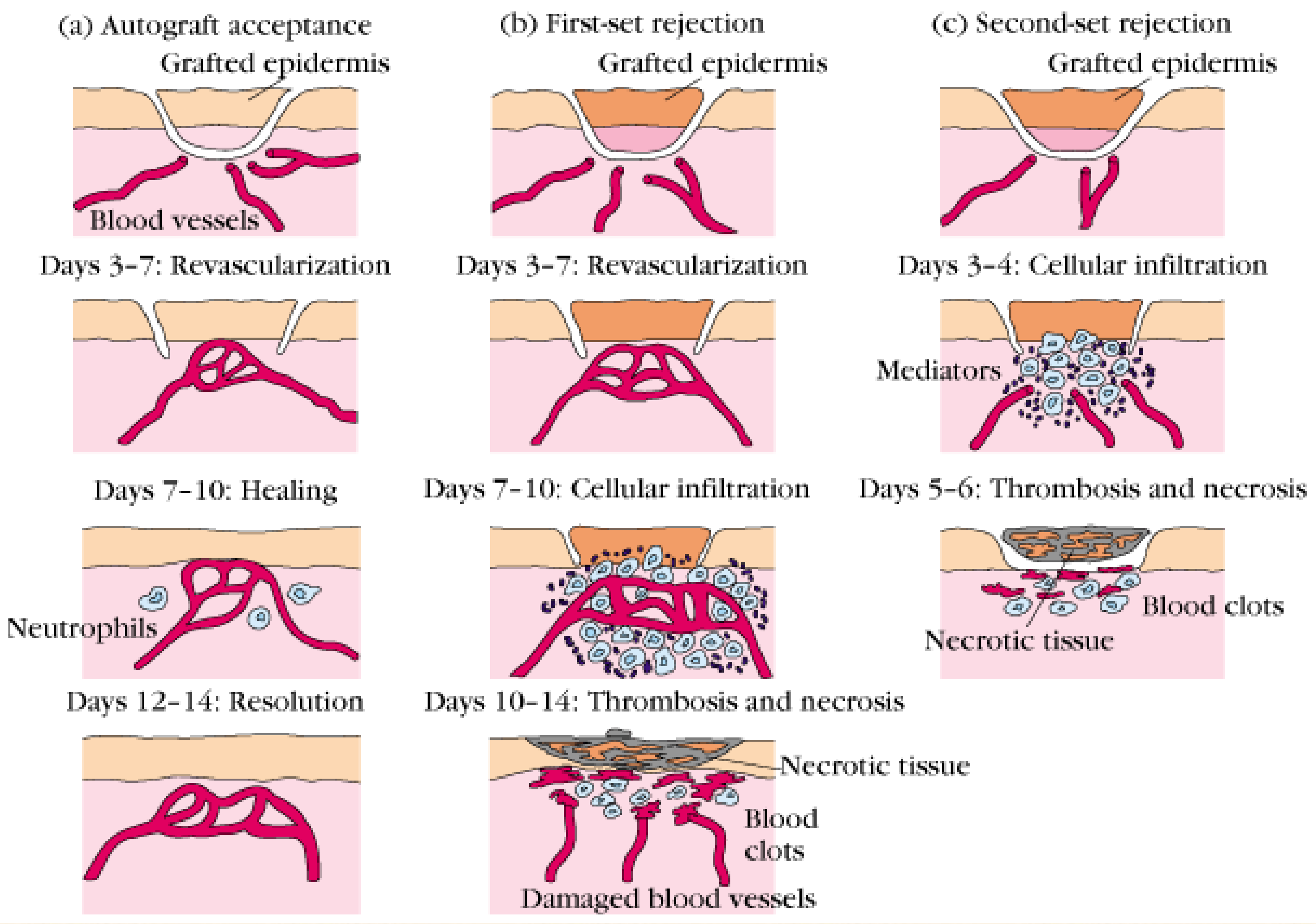
- autolog, allogeneic, xenogeneic graft

- auto-, allo-, xeno-transplantation

Allograft rejection



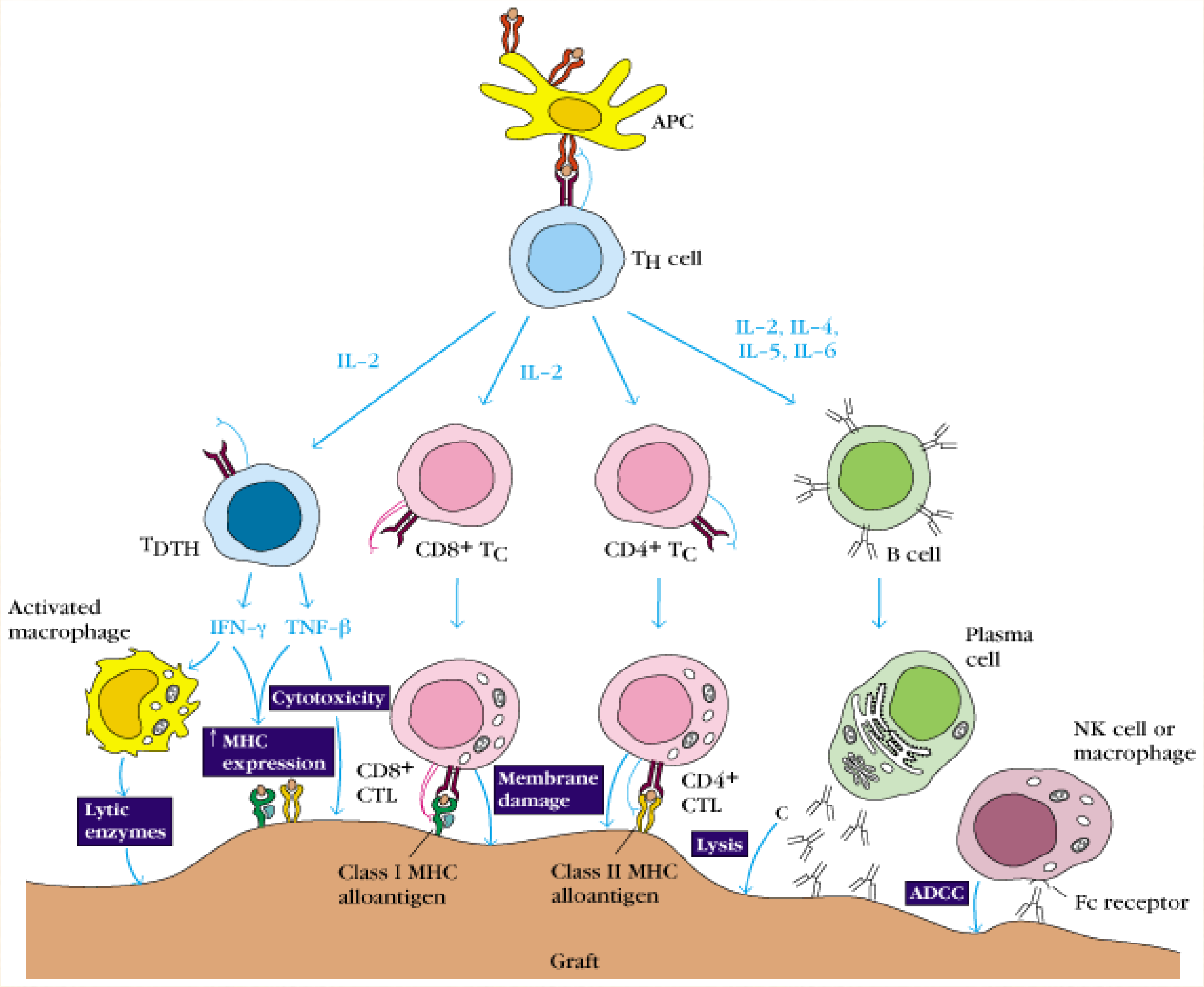
Graft acceptance and rejection



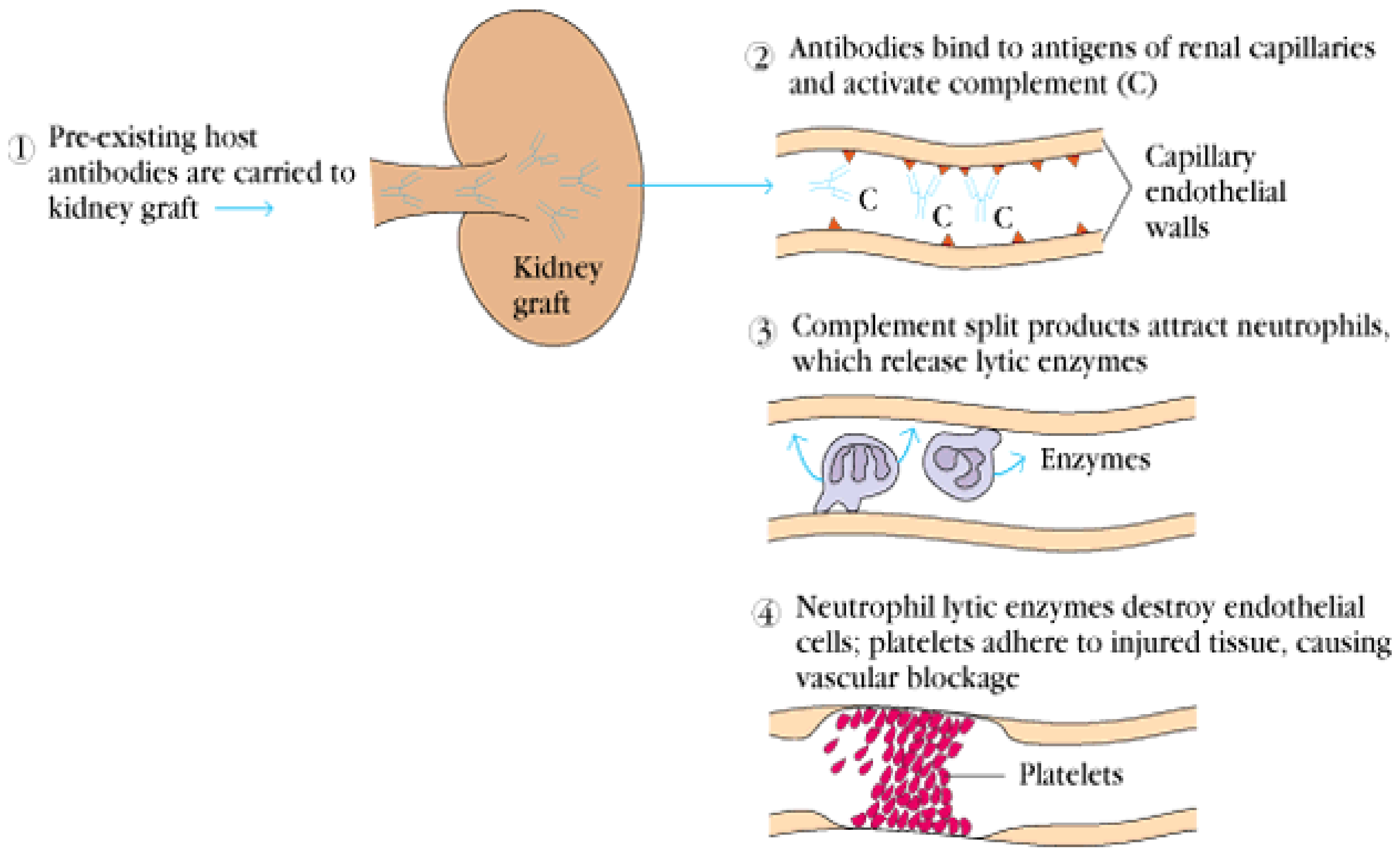
Host versus graft reaction

- **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**

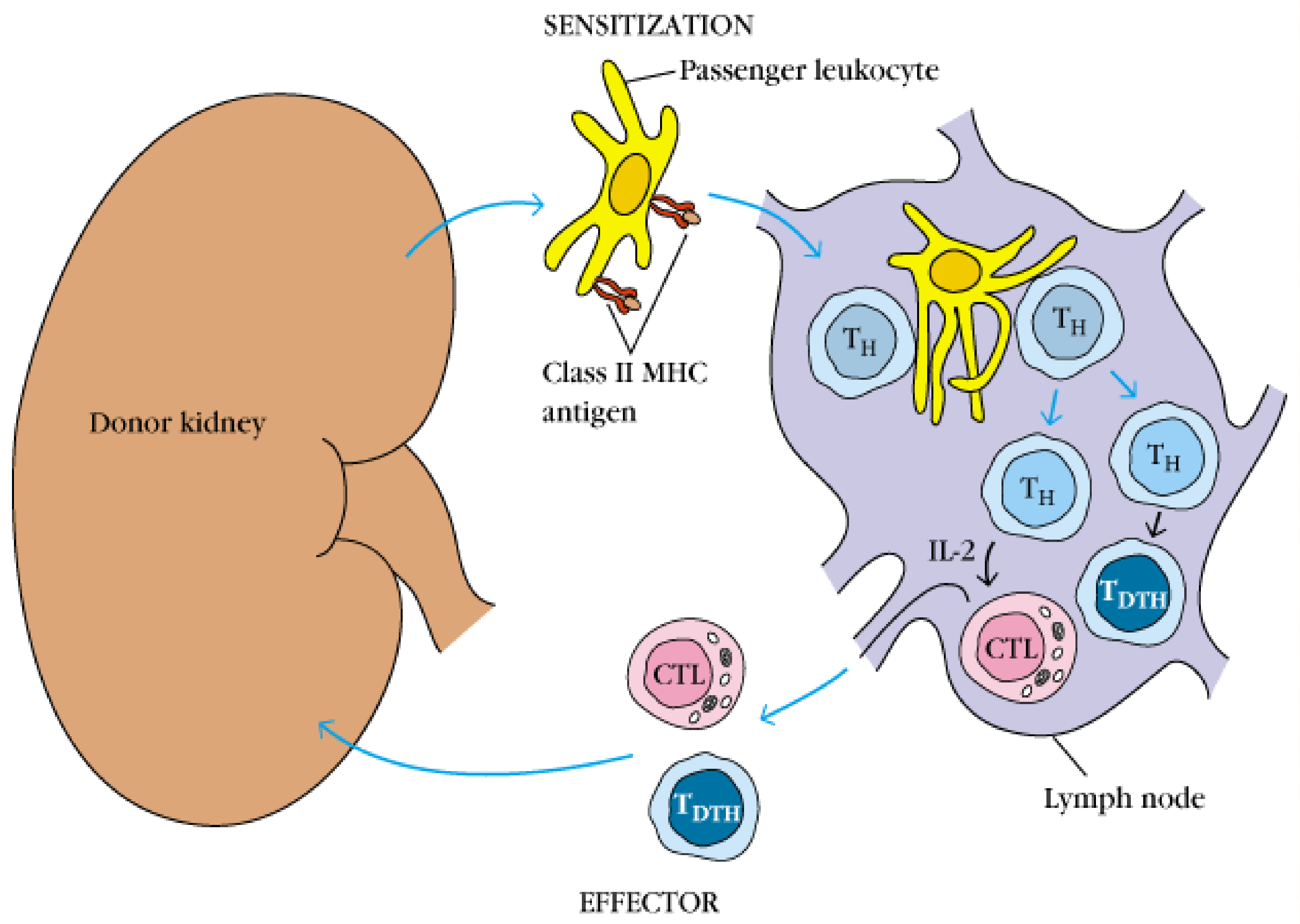
Mechanisms of host versus graft reactions



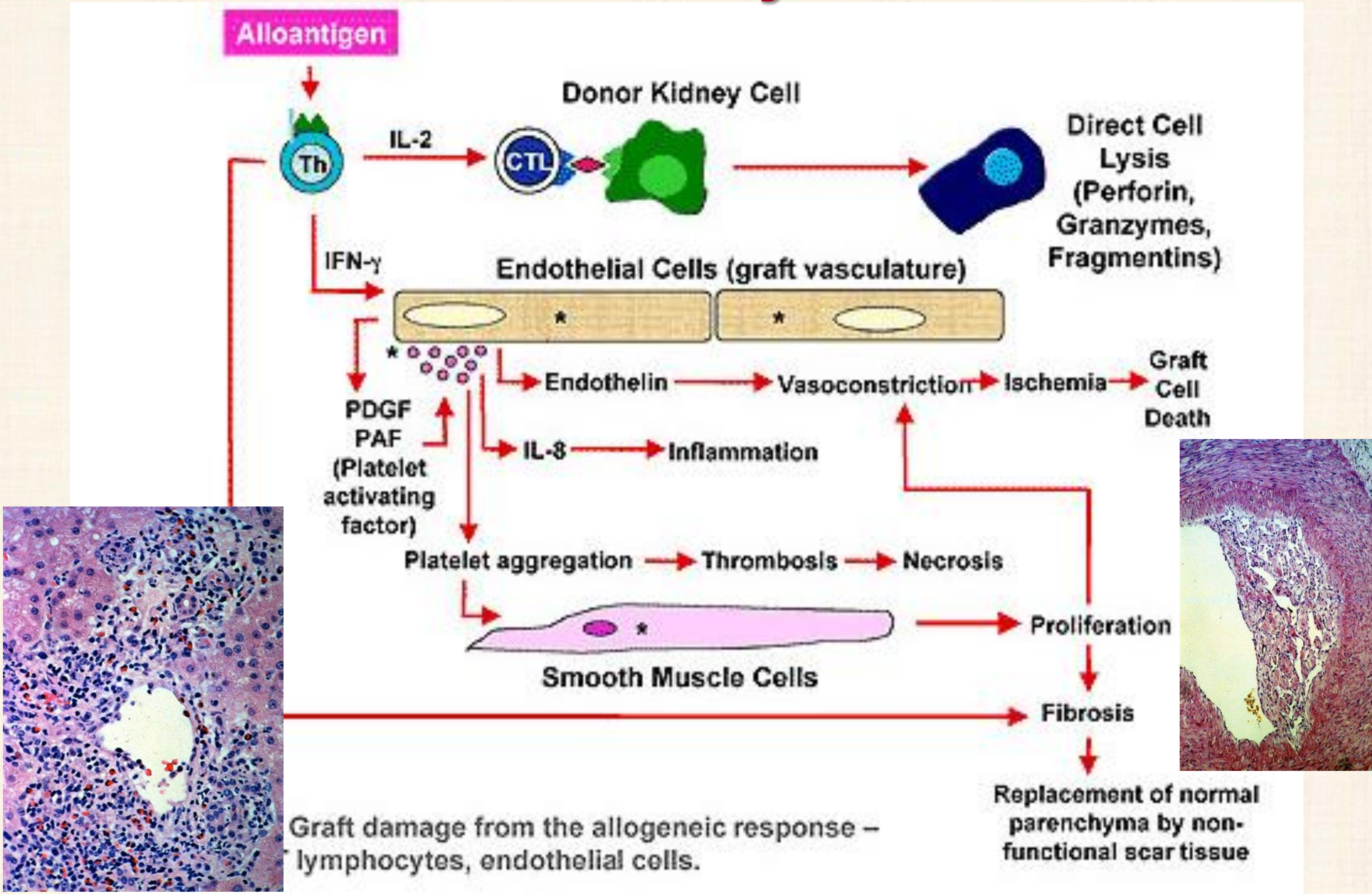
Hyperacute rejection



Acute rejection



Chronic rejection



Graft versus host reaction

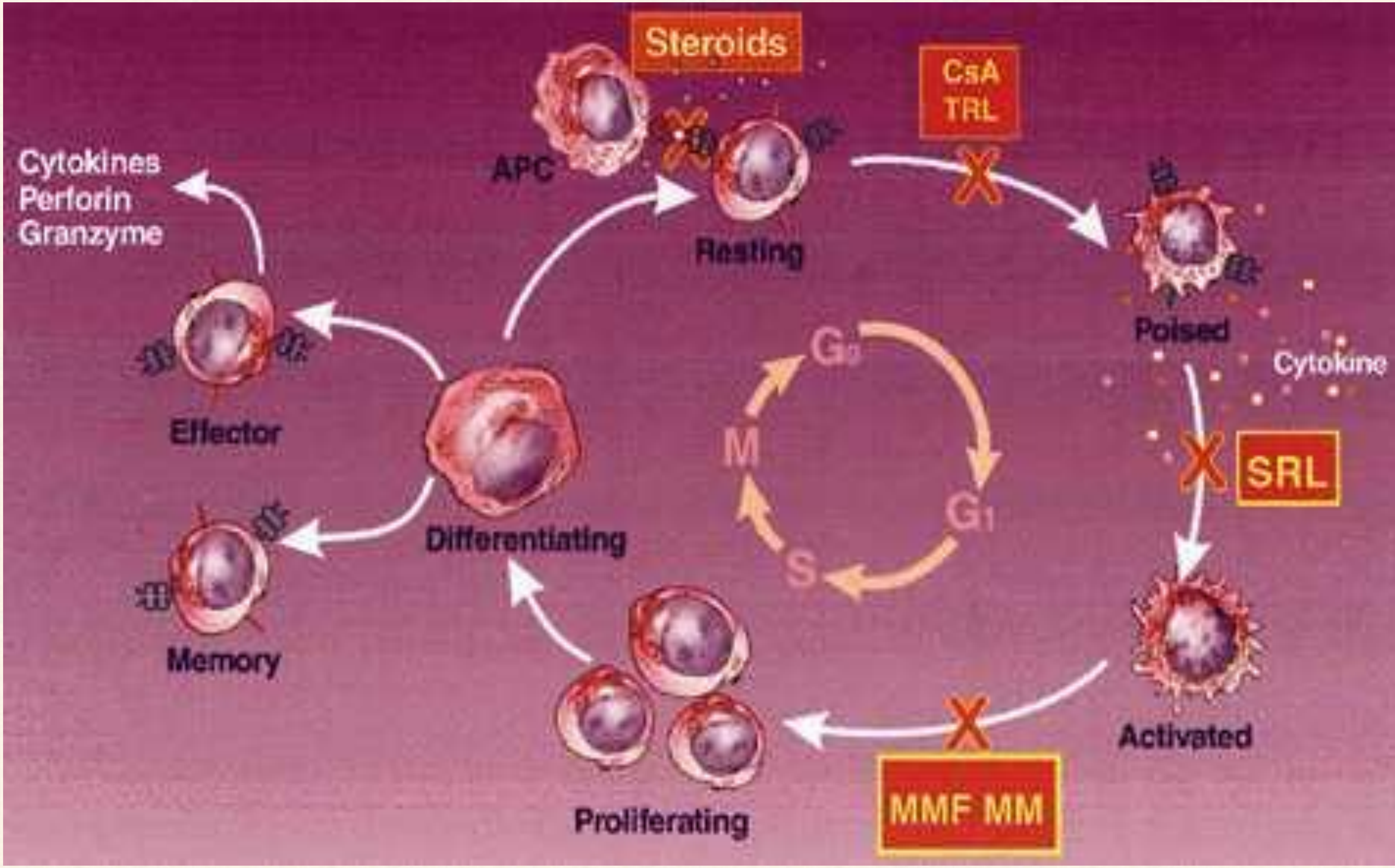
- **acute GVHD (acute tissue necrosis of the targeted organs)**

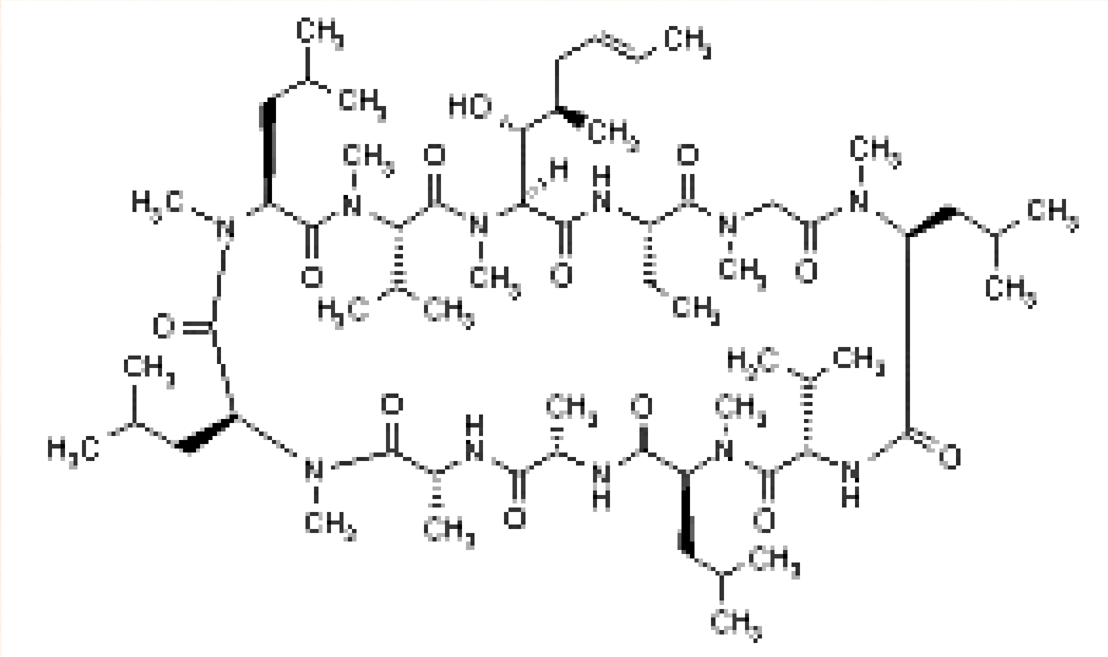
- **chronic GVHD (autoimmune-like phenomenon)**

Bone marrow transplantation

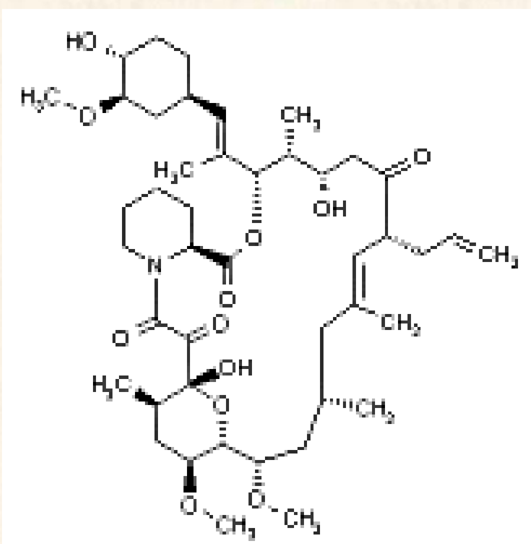
Advantage	Disadvantage
Autologous	**Allogeneic**
no GVH no rejection no matching needed	GVH rejection need matching tumour in donor cells
Allogeneic	**Autologous**
no tumour transfer graft vs. tumour myelosuppression avoided	grafting tumour cells (myelosuppression possible)

Immunosuppression



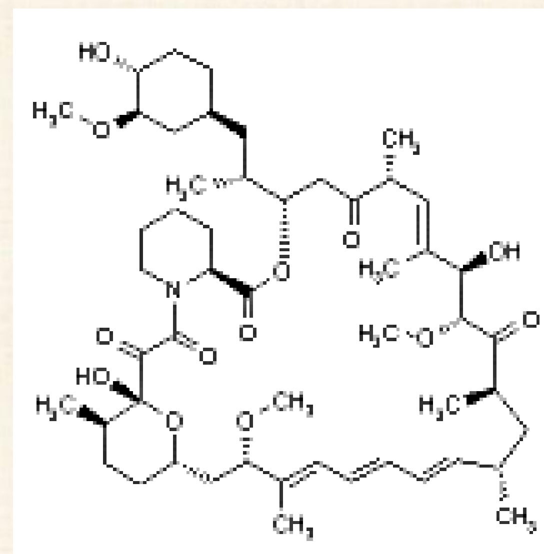


Cyclosporine A

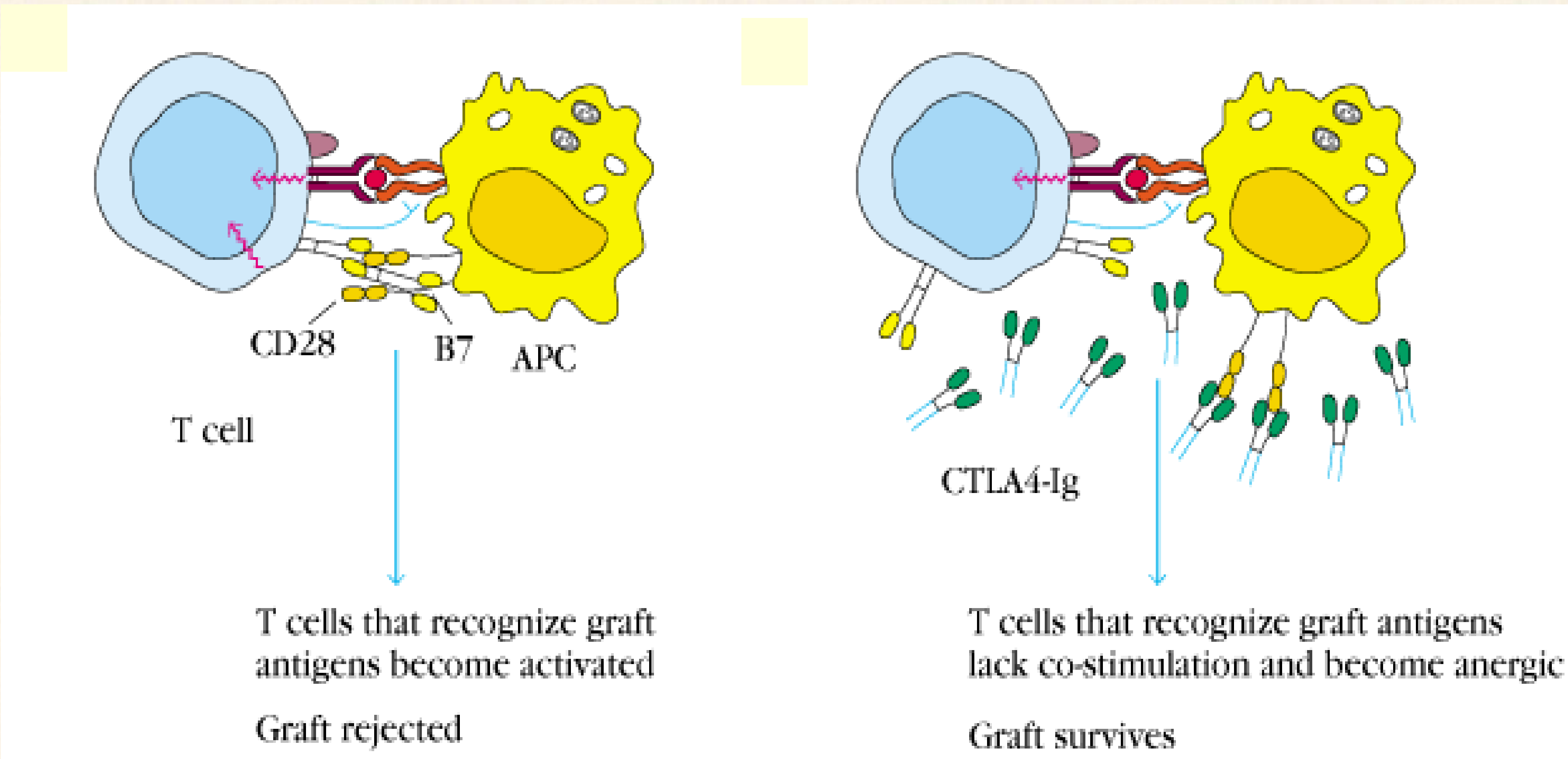


Tacrolimus

Sirolimus



Blocking co-stimulatory signals



Co-stimulation inhibition by *Abatacept*