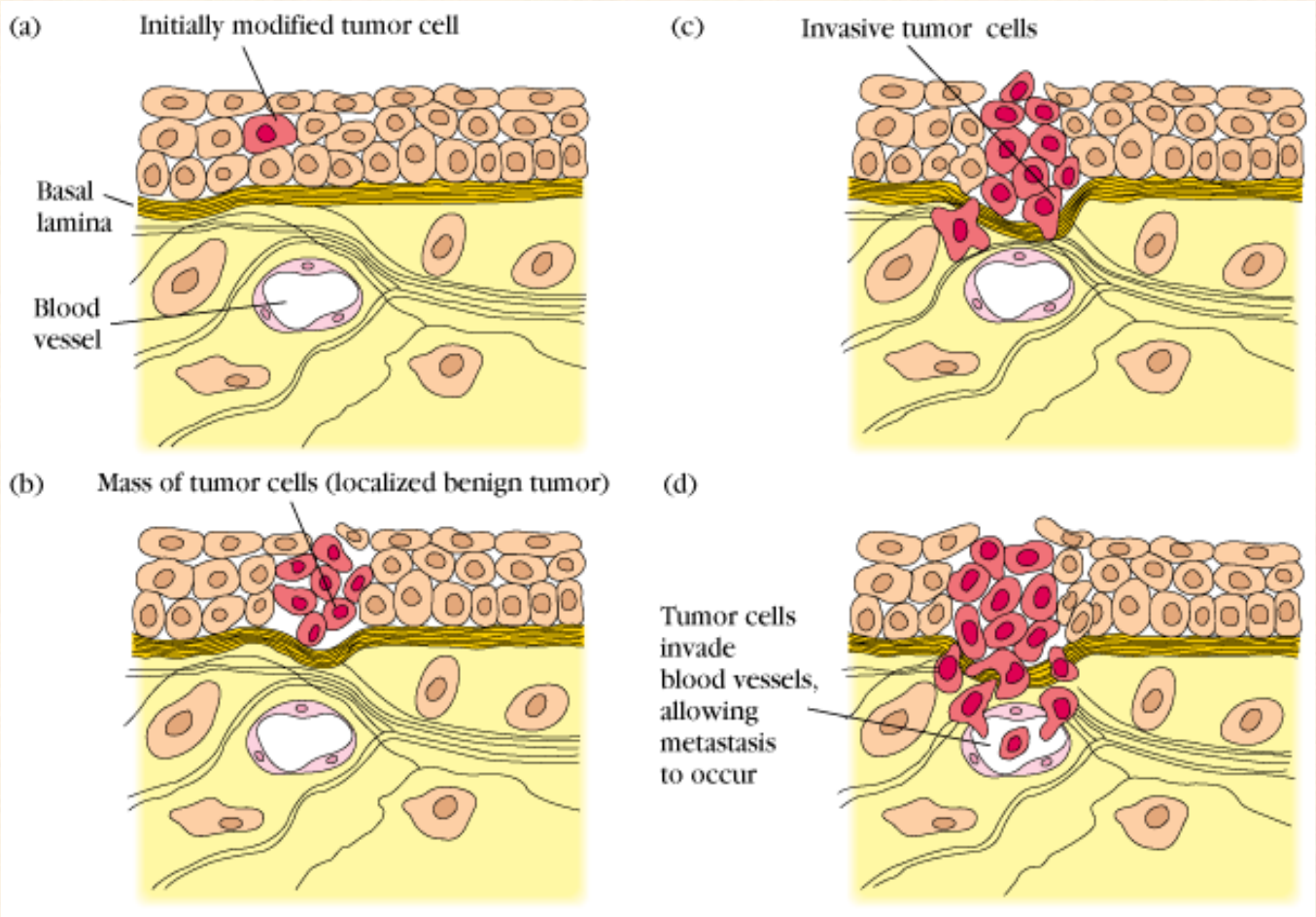
Basic Immunology

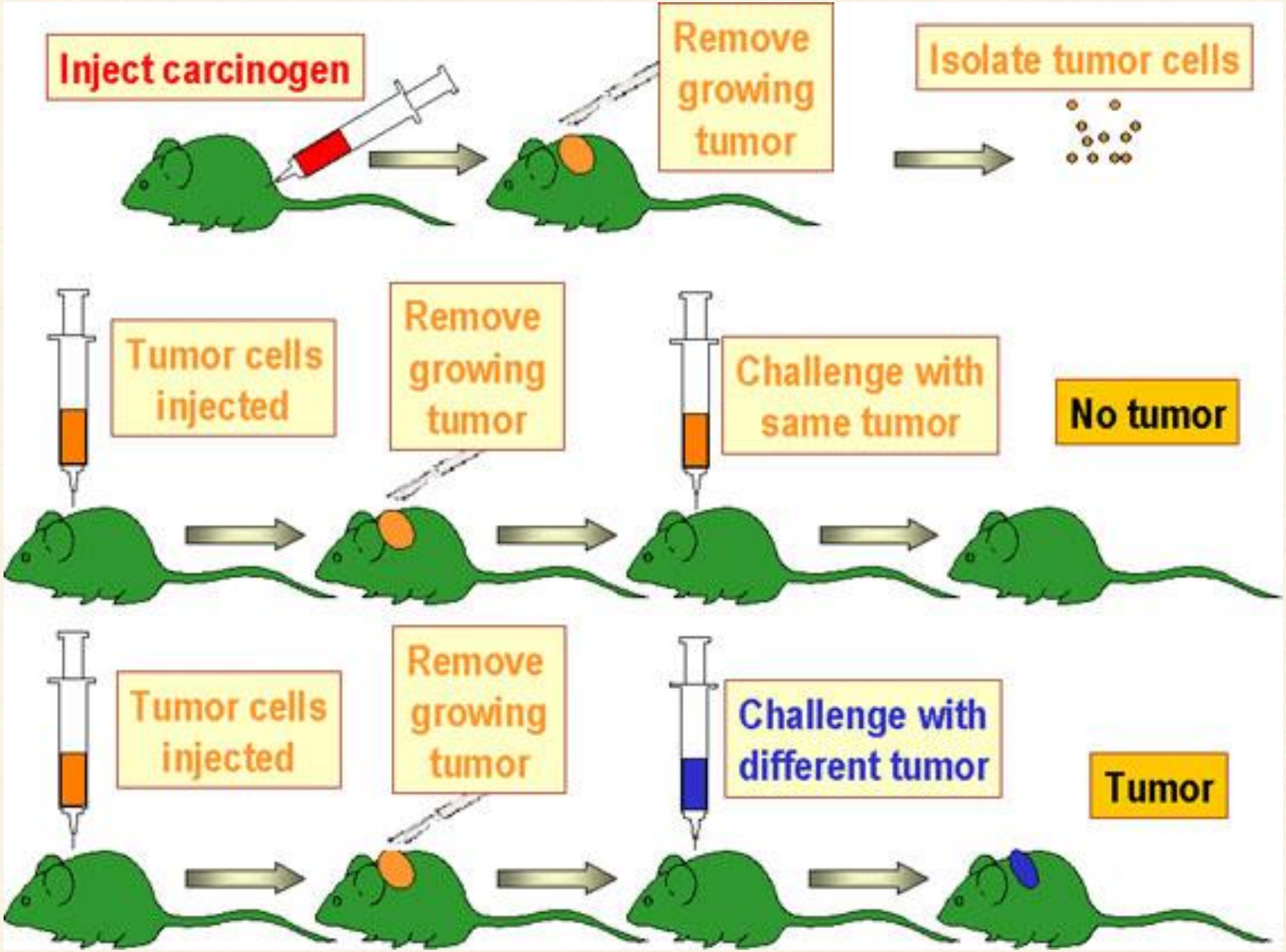
Lecture 26th

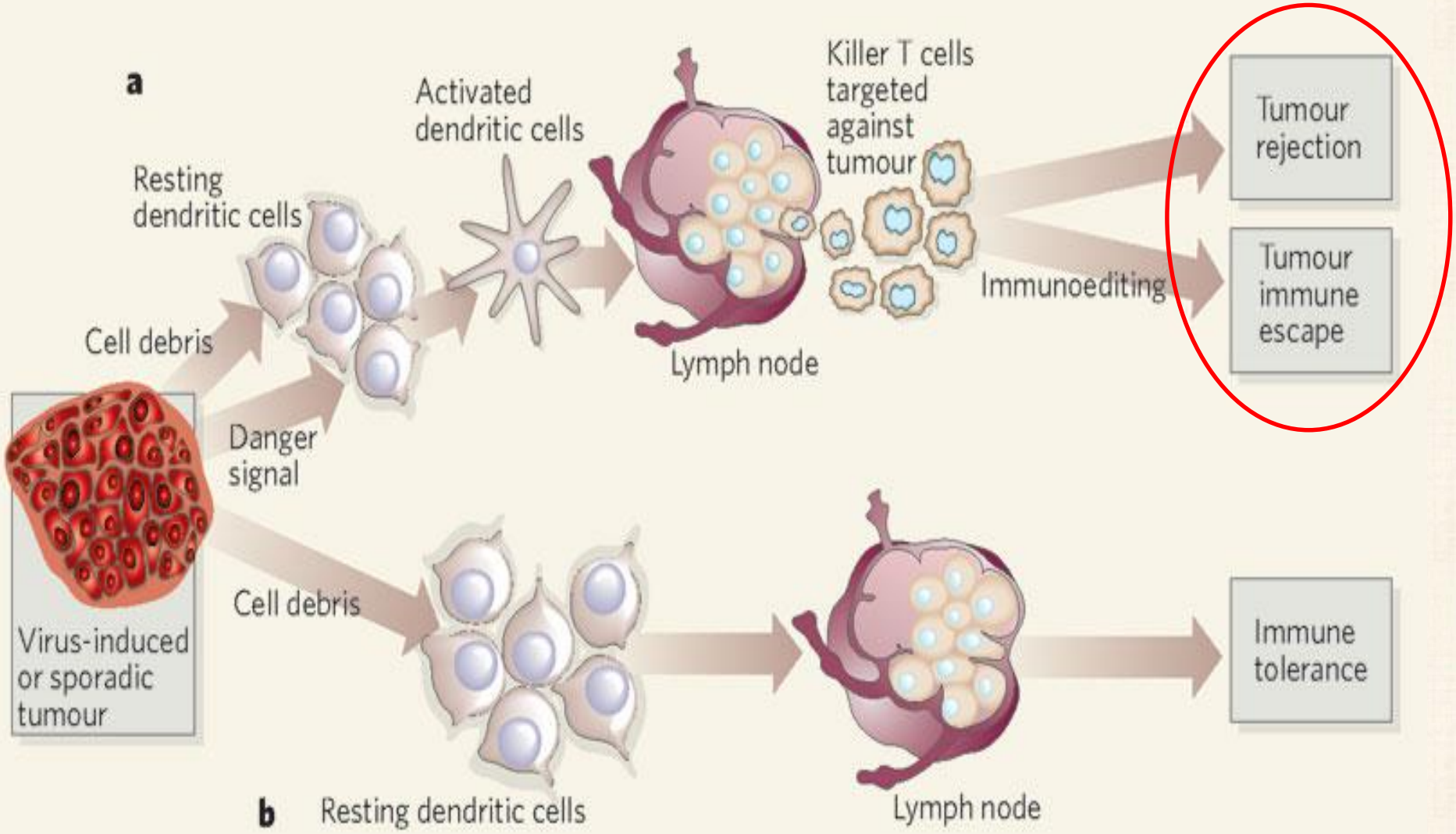
Immunity against tumors

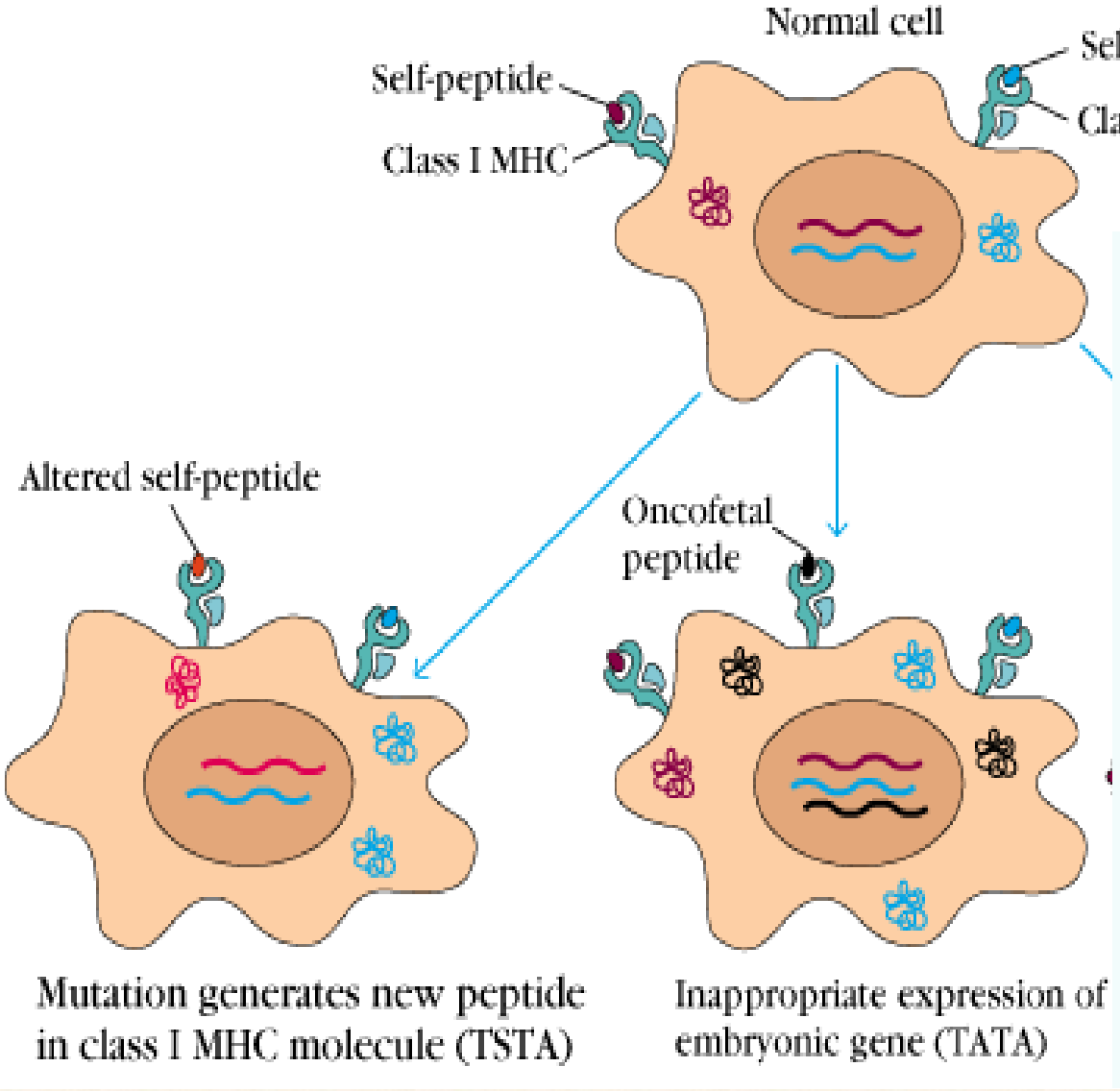
Tumor- and tumor associated antigens. Tumor escape. Trends in immunotherapy against cancer.



- Carcinogenesis is a multistep process with accumulation of multiple mutations
- Non-lethal genetic damages
- Clonal expansion (tumors are monoclonal)
- Tumor development (tumor escape or involvement)


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



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!**

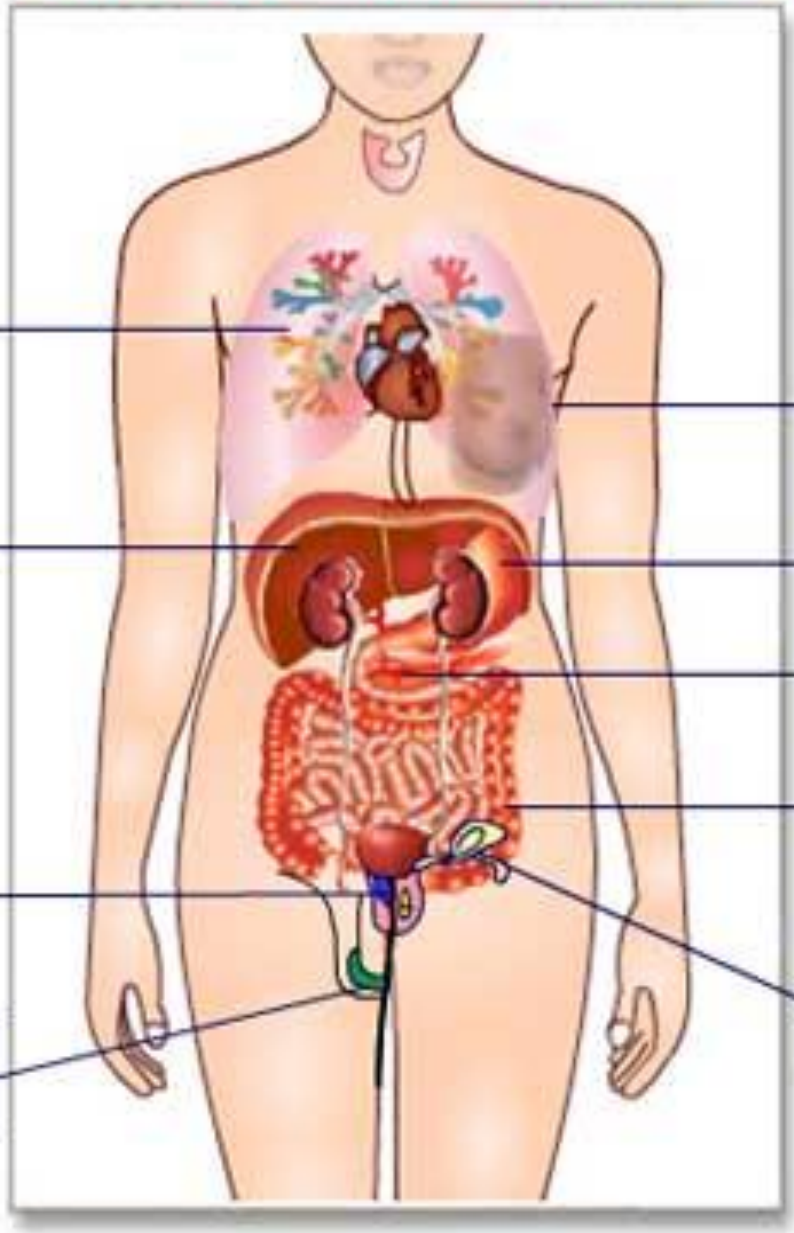
- **TSA is recognized** (according to the individual MHC haplotype) **by the immune system and induces targeting type immune response or tolerance**

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

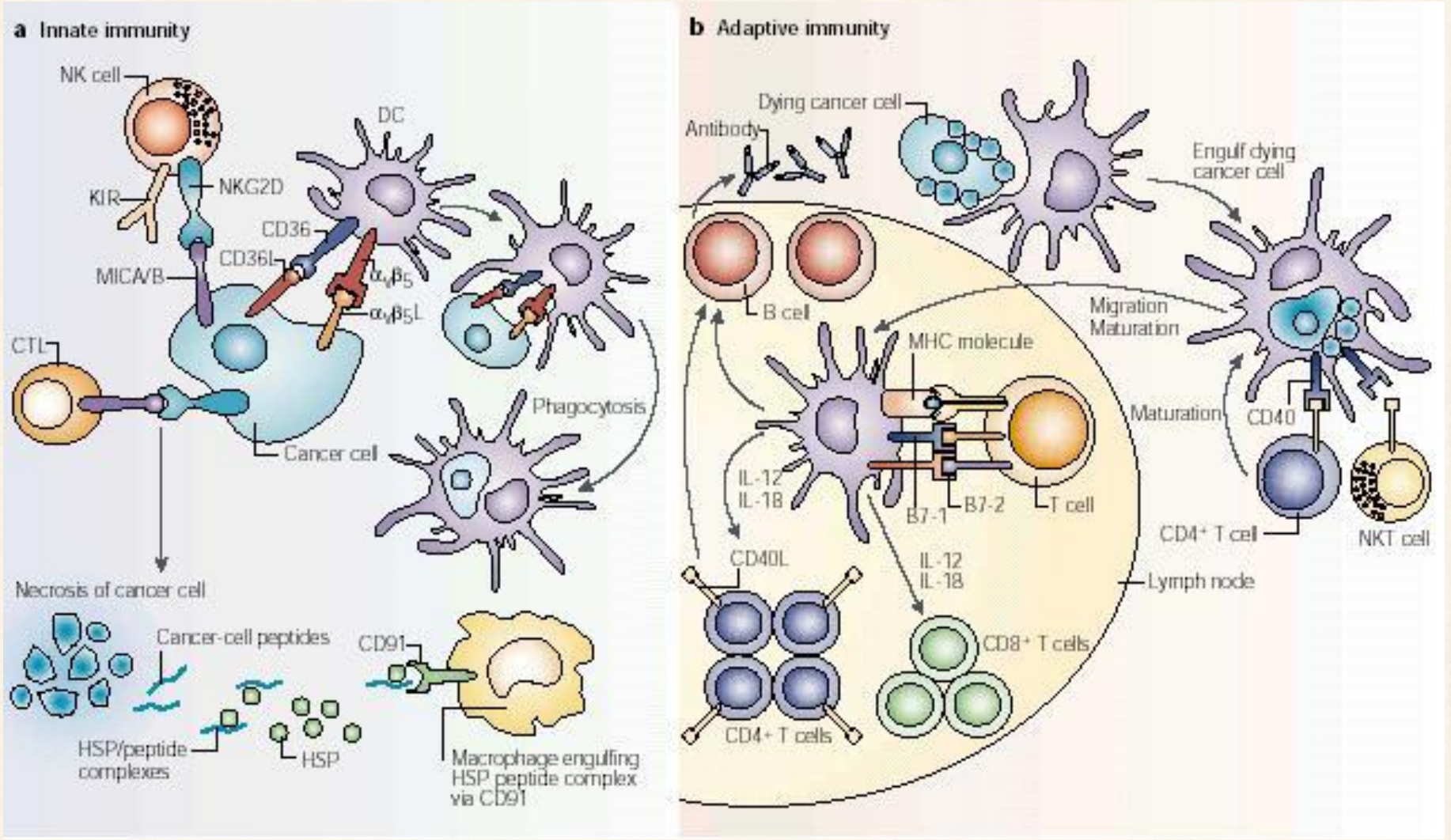
Tumor markers	Abbreviation	Oncological application
Alfa-foetoprotein	AFP	Liver and germ cell tumors
Cancer antigen 125	CA 125	ovarian tumors
Cancer antigen 15,3	CA 15,3	Breast cancer
Cancer antigen 72,4	CA 72,4	Gastric cancer
Cancer antigen 19,9	CA 19,9	Pancreatic cancer
Carcinoembrional antigen	CEA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

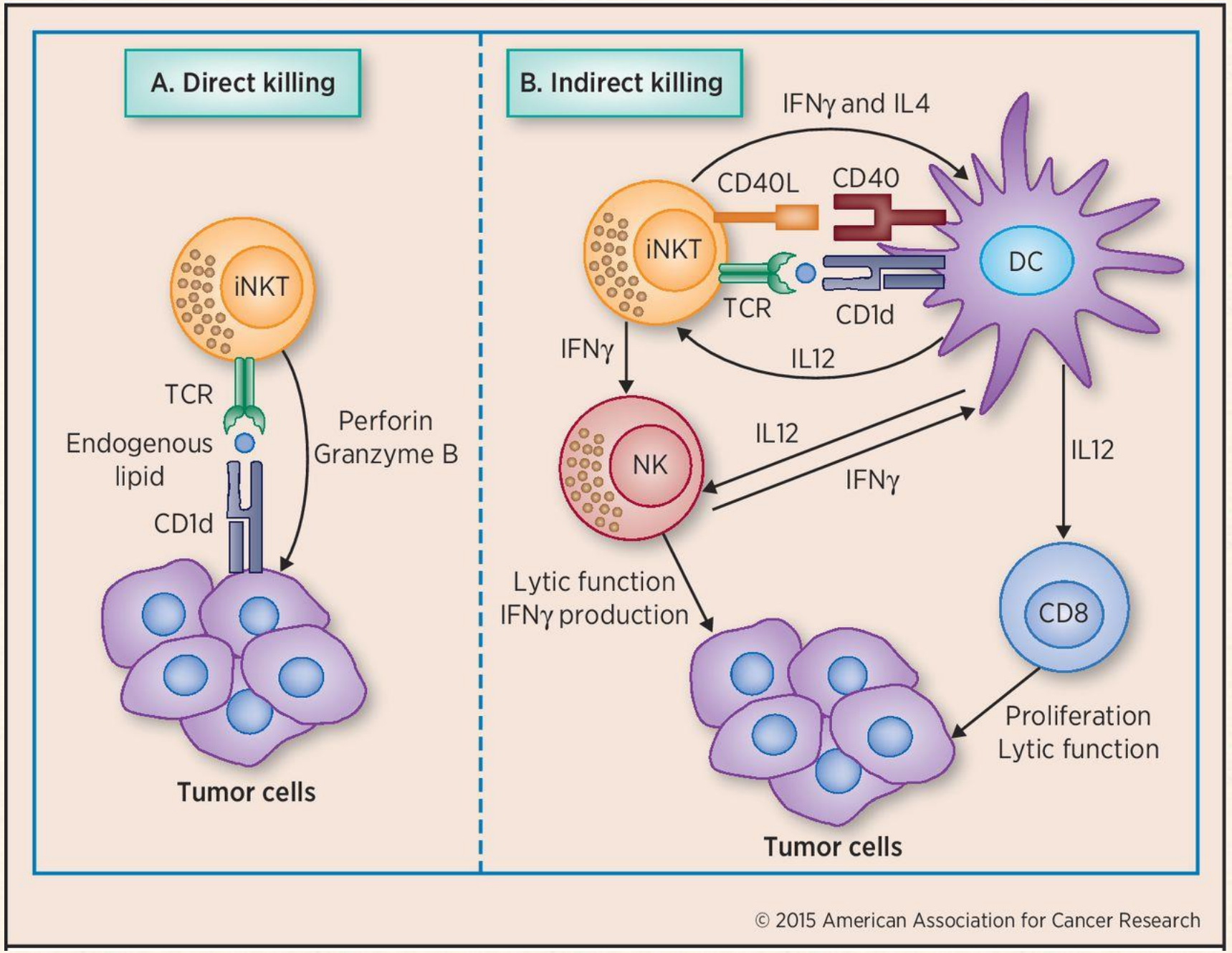
Immune reactions against tumor cells

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

NETWORK !!!

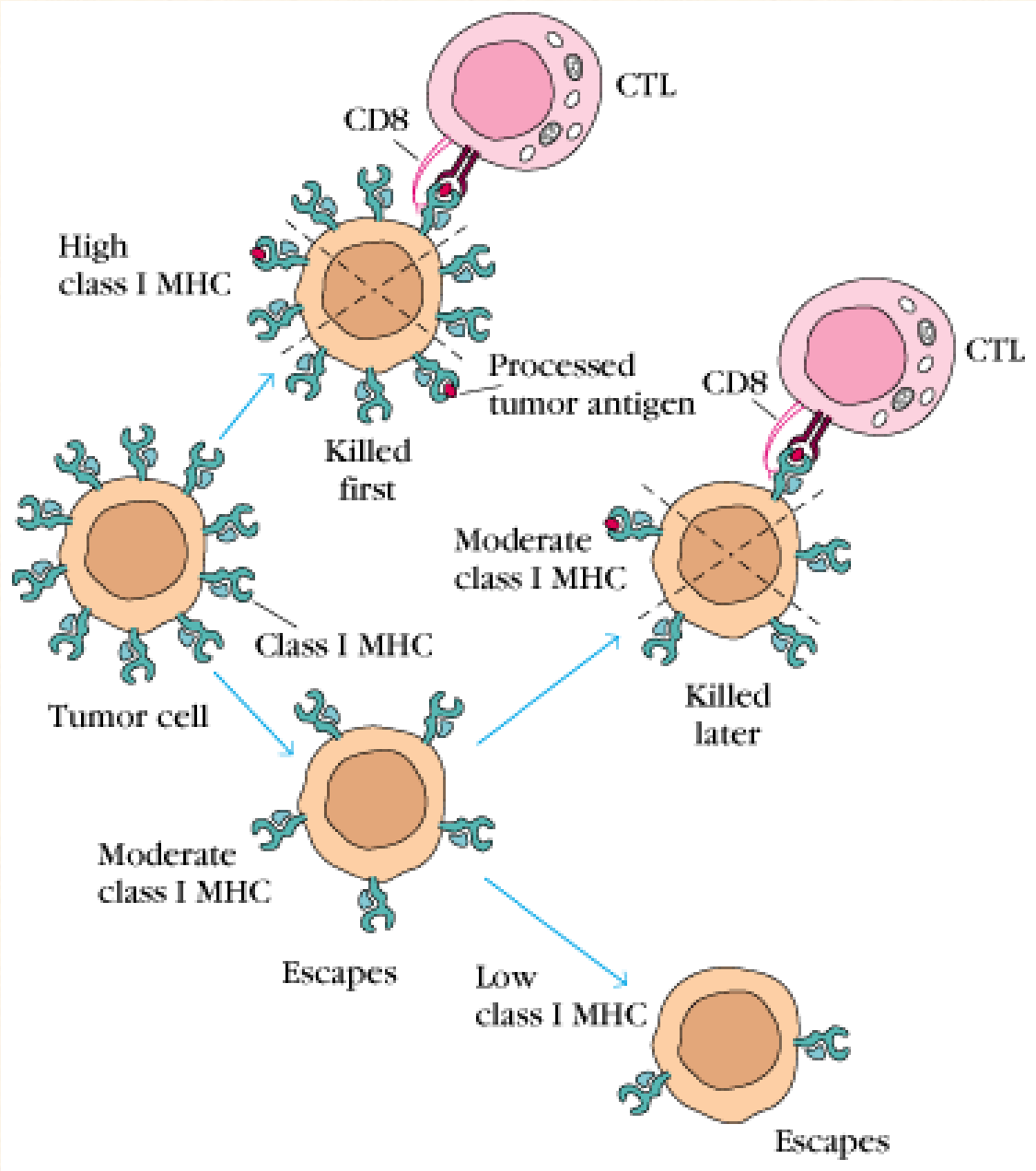
Cell mediated immunity against malignant tumors



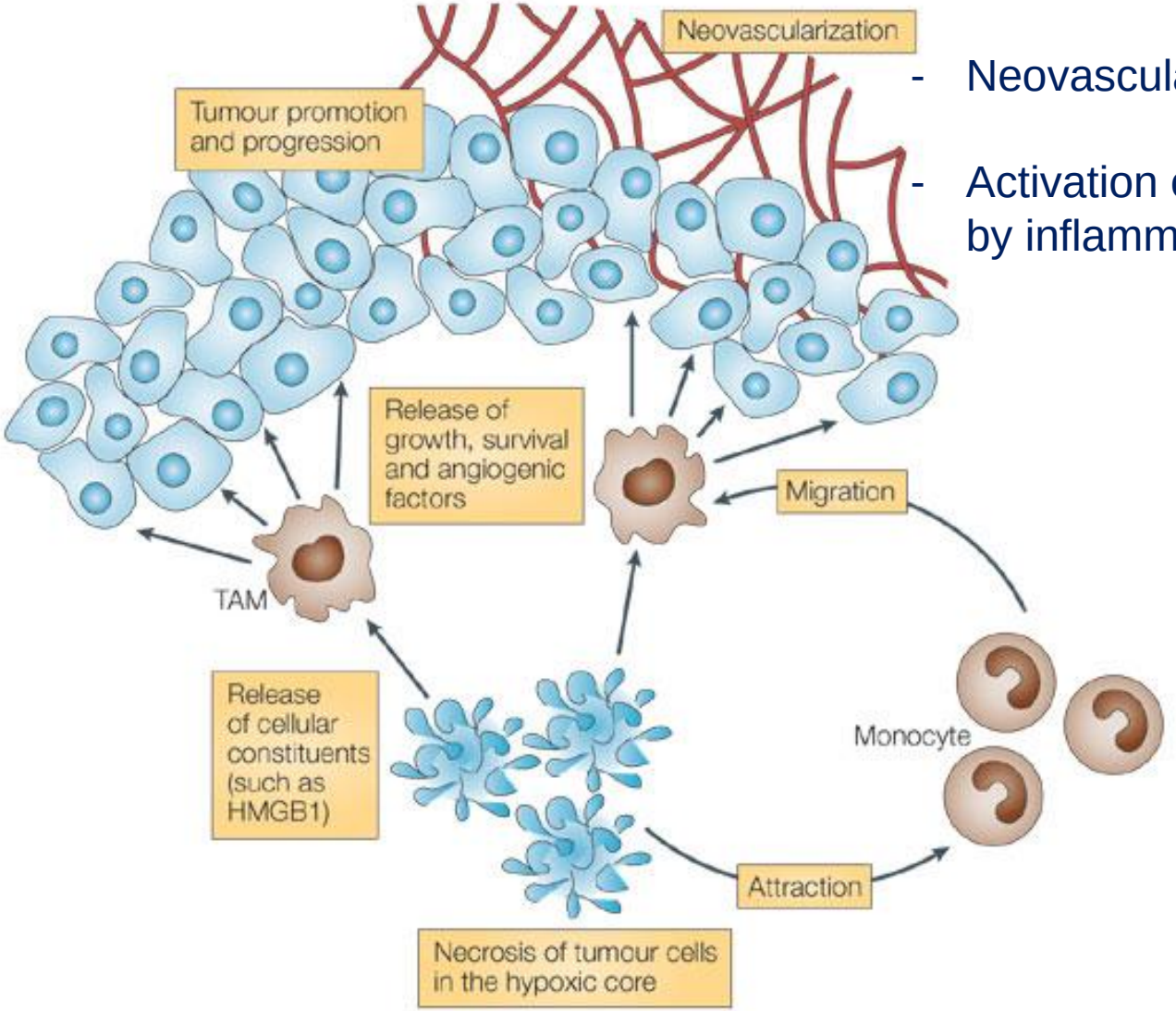


Tumor escape

- 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

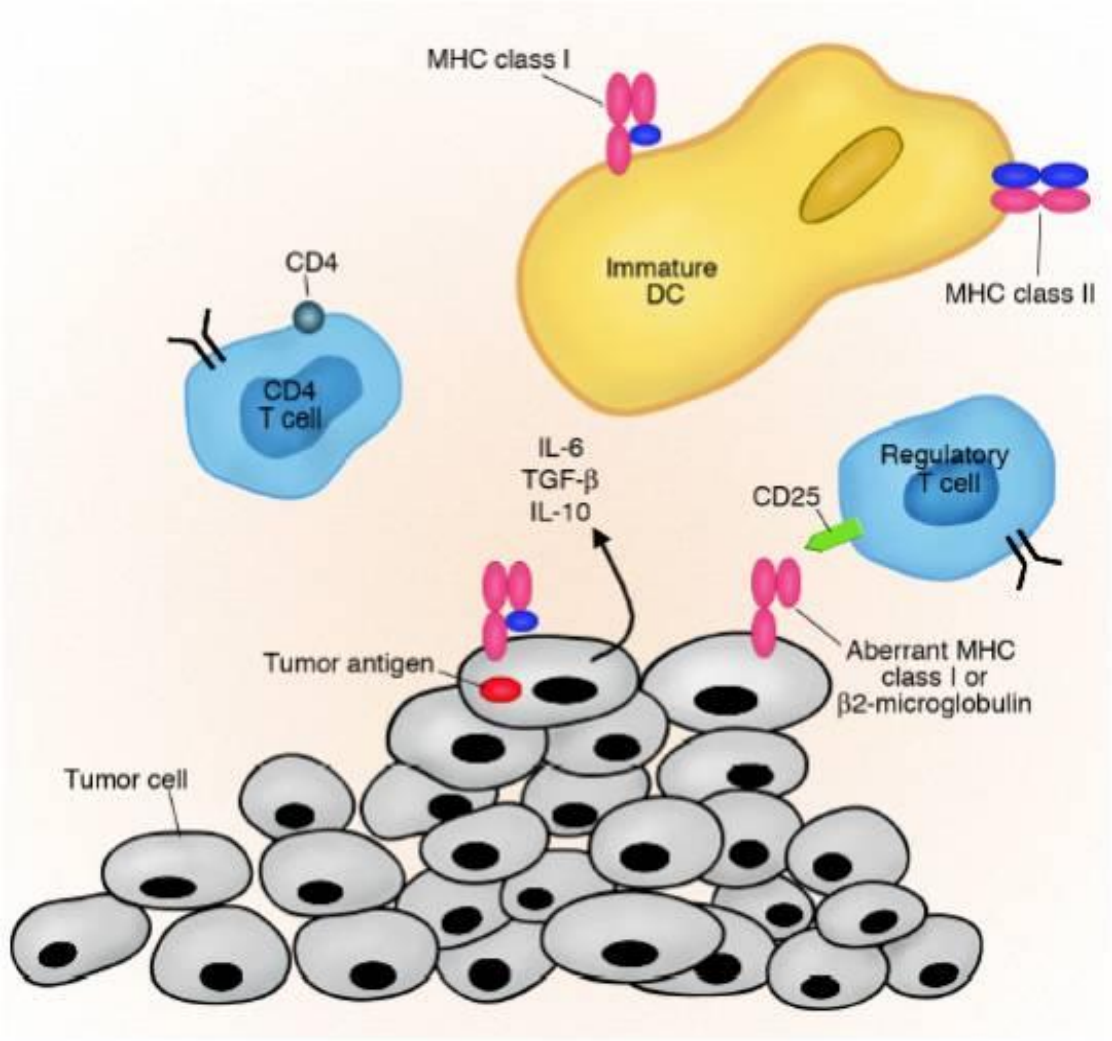

CTL
CD8
High
class I MHC
Processed
tumor antigen
Killed
first
CTL
CD8
Moderate
class I MHC
Class I MHC
Tumor cell
Killed
later
Moderate
class I MHC
Escapes
Low
class I MHC
Escapes

Tumor infiltrating macrophages: double-edged sword

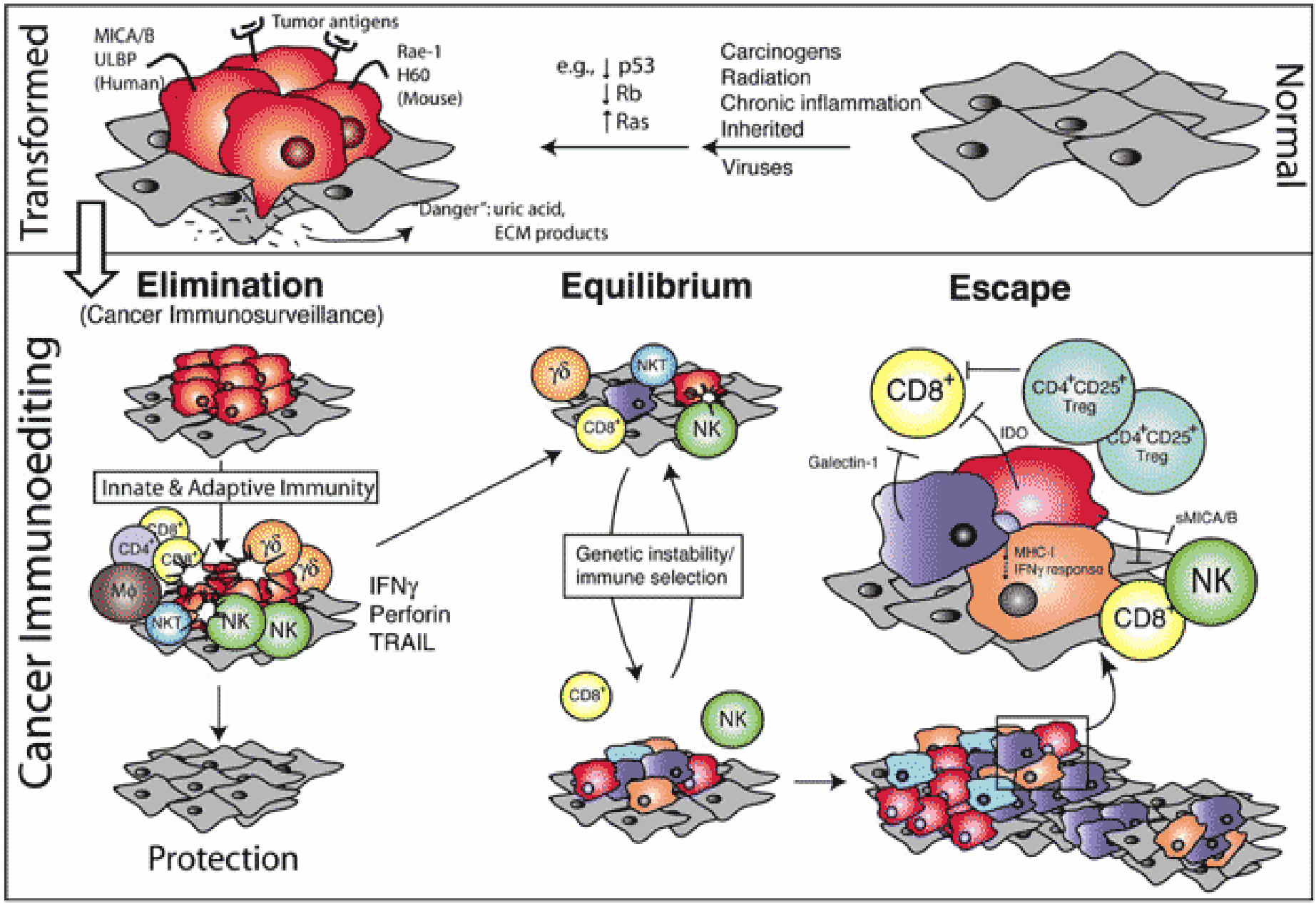


- Neovascularization
- Activation of cancer cells by inflammatory cytokines

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.

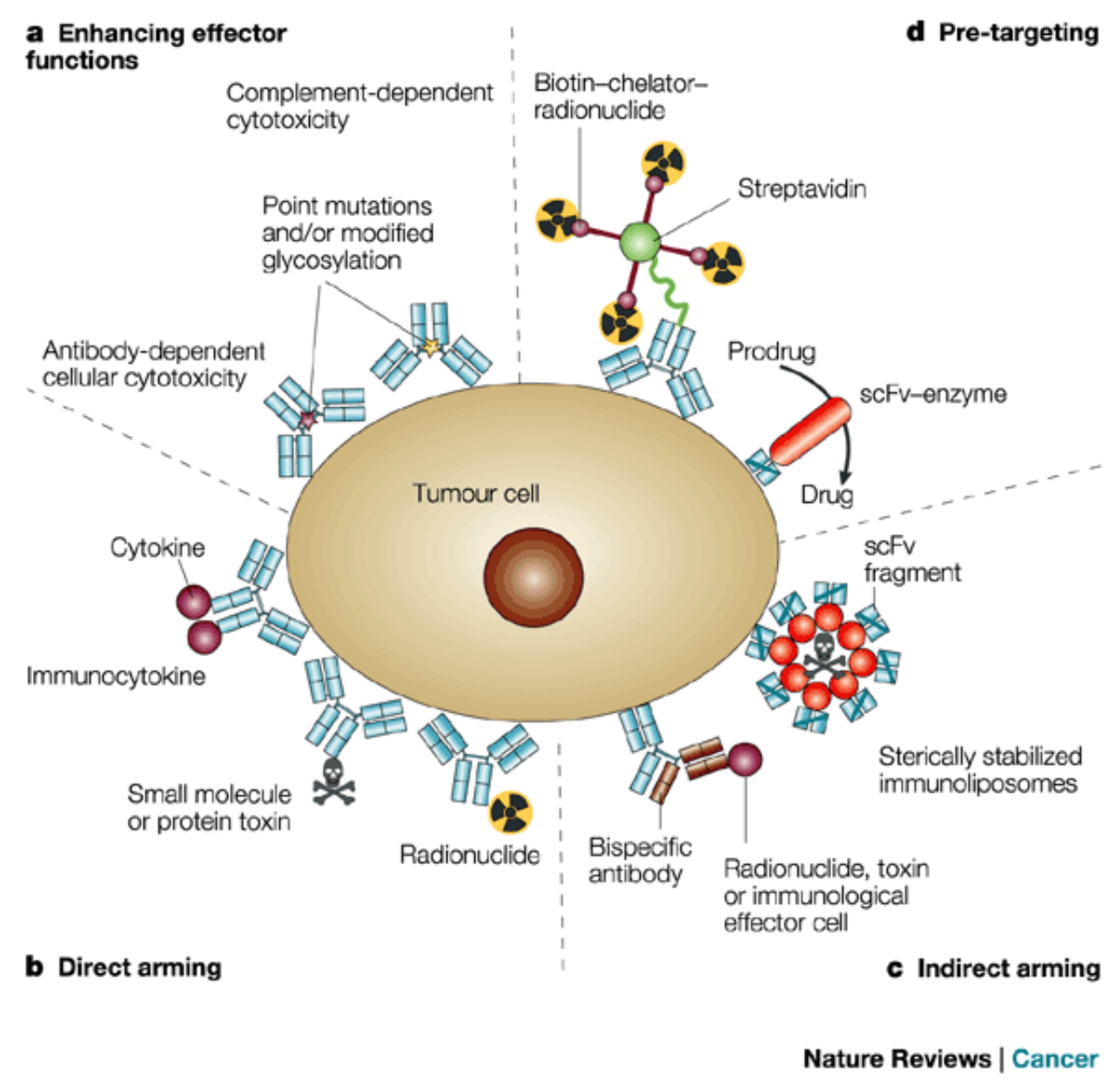

Transformed
MICA/B
ULBP
(Human)
Tumor antigens
Rae-1
H60
(Mouse)
e.g., ↓ p53
↓ Rb
↑ Ras
Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses
Normal
"Danger": uric acid,
ECM products
Cancer Immunoediting
Elimination
(Cancer Immunosurveillance)
Innate & Adaptive Immunity
IFNγ
Perforin
TRAIL
Protection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

Cancer immunotherapy

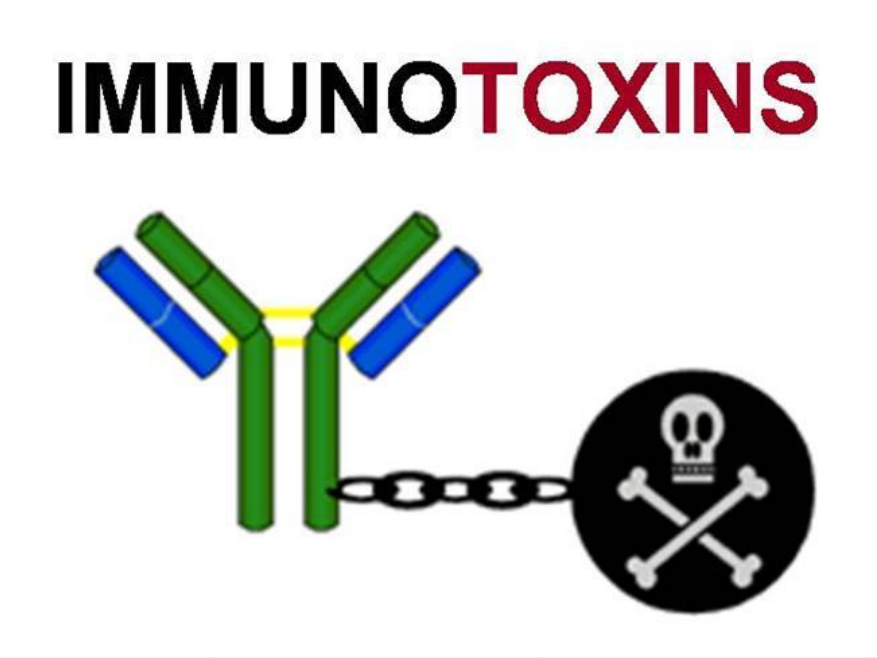
Complementary therapeutic tools after the surgical, chemotherapeutic and/or irradiation treatments:

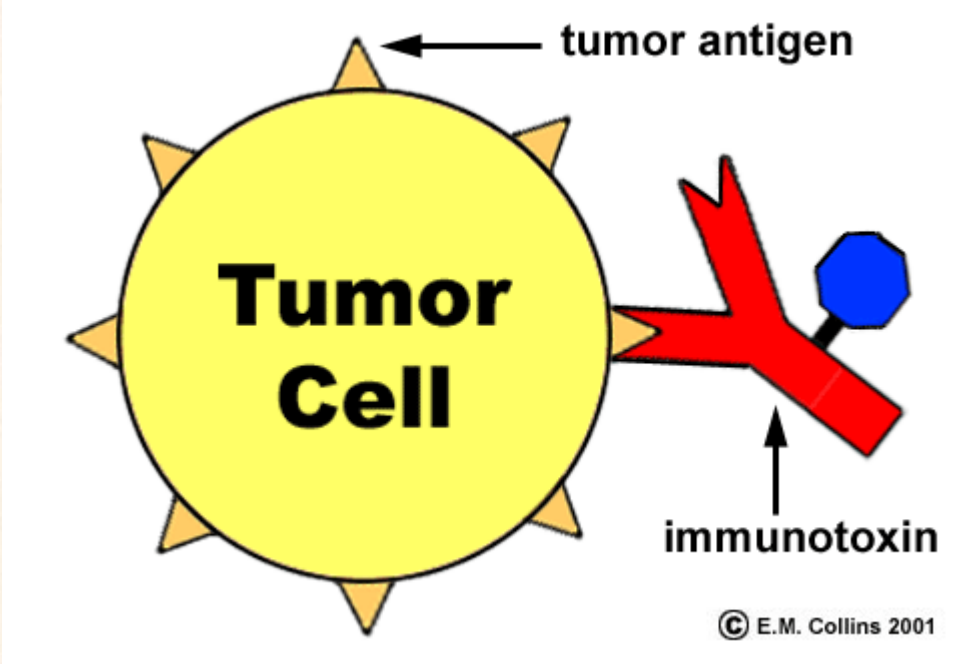
- **Therapeutic monoclonal antibodies**
- **Checkpoint inhibitors (PD-1/PDL-1)**
- **Immuno-modulation**
- **Cancer vaccines**
- **Oncolytic viruses**

Monoclonal antibodies for therapeutic use



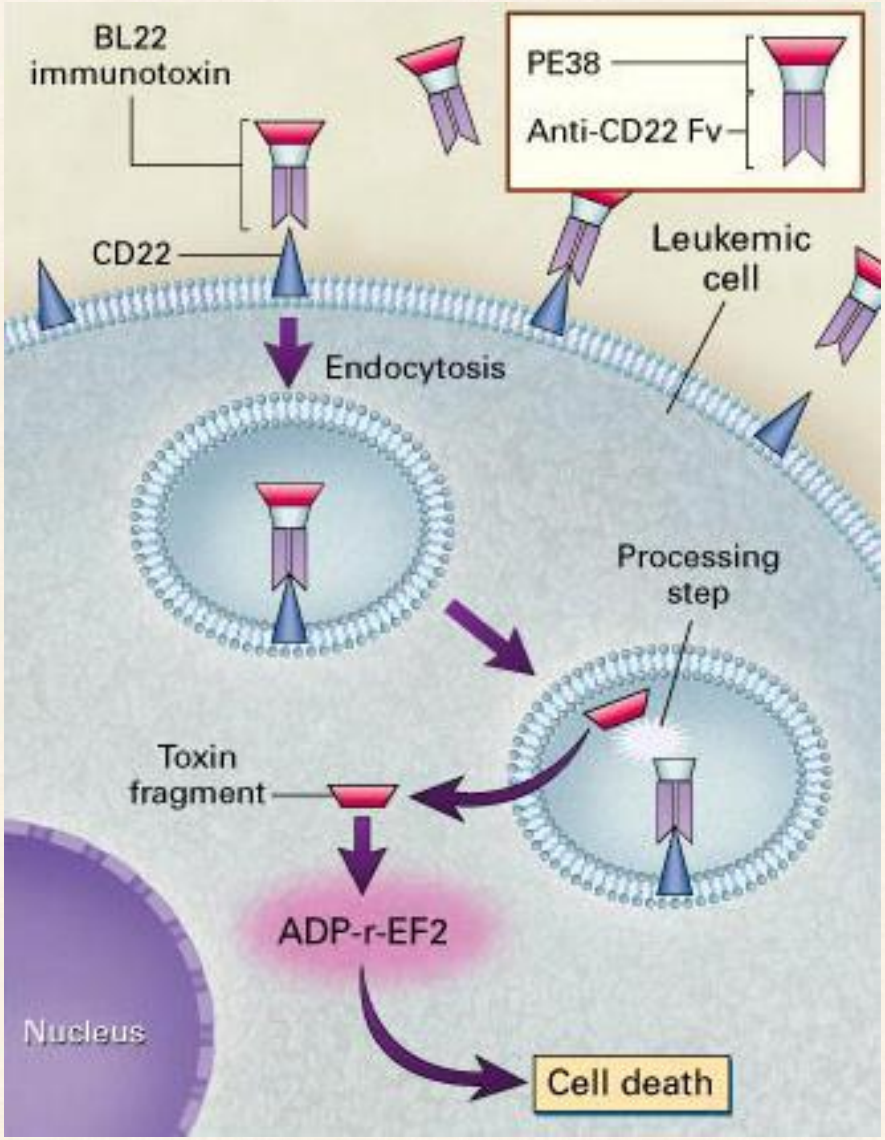
Immunotoxins in cancer therapy



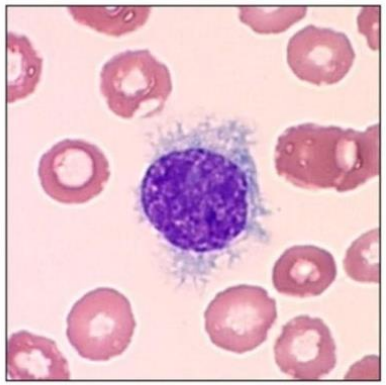


Monoclonal antibodies that bind target cell-surface antigens are themselves non-cytotoxic, but after conjugation with toxins they are able for clinical application in cancer therapy.

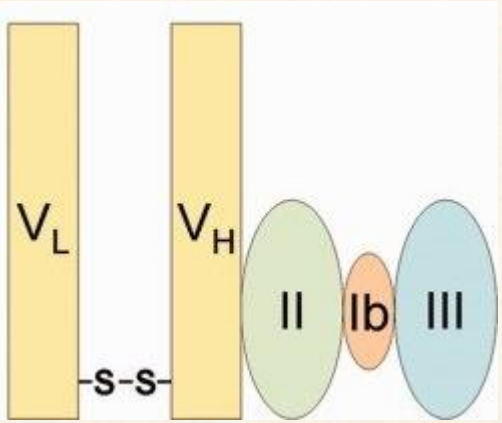
Immunotoxin therapy of „Hairy Cell" leukaemia by BL22



- 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

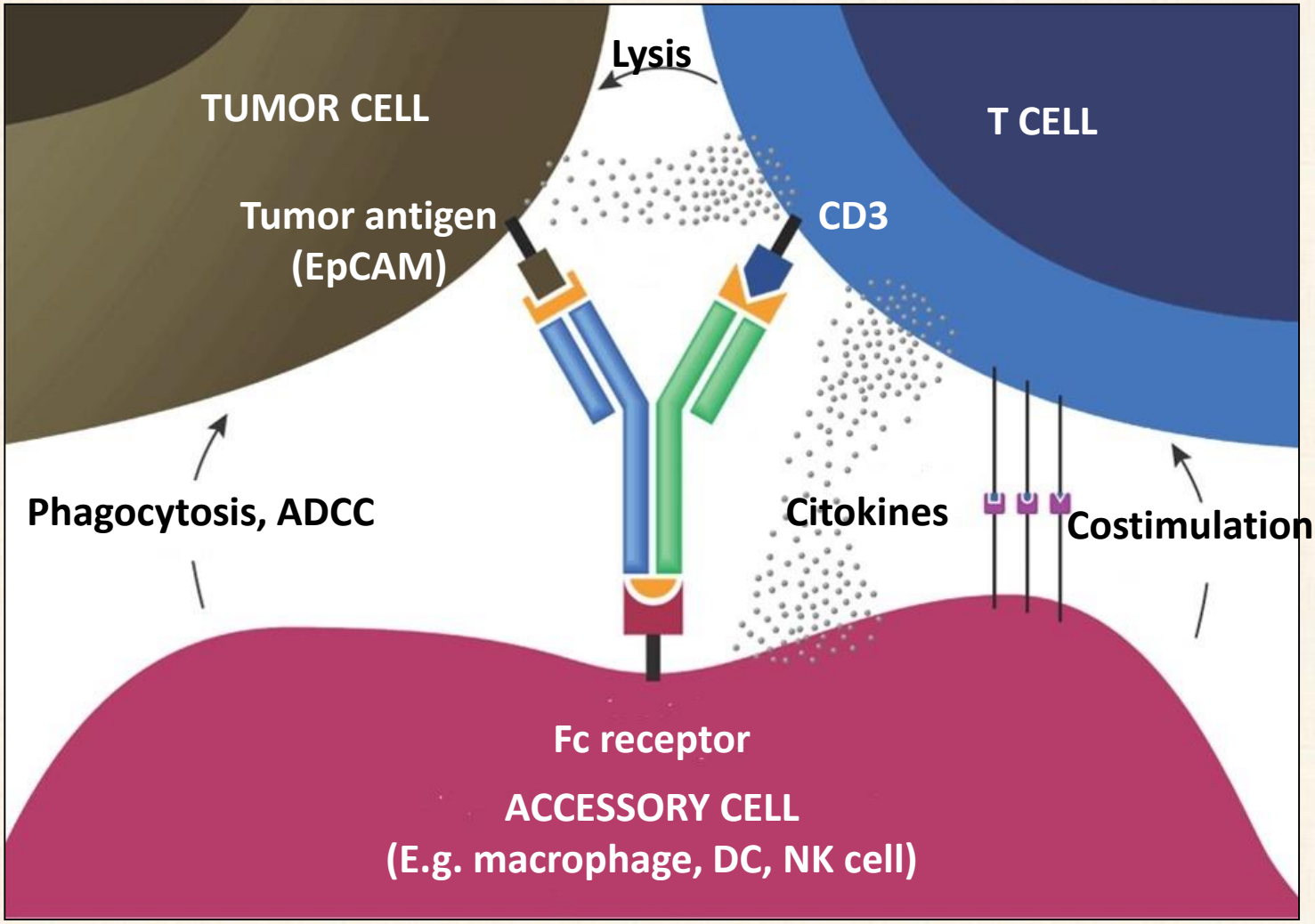


Hair-like projections of cytoplasmic membrane characteristic of hairy cell leukemia[c]



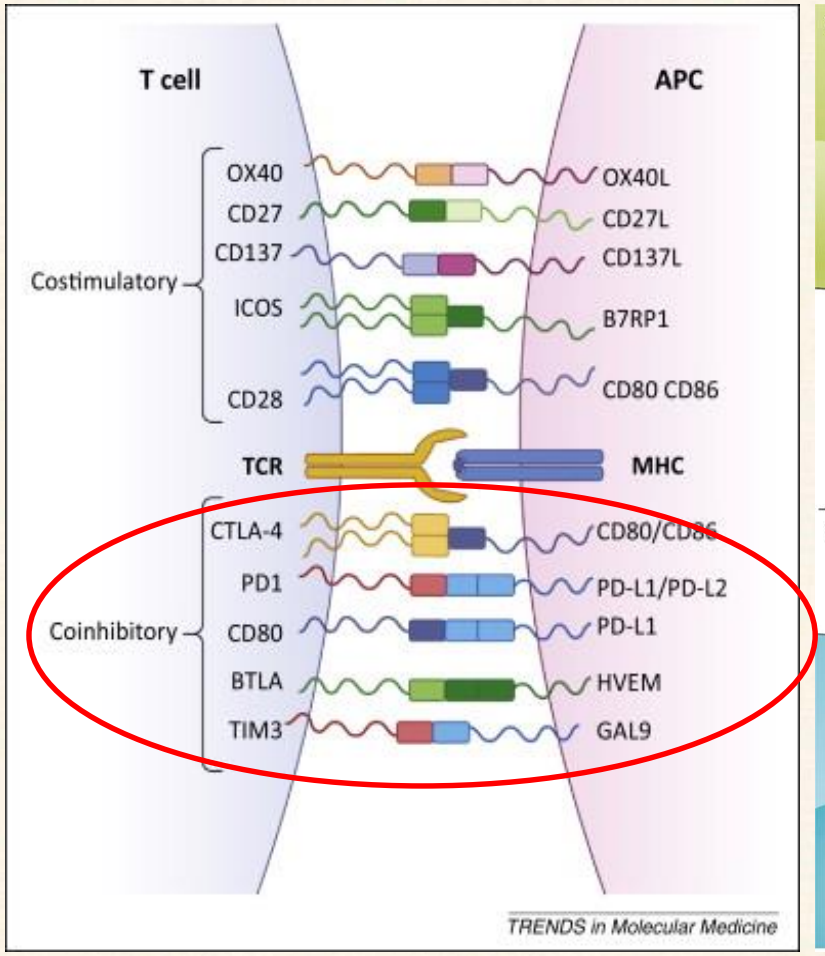
Pseudomonas exotoxin (**pe38**) conjugate to Ig variable H and L chains

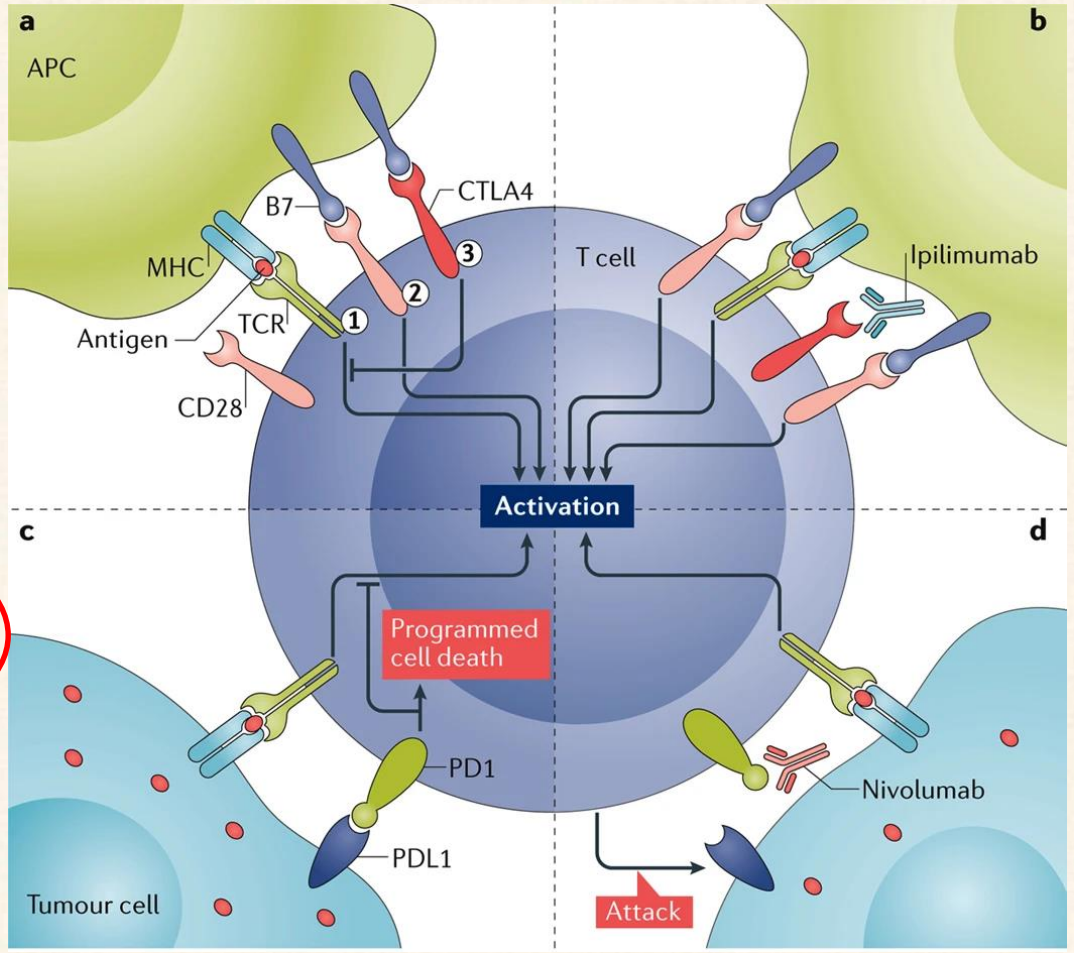
Bispecific therapeutic monoclonal antibodies



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

Immune checkpoint inhibitors

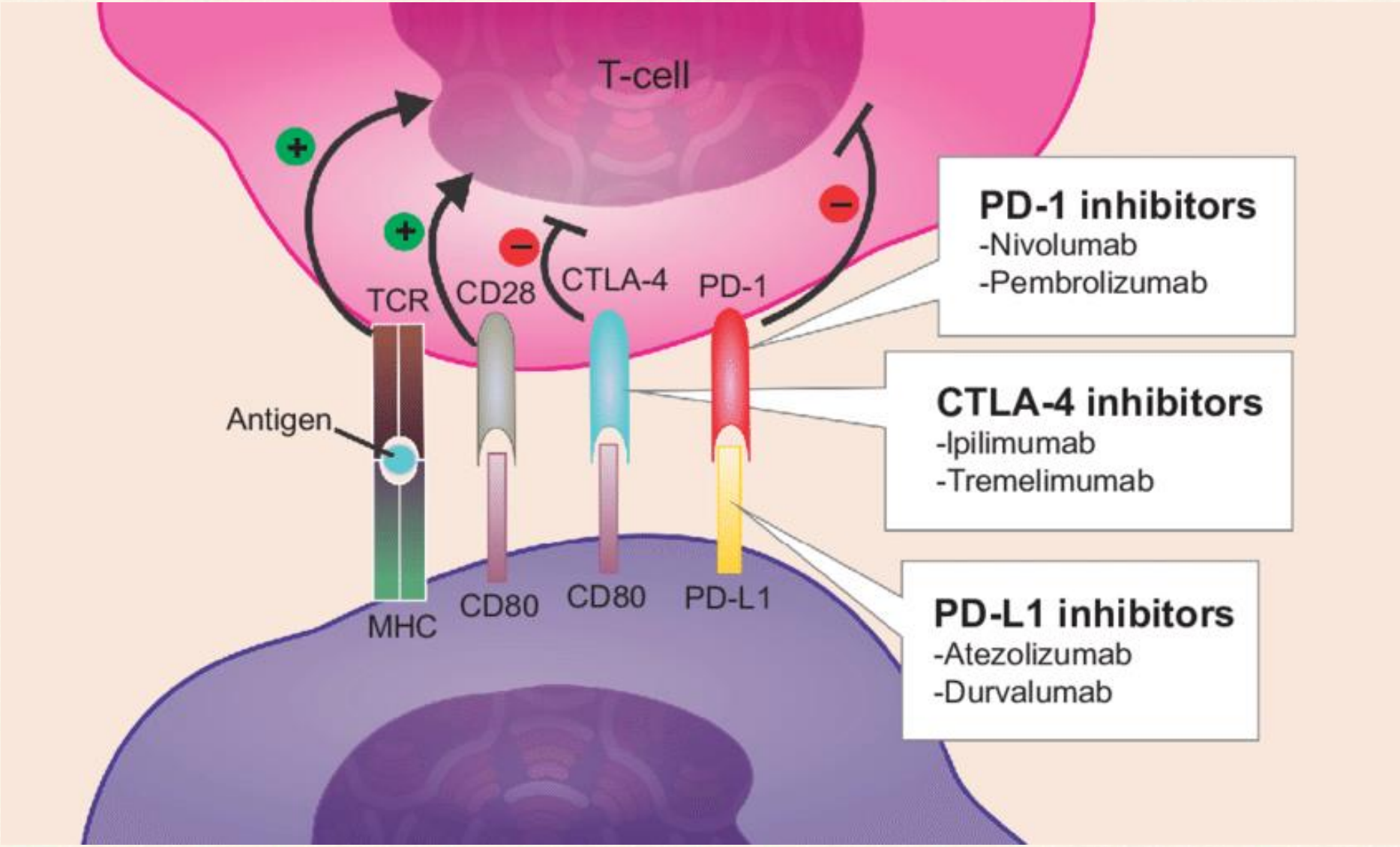


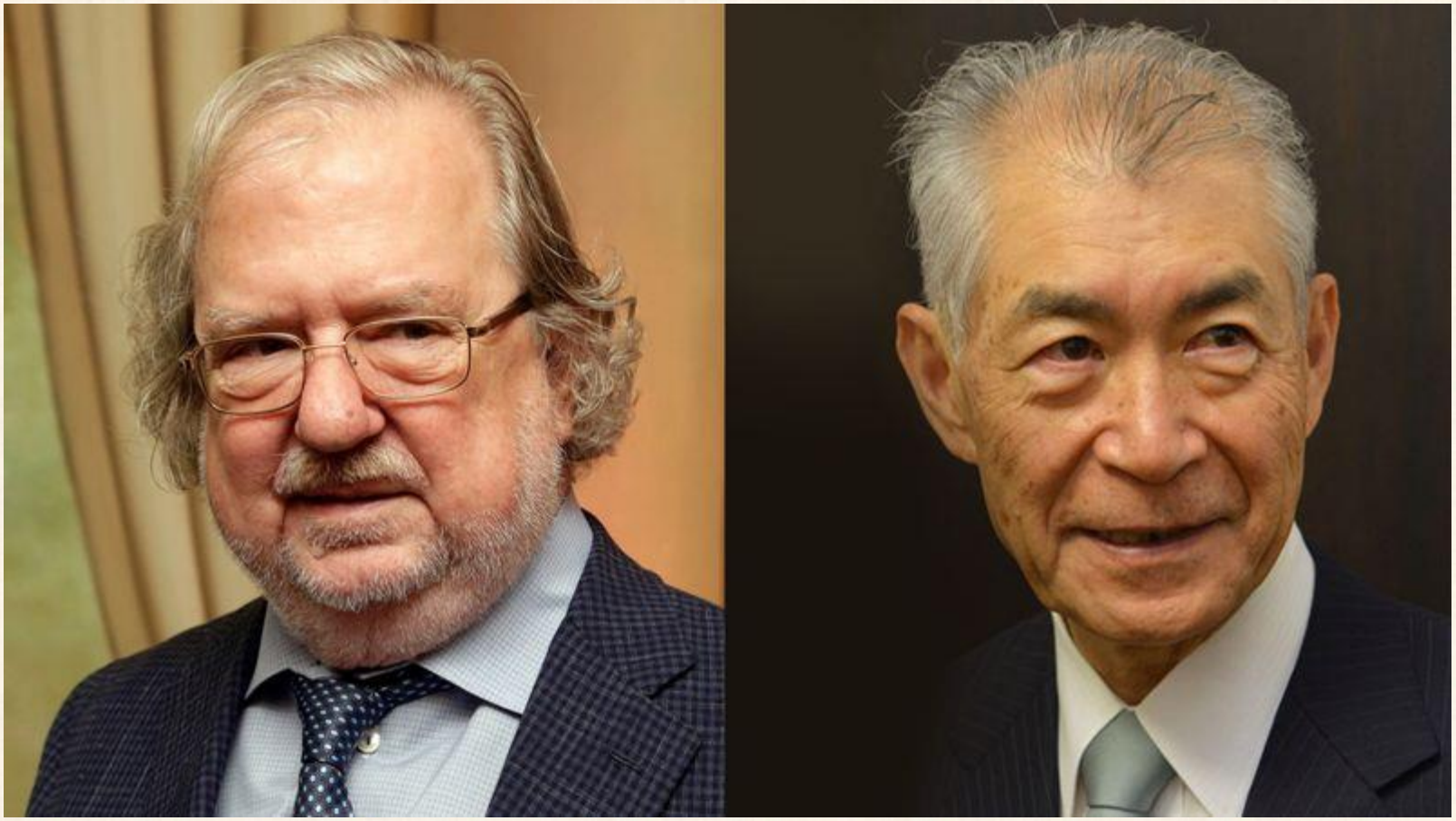


Blocking of CTLA-4, PD-1 and PD-L1 is able to delete the T cell inhibition induced by cancer cells.

Blocking the T cell blockade = T cell activation

Immune checkpoint inhibitors



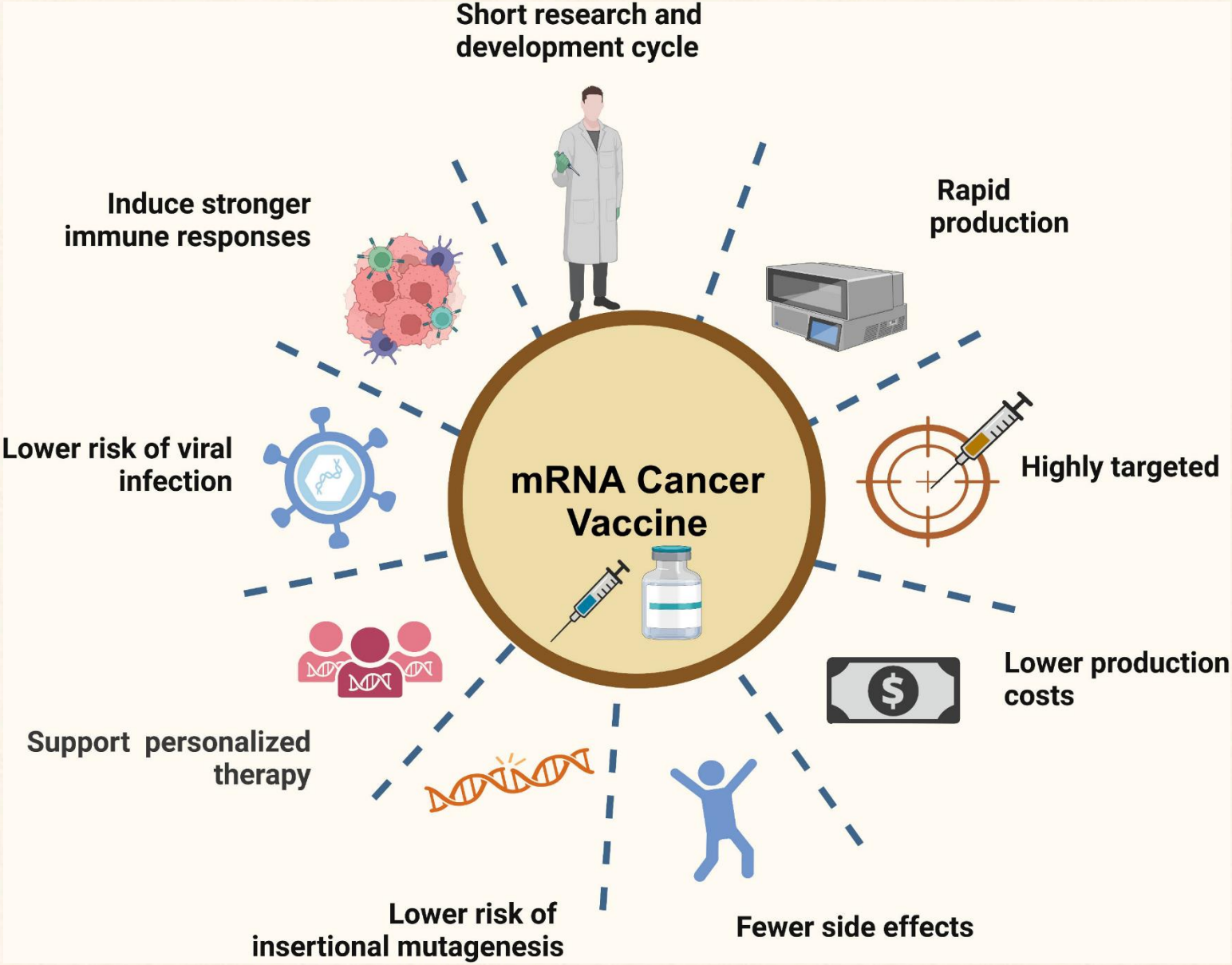


James P. Allison, PhD **Tasuku Honjo**, MD, PhD

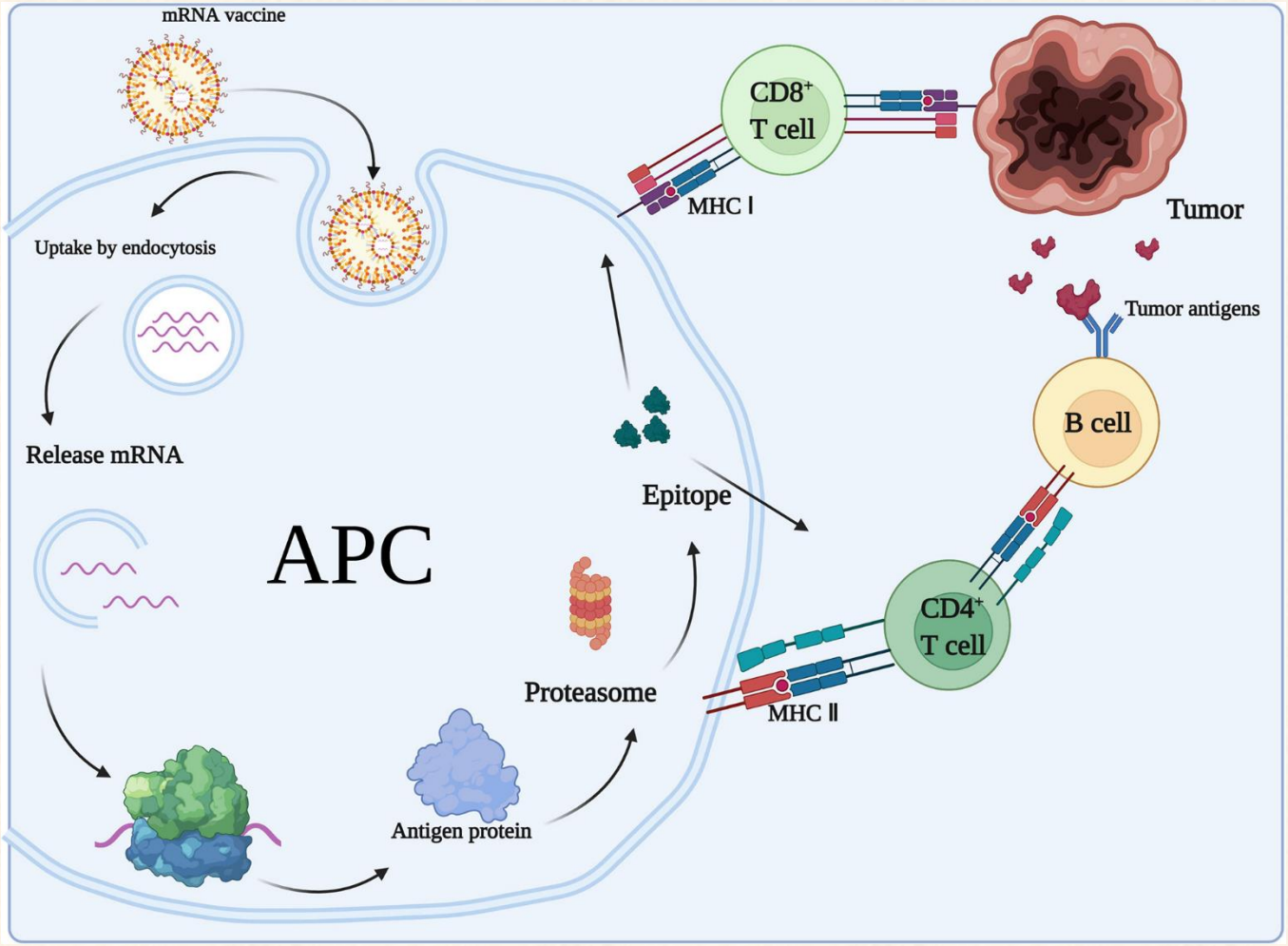
Immunotherapy pioneers have won the ***2018 Nobel Prize*** in Physiology or Medicine for their research that eventually led to the use of immune checkpoint inhibitors to treat cancer.

Nobel prize 2023’ for mRNA technology

The closed future: mRNA-based cancer vaccines

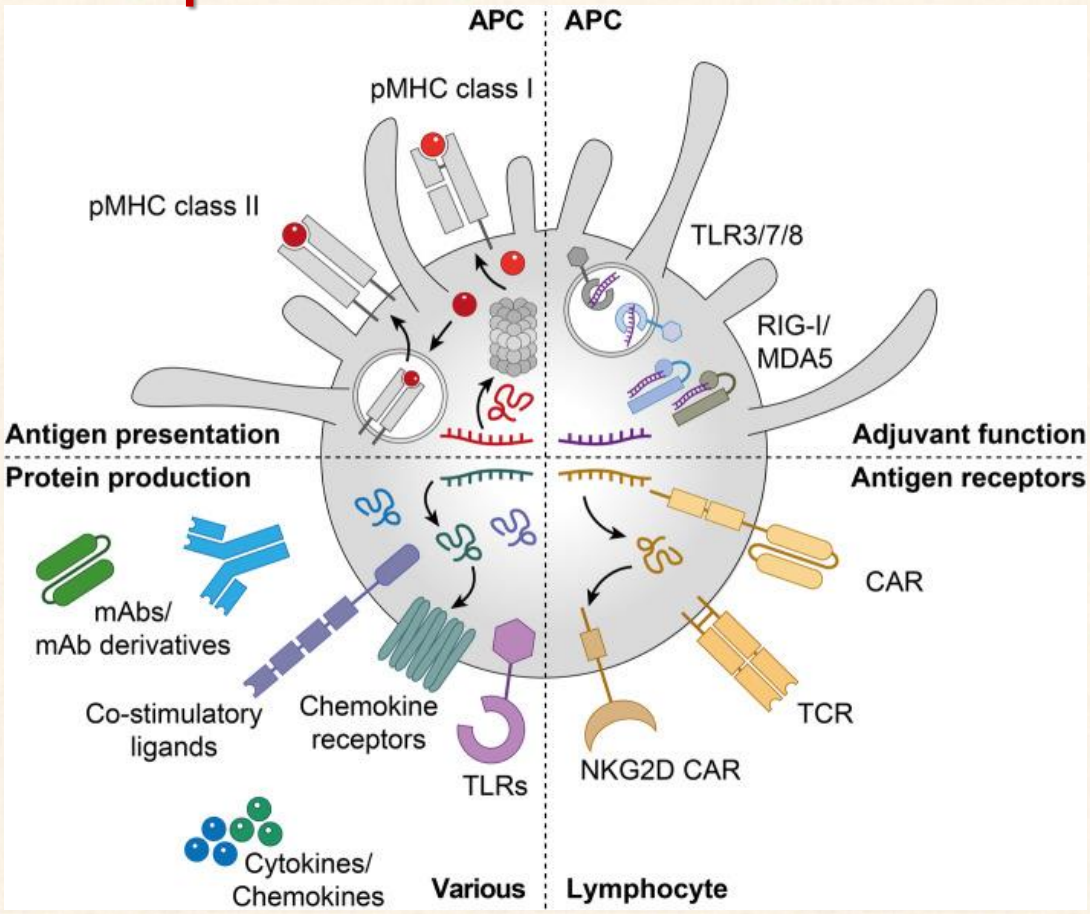


Adaptive immune response to mRNA vaccines



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).