Medical Biotechnology 2026'

Biological therapies

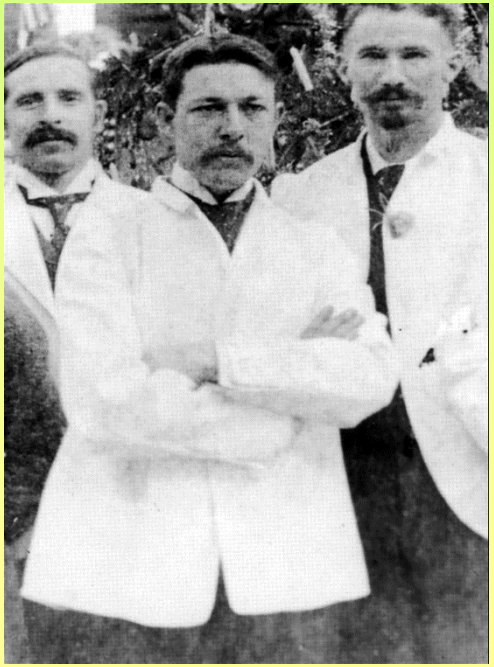
Lecture 17-18th

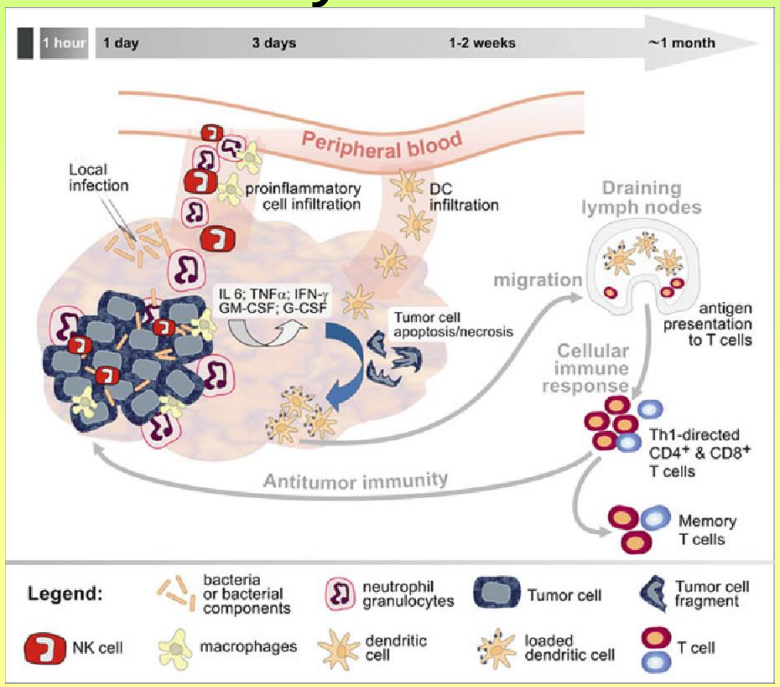
Introduction to biotherapies for malignant tumours

History

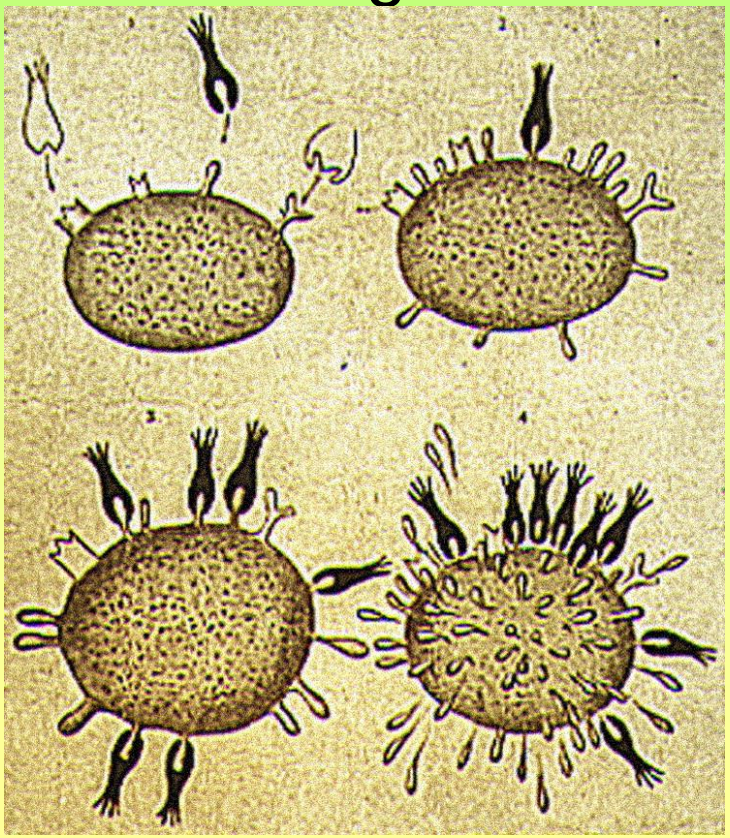
- Tumor immunotherapy: ***William Coley*** an American bone surgeon (1862-1936) used Streptococcus pyogenes injection into bone tumours (*TNFalpha induction, DC activation*)
- Idea of combination of bio- and chemotherapy: ***Paul Ehrlich*** (1854-1915): “magic bullet” (*therapeutic monoclonal antibodies*) winning the 1908 Nobel Prize in Medicineand
- Tumor vaccines and gene therapy: ***Steven Rosenberg*** pioneered the development of effective immunotherapies and gene therapies for patients with advanced cancers
- 2018 Nobel Prize: ***James P. Allison*** and ***Tasuku Honjo*** immune checkpoint inhibitors to treat cancer.

William Coley (1862–1936) was an American surgeon recognized as the "Father of Immunotherapy" for developing „Coley's Toxins", a mixture of heat-killed *Streptococcus* and *Serratia marcescens* bacteria designed to stimulate the immune system to fight cancer. By injecting these toxins, he successfully treated various inoperable sarcomas, sparking early interest in harnessing the immune system for cancer treatment.

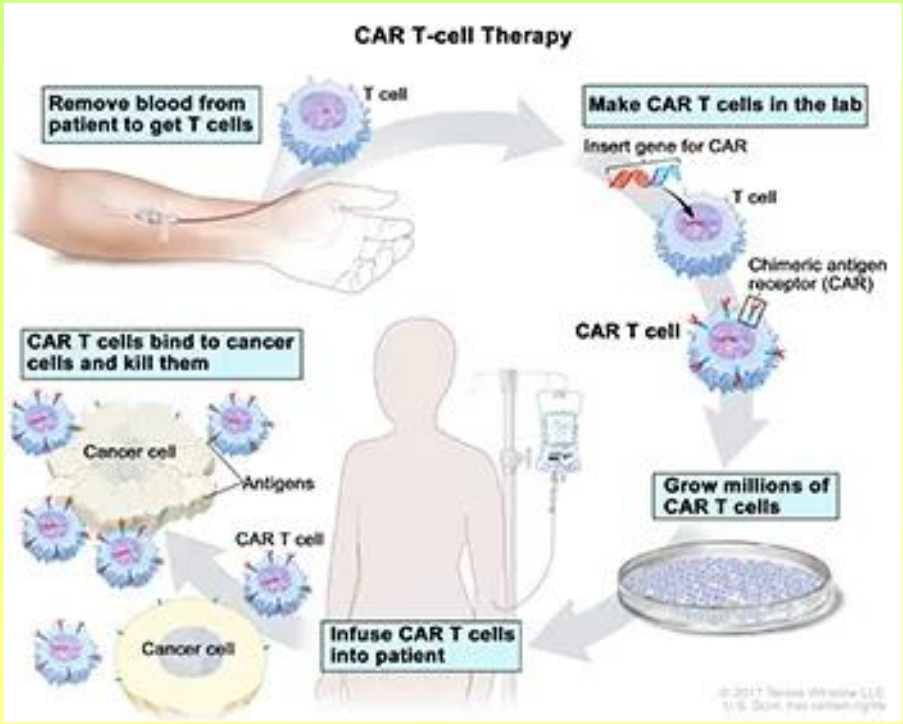


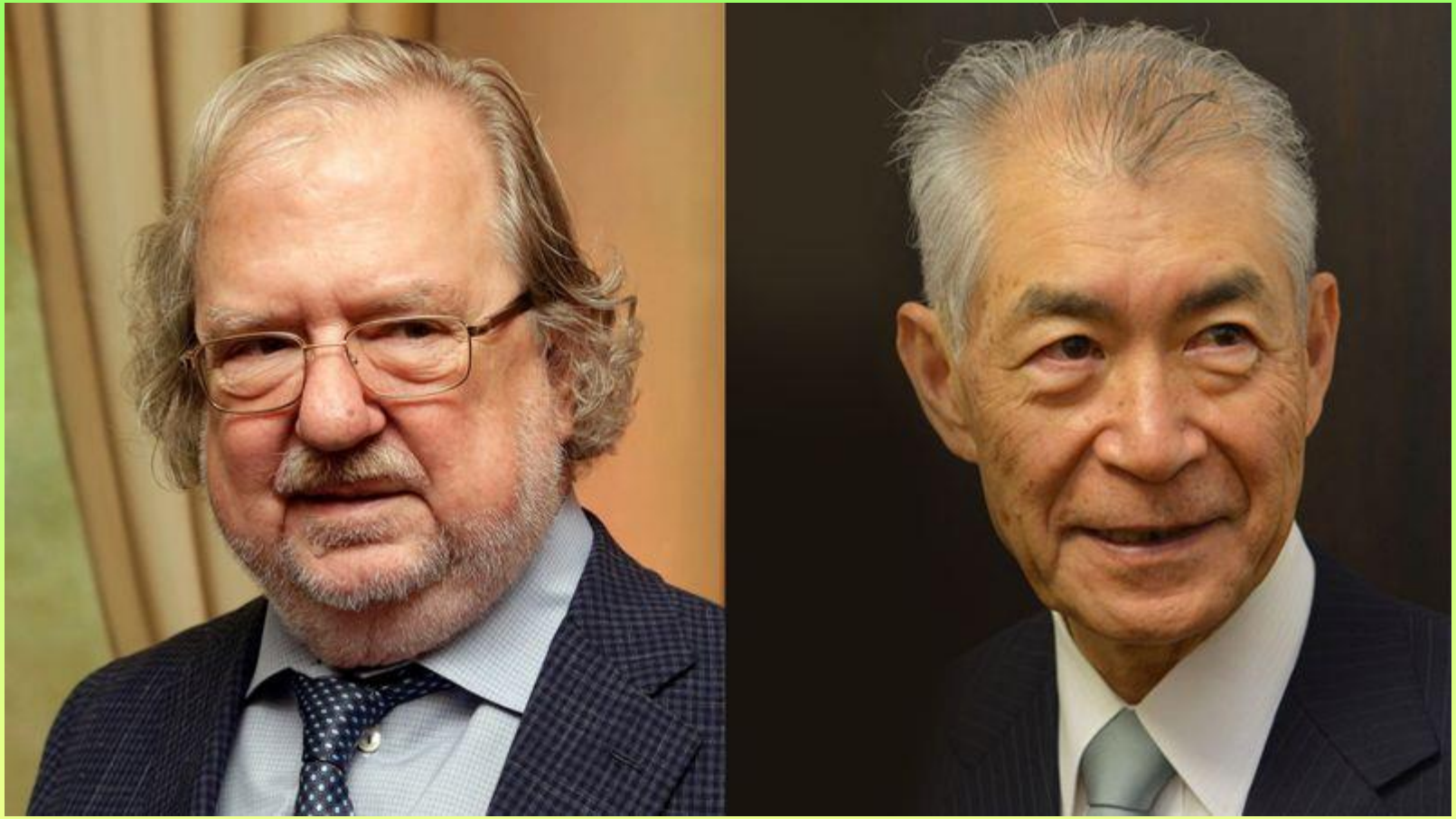


Paul Ehrlich (1854–1915) was a pioneering German physician and scientist who laid the foundations for modern immunology, hematology, and chemotherapy. He is best known for developing the "magic bullet" concept of targeted drug therapy, winning the 1908 Nobel Prize in Medicine, and discovering the first effective syphilis treatment.



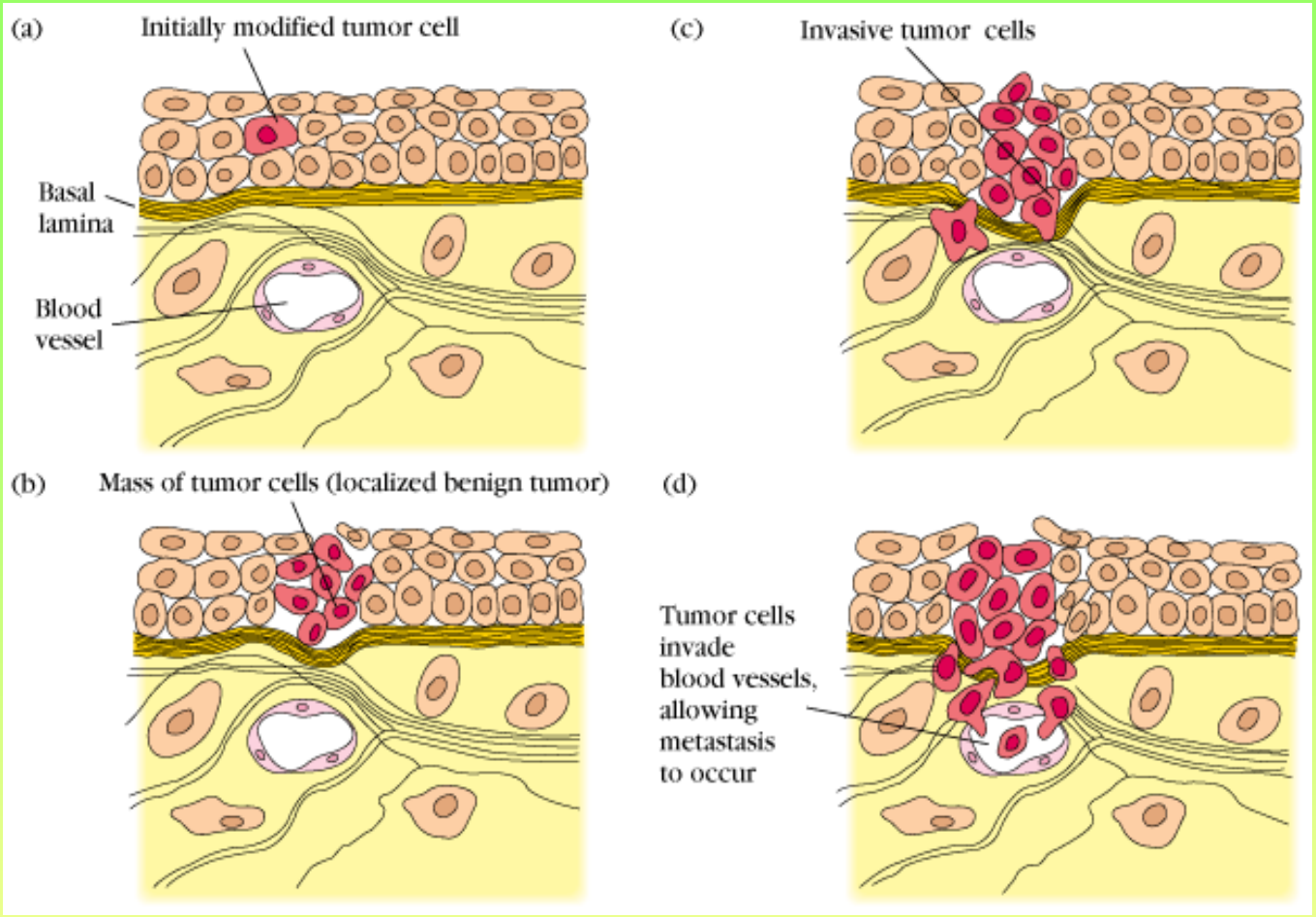
Steven A. Rosenberg, M.D., Ph.D., is a pioneering American surgeon and oncologist known for developing cancer immunotherapy, including adoptive cell transfer and IL-2 treatment, which have led to durable regressions in advanced cancer patients. While widely considered a pioneer worthy of the honor, he did not win the Nobel Prize in 2012.



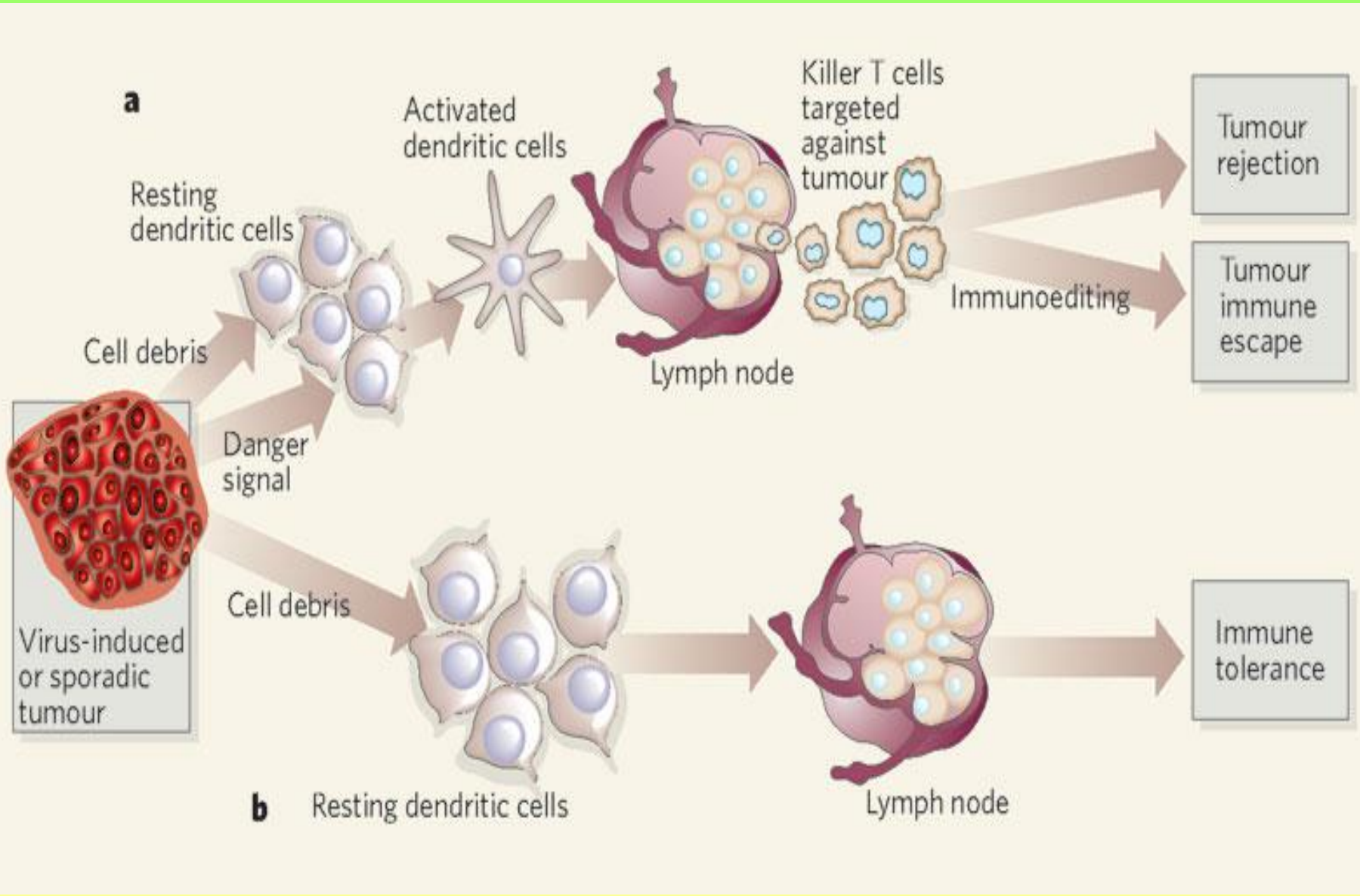


James P. Allison, PhD **Tasuku Honjo**, MD, PhD

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.



- 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)


a
Activated dendritic cells
Killer T cells targeted against tumour
Tumour rejection
Resting dendritic cells
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

Immune response against tumors

- Components of all innate, natural and adaptive immunity
- T cell mediated immune responses (CD8+, CD4+Th1, γδT cells, NK, NK T cells, iNKT, MAIT, iγδT cells)
- Macrophage mediated immune response
- Immunoglobulin mediated (ADCC)
- Network of cytotoxic cytokines

The whole network of the innate, natural and adaptive immune system participate in defence against tumors!

Tumor Specific Antigen

- **TSA – mutations of somatic cells induced by chemical carcinogenesis, viruses, x-rays or spontaneous mutations**

- **Each carcinogenic factor induces a unique and specific class of antigens.**

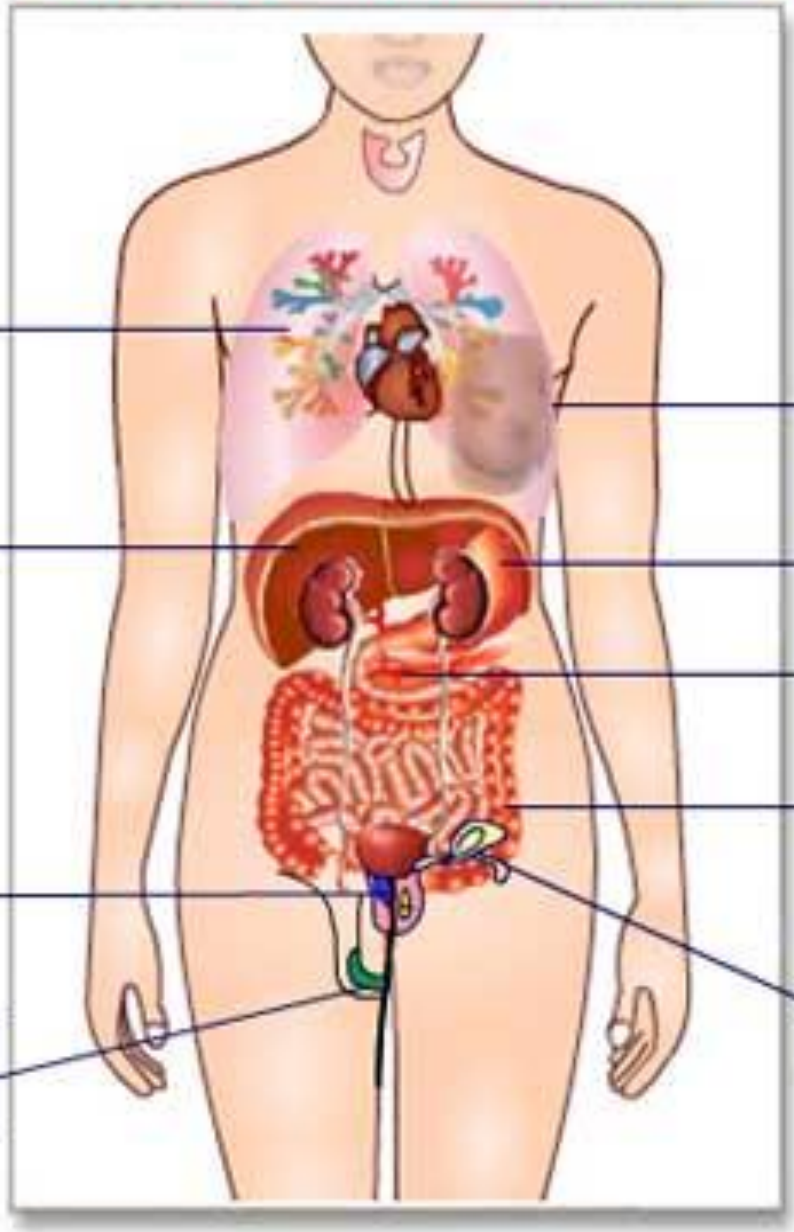
- **TSA is the result of somatic mutations which is recognized (according to the individual MHC haplotype) by the immune system.**

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, but 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

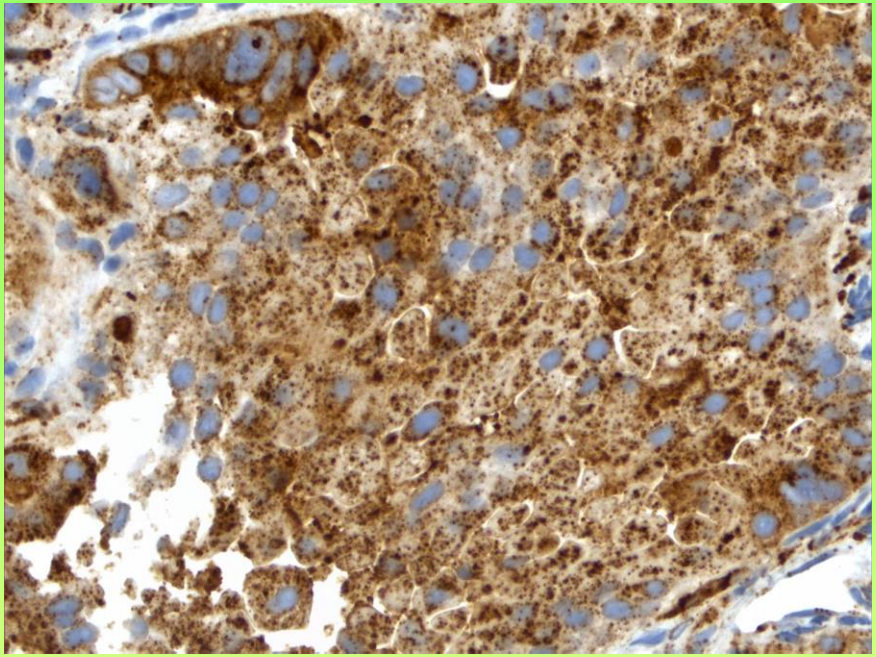
Pancrease Cancer
CA125,CEA

Colon Cancer
CEA

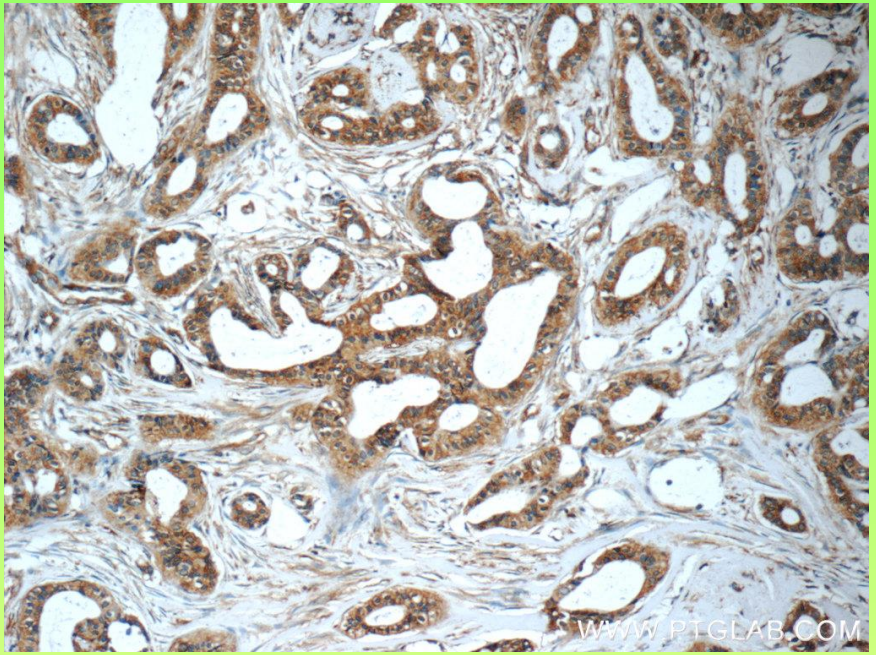
Ovaries Cancer
CA125,CEA

Often tumor markers

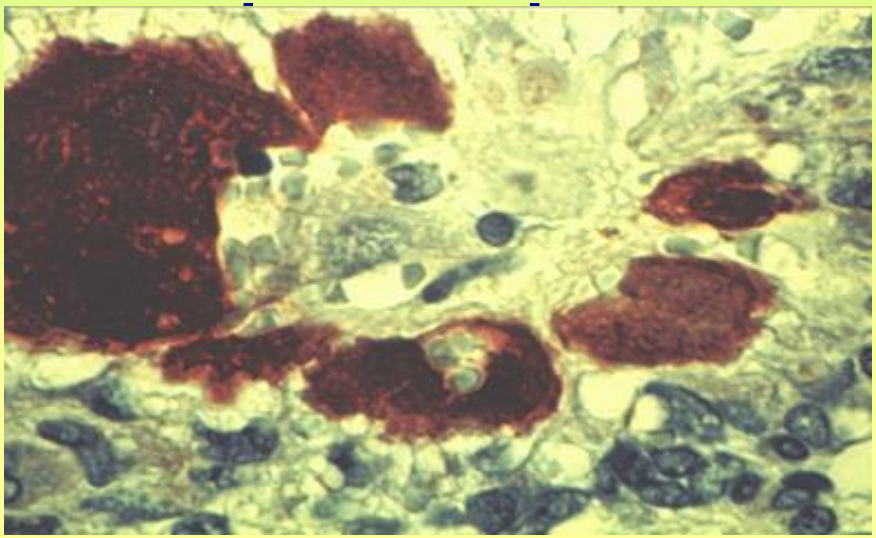
Tumor markers	Abbreviation	Oncological application
Alfa-foetoprotein	AFP	Liver and germ cell tumors
Cancer antigen 125	CA 125	ovarian tumors
Cancer antigen 15,3	CA 15,3	Breast cancer
Cancer antigen 72,4	CA 72,4	Gastric cancer
Cancer antigen 19,9	CA 19,9	Pancreatic cancer
Carcinoembrional antigen	CEA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



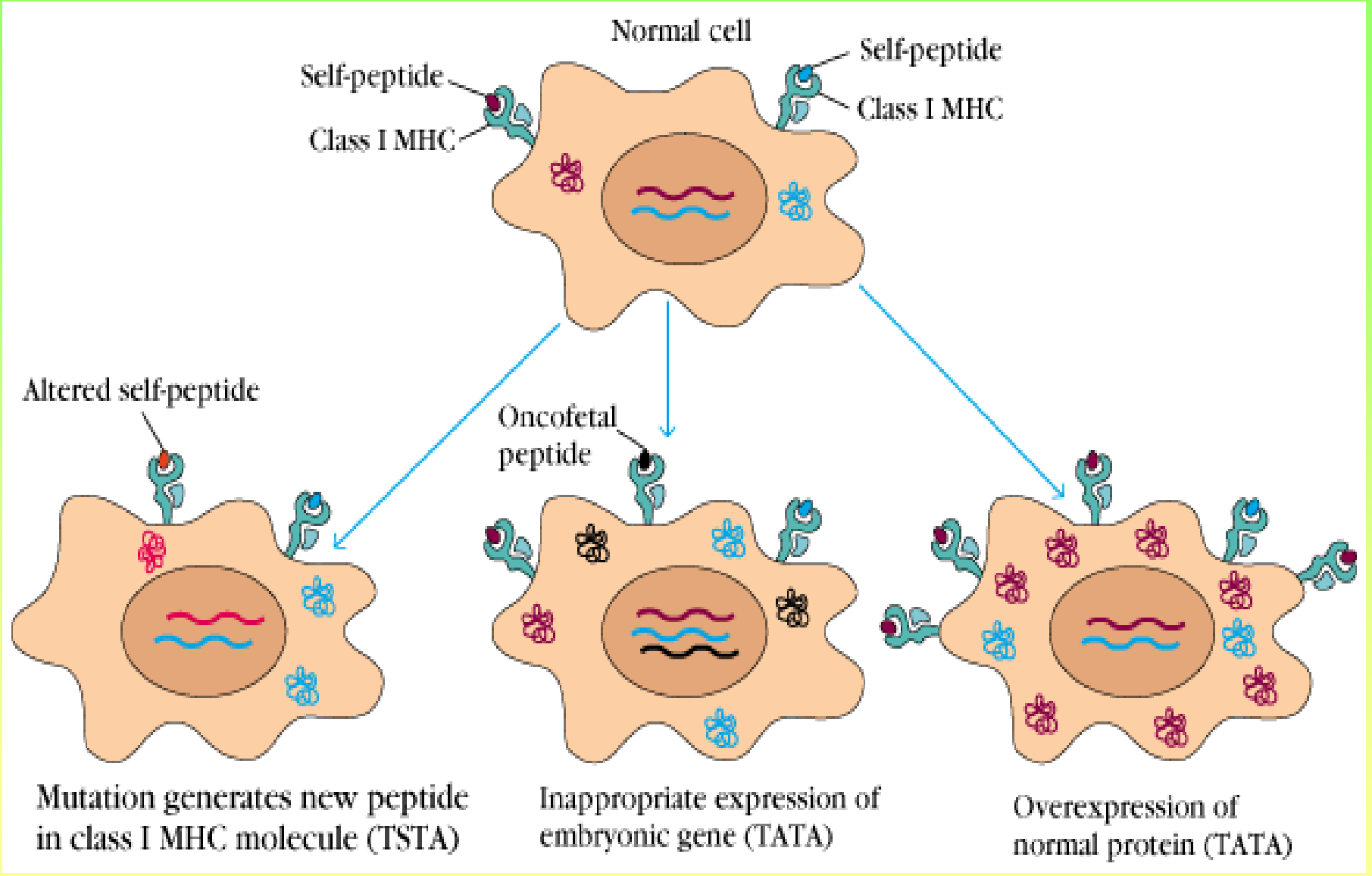
Naspin A in bone metastasis of lung



LGALS3BP Galectin 3 binding in breast cancer metastasis



hCGβ in choriocarcinoma


Normal cell
Self-peptide
Class I MHC
Self-peptide
Class I MHC
Altered self-peptide
Oncofetal peptide
Mutation generates new peptide in class I MHC molecule (TSTA)
Inappropriate expression of embryonic gene (TATA)
Overexpression of normal protein (TATA)

Tumor-specific antigen – antigen expressed on tumor cells but not on normal cells.

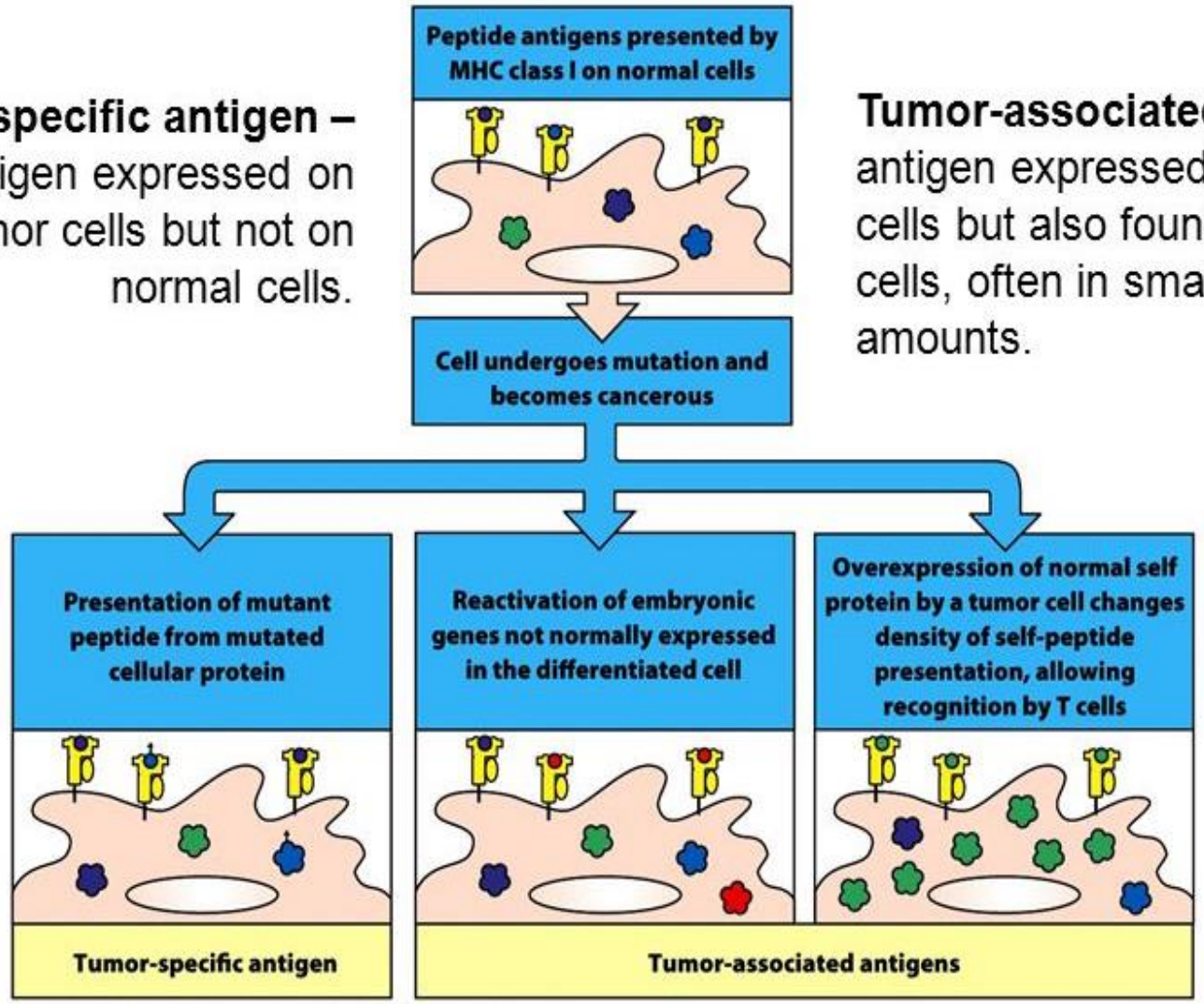
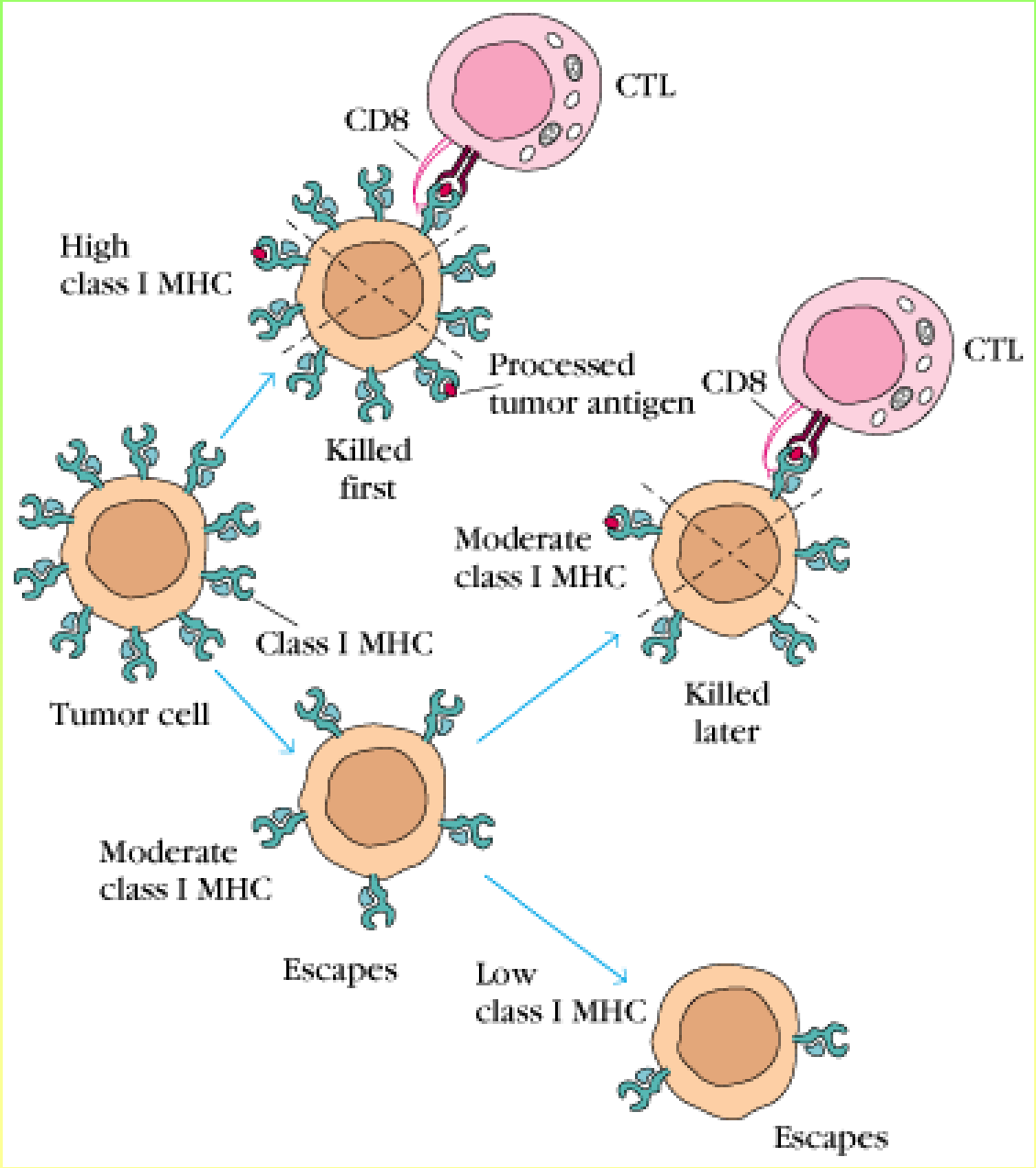


Figure 16.9 The Immune System, 3ed. (© Garland Science 2009)

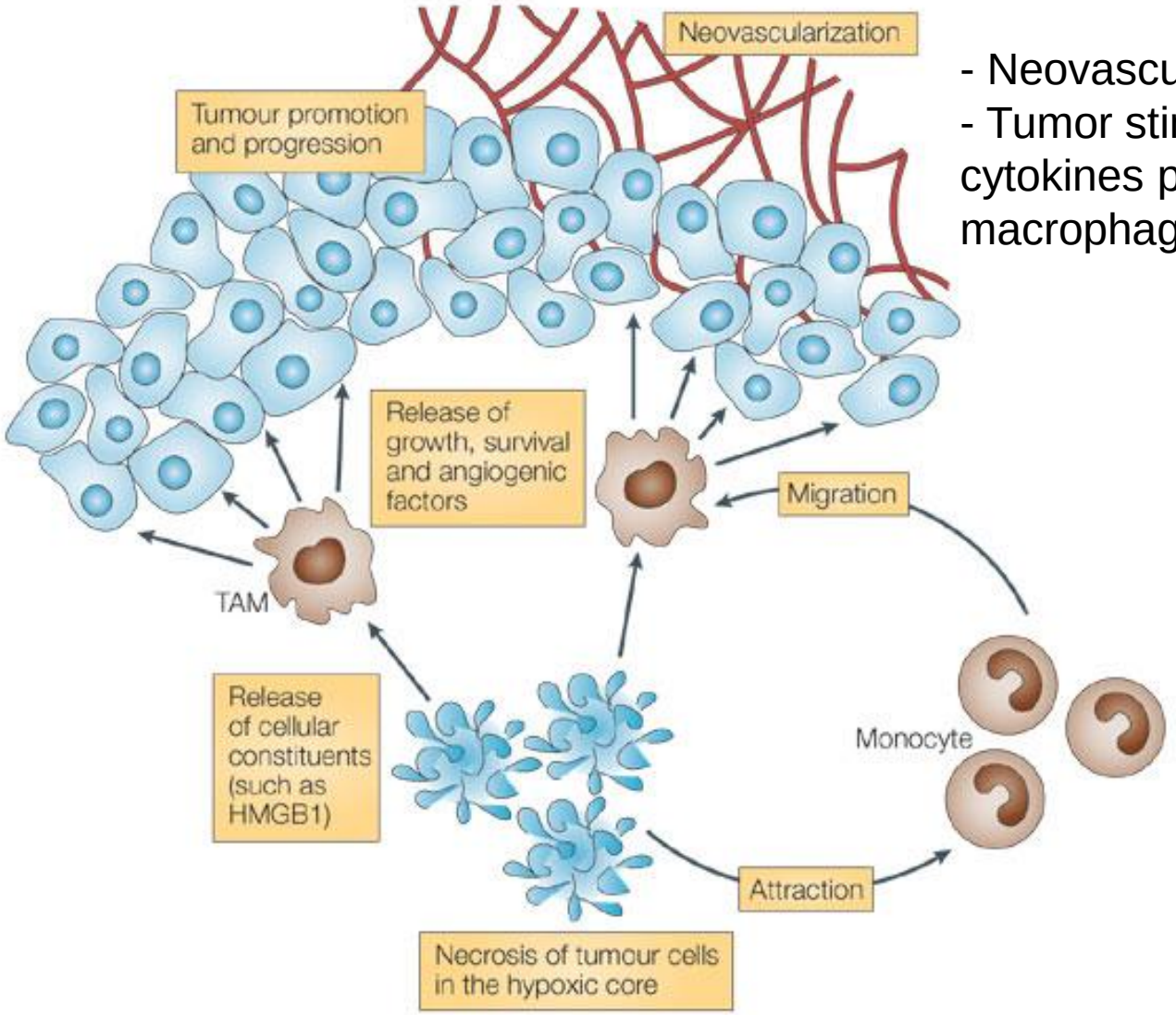
Tumor-associated antigen – antigen expressed on tumor cells but also found on normal cells, often in smaller amounts.

„Tumor escape”

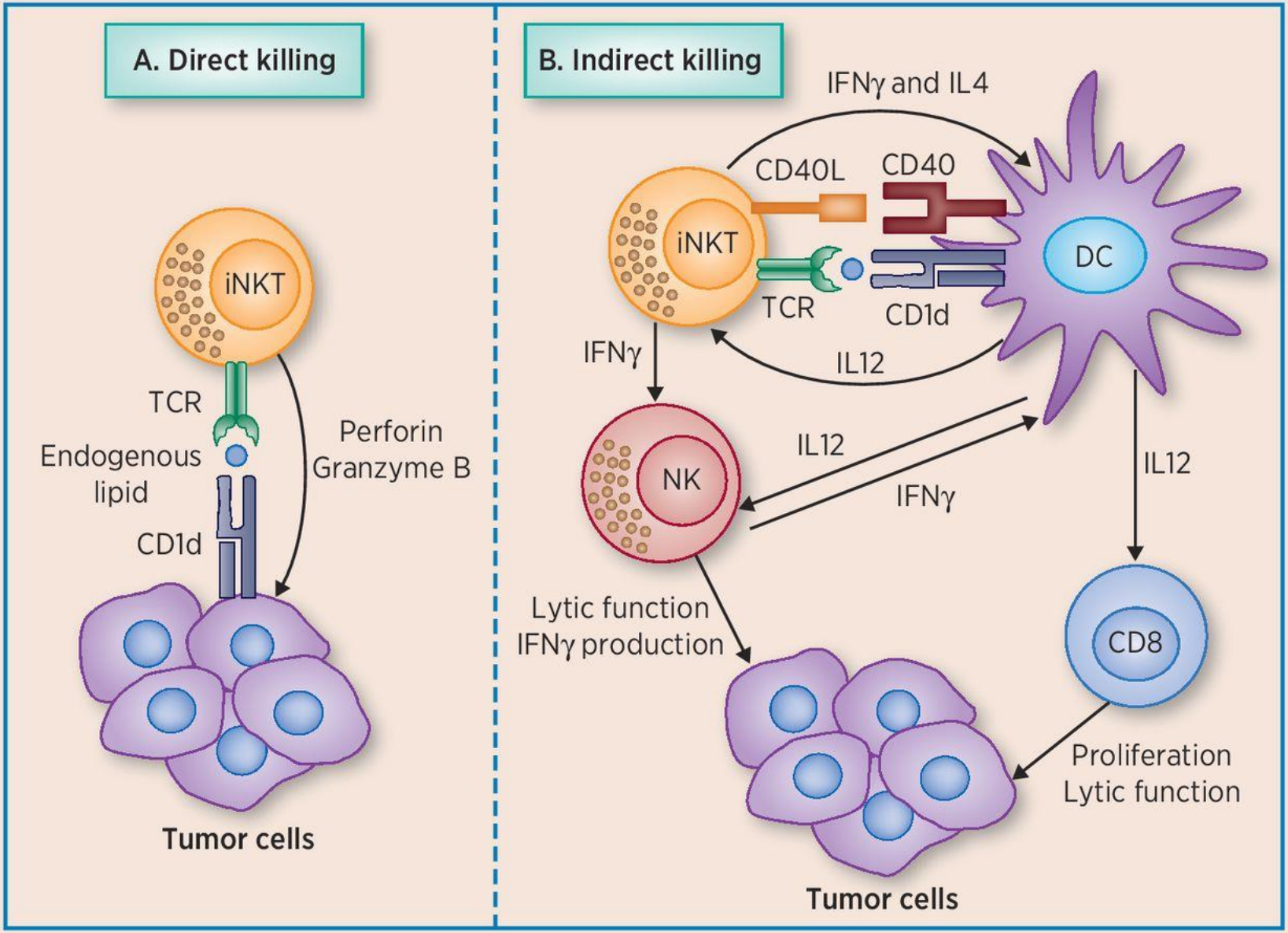
- **Downregulation or owerexpression of MHC class I.**
- **Owerexpression of FcRs.**
- **Failed cytokine receptors.**
- **Masking and blocking glykoproteines.**
- **Production of tumor associated cytokines.**
- **Blocking cytokines produced by macrophages or dendritic cells.**
- **Activation of T**reg **cells.**
- **Expression of blocking adhesion molecules.**

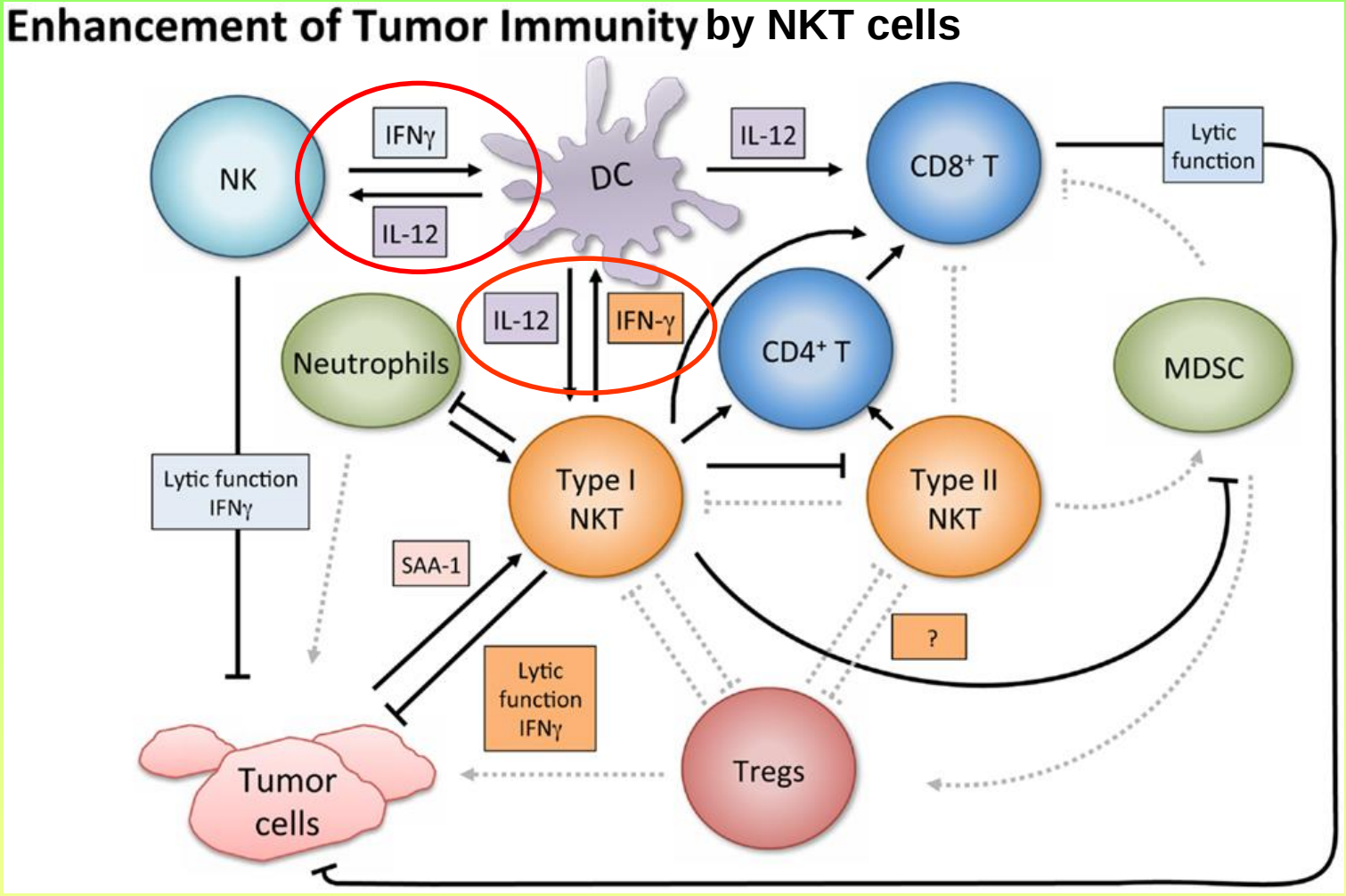

CTL
CD8
High
class I MHC
Processed
tumor antigen
Killed
first
CTL
CD8
Moderate
class I MHC
Killed
later
Class I MHC
Tumor cell
Moderate
class I MHC
Escapes
Low
class I MHC
Escapes

Tumor infiltrating macrophages: „double edged sword”

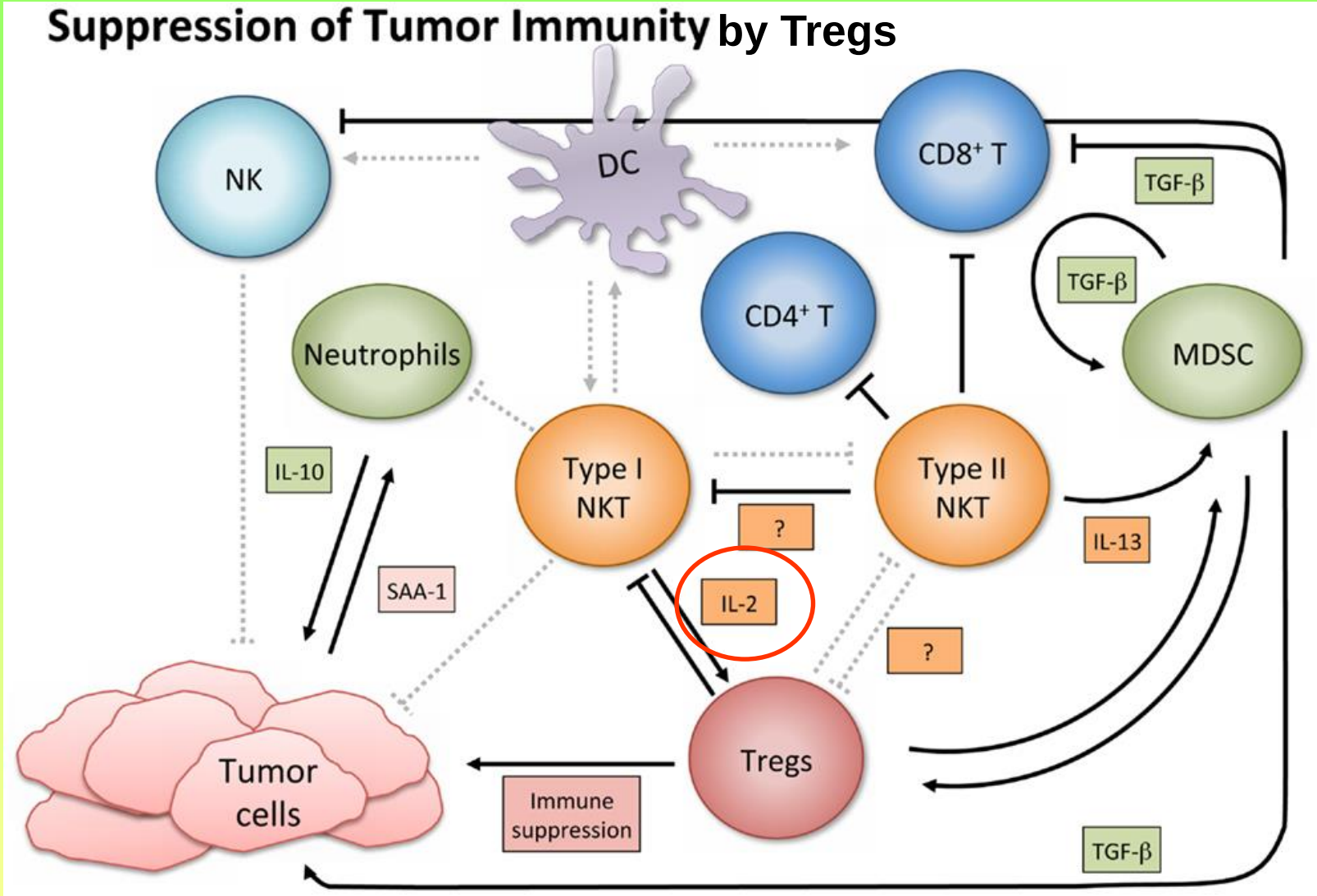


- Neovascularization
- Tumor stimulating cytokines produced by macrophages



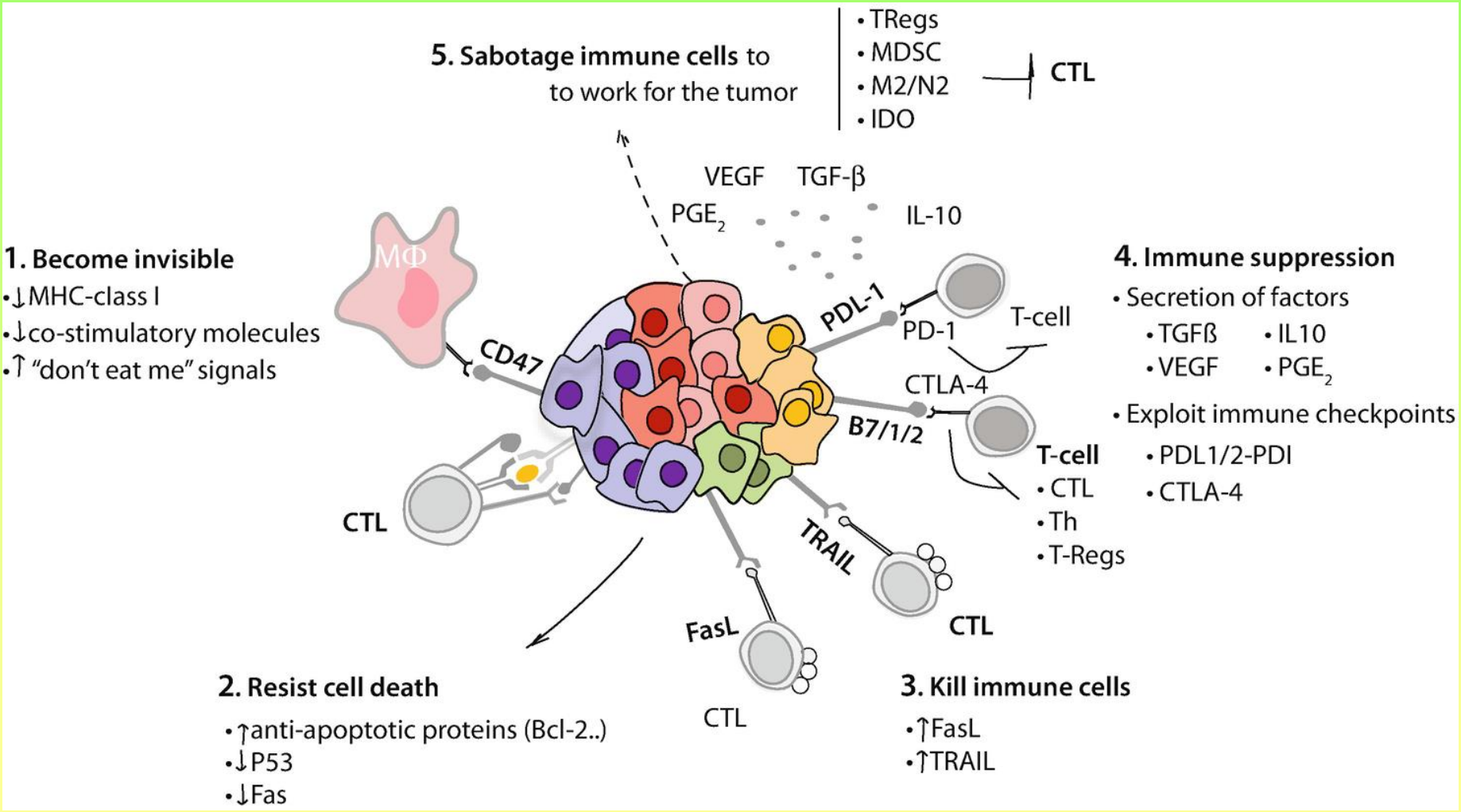


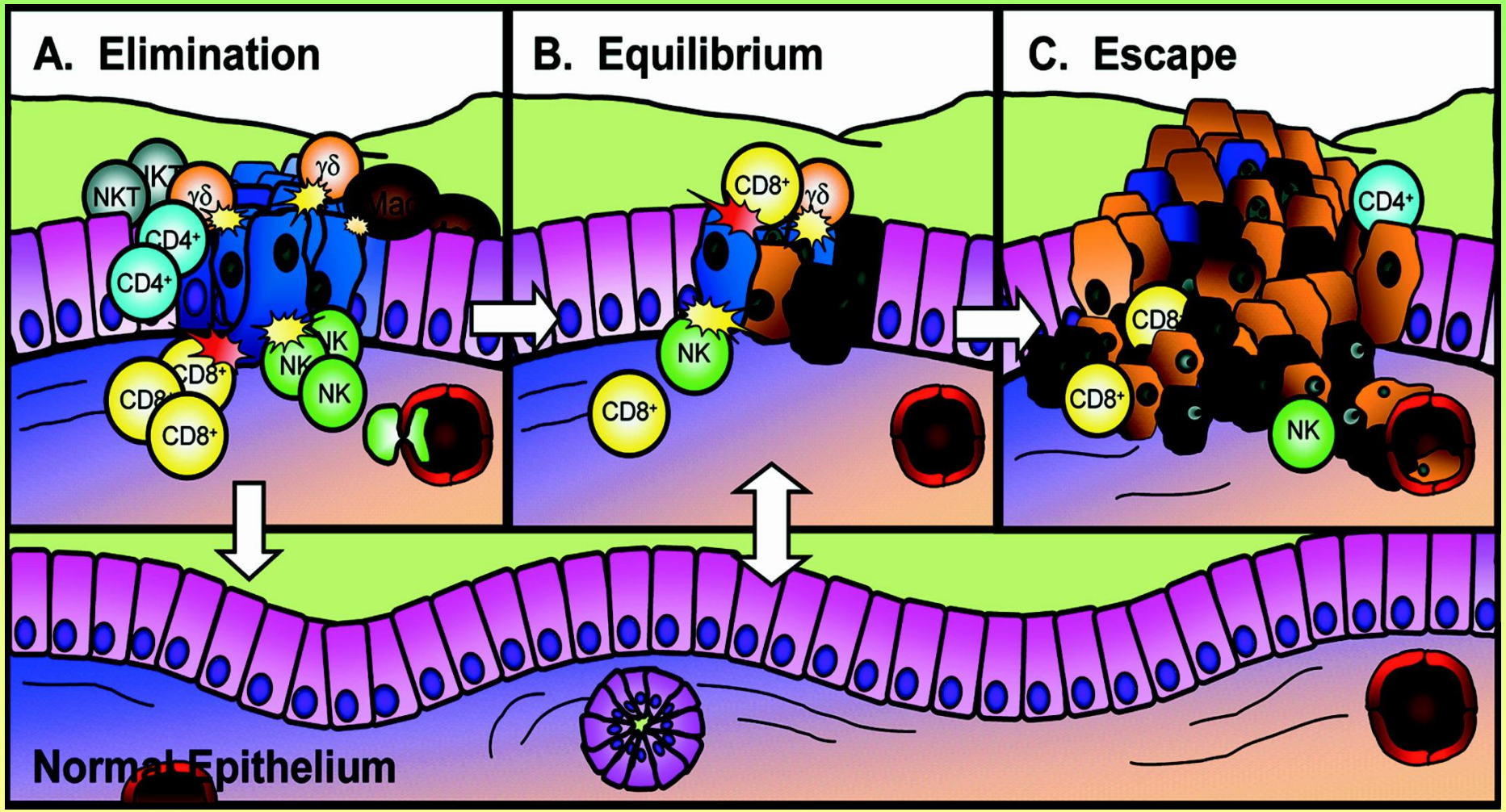
Upon antigenic stimulation, type I NKT cells produce **IFN-γ** activate both CD8+ T cells and DCs. NKT cells specifically induce DC maturation by engaging the CD1d-TCR complex and CD40–CD40L interaction and **upregulate costimulatory receptors of CD8+ T cells**. Additionally, **IL-12** production by DCs stimulates NK, NKT, and other T cells to produce more IFN-γ and the two cytokines together significantly impact the activation of downstream effector populations.



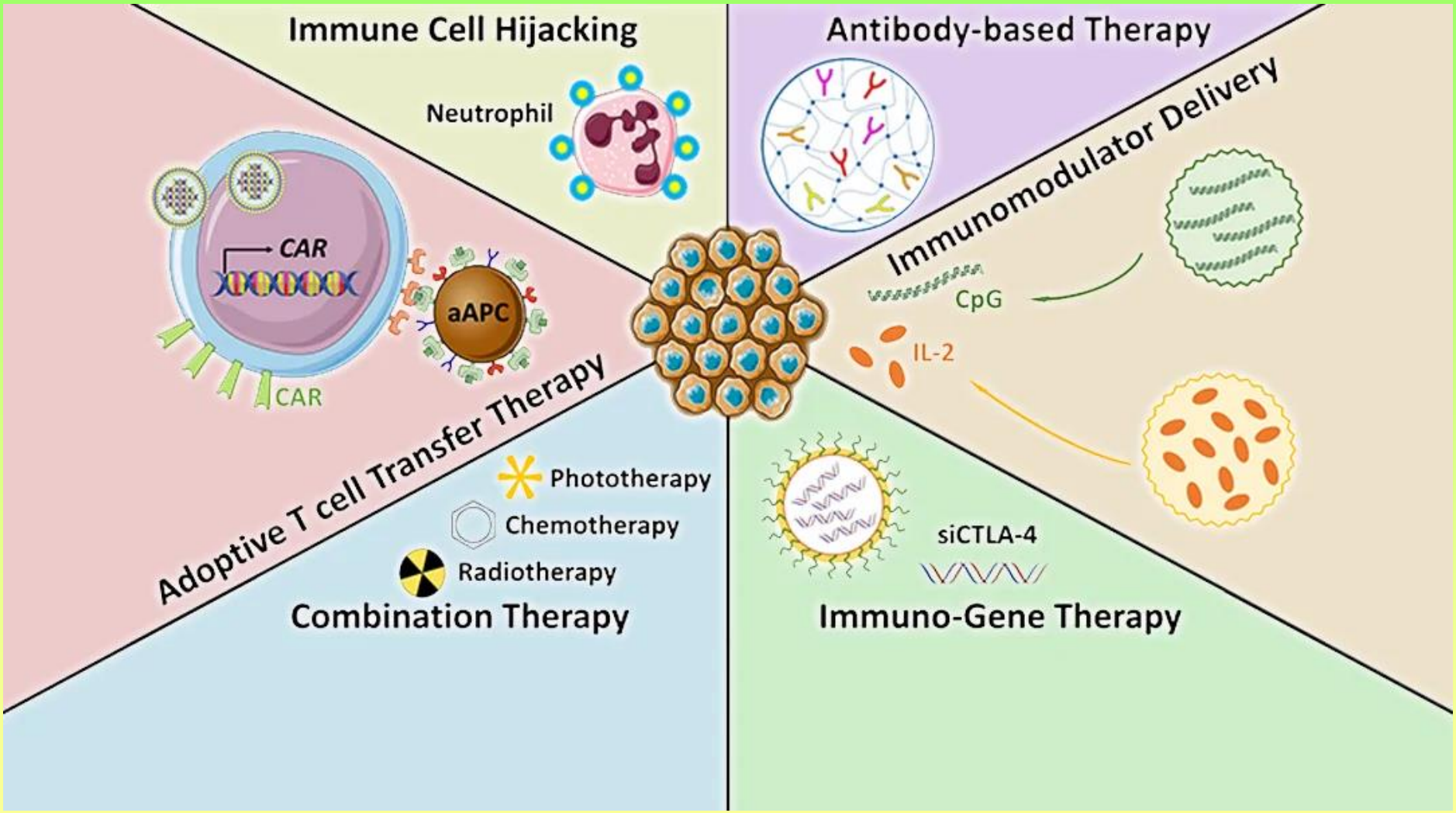
Activated type I NKT cells can support immunosuppressive Tregs through **IL-2** production, and they are then suppressed by Tregs in a cell-contact-dependent manner. Treg cells can then suppress CD8+ and CD4+ T cells and NK cells as well at the same time.

Cancer Immunoediting and Hijacking of the Immune System




A. Elimination
B. Equilibrium
C. Escape
NKT
γδ
CD4+
CD8+
NK
Normal Epithelium

Cancer immunotherapy



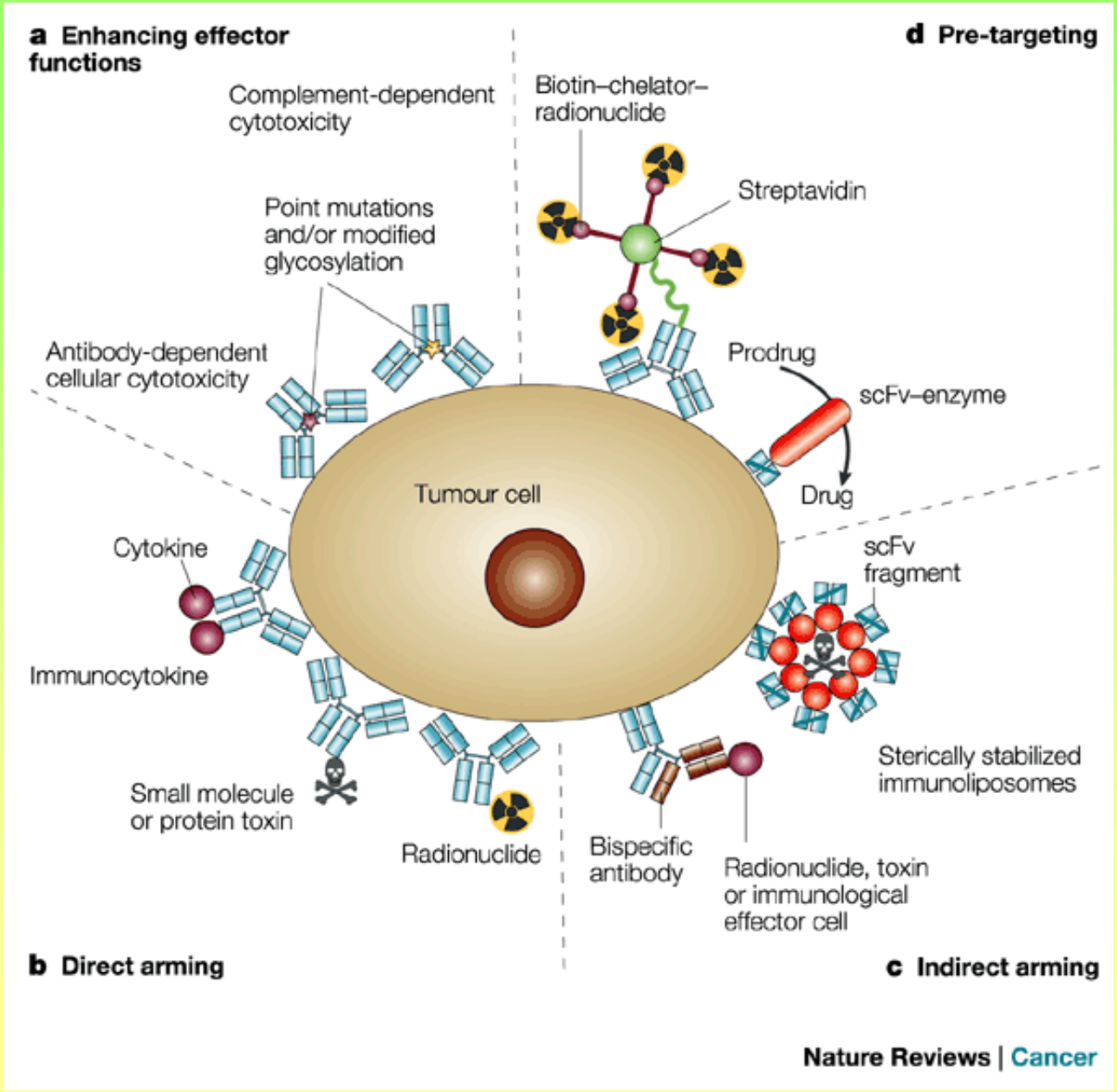
Cancer immunotherapy is an emerging treatment that harnesses the power of a patient's own immune system to fight cancer.

Cancer immunotherapy

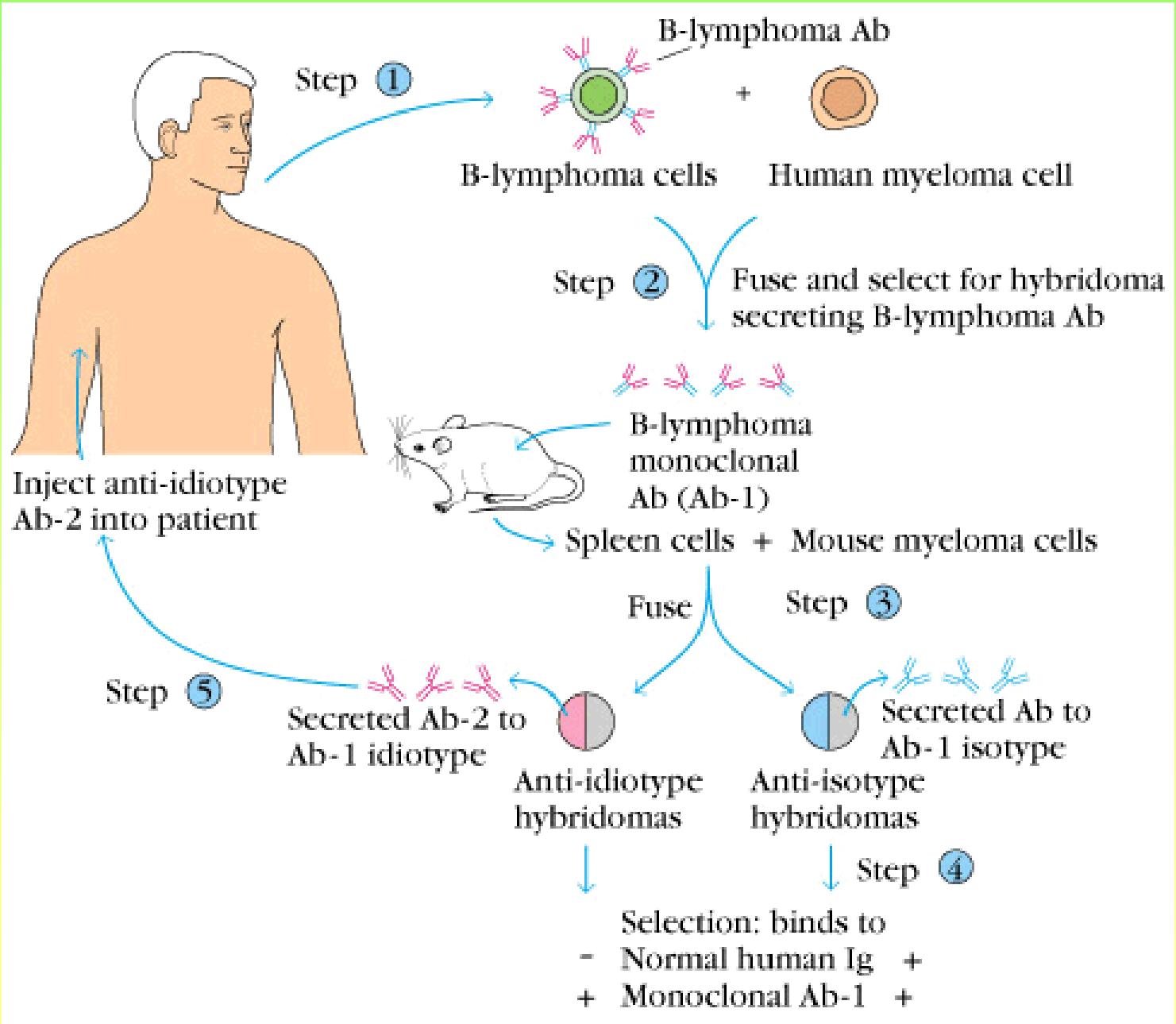
Complementary therapeutic tools after the surgical, chemotherapeutic and/or irradiation treatments:

- Therapeutic monoclonal antibodies
- Checkpoint inhibitors (CTLA4/PD-1/PDL-1)
- Immuno-modulation
- Cancer vaccines
- Oncolytic viruses

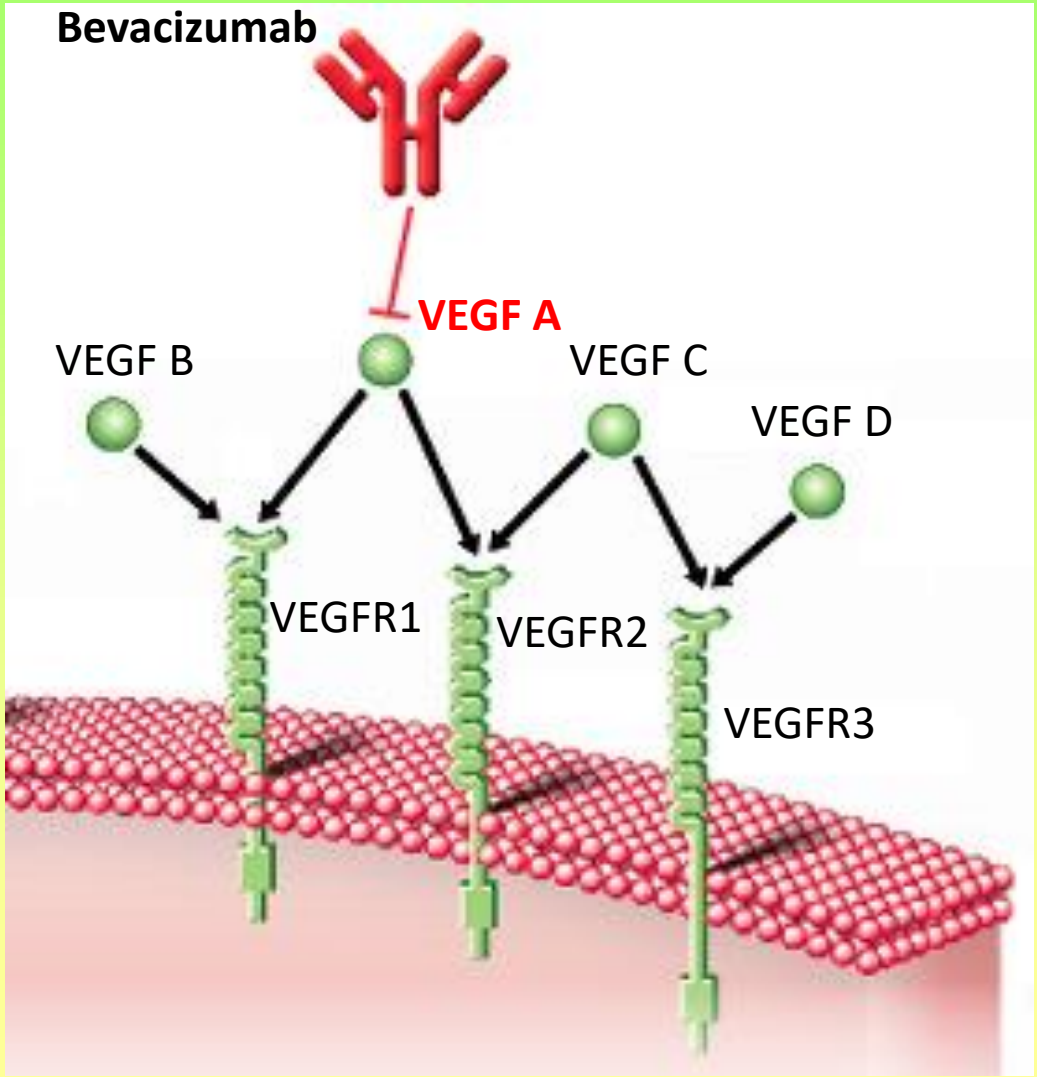
Monoclonal antibodies for therapeutic use



Anti-idiotype therapy of B cell malignant lymphomas



Therapeutic monoclonal antibodies I.

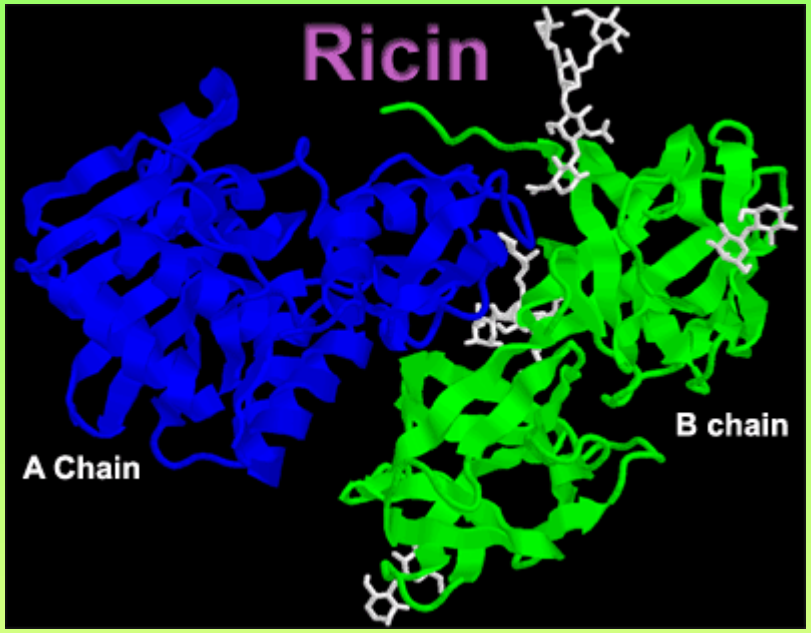


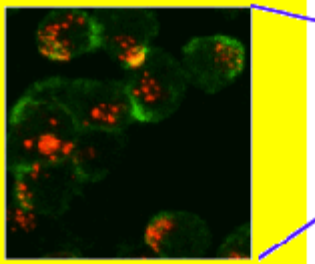
Bevacizumab (Avastin®)
Anti-VEGF A antibody

Blockin of angioneogenesis

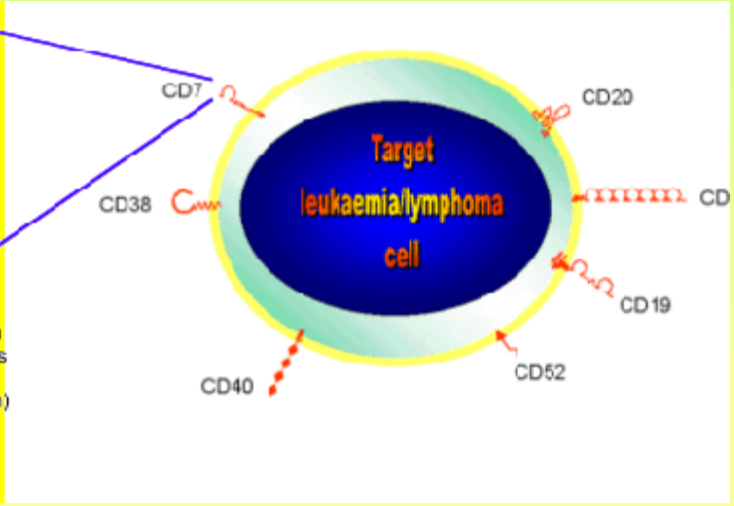
Applicable in some solid tumors:

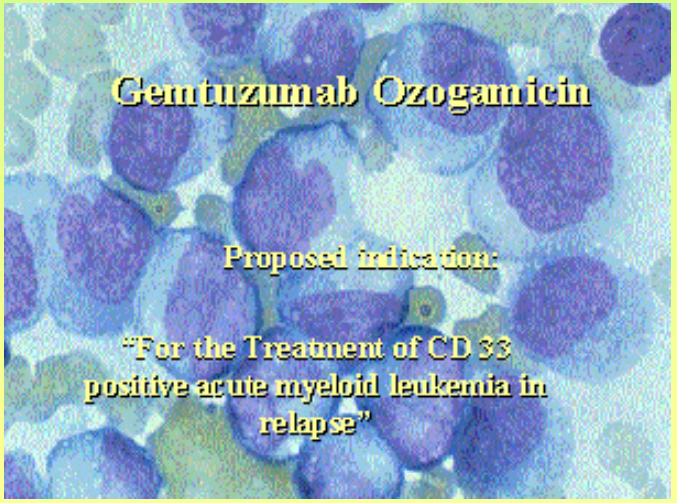
- Colon cancer
- Lung cancer
- Ovarian cancer
- Kidney cancer
- Glioblastoma

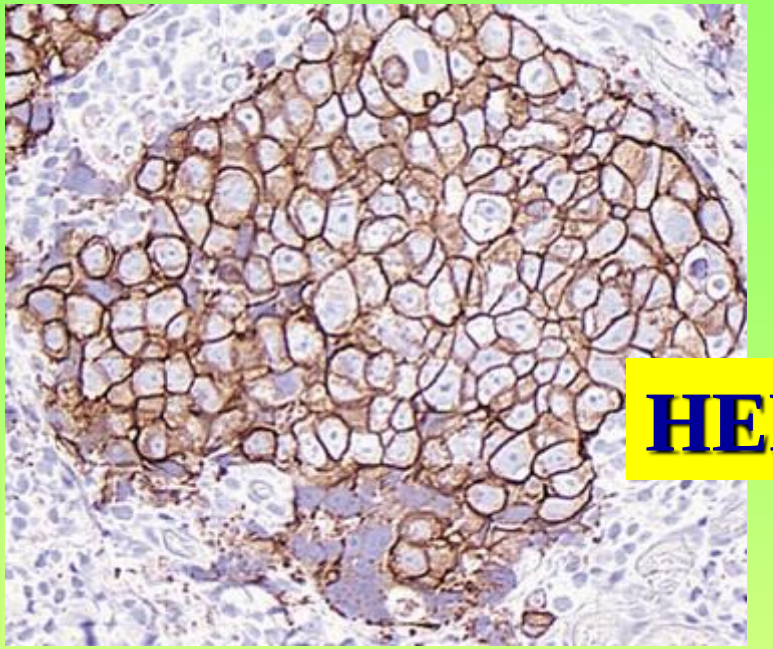




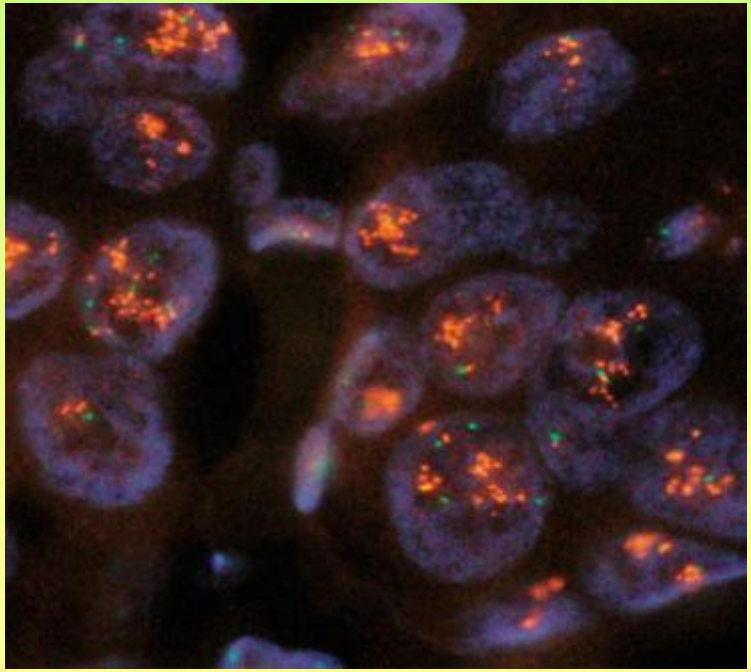
Confocal microscope image showing the internalisation of an anti-CD7 saporin immunctoxin by human T- leukaemia cells into intracellular vesicles (green stain) in relation to the trans-golgi region (red stain)

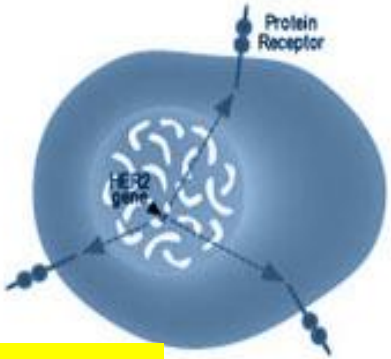






HER-2/neu



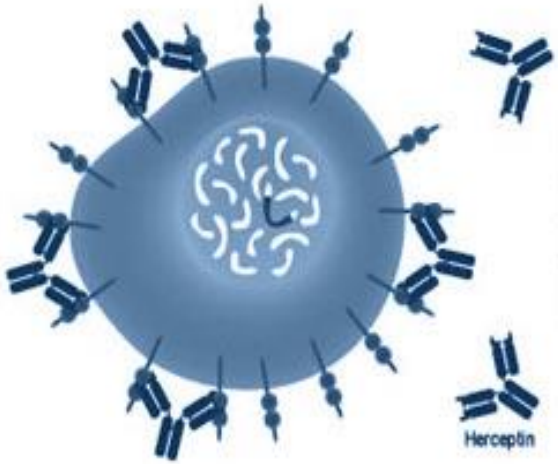


Normal Cell

In normal breast tissue cells, the HER2 gene produces a protein receptor on the cell surface. These growth factor-like receptors are thought to play a role in normal cell growth by signaling the cell to divide and multiply.

HER2 Overexpressing Cancer Cell

Cancerous breast tissue cells that overexpress (or overproduce) the HER2 gene produce extra protein receptors on the cell surface. The higher density of receptors triggers the cell to divide and multiply at an accelerated rate, thus contributing to tumor growth. Approximately 25-30% of all women with metastatic breast cancer overexpress the HER2 protein.



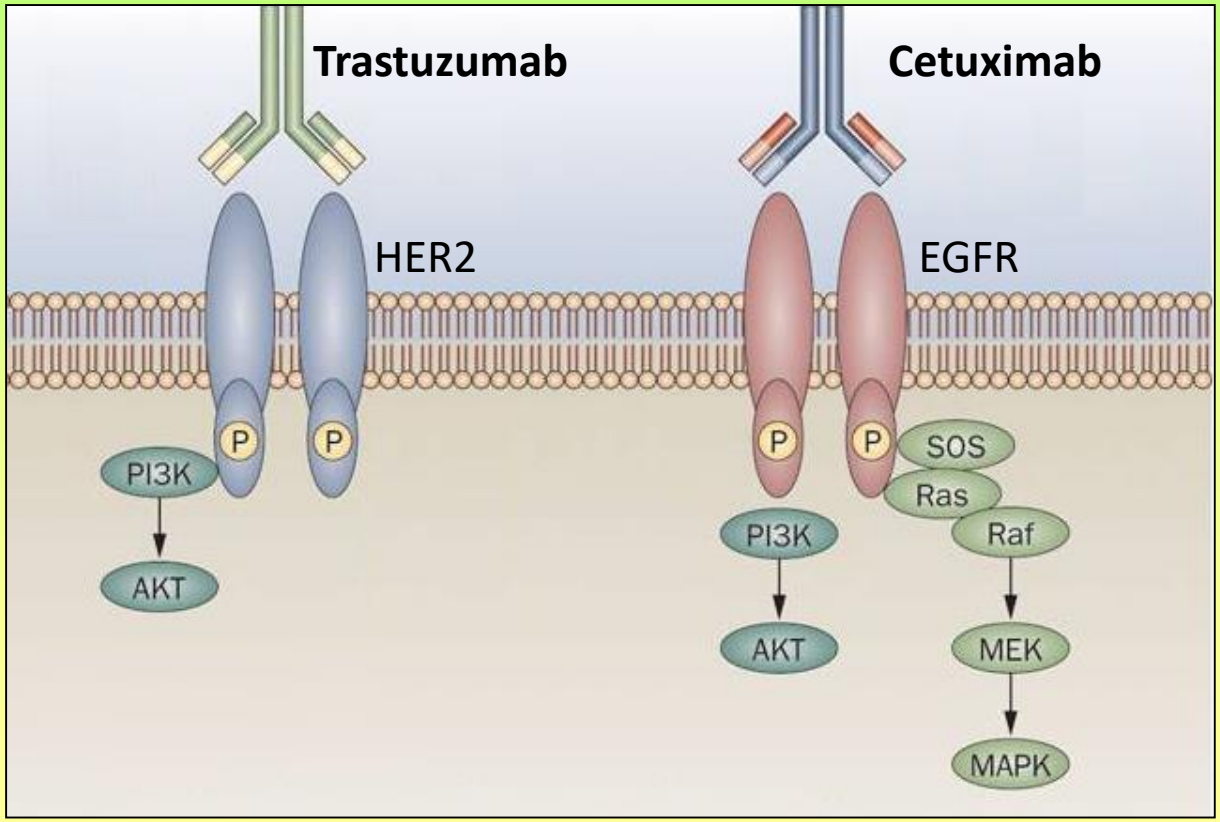
Herceptin® (Trastuzumab)

It is thought that Herceptin (a HER2 antibody) binds to numerous HER2 receptor sites found on the cell surface, blocking the receptor sites and possibly preventing further growth by interrupting the growth signal. As a result, the HER2 antibody may slow progression of the disease.

Therapeutic monoclonal antibodies II.

EGFR blockers:

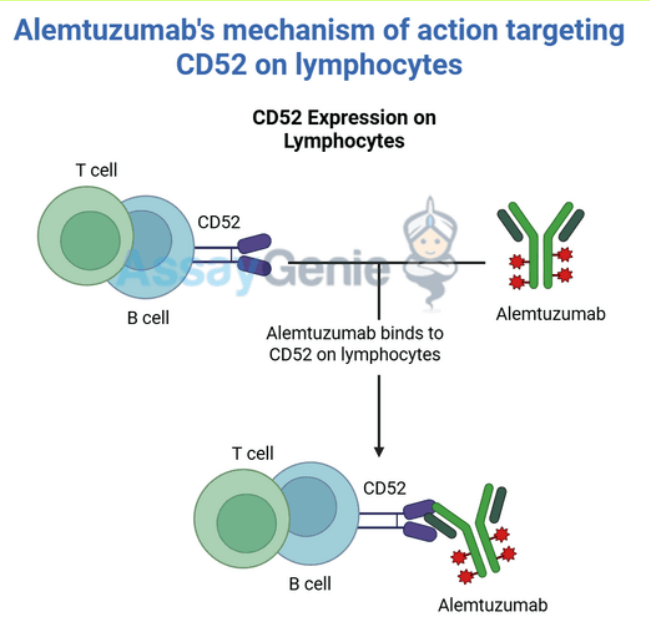
- **Trastuzumab** (Herceptin®): anti-EGFR2 (HER2) → **HER2 positive breast cancer and gastric cancer**
- **Cetuximab** (Erbitux®) → colon cancer, lung cancer, head and neck cancers



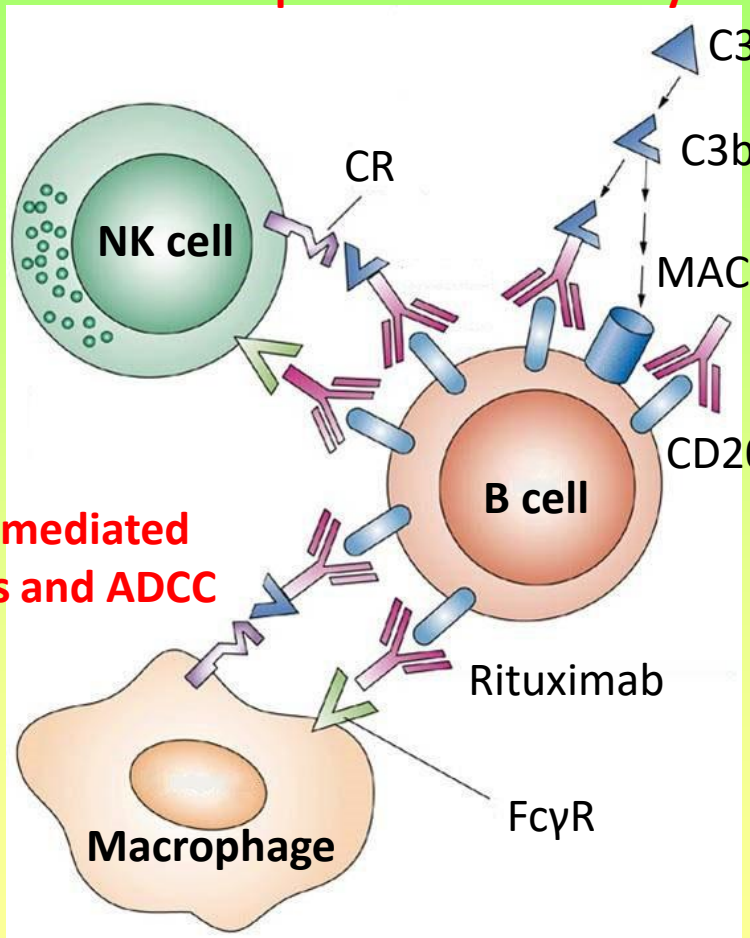
Therapeutic monoclonal antibodies III.

Antibodies against trageted cells:

- **Rituximab** (MabThera®): anti-CD20 → **B cell deplation** (E.g. B cell lymphomas, autoimmune diseases
- **Alemtuzumab:** anti-CD52 → CLL, sclerosis multiplex



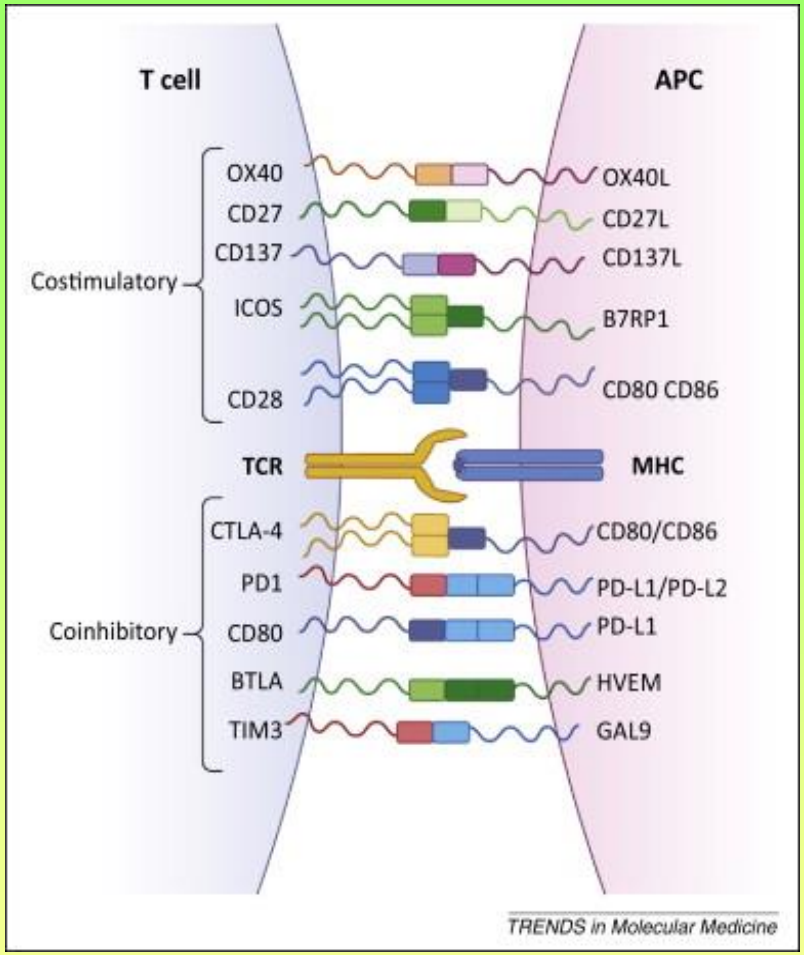
Complement mediated lysis

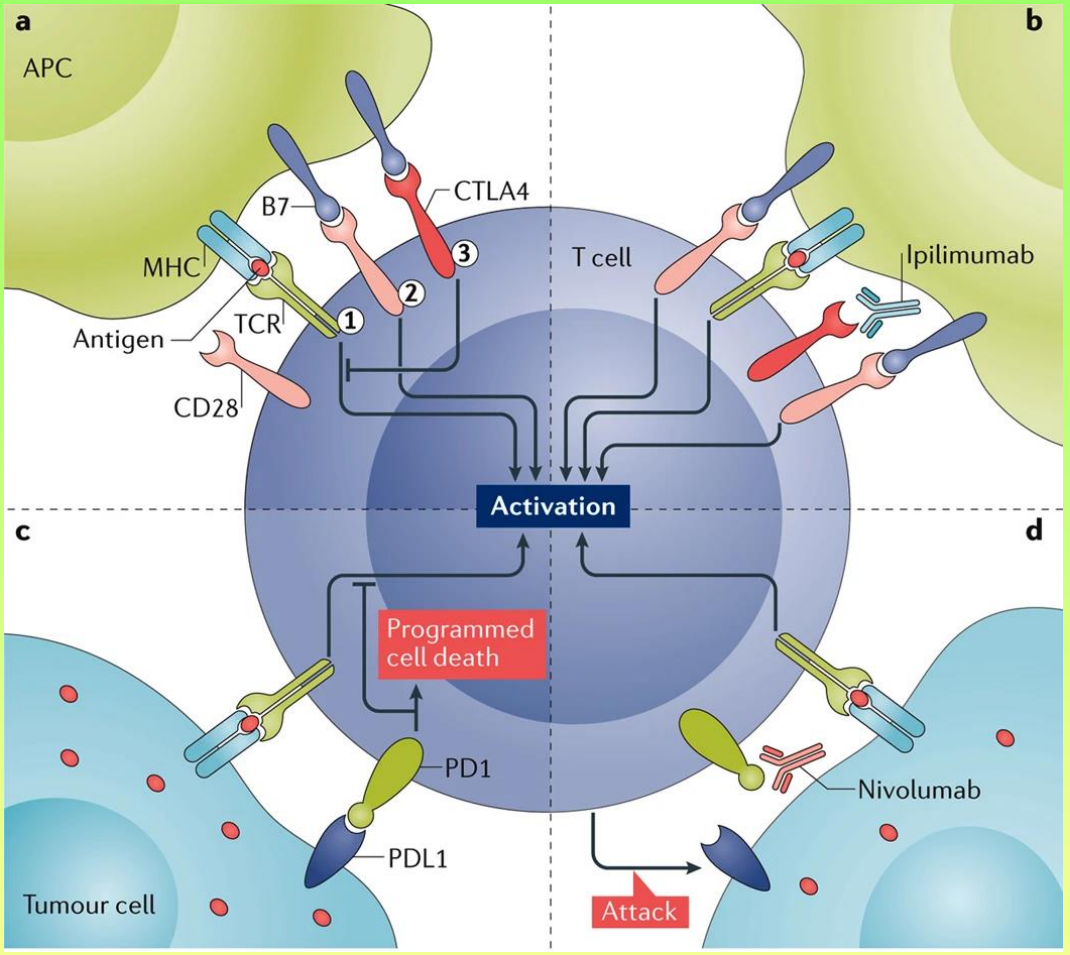


FcγR or CR-mediated phagocytosis and ADCC

Mechanism of action of the Rituximab

Checkpoint inhibitors





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

Blocking the T cell blockade = T cell activation

Therapeutic monoclonal antibodies V.

T cell activating check point inhibitor antibodies

Nivolumab:
Anti-PD1 antibody

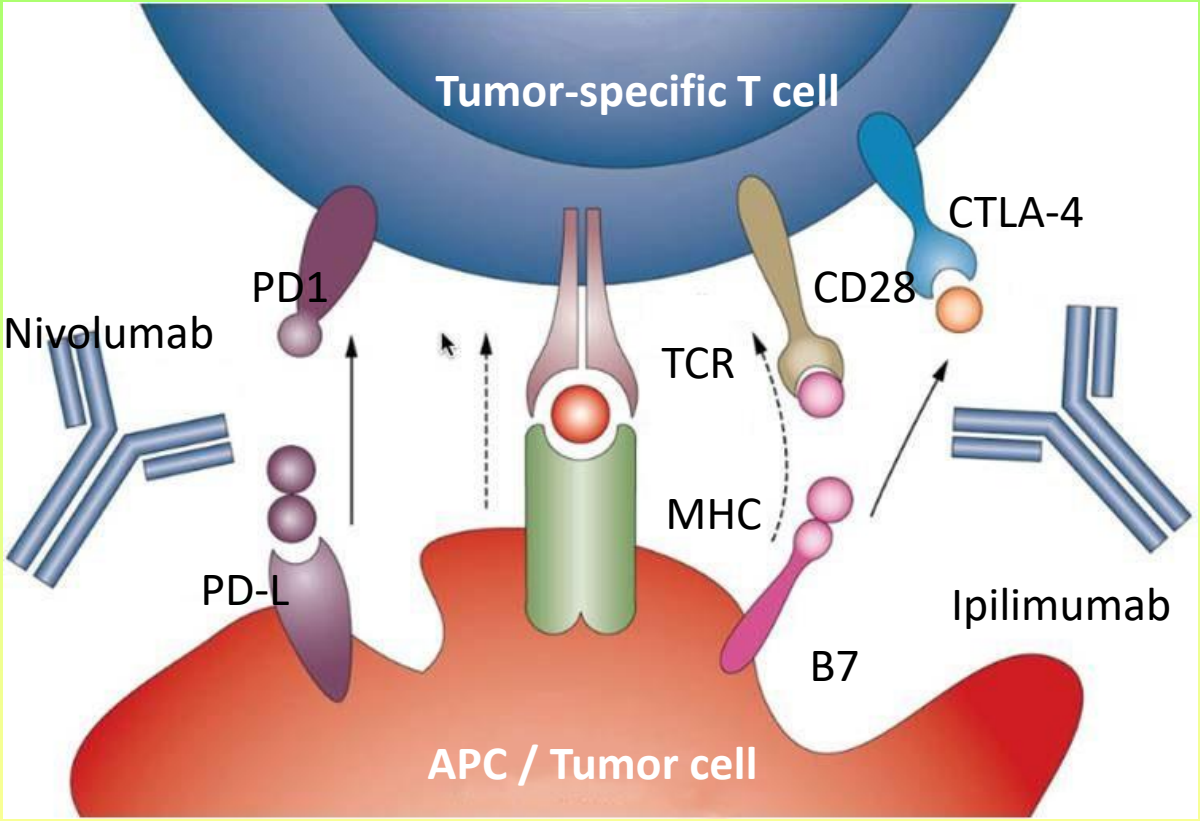
Ipilimumab:
Anti-CTLA-4 antibody

↓

Neutralization of the blocking effects of PD1 and CTLA-4

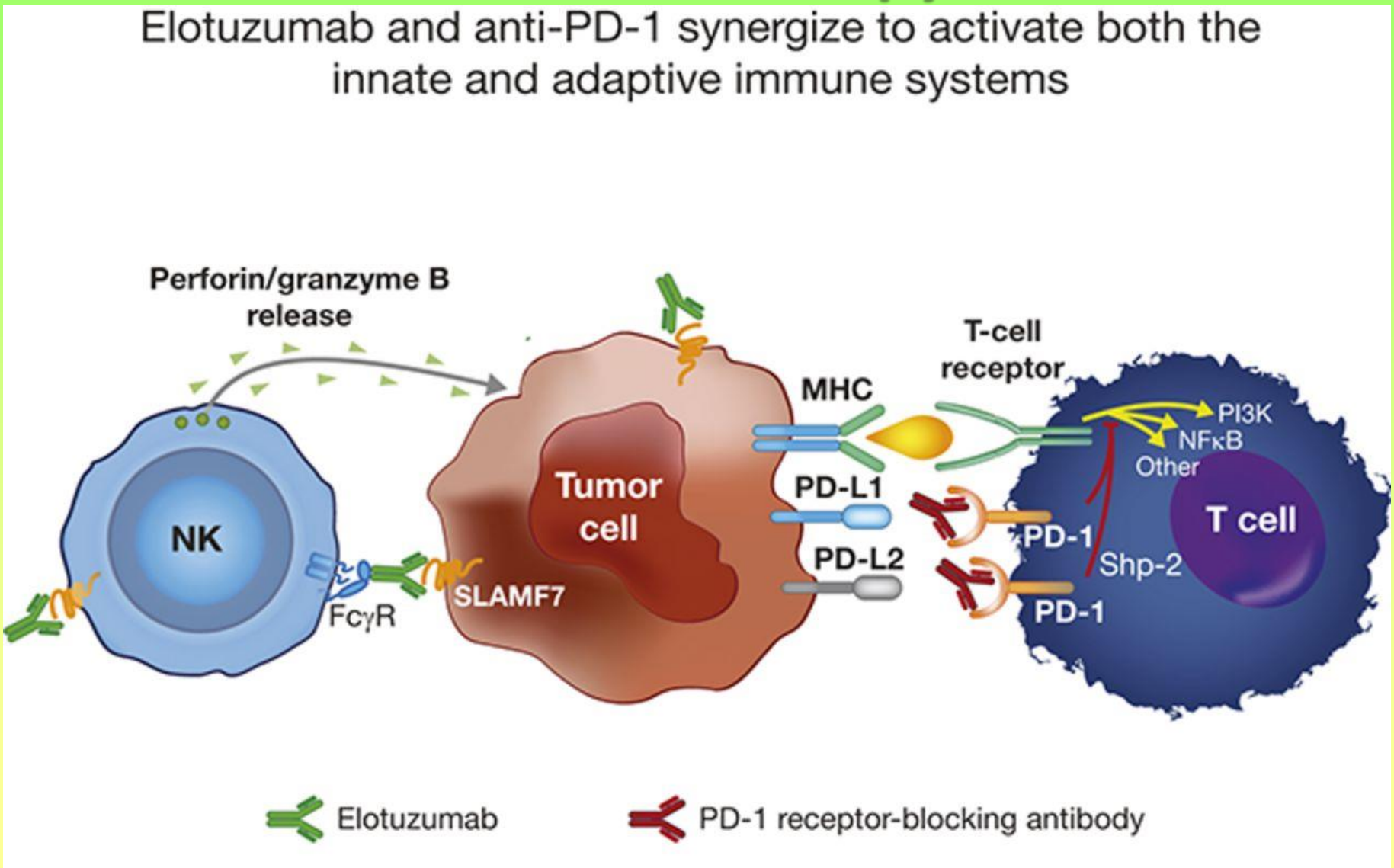
↓

T cell tolerance is decreasing

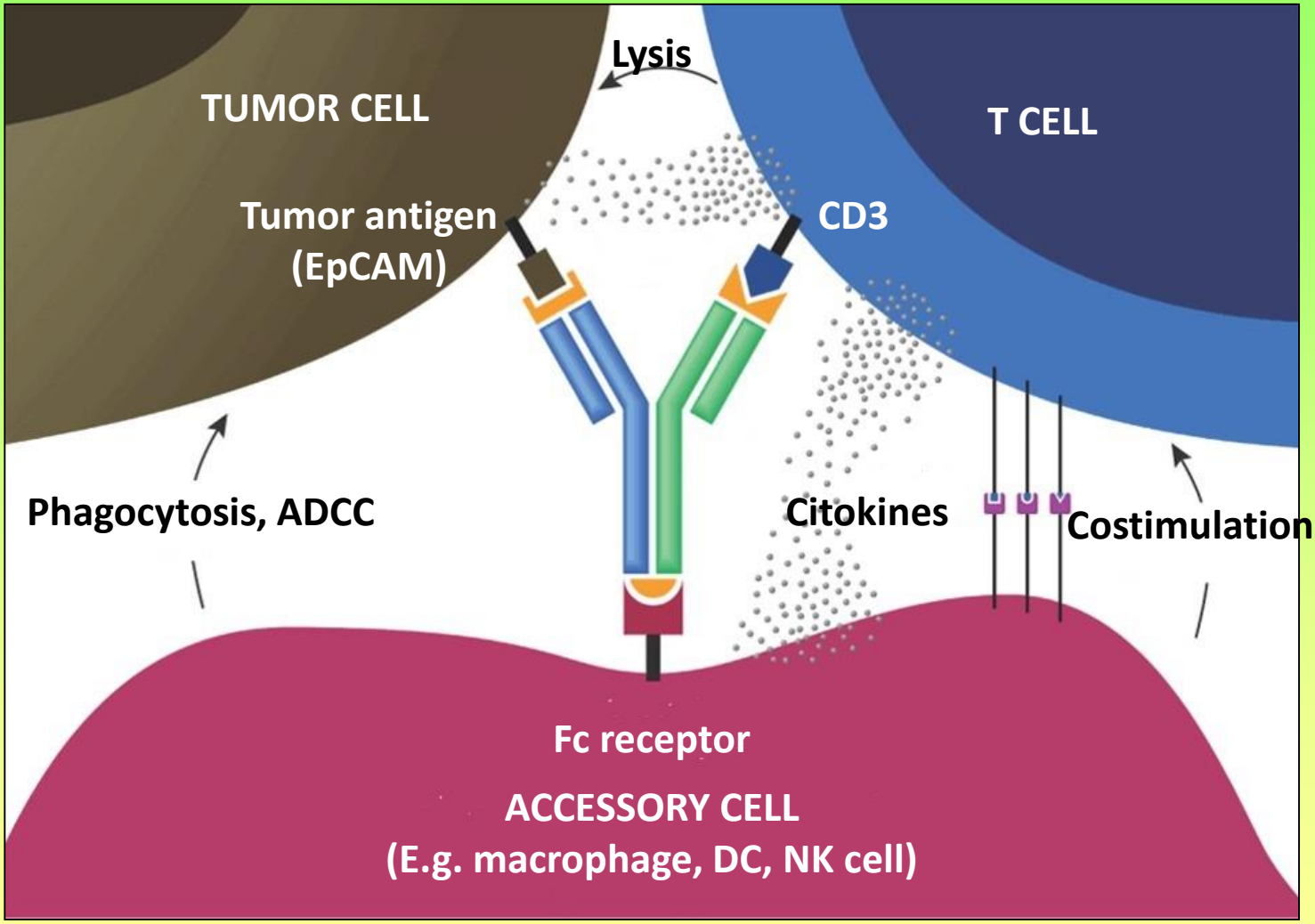


Therapeutic tool in melanoma malignum. (T cells are able to kill tumor cells without inhibition.
Inhibition of inhibitors = activation!)

Combined checkpoint inhibitor and NK activator therapy

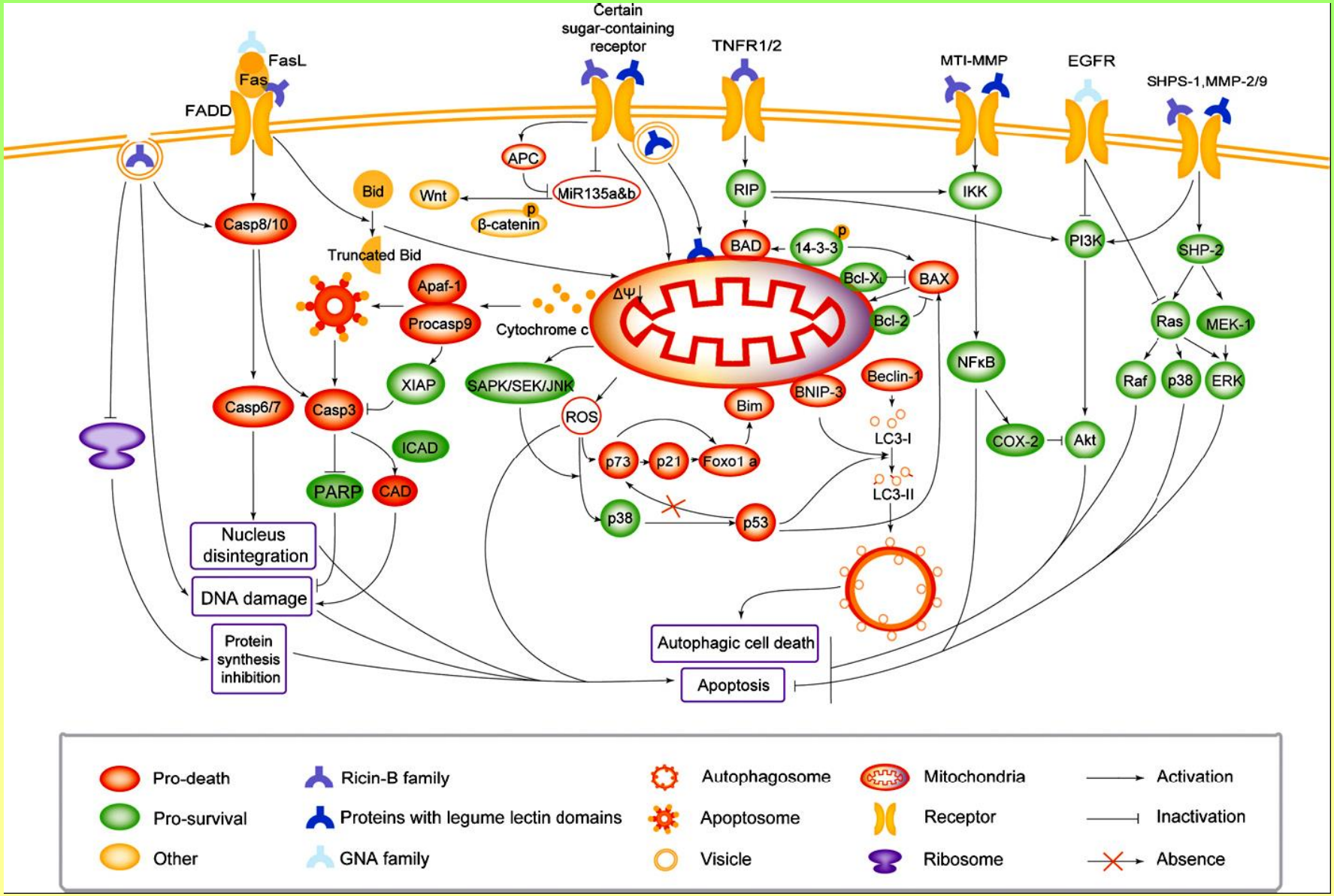


Bispecific therapeutic monoclonal antibodies

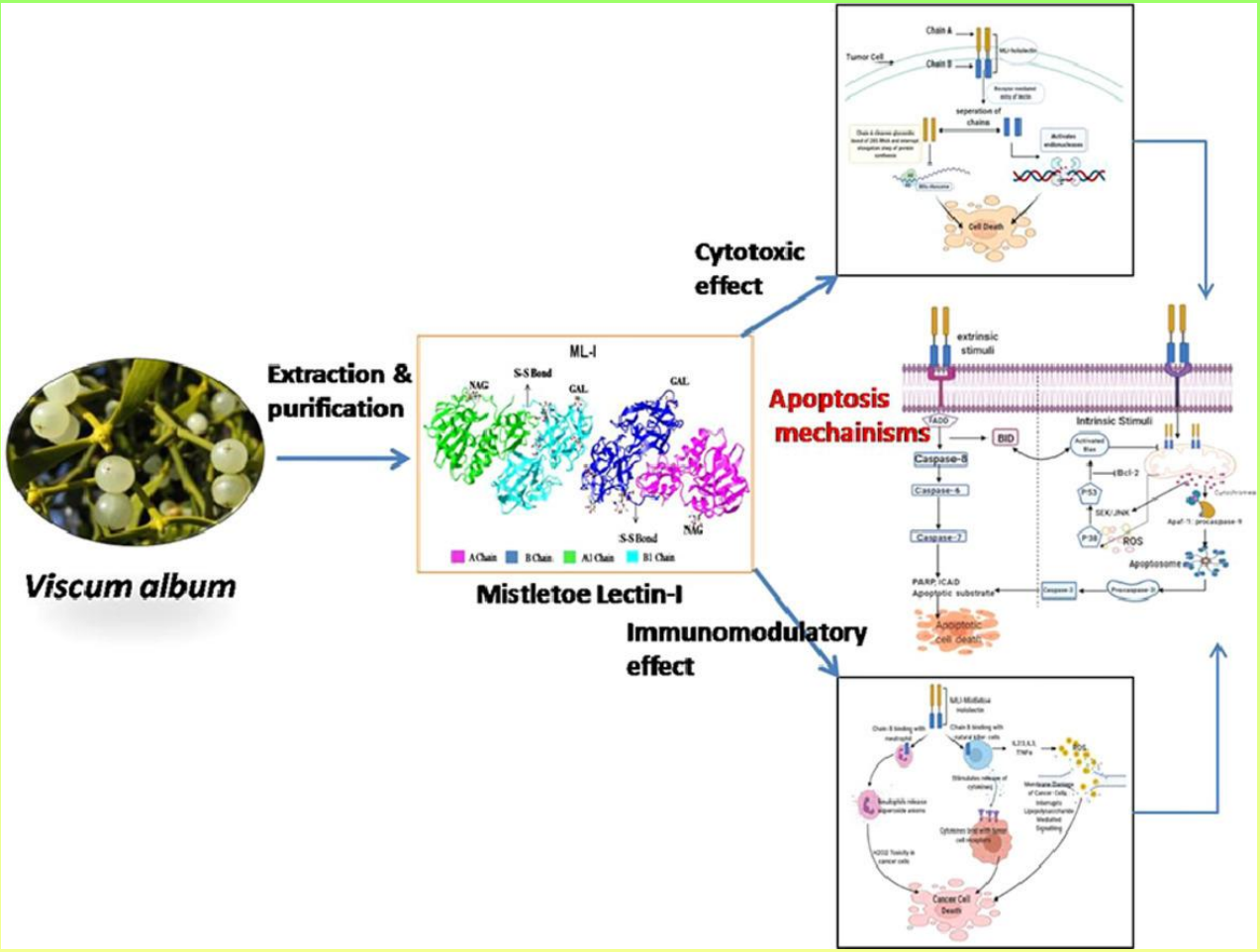


Mechanism of action of Catumaxomab (the first approved bispecific and és trifuntional antibody). (EpCAM: Epithelial cell adhesion molecule)

Plant lectins induce cancer cell death via targeting programmed cell death (PCD) signaling network.



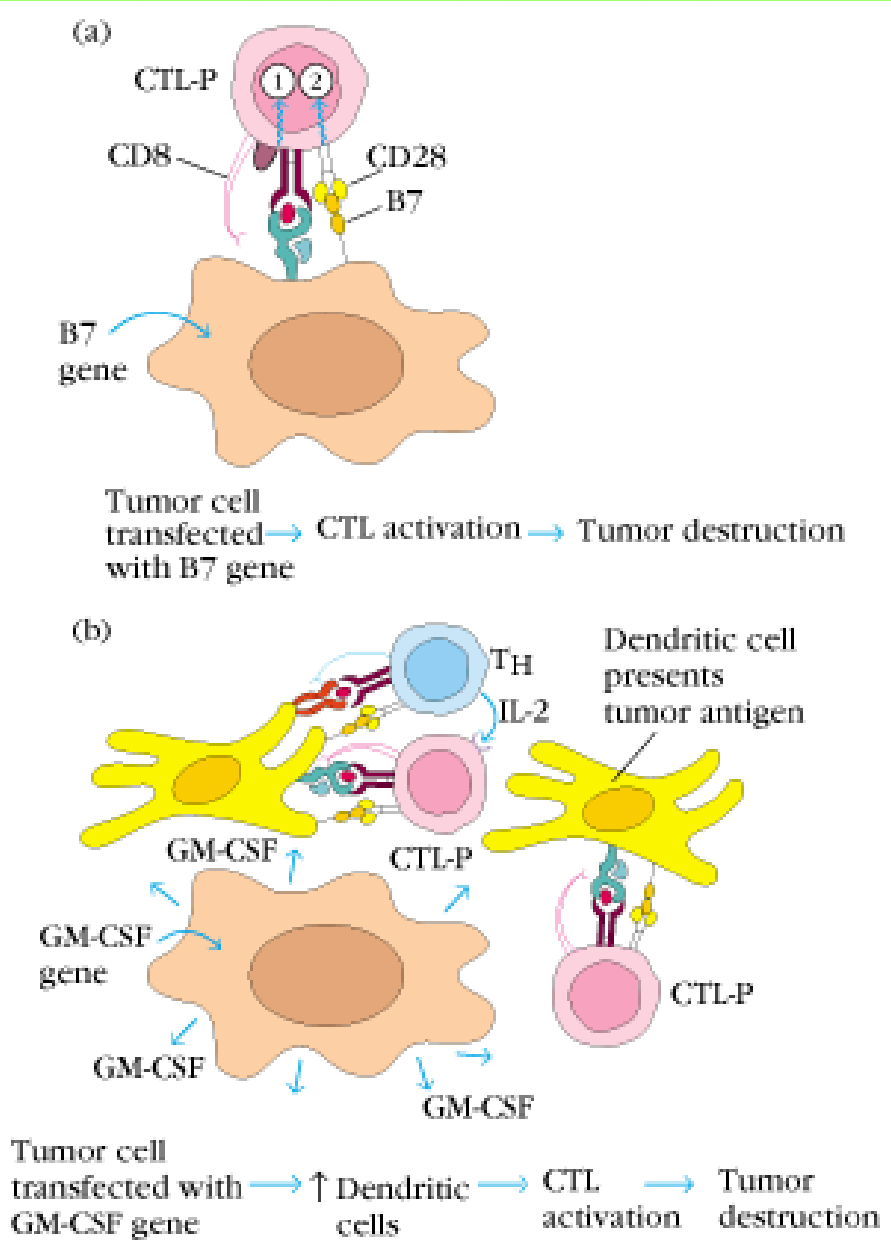
Misletoe lectin for malignant tumor's therapy



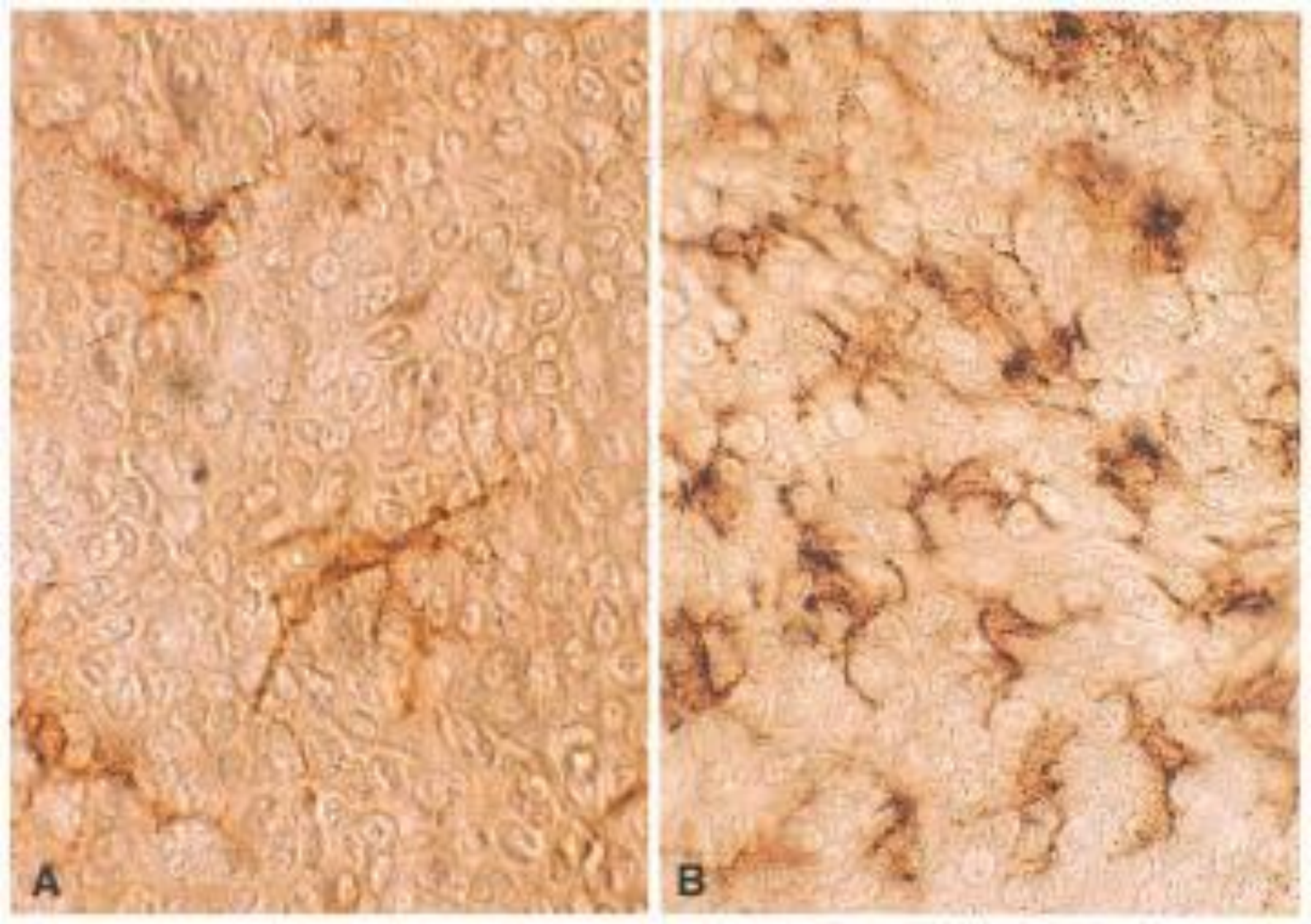
Sugar binding „B cahian" (34 kD) is responsible for the imunomodulant activity.

Enhance the T cell and NK cell maturation and activation in dose dependent manner.

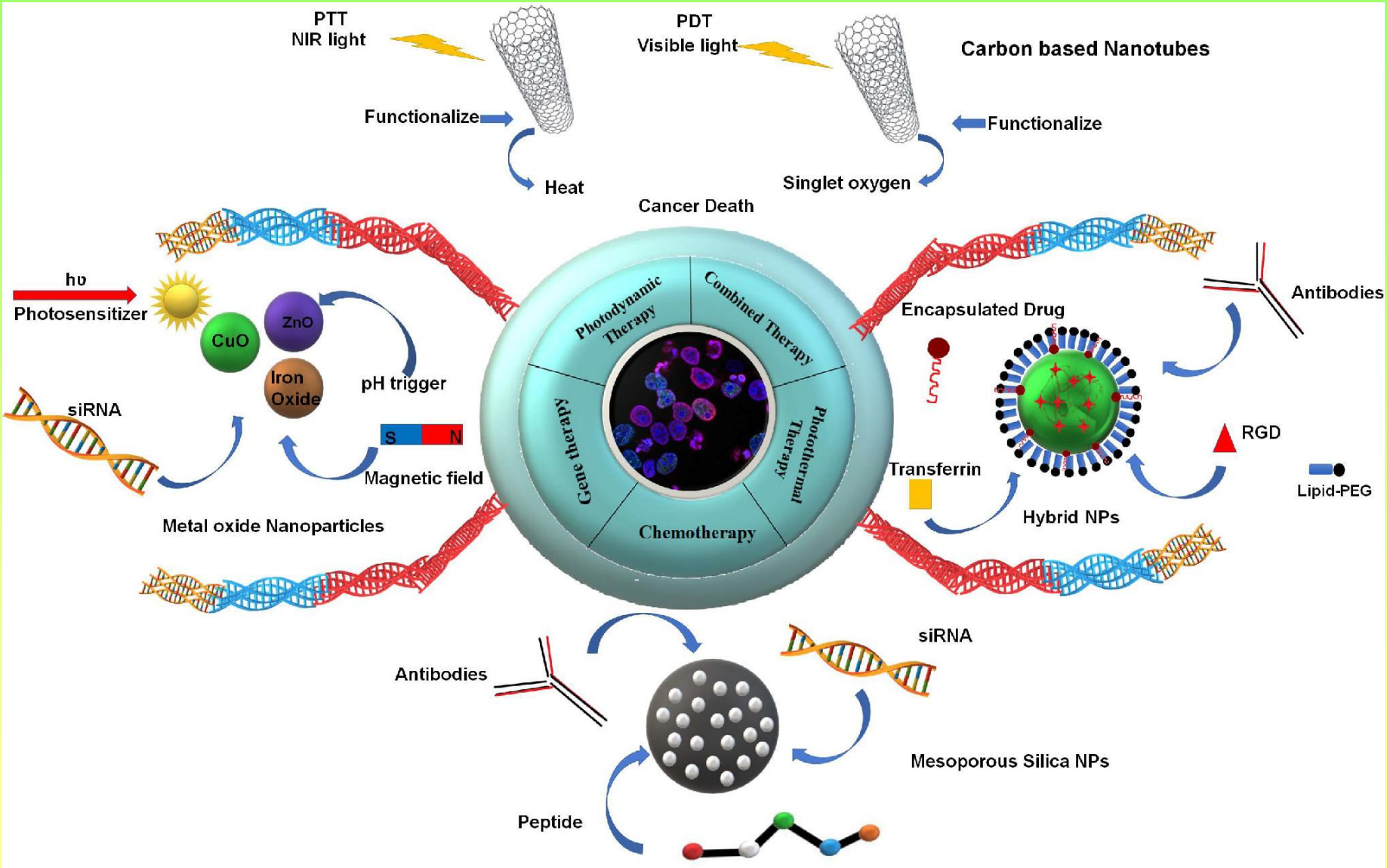
Development of cancer vaccines



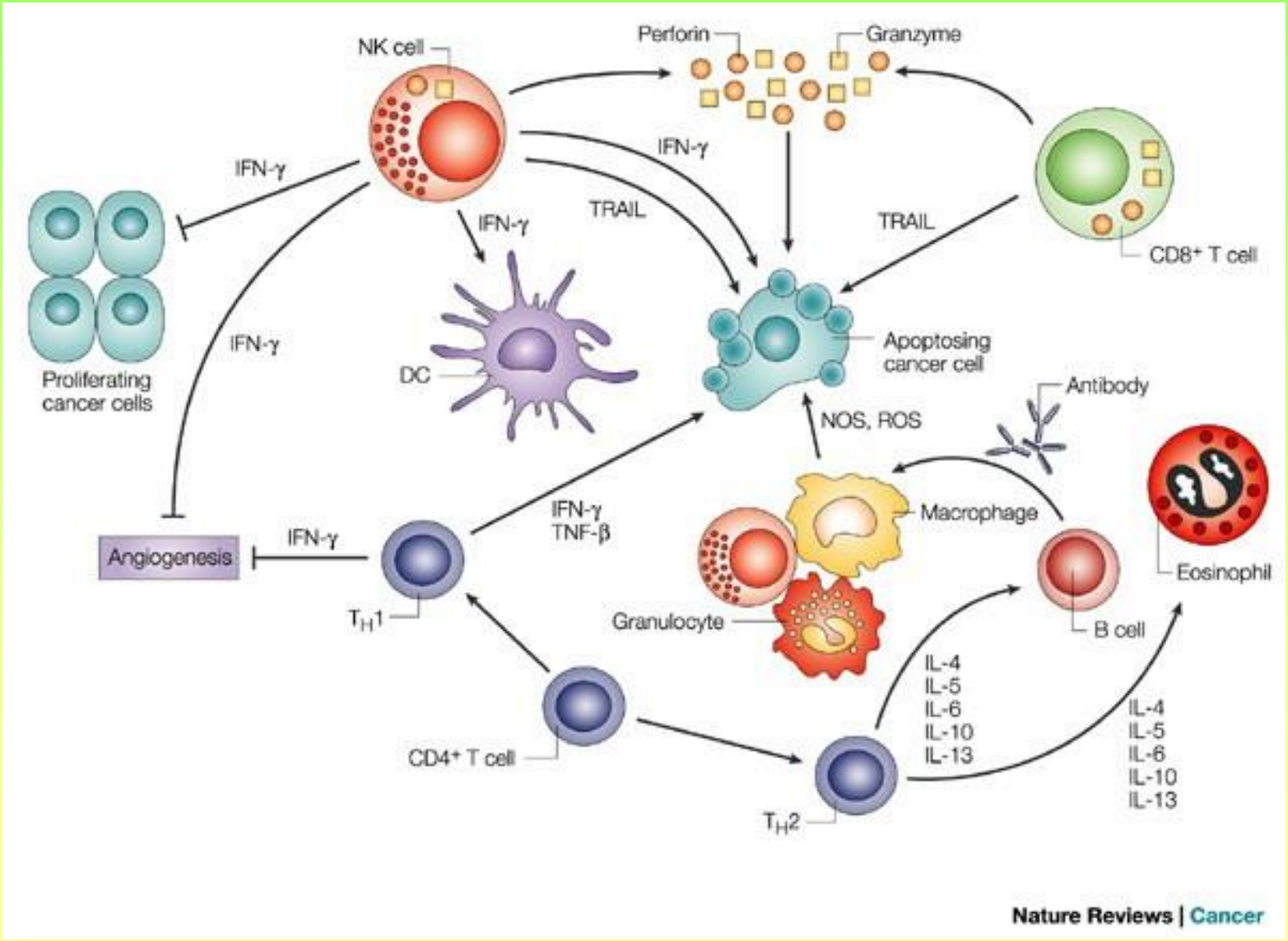
Recruitment of dendritic cells by DNA vaccine of GM-CSF



Nanoparticles for cancer therapy

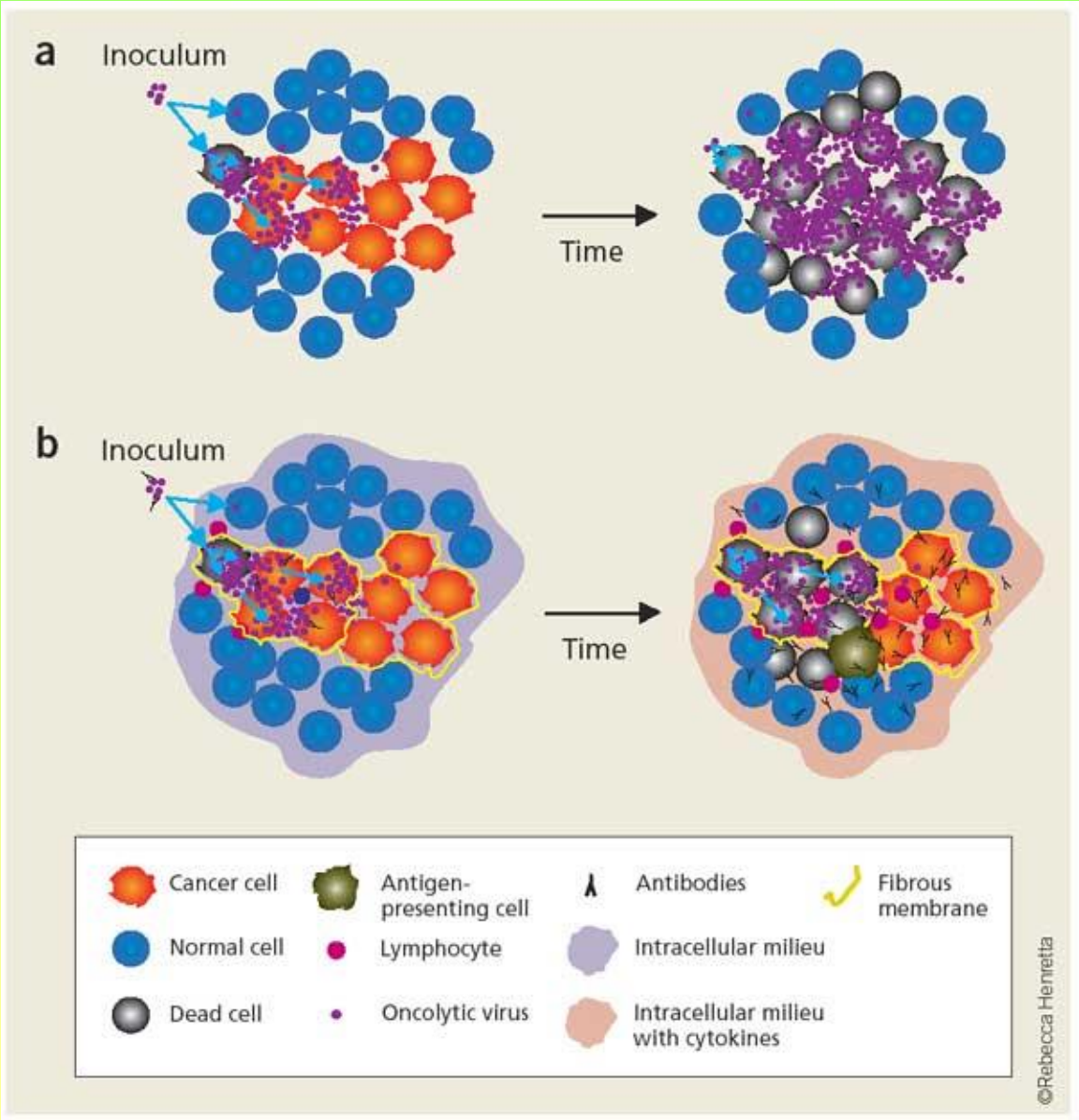


Possible pathways for cytokine therapy of cancer



Cytokine	Cell sources	Cell targets	Role in tumor formation	Therapeutic Action	Cancer type
IL-1	Macrophages, Lymphocytes Keratinocytes, Dendritic cell,	Epithelial and endothelial cells	Tumor invasion Angiogenesis	Induction of proinflammatory proteins	Fibrosarcoma
IL-6	Endothelial cells, fibroblasts, macrophages	Hepatocytes, leukocytes, T cells, B cells,	Required for chemically induced lymphomas	Enhances T-cell and B-cell function	Melanoma
IL-12	Macrophages, dendritic cells, neutrophils	T cells (Th1 cells), NK cells	Inhibits chemical carcinogenesis	Enhances TH1 immunity and cytotoxicity; inhibits angiogenesis	Colon, breast, Merkel cell carcinoma, malignant melanoma
IL-15	Monocytes, activated CD4+ T cells, keratinocytes, skeletal muscle cells	Natural killer cells	Promotes natural killer T cell leukemias	Enhances Cytotoxicity	Melanoma
IFN-γ	Natural killer cells, natural killer T cells, B cells, macrophages	Macrophage	Inhibits lymphomas, Stat1 and Rag2	Enhances tumour antigen presentation cytotoxicity	Prostrate
Gm-CSF	T cells, natural killer cells, macrophages, eosinophils, endothelial cells,	macrophage, neutrophils, and eosinophils	Inhibits lymphomas and carcinomas	Enhances Tumor antigen presentation	Colorectal
TNF-α	Macrophages, natural killer cells, B cells, T cells, neutrophils, fibroblasts, keratinocytes	Activation of MAPK pathway	Required for chemically-induced skin cancers	Induces Tumor-cell apoptosis;	Bladder

Oncolytic virus therapy



COMBINATORIAL IMMUNOTHERAPY

A Promising New Way To Kill Cancer