Università degli Studi di Firenze

Principles of Immunology and Immunotherapy

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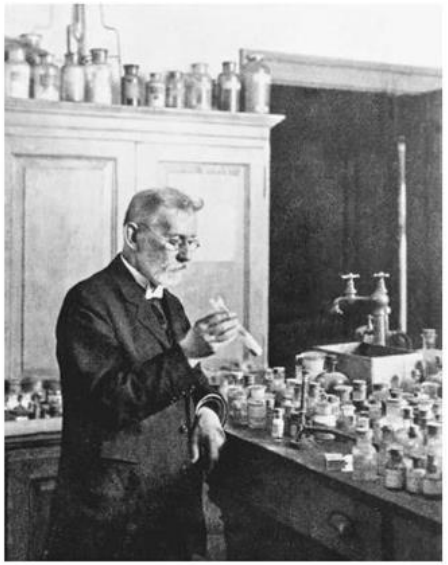
Florence, 21/01/2020

"Basic and translational oncology"
Italian-French Erasmus Intensive Course in Oncology organized in collaboration with
European Master of Genetics - University Paris7-Paris5

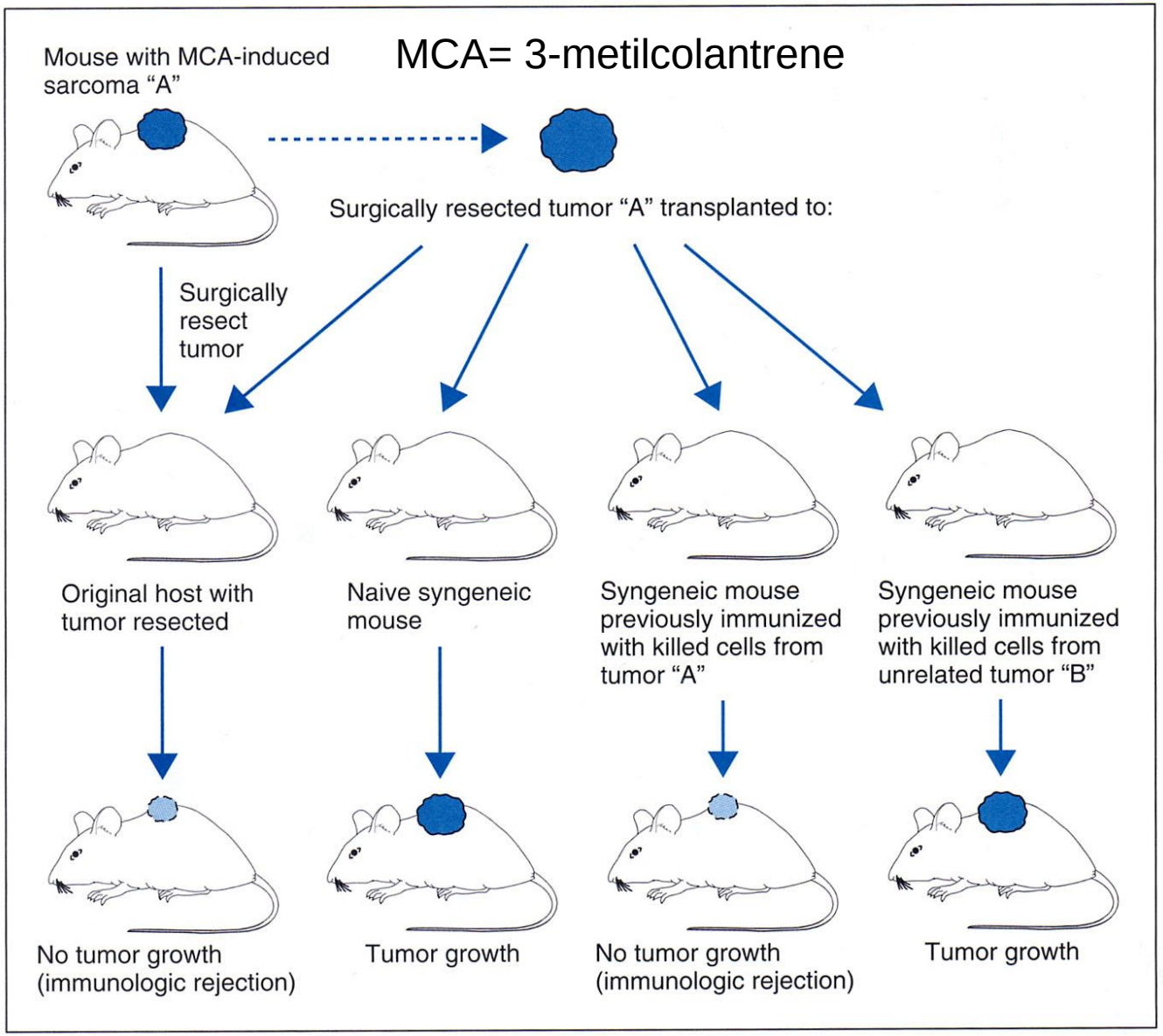
The concept of immune surveillance against tumors

In 1909, Paul Ehrlich formulated the hypothesis that host defense may prevent neoplastic cells from developing into tumors. He stated that: “in the enormously complicated course of fetal and post-fetal development, aberrant cells become unusually common. Fortunately, in the majority of people, they remain completely latent thanks to the organism's positive mechanisms.”

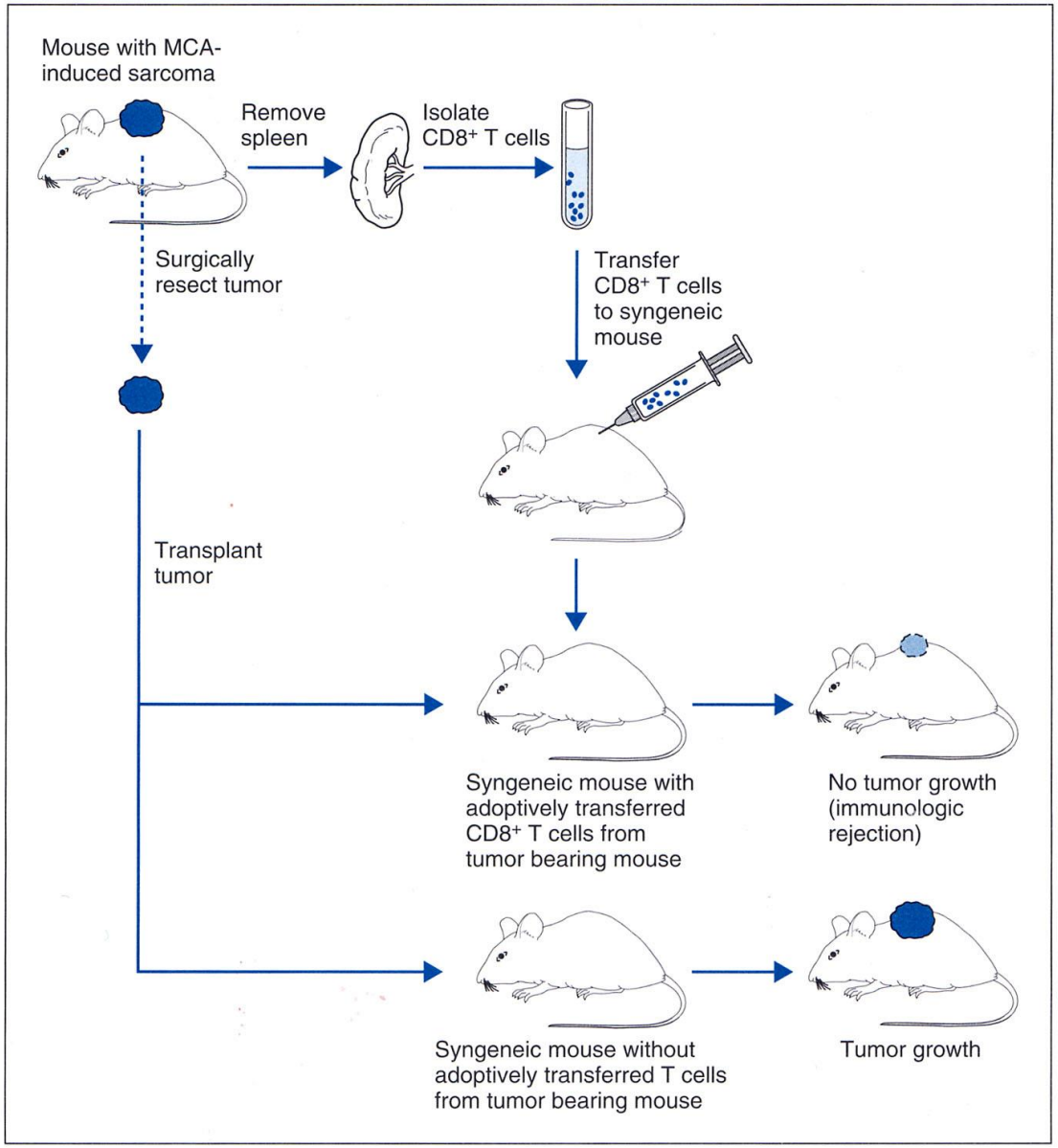


In 1970, Burnet hypothesized that tumor cell neo-antigens induce an immunological reaction against cancer and subsequently formulated the **immune surveillance theory**. He wrote that: “It is by no means inconceivable that small accumulation of tumor cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumor and no clinical hint of its existence.”

Experimental demonstration of immune response against tumor (1)



Experimental demonstration of immune response against tumor (2)



Evidences confirming the theory of immunesurveillance

Immune cells (mainly T cells, NK and macrophages) are found in the infiltrates of tumor tissue and in the draining lymph nodes.

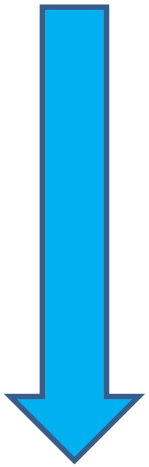
Events interfering with immune system activation status, are associated with an increase of cancer incidence:

- Immune competence decreases with age, the so-called “immunosenescence”, implying that decreased immunosurveillance against cancer contribute to increased disease in the elderly
- Clinical and pathological conditions leading to immunodeficiency (i.e. AIDS, primary or secondary immunodeficiences and transplanted patients)

From immunesurveillance to the tumor development

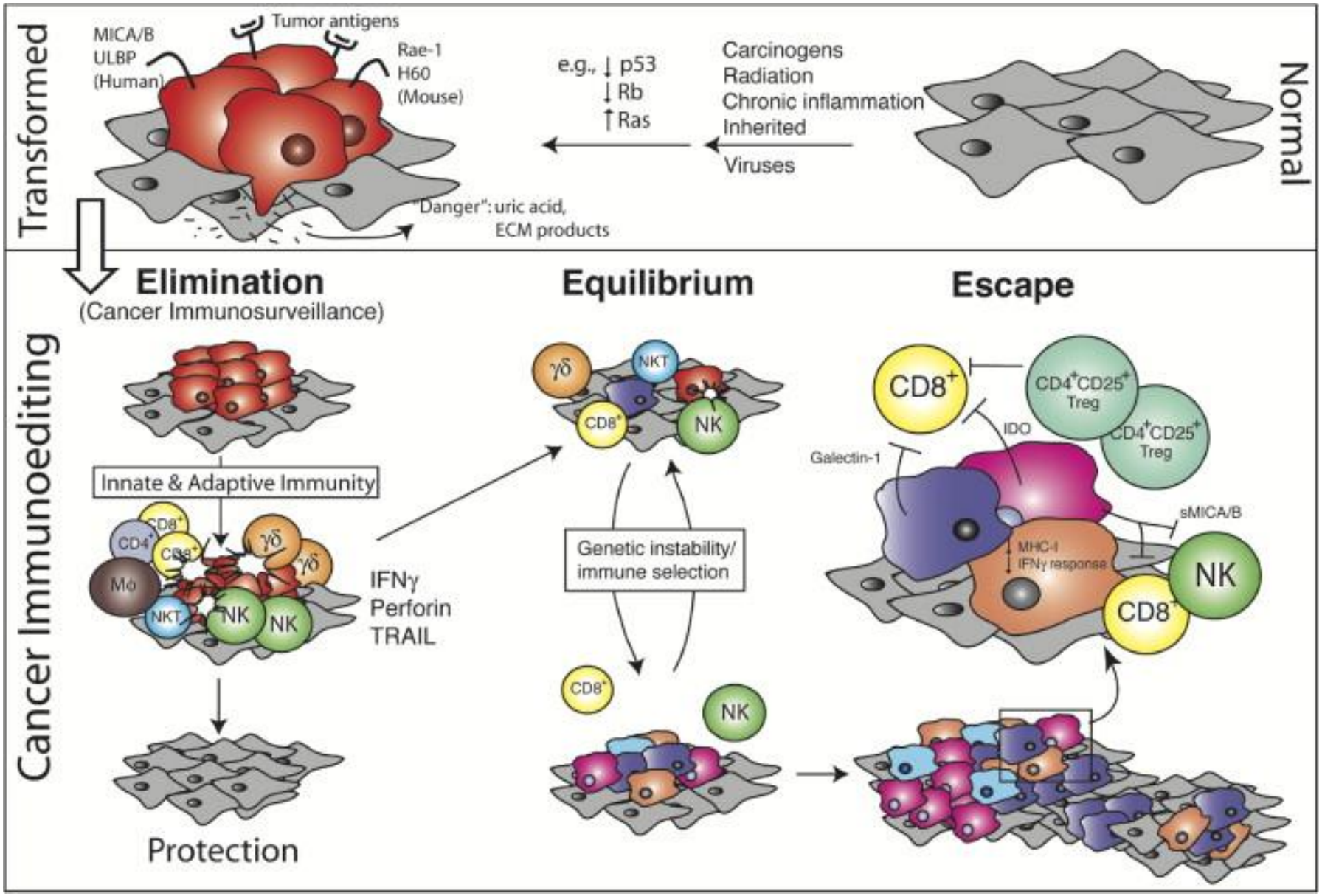
Immune surveillance against tumors could **fail**:

- Low immunogenic antigens (self)
- High growth rate of tumor cells
- Tumor escape mechanisms



The concept of cancer immunoediting

CANCER IMMUNOEDITING



Gavin P. et al, Immunity 2004

Tumor antigens

Tumor cells, despite their development from self-cells in the body, express tumor antigens. These could be useful tumor markers in identifying tumor cells with diagnostic tests and are potential candidates for use in cancer therapy.

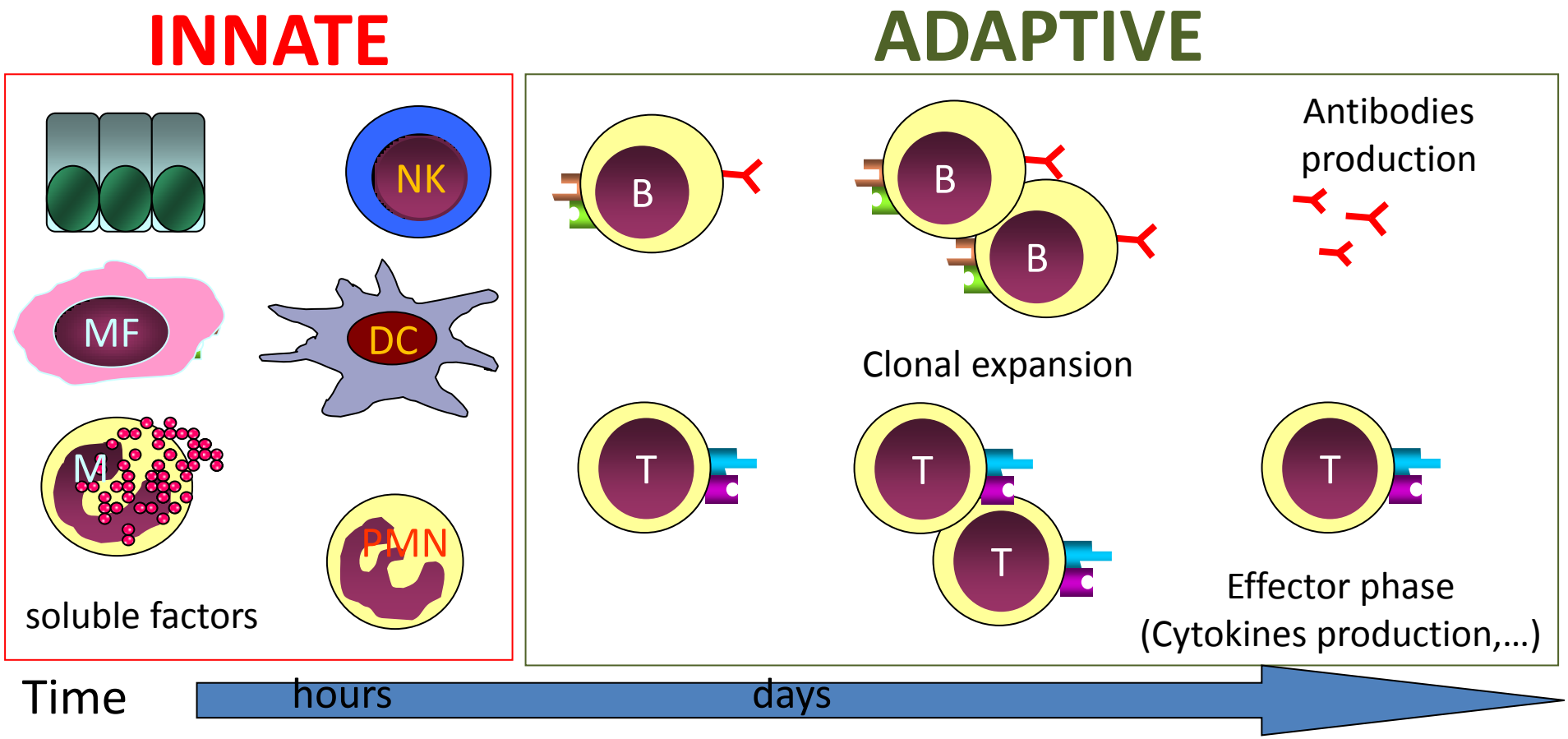
- **Tumor-Specific Antigens (TSA),** which are present only on tumor cells and not on any other cells

- **Tumor-Associated Antigens (TAA),** which are present on some normal cells, usually associated to a specific differentiation phases or to a specific tissues and that are an aberrant expression on tumor cells.

Tumor antigens

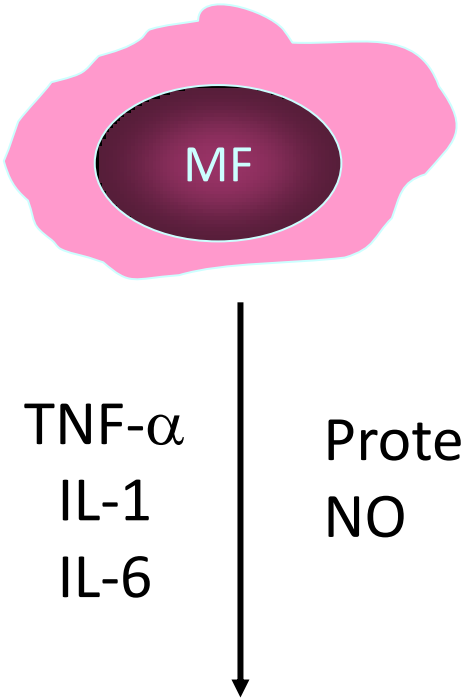
- Products of Mutated Oncogenes and Tumor Suppressor Genes
- Overexpressed or Aberrantly Expressed Cellular Proteins
- Tumor Antigens Produced by Oncogenic Viruses
- Oncofetal Antigens
- Altered Cell Surface Glycolipids and Glycoproteins
- Cell Type-Specific Differentiation Antigens

Main actors of immune response against the tumor



Macrophages

Macrophages are large cells that recognize, phagocyte cellular debris, foreign substances, microbes, cancer cells, and anything else that does not have the type of proteins specific to healthy body cells on its surface.

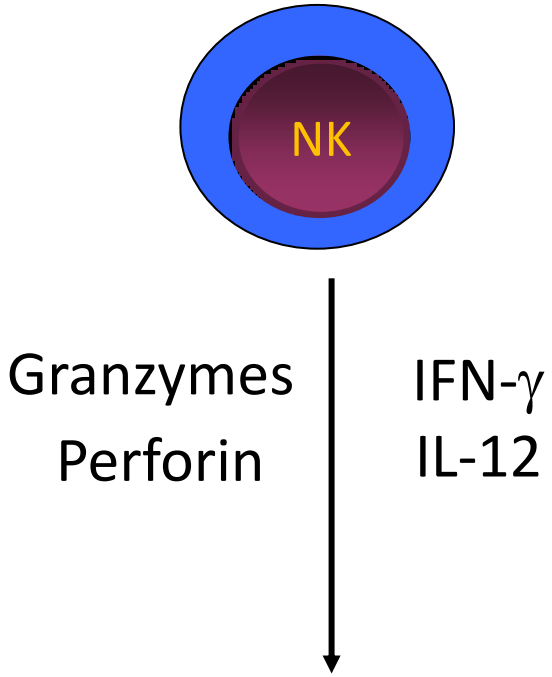


- Lymphocytes recruitment and antigen presentation
- Direct citotoxicity against tumor cells

- Substain local chronic inflammation
- Production of pro-angiogenetic factors (VEGF)
- Tumor-associated macrophages (TAMs) have a M2 phenotype (IL-4, IL-13, IL-10, TGF-β)

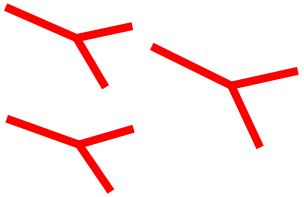
NK cells

Natural killer cells are cytotoxic lymphocytes. Their activation is determined by the balance of inhibitory and activating receptor stimulation or by Antibody-dependent cell-mediated cytotoxicity (ADCC).

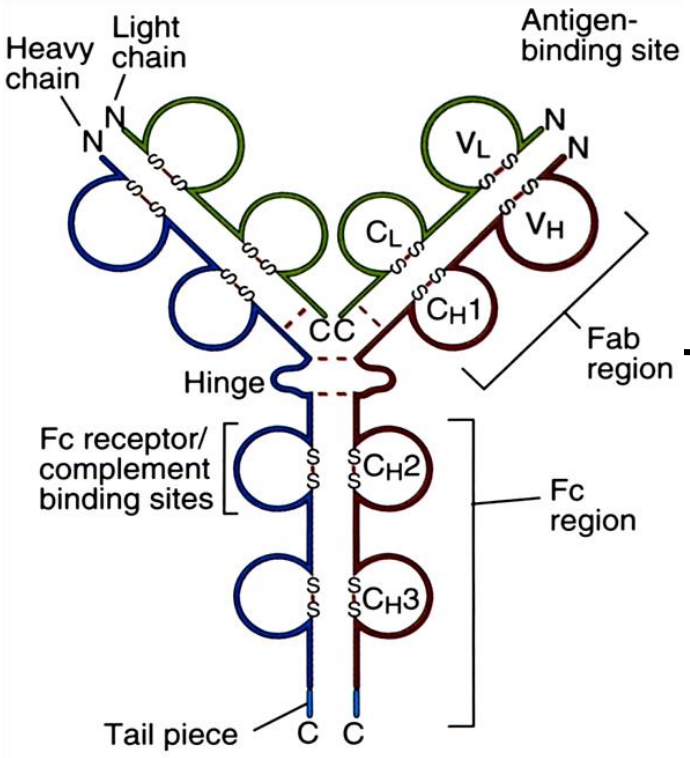


- Direct citotoxicity against tumor cells (dependent on low MHC I levels)
- Direct activation by specific ligands expressed by tumor cells (MIC-A e B/NKG2D)
- Direct citotoxicity against tumor cells mediated by ADCC

Antibodies



Antibodies are produced and secreted by B cells and plasmacells and belong to the adaptive humoral immunity

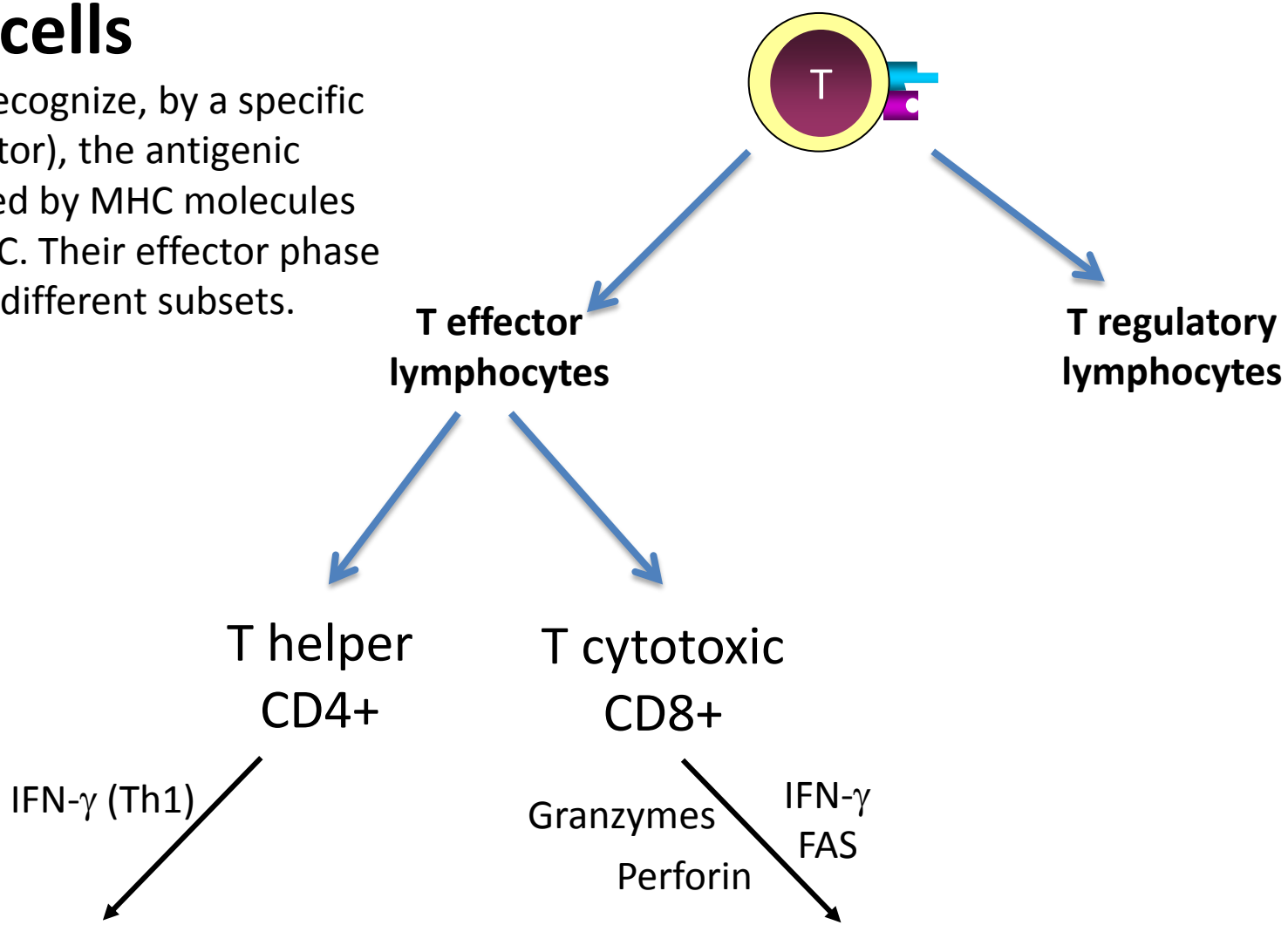


The presence of antibodies specific for TSA or TAA, as tumoral neo-antigens or viral antigens expressed by tumor cells, is clearly demonstrated in different types of cancers.

Mechanisms of action: ADCC, macrophages activation, complement cascade activation.

T cells

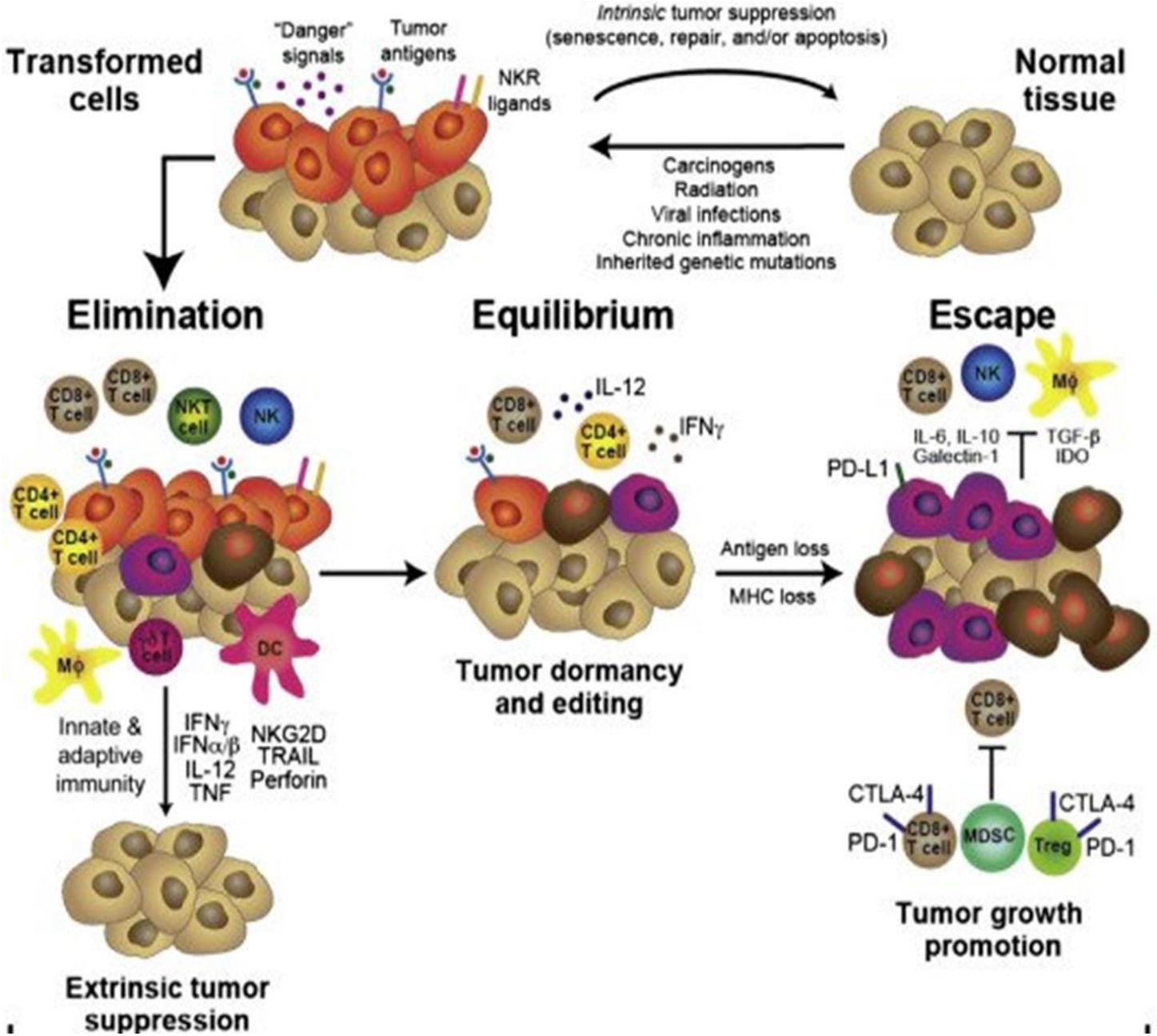
T lymphocytes recognize, by a specific TCR (T cell receptor), the antigenic peptide presented by MHC molecules expressed on APC. Their effector phase is different from different subsets.



- Increased levels of MHC I on tumor cells
- M1 macrophages activation
- Induction T cytotoxic CD8 differentation
- NK cells activation

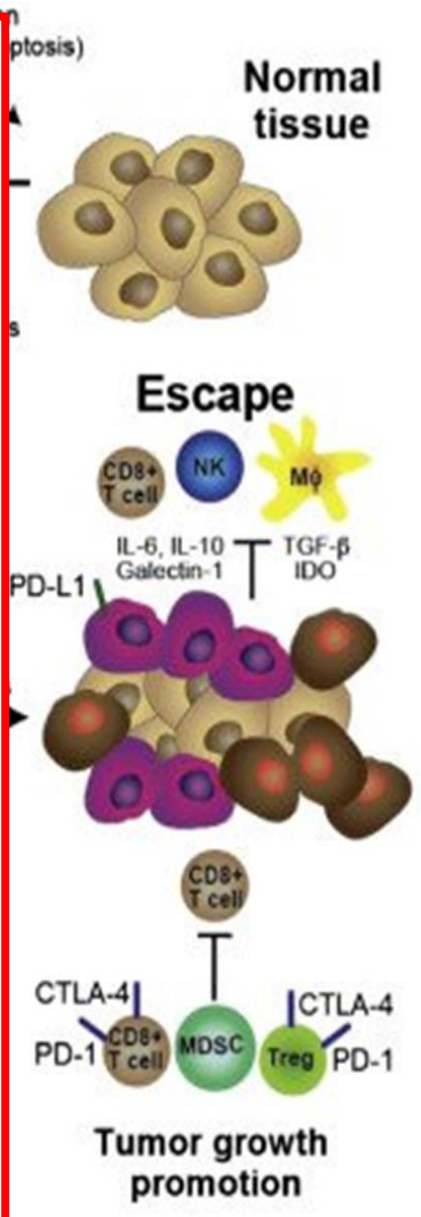
- Direct citotoxicity against cells showing peptide of TSA or TAA antigen associated to MHC I molecules

Mechanisms of tumor «escape»



Mechanisms of tumor «escape»

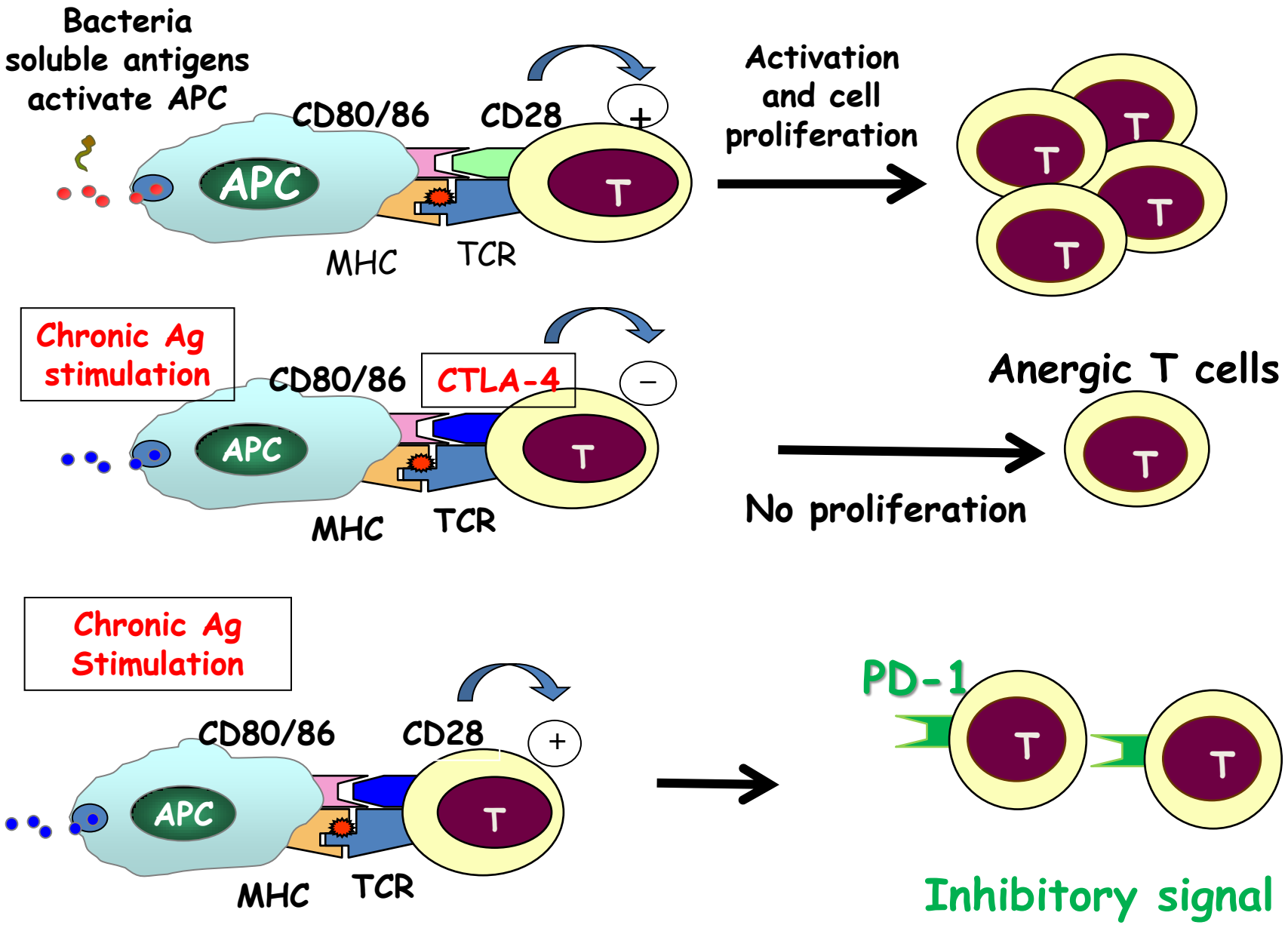
- Reduction of expression of MHC I molecules
- Activation of signaling pathway of CTLA-4, PD-1 and FAS on T cells
- Increase of glicocalix production to mask the membrane proteic antigens
- Production of IL-10 and TGF-b inhibiting activity of phagocytes and lymphocytes
- Many tumor antigens are self-antigens and are regulated by peripheral tollerance



The peripheral tollerance

- Ignorance
- Clonal deletion
- Anergy
- Immune suppression

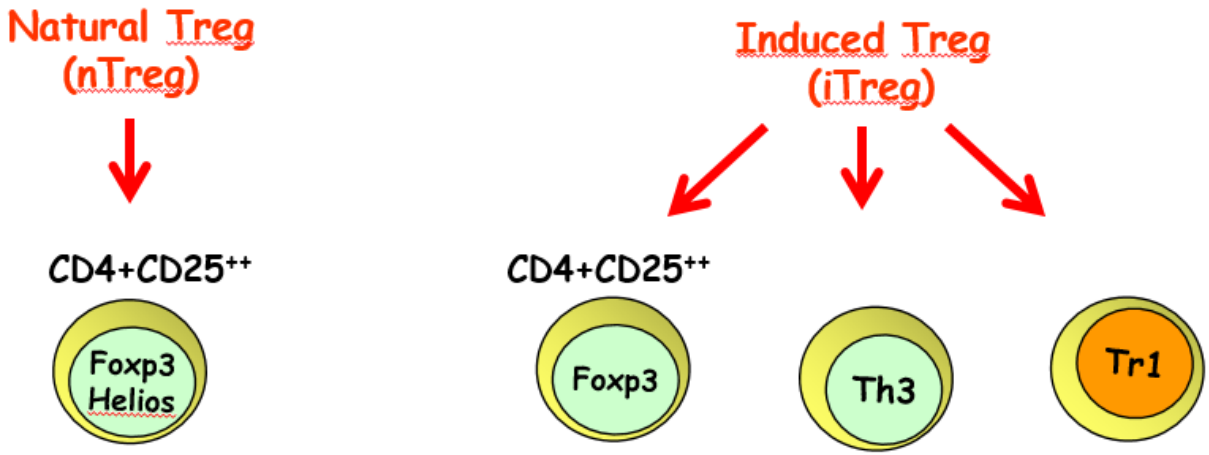
Molecular mechanism of anergy



Immune suppression

- T reg cells

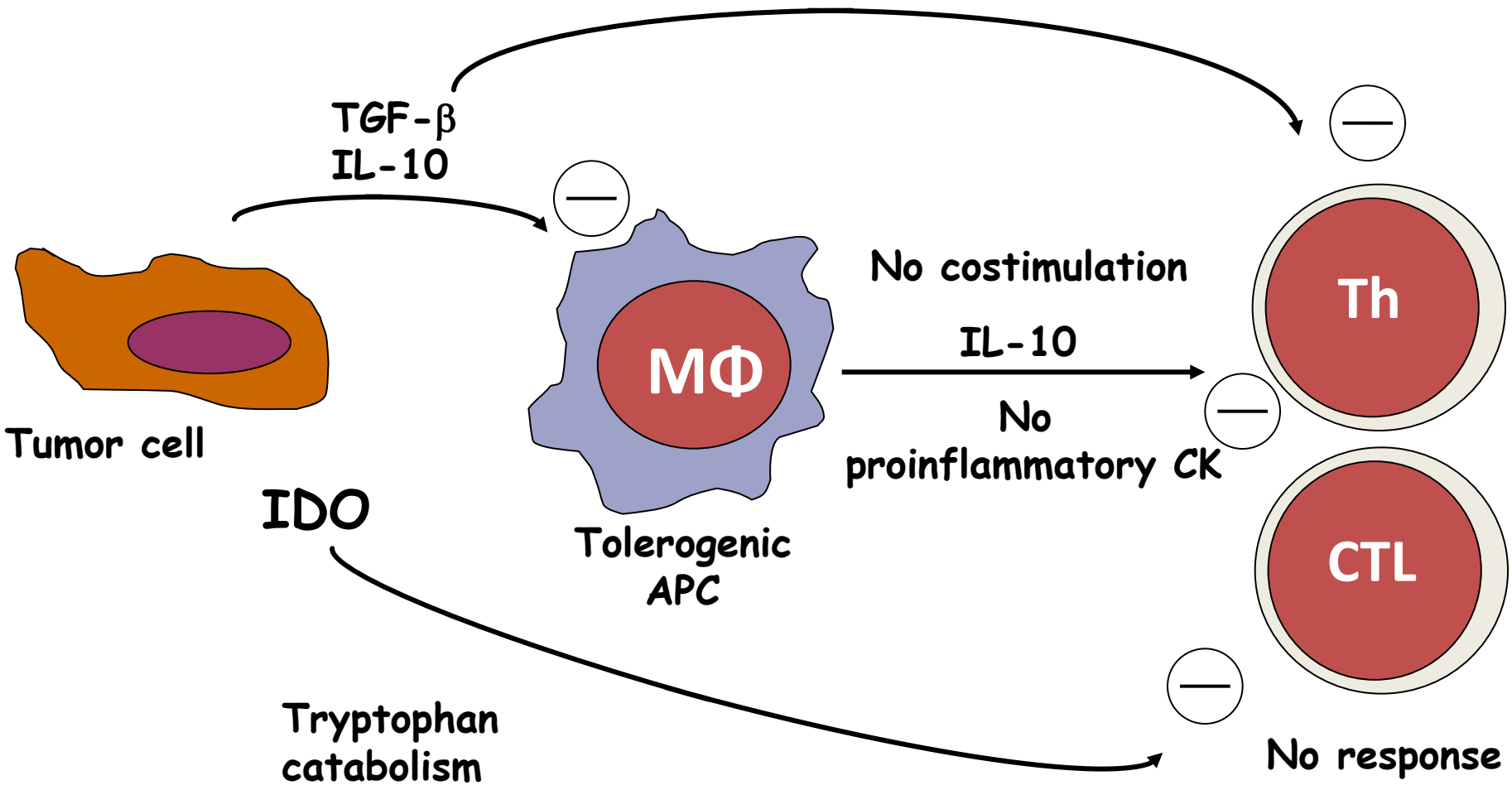
IL-10
TGF-β



The frequency of circulating and tumor-infiltating Treg cells is high in many cancers, it positively correlates with tumor grade and negatively correlates with the prognosis.

- Mesenchimal Stem cells (MSC)
- Myeloid derivative suppressor cells
- M2 macrophages
- Tumor cells and tumor-derived MSC

Immunosuppressive activity of tumor



IDO: Indoleamine 2,3-dioxygenase

Cancer Immunotherapy

1. Immunization:

    - active

    - passive

2. Reinforcing/modulating the pre-existing anti-tumor immunity

Immunization

Stimulating immune responses with a foreing agent

Active:

Active immunization entails the introduction of a foreign molecule into the body, which causes the body itself to generate immunity against the target. This immunity comes from the T cells and the B cells with their antibodies (adaptive immune system).

Passive:

Passive immunization is where pre-synthesized elements of the immune system are transferred to a person so that the body does not need to produce these elements itself. **Currently, antibodies can be used for passive immunization.** This method of immunization begins to work very quickly, but it is short lasting, because the antibodies are naturally broken down, and if there are no B cells to produce more antibodies, they will disappear.

Active Immunization against tumor

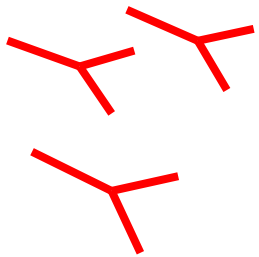
- Prophylactic vaccination

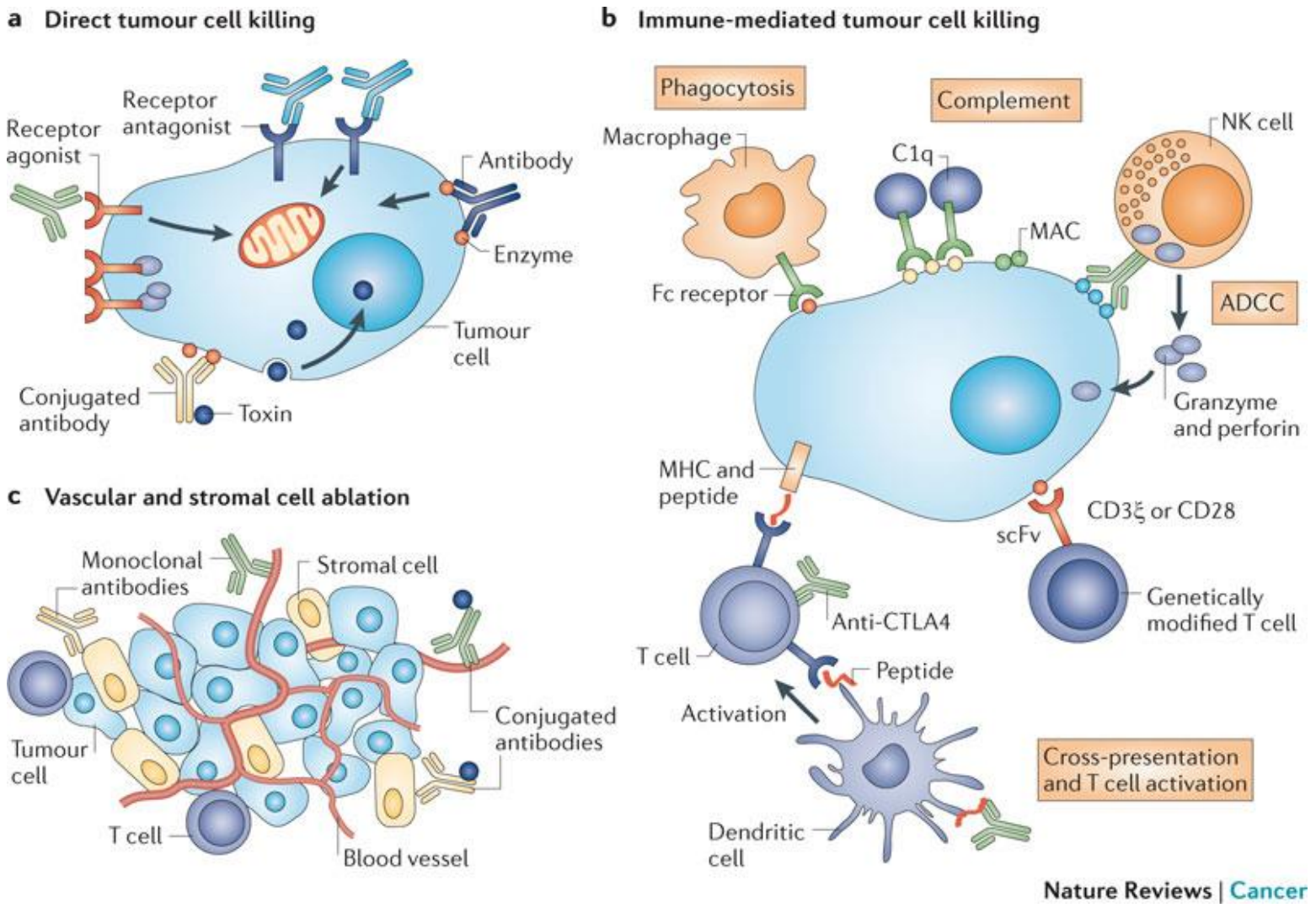
- Human papillomavirus (HPV) and tumor of the uterine cervix
- Hepatitis B Virus (HBV) and liver cancer

- Therapeutic vaccination

Passive Immunization

Administration of monoclonal antibodies against TSA or TAA

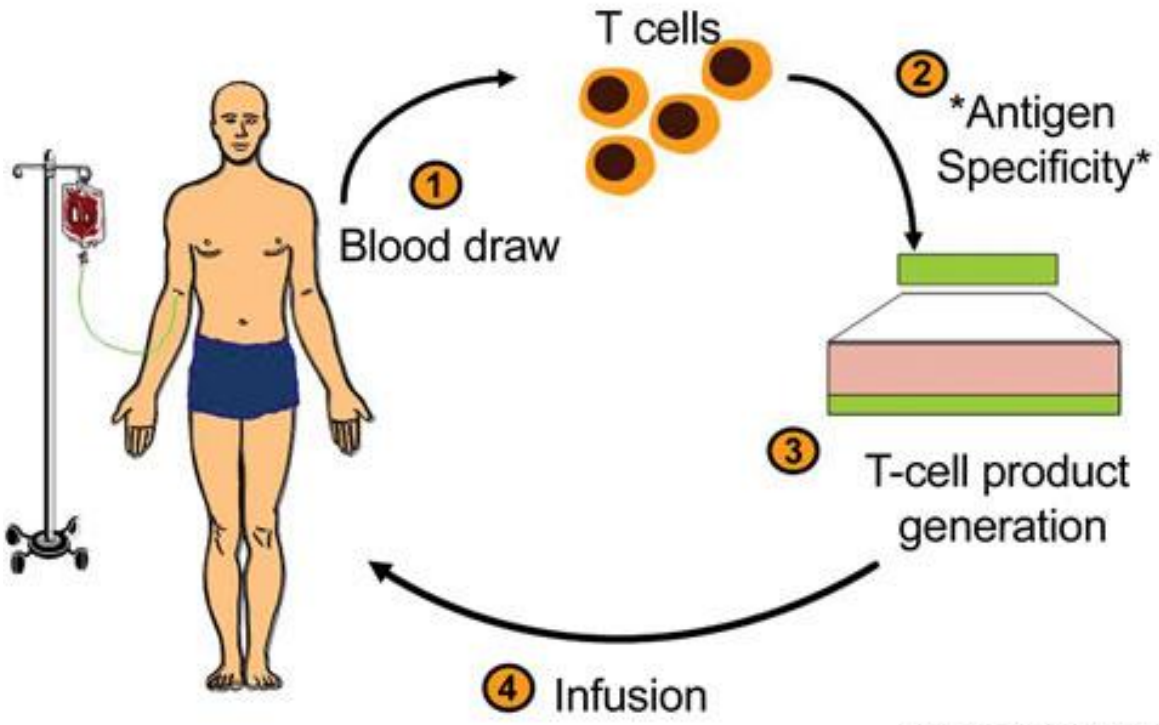




Passive immunization is not exclusively associated to antibodies administration

A new kind of passive immunity: to administrate tumor specific T cells

1964: Antigen-specific adoptive T cell therapy



The major advantage of T cells over the currently available immunotherapies that use antibodies:

- **Traffic to sites of disease**
- **Expand**
- **Persist after a single treatment**

Methodological approaches for antigen-specific adoptive T cell therapy

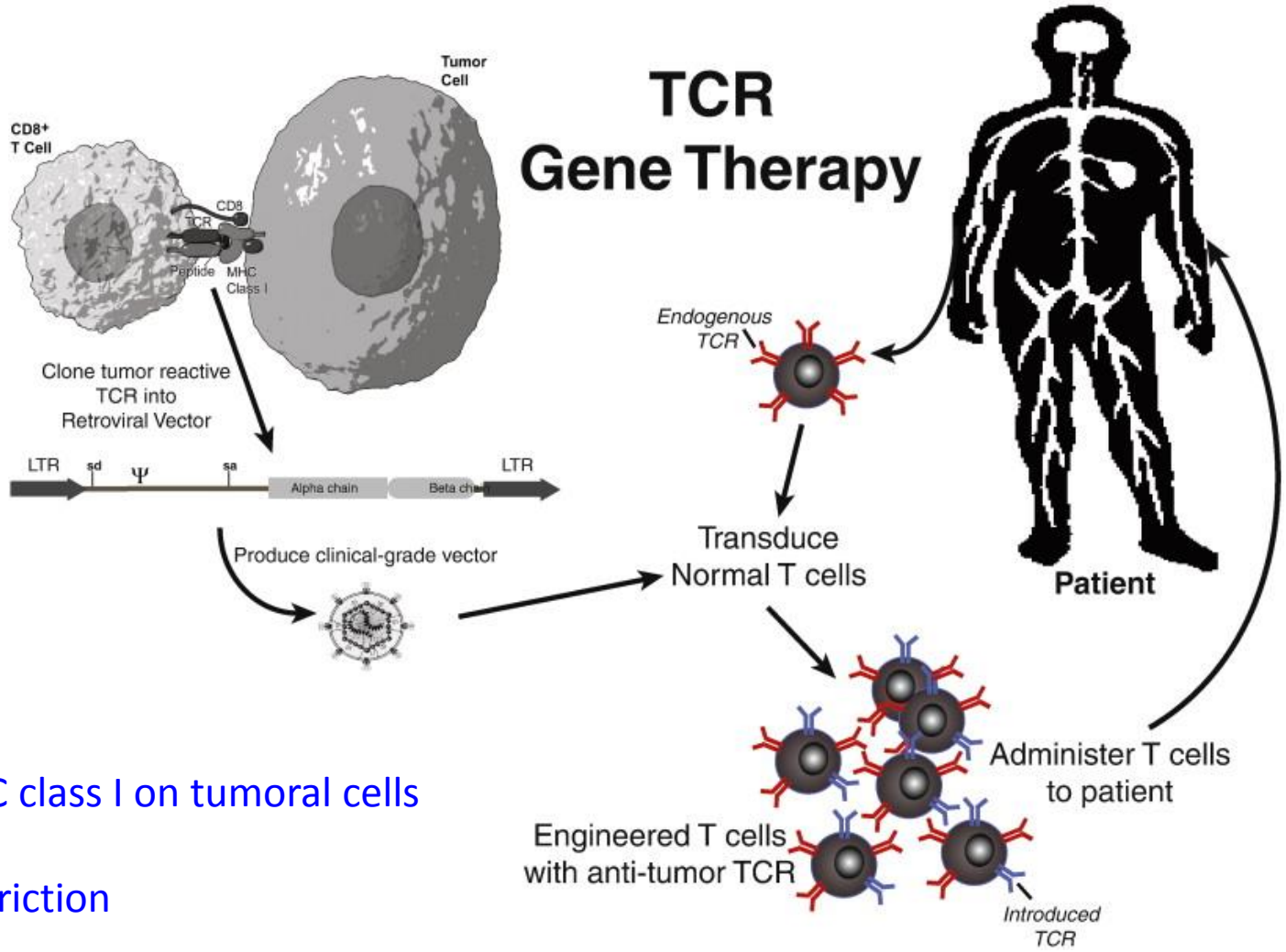
- The ex vivo expansion of antigen-specific T cells

- The direct isolation of antigen-specific T cells

Methods of adoptive T-cell transfer that relay on culture or selection of antigen-specific T cells require that the transplant donor has immunity to the relevant antigen (pathogen or tumor)

The TCR gene therapy

Genes encoding TCRs α and β chains can be isolated from T cells with high avidity to recognize the HLA/peptide complex. Retroviral or lentiviral vectors can be used to deliver TCR genes and redirect lymphocytes antigen specificity



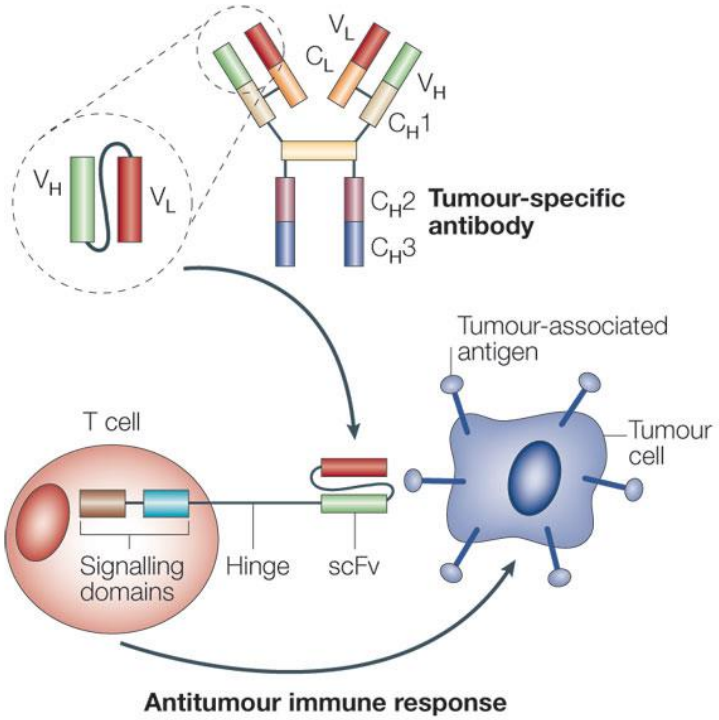
Limitations

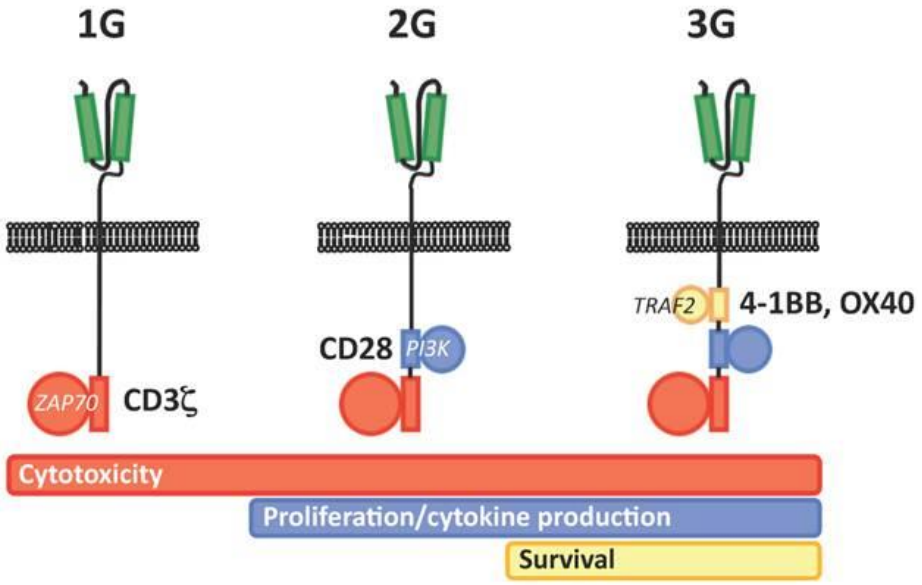
- Low levels of MHC class I on tumoral cells
- HLA aplotype restriction

The chimeric antigen receptors (CAR)

The chimeric antigen receptor (CAR) is generated by joining the light and heavy chain variable regions of a monoclonal antibody with the hinge domain, the transmembrane, and the cytoplasmic signaling domains derived from the CD3ζ chain or Fc receptor γ chain. Retroviral or lentiviral vectors can be used to deliver CAR genes and redirect lymphocytes antigen specificity

- they are not HLA-restricted
- they directly target cell-surface antigens
- do not require batteries of TCRs for different HLAs





Cancer Immunotherapy

1. Immunization:

    - active

    - passive

2. Reinforcing/modulating the pre-existing anti-tumor immunity

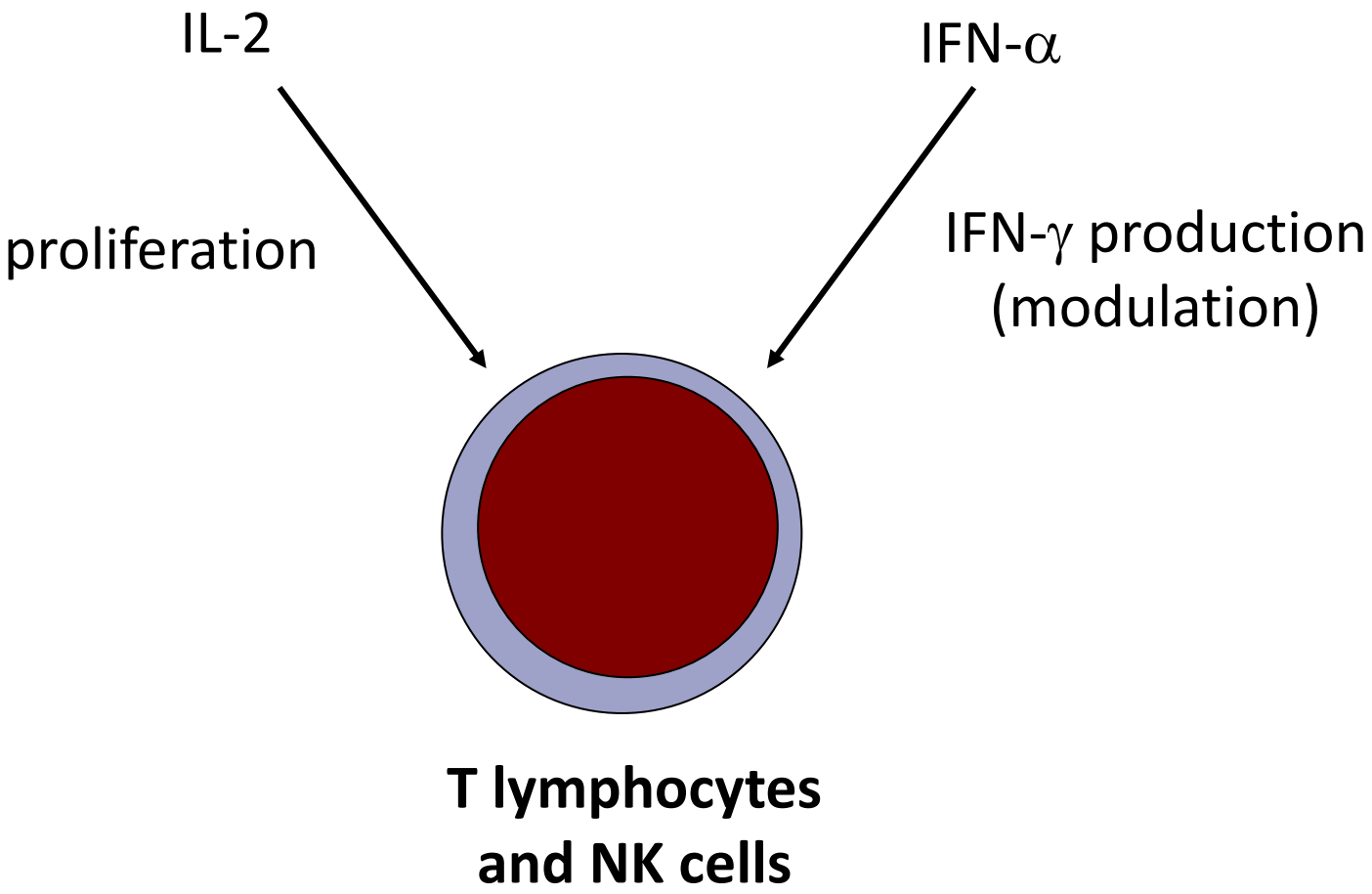
Tumor immunotherapy: reinforcing/modulating the pre-existing anti-tumor immunity

- Systemic administration of recombinant cytokines

(IL-2, IFN-α)

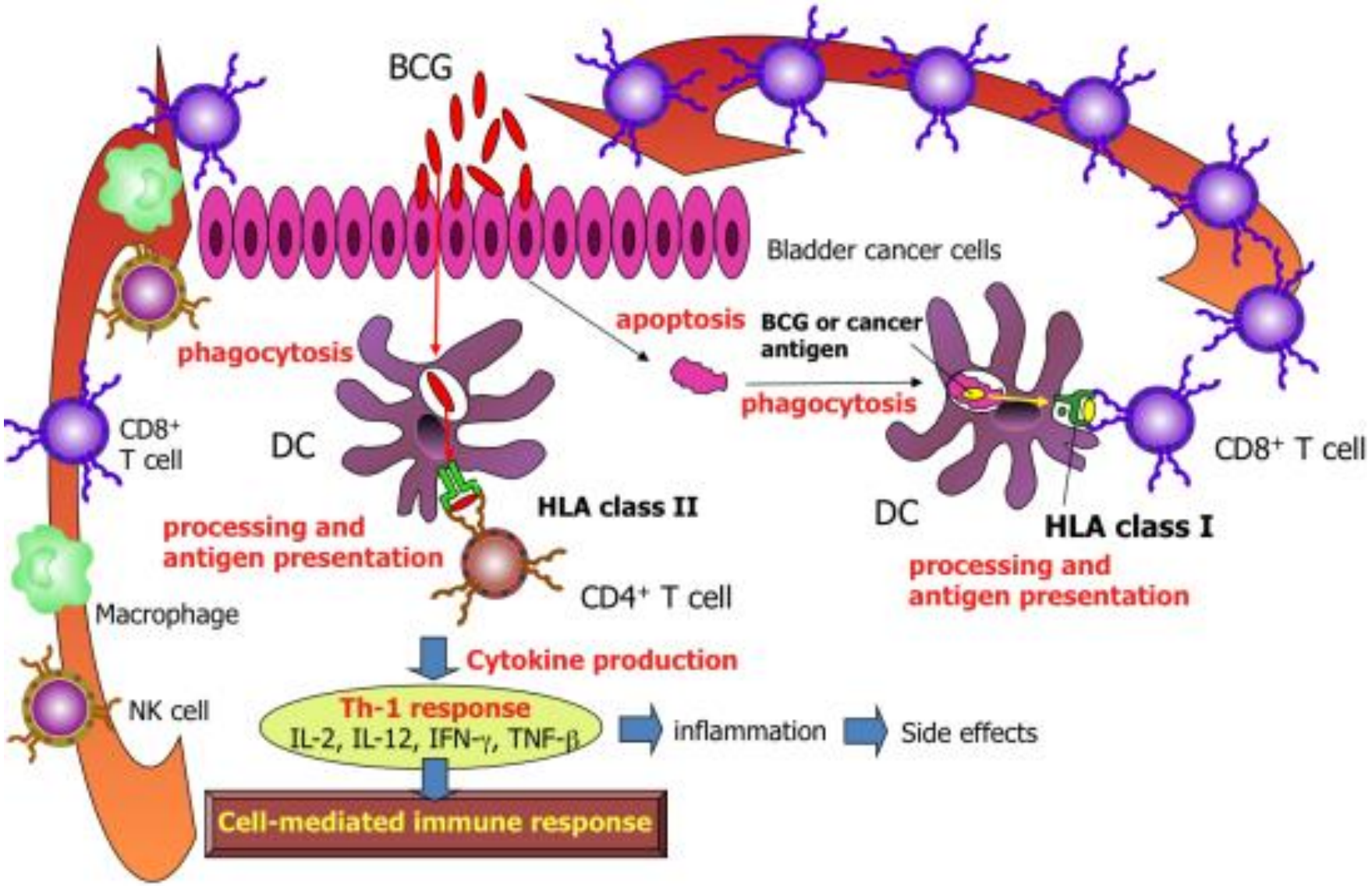
- Use of adjuvants to induce reactivation of immune response (i.e. Calmette Guerin Bacillus, BCG)
- To eliminate/to block T regulatory cells
- To interfere with inhibitory signals received by T cells in contact with APC and/or tumor cells

Systemic administration of recombinant cytokines



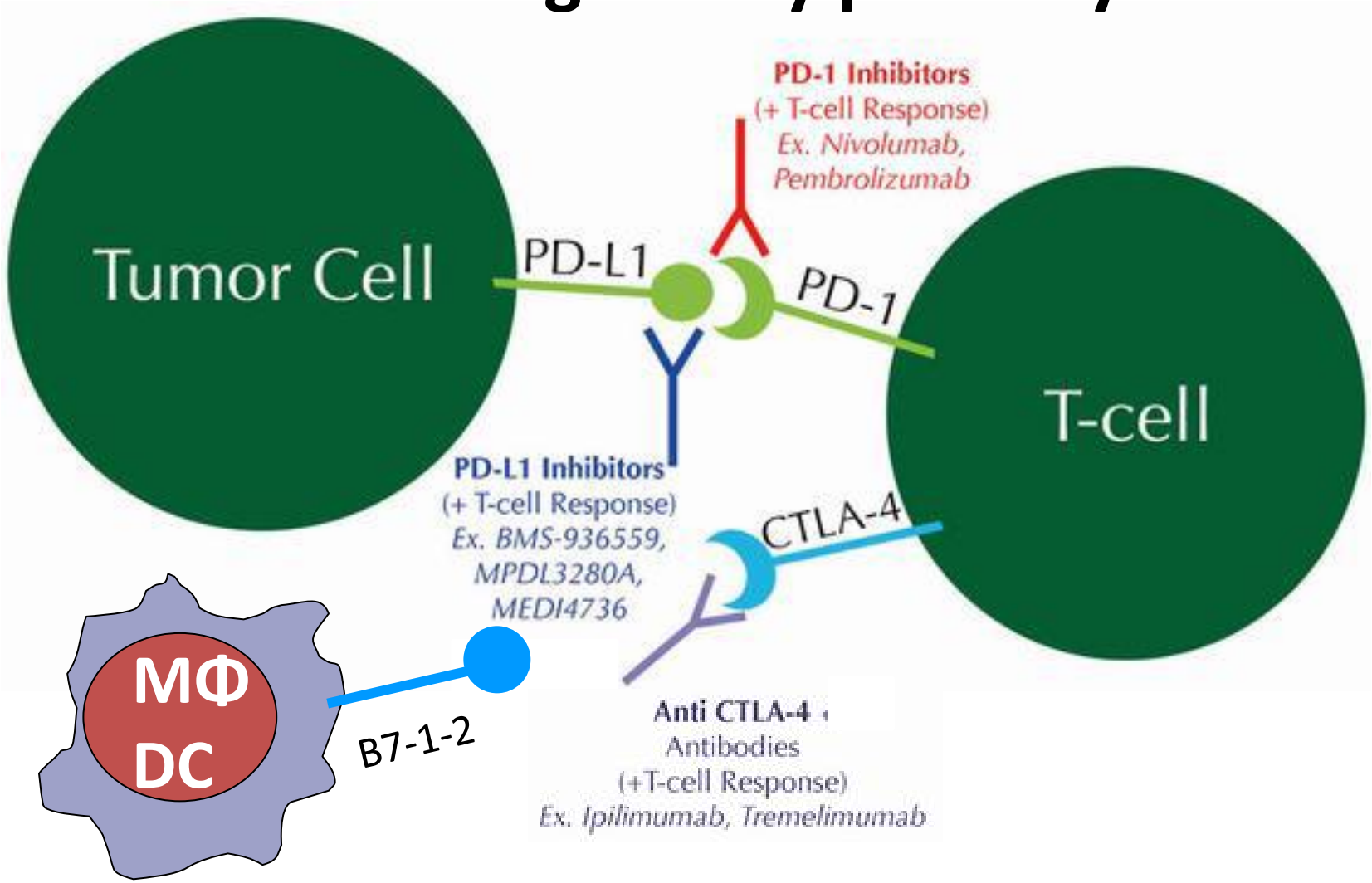
This therapy is mainly used in cancer with high grade of immune cells infiltating tumor tissue

Intravesical administration of BCG in bladder cancer



Cancers **2011**, *3*(3), 3055-3072; https://doi.org/10.3390/cancers3033055

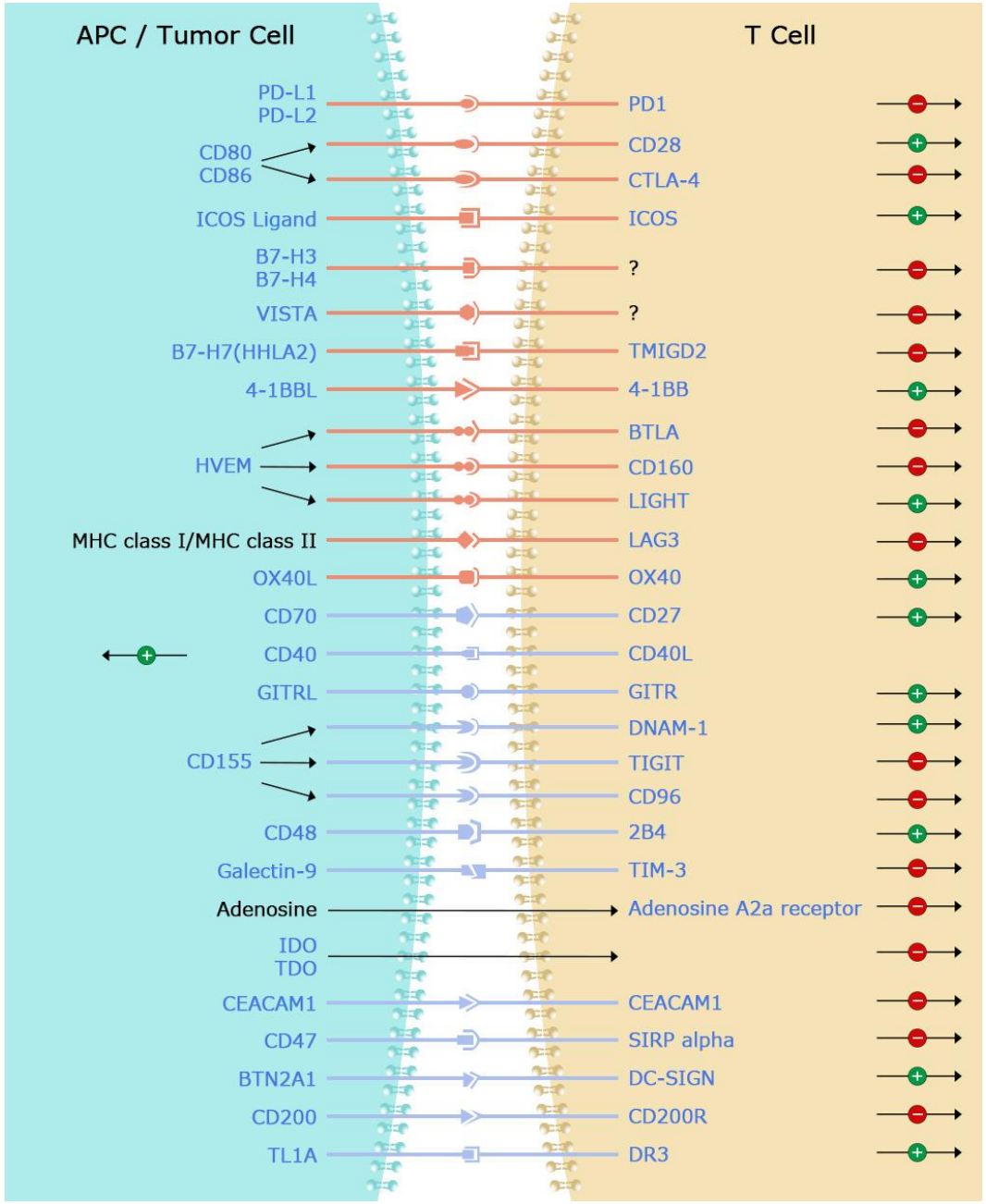
Targeting Immunocheckpoints: Immunoregulatory pathways



PD: Programmed cell Death receptor,

CTLA-4: Cytotoxic T Lymphocyte Antigen 4

Immunocheckpoints: new therapeutic targets



Drugs blocking **LAG-3, TIM-3, TIGIT, VISTA, or B7/H3**

Agonists of stimulatory checkpoint pathways such as **OX40, ICOS, GITR, 4-1BB, CD40**

Drugs interfering with **adenosine** pathway

At the clinical level, it is not yet clarified why certain patients respond to specific types of immunotherapies, while others do not.

The development of future treatments depends on finding effective immune-based **biomarkers** that can help to predict responses to treatment.

Precision medicine

Personalized medicine

The Italian Society of Immunology, Clinical Immunology and Allergology

announces

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L'Aquila 7-9 September 2020

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