TUMOR IMMUNOLOGY

INTRODUCTION

- Tumors look like an allograft in relation to rejection mechanisms by the body.
- **Immuno-surveillance** is the ability of the immune system to prevent the development of most tumors through early recognition and destruction of tumors cells.
- **tumor antigens**

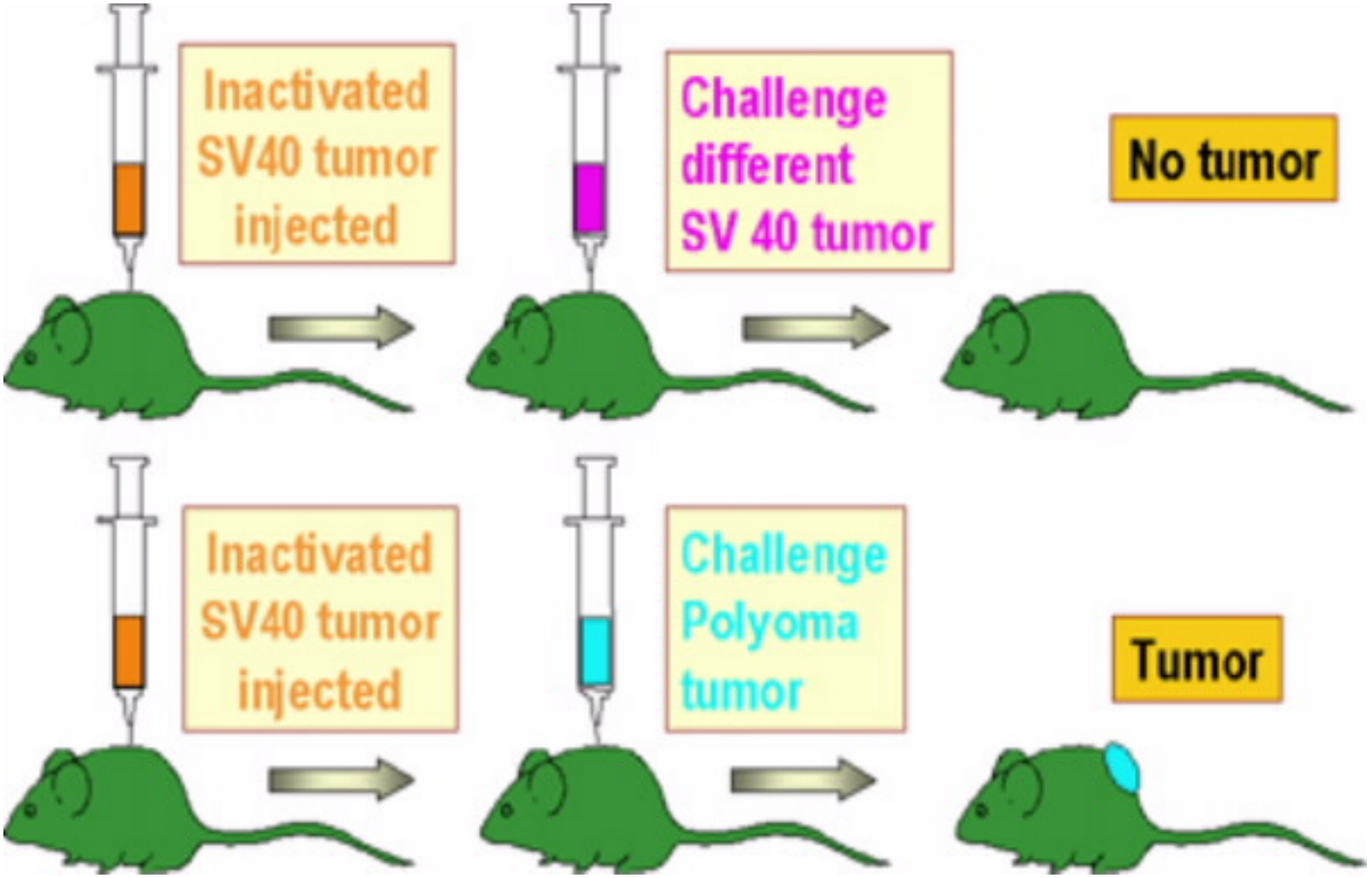
  Surface membrane molecules developed by tumor cells, which can be recognized by the immune system.

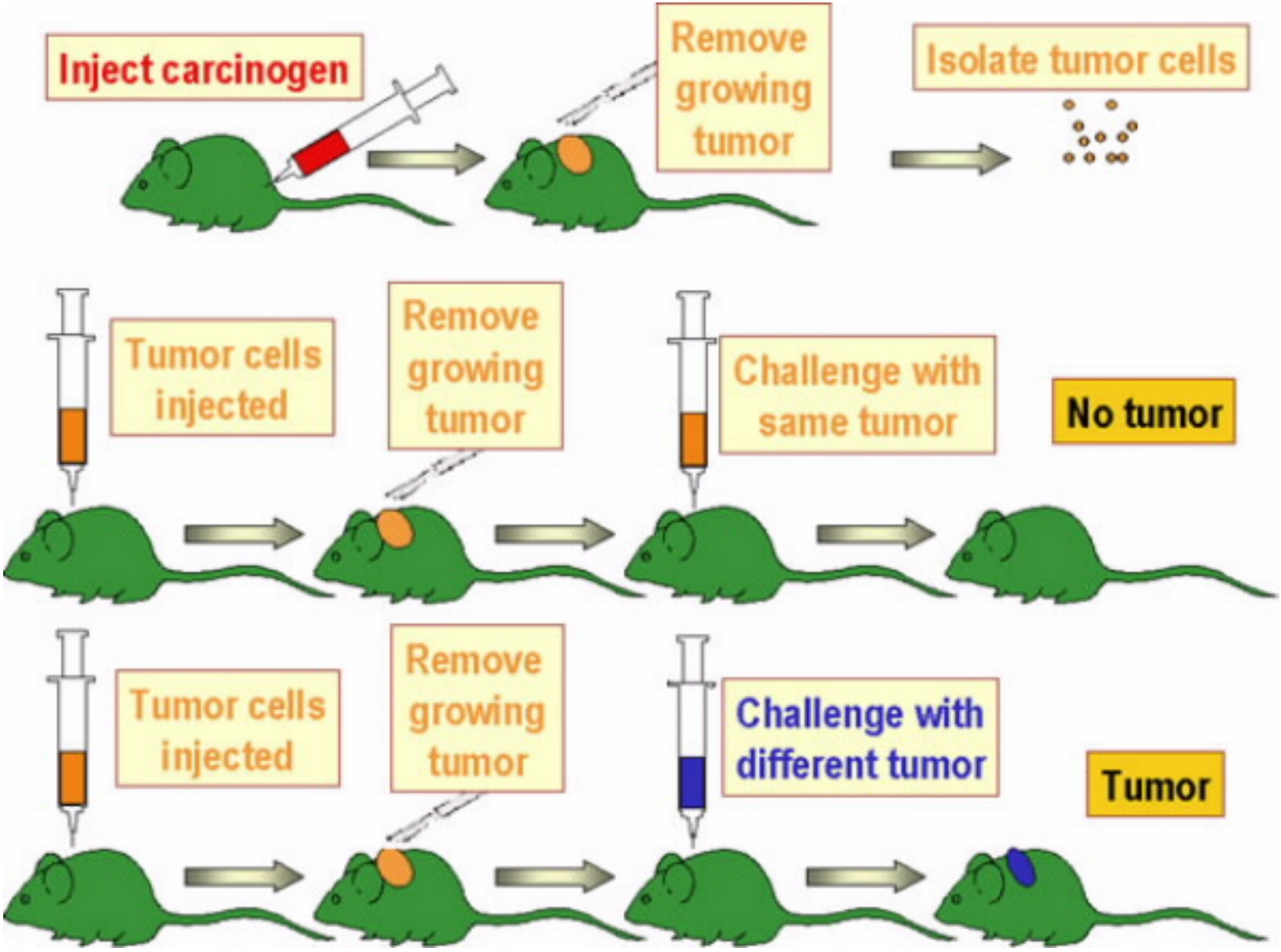
TUMOR ANTIGENS

Two groups of tumor antigens have been described:

- **Tumor-specific antigens (TSAs)**
  - antigens that are expressed on tumor cells but not on normal cells and might
  - induce an active immune response.
- **Tumor-associated antigens (TAAs)**
  - antigens that are relatively restricted to tumor cells but may also be present on normal tissue
  - may not be able to stimulate an effective response.

Any tumor antigen, from either group, that contributes to tumor rejection is referred to as **tumor-associated transplantation antigen** (TATA).


Inactivated SV40 tumor injected
Challenge different SV 40 tumor
No tumor
Inactivated SV40 tumor injected
Challenge Polyoma tumor
Tumor


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

ORIGIN OF TUMOR ANTIGENS

- **Oncofetal antigens:**
  - Present during normal fetal development but are lost during adult life.
  - They may reappear with the development of tumors.
  - Alpha feto-proteins (AFP) in hepatoma
  - Carcinoembryonic antigen (CEA) in colon carcinomas.

ORIGIN OF TUMOR ANTIGENS

- **Tumor associated transplantation antigens (TATA) on virally-induced tumors:**
  - These are virally derived peptides associated with surface MHC on the tumor cell.
  - They behave as powerful transplantation antigens.
  - They are present mainly on tumors produced by oncogenic viruses e.g. Epstein-Barr virus (EBV) in lymphomas, and hepatitis B virus in hepatic carcinoma.

ORIGIN OF TUMOR ANTIGENS

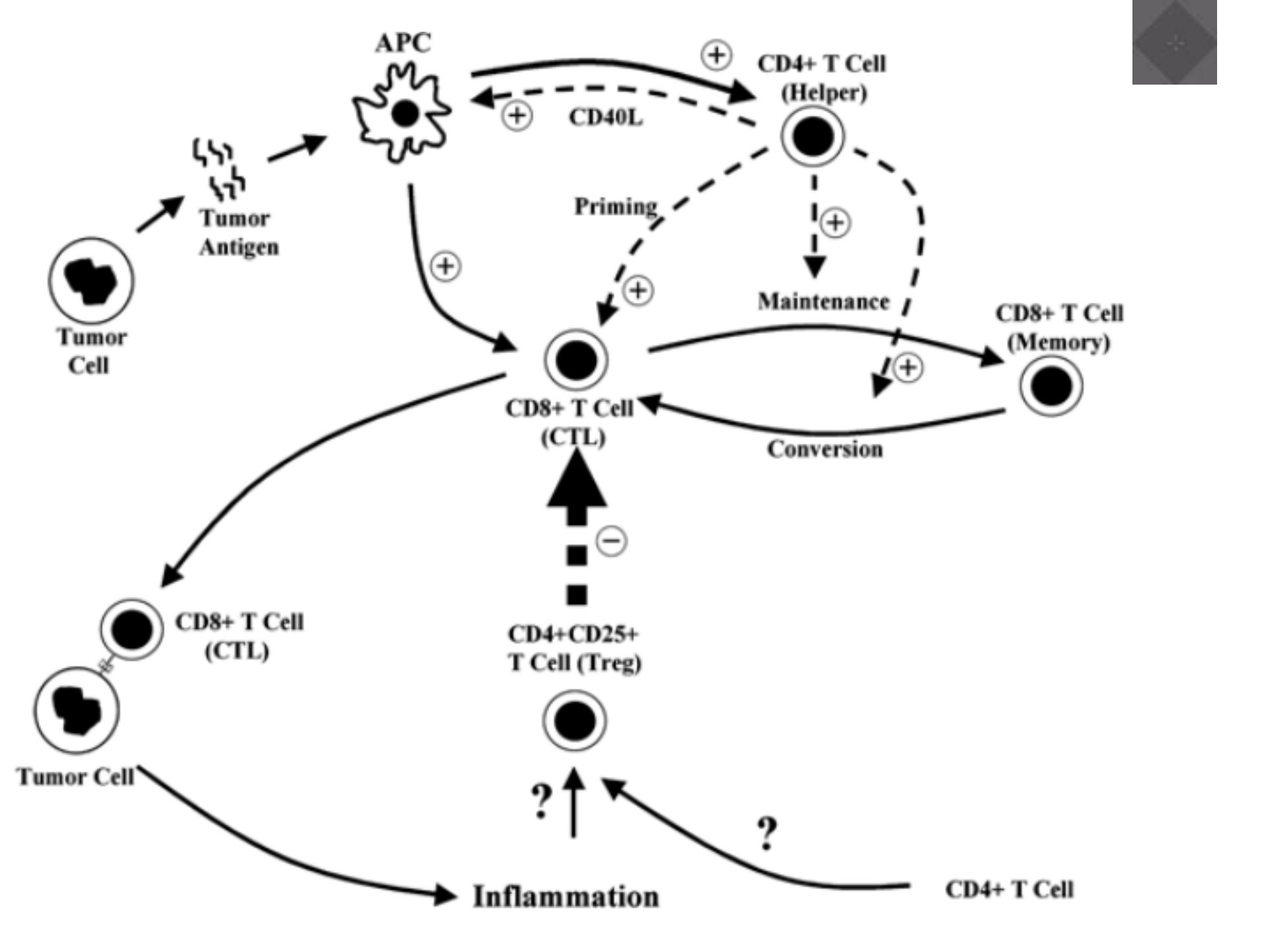
- **Tissue-specific differentiation antigens:**
  - A tumor arising from a particular tissue may express normal differentiation antigens specific for that tissue, e.g. prostate-specific antigen.

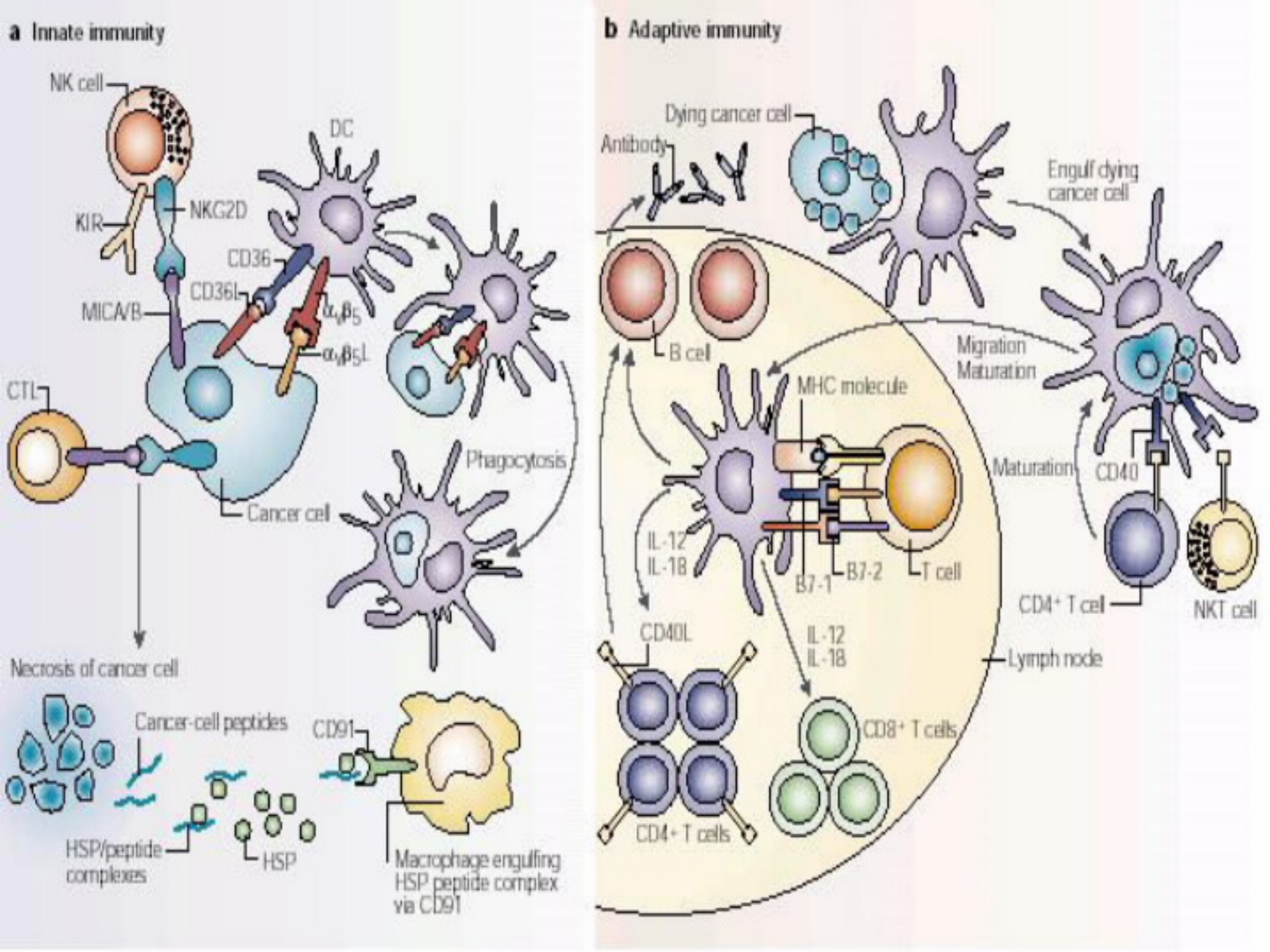
EVIDENCE FOR IMMUNE RESPONSE TO TUMORS

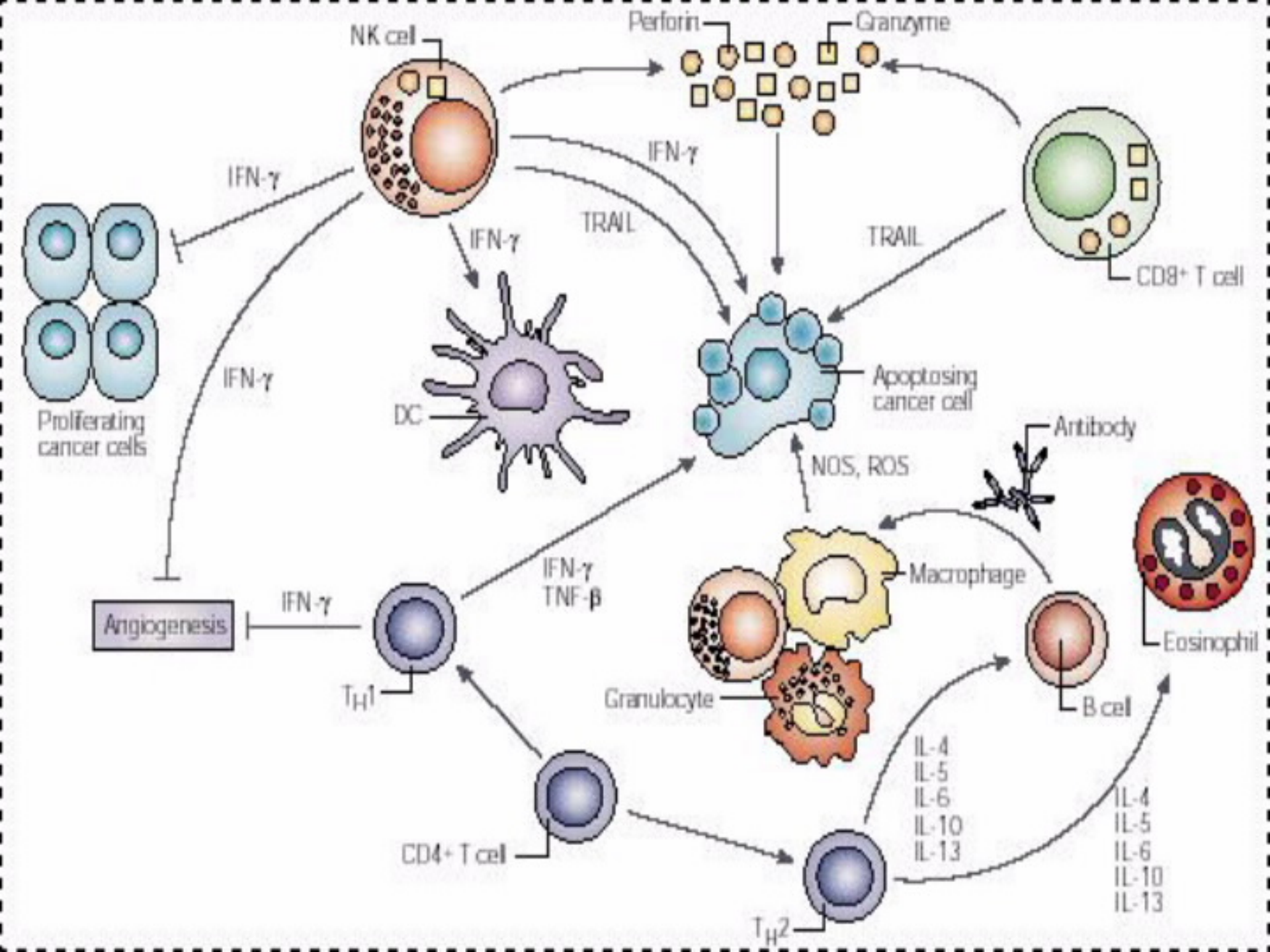
- Immunosuppressed patients (e.g. AIDS patients) develop tumors frequently.
- Extremes of age have an increased incidence of tumors.
- Antibodies and T lymphocytes against tumor antigens have been detected in patients with tumors.
- Animals can be specifically immunized against various types of tumors.

EFFECTOR IMMUNE MECHANISMS AGAINST TUMORS

I. **T Cells**: These are the main cells responsible for anti-tumor immunity:
   1. **Cytotoxic T cells** recognize antigens in association with class I MHC molecules on tumor cells and kill them. These cells are thought to play the most important role in recognition of tumor cells and their destruction.
   2. **Helper T cells** secrete cytokines which activate Tc cells, macrophages, NK cells and B cells. Th cells also produce TNF which is directly toxic to tumor cells.


APC
CD4+ T Cell
(Helper)
CD40L
Tumor
Antigen
Tumor
Cell
Priming
Maintenance
CD8+ T Cell
(Memory)
CD8+ T Cell
(CTL)
Conversion
CD8+ T Cell
(CTL)
CD4+CD25+
T Cell (Treg)
Tumor Cell
?
?
Inflammation
CD4+ T Cell


a Innate immunity
NK cell
DC
KIR
NKG2D
CD36
CD36L
MICA/B
$\alpha_v\beta_5$
$\alpha_v\beta_5$L
CTL
Phagocytosis
Cancer cell
Necrosis of cancer cell
Cancer-cell peptides
CD91
HSP/peptide complexes
HSP
Macrophage engulfing HSP peptide complex via CD91
b Adaptive immunity
Dying cancer cell
Antibody
Engulf dying cancer cell
B cell
Migration
Maturation
MHC molecule
Maturation
CD40
IL-12
IL-18
B7-1
B7-2
T cell
CD4+ T cell
NKT cell
CD40L
IL-12
IL-18
Lymph node
CD8+ T cells
CD4+ T cells


NK cell
Perforin
Granzyme
IFN-γ
IFN-γ
TRAIL
TRAIL
IFN-γ
IFN-γ
CD8+ T cell
Proliferating cancer cells
DC
Apoptosing cancer cell
NOS, ROS
Antibody
Macrophage
IFN-γ TNF-β
IFN-γ
Angiogenesis
Eosinophil
TH1
Granulocyte
B cell
IL-4 IL-5 IL-6 IL-10 IL-13
IL-4 IL-5 IL-6 IL-10 IL-13
CD4+ T cell
TH2

EFFECTOR IMMUNE MECHANISMS AGAINST TUMORS

II. B Cells and Antibody-Dependent Killing

B cells :

- Act as APCs → Th cell stimulation.
- Produce tumor reactive antibodies.

Antibodies may cause tumor cell lysis by:

- Fixing complement to the tumor cell membrane

↓

MAC causing tumor cell lysis.

- Antibody-dependent cellular cytotoxicity (ADCC) by NK cells & possibly macrophages.

EFFECTOR IMMUNE MECHANISMS AGAINST TUMORS

III. Natural Killer Cells

- NK cells recognize tumor cells and kill them.
- NK cell activity is enhanced by IL-2 and INF-γ produced by Th1 cells.
- NK cells also kill tumor cells by ADCC.

EFFECTOR IMMUNE MECHANISMS AGAINST TUMORS

IV. Monocytes/Macrophages

Monocytes/macrophages play an important role through:

- Antigen presentation and cytokine secretion.
- ADCC.
- Direct cytotoxicity of the tumor cells by releasing TNF-α, nitric oxide and hydrogen peroxide.

TUMOR EVASION OF THE IMMUNE RESPONSE

A number of mechanisms have been suggested for the escape of tumors from immuno-surveillance:

1. Host may be immunocompromised.
2. Factors related to tumor antigens:
   - Some tumors lack antigens that can stimulate the immune response.
   - Some tumor antigens cannot be processed and presented with MHC.
   - Amount of antigen may be too small to stimulate the immune system.
   - Some tumors may shed their antigens which block antibodies and T cells from reacting with the tumor cells.

TUMOR EVASION OF THE IMMUNE RESPONSE

3. Tumors localized at sites inaccessible to the immune system e.g. CNS.
4. Certain tumors (virally-induced) lack or are poor in expression of MHC I molecules.

TUMOR EVASION OF THE IMMUNE RESPONSE

5. Some viruses block expression of co-stimulatory molecules (e.g. B7) by antigen-presenting cells.
6. Blocking antibodies: Non-cytolytic (non-complement fixing) antibodies in the serum may bind to the tumor antigens, making them inaccessible to complement fixing antibodies. This prevents complement mediated lysis of tumor cells.
7. Fibrin coating leads to masking of tumor antigens.
8. Some tumors may secrete substances , such as TGF-ß, that suppress the immune response directly.

TUMOR IMMUNODIAGNOSTICS

- Tumor antigens can be very useful **tumor markers** in the diagnosis and follow-up of various tumors.
- An ideal tumor marker is:

1. Released only from tumor tissue,
2. Specific for a given tumor type,
3. Detectable early upon tumor formation,
4. Its concentration in the blood is proportional to the tumor mass
5. Present in all patients with the tumor.

TUMOR MARKERS

- **Carcinoembryonic antigen** (CEA): in colon carcinomas.
- **α-Fetoprotein** (AFP): in primary hepatoma.
- **β-Subunit of human chorionic gonadotrophin (β-HCG)**: in choriocarcinoma.
- **Prostate-specific antigen** (PSA): in cancer prostate.

TUMOR MARKERS

- **CA 125:** in ovarian cancer.
- **CA 19-9:** in colonic and pancreatic tumors.
- **CA 15-3:** in breast cancer.
- **Bence-Jones proteins:** in myeloma.
- **Pancarcinoma antigen** (TAG-72): is used to localize occult tumor secondaries by using radio-labeled monoclonal antibody.

TUMOR IMMUNOTHERAPY

1. **Passive Cellular Immunotherapy**

Passive cellular immunotherapy is a term used when activated cells are directly infused into a patient:

A. **Therapy with lymphokine-activated killer (LAK) cells**: The patient's lymphocytes (including NK cells) are cultured *in vitro* with IL-2 then re-infused.

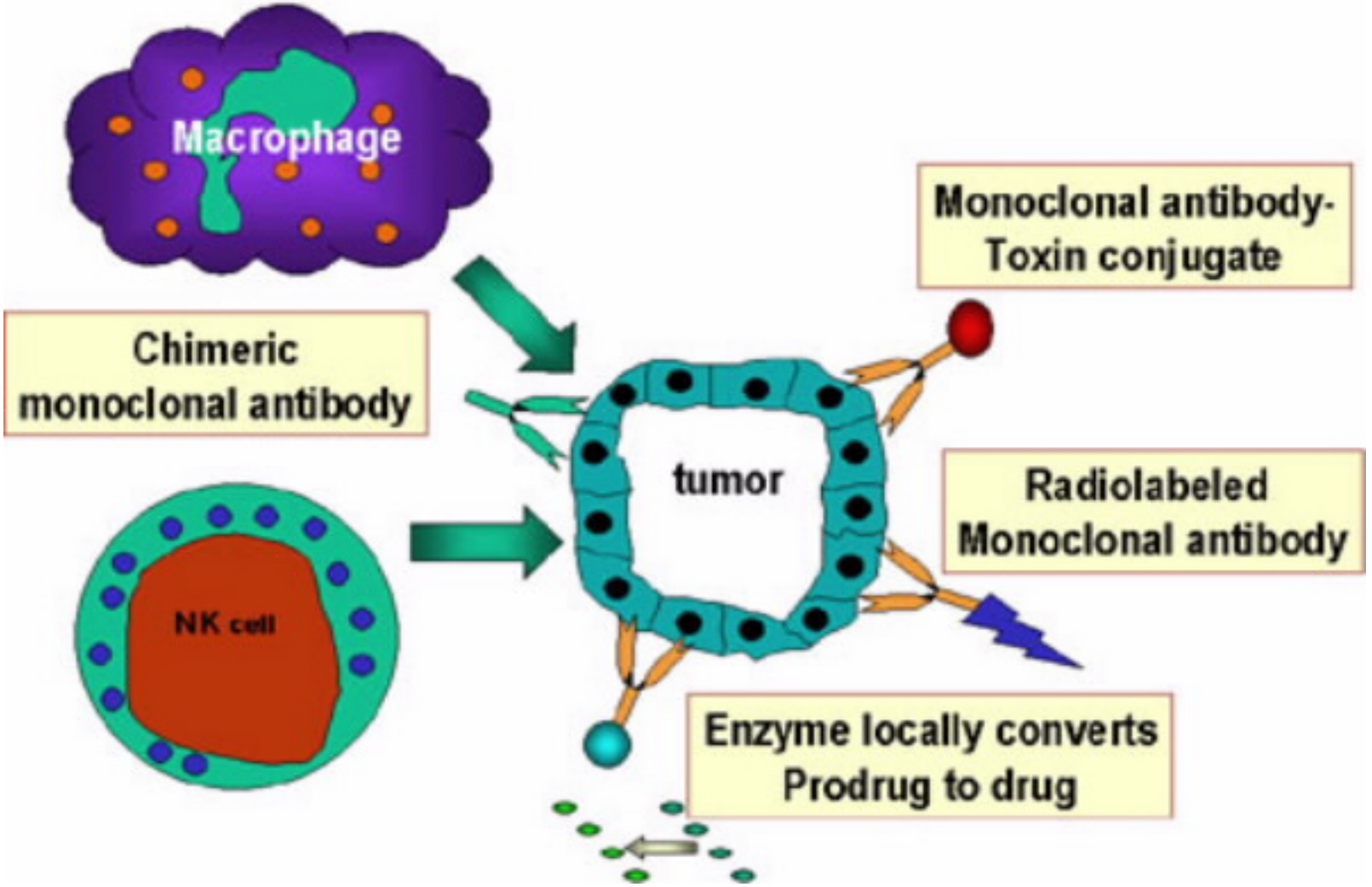
B. **Therapy with T cells**: In this approach, lymphocytes that have infiltrated tumors are extracted from tumor biopsies, stimulated *in vitro* using IL-2 and tumor antigen and then re-infused.

TUMOR IMMUNOTHERAPY

2. **Passive Humoral Immunotherapy**

Monoclonal antibodies directed against tumor antigens may be used either alone or coupled to radioisotopes, cytotoxic drugs, toxins (e.g. diphtheria toxin) or cytokines. Coupling has the advantage of delivering high doses of radioactivity or cytotoxic drugs directly to the site of the tumor **(magic bullet).**

TUMOR IMMUNOTHERAPY



TUMOR IMMUNOTHERAPY

3. **Passive Cellular and Humoral (Combined) Immunotherapy**

This is a new approach, based on the development of bi-specific (bi-functional) antibodies, which links one antibody reacting with the tumor cell to a second antibody reacting with a cytotoxic effector cell, targeting the latter directly to the tumor.

TUMOR IMMUNOTHERAPY

4. **Active Specific Immunotherapy**

   A. **Allogeneic tumor cells** : These are tumor cells taken from other patients, irradiated and then injected with BCG vaccine or other adjuvants.

   B. **Tumor antigen vaccines** are among the most promising approaches in cancer immunotherapy. Cellular immunity to specific, well-defined antigens can be induced by using short synthetic peptides.

TUMOR IMMUNOTHERAPY

5. Nonspecific Immunotherapy

A. **Interferons** (IFNs) have anti-tumor activity in leukemia and AIDS-associated Kaposi's sarcoma.

B. **Bacterial Adjuvants** e.g. BCG, or killed suspensions of *Corynebacterium parvum* have been used with or without tumor antigens, to treat a wide variety of cancers, usually along with intensive chemotherapy or radiotherapy.

THANK YOU