Tumor immunology

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Lession plan

- What is a tumor / neoplasm?
- Properties of tumor
- Role of immune system to prevent tumors
  - "Immune surveillance"
- Immunogenicity of tumors
  - TSTA, TAA
- Defence mechanisms against tumors
  - NK cells,
  - CTL,
  - Macrophage – Macrophage mediated cytotoxicity MTC
- Escape from immune surveillance
- Immunodiagnosis of tumors
- Immunotherapy against tumors

- In the year 2000 there were 10 million (1 crore) new cases of cancer and 6 million (60 lakh) deaths worldwide.

What is a Tumor?

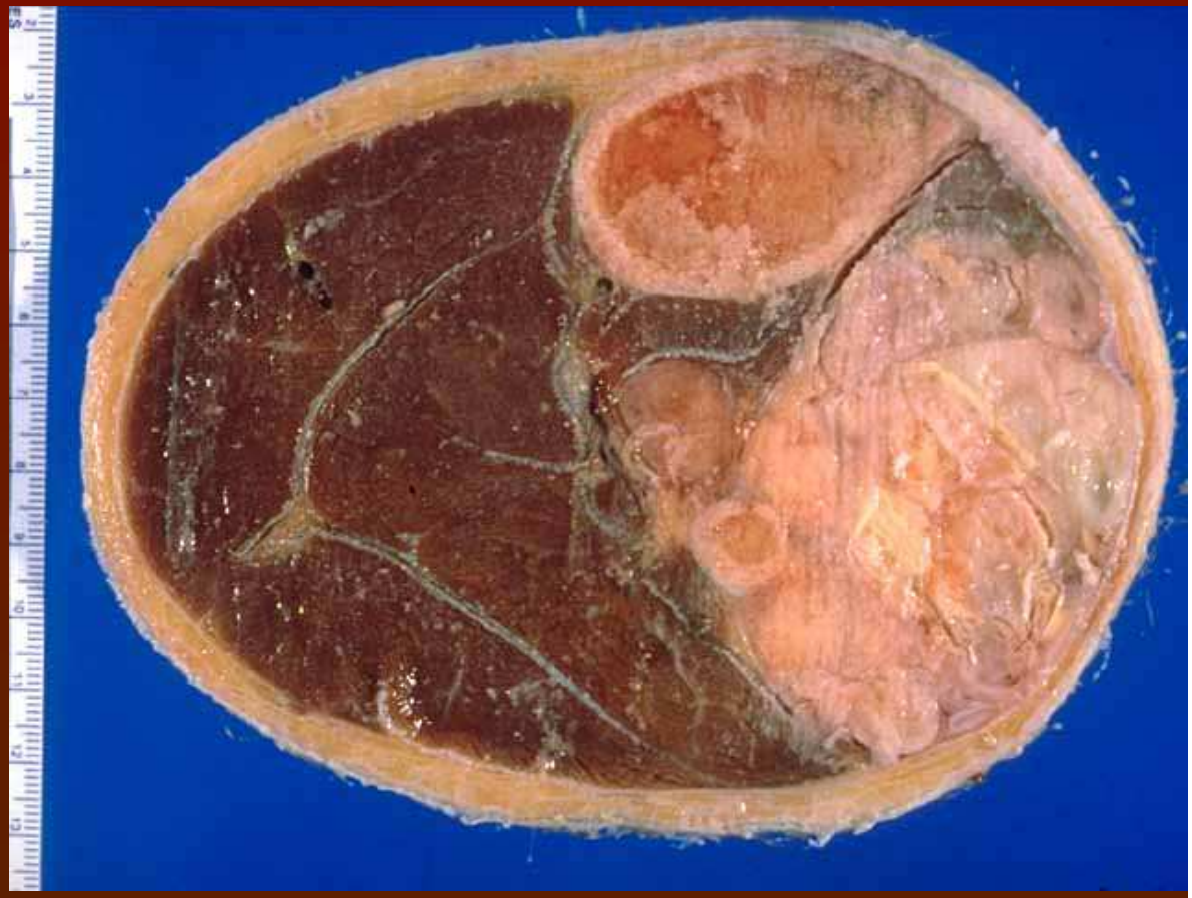
- Neoplasia means “New growth” and a new growth is called a neoplasm.
- “A neoplasm” is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change”

Definitions

Neoplasm

=

“Tumor”

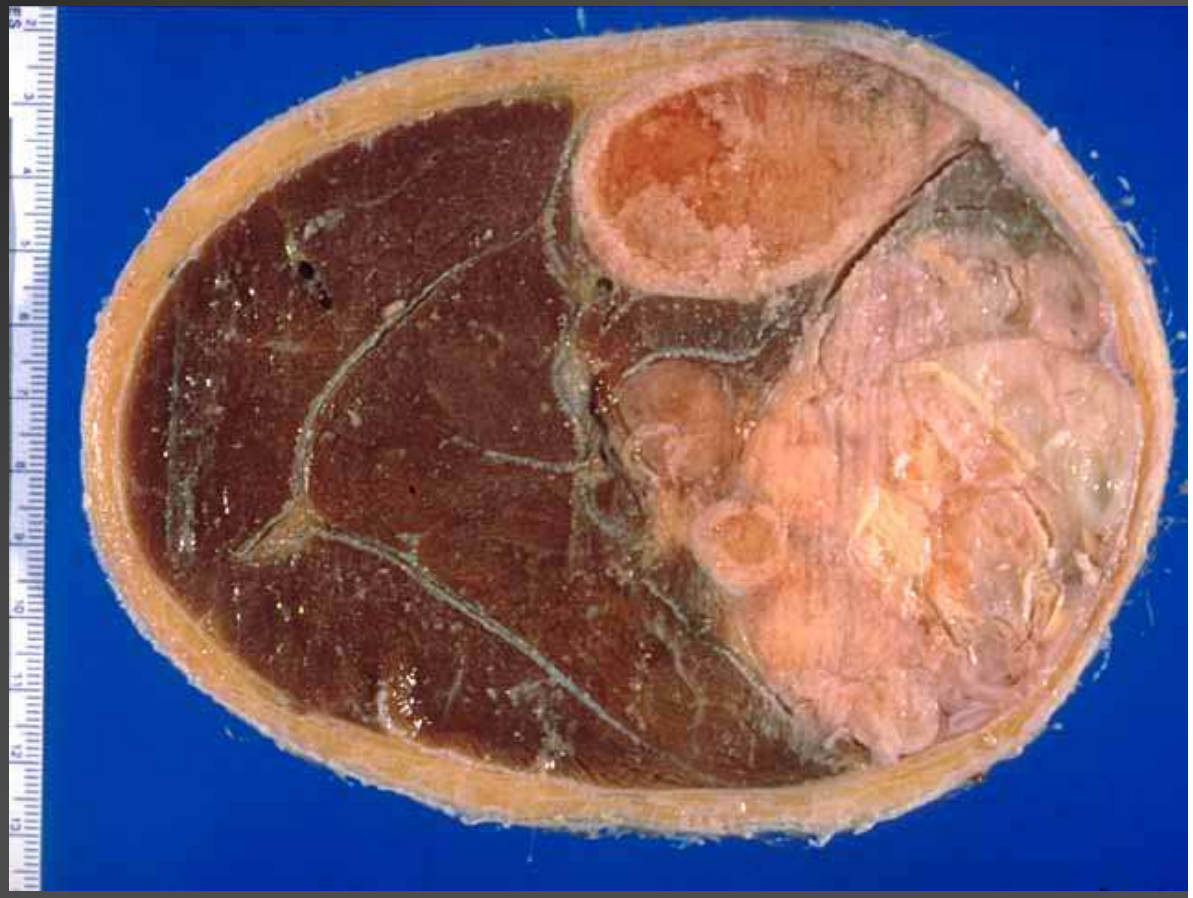


Definitions

Malignant neoplasm

=

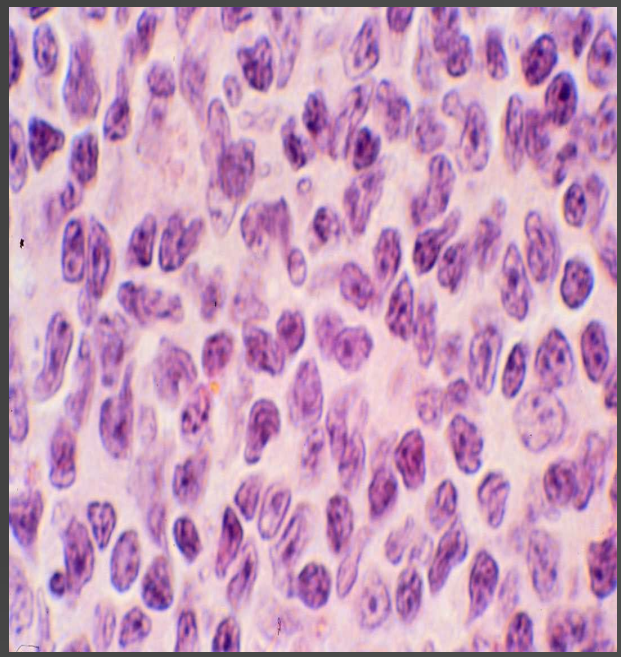
"Cancer"



Properties of tumor cells

- Monoclonality
- Autonomous proliferation

  (usually!)
- Many tumors have known abnormalities in genes controlling the *cell cycle:*
  - *oncogenes*
  - *tumor suppressor genes*
- A few slow-growing tumors have abnormalities in genes controlling *programmed cell death*



Immune surveillance

- This theory says
  - Immune system continually recognizes and eliminates tumor cells; when a tumor escapes immune surveillance and grows too large for the immune system to kill, cancer is the result.

Evidence for immune reactivity to tumors-1

1. Tumors that have severe lympho-reticular infiltration have a better prognosis than those that do not.
2. Certain tumors regress spontaneously (*e.g.*, melanomas, neuroblastomas).
3. There is an increased incidence of primary and secondary malignancies (particularly lympho-reticular tumors) in immunodeficient patients).

Evidence for immune reactivity to tumors-2

4. Antibodies and immune T lymphocytes (in cytotoxicity and mitogenic response assays) have been detected in patients with tumors.
5. The young and the very old have an increased occurrence of tumors. These members of the population often have an immune system that is less effective.
6. Finally, animals can be specifically immunized against various types of tumors.

Immunogenicity tumors

- Two types of tumor antigens
  - Tumor associated antigens (TAA)
    - Are more common and found on tumor cells and on normal cells during fetal life (oncofetal antigens) after birth in selected organs at low conc.
  - Tumor specific antigens (TSTA)
    - Present only on tumor cells (usually vrial induced) but not normal cells

Tumor associated antigens-1

- A number of alterations occur in the cell during tumorigenesis (*e.g.*, enzymes, receptors, membrane antigens, *etc*.).

- Most relevant from the point of view of immuno-surveillance are surface membrane molecules which might be antigenically novel or suppression of membrane proteins that are essential for immune recognition and activation.

Tumor associated antigens-2

2. In animals, most chemically- or physically-induced tumors or or those produced as a result of a virus, have **neo-antigens**.

3. Spontaneously occurring tumors are often weakly immunogenic or non-immunogenic.

Tumor associated antigens-3

4. Antigenic changes observed in malignant cells include
   - reappearance of fetal antigens (**onco-fetal antigens**),
   - expression of unique antigens not expressed by normal cells.
5. Some of these antigens may be secreted while others are membrane-associated molecules.
6. Neo-antigens that contribute toward tumor rejection are referred to as **tumor associated transplantation antigens** (**TATA**).

Onco-fetal antigens

- Onco-fetal antigens may appear due to de-repression of genes that were only expressed early in life.
- Two major onco-fetal antigens are
  - **alpha-fetoprotein** (**AFP)** and
  - **carcino-embryonic antigen** (**CEA**).
- AFP is produced only as a secreted protein whereas CEA is found both on cell membranes and in secreted fluids.
- Since secreted antigens contribute little toward immunity against tumors, the role of these neo-antigens in immuno-surveillance is questionable.

Alpha-fetoprotein

- The normal range of AFP concentrations in humans is 0-20 ng/ml. This level rises considerably in patients with hepatomas and non-seminal testicular carcinoma.
- A 5-fold or higher rise in this protein is used for monitoring hepatomas and testicular cancers.
- AFP level may also be raised in some non-malignant conditions, such as
  - cirrhosis,
  - in hepatitis and
  - other forms of liver damage.

Carcinoembryonic antigen

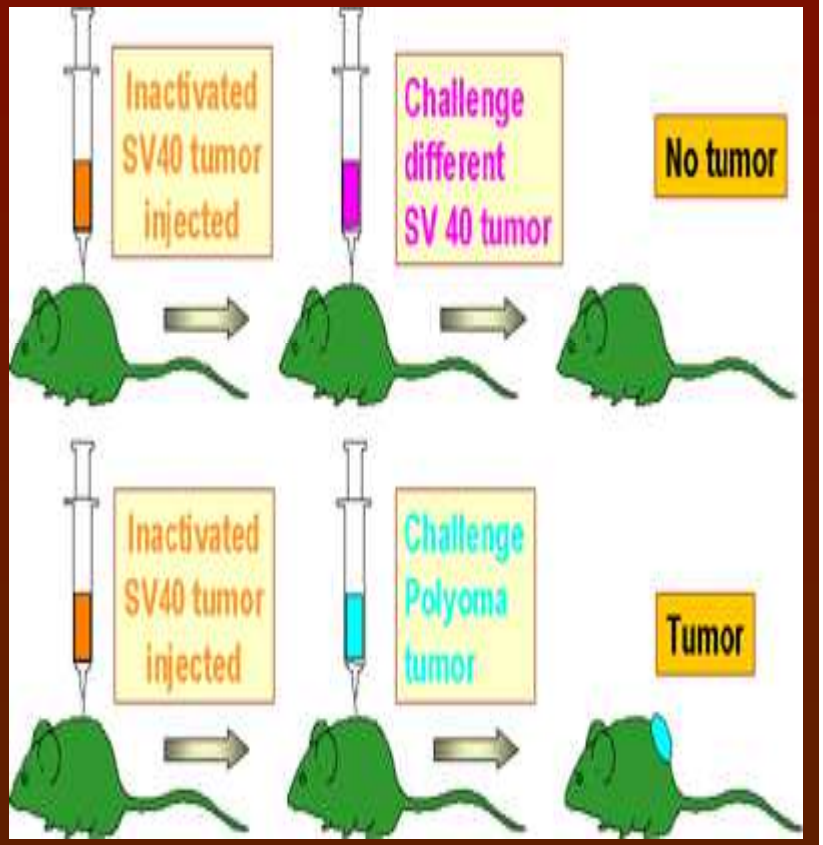
- CEA levels in normal people range up to 2.5 ng/ml,
- they increase significantly in certain malignancies,
  - particularly colo-rectal cancers.
- They may also rise in some non-malignant conditions
  - chronic cirrhosis,
  - pulmonary emphysema and
  - heavy smoking
- Levels that are 4-5 times normal have been used to predict recurrence of colo-rectal tumors.

Tumor associated transplantation antigens (TATA) on viral tumors

- A number of viruses cause different types of tumors in animals (SV-40 virus, adenovirus, Rous sarcoma virus, Friend erythroleukemic virus, Moloney Rauscher and Gross viruses).
- Viruses are involved or suspected to be involved in some human malignancies (HTLV-1 in leukemia, hepatitis-B virus in hepatic carcinoma, papilloma virus in cervical cancer).

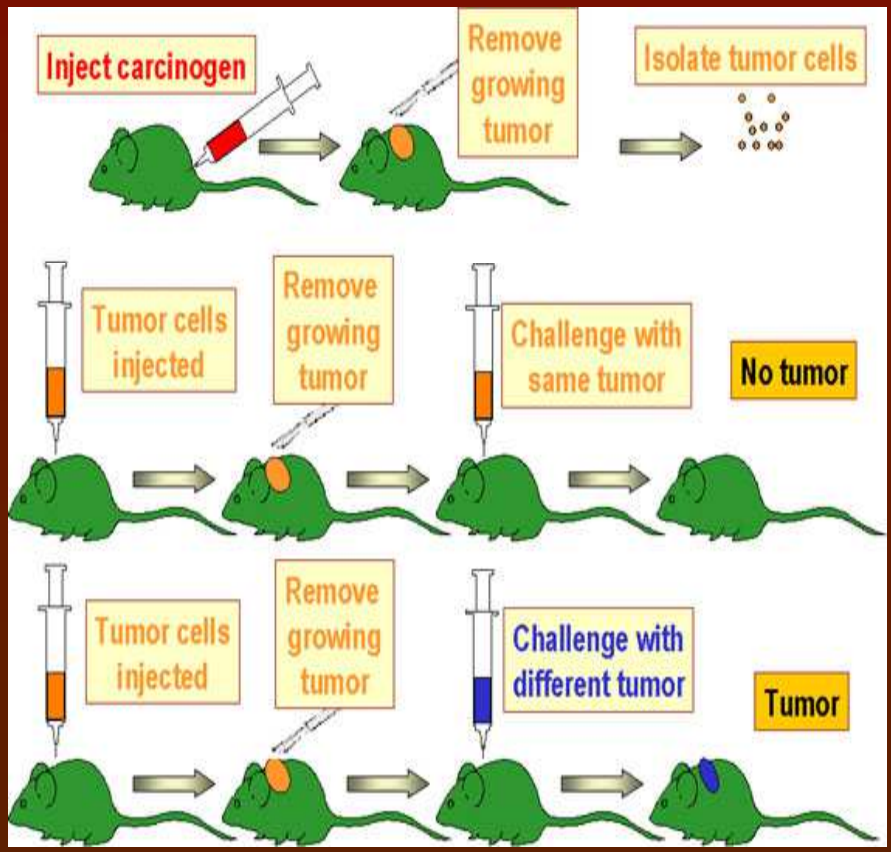
Tumor associated transplantation antigens (TATA) on viral tumors

- Virus-induced tumors express cell surface antigens (distinct from antigens of the virion itself) which are shared by all tumors induced by the same virus. These antigens are characteristic of the tumor-inducing virus, regardless of tissue origin of the tumor or animal species in which the tumor exists (Figure 1).



Tumor specific transplantation antigens on chemically-induced tumors

- Chemically-induced tumors are different from virally-induced tumors in that they are extremely heterogeneous in their antigenic characteristics. Thus, any two tumors induced by the same chemical, even in the same animal, rarely share common tumor specific antigens (Figure 2). These unique antigens on chemically-induced tumors are referred to as **tumor specific transplantation antigens (TSTA)**.



Immunity against tumors

- Evidence for immunity against malignancy comes mostly from experimental tumors, although there is ample evidence for anti-tumor immune reactivity in humans.
- In experimental studies, animals can be immunized by administering inactivated tumor cells or by removal of a primary tumor.
- Also, immunity can be transferred from an animal, in which a tumor has regressed, to a naive animal by injection of lymphocytes (T cells).
- All components of the immune system (non-specific and specific; humoral and cellular) can affect the growth and progression of a tumor.

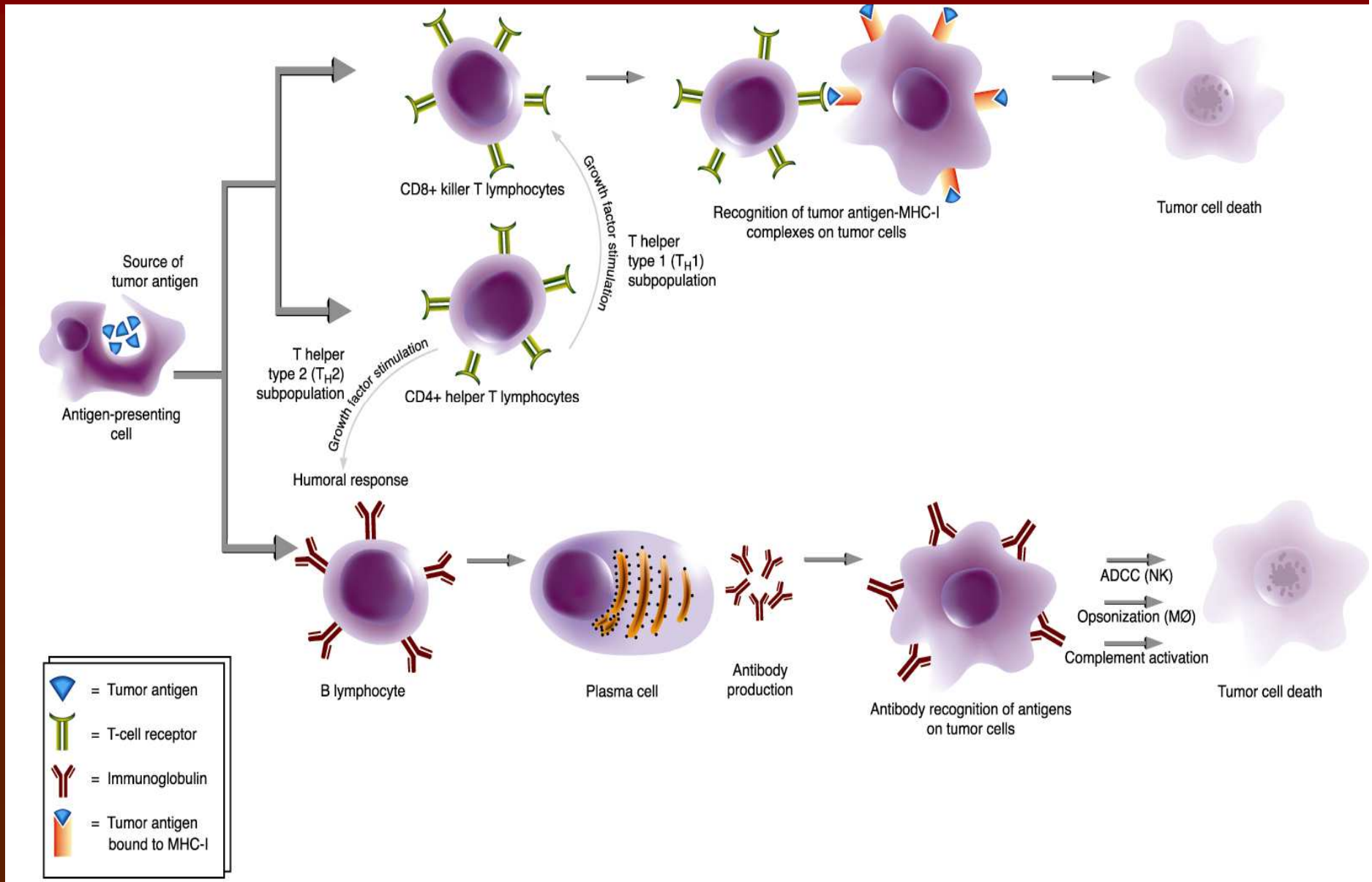
Mechanisms of immune surveillance

- All components take part.
  - NK cells
  - CTL
  - Macrophage play predominant role

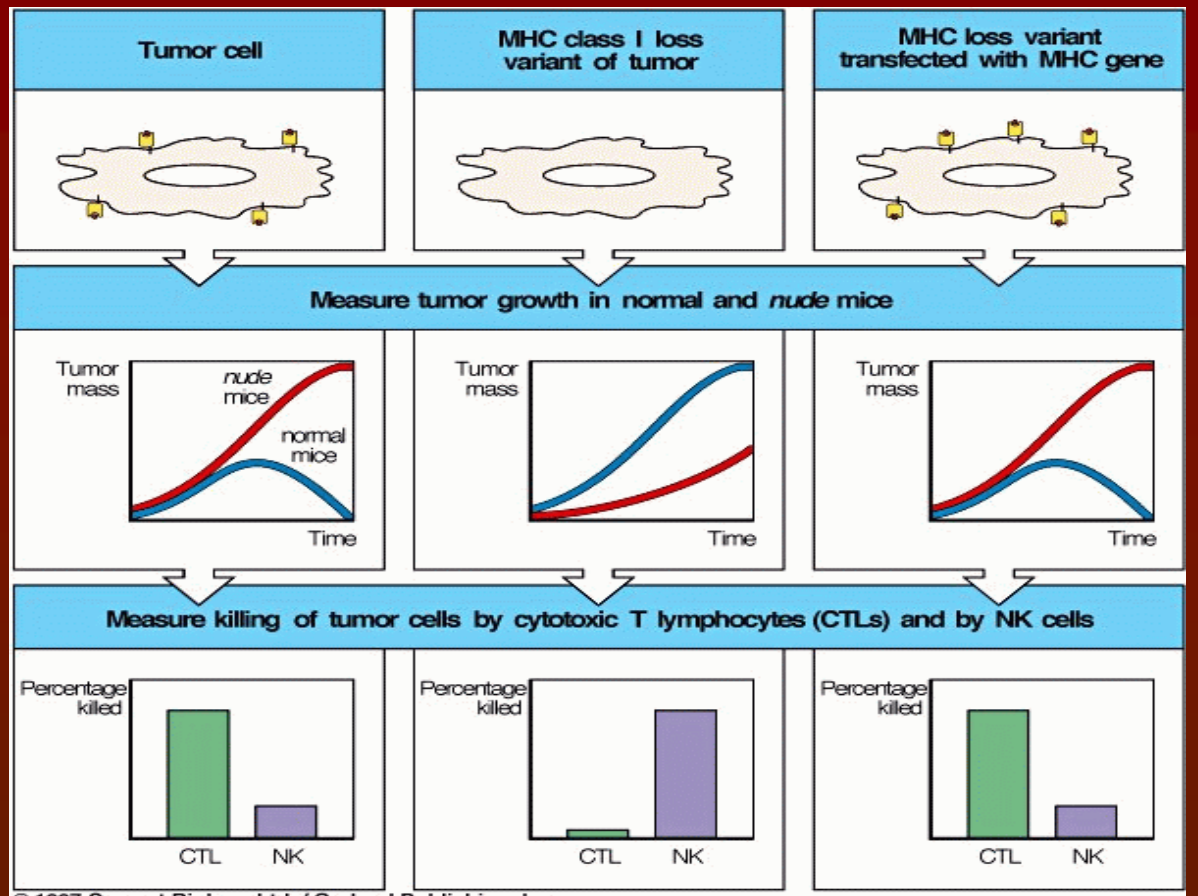
Natural Killer (NK) Cells

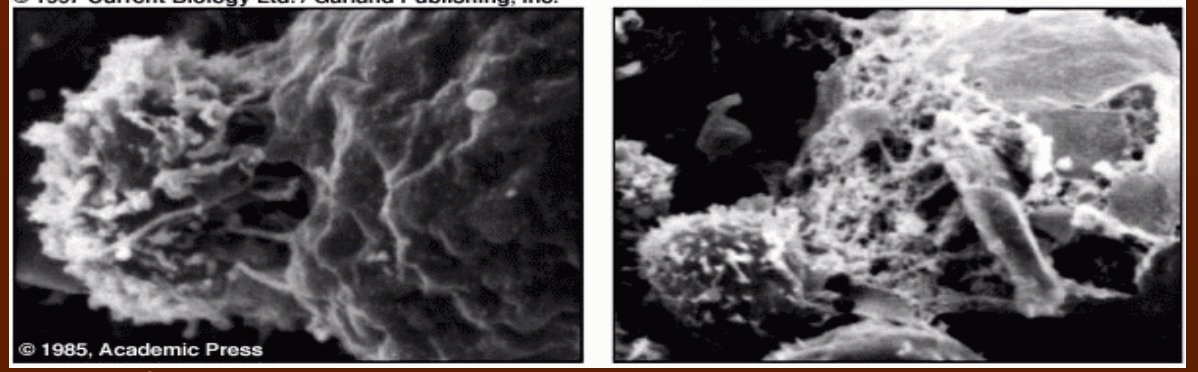
- Lymphocytes that are related to, but distinct from T cells.
- Provide first line of cell-mediated defense.
  - NK cells destroy tumors in a nonspecific fashion.
    - NK cells attach to cells that lack class-1 MHC antigens.
      - Release perforins and granzymes.
- Do not require prior exposure for sensitization to the tumor antigens.
- Stimulated by interferon.

The Antitumor Immune Response

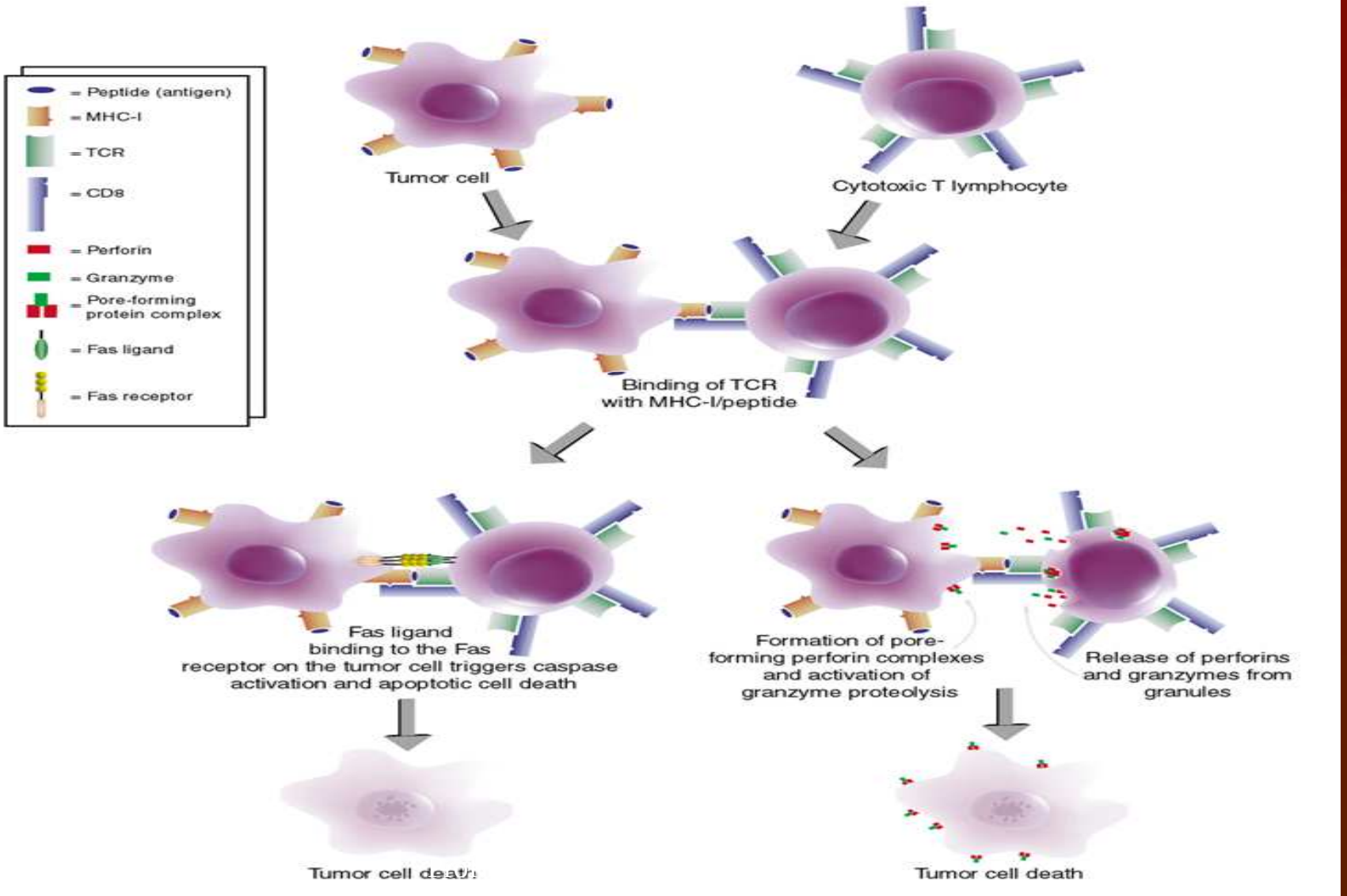


Reciprocal effectiveness of CTLs and NK cells against tumors

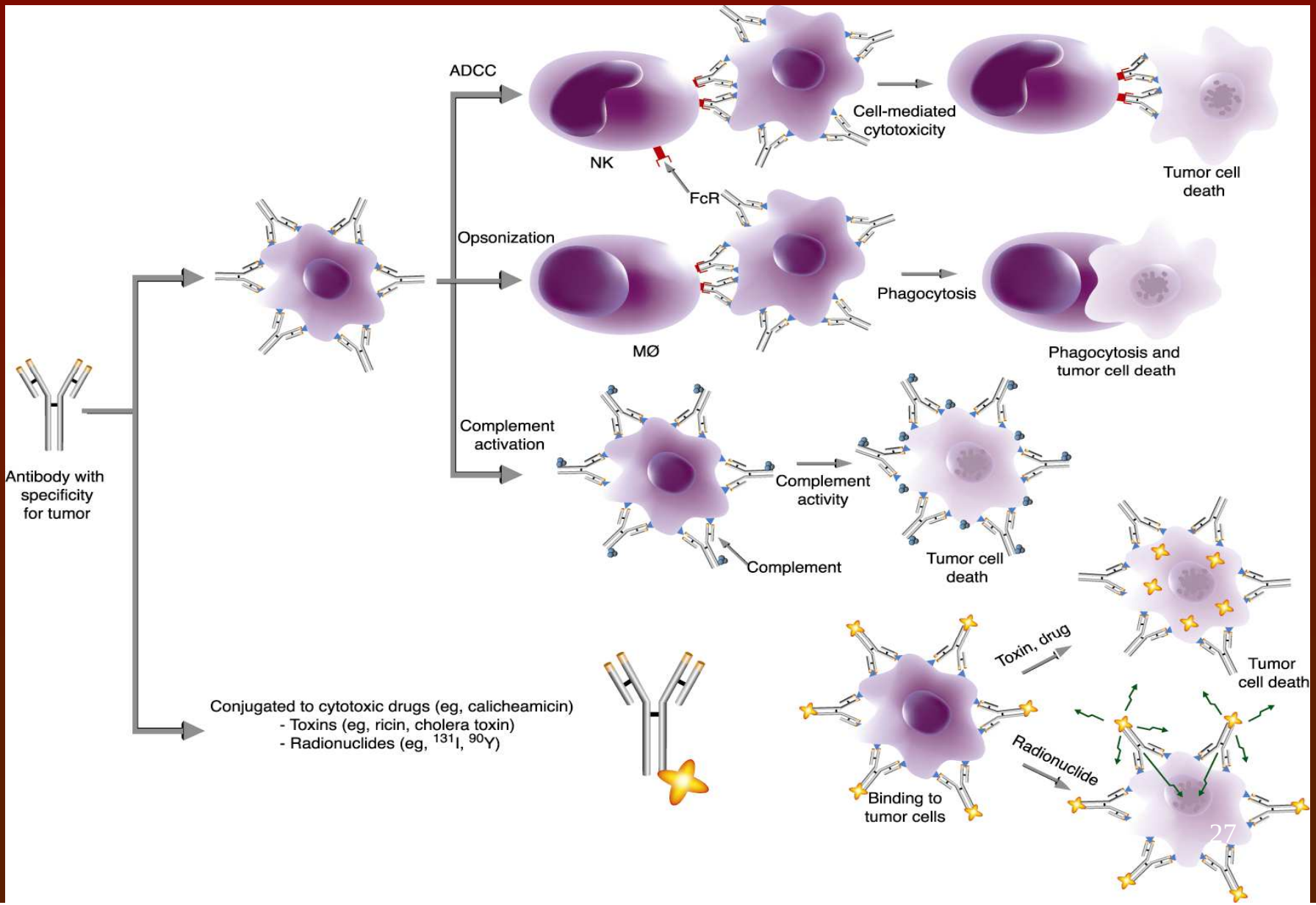




Effector Mechanisms of Tumor Cell Killing by Cytotoxic T Cells (CTLs)



Direct and Indirect Mechanisms Through Which Antitumor Antibody Can Mediate Tumor Cell Killing Directly



Escape from immuno-surveillance-1

- A number of mechanisms have been suggested
  1. Tumors may not express neo-antigens that are immunogenic or
  2. they may fail to express co-stimulatory molecules for the activation of T-cells.
  3. In addition, certain tumors are known to lack or be poor expressers of MHC antigen.

Escape from immuno-surveillance-2

4. Another reason for failure of immunosurveillance may be the fact that in the early development of a tumor, the amount of antigen may be too small to stimulate the immune system and, due to the rapid proliferation of malignant cells, the immune system is quickly overwhelmed.
5. In addition, some tumors may evade the immune system by secreting immunosuppressive molecules and others may induce suppressor cells.
6. Also, some tumors may shed their unique antigens which block antibodies and T cells from reacting with malignant cells.

Use of tumor neo-antigens in patient management

- **Immuno-diagnosis**
- **Immunotherapy**

Use of tumor neo-antigens in **Immuno-diagnosis**

1. Monoclonal antibodies labeled with radioisotope have been used for *in vivo* detection of relatively small tumor foci.
2. Antibodies have also been used *in vitro* to identify the cell origin of undifferentiated tumors, particularly of lymphocytic origin.
3. immuno-histological staining is used to confirm suspected metastatic foci, especially in bone marrow.
4. Tumor marker antigens e.g. CEA, AFP etc

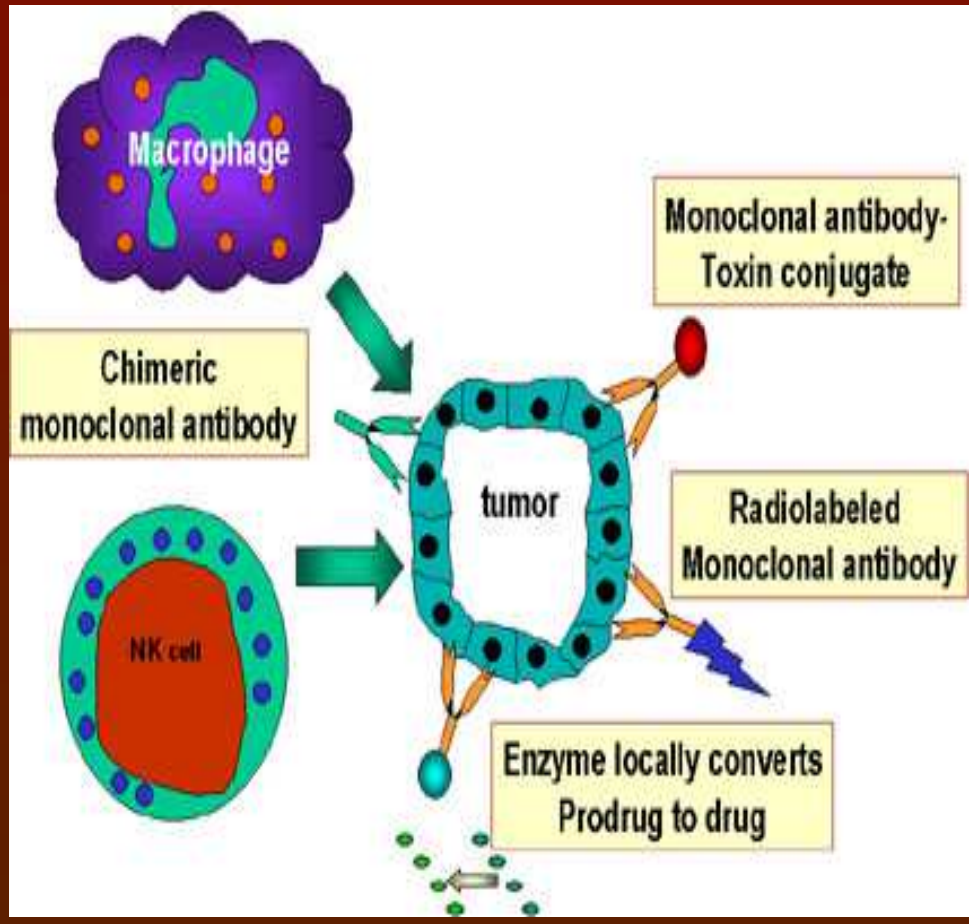
Immunotherapy for Cancer…

1. Monoclonal antibodies tagged with anticancer agents
2. Interleukin-2 activates both killer T and B lymphocytes.

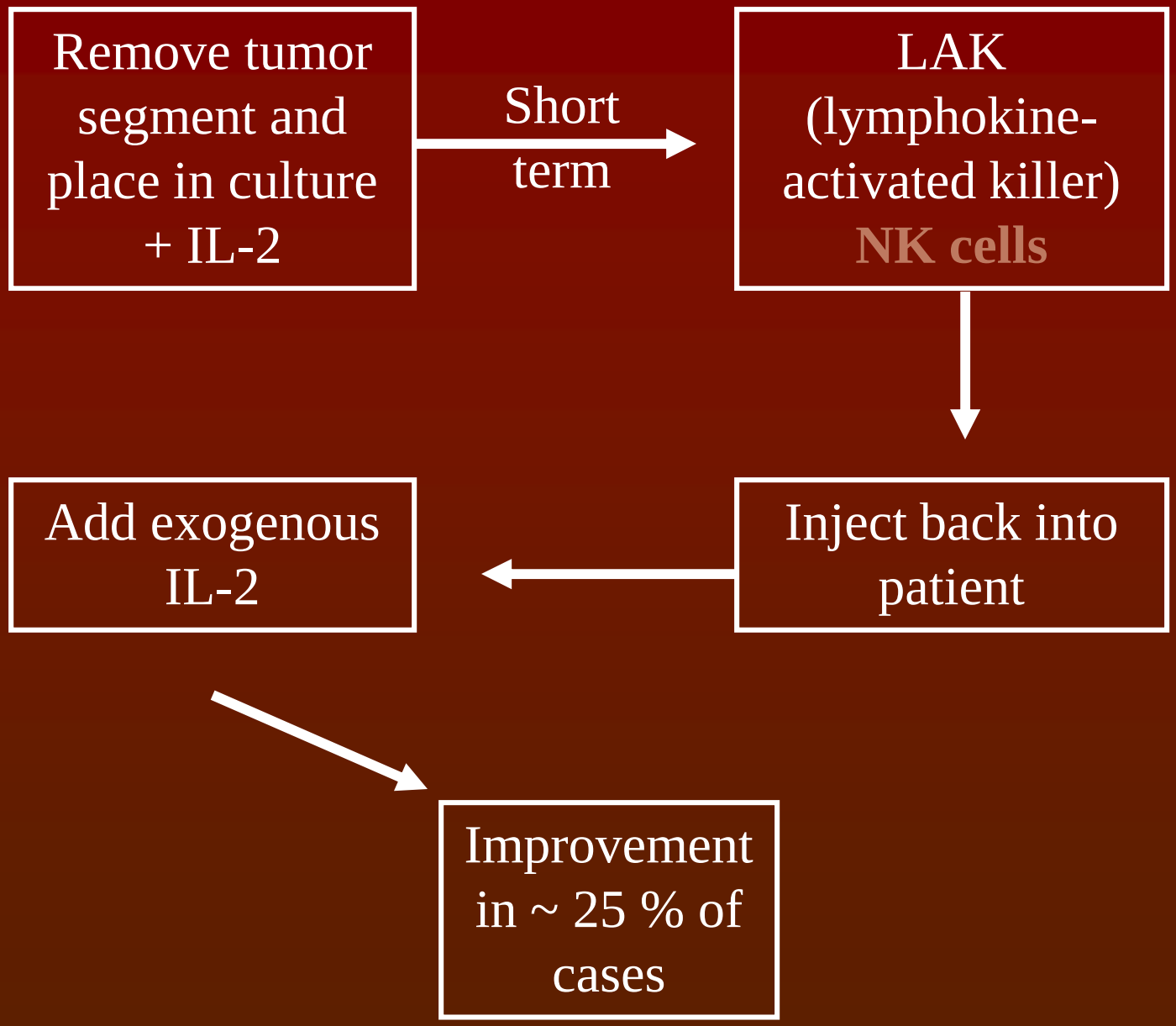
3. Gamma interferon is used to treat particular forms cancer. Lymphomas, renal carcinomas, melanoma, Kaposi's sarcoma.
4. Tumor infiltrating lymphocyte is promising.
5. Antitumor Vaccine

Use of monoclonal antibodies in immunotherapy (magic bullet)

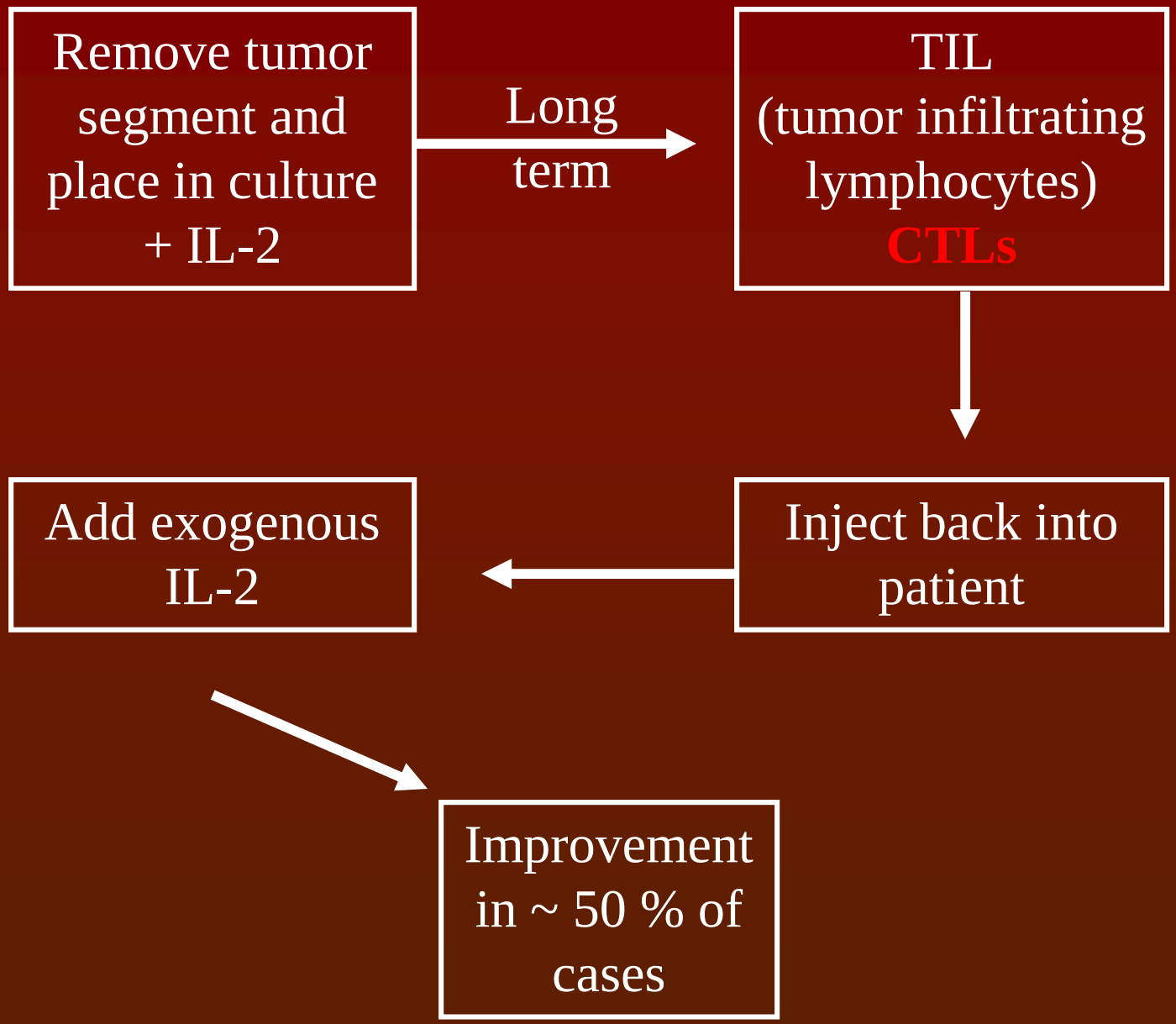
- Monoclonal anti-tumor antibodies have been used in different forms for the treatment of cancer, either because of their direct effect or as vehicles to target anti-cancer drugs, toxins and the non-specific components of the host's immune system to the site of tumor (Figure 3). In addition, such specific antibodies are also used in the diagnosis of metastatic lesions, otherwise not detectable by conventional radiologic means.



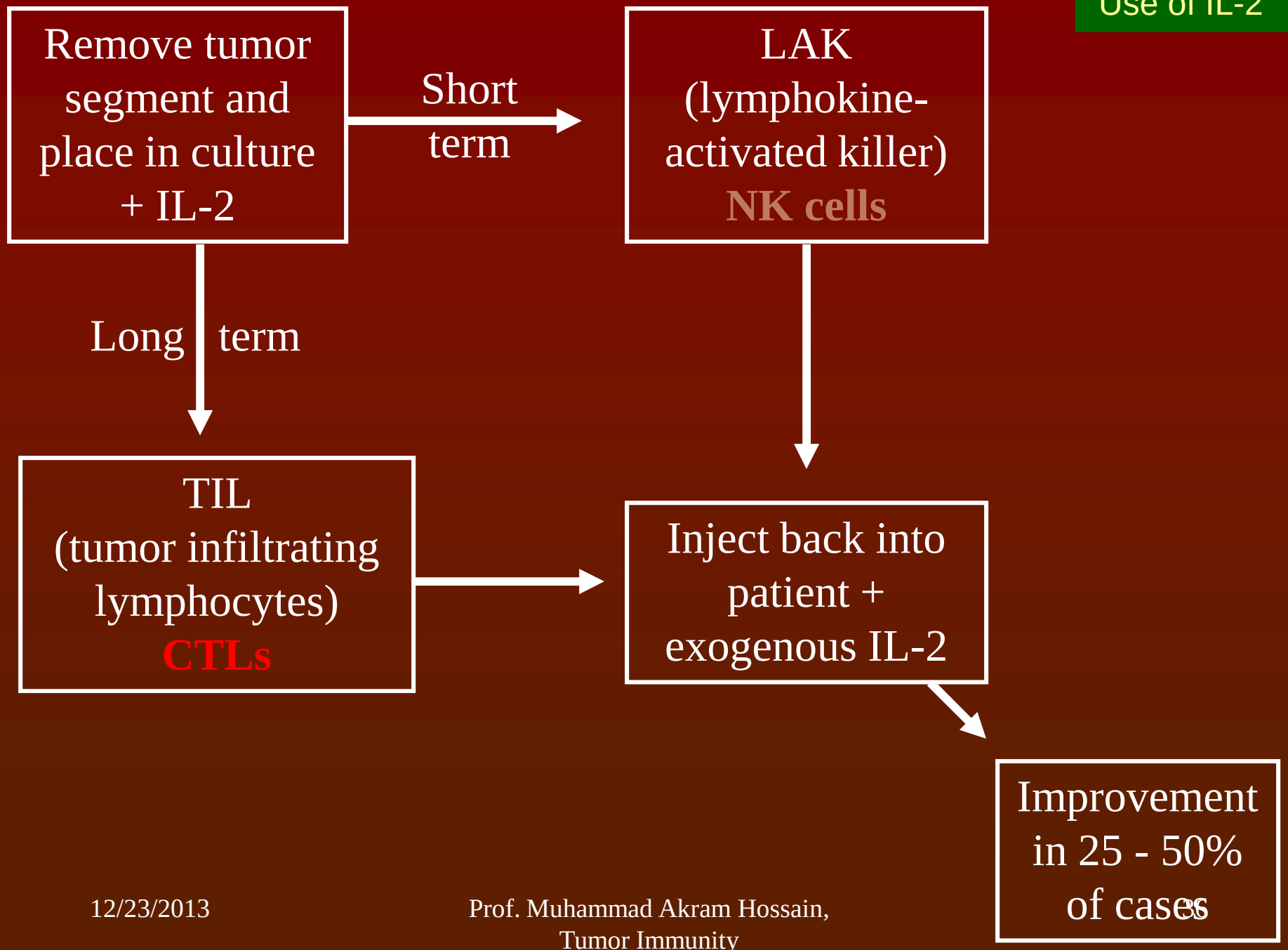
Use of IL-2


Remove tumor segment and place in culture + IL-2
Short term
LAK (lymphokine-activated killer) NK cells
Inject back into patient
Add exogenous IL-2
Improvement in ~ 25 % of cases

Use of IL-2


Remove tumor segment and place in culture + IL-2
Long term
TIL (tumor infiltrating lymphocytes) CTLs
Inject back into patient
Add exogenous IL-2
Improvement in ~ 50 % of cases

Use of IL-2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LAK (lymphokine-activated killer) NK cells
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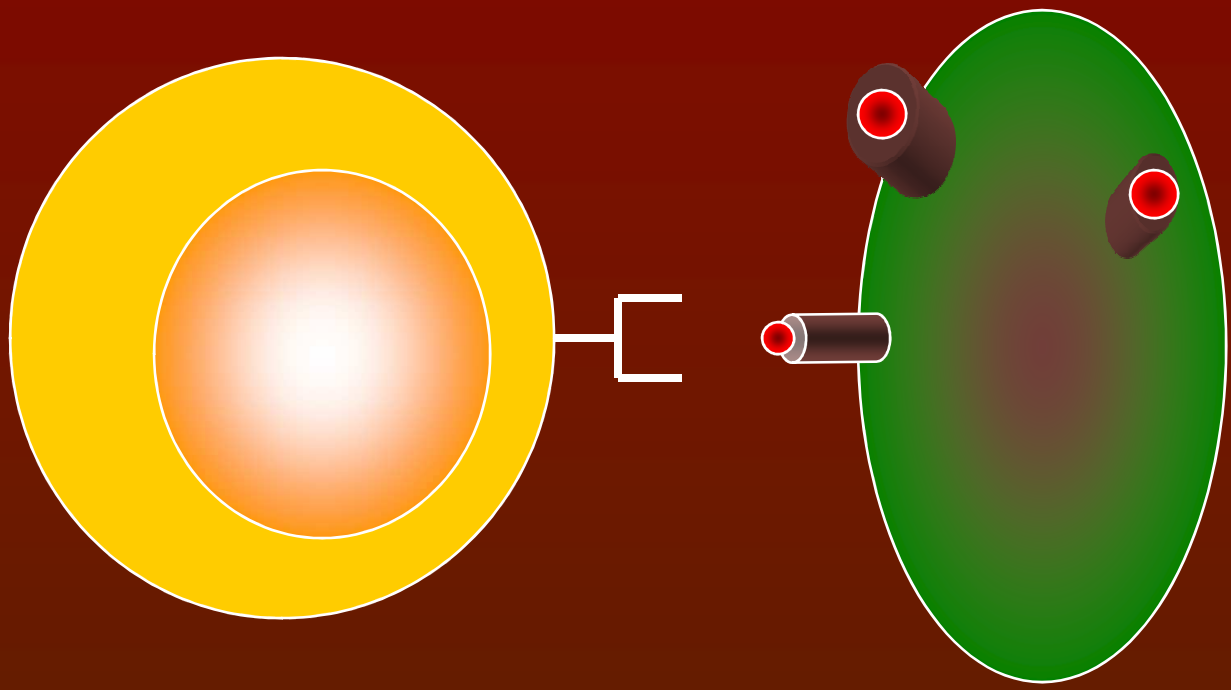
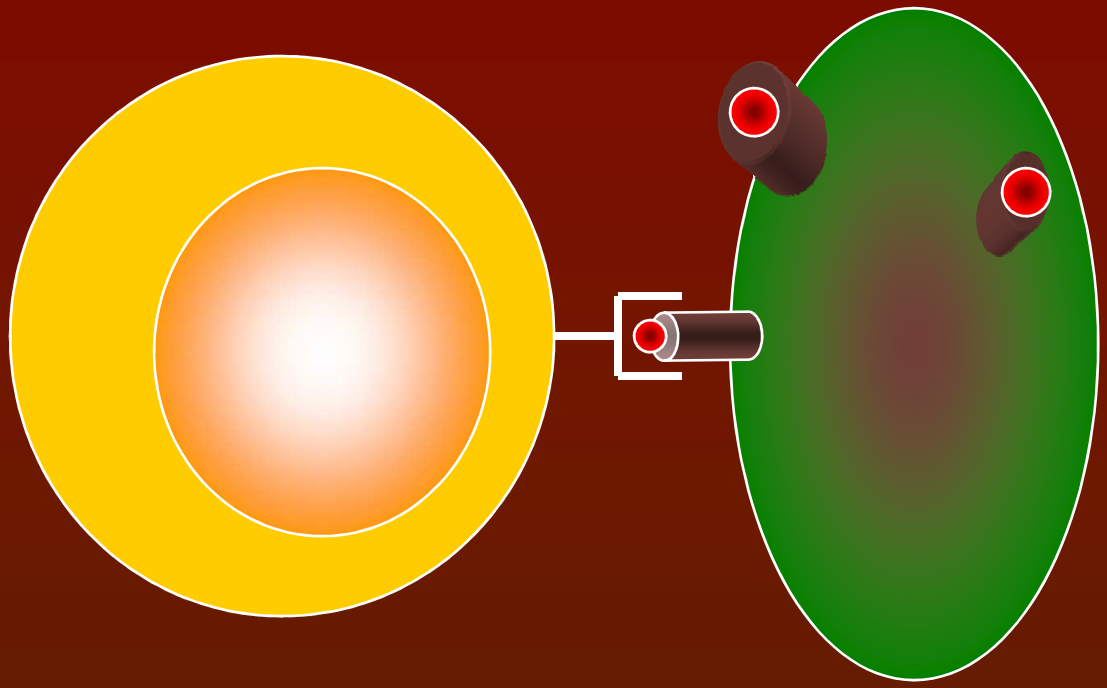
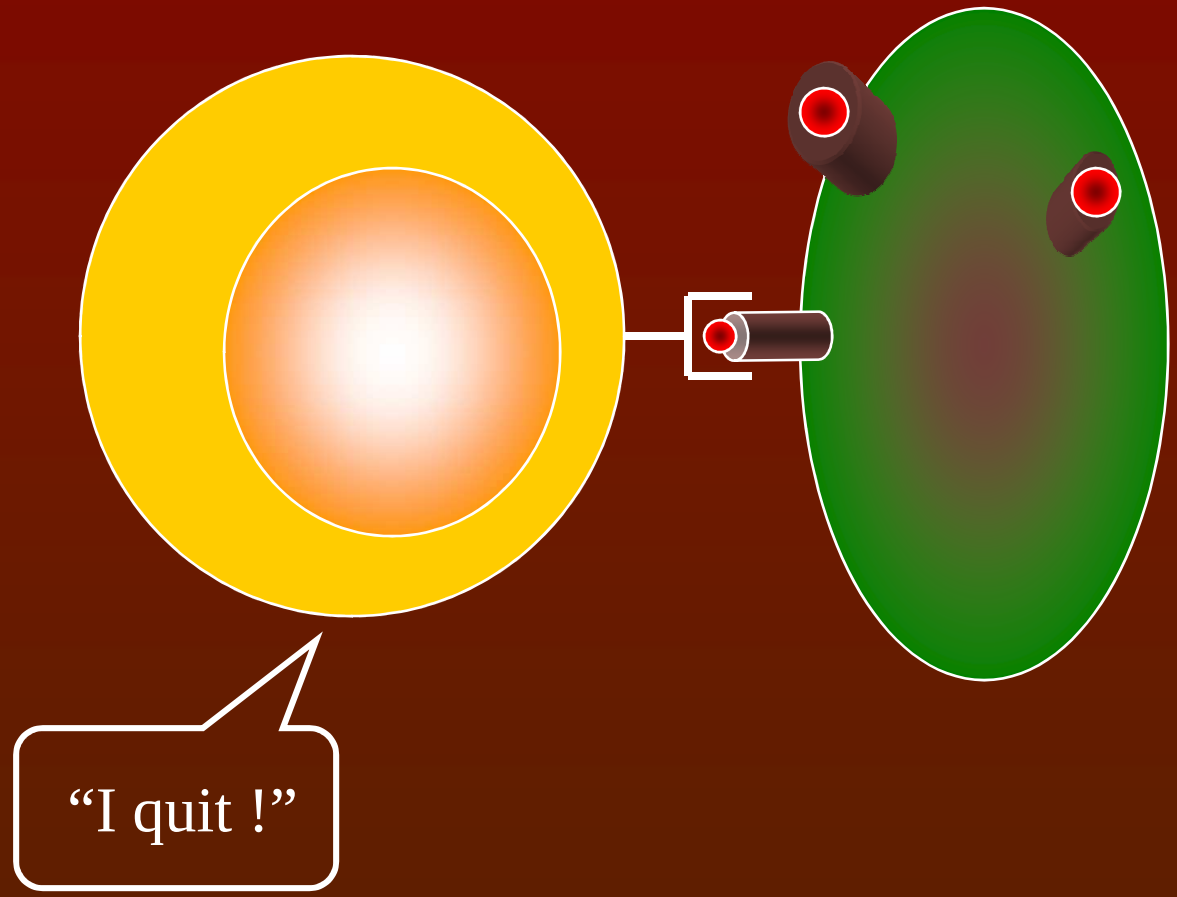
Improvement in 25 - 50% of cases



“Naive” CTL

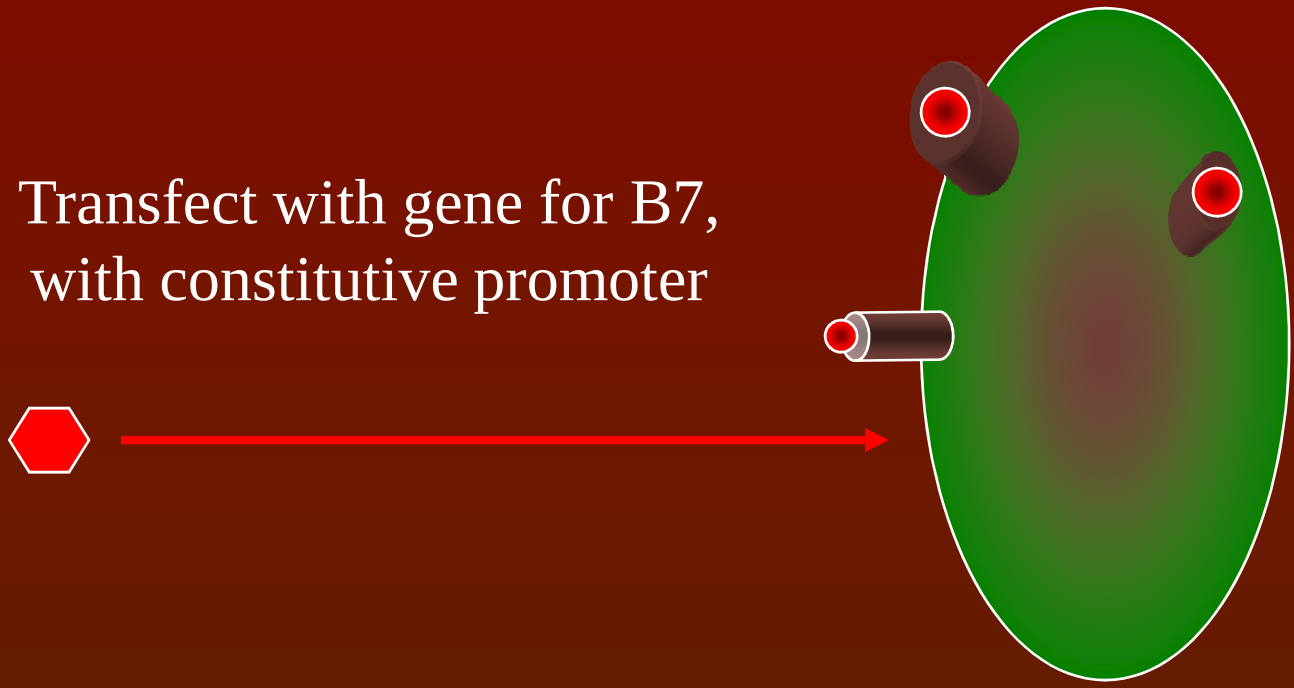
Tumor Cell



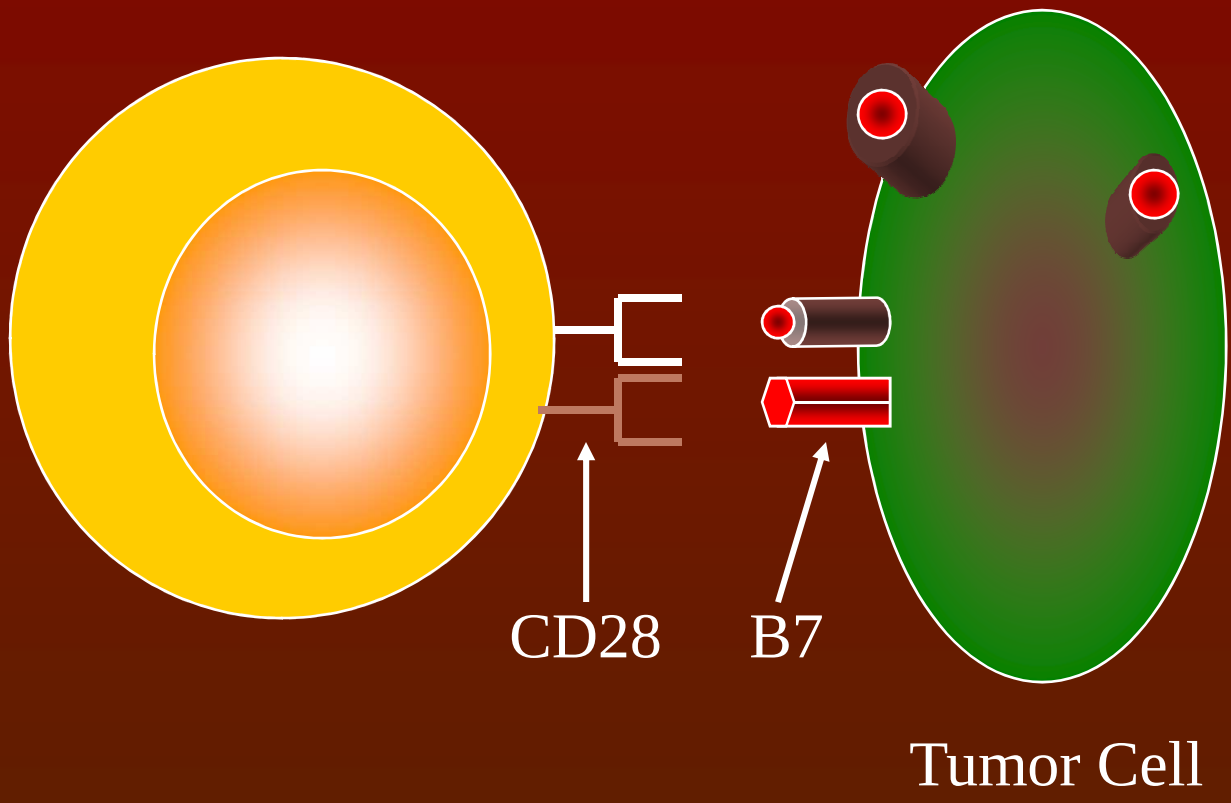

“I quit !”

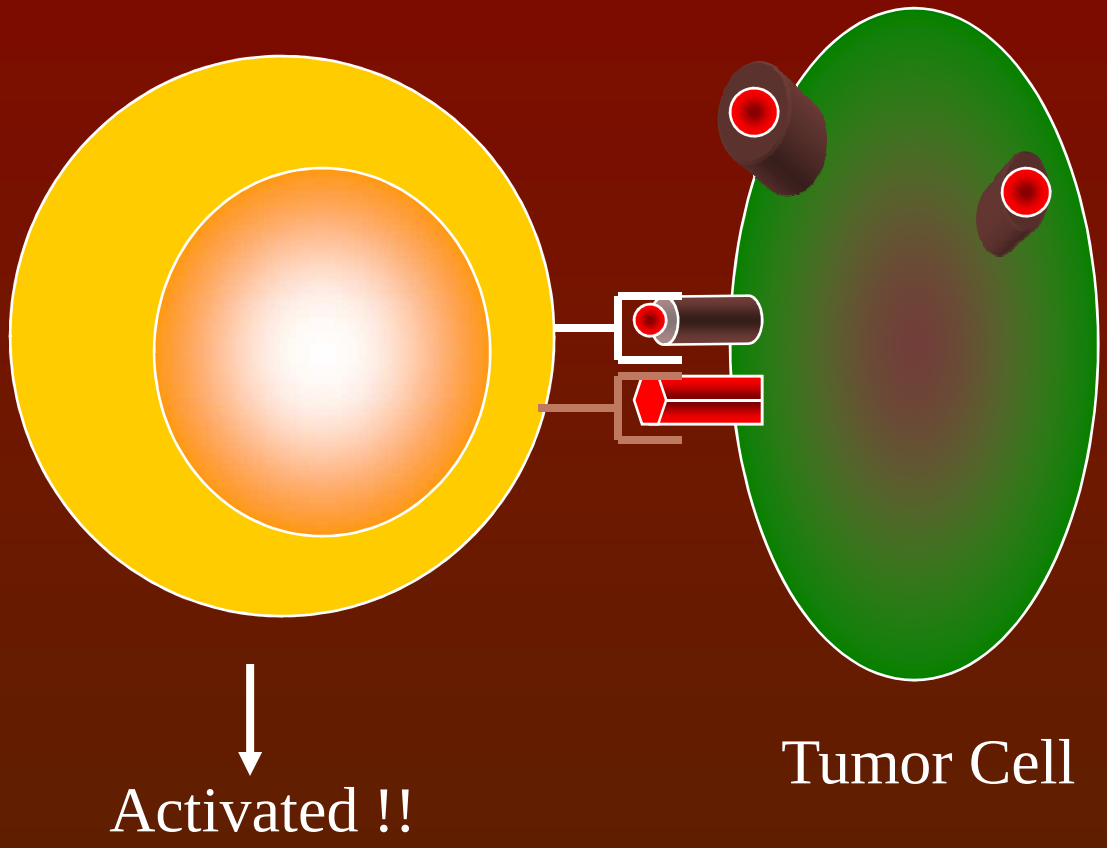
Can we turn the tumor cell into an antigen-presenting cell??

Transfect with gene for B7,
with constitutive promoter



Tumor Cell


CD28
B7
Tumor Cell


Activated !!
Tumor Cell

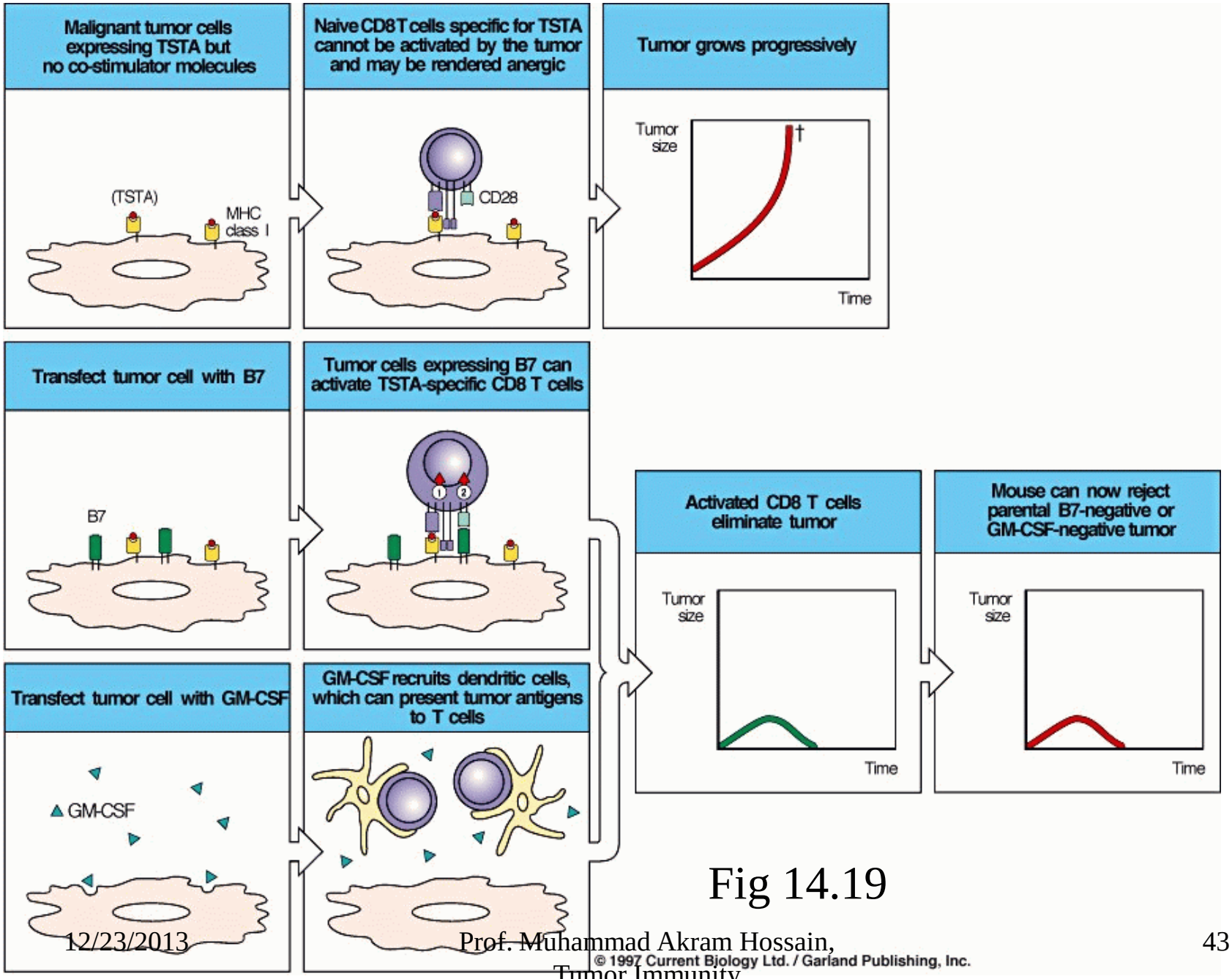

Malignant tumor cells expressing TSTA but no co-stimulator molecules
(TSTA)
MHC class I
Naive CD8 T cells specific for TSTA cannot be activated by the tumor and may be rendered anergic
CD28
Tumor grows progressively
Tumor size
Time
Transfect tumor cell with B7
B7
Tumor cells expressing B7 can activate TSTA-specific CD8 T cells
Activated CD8 T cells eliminate tumor
Tumor size
Time
Mouse can now reject parental B7-negative or GM-CSF-negative tumor
Tumor size
Time
Transfect tumor cell with GM-CSF
GM-CSF
GM-CSF recruits dendritic cells, which can present tumor antigens to T cells
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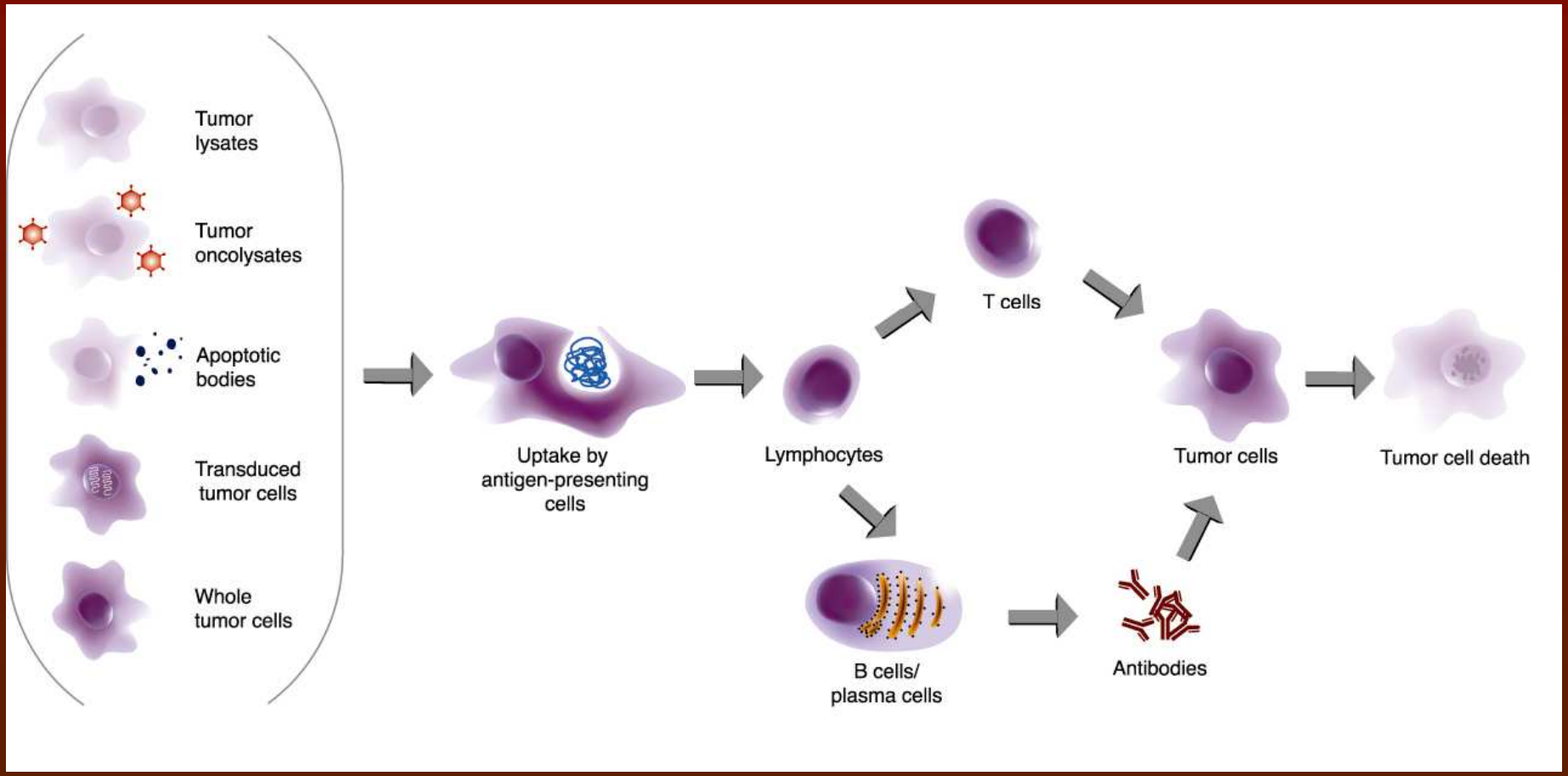
Fig 14.19

Sources of Antigens for Vaccines Stimulating Cell-Mediated Antitumor Immune Responses



Tumor-Associated Antigen-Based Cancer Vaccines and Roles of Antigen-Presenting Cells (APCs) in Antigen Uptake and Presentation

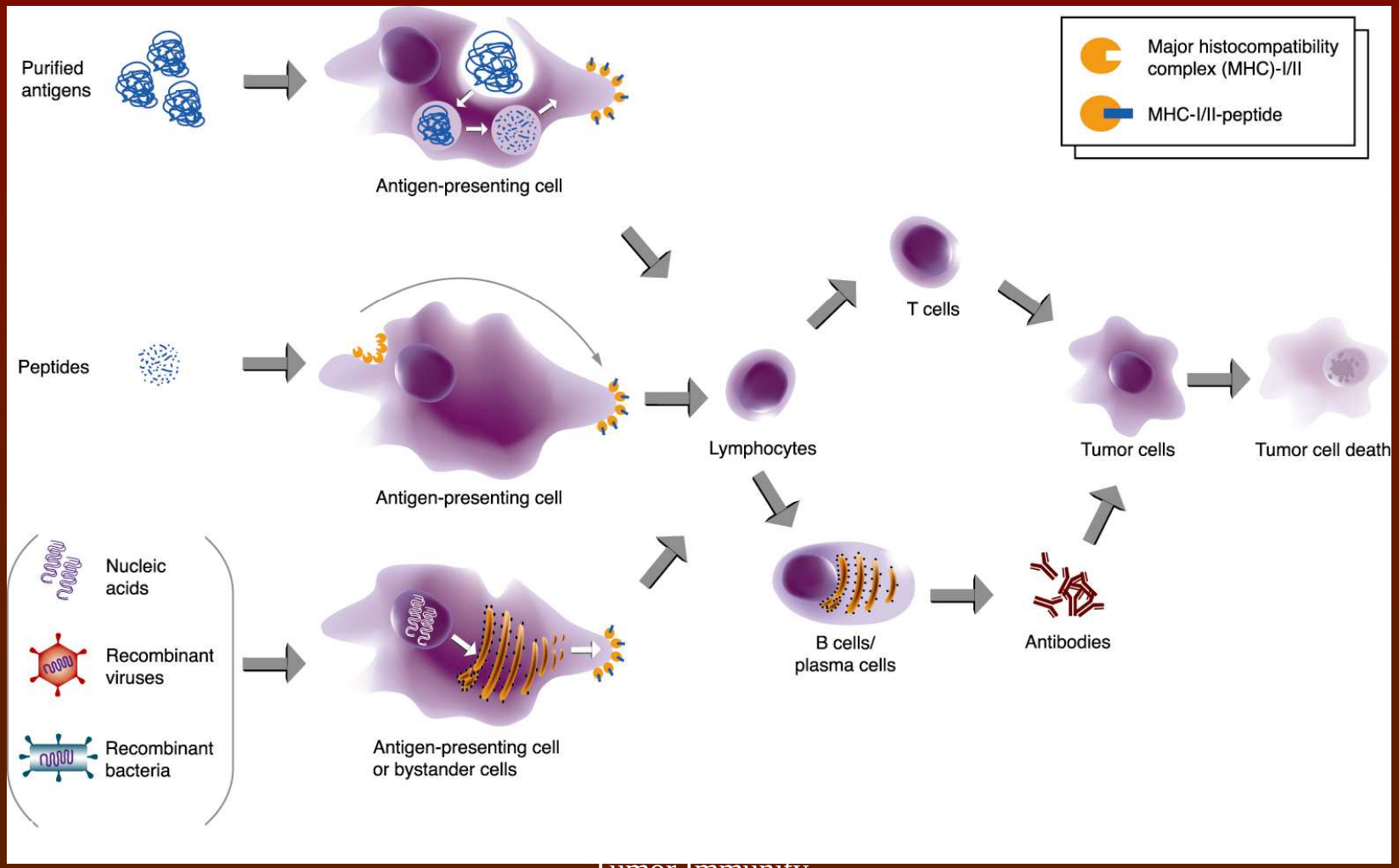


Table 1. Immunotherapy of tumors

Active	Specific	**BCG, *Propionibacterium acnes*, levamisole, cytokine genes, *etc***
	Non Specific	**killed tumor cells or their extract, recombinant antigens, idiotype, co-stimulatory molecule genes, *etc*.**
Passive	Specific	LAK cells, cytokines
	Non Specific	antibodies alone or coupled to drugs, pro-drug toxins or radioisotope; bispecific antibodies; T-cells
	Combined	LAK cells and bispecific antibody

Nonspecific biological products

- A variety of immunopotentiating agents (biological response modifiers) are used to enhance anti-tumor immunity.
- They include
  - bacterial products,
  - synthetic chemicals
  - and cytokines (Table 2).
- Most of these agents exert their effects by activating macrophages and natural killer (NK) cells, eliciting cytokines or enhancing T-cell functions

Table 2. Non-specific active immunotherapy: biological response modifiers (BRMs)

Type of BRM	Examples	Major effect
Bacterial product	BCG, *P. acnes*, muramyl di-peptide, trehalose dimycolate	activate macrophages and NK cells (via cytokines)
Synthetic product	pyran, poly I:C, pyrimidines	induce interferon production
Cytokines	interferon-alpha, -beta, -gamma, IL-2, TNF	activate macrophages and NK cells

Table 3. Cytokine therapy of tumors		
Cytokine	**Tumor type and result**	**Anti-tumor mechanism(s)**
IFN-alpha, beta	remission of hairy cell leukemia, weak effect on some carcinomas	increased expression of class I MHC, possible cytostatic anti-tumor effect,
IFN-gamma	remission of peritoneal carcinoma of ovary: ineffective systemically	increased MHC antigens; macrophage, Tc and NK cell activation
IL-2	remission in renal carcinoma and melanoma	T-cell proliferation and activation, NK cells activation
TNF-alpha	can reduce malignant ascites	macrophage and lymphocyte activation

Thank you for patience hearing