Tumor Immunology

Immunology Lecture 11

Ashraf Khasawneh
Faculty of Medicine
The Hashemite University

Objectives:

- Introduction to tumors types and aetiology
- Tumors associated antigens and markers
- Evidence for Immune Reactivity to Tumors
- Discuss immune protection against tumors and immune surveillance system
- Discuss immune mediated tumor growth
- Provide an overview of experimental cancer therapies

Introduction

- Pathological cell masses derived by abnormal and uncontrollable clonal expansion of a single cell
- Cells that continue to replicate, fail to differentiate into specialized cells, and become immortal.
- Cells become antigenically different from normal cells
- They are recognized and destroyed by immune system
- Tumors can be:

1. Malignant: A tumor that grows indefinitely and spreads (metastasis)--also called cancer: kills host
2. Benign: A tumor that is not capable of metastasis: does not kill host

Types of Cancer

- **Carcinoma:** arising from epithelial tissue, such as glands, breast, skin, and linings of the urogenital, digestive, and respiratory systems (89.3% of all cancers)
- **Sarcoma:** solid tumors of muscles, bone, and cartilage that arise from the embryological mesoderm (1.9% of all cancers)
- **Leukemia:** disease of bone marrow causing excessive production of leukocytes (3.4% of all cancers)
- **Lymphoma, Myeloma:** diseases of the lymph nodes and spleen that cause excessive production of lymphocytes (5.4% of cancers)

Etiology of Tumor

- Inherited :
  - Expression of inherited oncogene: Breast, colon, prostate cancers
- Viral:
  - Viral genome incorporated into host gene
  - Human papilloma, herpes type 2, HBV, EBV (DNA)
  - Human T-cell leukemia virus (RNA)
- Chemical:
  - Poly cyclic hydrocarbons cause sarcomas
  - Aromatic amines cause mammary carcinoma
  - Alkyl nitroso amines cause hepatoma
- Radiological: Ultraviolet & ionizing irradiation
- Spontaneous: failure in the cellular growth control

Tumor Associated Antigens

- **Viral Antigen:** Viral proteins and glycoproteins

  New antigens produced by virally infected host cells under control of viral nucleic acid
- **Tumor specific antigens:** Tumor cells develop new antigen specific to their carcinogen
- **Tumor specific transplantation antigens:** Tumor cells express new MHC antigens due to alteration of normally present MHC antigens
- **Oncofetal antigens:**

1. **Carcino-embryonic antigens (CEA)**

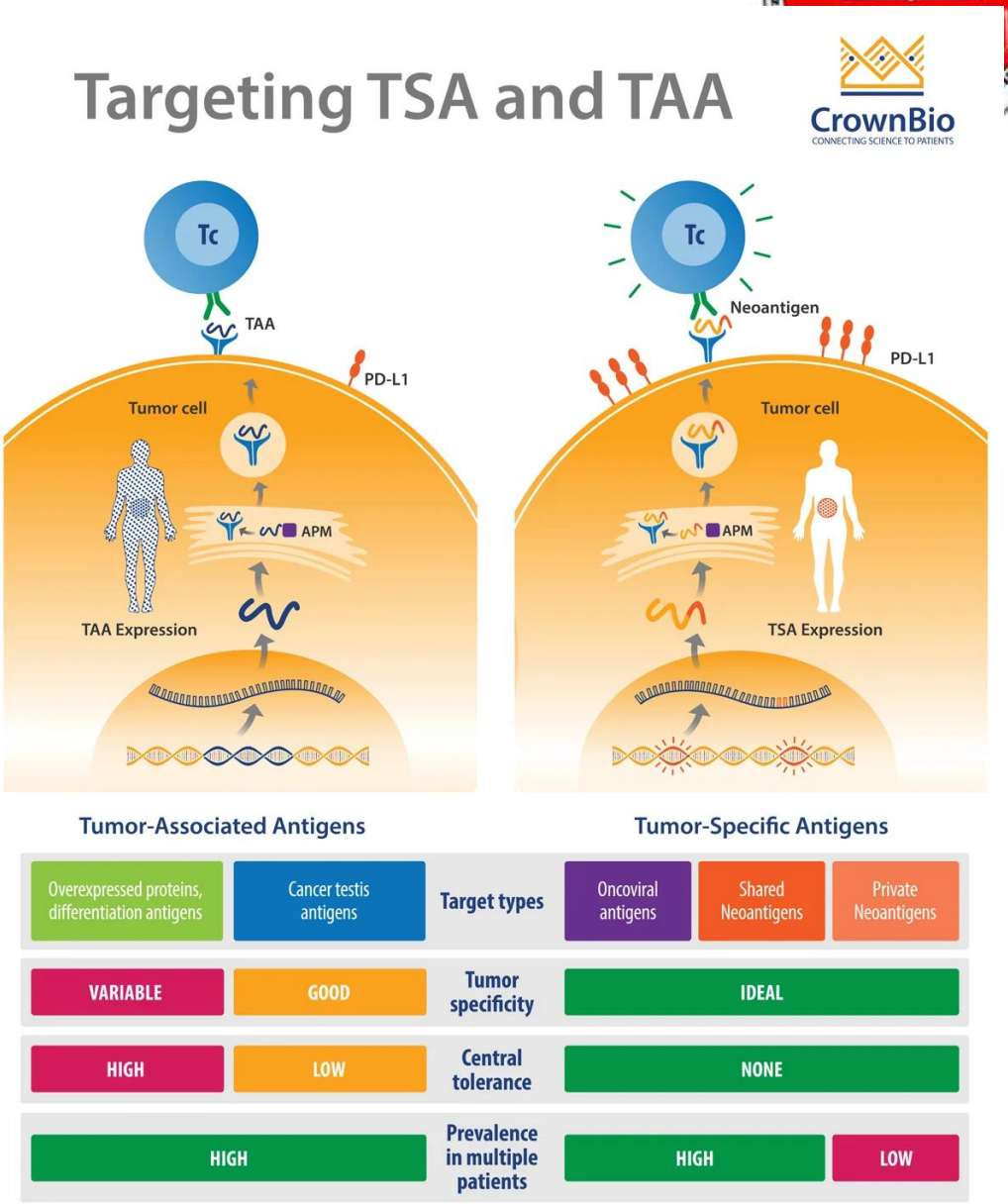
   Normally expressed during fetal life on fetal gut

   Reappearance in adult life:

   GIT, pancreas, biliary system and breast cancers
2. **Alpha fetoprotein:**

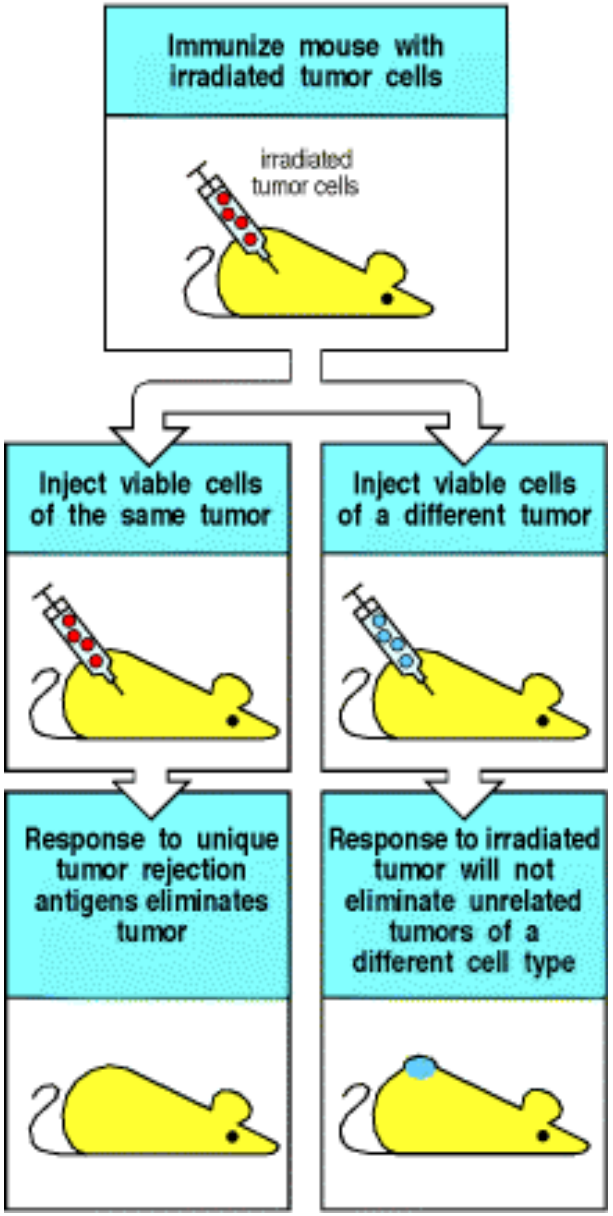
   Normally expressed in fetal life

   Reappearance in adult life; hepatoma



Evidence for Immune Reactivity to Tumors

- Tumors that have severe lympho -reticular infiltration have a better prognosis than those that do not.
- Certain tumors regress spontaneously
- There is an increased incidence of primary and secondary malignancies (particularly lympho-reticular tumors) in immunodeficient patients
- Antibodies and immune T lymphocytes have been detected in patients with tumors.
- The young and the very old have an increased occurrence of tumors.
- Finally, animals can be specifically immunized against various types of tumors



Animal models showed that pre-treatment of mice with killed tumour material could protect against a subsequent challenge.

T cell ablation or T-cell deficient mice removed this protection.

Transfer of T cells from an immunized mouse could protect a naïve mouse from tumour challenge. (Adoptive immunotherapy)

Immune Surveillance System

- During neoplastic transformation, new antigen develop
- The host recognize them as non-self antigens
- Cell mediated immune reactions attack these non-self tumor cells
- Immune response act as surveillance system to detect and eliminate newly arising neoplastic cells

This system include :

1) Natural killer (NK) cells

They kill directly tumor cells, helped by interferon, and IL-2

2) Cytotoxic T-cells

They also kill directly tumor cells

3) Cell mediated T-cells (effector T-cells)

They produce and release a variety of lymphokines :

a-Macrophage activation factor that activate macrophages

b-Gamma interferon and interleukin-2 that activate NK

c-Tumor necrosis factor (cachectine): apoptosis, necrosis, immune cell activation, differentiation, and cell migration.

4) B-cells :

- Tumor associated antigens stimulate production of specific antibodies by host B-cells
- These specific antibodies bind together on tumor cell surface leading to destruction of tumor through:

1. Antibody mediated-cytotoxicity : Cytotoxic T-cells kill IgG-coated tumor cells
2. Activation of macrophages: Sensitized T-cells release macrophage activating factor which activate macrophages
3. Activation of classical pathway of complement leading to Lysis of tumor cells

Tumor Escape

Mechanisms by which tumor escape immune defenses:

1) **Reduced levels or absence of MHCI molecule on tumor cells so that they can not be recognized by CTLs**

2) **Some tumors stop expressing the antigens** (not essential for tumor growth)

These tumors are called "antigen loss variants"

3) **Production of immunosuppressive factors by tumor e.g. transforming growth factor (TGF-β)**: the early stages it inhibits cellular transformation and prevents cancer progression. In later stages TGF-β plays a key role in promoting tumor progression through mainly 3 mechanisms: facilitating epithelial to mesenchymal transition, stimulating angiogenesis and inducing immunosuppression

4) **Tumor antigens may induce specific immunological tolerance**: state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response in a given organism.

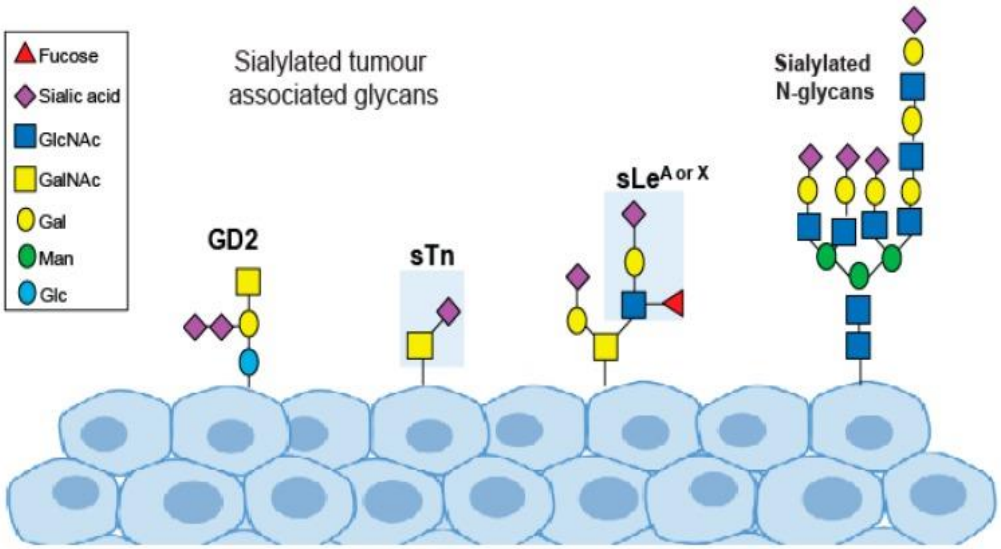
5) Tumor cells have an inherent defect in antigen processing and presentation

6) Blocking of receptors on T-cells by specific antigen antibodies complex (after shedding of tumor Ag) prevents them from recognizing and attacking tumor cells

7) Antigens on the surface of tumors may be masked by sialic acid-containing mucopolysaccharides

8) Immune suppression of the host as in transplant

patients who show a higher incidence of malignancy



Tumor Markers

- Anything present in or produced by cancer cells or other cells of the body in response to cancer or certain benign (noncancerous) conditions that provides information about a cancer

- Tumor markers : They are either

1. Tumor antigens
   - diagnose, stage, and/or classify cancer
   - estimate prognosis
   - select an appropriate treatment
2. Tumor products (enzymes and hormones)
   - found in the blood, urine, stool, or other bodily fluids of some patients with cancer
   - USED TO:
   - Estimate prognosis
   - Determine the stage of cancer
   - Detect cancer that remains after treatment (residual disease) or that has returned after treatment
   - Assess how well a treatment is working
   - Monitor whether the treatment has stopped working

Tumor Antigens

1) Alpha fetoprotein antigen (AFP) in cases of hepatoma

2) Carcinoembryoinic antigen (CEA) in gastrointestinal tumors, tumors of biliary system and cancer breast

3) Cancer antigen 125 (CA 125) in ovarian carcinoma

4) Cancer antigen 15-3 (CA15-3) in breast cancer

5) Cancer antigen 19-9 in colon and pancreatic tumor

6) Prostatic specific antigen (PSA) in prostatic tumors

Tumor Products

a) Hormones:

Human chorionic gonadotrophins (HCG) are secreted in cases of choriocarcinoma

Thyroxin (T3 & T4) is secreted in cases of cancer of thyroid gland

b) Enzymes:

Acid phosphatase enzymes in cases of cancer prostate

Alkaline phosphatase, lipase and amylase enzymes in cases of pancreatic cancer

Applications of Tumor Immunology

- **Diagnosis:** Immunodiagnostics is a diagnostic methodology that uses an antigen-antibody reaction as their primary means of detection.
  - Monoclonal antibodies labeled with radioisotope have been used for in vivo detection of relatively small tumor foci.
  - Antibodies have also been used in vitro to identify the cell origin of undifferentiated tumors, particularly of lymphocytic origin.
  - Immuno-histological staining is used to confirm suspected metastatic foci, especially in bone marrow

- **Treatment (immune therapy):** Immunotherapy is a type of cancer treatment that helps your immune system fight cancer.

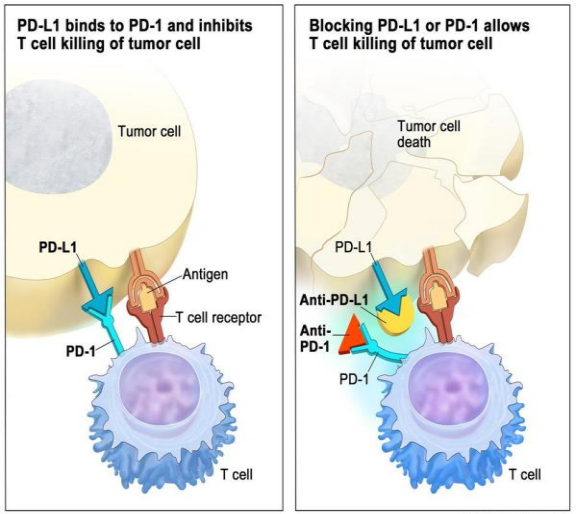
- **T-cell transfer therapy**, which is a treatment that boosts the natural ability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein.T-cell transfer therapy may also be called adoptive cell therapy, adoptive immunotherapy, or immune cell therapy.

- **Monoclonal antibodies**, which are immune system proteins created in the lab that are designed to bind to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system. Such monoclonal antibodies are a type of immunotherapy.Monoclonal antibodies may also be called therapeutic antibodies.

- **Treatment vaccines**, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.

- **Immune system modulators**, which enhance the body's immune response against cancer. INF, ILs, EPO, GM-CSF, and BCG.

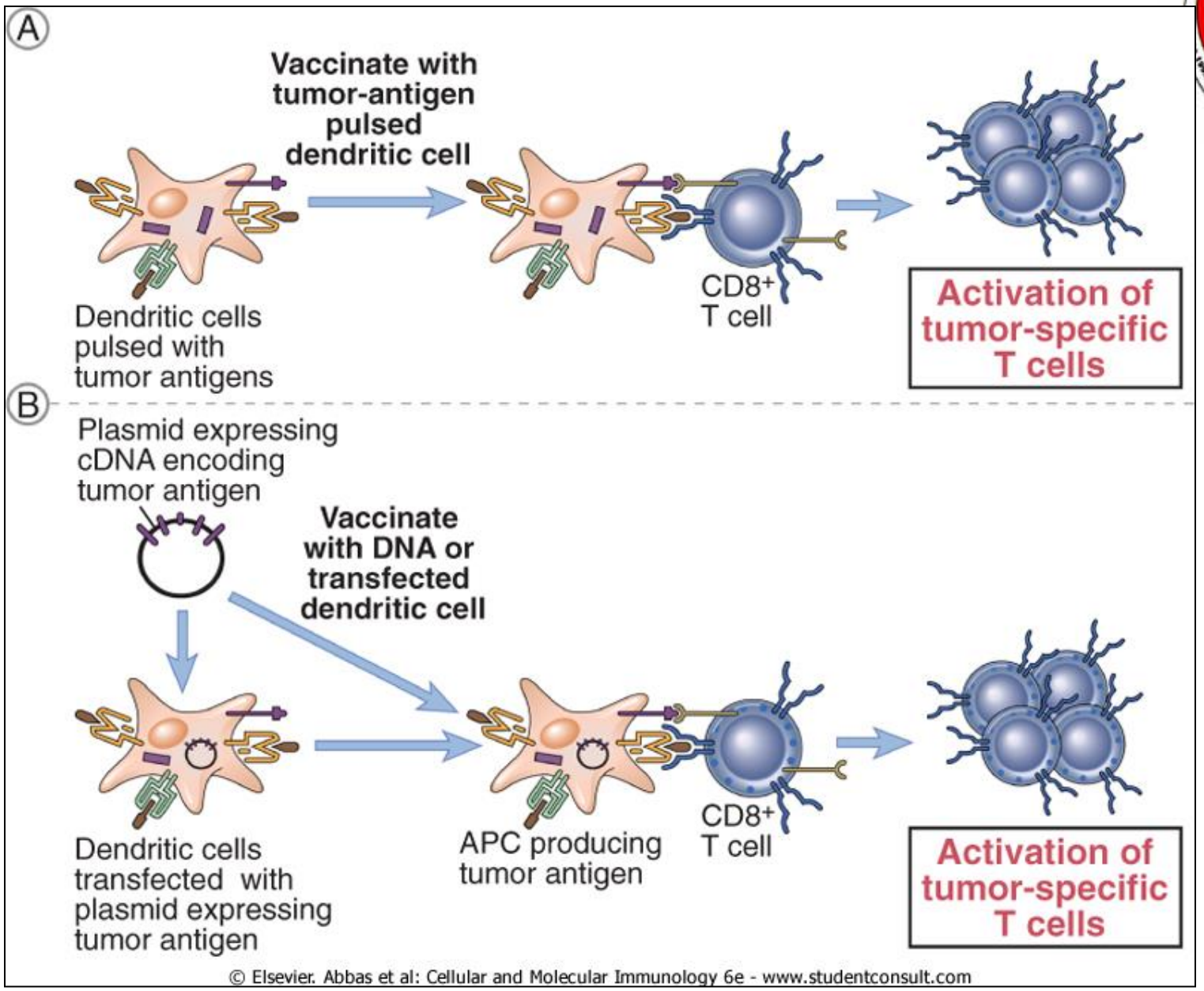
- **Immune checkpoint inhibitors**, which are drugs that block immune checkpoints.



Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body (left panel). Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells (right panel).

Tumor vaccines

Type of vaccine	Vaccine preparation	Clinical trials
Killed tumor	killed tumor cells + adjuvants	Melanoma, colon cancer
	tumor cell lysates + adjuvants	Melanoma
Purified tumor antigens	Melanoma antigens	Melanoma
	Heat shock proteins	Melanoma, renal cancer, sarcoma
APC based	DC pulsed with TAA	Various
	DC transfected with TAA	
Cytokine and costimulator-enhanced	Cytokine or B7 gene transfected tumor cells	Various
	APC transfected with cytokines and pulsed with TAA	
DNA	plasmids encoding TAA	Melanoma
Viral vectors	Adenovirus, vaccinia virus encoding TAA +/- cytokines	Melanoma



Monoclonal antibodies

Antibody name generic/trade	Antibody format	Target antigen	Therapeutic area	Approved year
Rituximab/Rituxan	Chimeric IgG1	CD20	B-cell lymphoma, NHL Chronic lymphocytic leukemia	1997 2010
Trastuzumab/Herceptin	Humanized IgG1	HER-2	Metastatic breast cancer Early stage breast cancer Metastatic stomach cancer	1998 2006 2010
Gentuzumab Ozogamicin/Mylotarg	Humanized IgG1	CD33	Acute myeloid leukaemia	2000
Alezumtumab/ Campath	Humanized IgG1	CD52	Chronic myeloid leukaemia	2001
Ibritumomab Tiuxetan/ Zevalin	Mouse IgG1 conjugated to ^{90}Y)	CD20	NHL	2002
Tositumomab/Bexxar	Mouse IgG1 conjugated to ^{131}I	CD20	NHL	2003
Bevacizumab/Avastin	Humanized IgG1	VEGF	Metastatic colorectal cancer Non-small-cell lung cancer Metastatic renal cancer GBM Ovarian cancer (in Europe only)	2004 2006 2009 2009 2011
Cetuximab/Erbitux	Chimeric IgG1	EGFR	Metastatic colorectal cancer Head and neck cancer Metastatic colorectal cancer (first-line treatment)	2004 2006 2012
Panitumumab/Vectibix	Human IgG2	EGFR	Metastatic colorectal cancer	2006
Ofatumumab/Arezera	Human IgG1	CD20	Chronic lymphocytic leukaemia	2009
Removab®	Bi-sepecific mouse/ rat Hrbrid IgG	EpCAM X CD3	Patients with malignant ascites (in Europe)	2009
Ipilimumab/Yervoy	Human IgG1	CTLA-4	Metastatic melanoma	2011
Brentuximab/Adcetris	Chimeric IgG1	CD30	ALCL and Hodgkin lymphoma	2011
Pertuzumab/Perjecta	Humanized IgG1	HER2	Metastatic breast cancer	2012

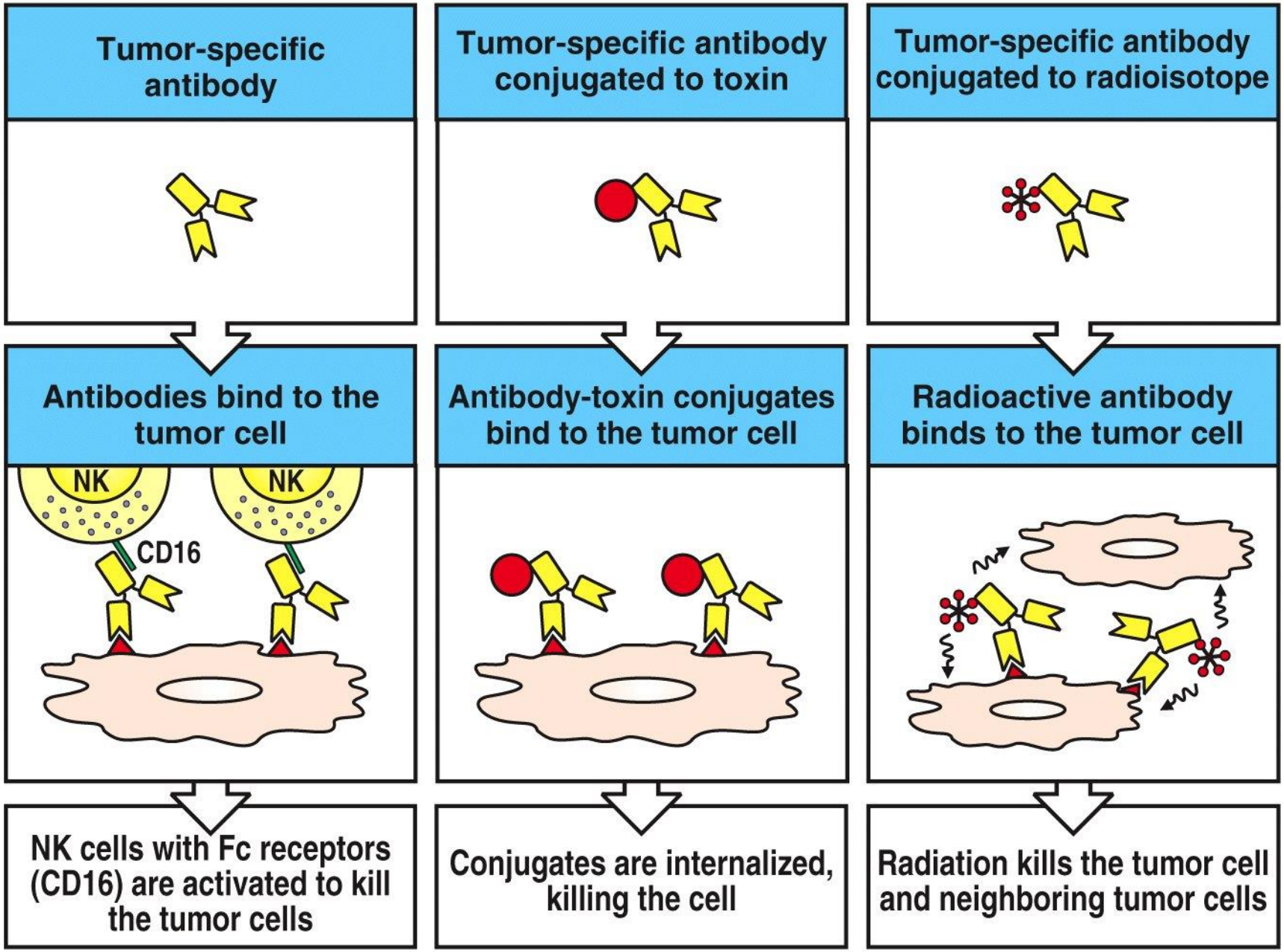


Figure 14-17 Immunobiology, 6/e. (© Garland Science 2005)