- Nama : Prof.DR.Dr.Hj.Eryati Darwin,PA(K)
- NIP : 195311091982112001
- Pangkat/Gol : Pembina Utama/IVd
- Tempat/Tanggal lahir : Pasar Usang/ 9 November 1953
- Agama : Islam
- Pekerjaan : Guru besar tetap Fakultas Kedokteran Unand
- Alamat : Jl. Veteran No.13 A Padang 25116
- No. Sertifikat Dosen Profesional : 08100601124

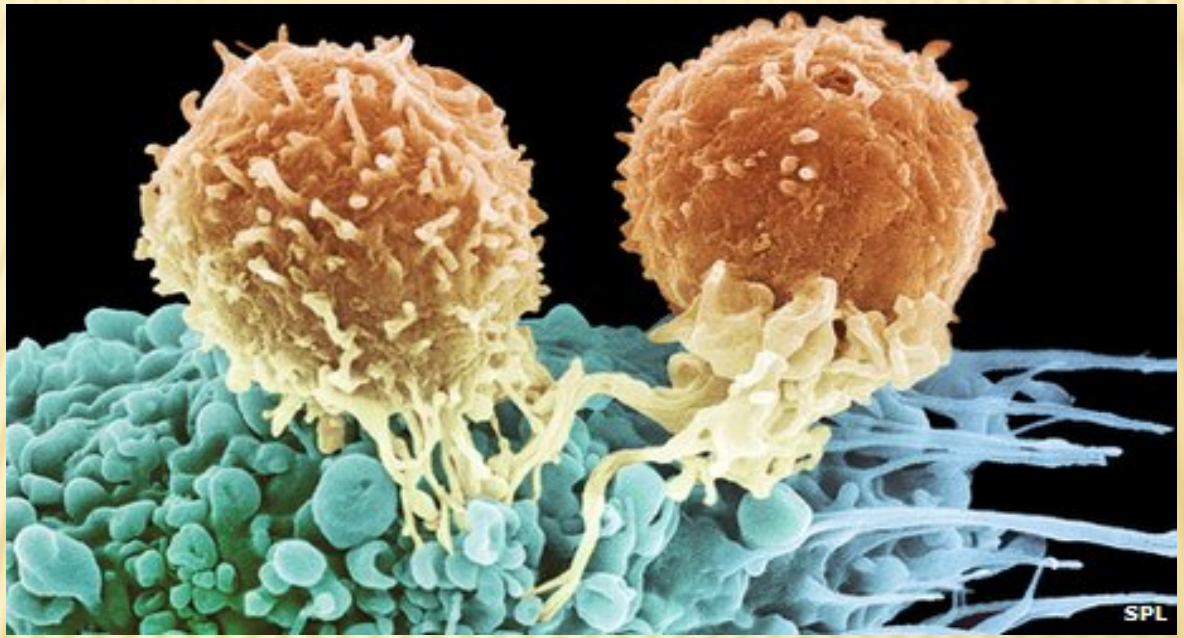
PENDIDIKAN :

- Sekolah Rakyat Patrakomala Bandung, SD Adabiah Padang, 1967
- SMP Adabiah Padang, 1970
- SMA Adabiah Padang, 1973
- Fakultas Kedokteran Unand Padang, 1981
- Institut für Experimentelle Immunologie Philipps Universität. Marburg- West Germany , 1989
- Program Pascasarjana S3 Unair (predikat Cum-Laude) ,2004
- Brevet Pakar Anatomi, 2005
- Brevet Pakar Anatomi Konsultan, 2007

JABATAN

- Dosen Histologi dan Imunologi FK Universitas Andalas 1981-skr
- Dosen Histologi dan Imunologi FK Universitas Baiturrahmah 1999-2003
- Ketua Unit Penelitian dan Kegiatan Ilmiah (UPKI) FK Unand 1998-2002; 2002-2006
- Dosen Histologi dan Imunologi FK Universitas Riau 2002-2007
- Kepala Bagian Diklat-Litbang Perjan RS Dr M Jamil Padang 2003-2005
- Direktur SDM dan Litbang Perjan RS Dr M Djamil Padang 2004-2006
- Dosen Program Pascasarjana S2 Biomedik Universitas Andalas 2005-skr
- Koordinator Peminatan Imunologi Program Pascasarjana Biomedik Universitas Andalas 2005-skr
- Dosen Program Pascasarjana S3 Biomedik Universitas Andalas 2006- skr
- Ketua Komite Etik Penelitian FK Unand 2008-skr
- Pembantu Dekan 1 Fakultas Kedokteran Universitas Andalas 2008-2012
- Ketua Majelis Kehormatan Etika Kedokteran (MKEK) IDI Sumbar 2008-skr

CANCER IMMUNOPATHOLOGY



Eryati Darwin

Faculty of Medicine Andalas University

Padang 18 Mei 2013

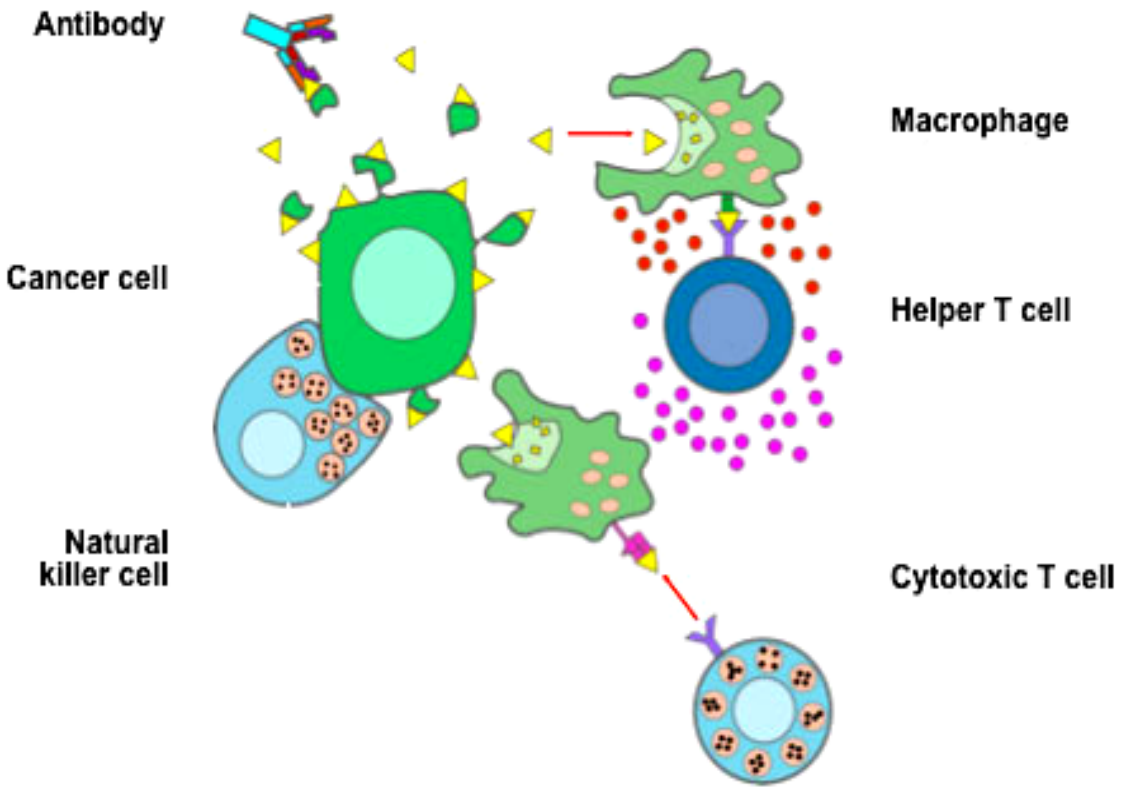
INTRODUCTION

Tumor: cells that continue to replicate, fail to differentiate into specialized cells, and become immortal.

- **Malignant: A tumor that grows indefinitely and spreads →cancer**
- **Benign: A tumor that is not capable of metastasis**

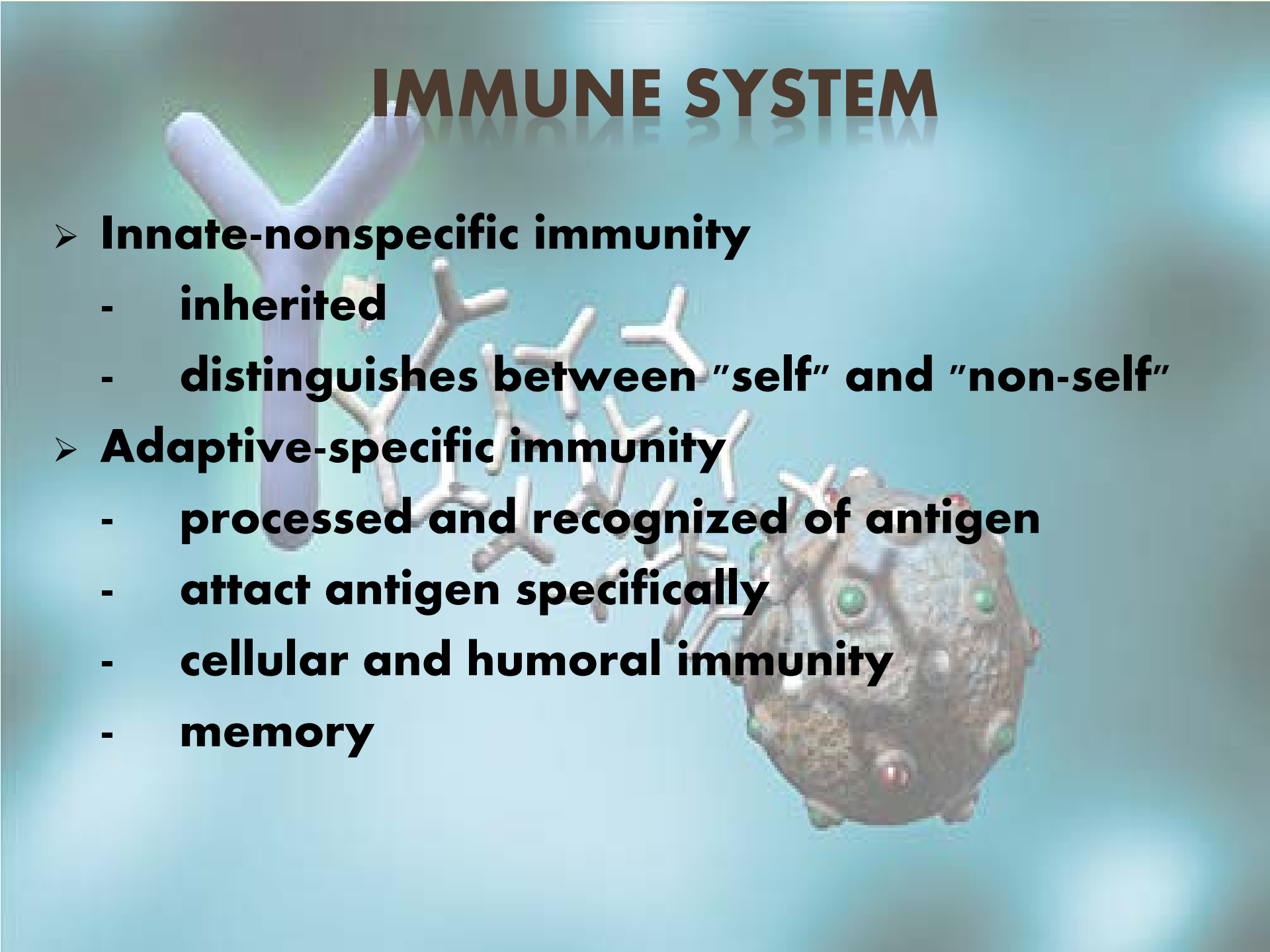
Body's defenses against cancer

- **When normal cells turn into cancer cells, surface antigens changes.**
- **Patrolling cells of the immune system provide continuing bodywide surveillance, spying out and eliminating the cells by:**
  - **cytotoxic T cells**
  - **natural killer cells**
  - **macrophages.**



IMMUNE SYSTEM

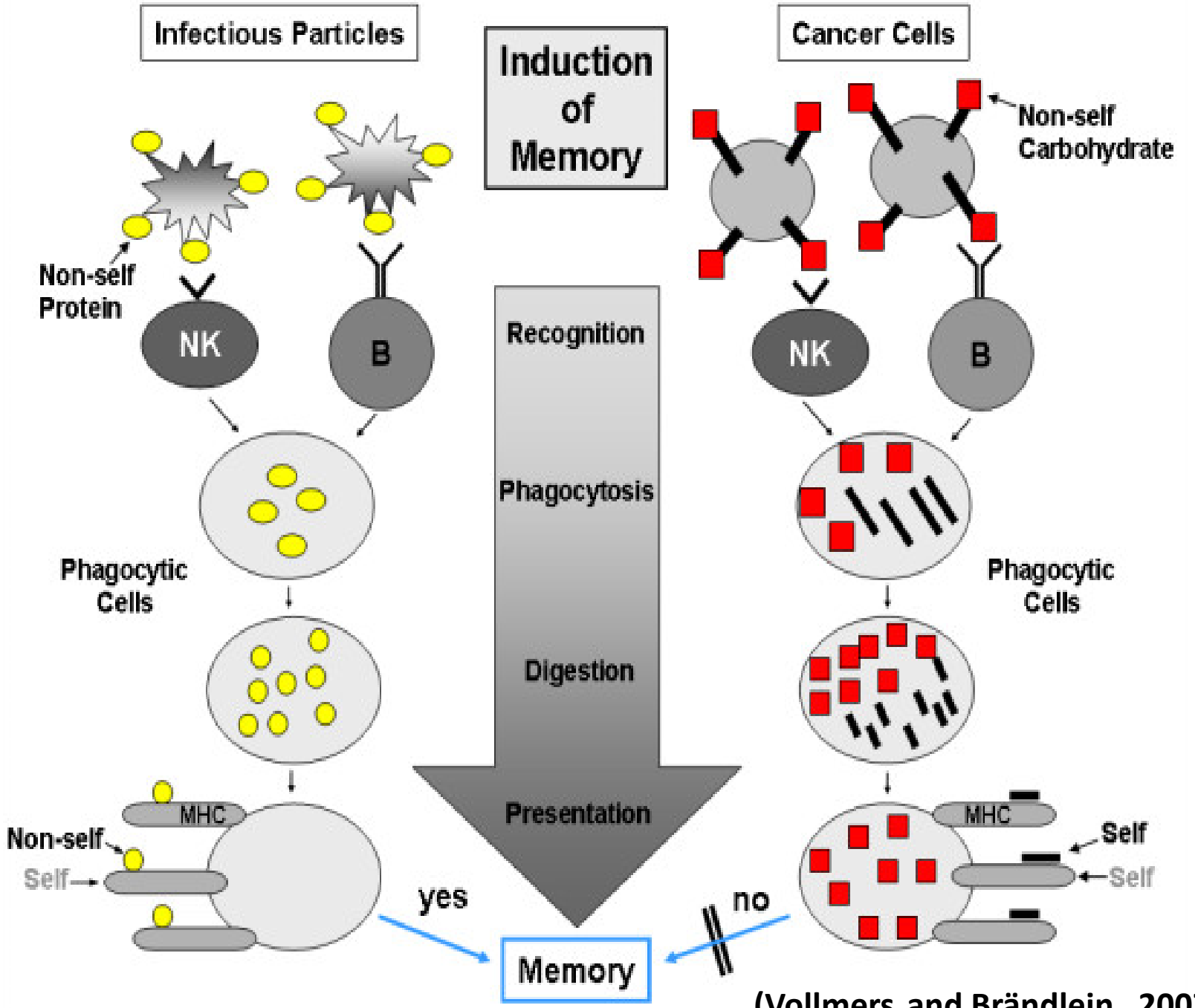
- **Innate-nonspecific immunity**
  - **inherited**
  - **distinguishes between "self" and "non-self"**
- **Adaptive-specific immunity**
  - **processed and recognized of antigen**
  - **attact antigen specifically**
  - **cellular and humoral immunity**
  - **memory**



IMMUNE RESPONSE TO TUMOR CELLS

- The natural immunity → immune surveillance
- NK cells recognizes and destroys all invasive/ change particles
- Phagocytic cells clean and transport the garbage
- Memory ?

- Infectious particles (protein-epitope)→ Th are stimulated → CTL and B cells are generated → memory
- Cancer cells (carbo-epitope)→ recognition fails
- phagocytic cells cannot present carbohydrat structures
- Peptides associated with carbohydrate structures are "self" structures → memory does not occur.



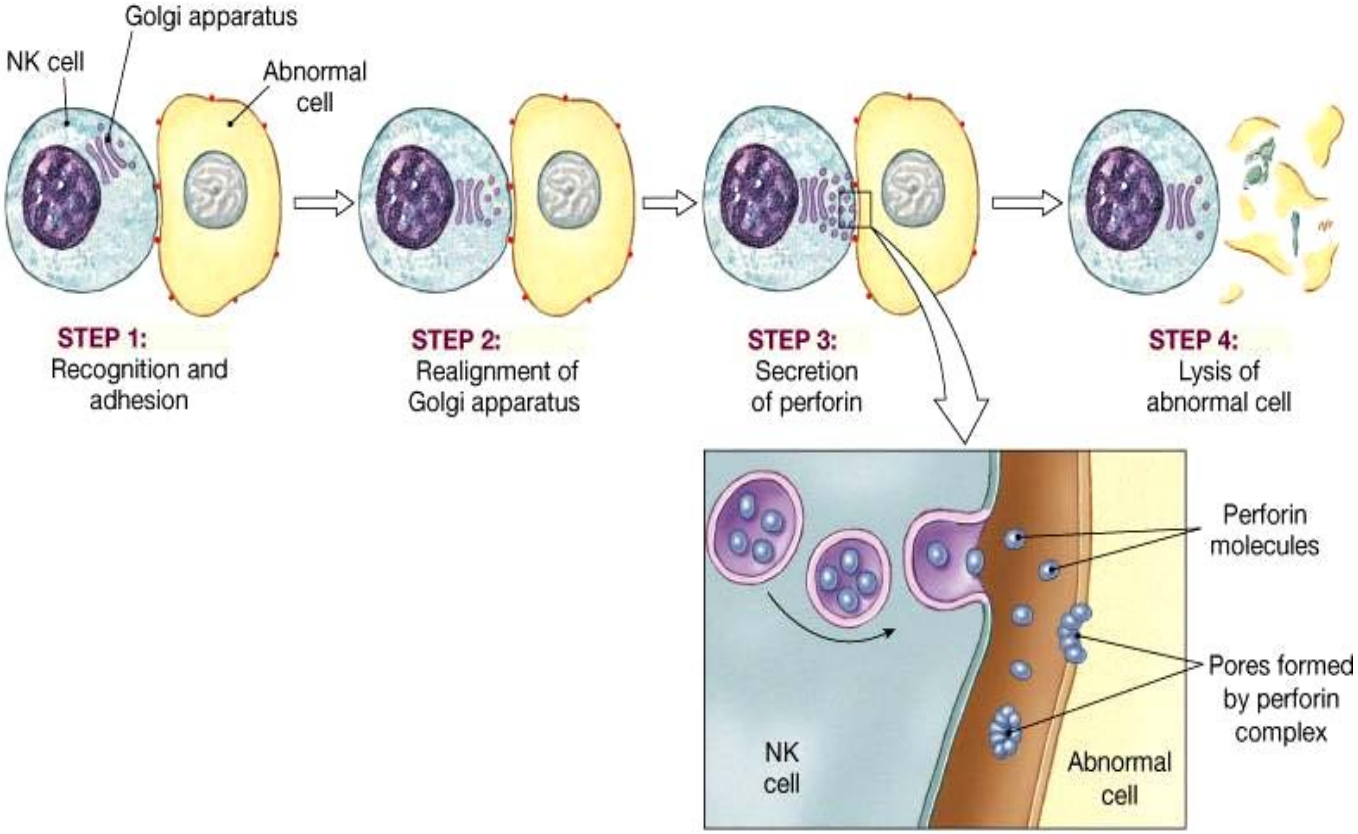
(Vollmers and Brändlein , 2007)

TUMOR CELLS KILLING

- **Non-specific:**
  - NK cells
  - γδ T cells (NKG2D)
  - Macrophages
  - NK T cells
- **Antigen-specific:**
  - Antibody (ADCC, opsinization)
  - T cells (cytokines, Fas-L, perforin/granzyme)

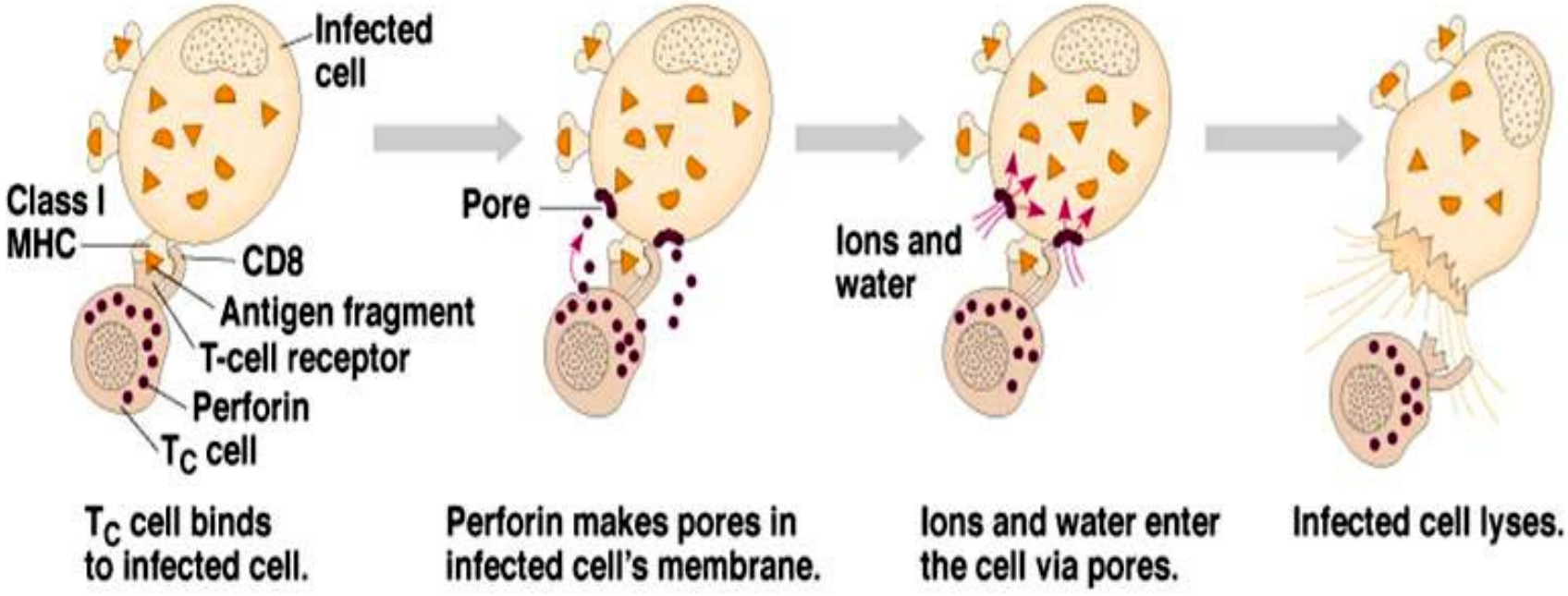
Natural Killer Cells

- Patrol the body and attack virus-infected / cancer cells
- Recognize cell surface markers on foreign cells
- Destroy cells with foreign antigens
- Rotation of the Golgi toward the target cell and production of perforins
- Release of perforins by exocytosis
- Interaction of perforins causing cell lysis+



Cytotoxic T (Tc) Cells

- Killer Ts or CD8
- Destroy target cells
- Recognize and kill all infected/cancer cells
- Release perforin → lysis of infected/cancer cells.
- Produce cytokines →phagocytosis and inflammation



CANCER IMMUNOSURVEILANCE

- **Past:**
  - a host-protective function
  - carried out by the adaptive immune system only at the earliest stages of cellular transformation
- **Now:**
  - the broader term “cancer immunoediting”
  - recognize the innate and adaptive immune system
  - not only to protect the host from tumor development but also to sculpt, or edit, the immunogenicity of tumors that may eventually form.

CANCER IMMUNOEDITING (three "E"s)

1. **Elimination phase**

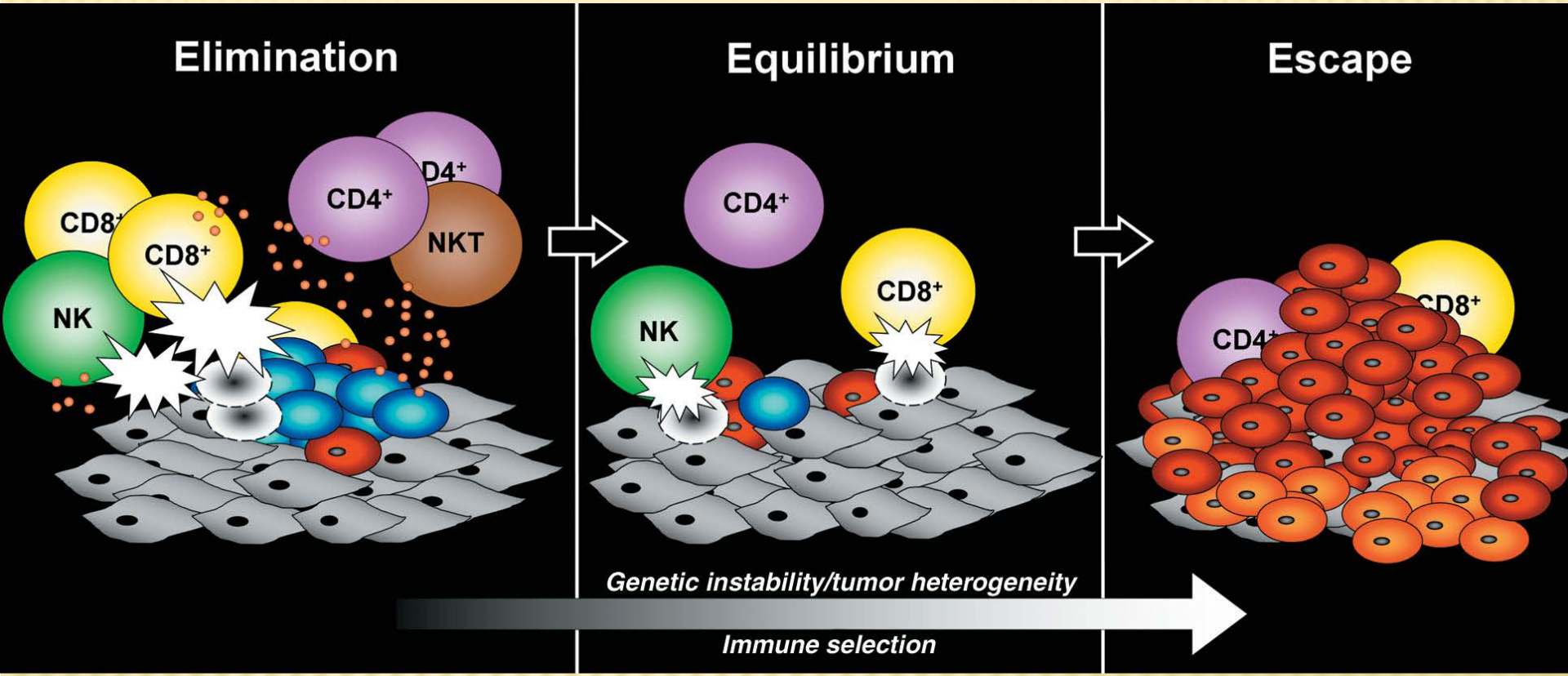
   eradicates the developing tumor

2. **Equilibrium phase**

   - tumor bed containing many genetically unstable and mutating tumor cells
   - many of the original tumor cell escape variants are destroyed
   - new variants arise →resistance to immune attack.
   - new population of tumor clones with reduced immunogenicity
   - the longest of the three phases and may occur over a period of many years in humans

3. **Escape phase**

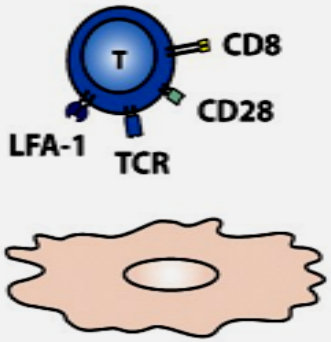
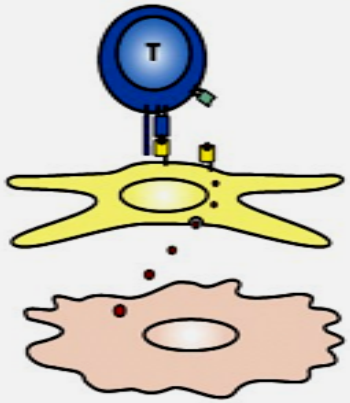
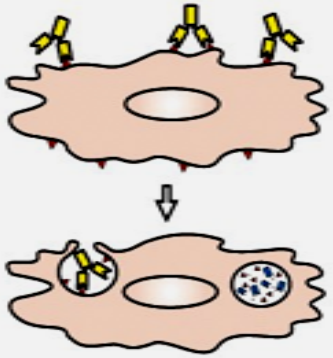
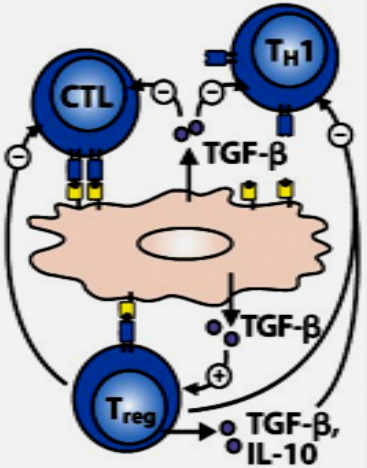
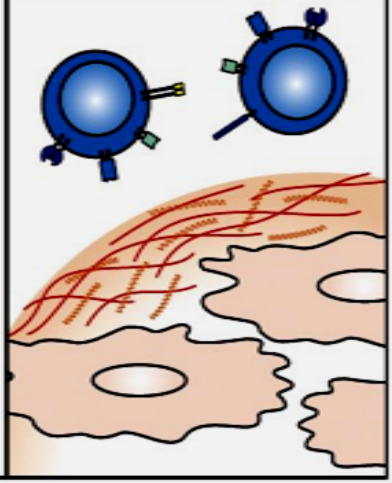
   - tumor cell variants selected in the equilibrium phase now can grow in an immunologically intact environment
   - tumor expand in an uncontrolled manner



- developing tumor cells
- tumor cells variants
- additional tumor variants
- Underlying stroma and nontransformed cells

CANCER CELLS ESCAPE FROM IMMUNOSURVEILLANCE

- Low immunogenicity
- Tumor cells as self antigen
- Antigenic modulation
- Tumor-induced immunosupression
- Tumor-induced privileged site

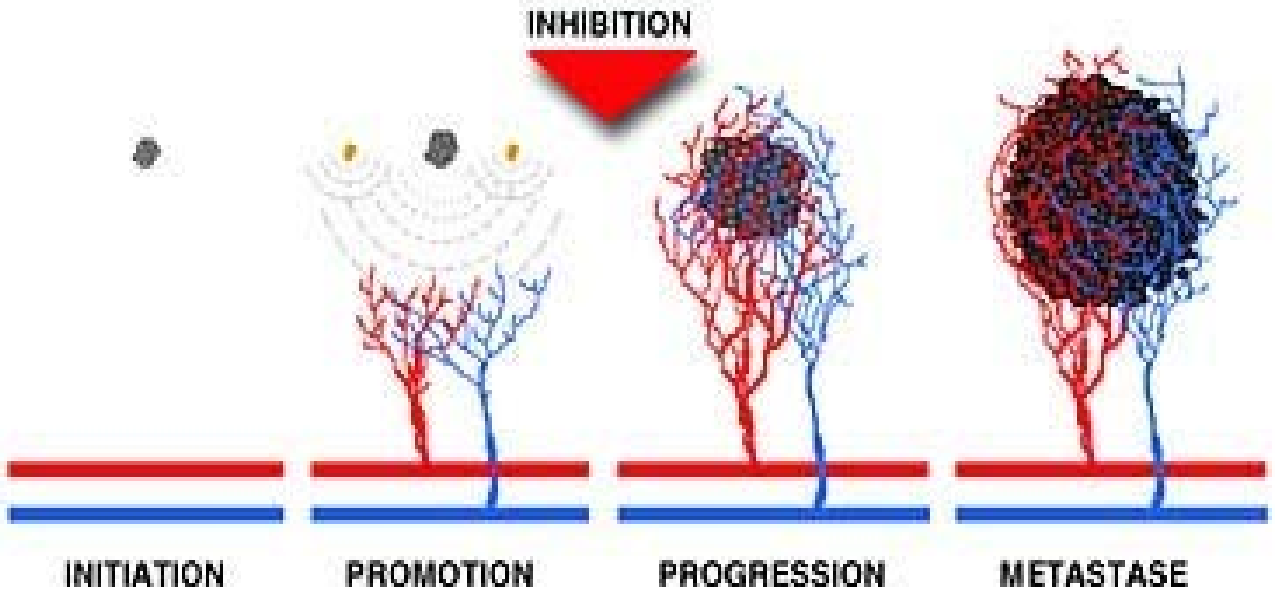
Low immunogenicity	Tumor treated as self antigen	Antigenic modulation	Tumor-induced immune suppression	Tumor-induced privileged site
No peptide:MHC ligand No adhesion molecules No co-stimulatory molecules	Tumor antigens taken up and presented by APCs in absence of co-stimulation tolerize T cells	Antibody against tumor cell- surface antigens can induce endocytosis and degradation of the antigen. Immune selection of antigen-loss variants	Factors (e.g.,TGF-β) secreted by tumor cells inhibit T cells directly. Induction of regulatory T cells by tumors	Factors secreted by tumor cells create a physical barrier to the immune system
				

TUMOR ANTIGENS

- **Tumor-specific transplantation antigens (TSTA)**
  - unique to tumor cells, not expressed on normal cells
  - responsible for rejection of the tumor
- **Tumor associated transplantation antigens (TATA)**
  - expressed by tumor cells and normal cells
  - Tumour-associated developmental Ag (TADA)
  - Tumour-associated viral Ag (TAVA)
- **Tumor-associated developmental antigens or onco-fetal antigens**
  - alpha-fetoprotein (AFP)
  - carcino-embryonic antigen (CEA)
- Prostate-specific antigen (PSA)

Cancer angiogenesis

- New blood vessel development is an important process in cancerous growths
- Play a role in the dissemination of cancer leading to metastasis formation
- supplying nutrients and oxygen and removing waste products
- growth factors and cytokines can promote angiogenesis,
- most important is vascular endothelial growth factor (VEGF)



CANCER AND INFLAMMATION

- Inflammation can cause cancer
  - Chronic infection (HPV/Hepatitis B and C virus) leads to cervical and hepatocellular carcinoma
  - Intrinsic mechanisms of cells prevent unregulated proliferation or the accumulation of DNA mutations.
  - Tumor suppressor pathways that mediate DNA repair, cell cycle arrest, and apoptosis

Cancer can cause inflammation

- Pre-malignant tumors are “wound-like”
- First phase→body treats early tumors as wounds
- mast cells are responsible for providing MMP→ biological active form of VEGF → stimulate the pro-tumorigenic angiogenic switch
- Early tumor→ COX-2 is expressed by stromal cells
- In larger tumors→COX-2 is expressed by the dysplastic epithelium
- Later tumor growth→pro-inflammatory factors (MMPs) come under direct control by the tumors

EFFECT OF AGING AND STRESS TO CANCER

- **Cancer risk increases with age**
  - aging lymphocytes accumulate genetic errors → decrease effectiveness
  - thymus function declining with age →decrease in cell-mediated immune competence.

- **Stressfull experience decrease immunological function → cancer**
  - The end result of chronically stressed → stimulatory signals to adrenal glands → stress hormones (cortisol and epinephrine)

STRESS HORMON

- Increase the production of free radicals → DNA damage and impaired immune function
- Increase inflammation through the production of pro-inflammatory cytokines → impair immune function and promote cancer growth
- Reduce the ability of abnormal cells to undergo apoptosis and DNA repair, important self-regulating anticancer mechanisms
- Stimulate the production of IGF-1, VEGF and other growth factors that can promote tumor cell growth

IMMUNOTHERAPY

- **Active Immunotherapy**
  Stimulation of active host immune responce to tumor
- **Passive Immunotherapy**
  transfer of immune effectors
- **Antiangiogenesis**

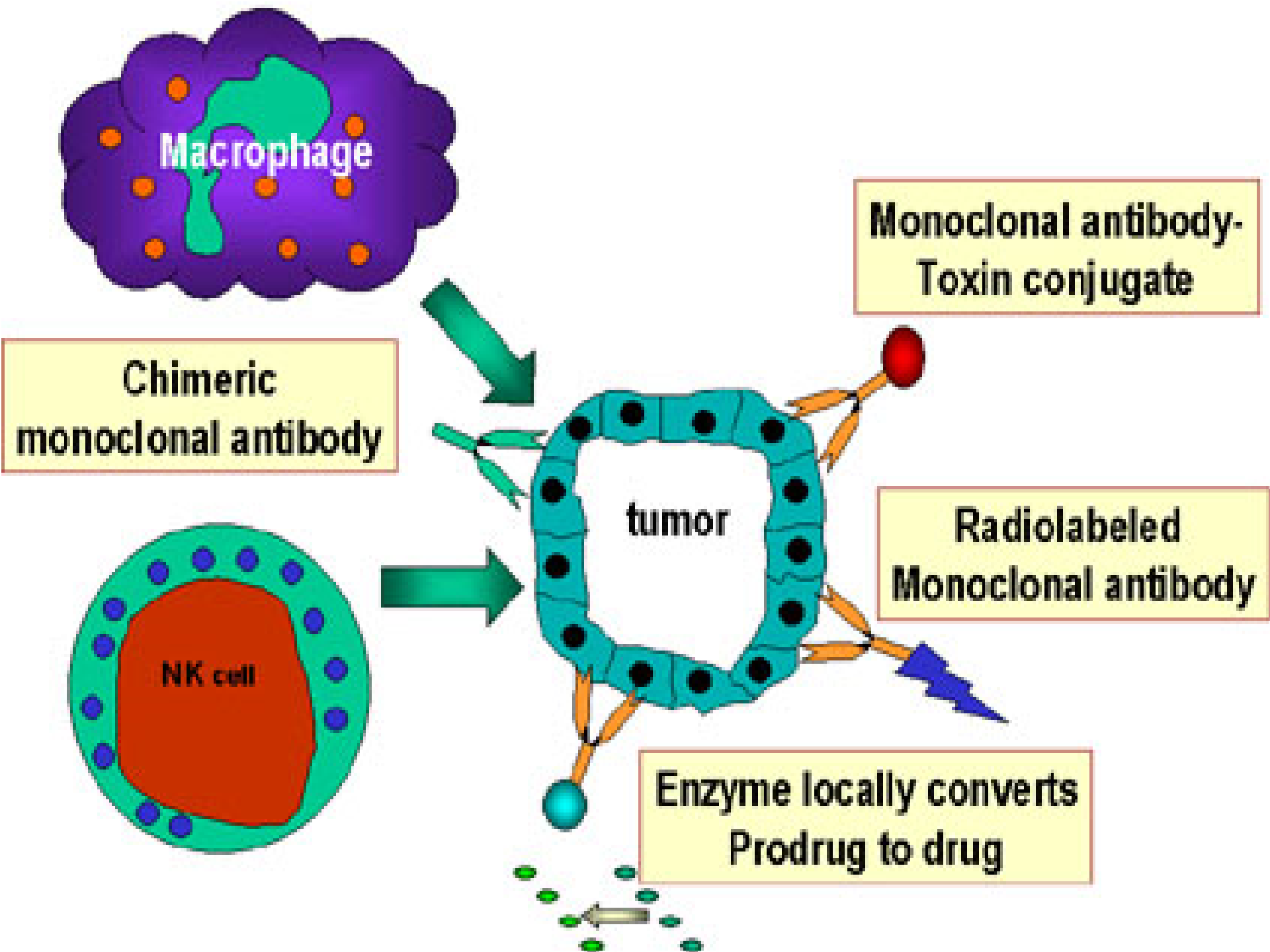
  inhibiting angiogenesis can slow down or prevent the growth and spread of cancer cells in humans

1. ACTIVE IMMUNOTHERAPY

- Vaccination with tumor cells and tumor antigens (type 16 HPV, adenovirus, melanoma, plasmids dendritic cells and cytokine vaccines)
- Augmentation of host immunity to tumors with costimulators and cytokines (IL-2, IL-4, IFN-γ, GM-CSF)
- Blocking inhibitory pathways to promote tumor immunity (CTLA)
- Nonspecific stimulation of the immune system (BCG)

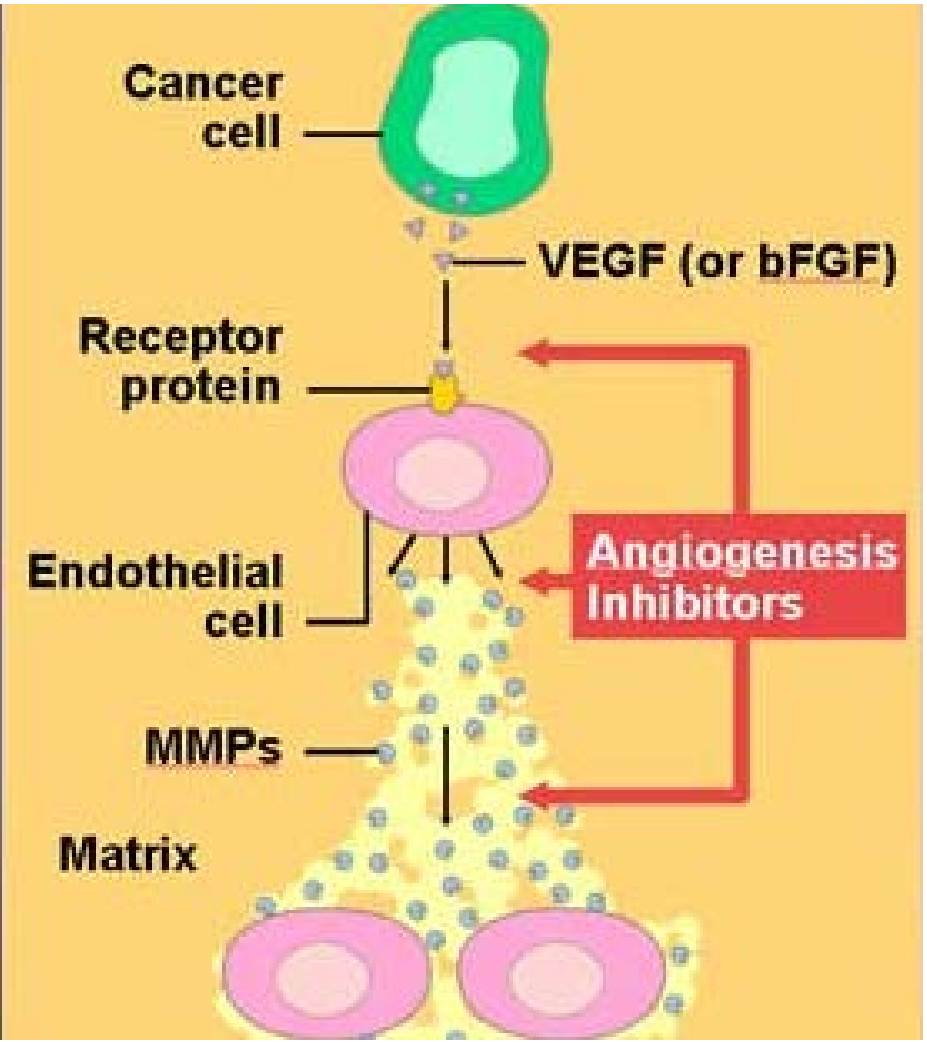
2. PASSIVE IMMUNOTHERAPY FOR TUMOR

- Antibodies against tumor cells
  - Monoclonal antibodies against specific tumor antigen (CD20/Her2/CD 33/VEGF)
  - Monoclonal antibodies attached with toxin or radioactive isotop
- Adoptive cellular therapy
  - Transfer of lymphocytes : lymphokine- activated killer (LAK) → IL-2 activated T and NK cells,
  - Tumor-infiltrating lymphocytes (TIL)
  - NK cells and dendritic cells

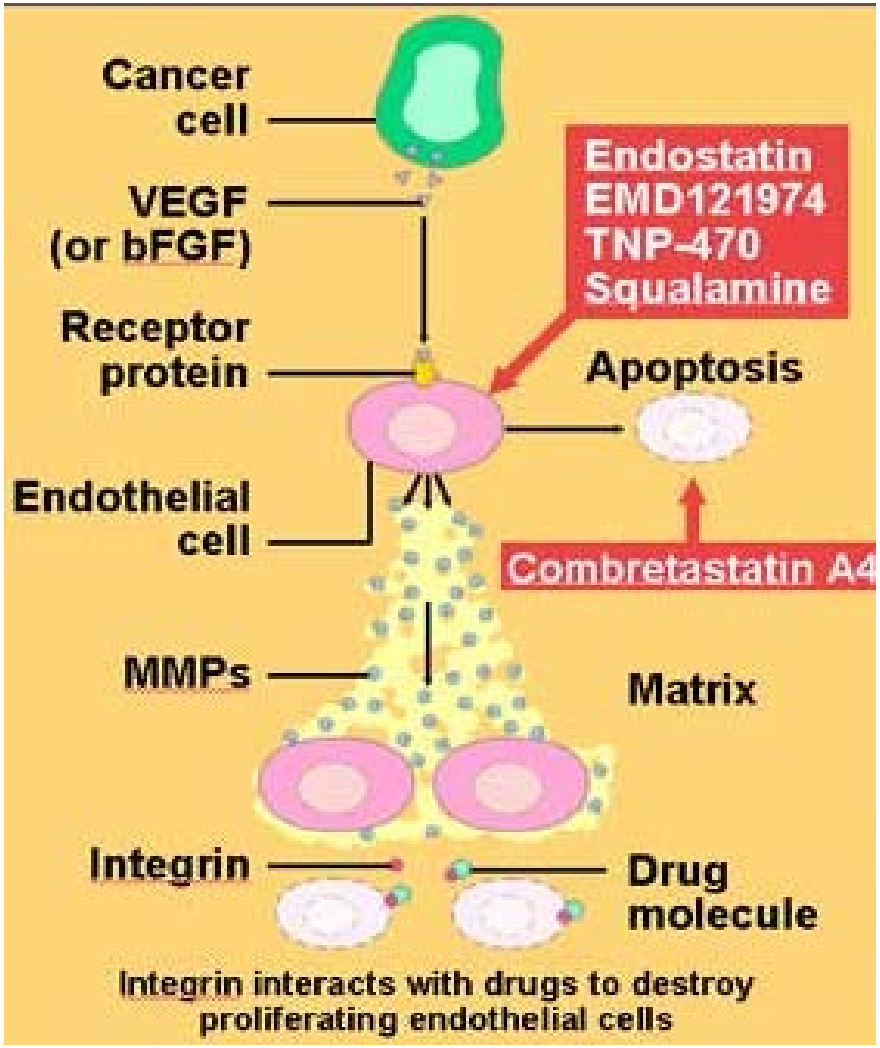

Macrophage
Monoclonal antibody-
Toxin conjugate
Chimeric
monoclonal antibody
tumor
Radiolabeled
Monoclonal antibody
NK cell
Enzyme locally converts
Prodrug to drug

3. ANTIANGIOGENESIS

- Inhibiting endogenous angiogenic factors: bFGF (basic Fibroblast Growth Factor) and VEGF
- Inhibiting degradative enzymes (MMPs) →degradation of the basement membrane of blood vessels
- Inhibiting endothelial cell proliferation
- Inhibiting endothelial cell migration
- Inhibiting the activation and differentiation of endothelial cells



Angiogenesis inhibitors



Inhibit angiogenesis directly


Thank You