

# **Immunology and Immunotherapy 101 for the Non-Immunologist**

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# Disclosures

I have the following relationships with industry:

Amgen	Scientific Advisory Board, Clinical trial funding
BMS	Clinical trial Funding
Celldex	Scientific Advisory Board
EMD Serono	Scientific Advisory Board , Clinical trial funding
Merck Rutgers)	Scientific Advisory Board, Speaker's Bureau (funds to
Prometheus	Scientific Advisory Board, Clinical trial funding
Sanofi	Consulting services
Turnstone Biologics	Scientific Advisory Board
Viralytics	Clinical trial funding

*-I will NOT be discussing non-FDA treatments during my presentation.*

# What is Immunology?

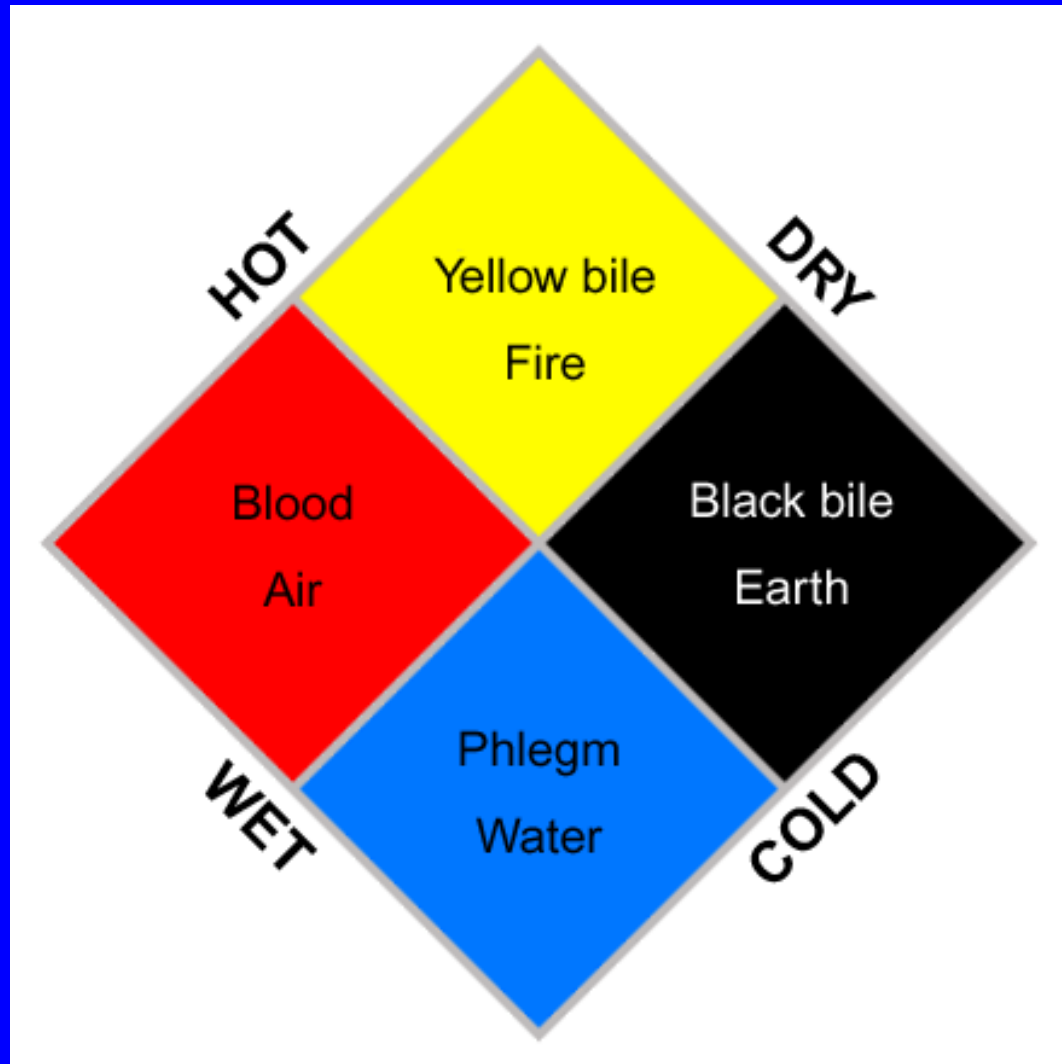
- Study of body's immunity (defense) against invaders
  - External (viruses, bacteria, etc.)
  - Internal (tumors, self)
- Divided into two major functions
  - Afferent arm (“recognition”)
  - Efferent arm (“effector functions”)

# Thucydides, 460-395, B.C.



- Historian
- Philosopher
- General
- First to foster 'cause and effect' relationships and use evidence to document facts
- First to notice that people exposed to plague were "protected" or "immune"

# Disease and the four humors

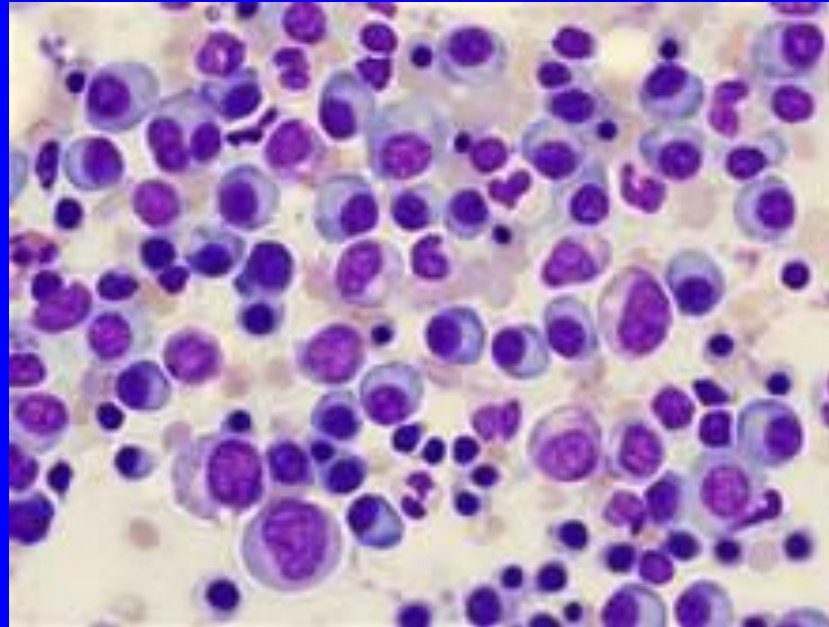


# 18<sup>th</sup> Century and Vaccination





# 19<sup>th</sup> Century and the microscope

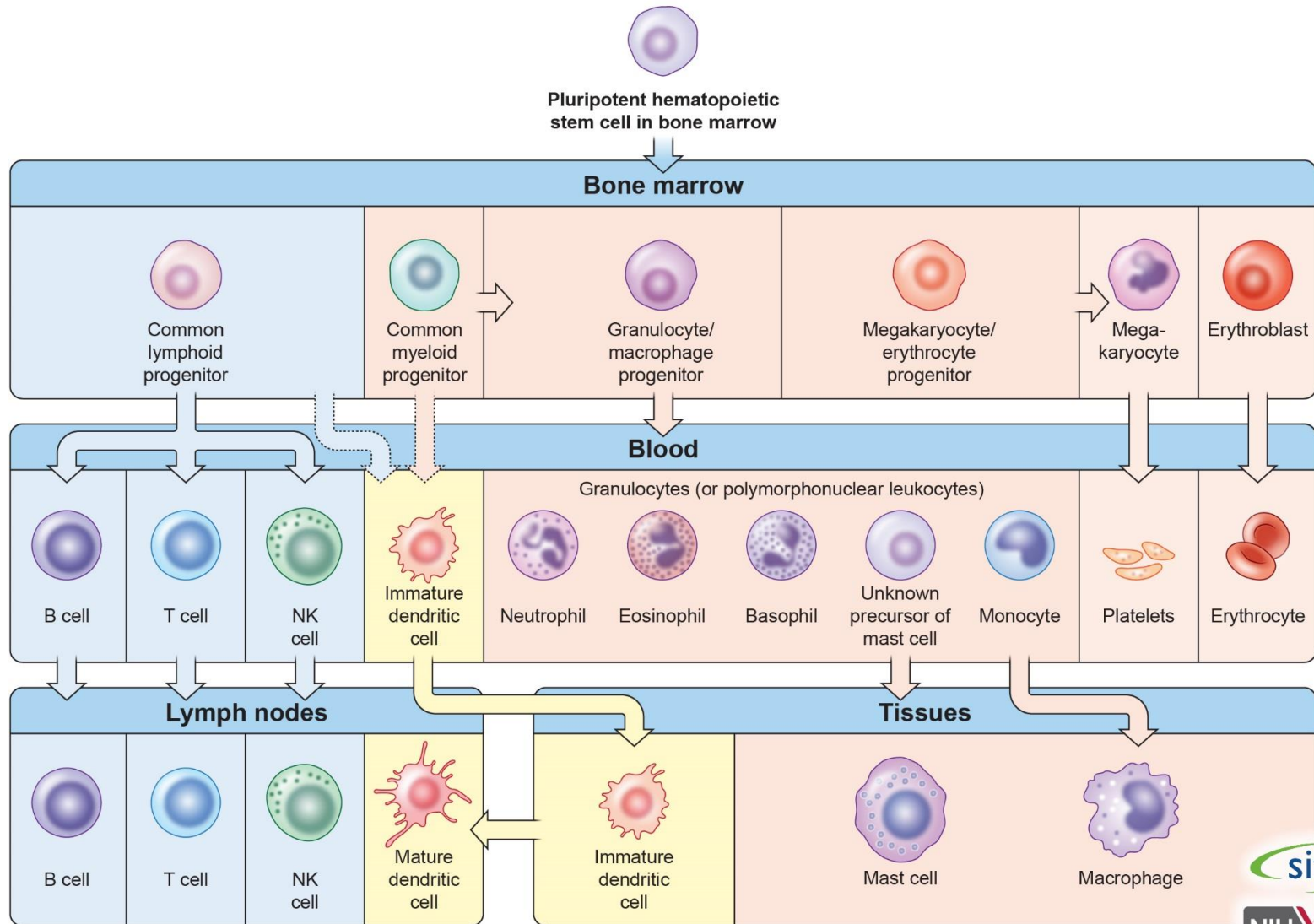


Cells

Microbes



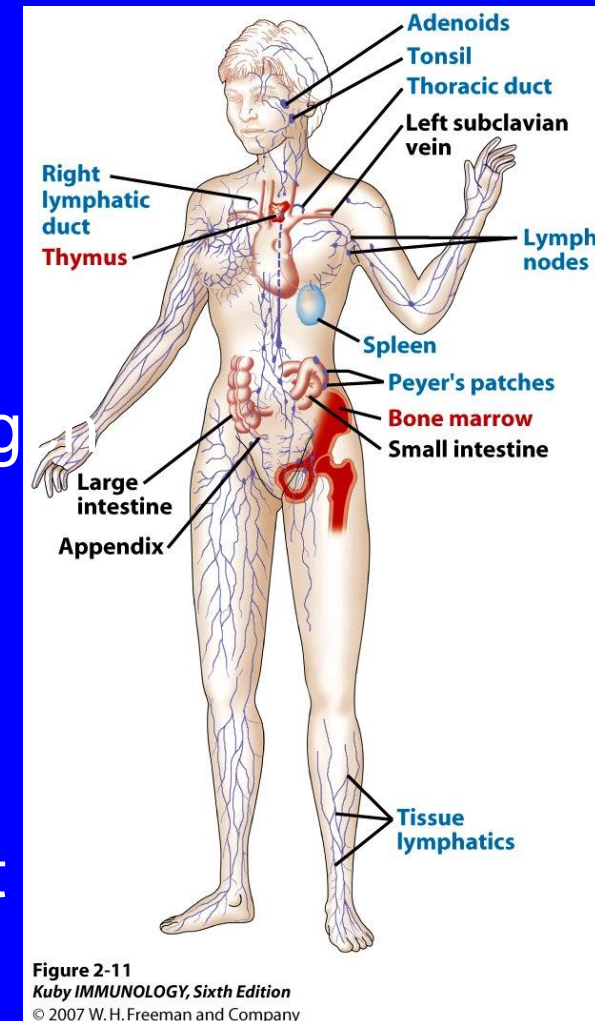
# Immune cells are derived from stem cells in the bone marrow



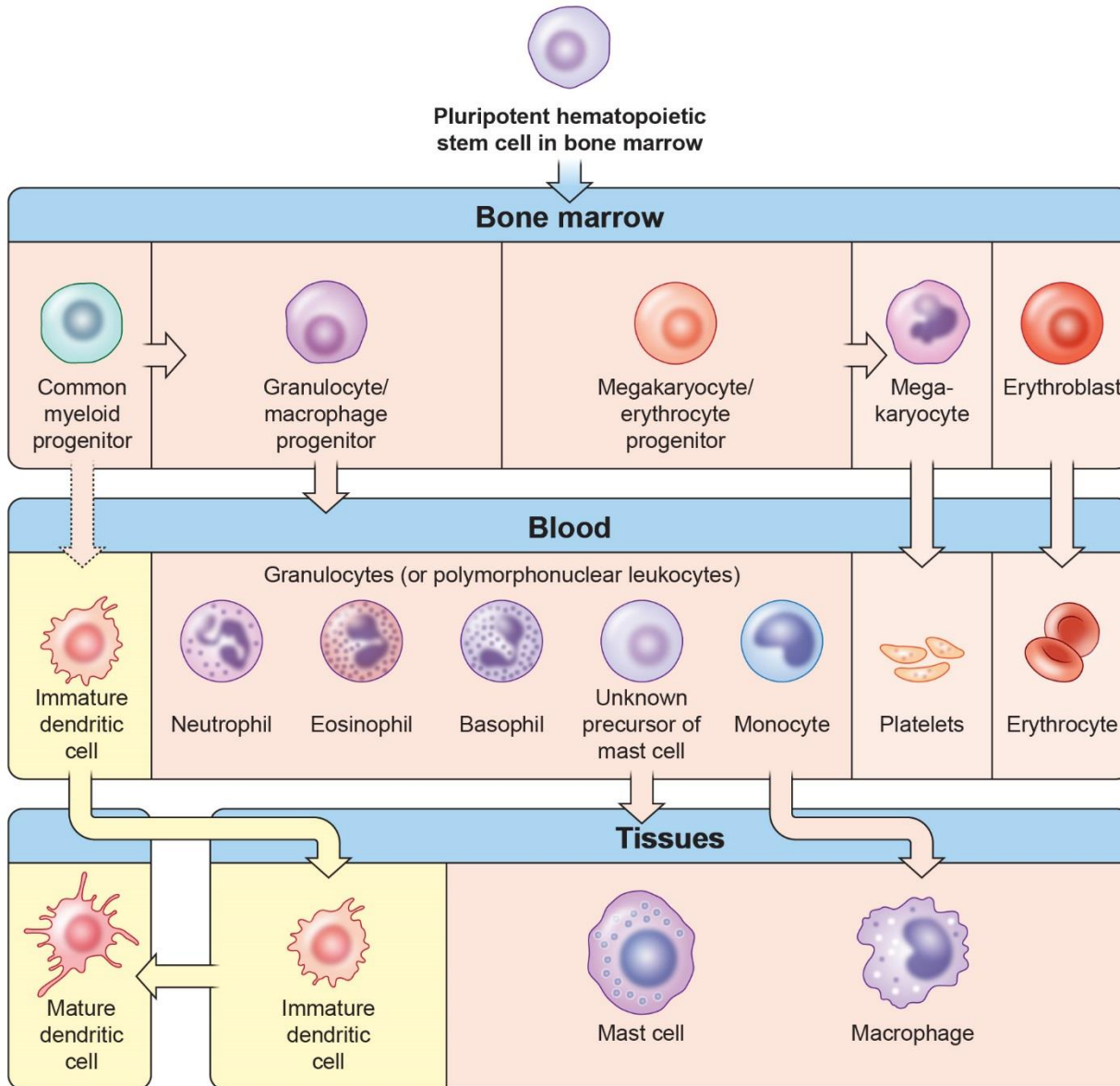


# Lymphoid Organs

- Primary (central)
  - Sites of cell maturation
    - Thymus (T cells)
    - Bone marrow (B cells)
- Secondary (peripheral)
  - Sites of cell interaction with antigens
    - Lymph nodes
    - Spleen
    - ALTs (MALT, GALT, CALT)
- Lymphatic system
  - Site of fluid recycling
  - Method of immune cell transport



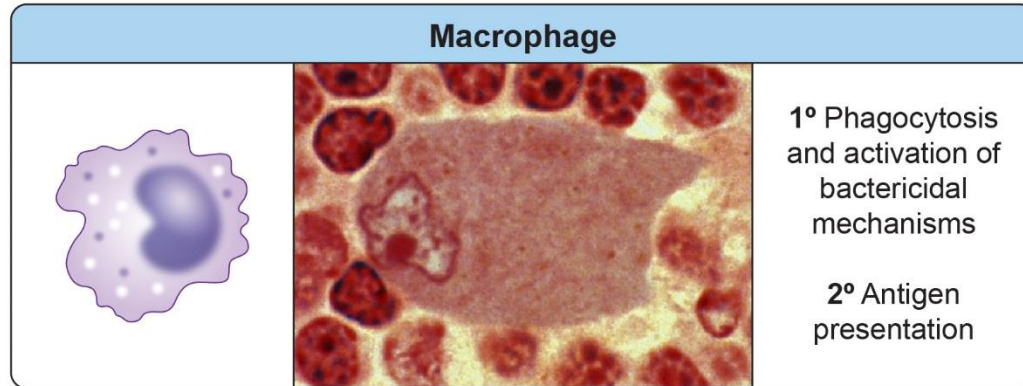
# Myeloid cells



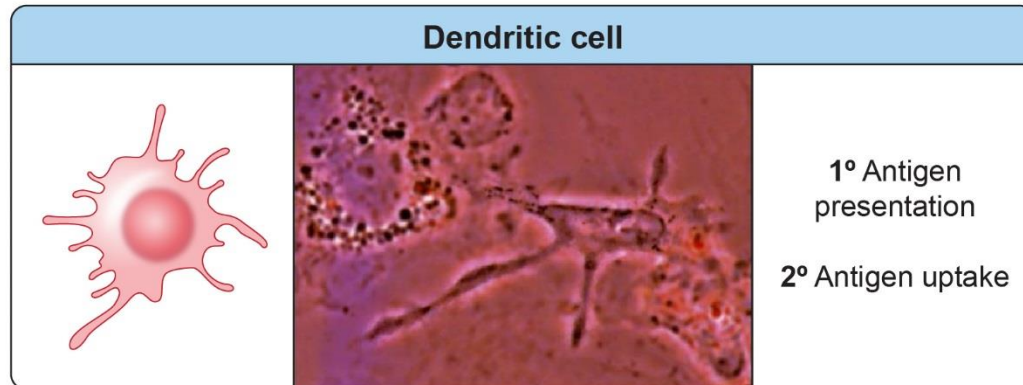
- Derived from a common progenitor
- Comprises most of the cells of the innate immune system
- Functional maturation may happen in tissue in response to danger signals

# Phagocytes

Neutrophils, macrophages and dendritic cells



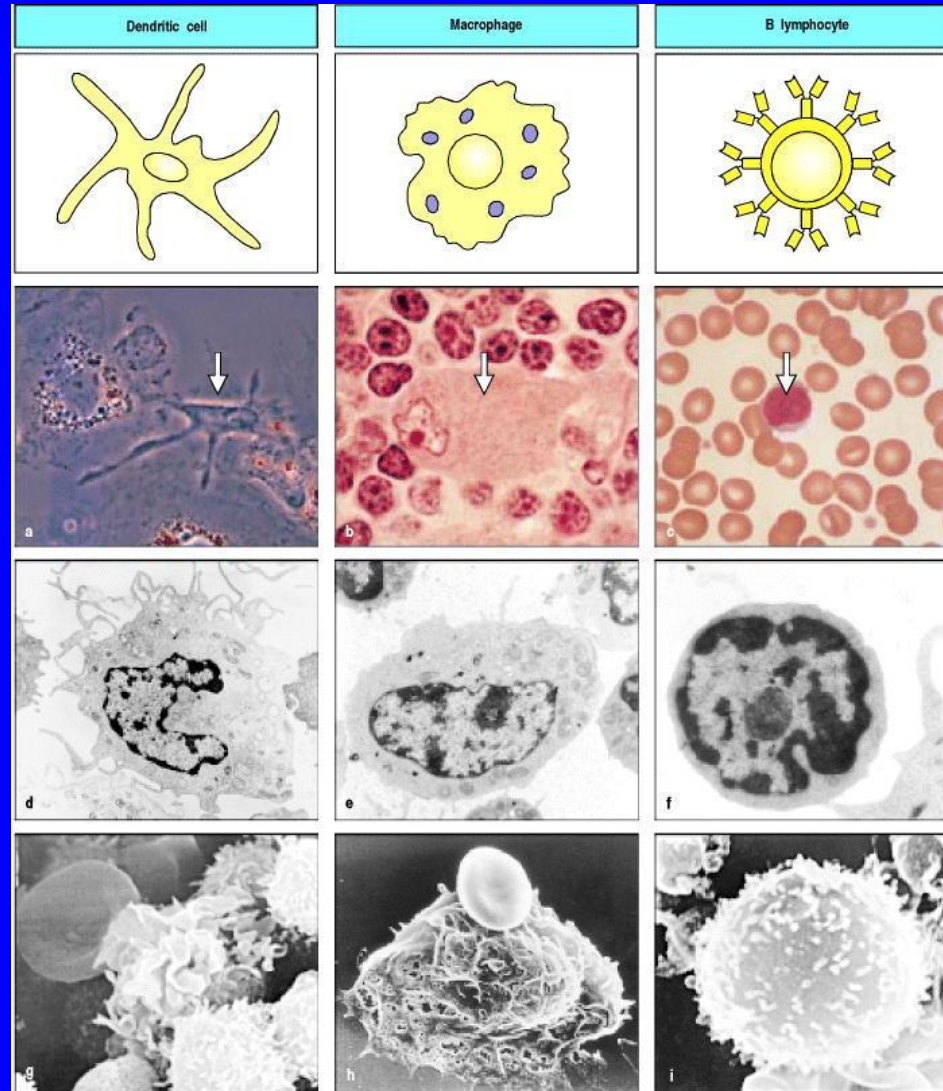
Reside in tissues



Main role is not clearance of pathogen but rather immune cell activation; patrolling population in lymphoid tissues as well as non-lymphoid tissues

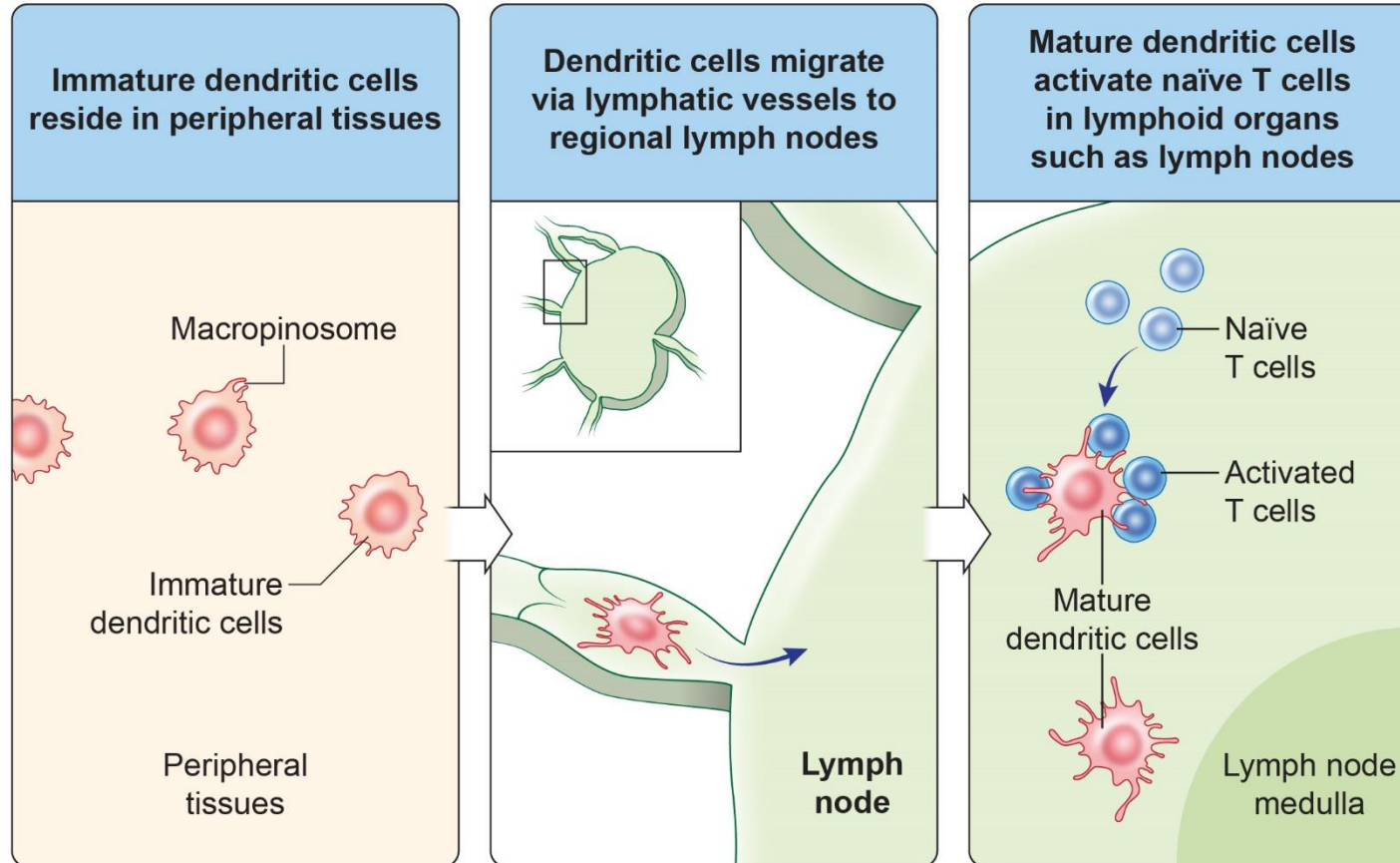
Dendritic cells and macrophages are two types of professional antigen presenting cells (APCs)

# Function of Myeloid Cells: Antigen-Presenting Cells



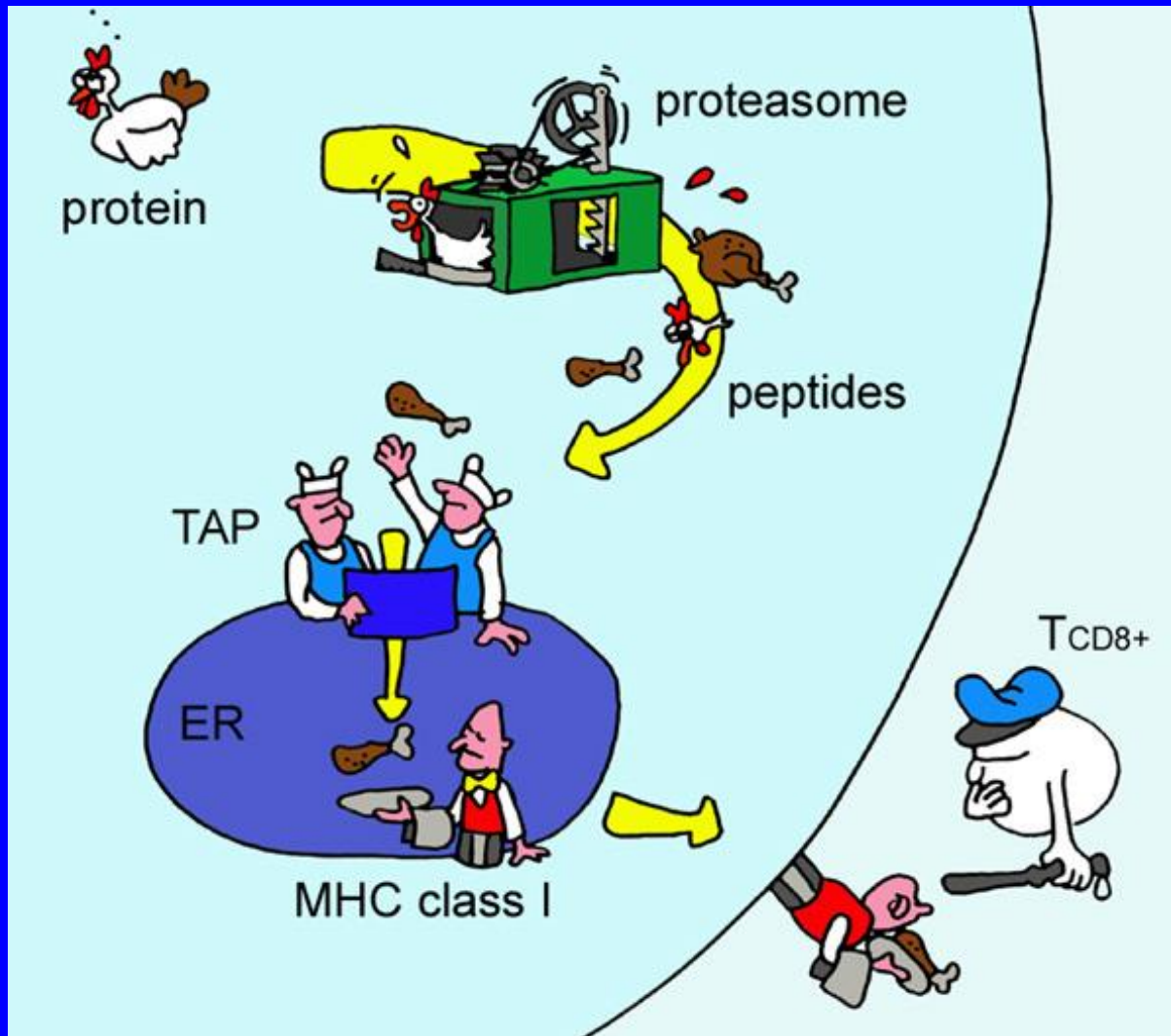


# DCs are important for initiating adaptive immune responses





# Antigen processing and presentation



# Major Histocompatibility Complex (MHC) molecules

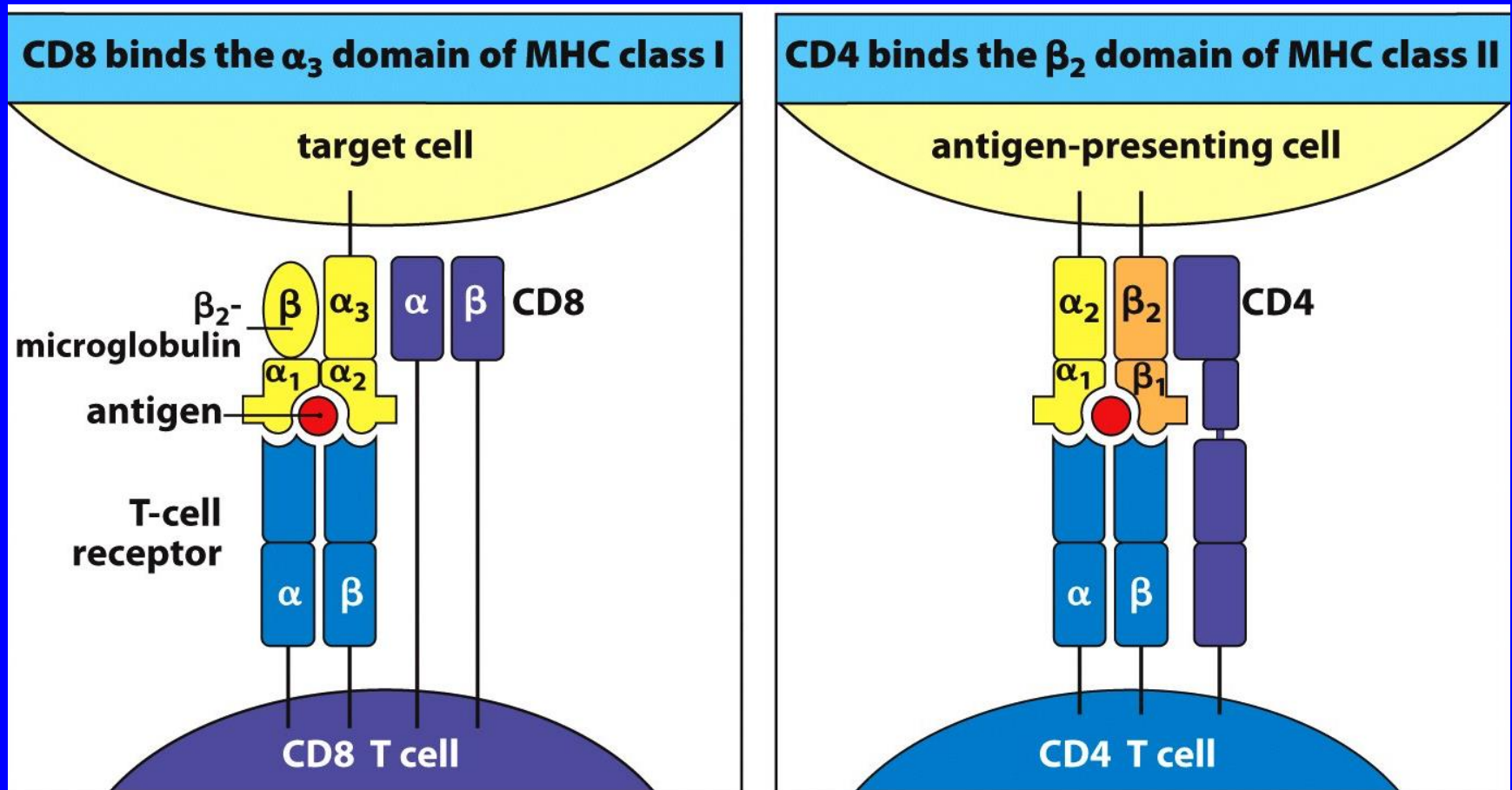
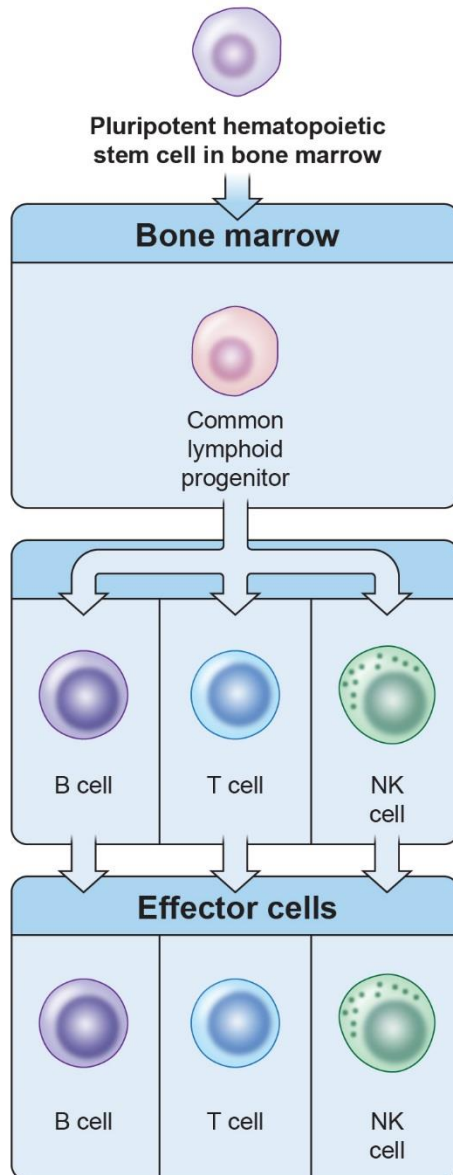


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

# Lymphocytes



## B cells

- Produce antibodies (Ab) that bind proteins

## T cells

- Change antigens to peptides

## Natural Killer (NK) cells

- Kill tumor and virus-infected cells
- Kill antibody-coated cells
- Play dominant role in mediating ADCC in vivo

## Adaptive

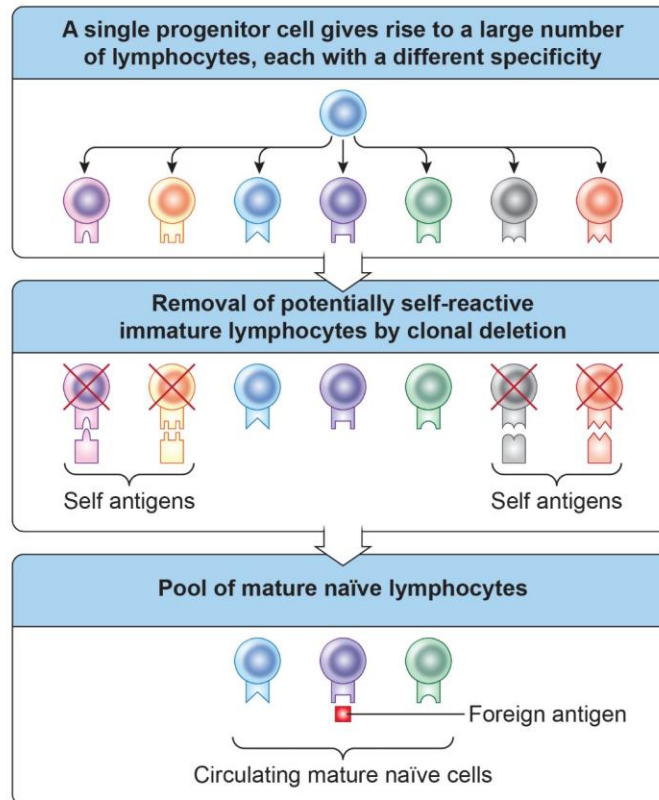
(recognize very specific antigens)

## Innate

(recognize general features)

# Lymphocyte Clonal Selection

## Generating lymphocytes that each have a unique specificity



### Generation of vast pool of cells

- Immature cells (non-functional)

### Elimination of cells that can recognize self Ags

- One barrier to inducing responses against tumor cells

### Mechanism of central tolerance

- Circulating mature naïve cells

# Result of Antigen Recognition: Clonal Expansion

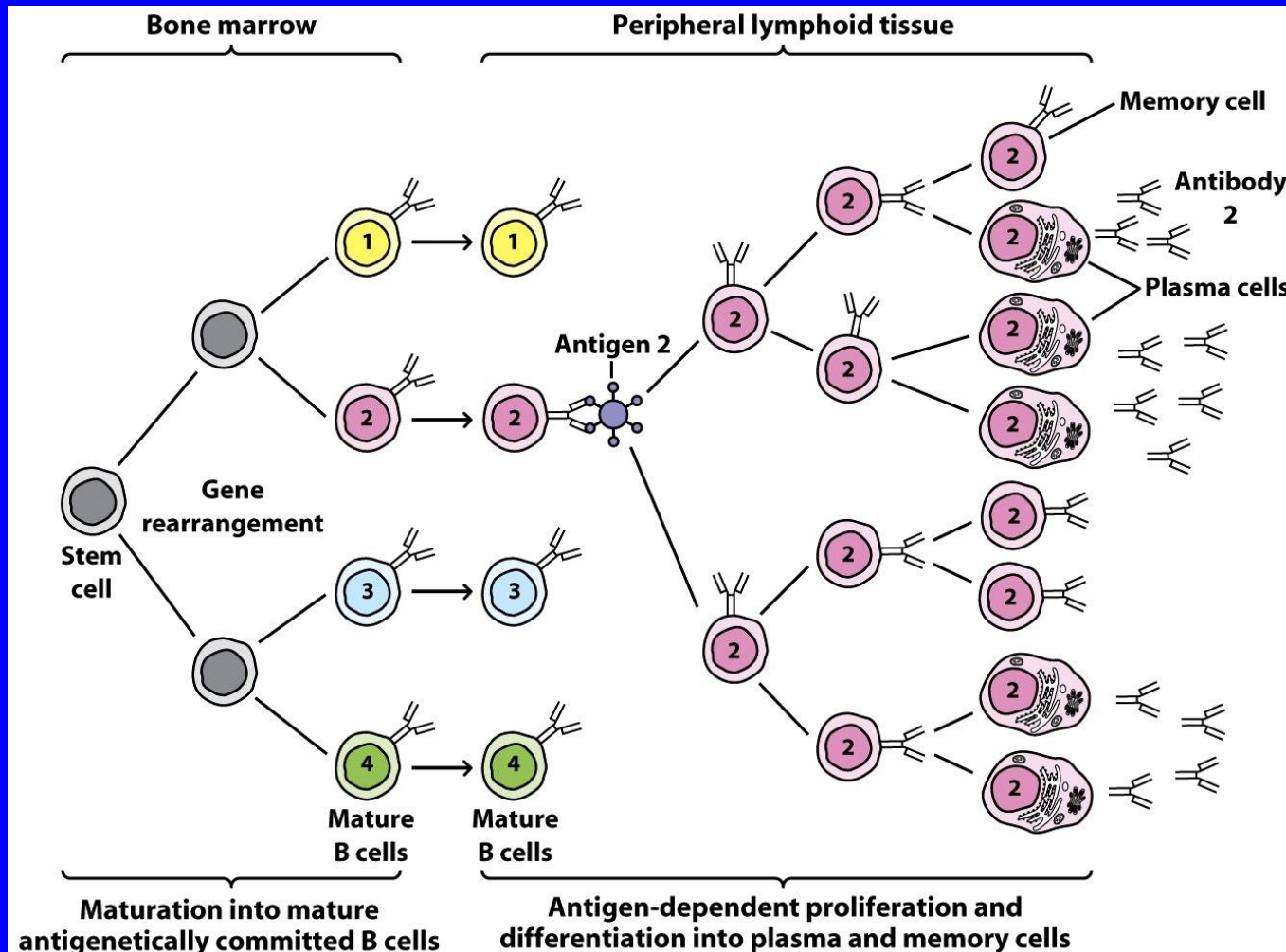
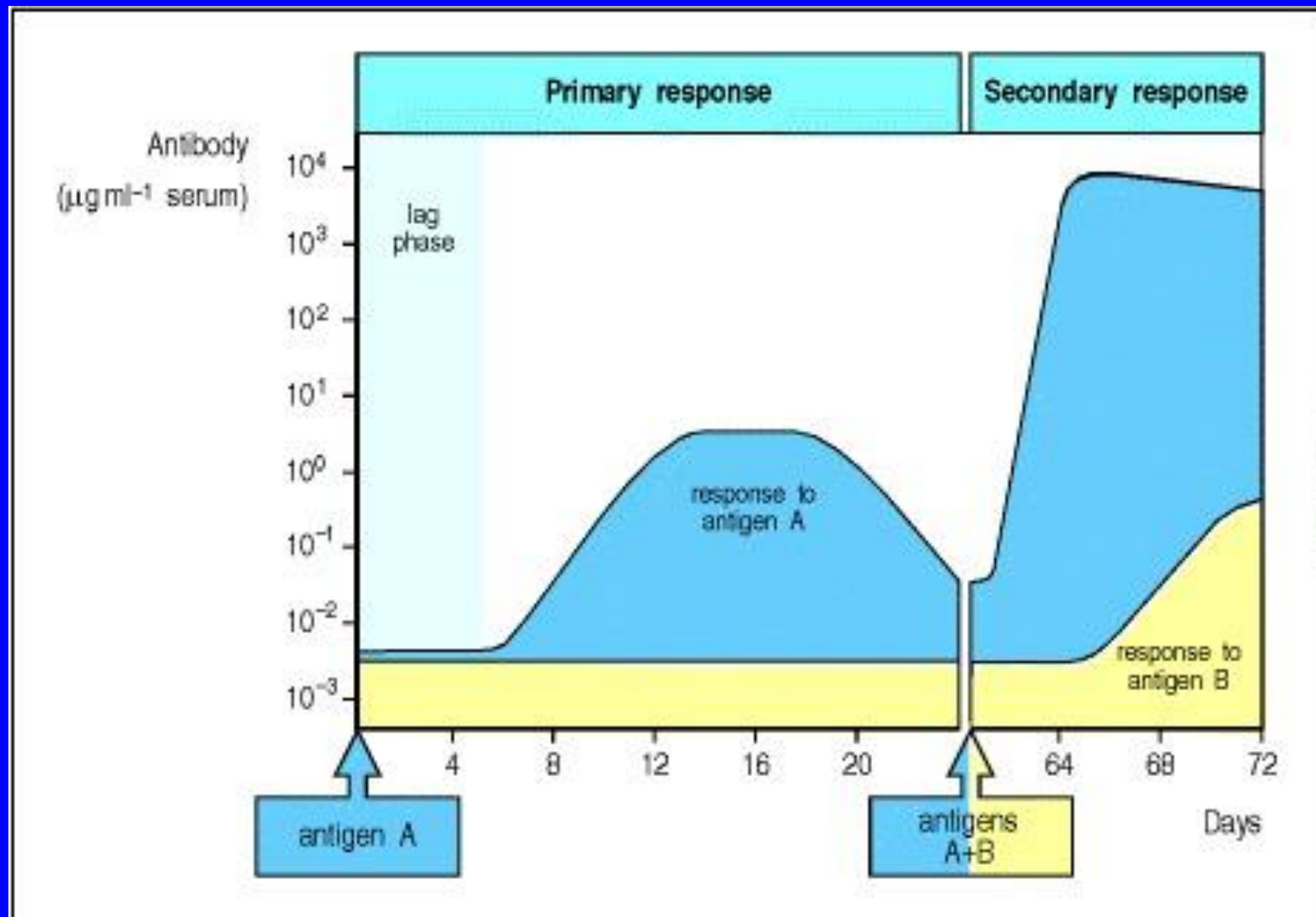


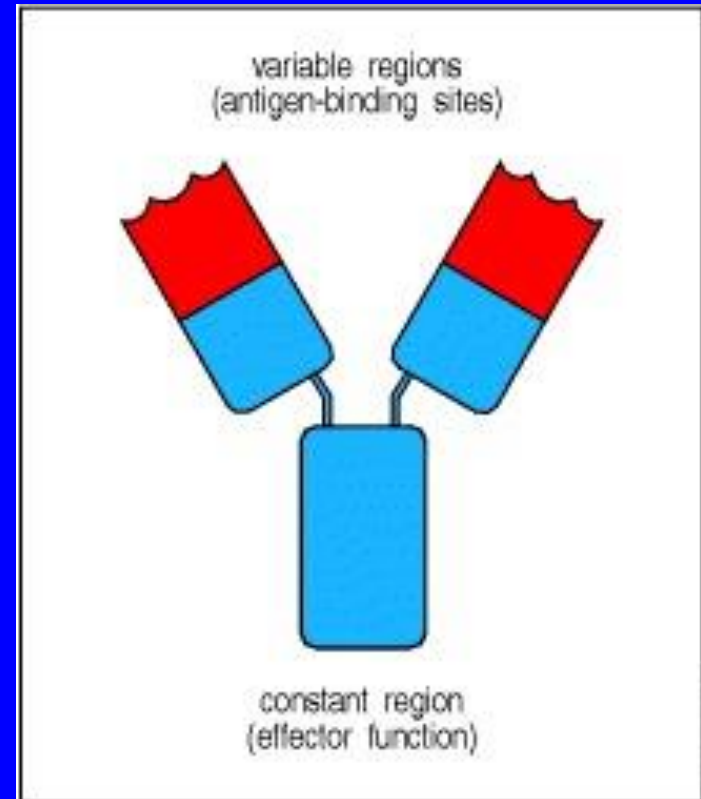
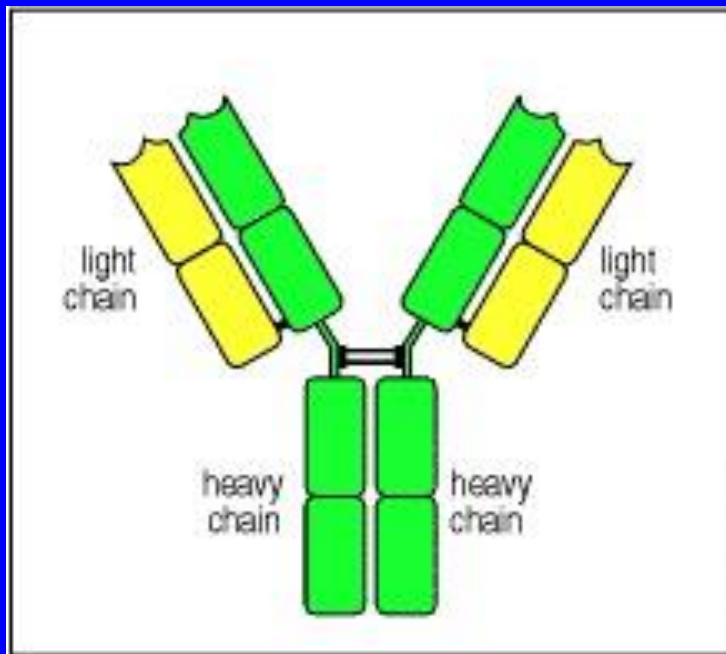
Figure 1-12  
Kuby IMMUNOLOGY, Sixth Edition  
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# Kinetics of the Immune Response



# Antibody Structure and Function



# Antibody classes and activity

– IgG

– IgM

– IgA

– IgD

– IgE

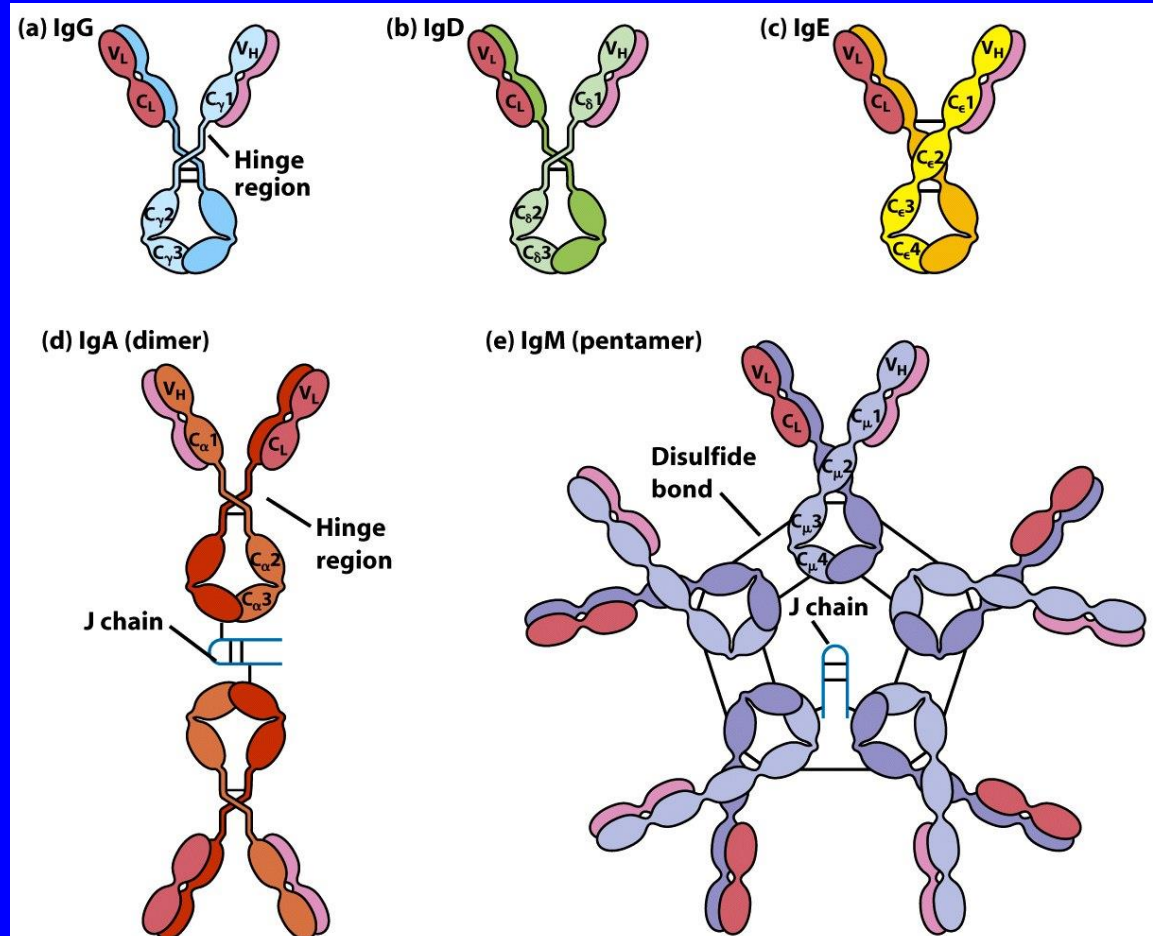
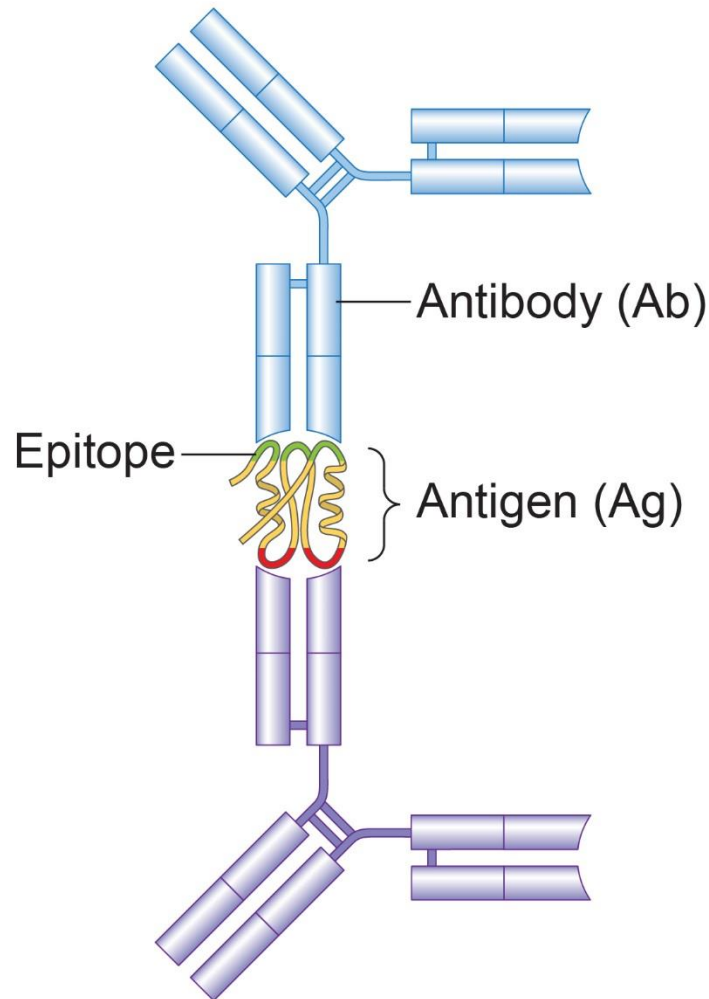


Figure 4-17  
Kuby IMMUNOLOGY, Sixth Edition  
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# Antigen recognition by antibodies

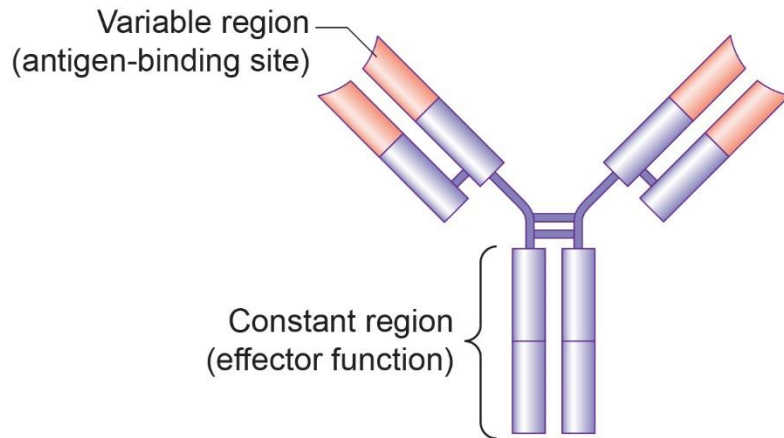
Ab recognizes portions of proteins in native structures, not processed proteins (may not be continuous portion of protein)



# Antigen receptors

## Antibody (Ab)

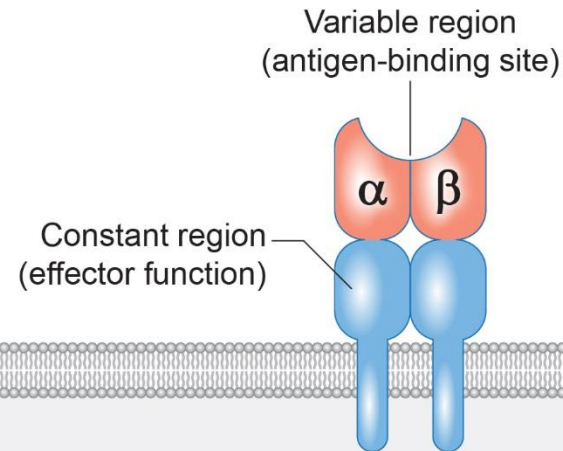
Schematic structure of an antibody molecule



Cell surface and secreted

## T cell receptor (TCR)

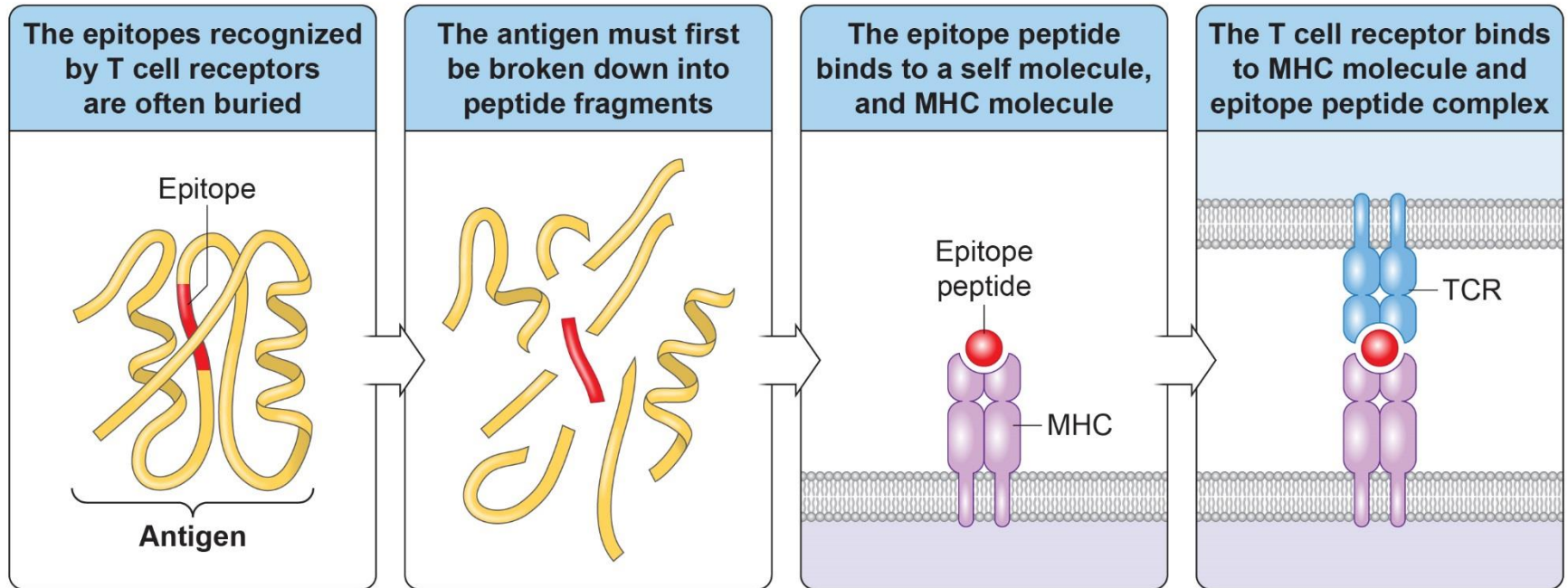
Schematic structure of the T cell receptor



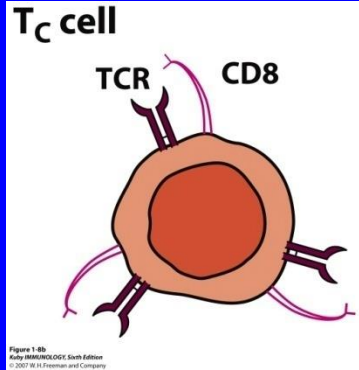
Cell surface only



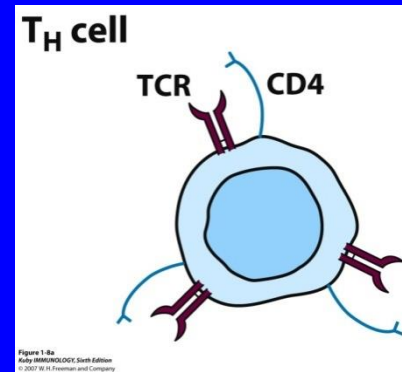
# T cell receptors (TCRs) recognize processed proteins presented by MHC



MHC = Major Histocompatibility Complex



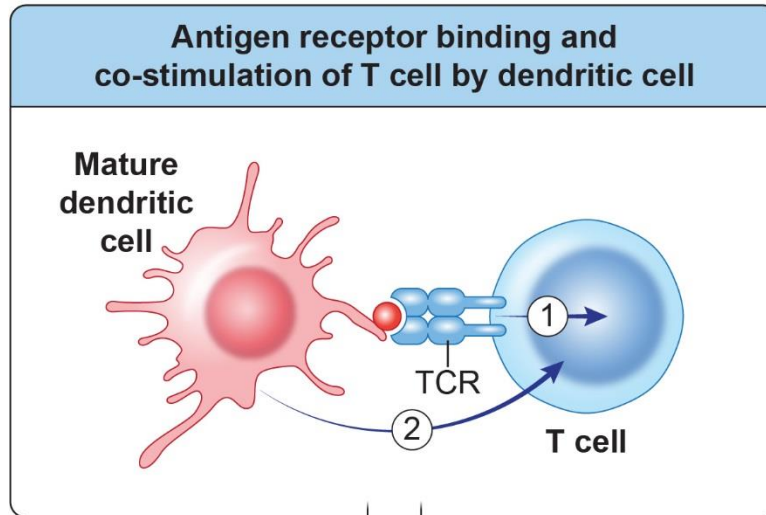
# Three major T cell categories



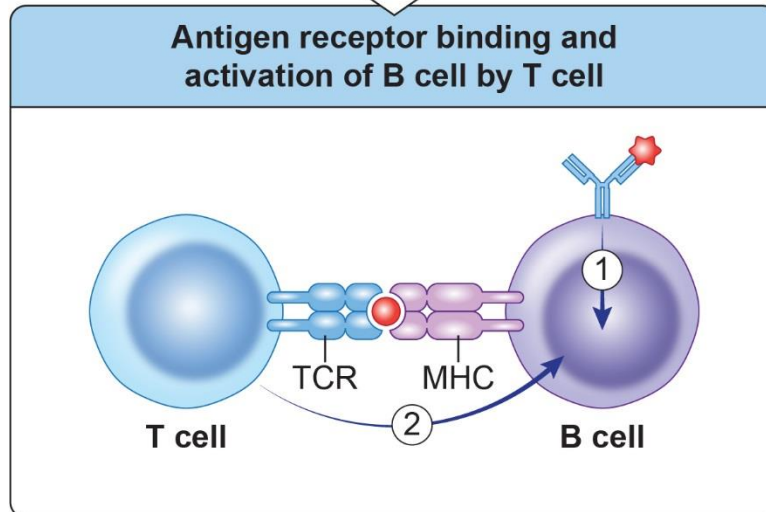
- Cytotoxic T cells (CD3+**CD8+**)
  - Recognize and kill infected (virus, tumor) cells
  - Recognize antigen presented by MHC-I
- Helper T cells (CD3+**CD4+**CD25-)
  - Help activate other cell types (B cells, cytotoxic T cells and macrophages)
  - Recognize antigen presented by MHC-II
  - Th1 helps cytotoxic T cells (cell-mediated immunity)
  - Th2 helps B cells (humoral immunity)
- Regulatory T cells (CD3+CD4+CD25+**FoxP3+**)
  - Regulate (suppress) the action of other cells

# Lymphocyte activation

T cells



B cells



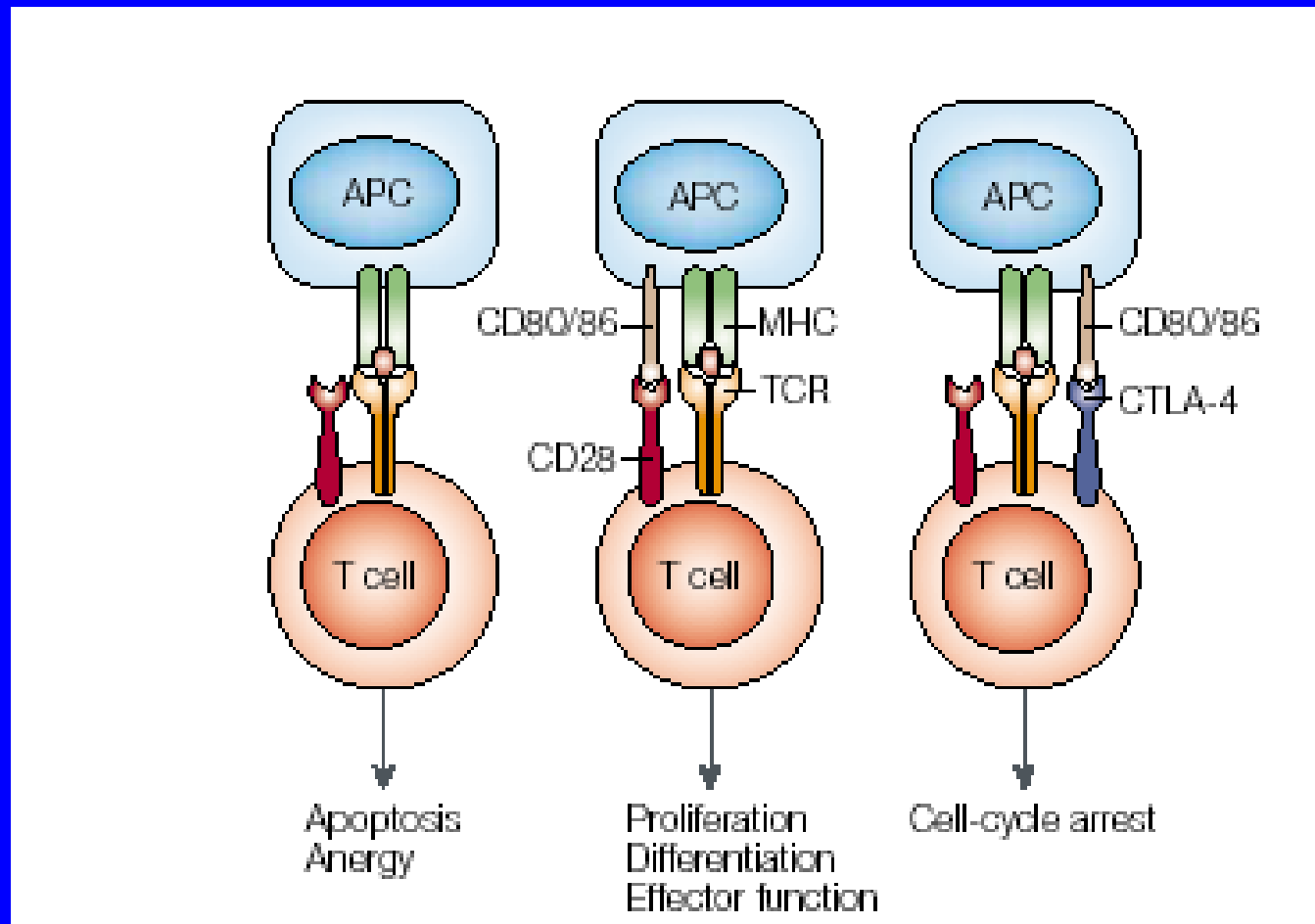
**Activation of T and B cells requires stimulation via:**

- Antigen receptor (Signal 1)
- Costimulatory molecules (Signal 2)

Absence of co-stimulation leads to unresponsiveness

Peripheral tolerance

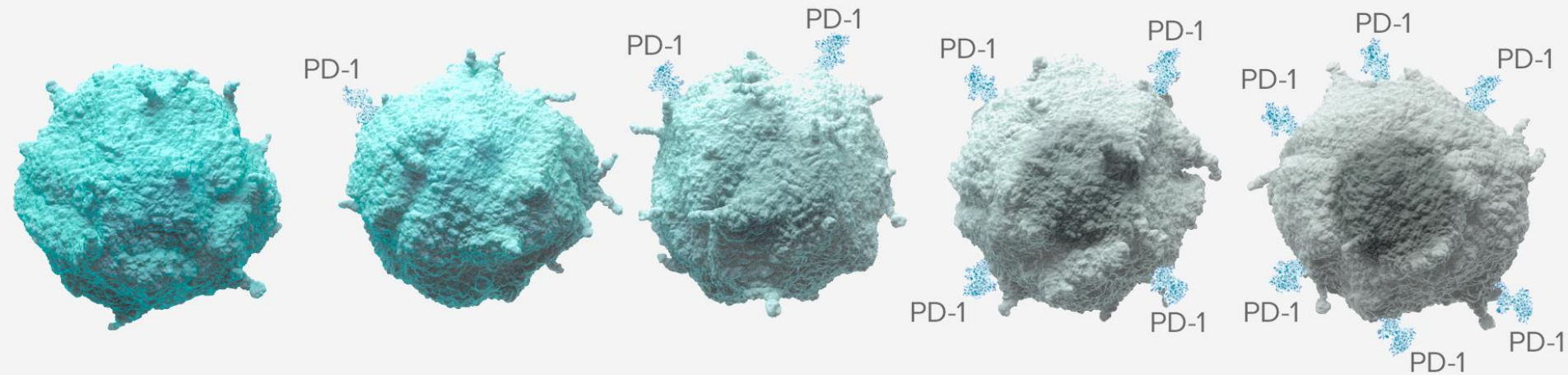
# Co-stimulation regulates T cell activation



# T cell life cycle

Activated T cell

Exhausted T cell

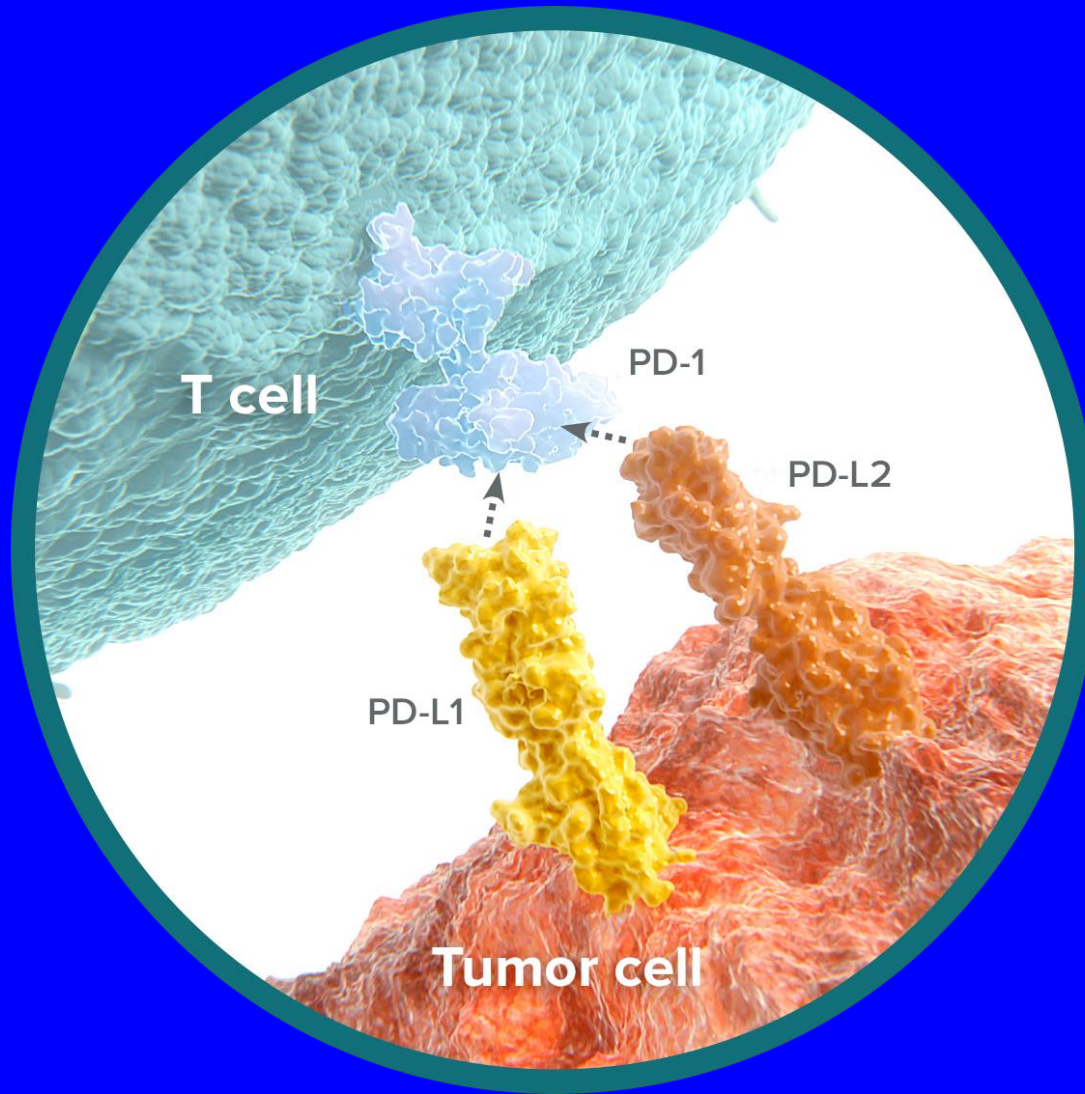


T-cell function

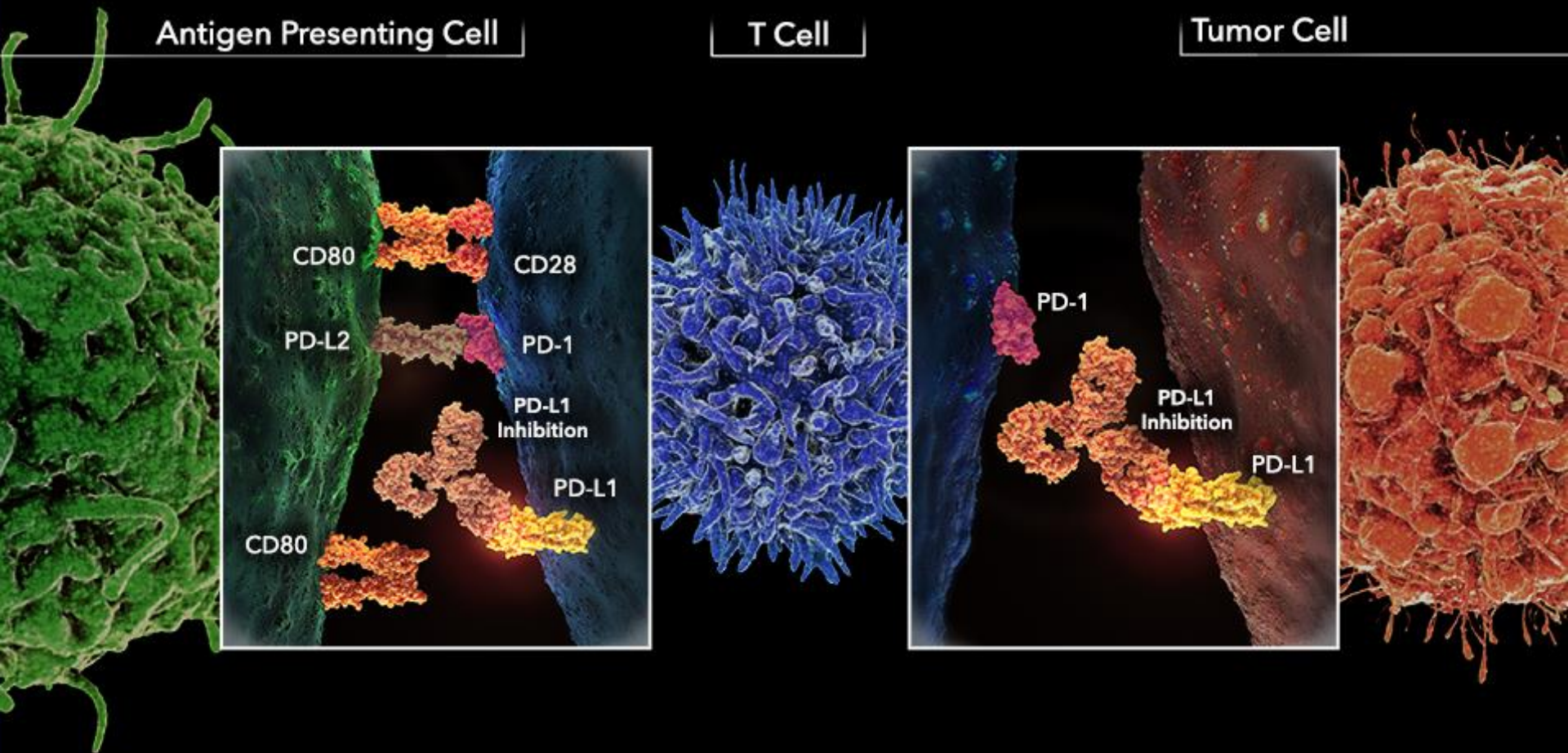
PD-1 expression



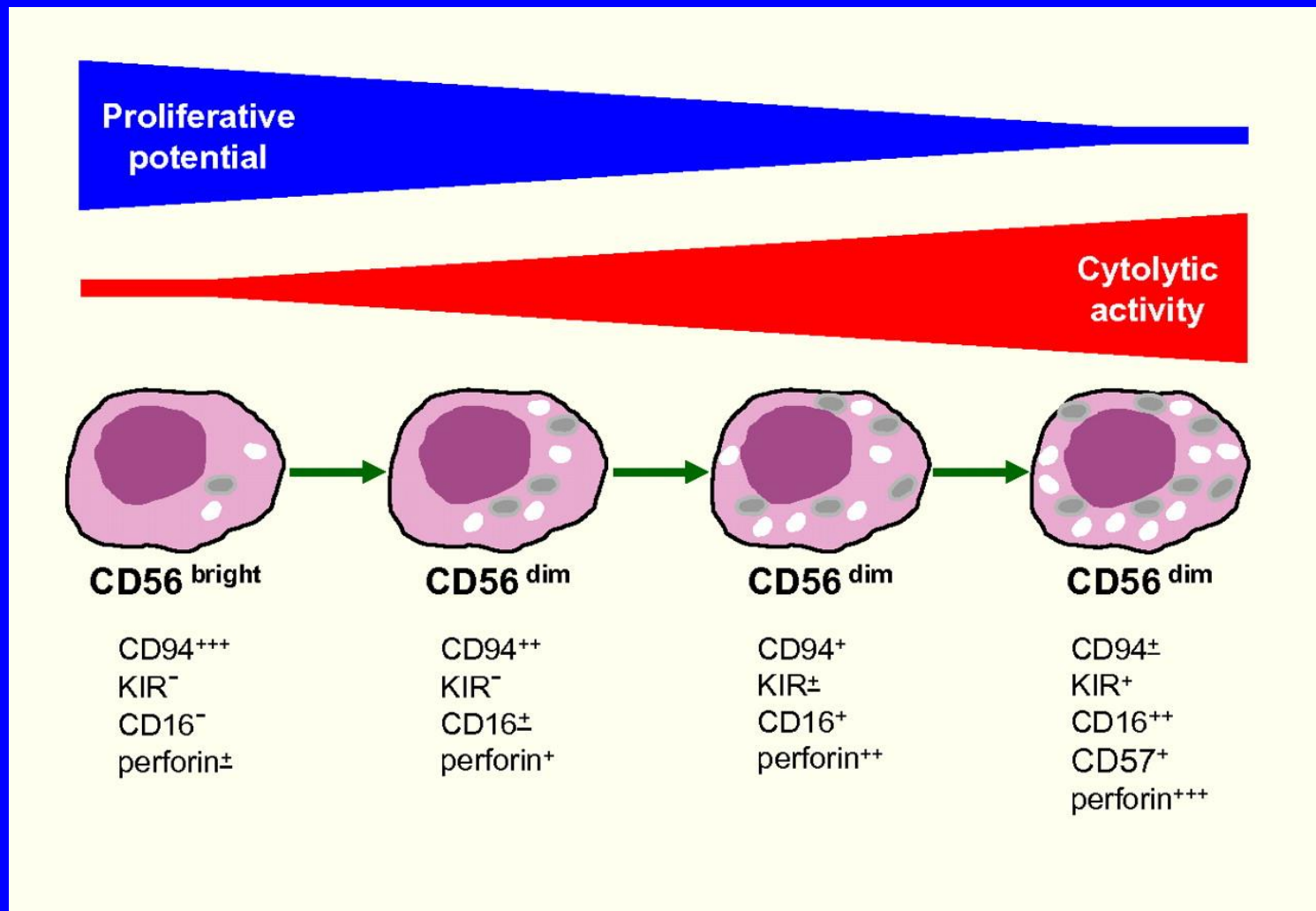
# PD-1:PD-L1 Interactions



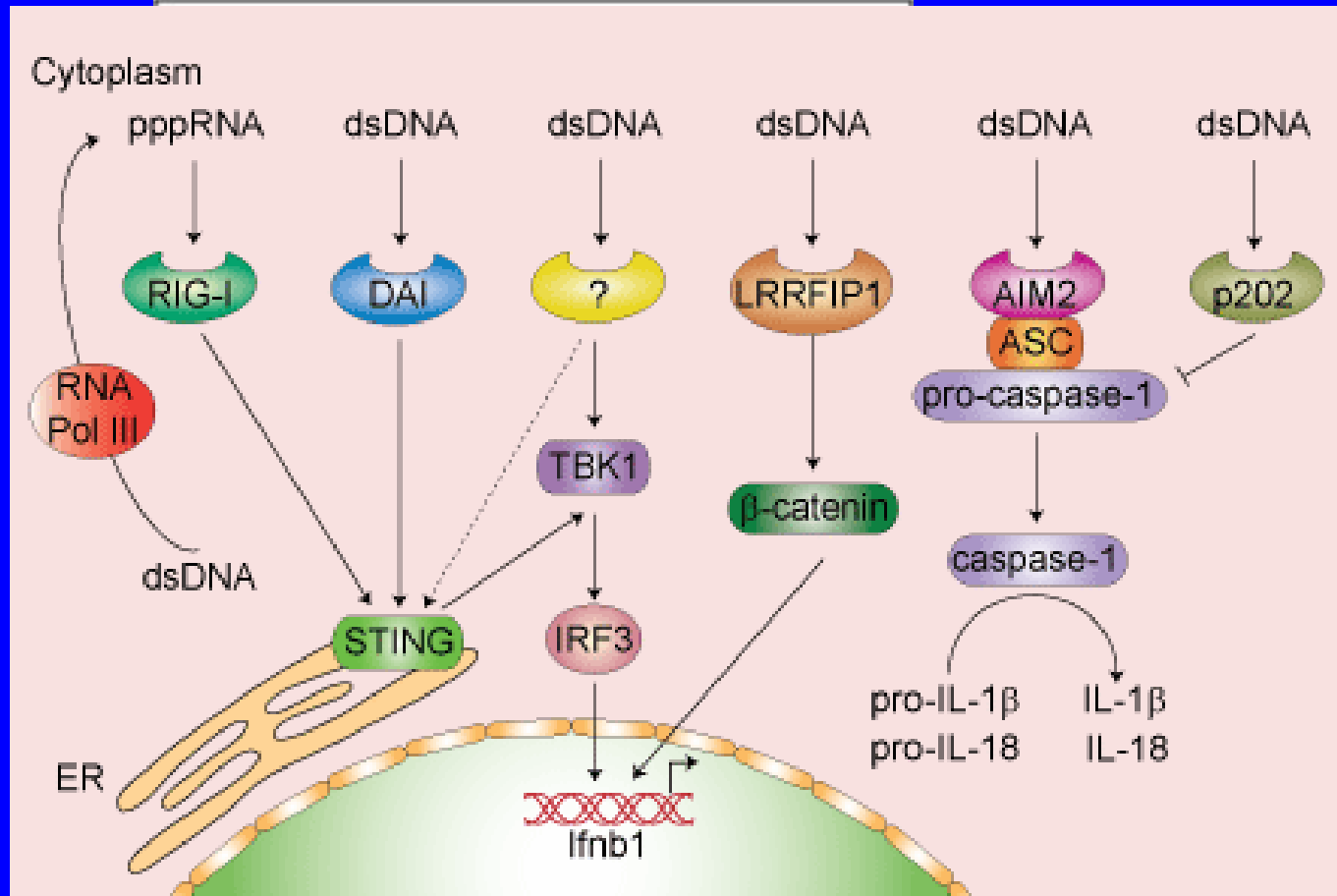
# Programmed cell death 1 (PD-1) and PD-ligand 1 (PD-L1)



# Natural Killer (NK) Cells



# Innate Immunity



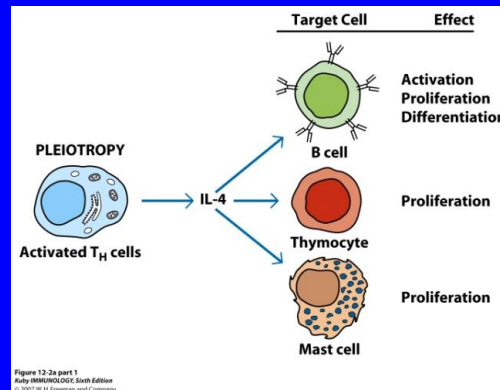
n-associated  
patterns (PAMPs)

associated  
patterns (DAMPs)

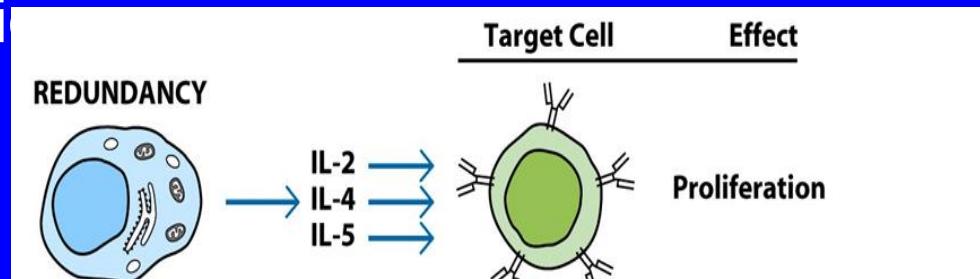
- Toll-like receptors (TLRs)

# Attributes of cytokines

- Pleiotropic
  - One cytokine has different actions on different target cells



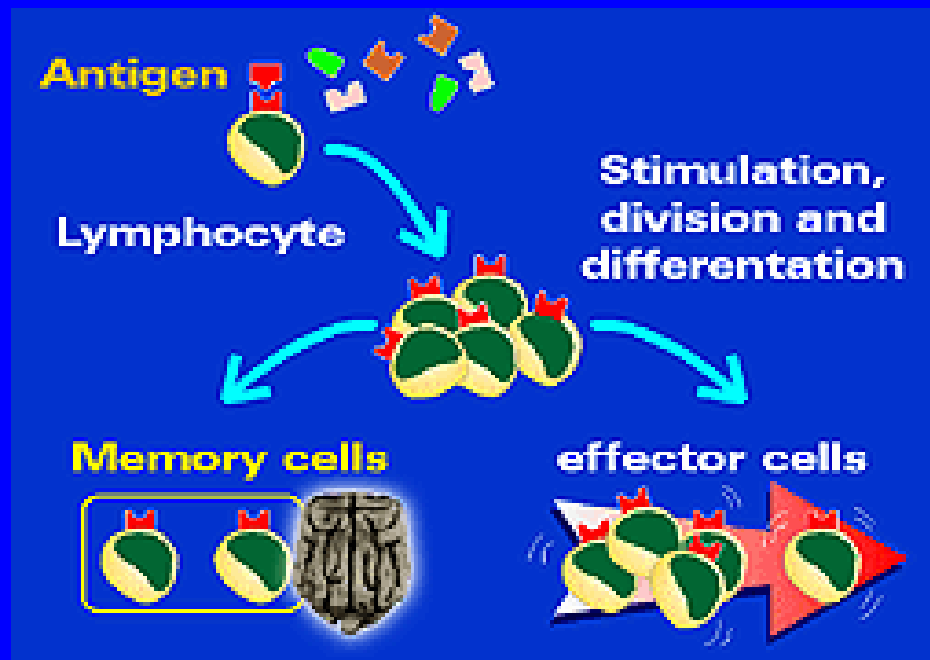
- Redundant
  - Two or more cytokines can mediate the same function





# Key Features of the Immune System

- Discrimination: self vs. foreign
- Specificity: single antigenic determinant (epitope)
- Memory: primary and secondary response



# Functions of the Immune System

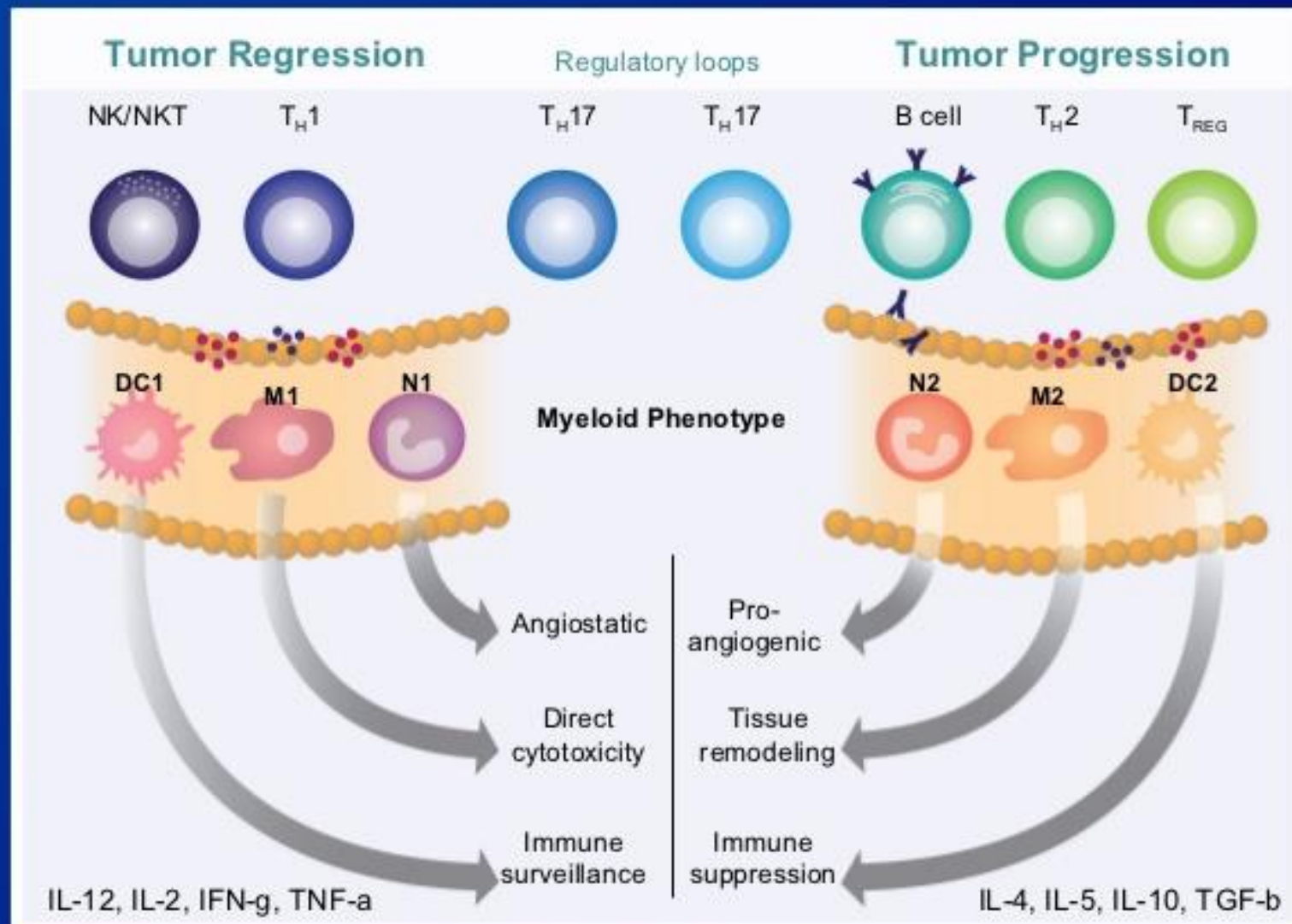
## Innate Immune Response

- First line of defense
- Barriers (e.g. skin, GI tract)
- Responds within hours
- Limited specificity
- Primary response only
- Phagocytes, NK cells
- Uses pathogen-associated molecular patterns (PAMPs)

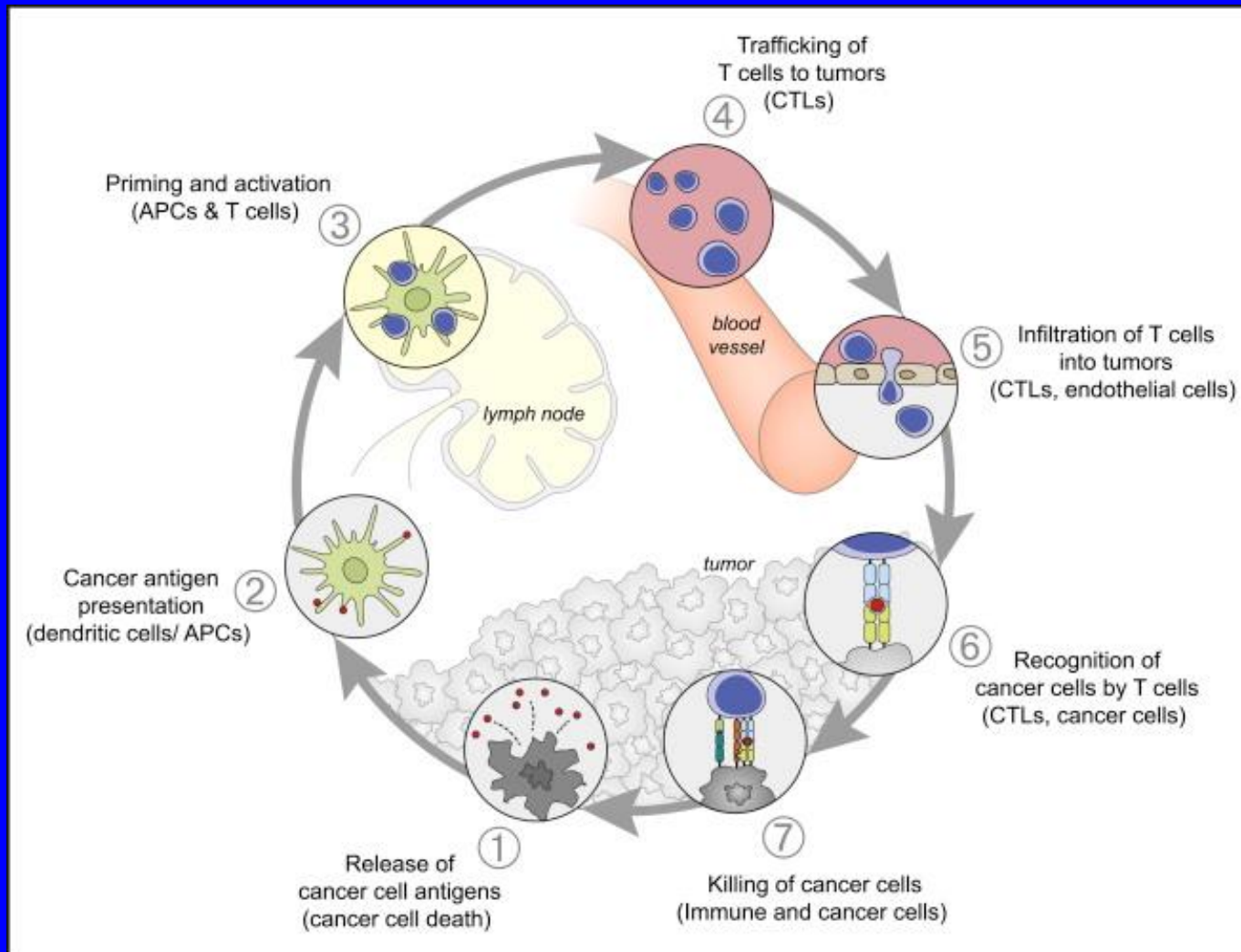
## Adaptive Immune Response

- Second line of defense
- Adapts to invader(s)
- Responds within days
- Highly diverse
- Secondary response (memory)
- T cells, B cells
- Uses antigen-specific antibodies and T cell receptors

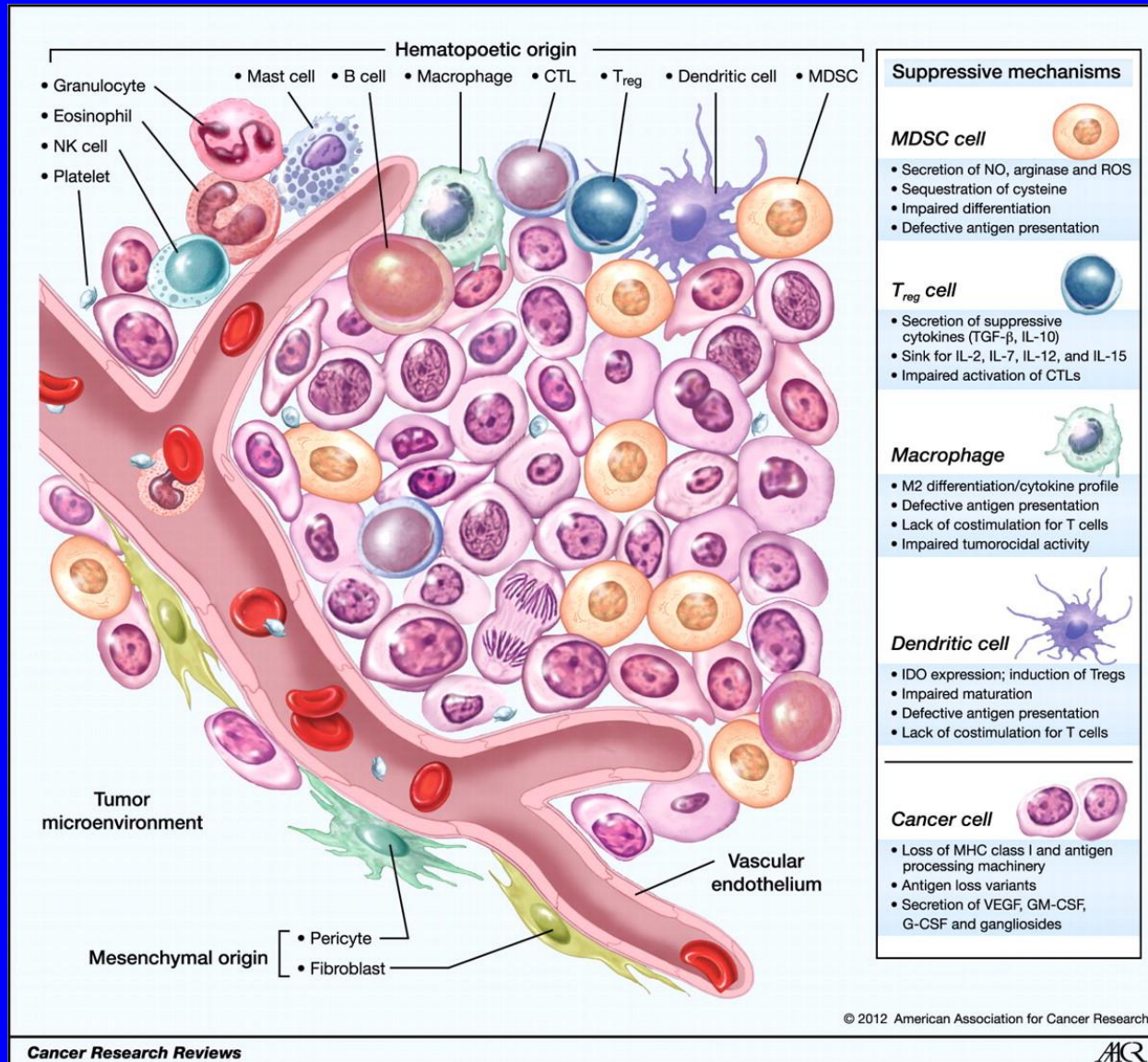
# The Immune System Is All About “Checks and Balances”



# The Cancer-Immunity Cycle



# Tumor Microenvironment





# Major Approaches to Cancer Immunotherapy

## Cytokines

- Interferon- $\alpha$
- Interleukin-2
- Modified IL-2

## Other Strategies in Development

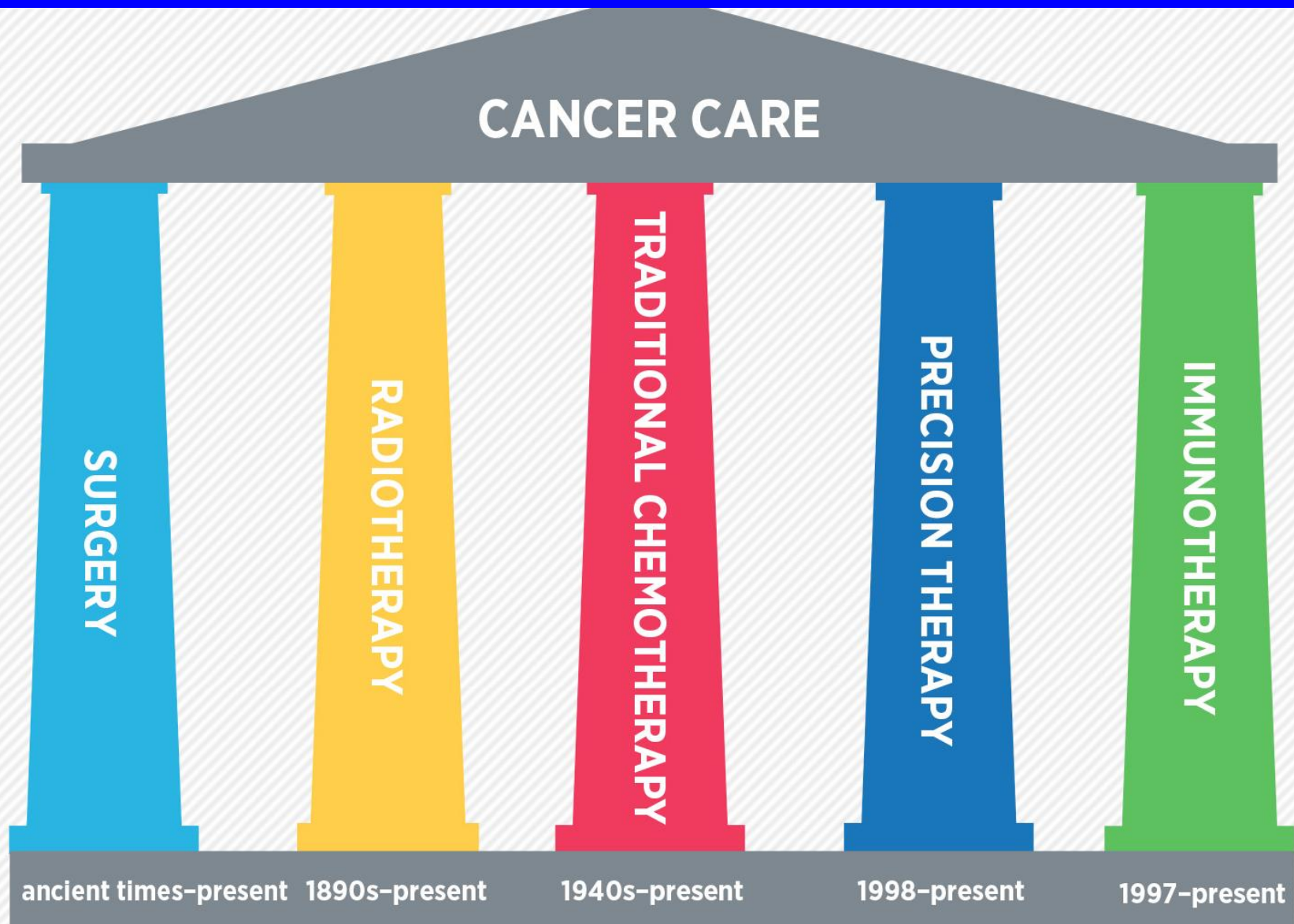
- Oncolytic Viruses  
(Talimogene laherparepvec; T-VEC)
- Adoptive T cell therapy
- Vaccines

## T cell Checkpoint Inhibitors

- Ipilimumab ( $\alpha$ -CTLA-4)
- Pembrolizumab ( $\alpha$ -PD1)
- Nivolumab ( $\alpha$ -PD1)
- Atezolizumab ( $\alpha$ -PD-L1)

\*FDA-approved

# Current approaches to cancer therapy



# Conclusions

- The immune system protects the host against internal and external danger (e.g. pathogens, cancers) and has three major features
  - Discrimination
  - Specificity
  - Memory
- The immune system utilizes a series of cells and molecular factors to communicate:
  - Recognition
  - Effector functions
- There are two major types of immunity
  - Innate
  - Adaptive
- The immune system has a system of check and balances
  - Activation
  - Suppression
- The immune system can be used to treat cancer (“immunotherapy”)