# Immunology and Immunotherapy 101 for the Non-Immunologist

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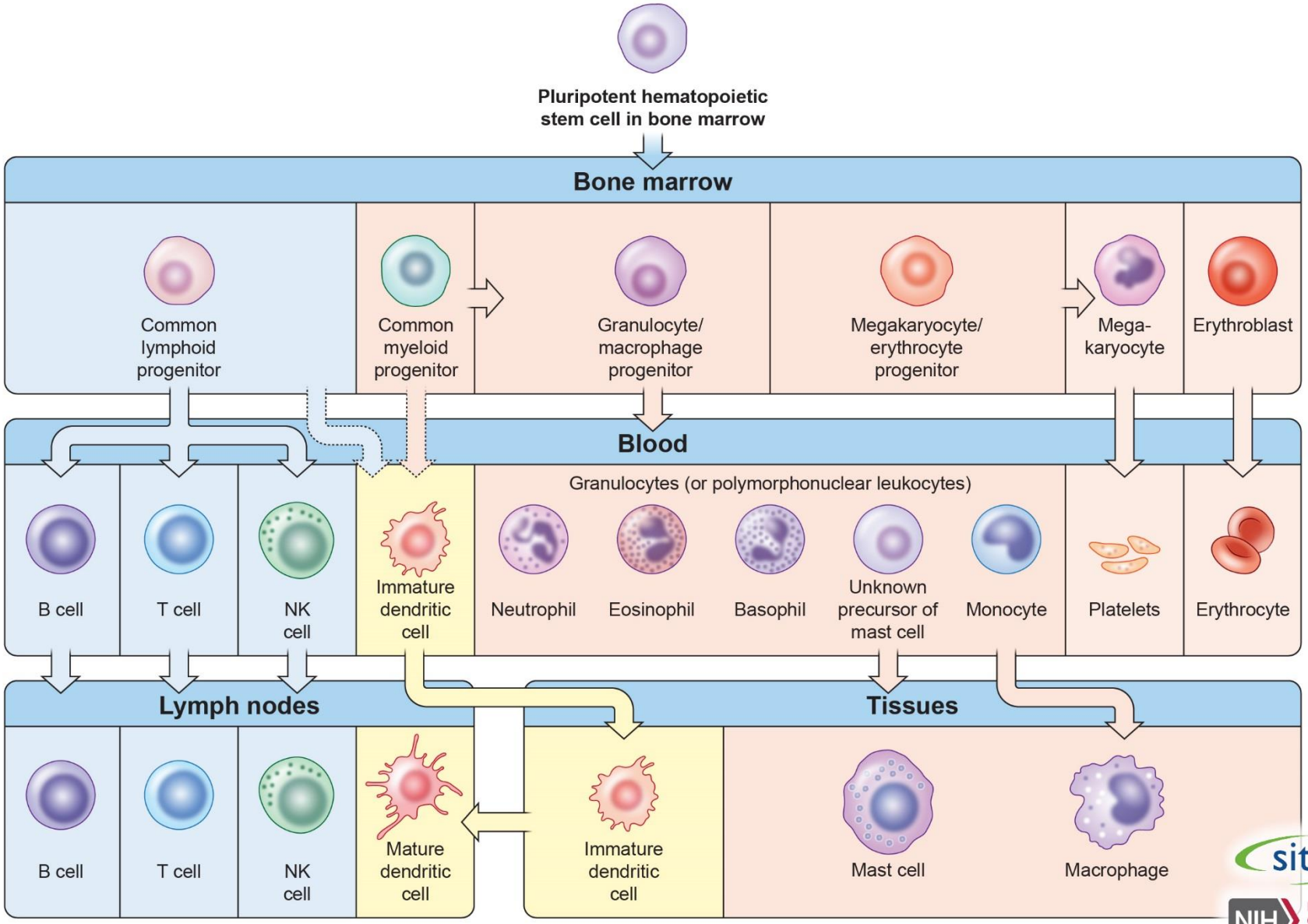
**I have no relevant conflicts of interest to disclose.**

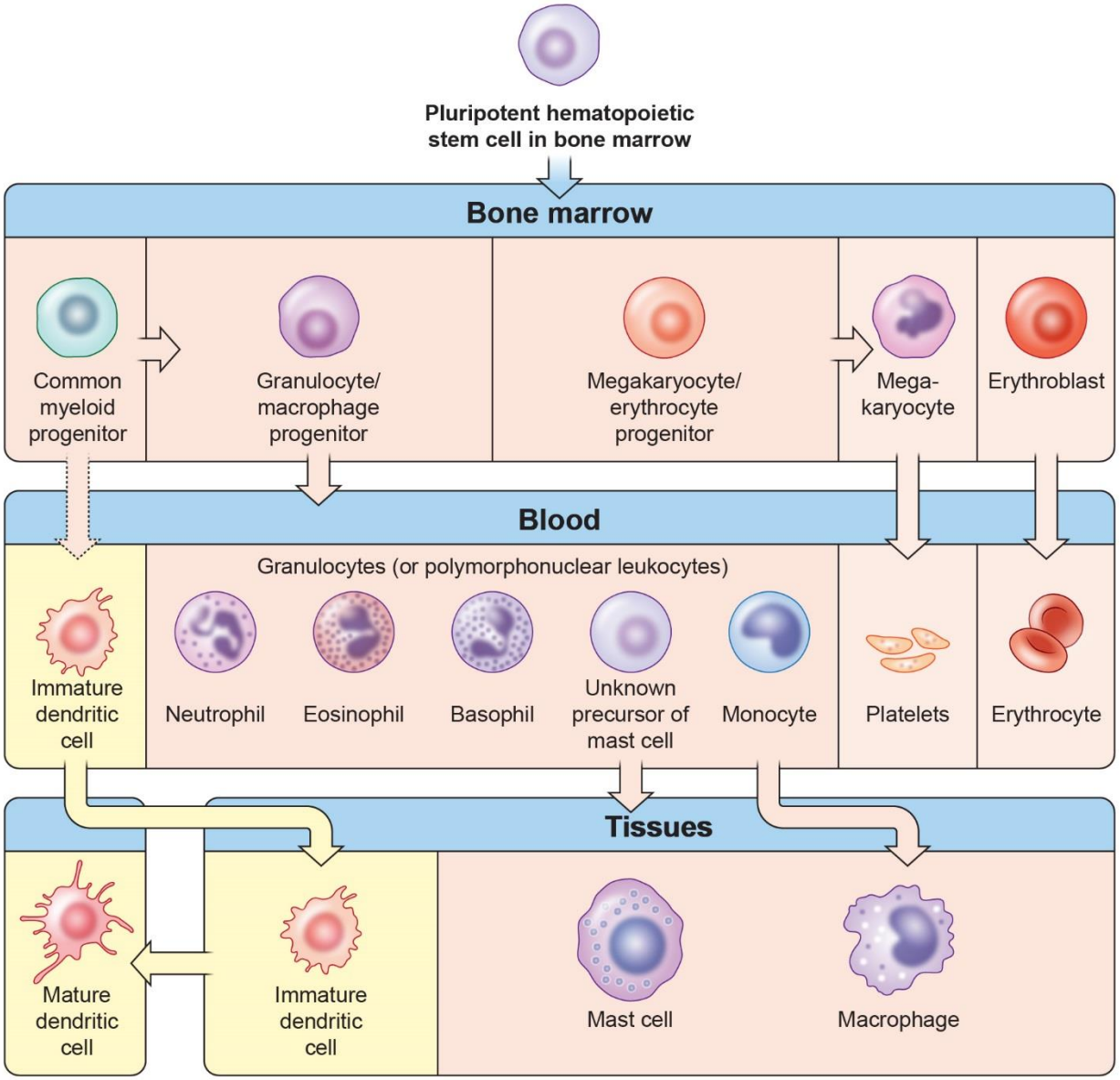
**I will not be discussing non-FDA approved treatments.**

# Immunology Basics

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



# 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

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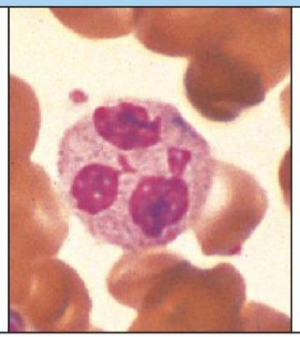
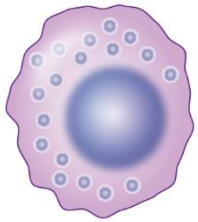
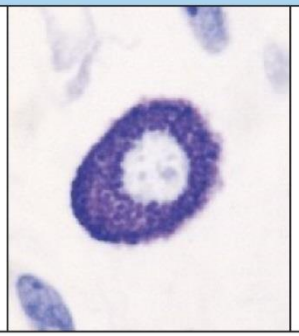
# Granulocytes

Short-lived cells that possess granules containing degradative enzymes and anti-microbial substances

| Neutrophil | | |
|---|---|---|
|  |  | Phagocytosis and activation of bacterial mechanisms |

| Mast cell | | |
|---|---|---|
|  |  | Release of granules containing histamines and other inflammatory mediators |

| Eosinophil | | |
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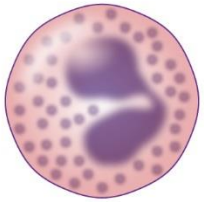
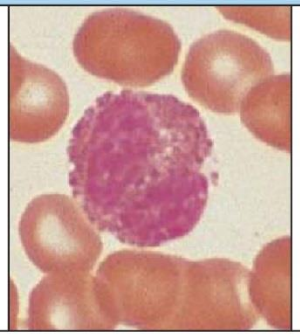
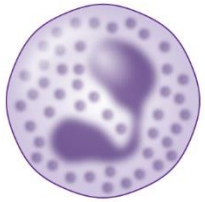
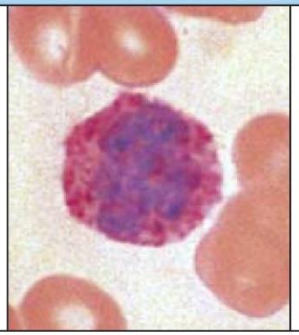
|  |  | Killing of antibody-coated parasites |

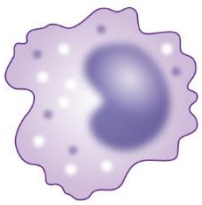
| Basophil | | |
|---|---|---|
|  |  | Promotion of allergic responses and augmentation of anti-parasitic immunity (Blood mast cells) |

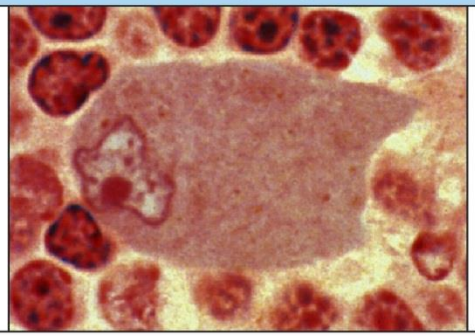
Neutrophils, eosinophils and basophils are sometimes referred to as polymorphonuclear leukoyctes (PMNs)

# Phagocytes

Neutrophils, macrophages and dendritic cells

**Macrophage**



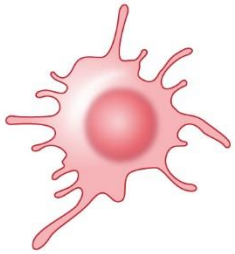


**1º** Phagocytosis and activation of bactericidal mechanisms

**2º** Antigen presentation

Reside in tissues

**Dendritic cell**



**1º** Antigen presentation

**2º** Antigen uptake

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)

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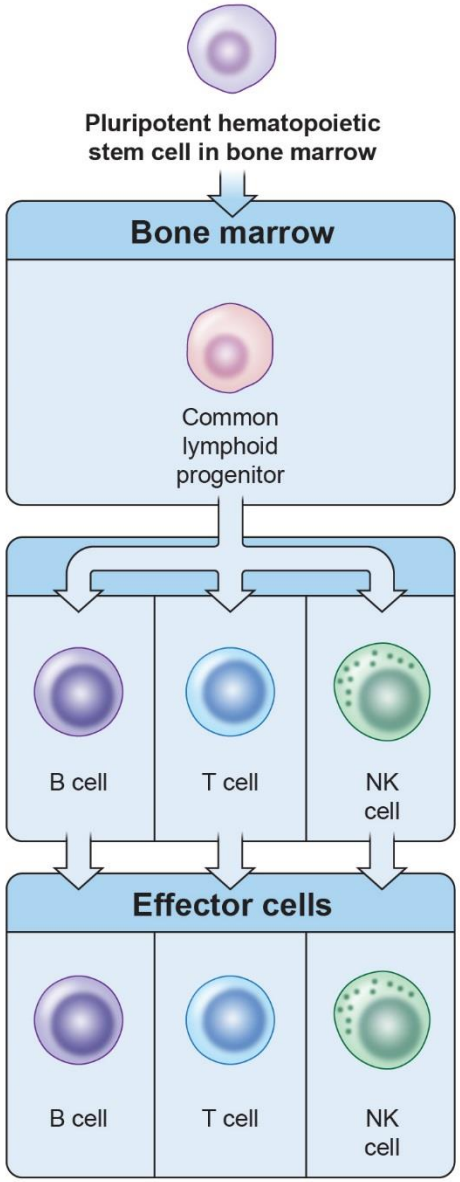
# Lymphocytes




**B cells**
- Produce antibodies (Ab) that bind proteins

**T cells**
- Various regulatory and cytotoxic functions

**Adaptive** (recognize very specific antigens)

**Natural Killer (NK) cells**
- Kill tumor and virus-infected cells
- Kill antibody-coated cells
- Play dominant role in mediating ADCC in vivo

**Innate** (recognize general features)

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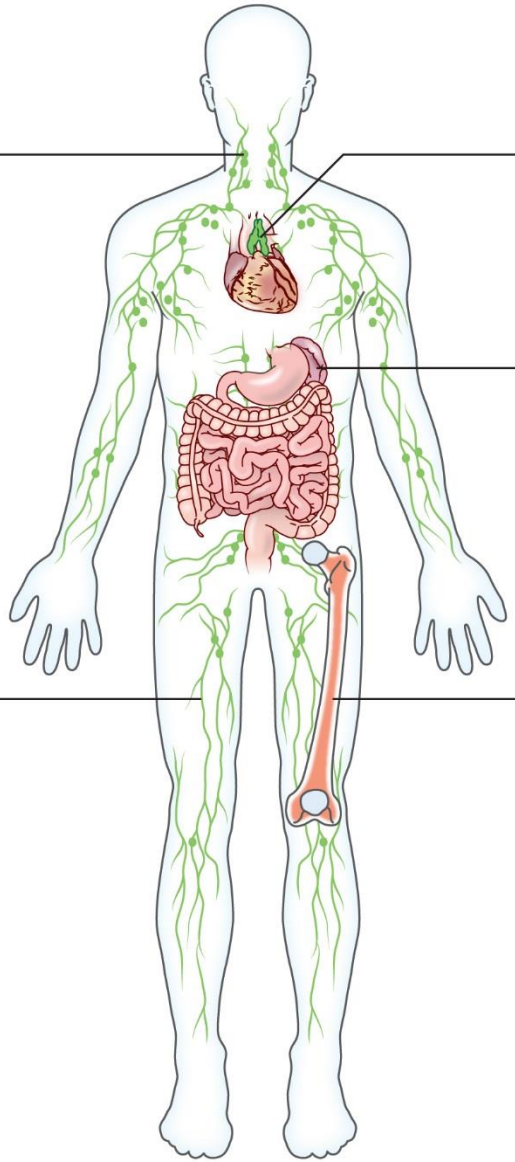
# Lymphoid organs

**Lymph nodes**

Collect lymph and antigen from peripheral sites through lymphatic vessels

**Lymphatic vessels**



**Thymus**

Site of T cell development

**Spleen**

Collects antigens from circulating blood

**Bone marrow**

Site of myeloid cell and B cell development

Note: Immmune cells and lymphoid aggregates are also found througout the body

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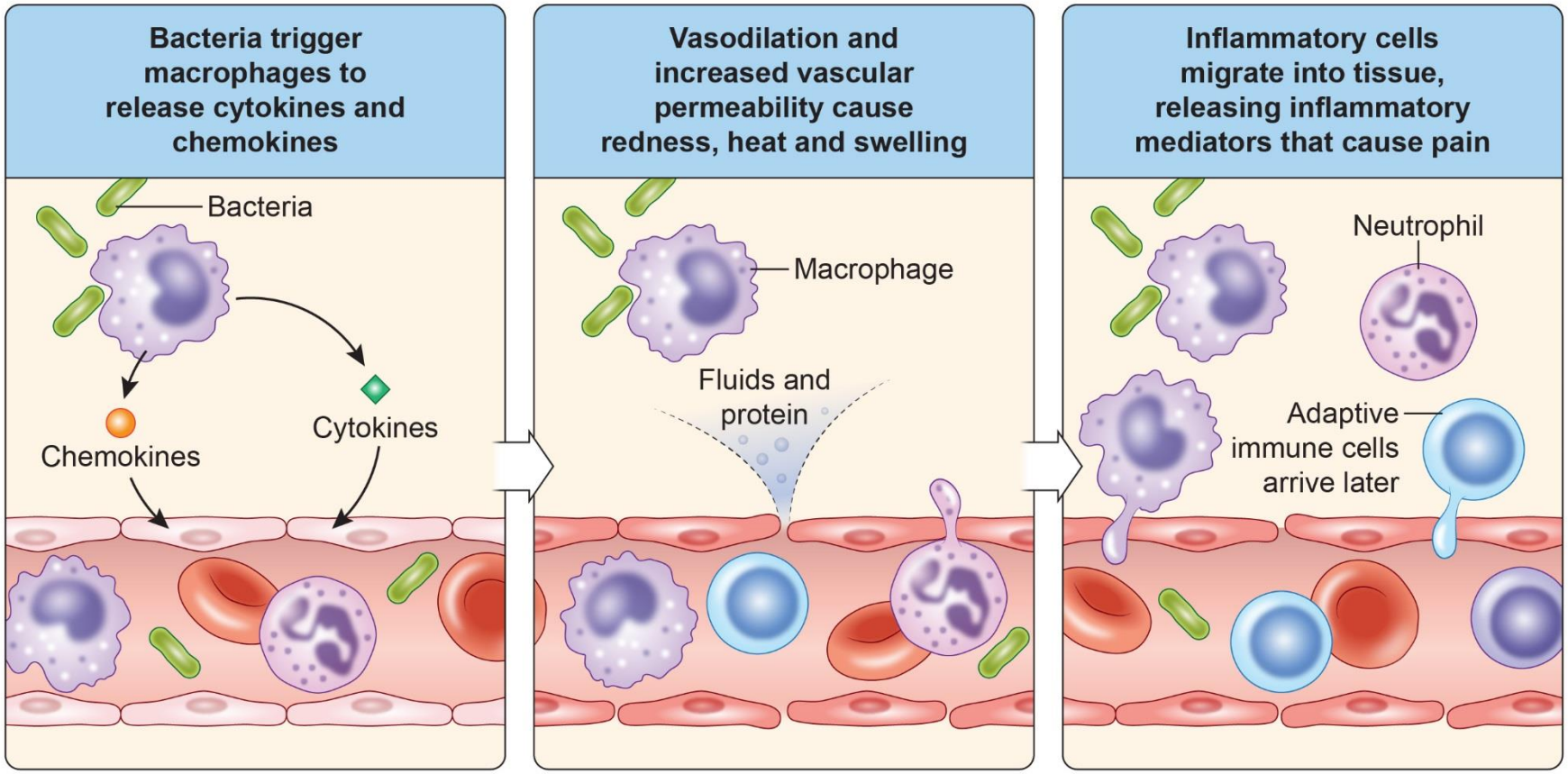
# Infectious agents first activate innate immune cells resulting in an inflammatory response




Cytokines are proteins that immune cells use to communicate/regulate other immune cells, not all cytokines are inflammatory

Chemokines are a group of cytokines that attract other immune cells

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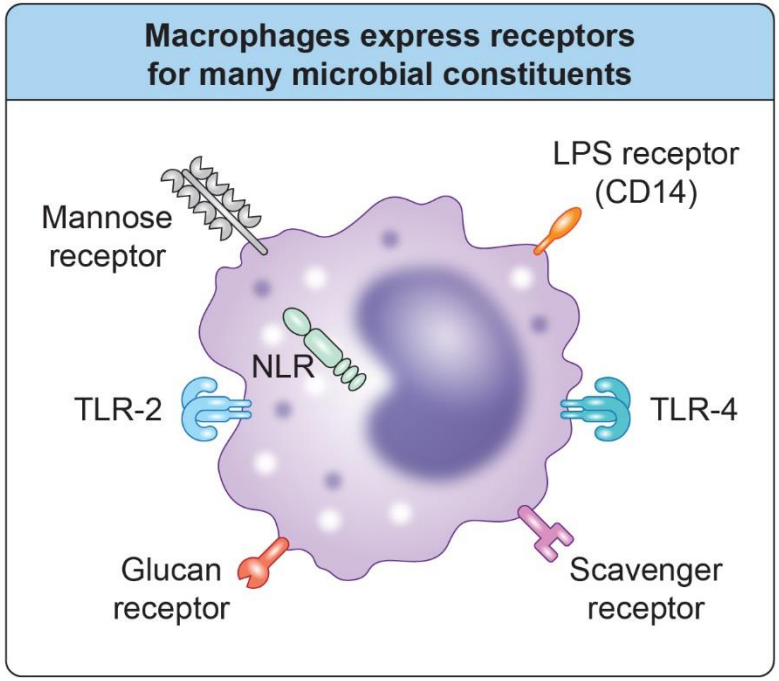
# Innate responses are initiated upon recognition of "danger signals" by pattern recognition receptors (PRRs)




**"Danger signals"**

- Pathogen-associated molecular patterns (PAMPs)
  - Bacteria proteins
  - viral DNA/RNA
- Damage-associated molecular patterns (DAMPs)
  - Products of dying cells

**Types of PRRs**

- Toll-like receptors (TLR)
- C-type lectin receptors
- NOD-like receptors (NLRs)
- RIG-I-like receptors

Receptors can be on the cell surface or intracellular (NLRs)

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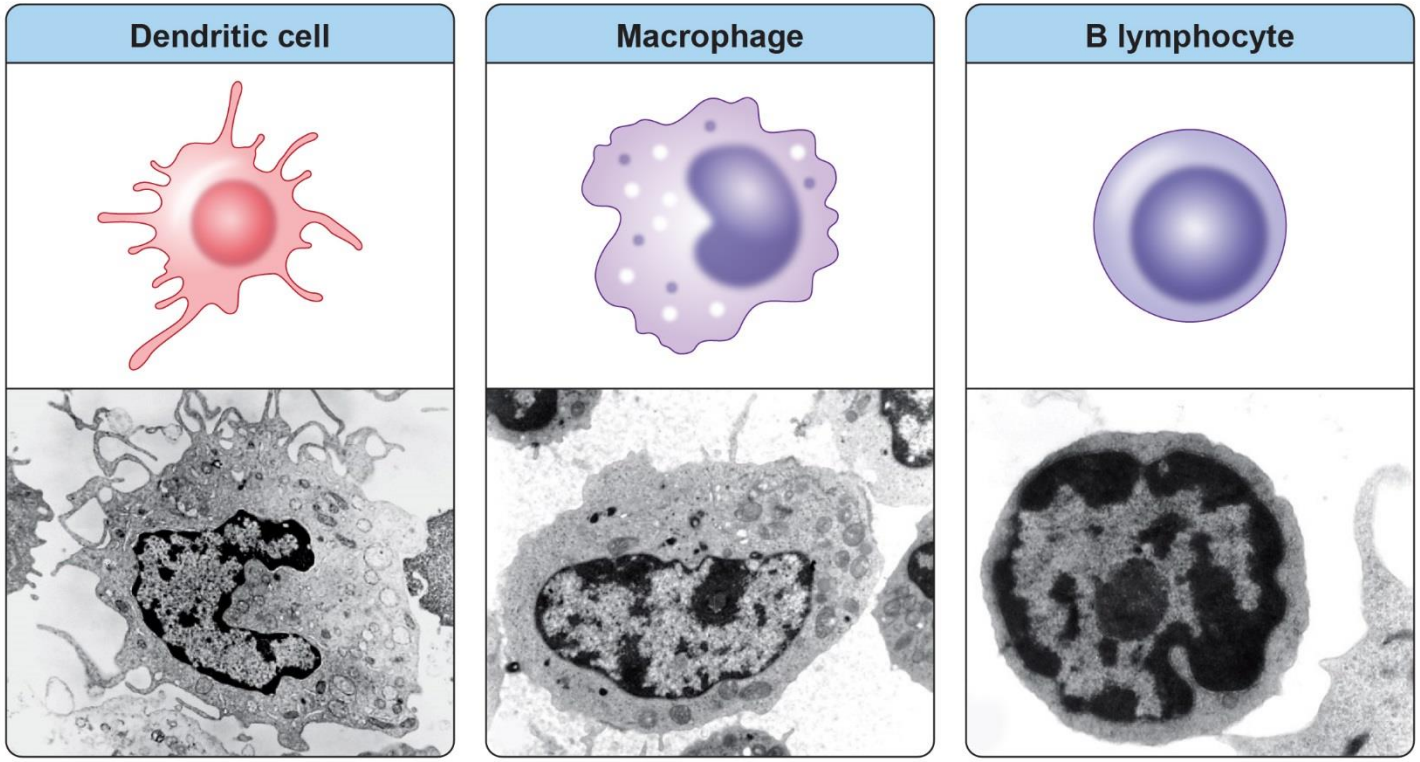
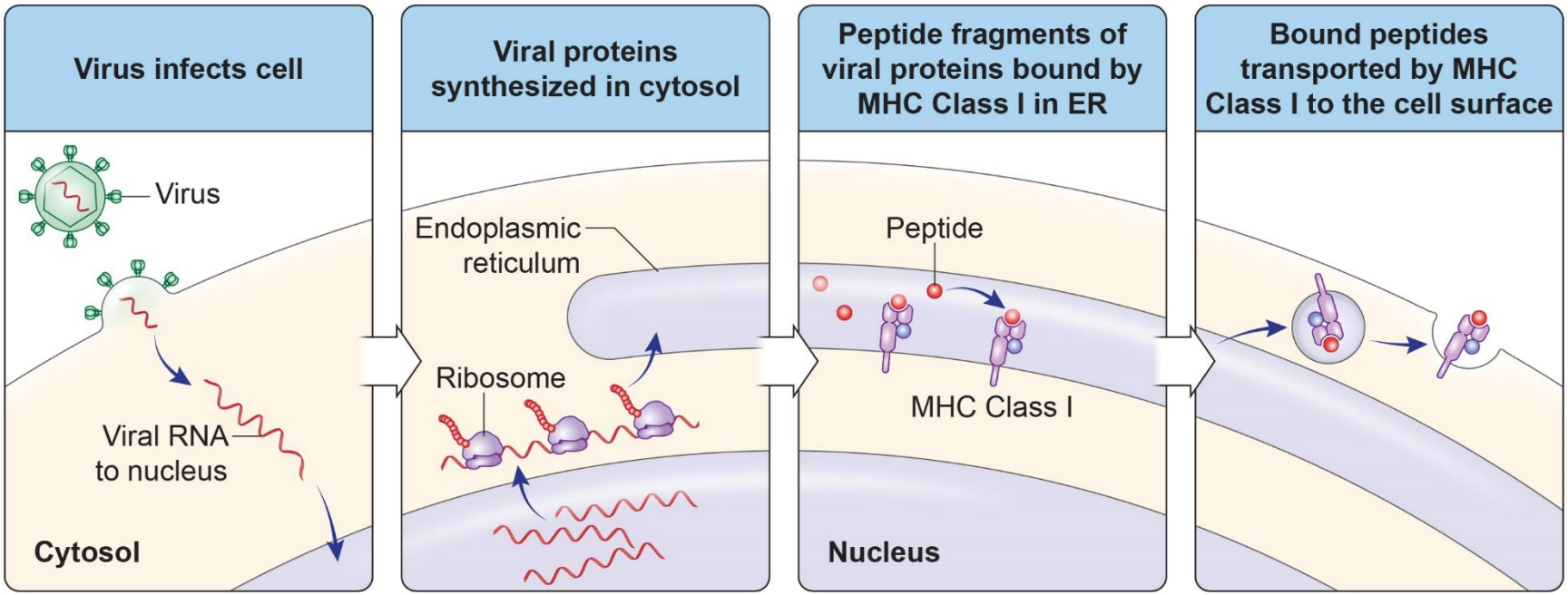
# Antigen processing and presentation

Professional APCs present Ag to naïve T cells and induce activation




Immature DCs very efficient at Ag processing (in tissues) → Mature DCs very efficient at Ag presentation (in LNs)

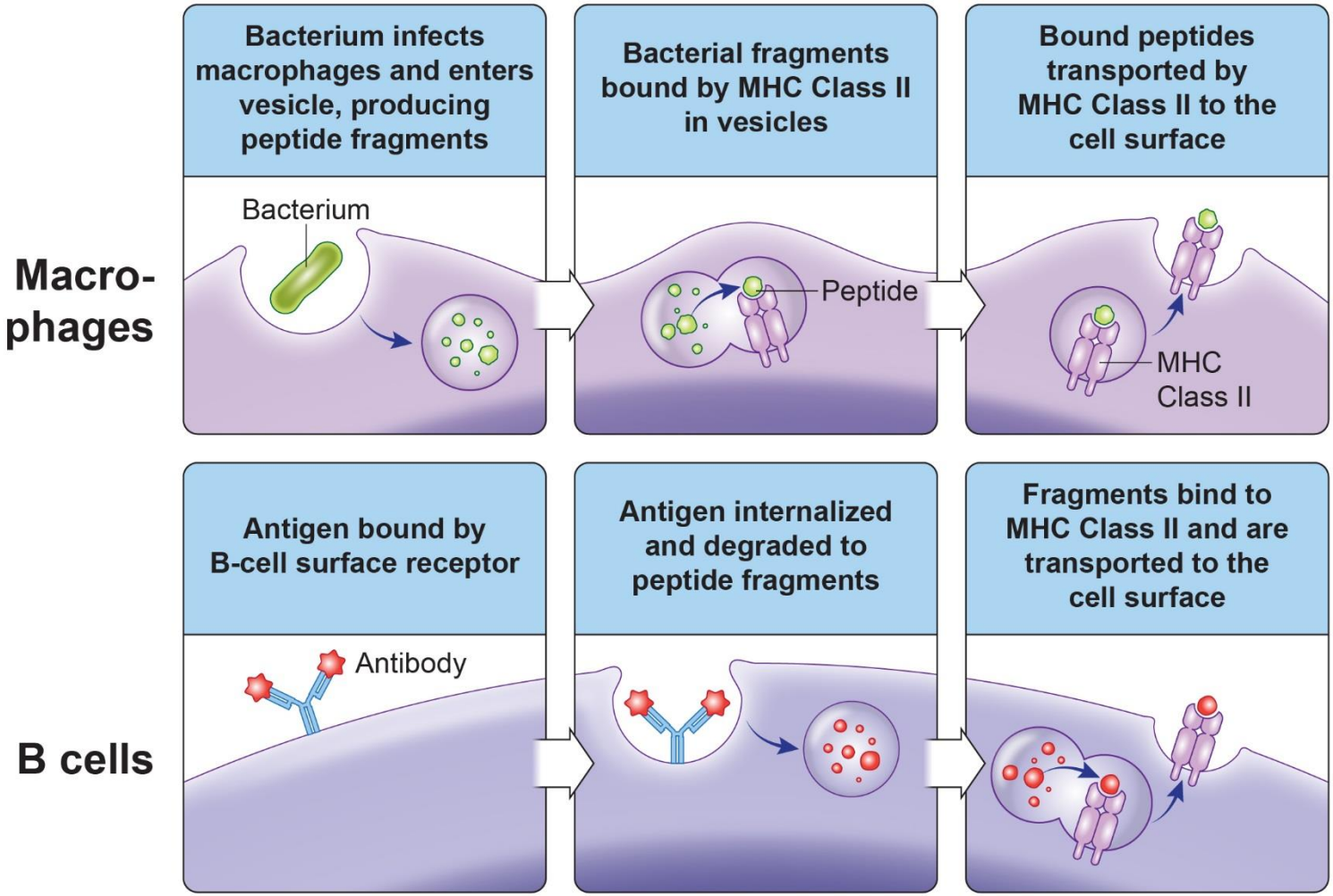
# MHC Class I presents peptide antigens to CD8 T cells




**Major Histocompatibility Complex (MHC) Class I**

- Expressed by all nucleated cells
- Presents peptides derived from endogenous proteins
- MHC Class I proteins are also recognized by NK cells

# MHC Class II presents antigens to CD4 T cells




**Major Histocompatibility Complex (MHC) Class II**

- Typically expressed by professional APCs
- Presents peptides derived from exogenous proteins

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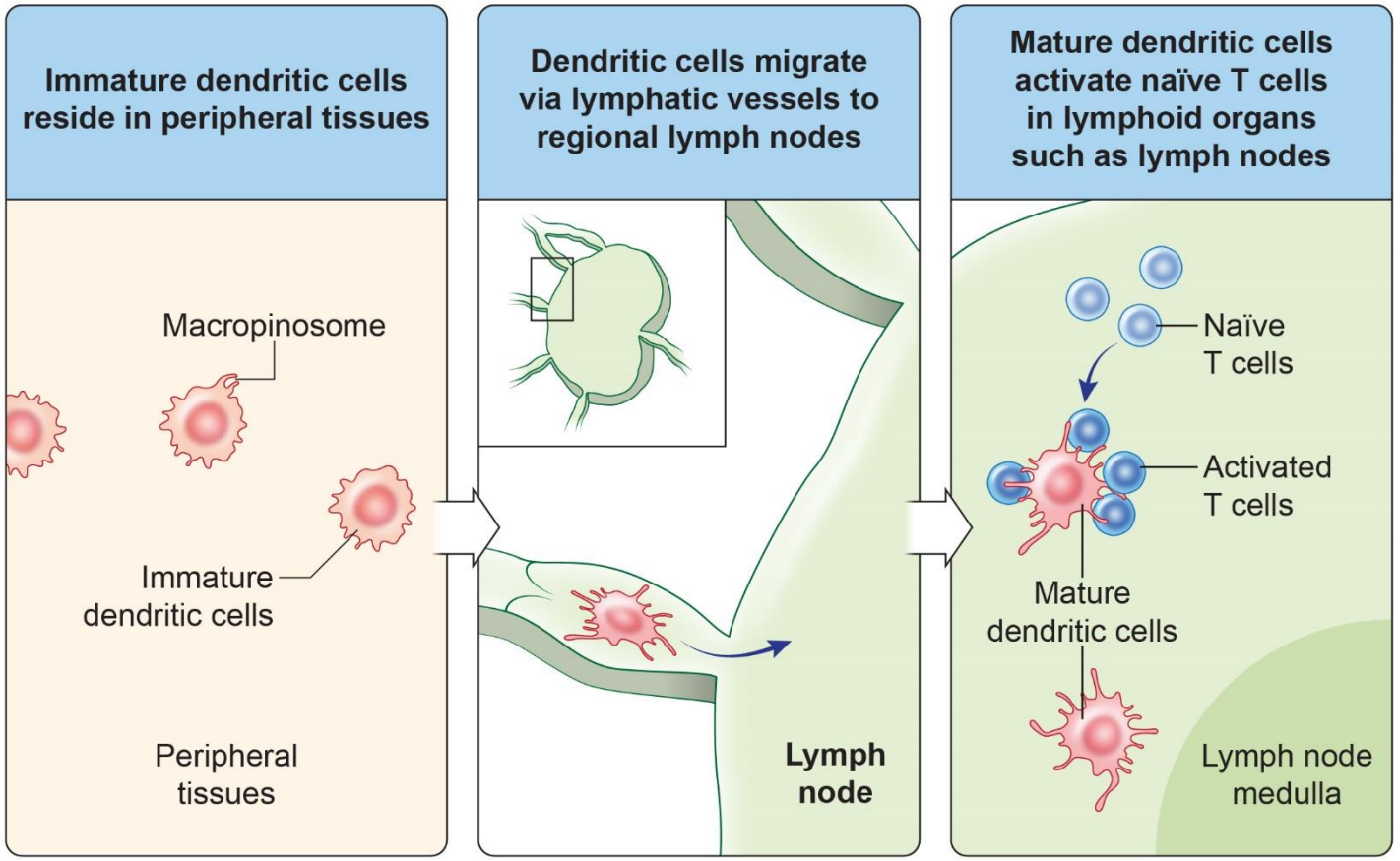
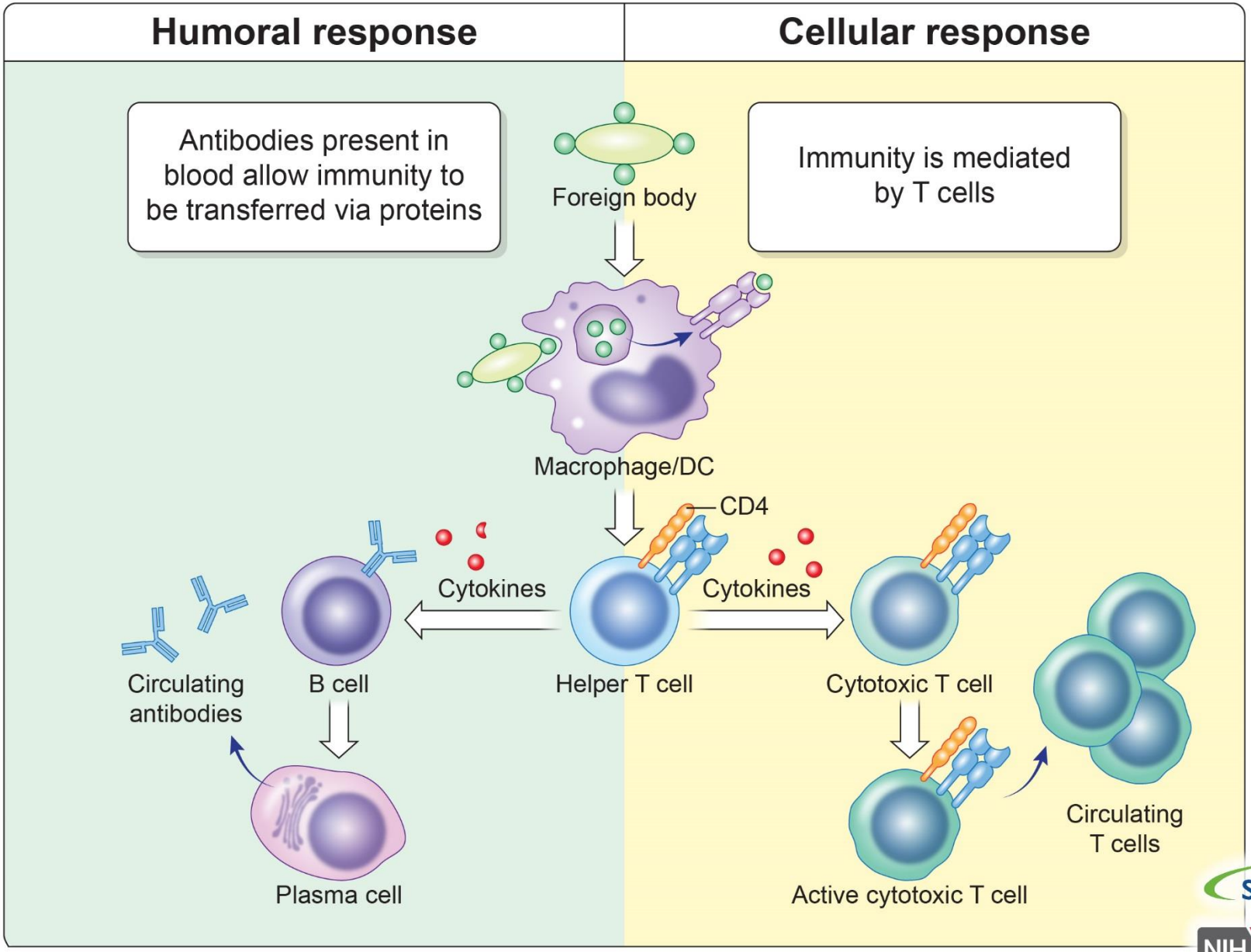
# DCs are important for initiating adaptive immune responses

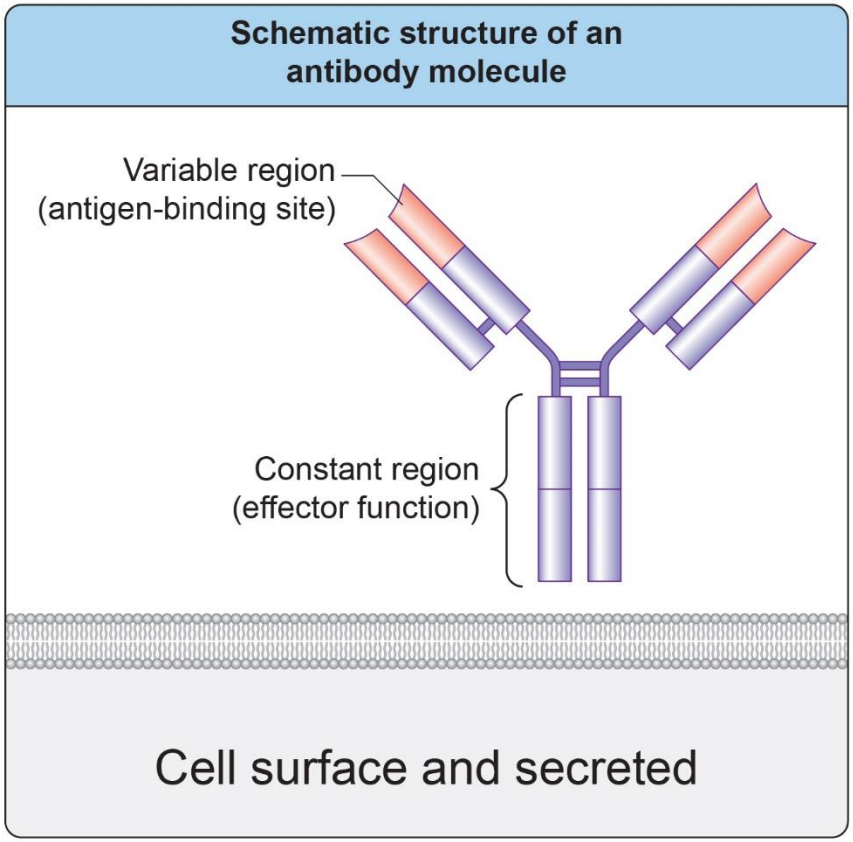


# Adaptive immune responses

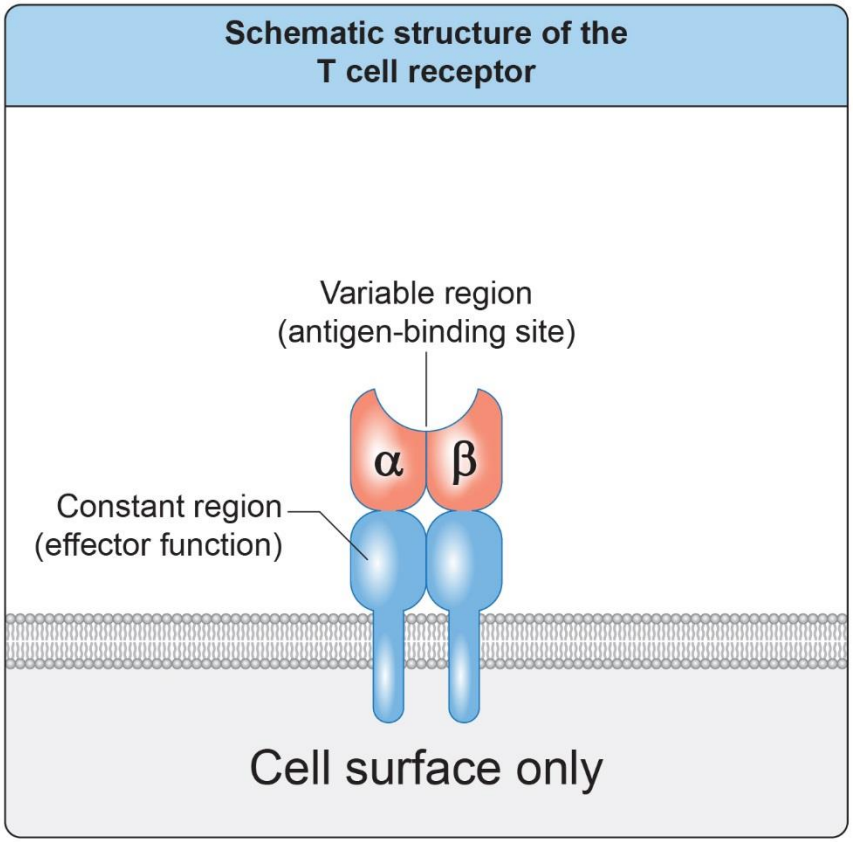


# Antigen receptors

## Antibody (Ab)

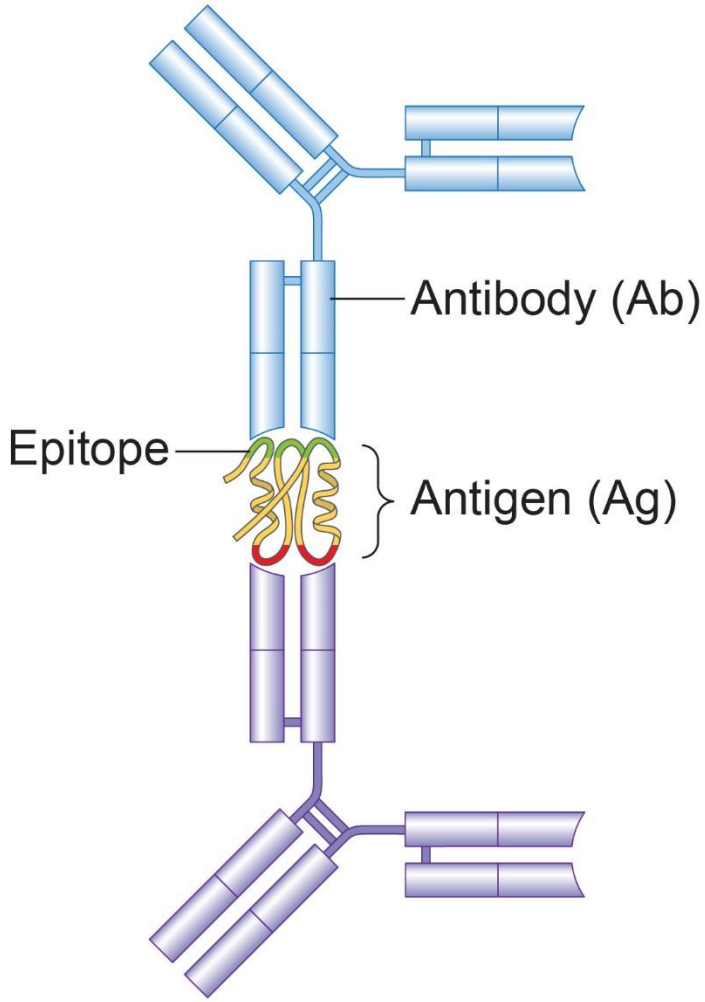



## T cell receptor (TCR)

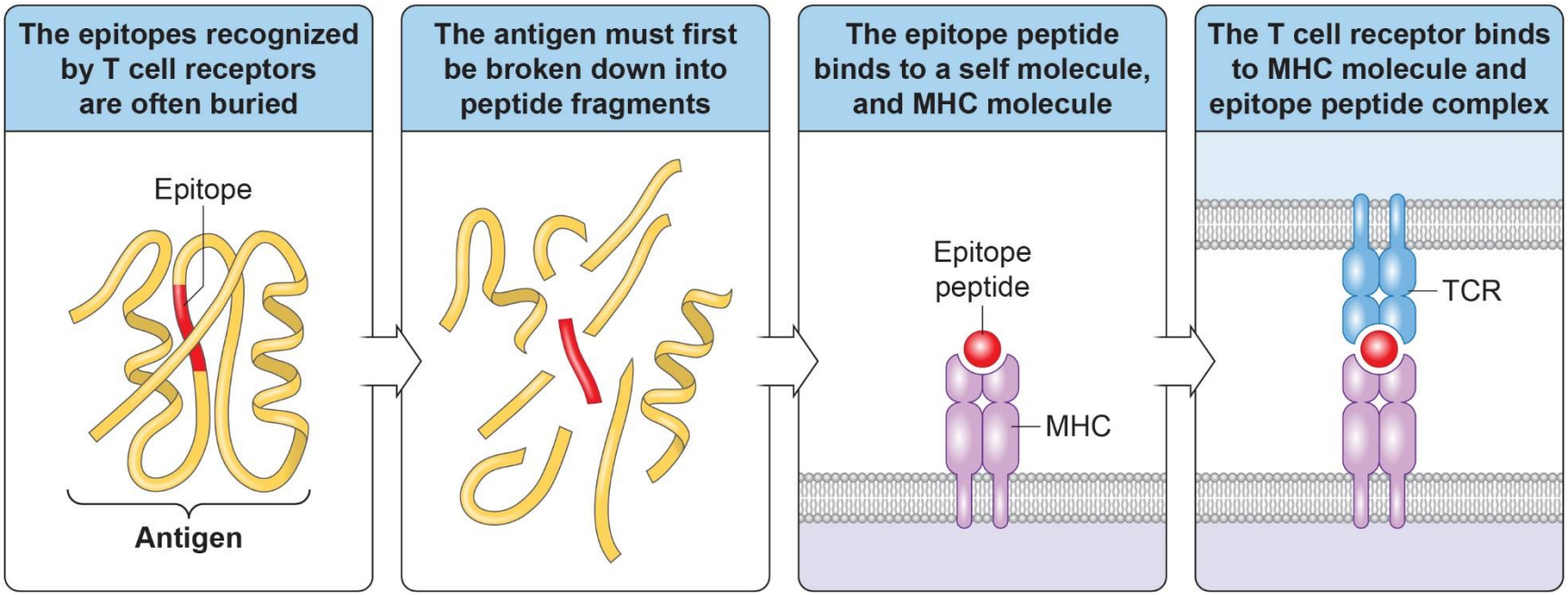


# Antigen recognition by antibodies

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

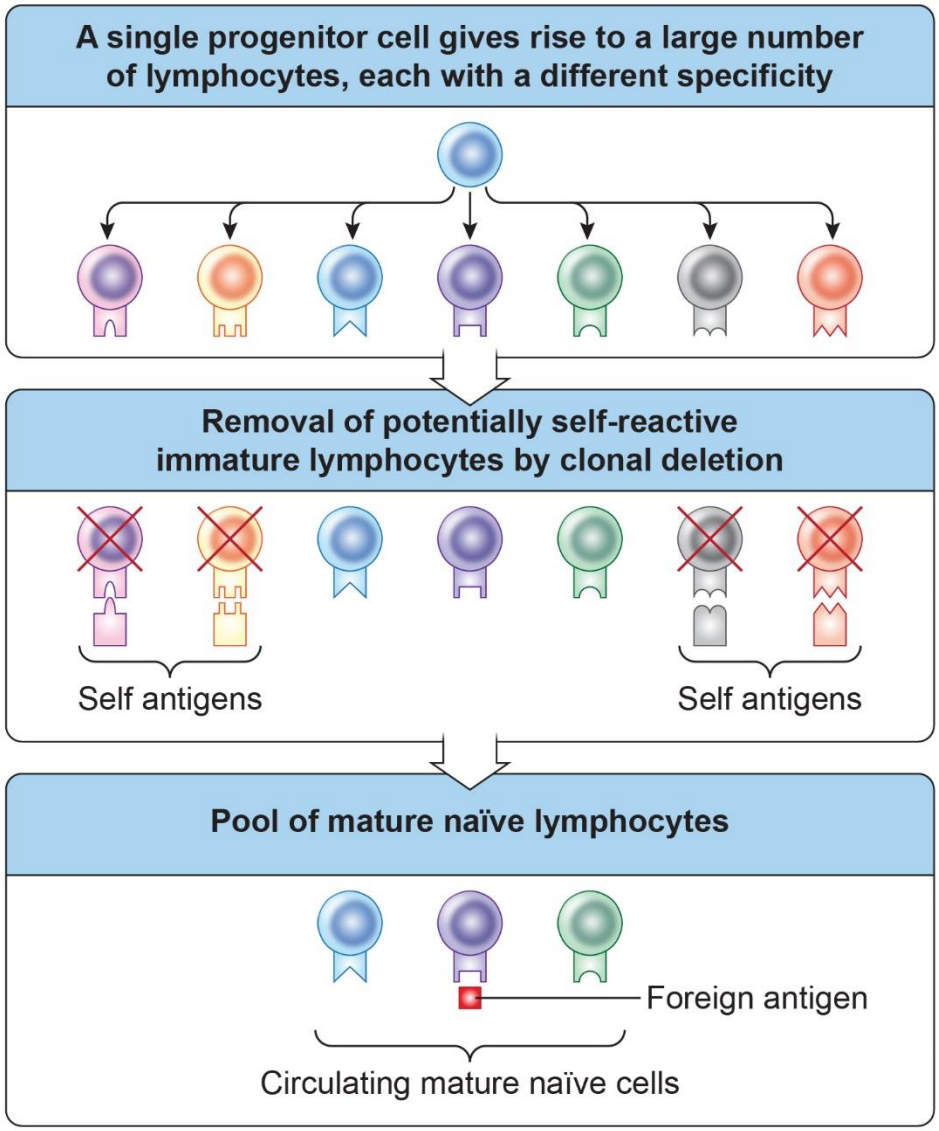


# T cell receptors (TCRs) recognize processed proteins presented by MHC




MHC = Major Histocompatibility Complex

# 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

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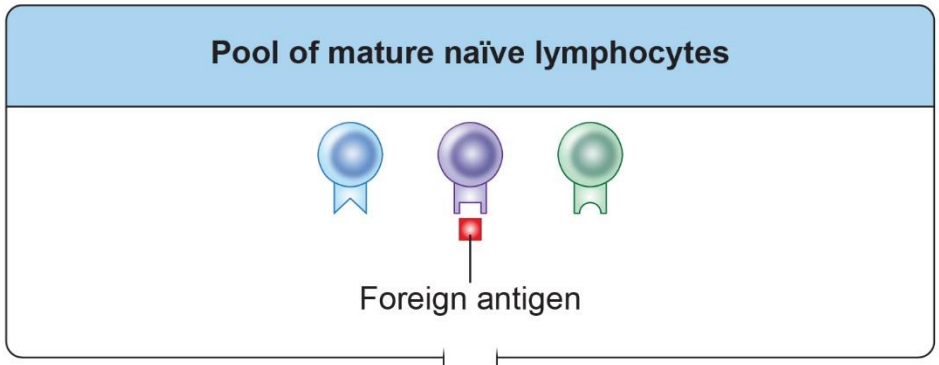
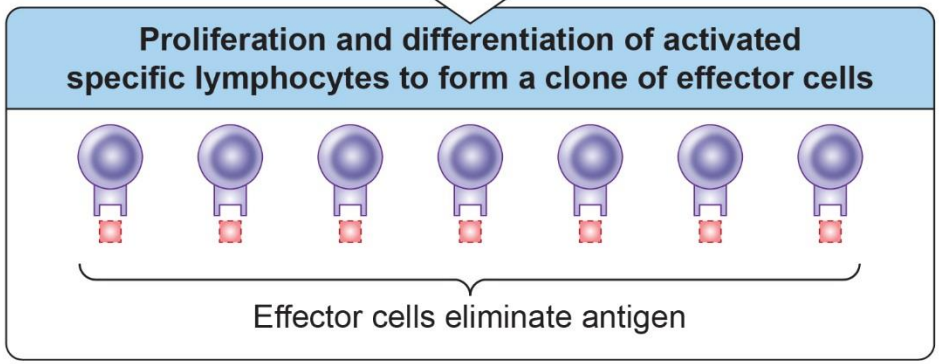
# Lymphocyte activation

**Naïve**




Cells that recognize specific Ag are very rare

**Activated or effectors**



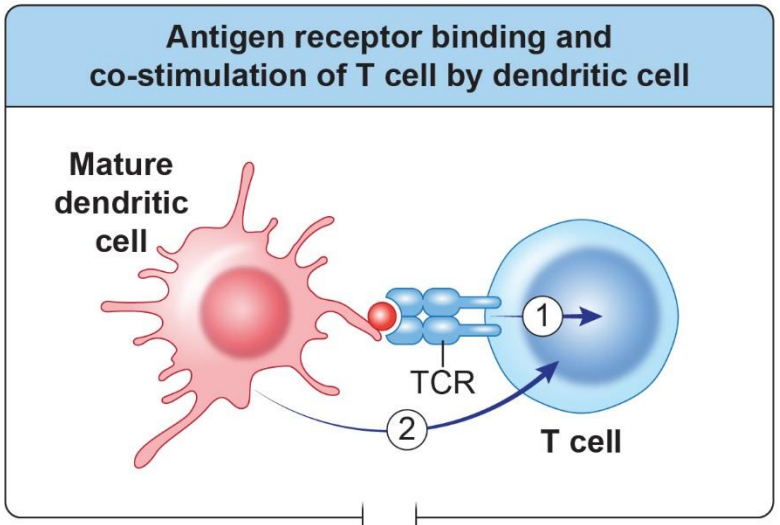

**Results in:**
- Expansion
- Acquisition of effector functions

What happens to T cells and B cells after immune response?

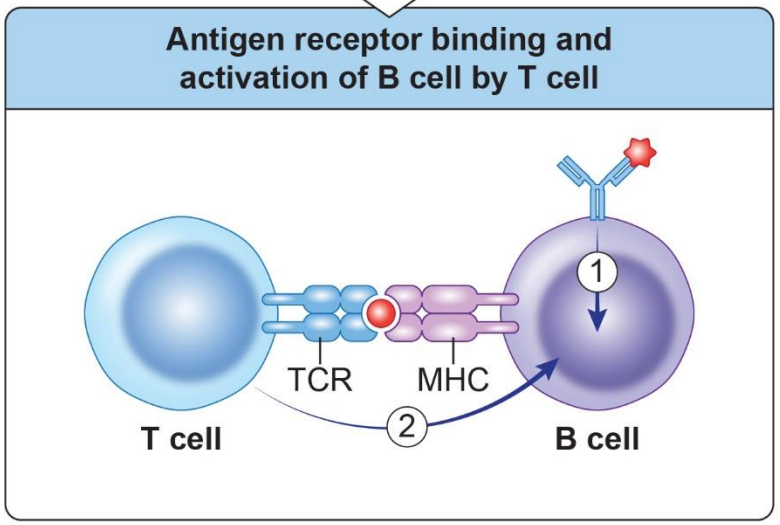
Differentiate into long-lived memory lymphocytes

# Lymphocyte activation

**T cells**




**B cells**




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

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

Absence of co-stimulation leads to unresponsiveness

Peripheral tolerance

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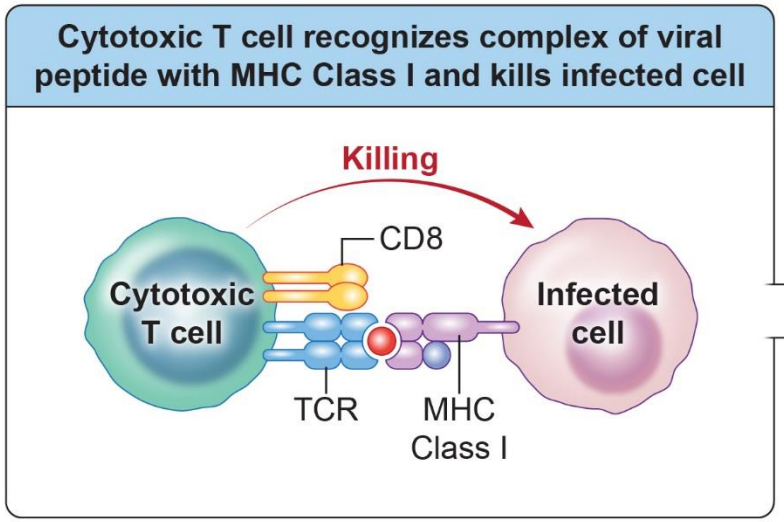
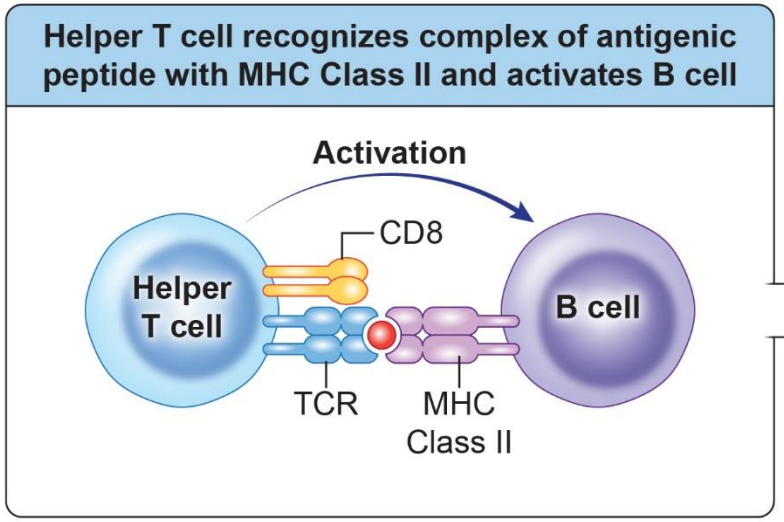
# Effector mechanisms of adaptive immunity

**CD8+ T cells**
(Cytotoxic T cells)




Produce proteins that lyse cells

**CD4+ T cells**
(Helper T cells)




Different subtypes:
Th1, Th2, Th17, Tregs

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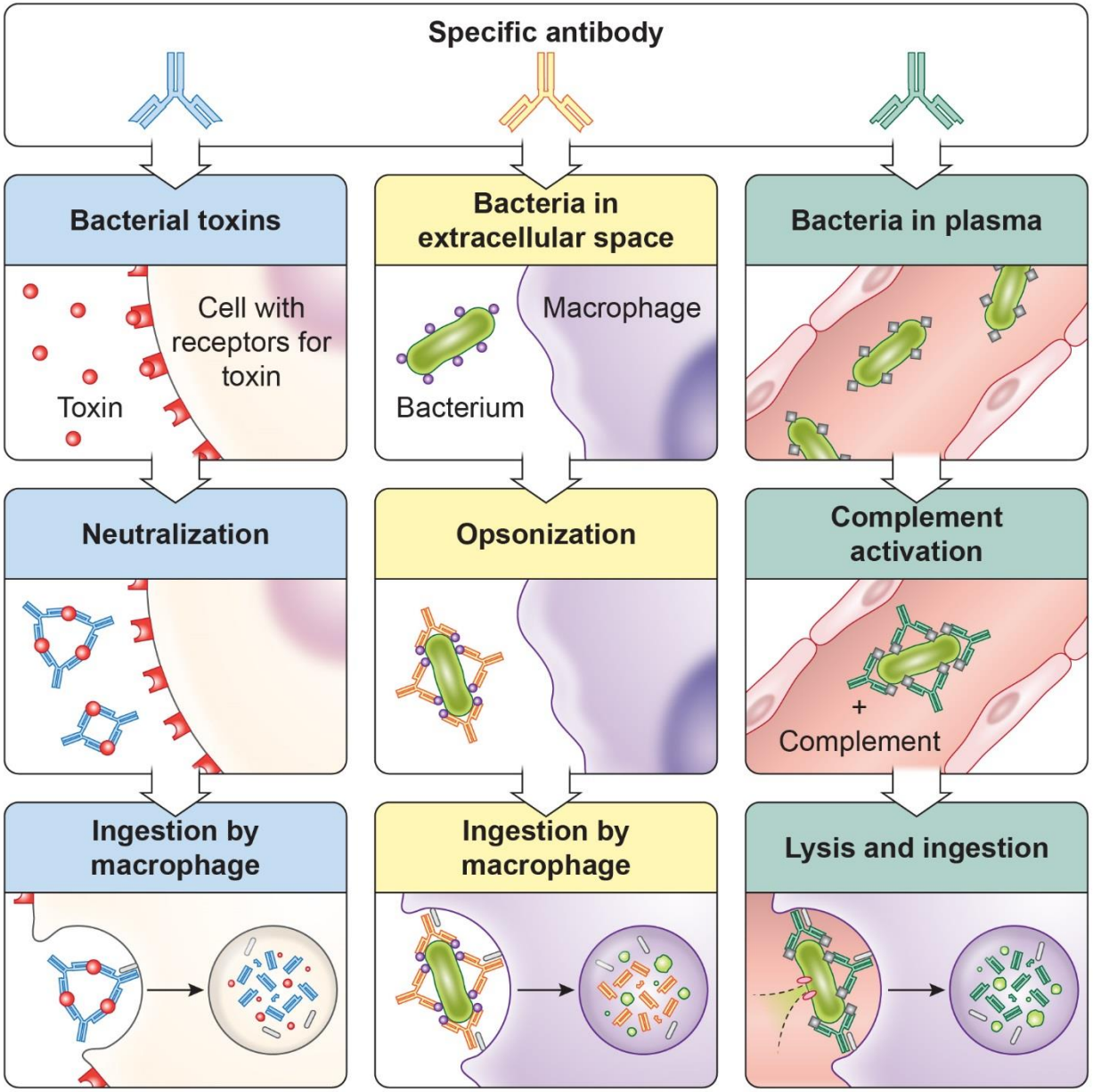
# Effector mechanisms of adaptive immunity




## B Cells

## Ab function:

- Neutralize
- Block protein functions
- Promote engulfement
- Induce complement-mediated cell lysis

## Different classes (isotypes) of Ab

- IgM
- IgG
- IgE
- IgA

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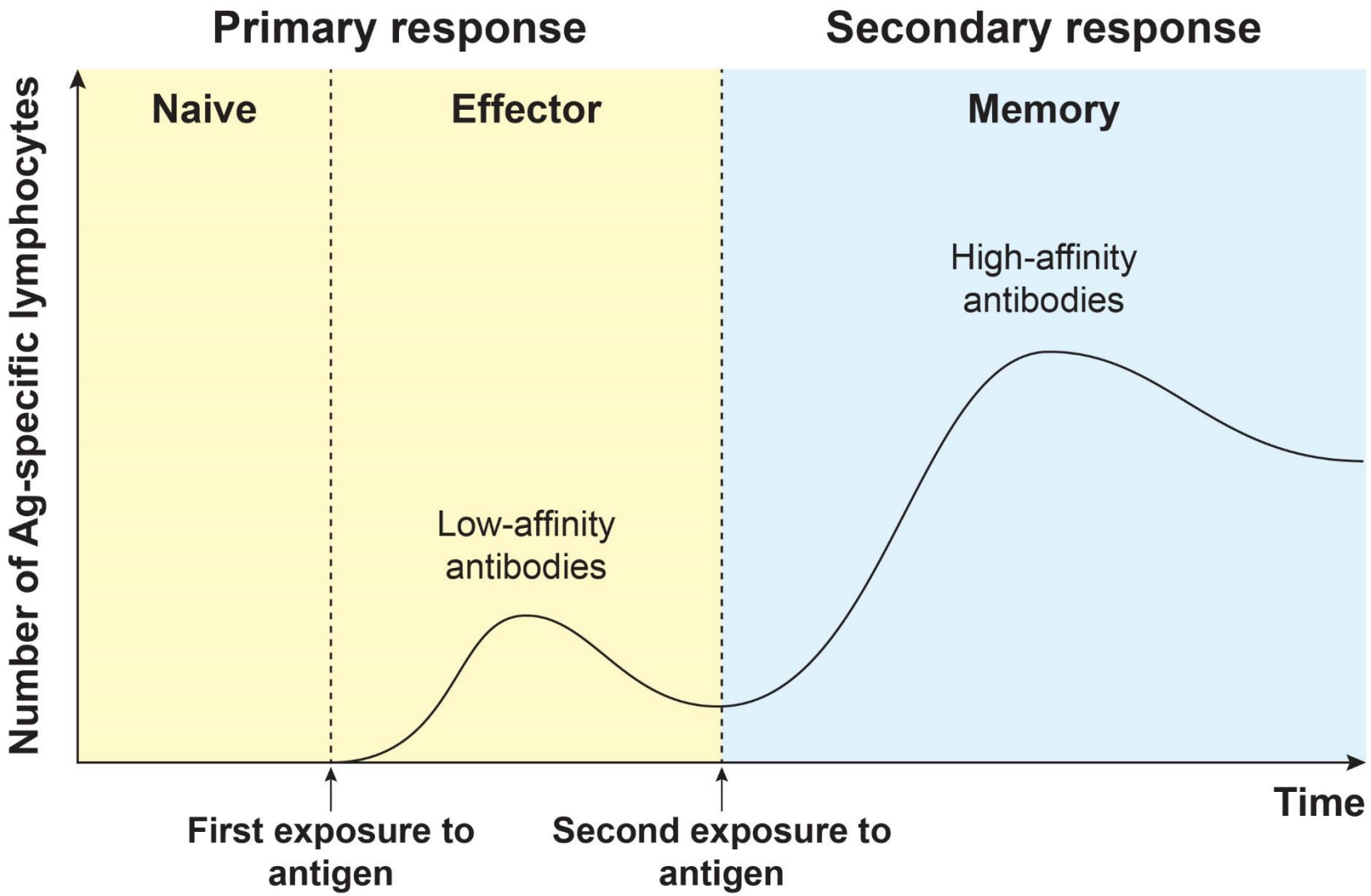
# Significance of immunological memory




- Typically expressed by professional APCs
- Presents peptides derived from exogenous proteins

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# Immune responses can be beneficial or harmful

| Antigen | Effect of response to antigen | |
|---|---|---|
| | Normal response | Deficient response |
| Infectious agent | Protective immunity | Recurrent infection |
| Innocuous substance | Allergy | No response |
| Grafted organ | Rejection | Acceptance |
| Self organ | Autoimmunity | Self tolerance |
| Tumor | Tumor immunity | Cancer |

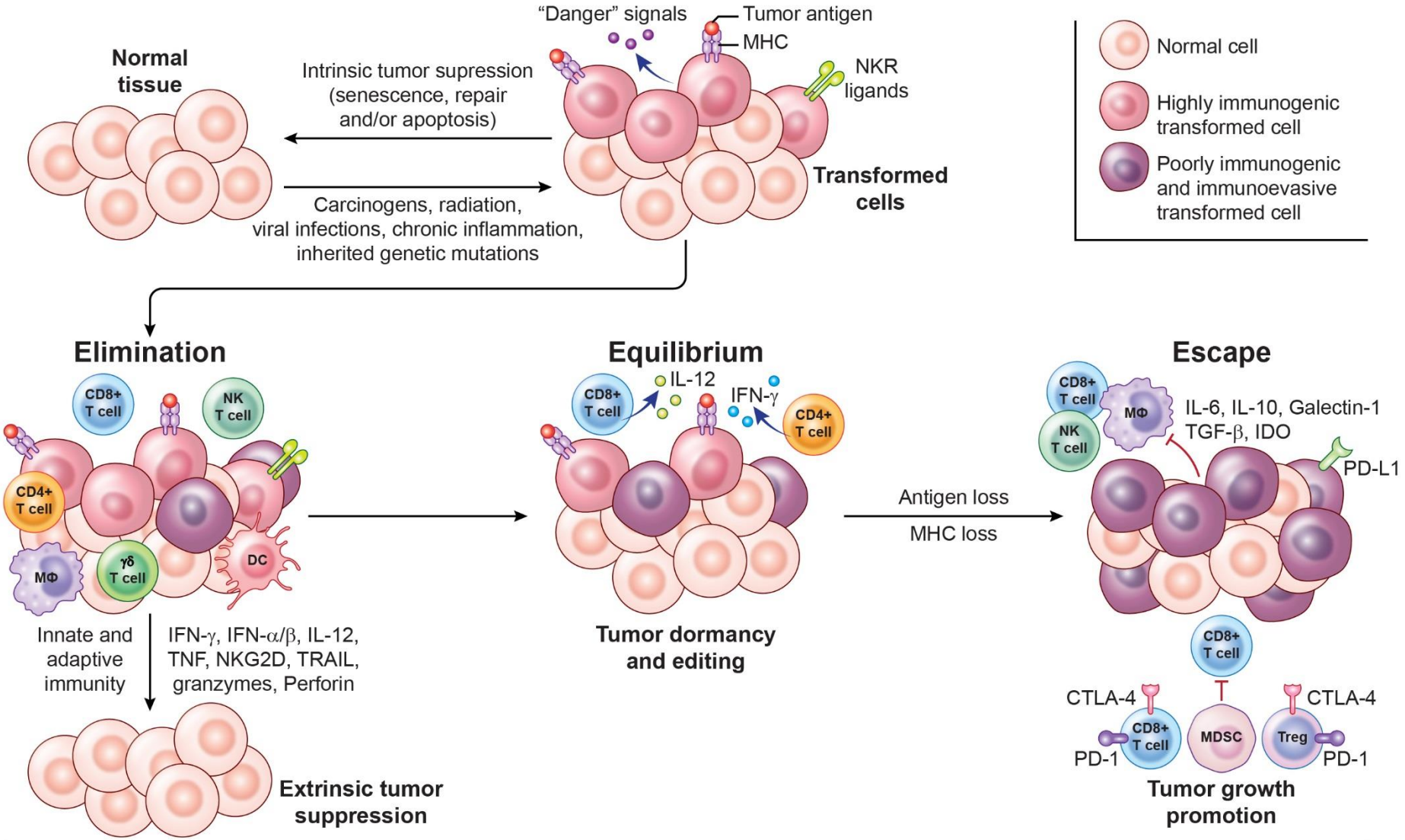
Effectiveness of mechanisms mediating immune tolerance and regulation

# Tumor Immunology

# Definitions

- Immunosurveillance: process of immune cells looking for and recognizing pathogens or tumor cells
- Neoantigens: antigens on tumor cells that give the immune system a way to differentiate them from normal cells. Examples: mutant proteins, oncogenic viruses, cancer testis antigens, or differentiation antigens
- Immunoediting: elimination of immunogenic tumor cells leads to a progressively more non-immunogenic tumor phenotype

# The 3 Es of cancer immunoediting

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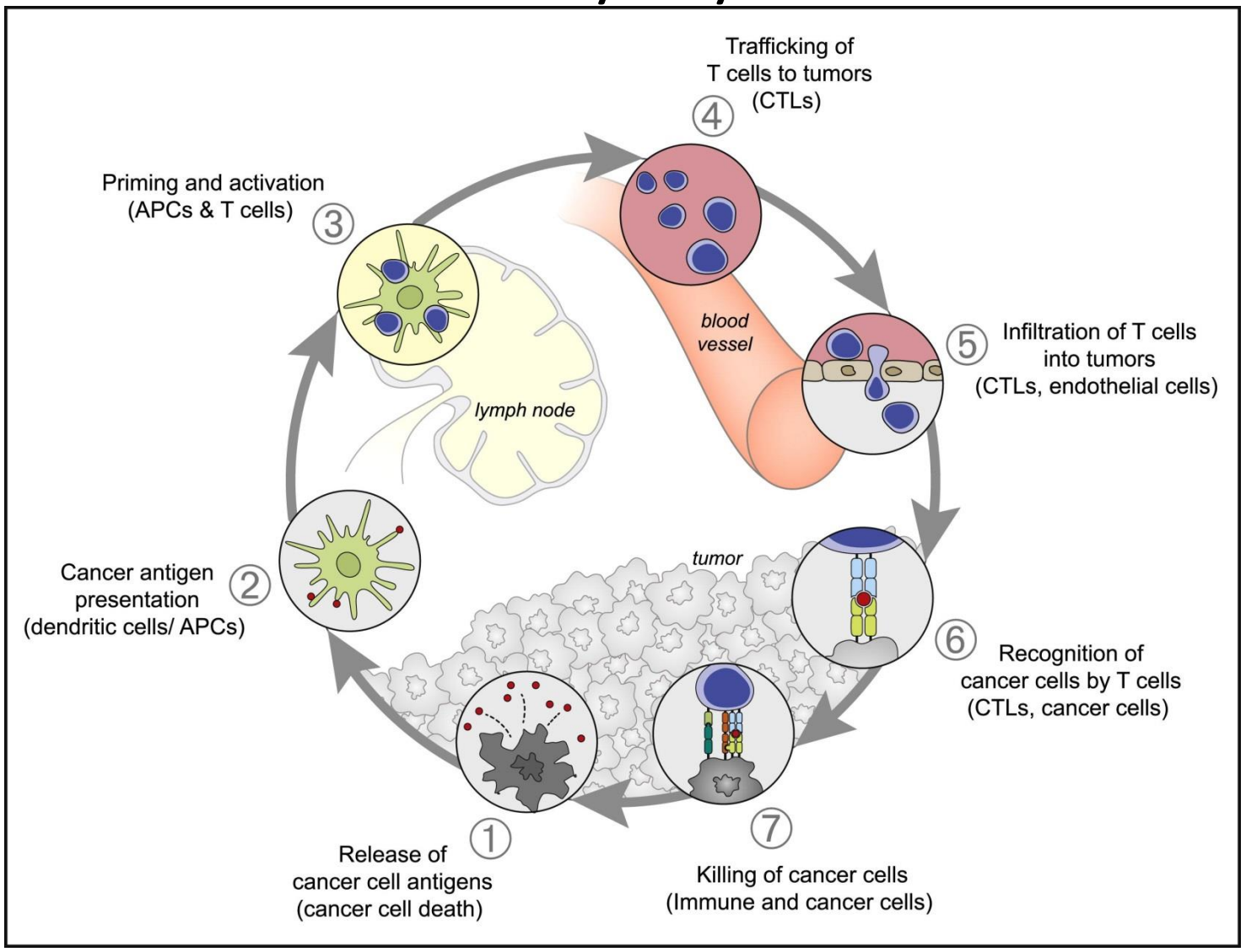
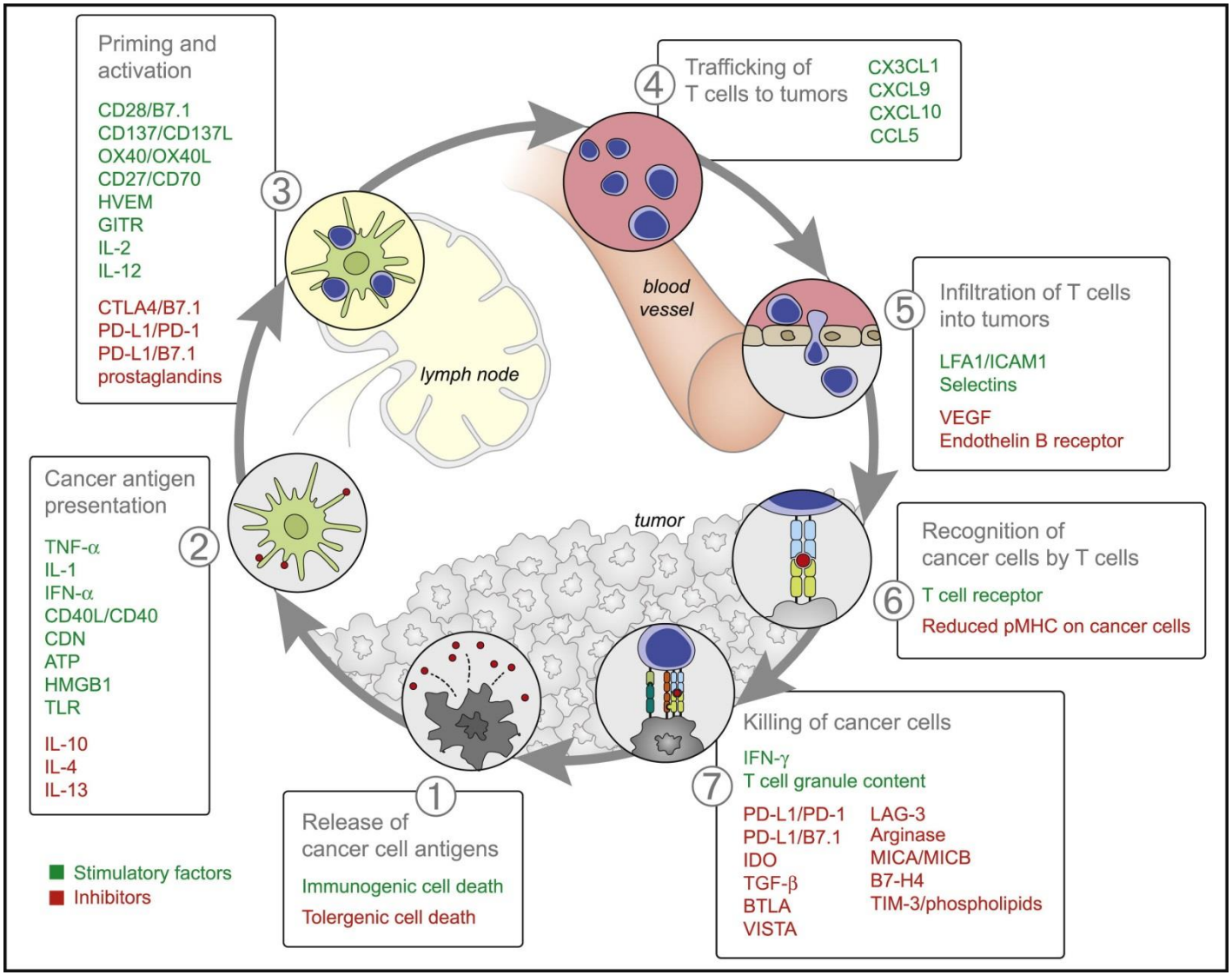
# Cancer-Immunity Cycle




*Immunity* 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

# Cancer-Immunity Cycle -- regulators

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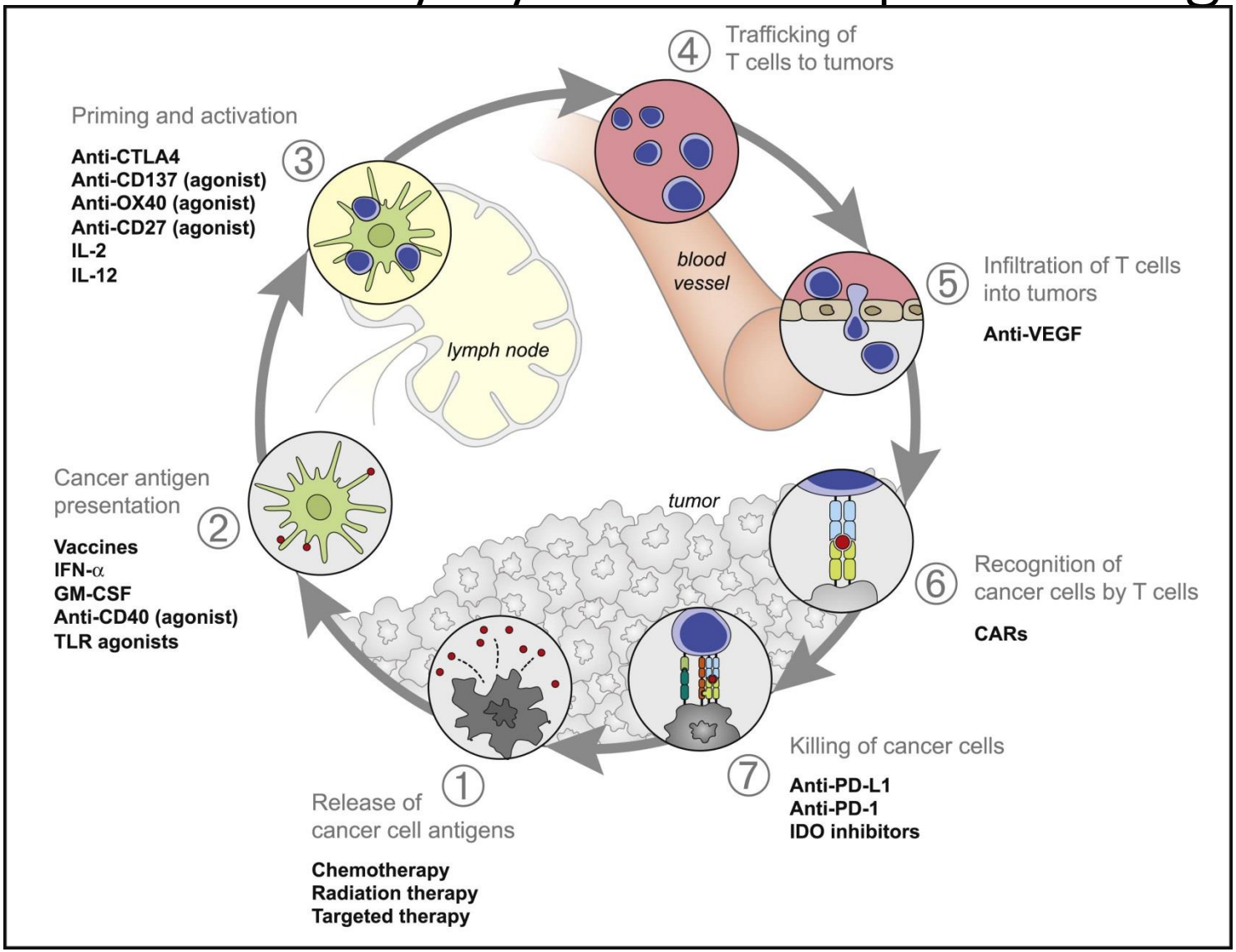
# Cancer-Immunity Cycle – therapeutic targets

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Thank you