Society for Immunotherapy of Cancer (SITC)

Immunology and Immunotherapy 101 for the Non-Immunologist

Christian Capitini, MD
Assistant Professor
Pediatric Hematology, Oncology & Bone Marrow Transplant
University of Wisconsin
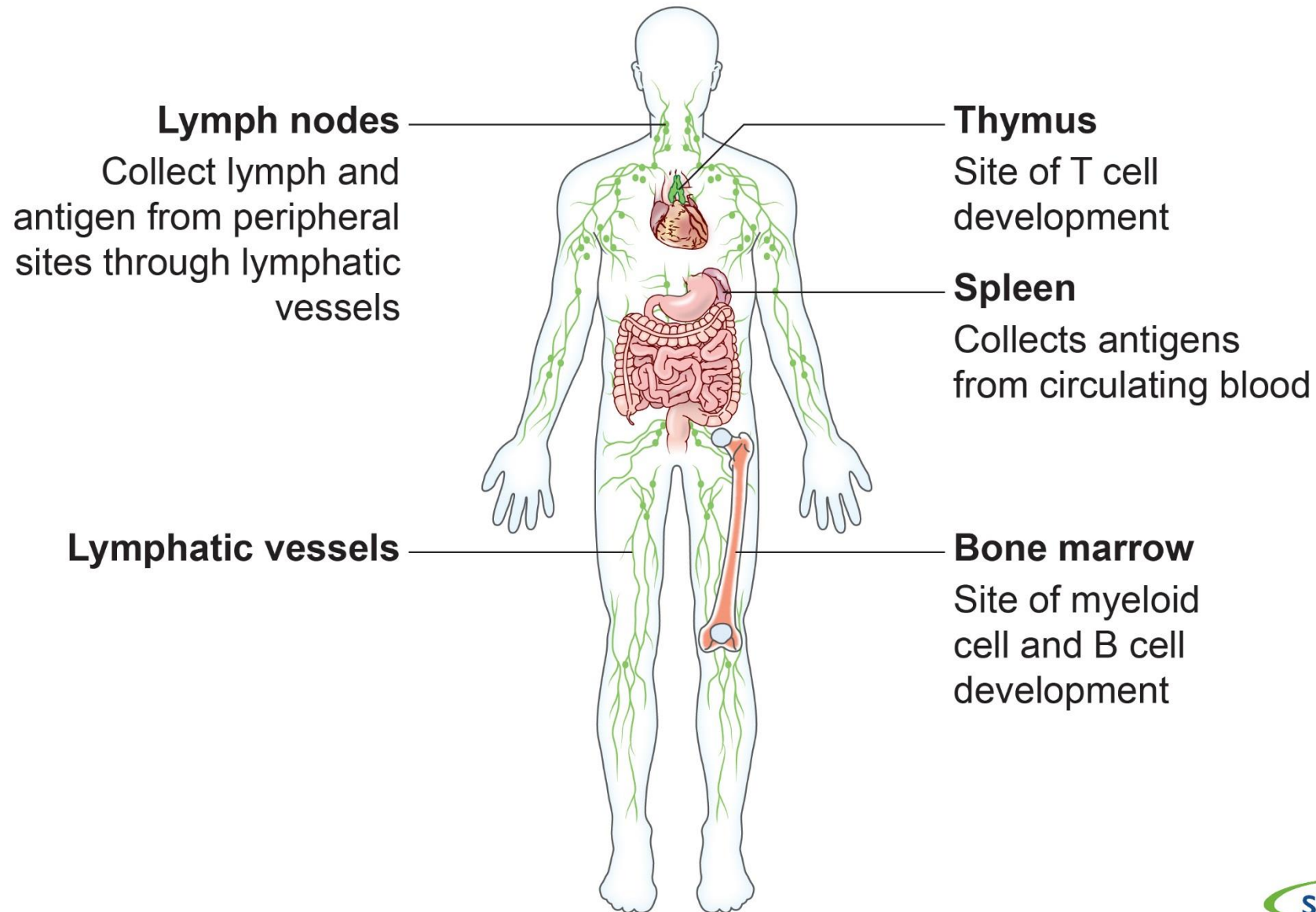
Annual Meeting
November 12, 2016

The following relationships exist related to this presentation:

- I have no relevant conflicts of interest to disclose

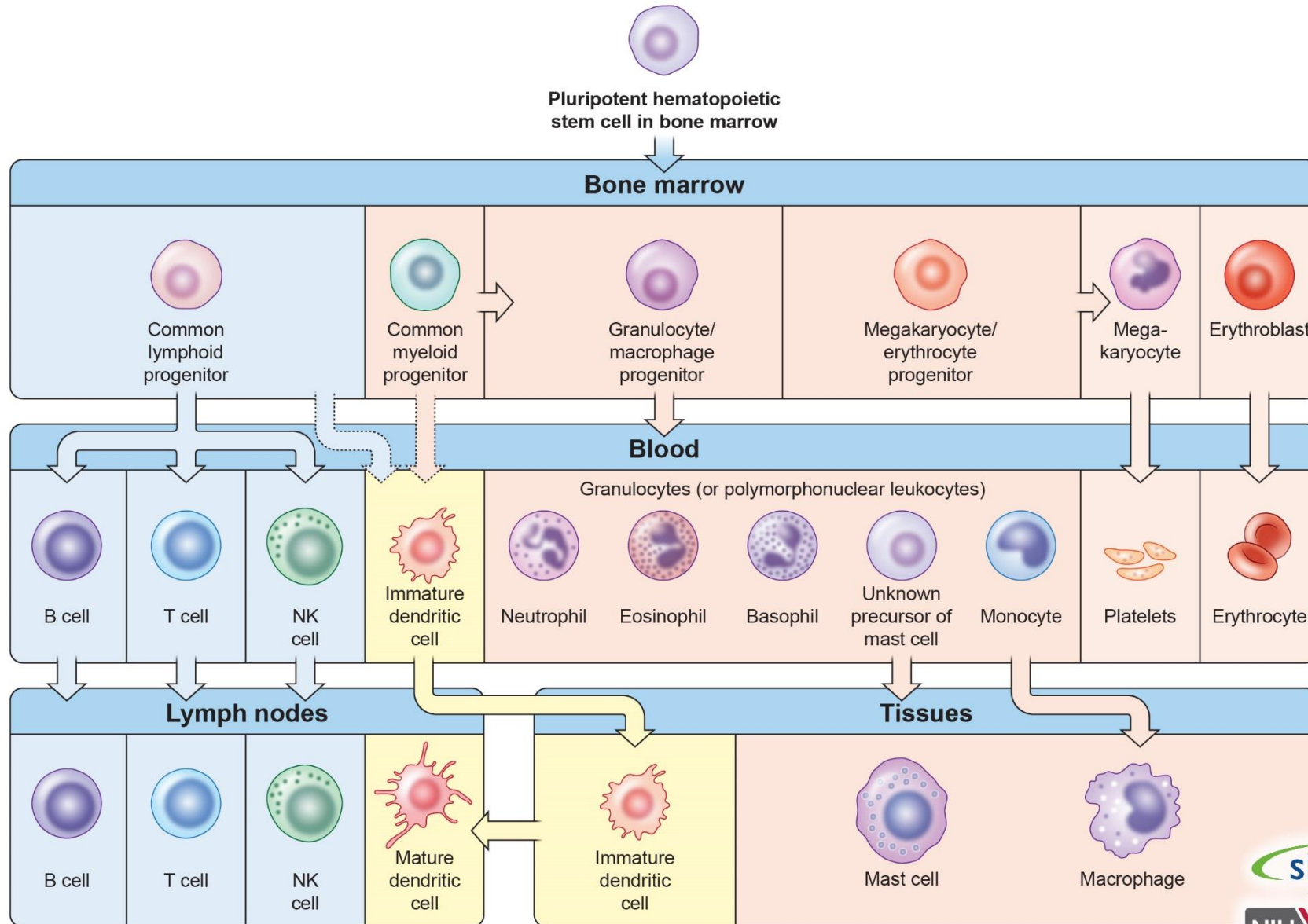- I will not discuss off-label usage of FDA-approved drugs

Objectives

- Understand the components of the immune system

- Differentiate between innate vs. adaptive immune system

- Understand the barriers to effective immunotherapy
  - Including the tumor microenvironment

Lymphoid organs

Lymph nodes
Collect lymph and antigen from peripheral sites through lymphatic vessels

Thymus
Site of T cell development

Spleen
Collects antigens from circulating blood

Lymphatic vessels

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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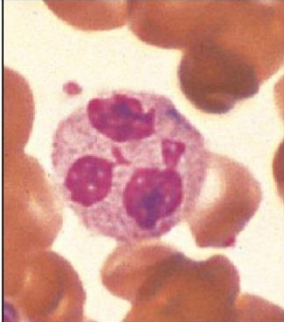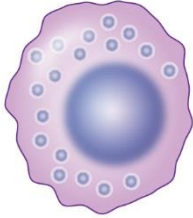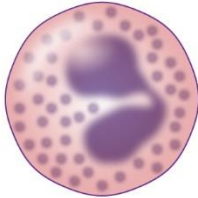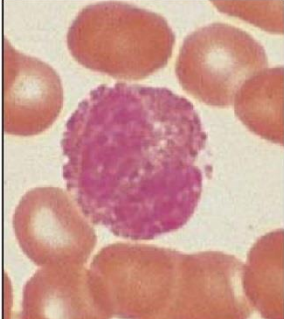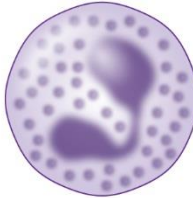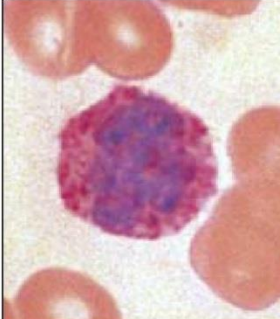
Immune cells are derived from stem cells in the bone marrow

Pluripotent hematopoietic stem cell in bone marrow

Bone marrow

Common lymphoid progenitor | Common myeloid progenitor | Granulocyte/macrophage progenitor | Megakaryocyte/erythrocyte progenitor | Mega-karyocyte | Erythroblast

Blood

Granulocytes (or polymorphonuclear leukocytes)

B cell | T cell | NK cell | Immature dendritic cell | Neutrophil | Eosinophil | Basophil | Unknown precursor of mast cell | Monocyte | Platelets | Erythrocyte

Lymph nodes | **Tissues**

B cell | T cell | NK cell | Mature dendritic cell | Immature dendritic cell | Mast cell | Macrophage

Innate Immunity

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	
	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)

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

Bacteria trigger macrophages to release cytokines and chemokines	Vasodilation and increased vascular permeability cause redness, heat and swelling	Inflammatory cells migrate into tissue, releasing inflammatory mediators that cause pain

Bacteria

Chemokines

Cytokines

Macrophage

Fluids and protein

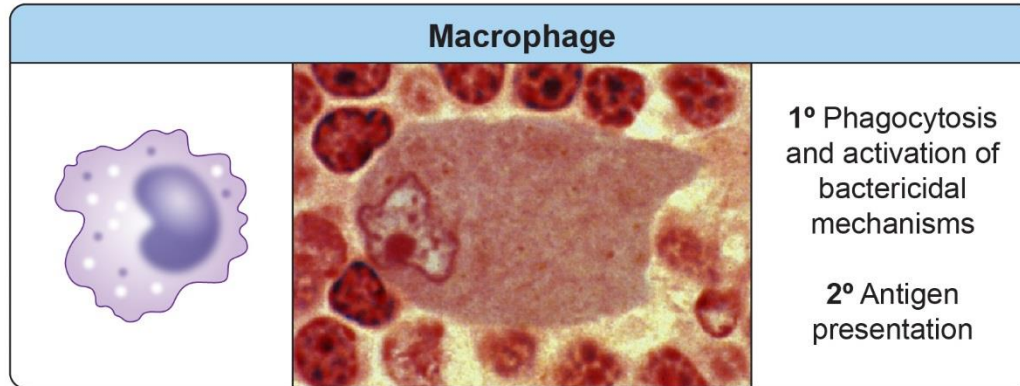Neutrophil

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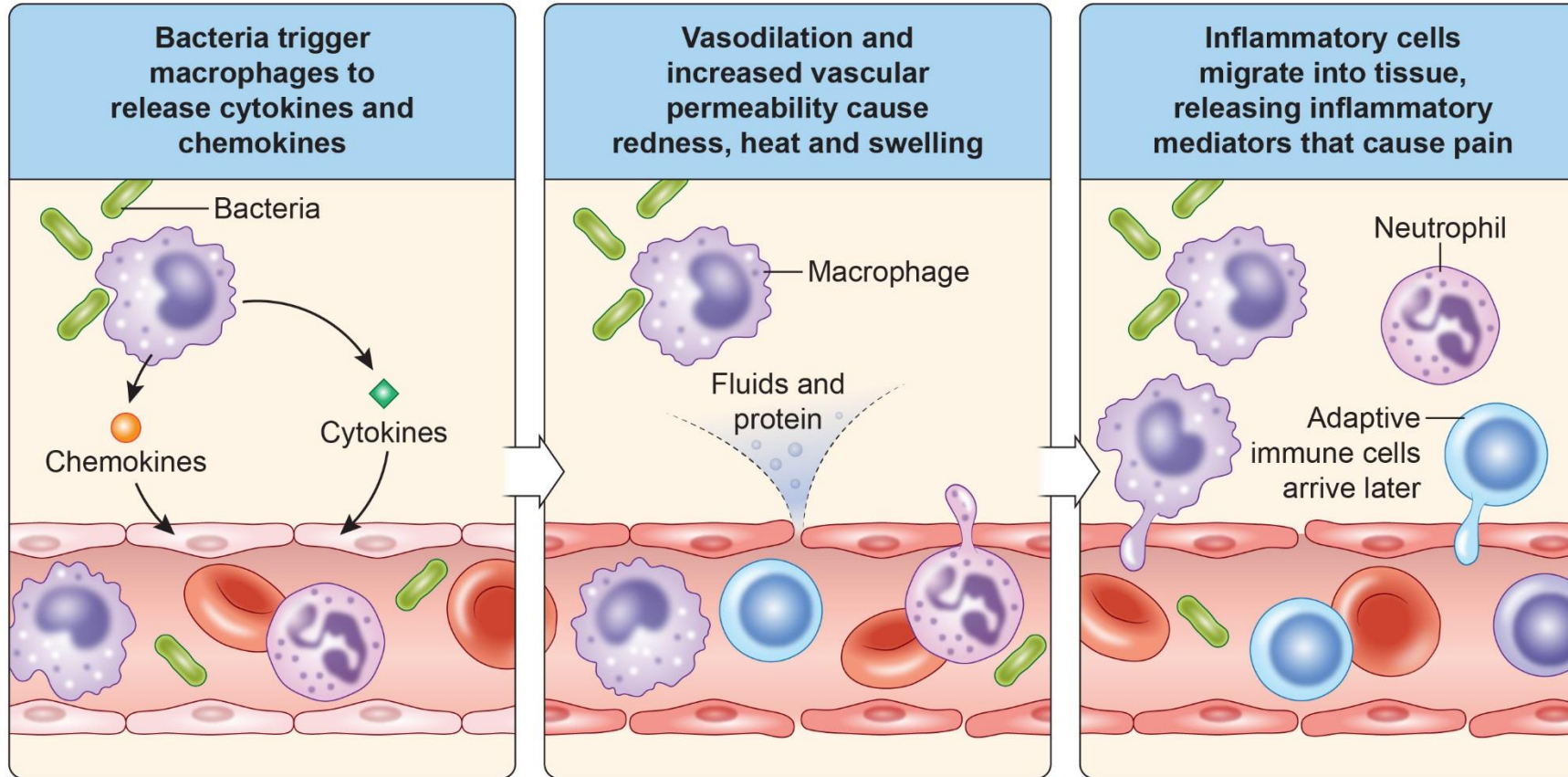
Cytokines are proteins that immune cells use to communicate/regulate other immune cells, not all cytokines are inflammatory

Chemokines are a group of cytokines that attract other immune cells
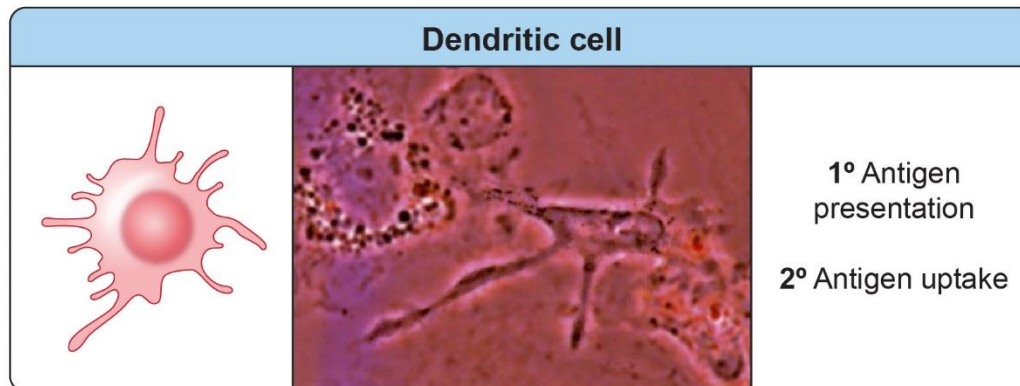
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Phagocytes

Neutrophils, macrophages and dendritic cells

Macrophage		
		1° Phagocytosis and activation of bactericidal mechanisms **2°** Antigen presentation

Reside in tissues

| Dendritic cell		
		1° Antigen presentation **2°** 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)

Antigen processing and presentation

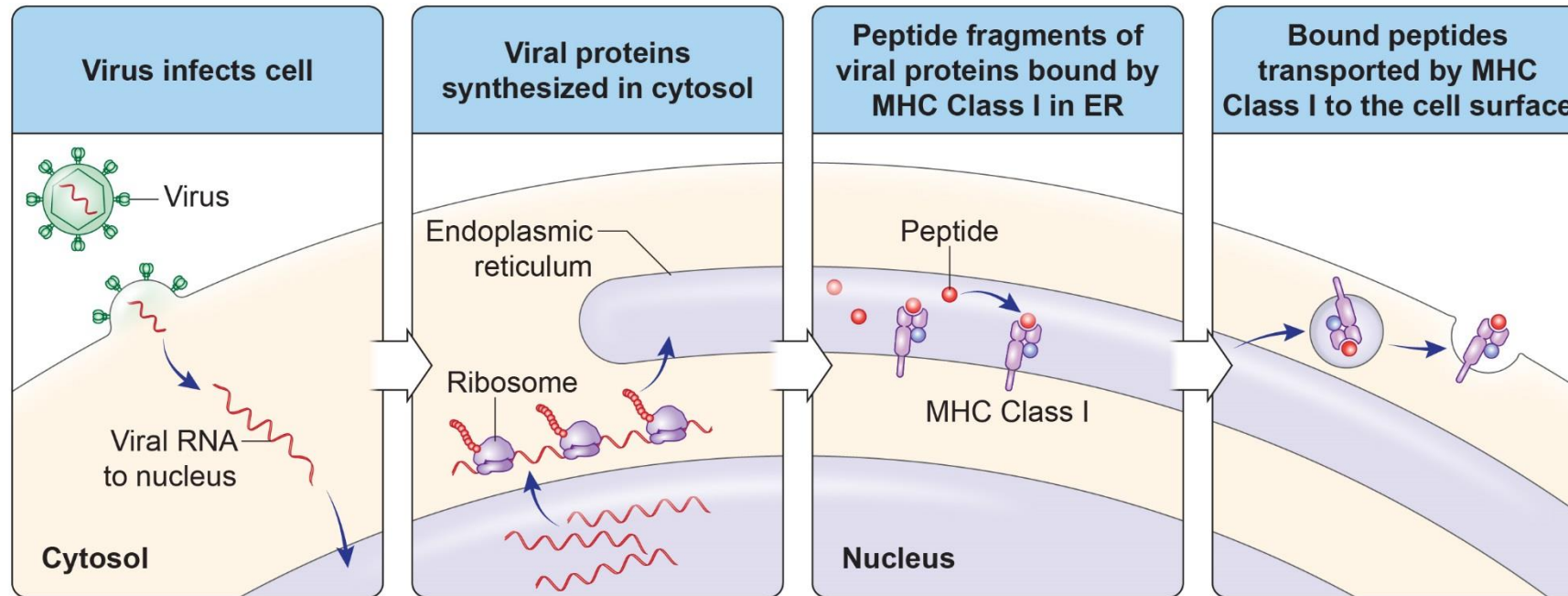Professional APCs present Ag to naïve T cells and induce activation
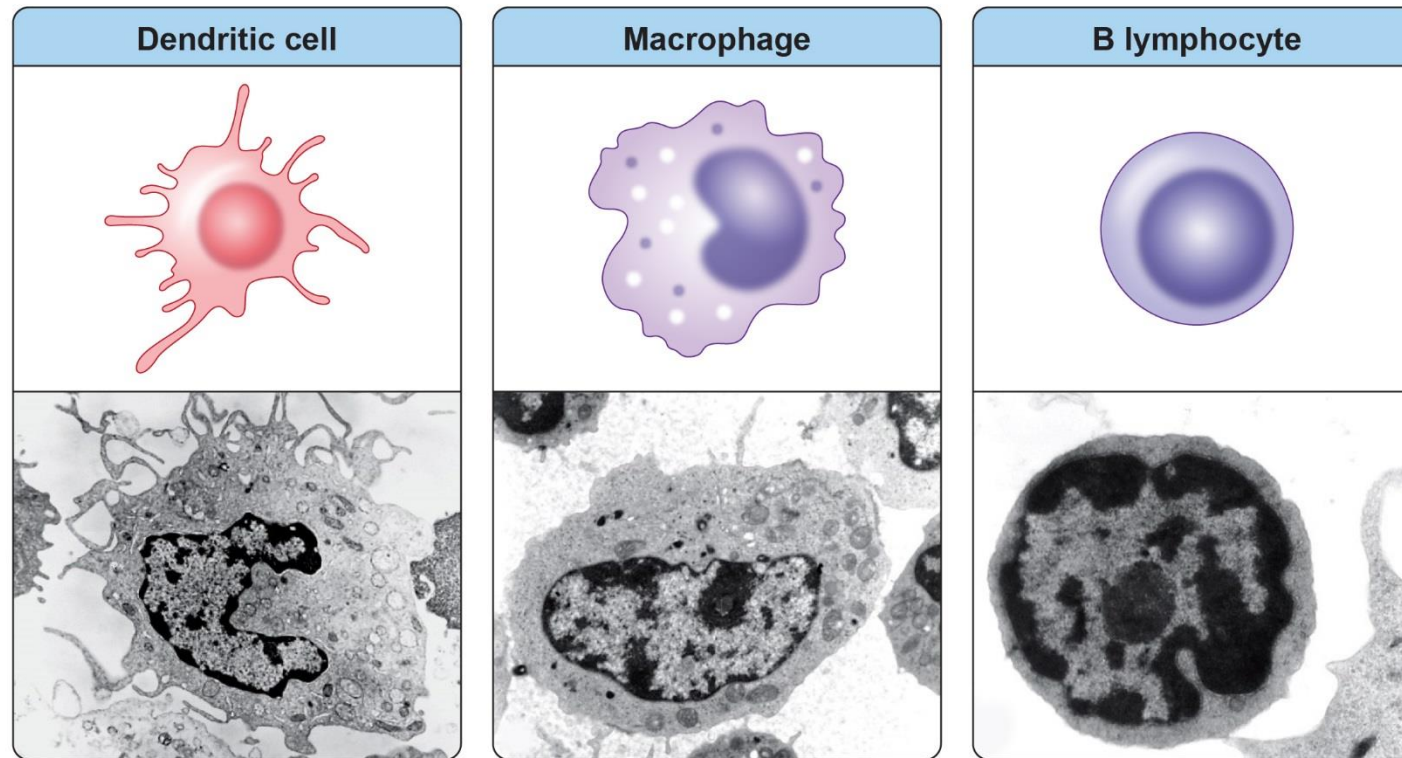
Immature DCs very efficient at Ag processing (in tissues) → Mature DCs very efficient at Ag presentation (in LNs)

MHC Class I presents peptide antigens to CD8 T cells

Virus infects cell

Virus

Viral RNA to nucleus

Cytosol

Viral proteins synthesized in cytosol

Endoplasmic reticulum

Ribosome

Peptide fragments of viral proteins bound by MHC Class I in ER

Peptide

MHC Class I

Nucleus

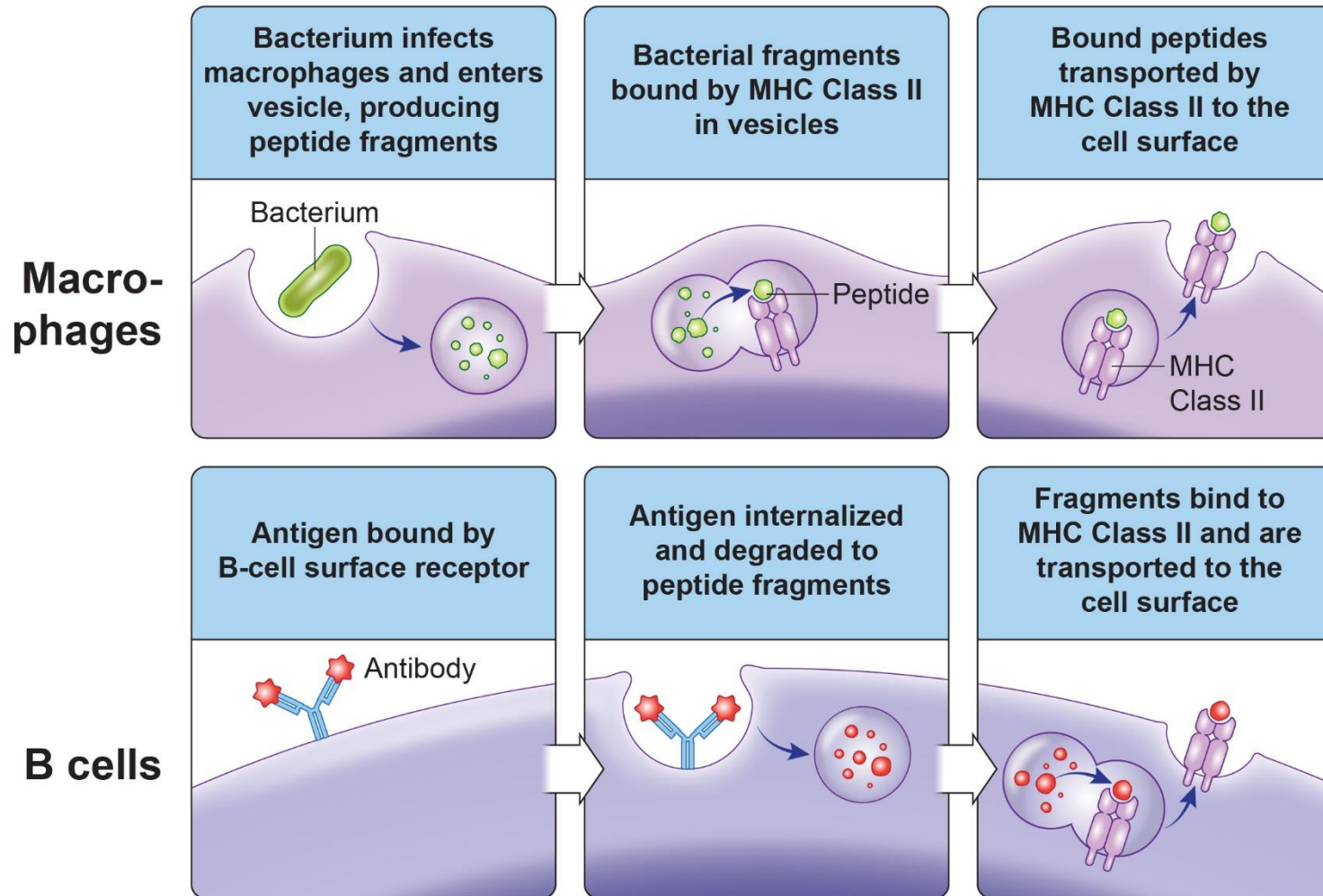**Bound peptides transported by MHC Class I to the cell surface**

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

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MHC Class II presents antigens to CD4 T cells

Macro-phages

| Bacterium infects macrophages and enters vesicle, producing peptide fragments | Bacterial fragments bound by MHC Class II in vesicles | Bound peptides transported by MHC Class II to the cell surface |

Bacterium

Peptide

MHC Class II

B cells

| Antigen bound by B-cell surface receptor | Antigen internalized and degraded to peptide fragments | Fragments bind to MHC Class II and are transported to the cell surface |

Antibody

Major Histocompatibility Complex (MHC) Class II
- Typically expressed by professional APCs
- Presents peptides derived from exogenous proteins

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Overarching Theories on the Immune System

Stranger Model	**Danger Model**
Self/Non-Self	

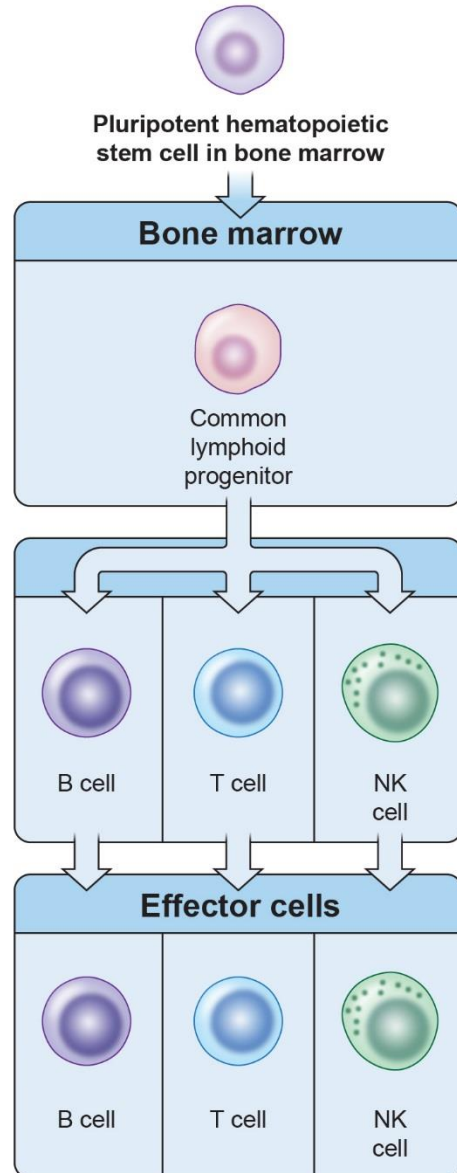| Stranger Model	Danger Model
• The primary goal of the immune system is to distinguish self from non-self.	• The primary goal of the immune system is to identify and respond to danger.
• Specificities of clonal receptors are selected such that they overwhelmingly recognize non-self.	• Specificities of clonal receptors predominantly recognize foreign antigens but can also recognize self antigens.
• Corollary: very few self-reactive T and B cells are normally found, because thymic and B cell selection processes are complete.	• Peripheral signals provide the primary signals which determine whether an immune response to a given antigen will occur at a given time.
• Peripheral mechanisms for preventing autoimmunity are deemphasized.	• Dendritic cells serve primarily to identify and initiate responses to danger signals.

Stranger model

Danger model

Pathogen

PAMPs

Necrotic cell death

Release of DAMPs

DC

PRR

DAMP receptor

DC maturation

Peptide–MHC complex

CD80 and/or CD86 co-stimulatory molecule

Lymph node

T cell

CD28

TCR

CD80 or CD86

Migration to lymph node

Kono & Rock, 2008

Lymphocytes

Pluripotent hematopoietic stem cell in bone marrow

Bone marrow

Common lymphoid progenitor

B cell   T cell   NK cell

Effector cells

B cell   T cell   NK cell

B cells
- Produce antibodies (Ab) that bind proteins

T cells
- Change antigens to peptides

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
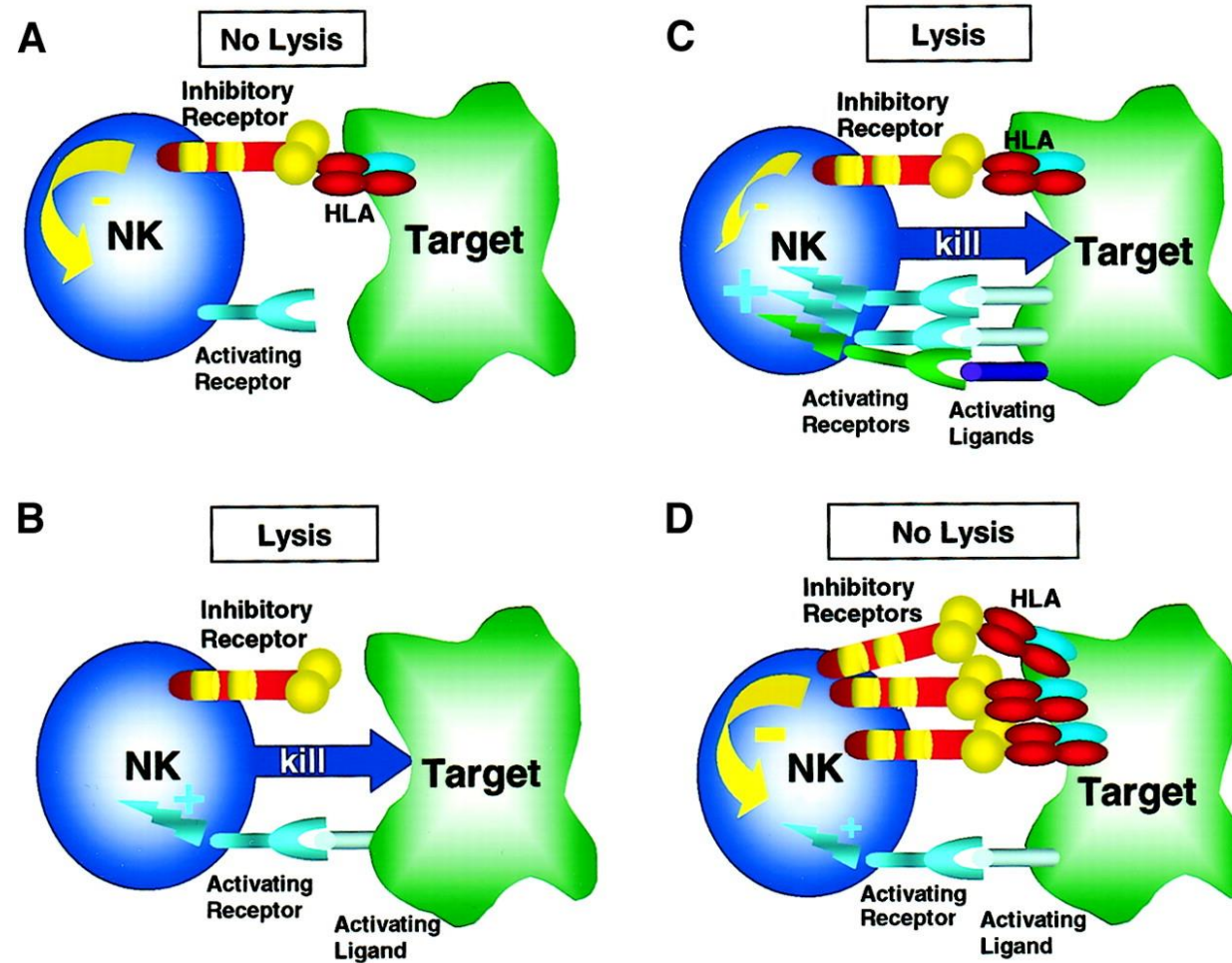
Innate
(recognize general features)

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NK cells

- Mediate non-MHC restricted killing of virally infected cells and tumors

- Produce cytokines like IFNγ and TNFα

- Mediate Antibody-Dependent Cellular Cytotoxicity

Figure 1.

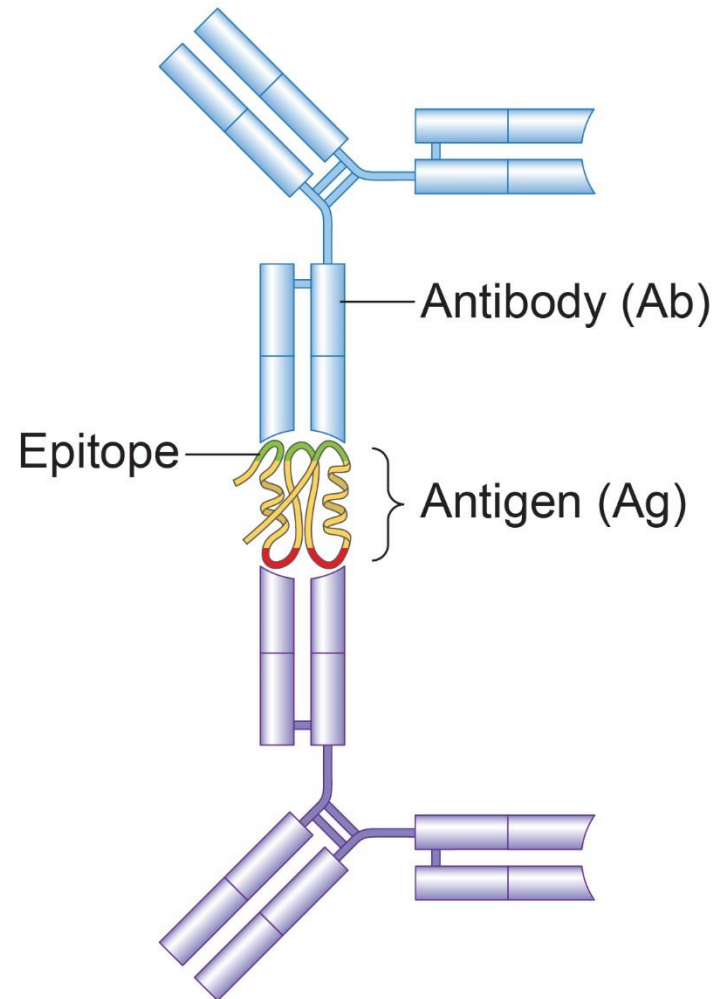Farag, S. S. et al. Blood 2002;100:1935-1947

Adaptive Immunity

B cells

- Produce antibodies

- Antigen presenting cell
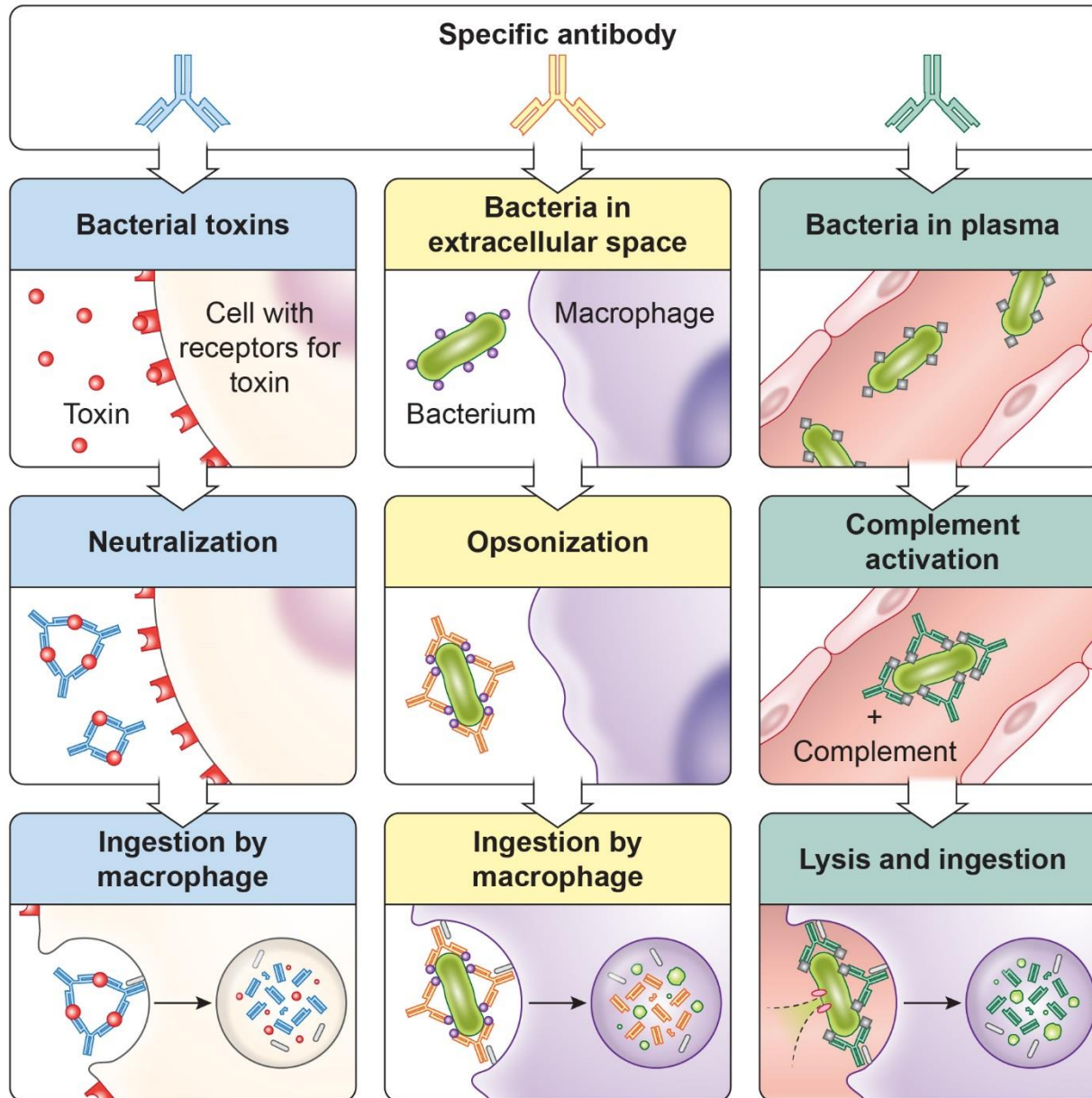
- Produce cytokines

- Have memory

Antigen recognition by antibodies

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

Effector mechanisms of adaptive immunity

B Cells

Ab function:
- Neutralize
- Block protein functions
- Promote engulfement
- Induce complement-mediated cell lysis
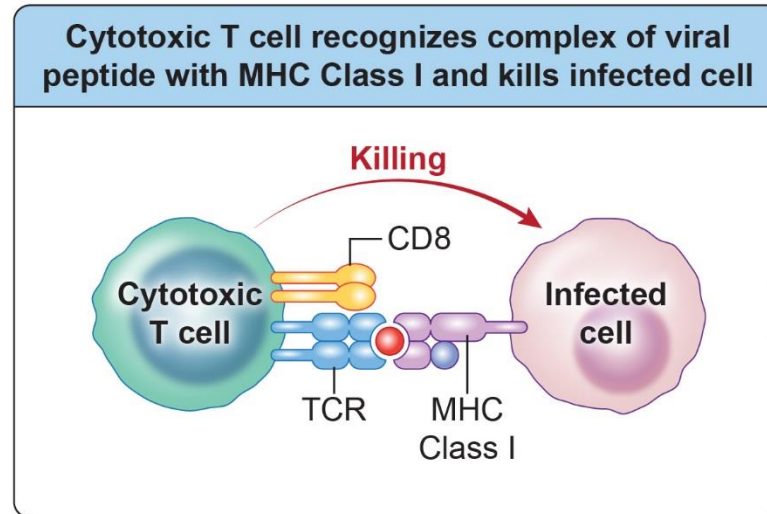
Different classes (isotypes) of Ab
- IgM
- IgG
- IgE
- IgA

T cells

- Mediate MHC-restricted killing of virally infected cells and tumors

- Main types include CD8$^+$ (Cytotoxic) and CD4$^+$ (Helper)
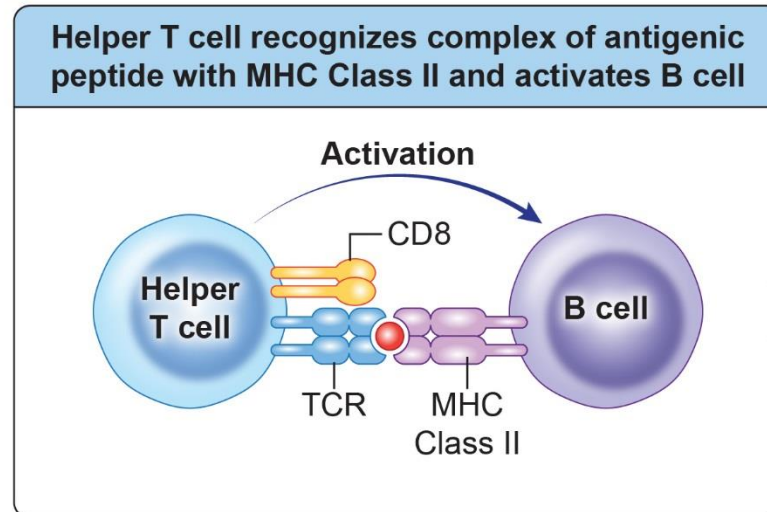
- Produce cytokines

- Have memory

Effector mechanisms of adaptive immunity

CD8+ T cells
(Cytotoxic T cells)

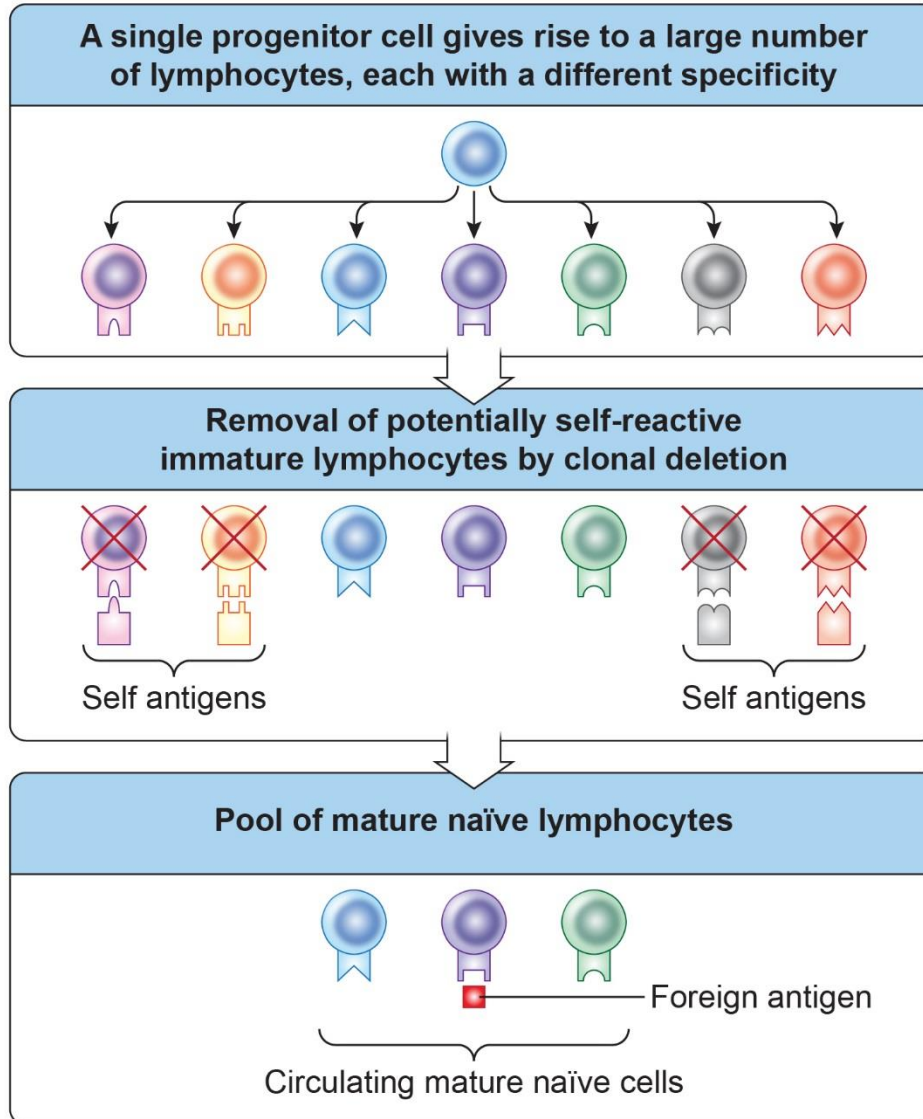Cytotoxic T cell recognizes complex of viral peptide with MHC Class I and kills infected cell

Killing

Cytotoxic T cell — CD8 — TCR — MHC Class I — Infected cell

Produce proteins that lyse cells

CD4+ T cells
(Helper T cells)

Helper T cell recognizes complex of antigenic peptide with MHC Class II and activates B cell

Activation

Helper T cell — CD8 — TCR — MHC Class II — B cell

Different subtypes: Th1, Th2, Th17, Tregs

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Achieving an adaptive immune response

Generating lymphocytes that each have a unique specificity

A single progenitor cell gives rise to a large number of lymphocytes, each with a different specificity

Removal of potentially self-reactive immature lymphocytes by clonal deletion

Self antigens

Self antigens

Pool of mature naïve lymphocytes

Foreign antigen

Circulating mature naïve cells

Generation of vast pool of cells
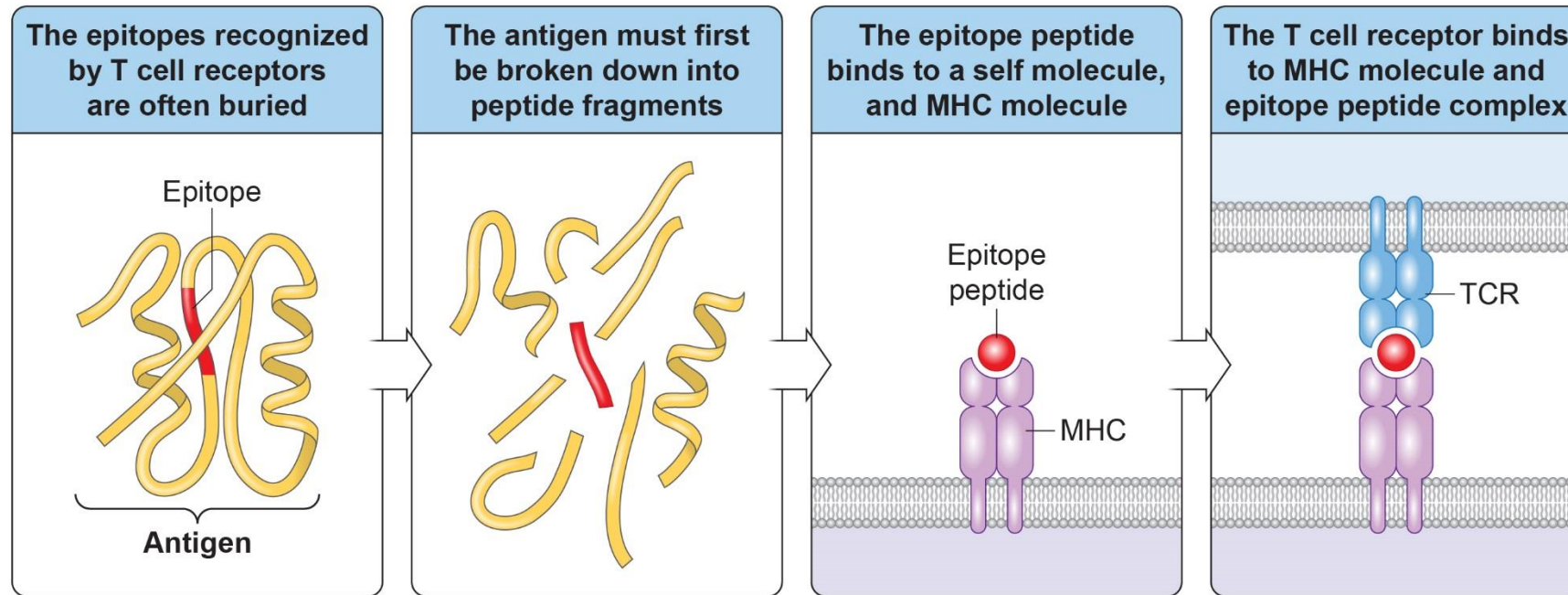- Immature cells (non-functional)

Elimination of cells that can recognize self Ags
- One barrier to inducing responses against tumor cells

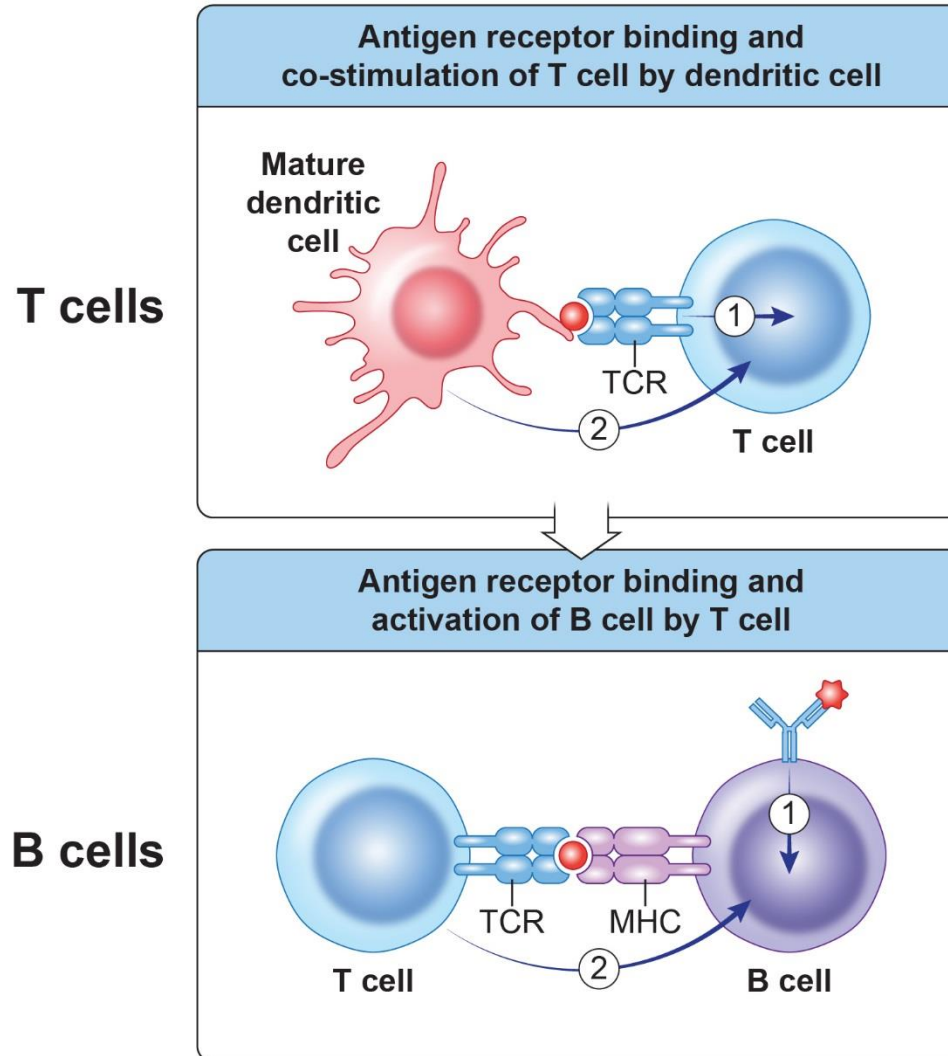**Mechanism of central tolerance**
- Circulating mature naïve cells

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

The epitopes recognized by T cell receptors are often buried

Epitope

Antigen

The antigen must first be broken down into peptide fragments

The epitope peptide binds to a self molecule, and MHC molecule

Epitope peptide

MHC

The T cell receptor binds to MHC molecule and epitope peptide complex

TCR

MHC = Major Histocompatibility Complex

Lymphocyte activation

The Immune Synapse

T CELL

4-1BB +

OX40 +

LFA-1 +

CD40L +

CD4 +

TCR +

CD28 +

CTLA4 −

PD-1 −

peptide

DENDRITIC CELL

4-1BBL

OX40L

ICAM-1

CD40 +

class II

B7-1/ B7-2

B7-H1/ B7-DC

Lymphocyte activation

Pool of mature naïve lymphocytes

Naïve

Foreign antigen

Cells that recognize specific Ag are <u>very rare</u>

Proliferation and differentiation of activated specific lymphocytes to form a clone of effector cells

Activated or effectors

Effector cells eliminate antigen

Results in:
- Expansion
- Acquisition of effector functions
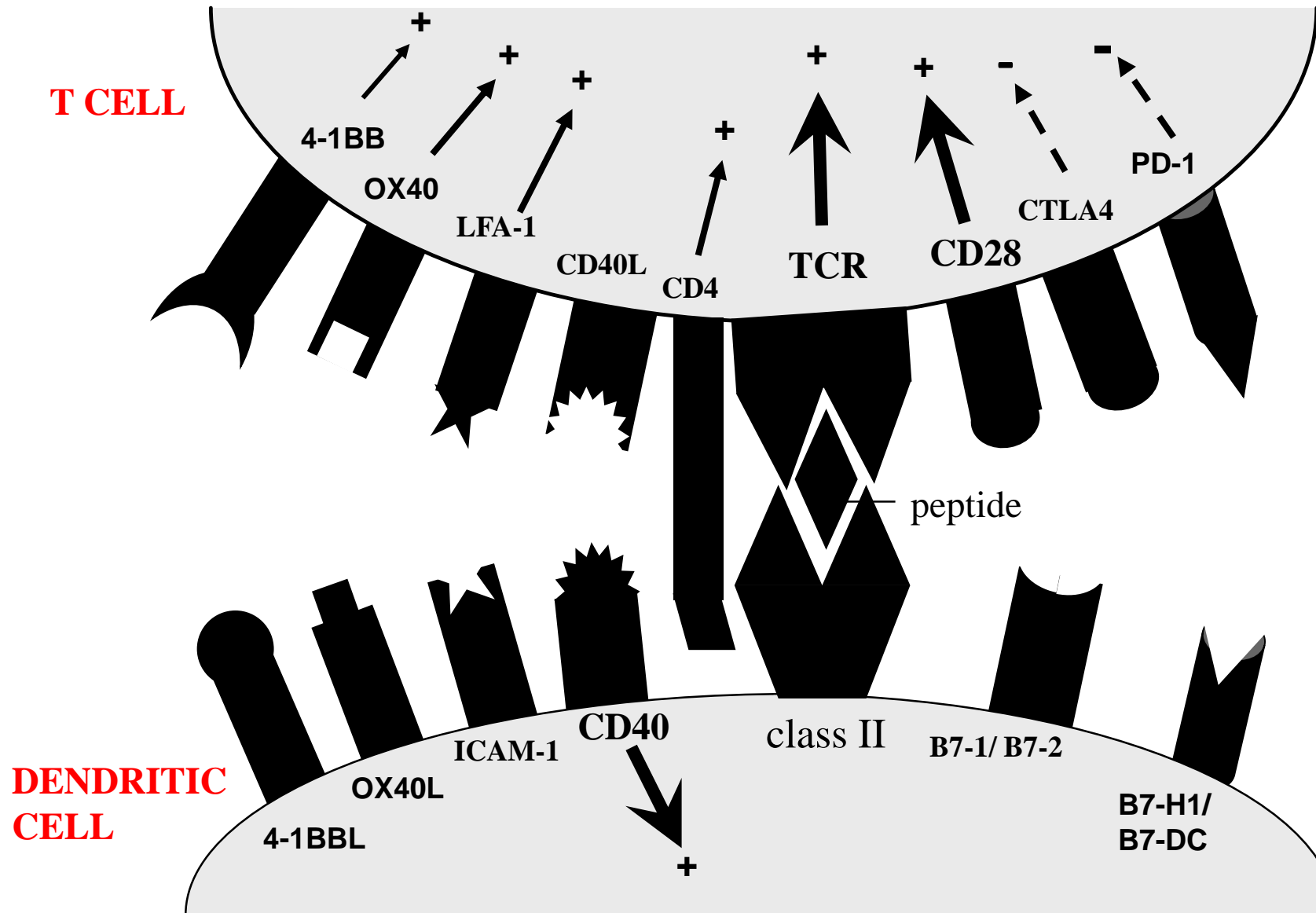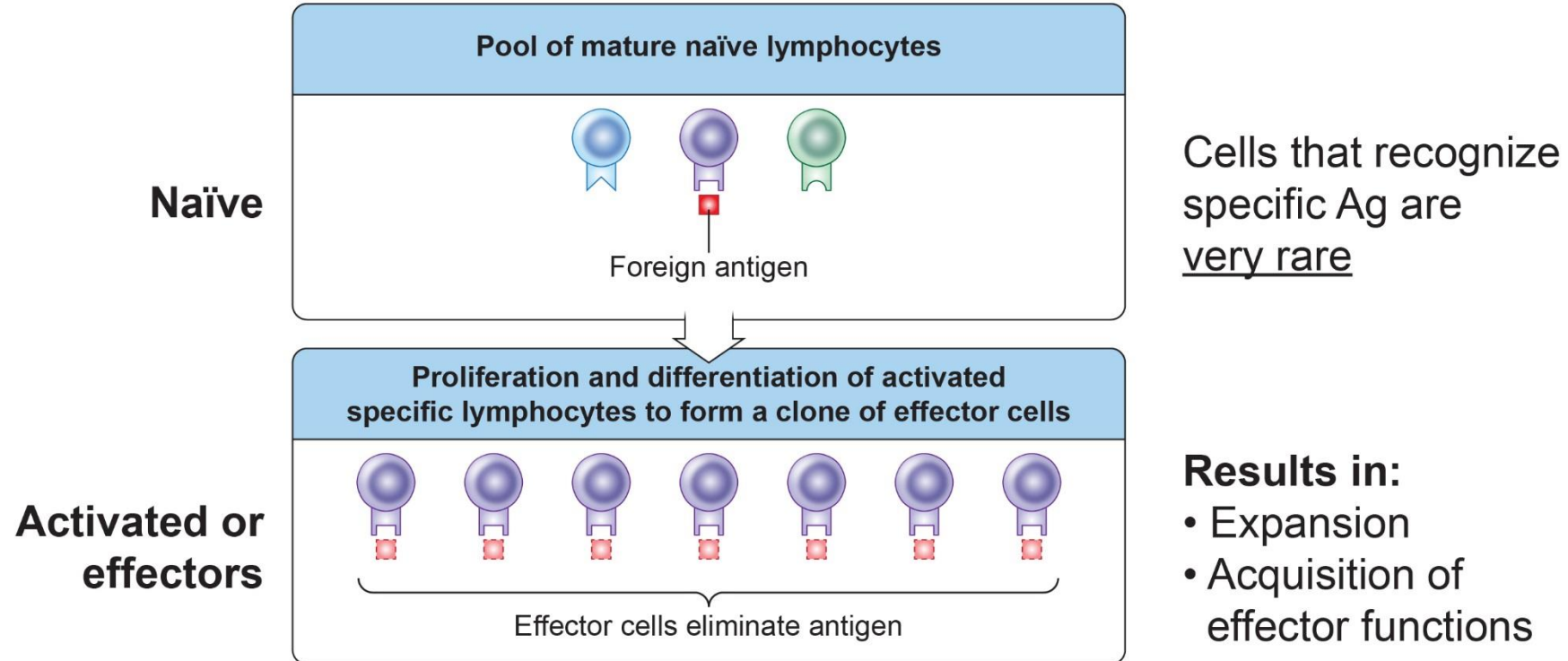
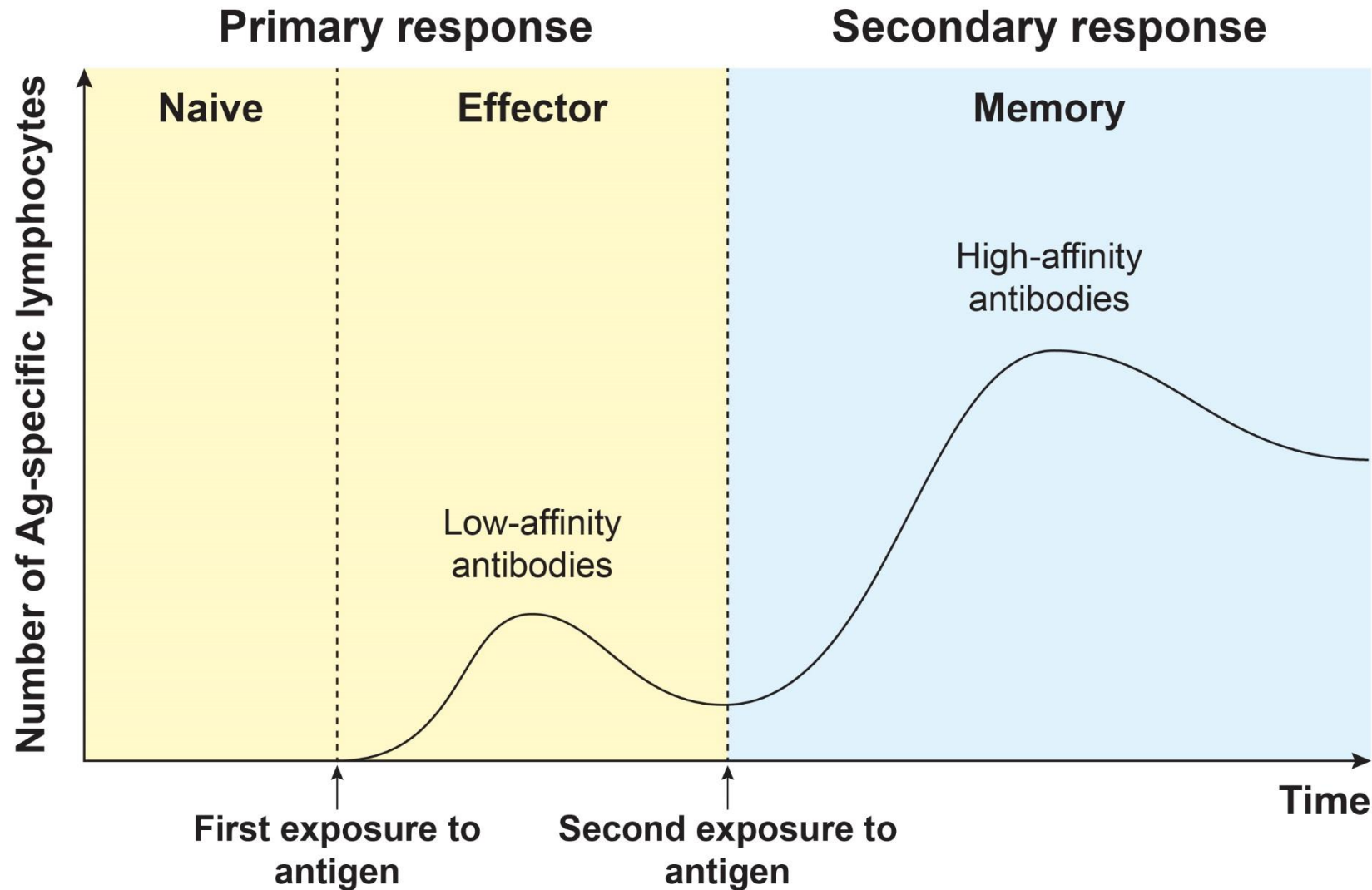What happens to T cells and B cells after immune response?

Differentiate into long-lived memory lymphocytes

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Adaptive immune responses

| Humoral response | Cellular response |

Humoral response — Antibodies present in blood allow immunity to be transferred via proteins

Cellular response — Immunity is mediated by T cells

Foreign body

Macrophage/DC

CD4

Cytokines

Cytokines

Circulating antibodies

B cell

Helper T cell

Cytotoxic T cell

Circulating T cells

Plasma cell

Active cytotoxic T cell

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Significance of immunological memory

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

Tumor Microenvironment
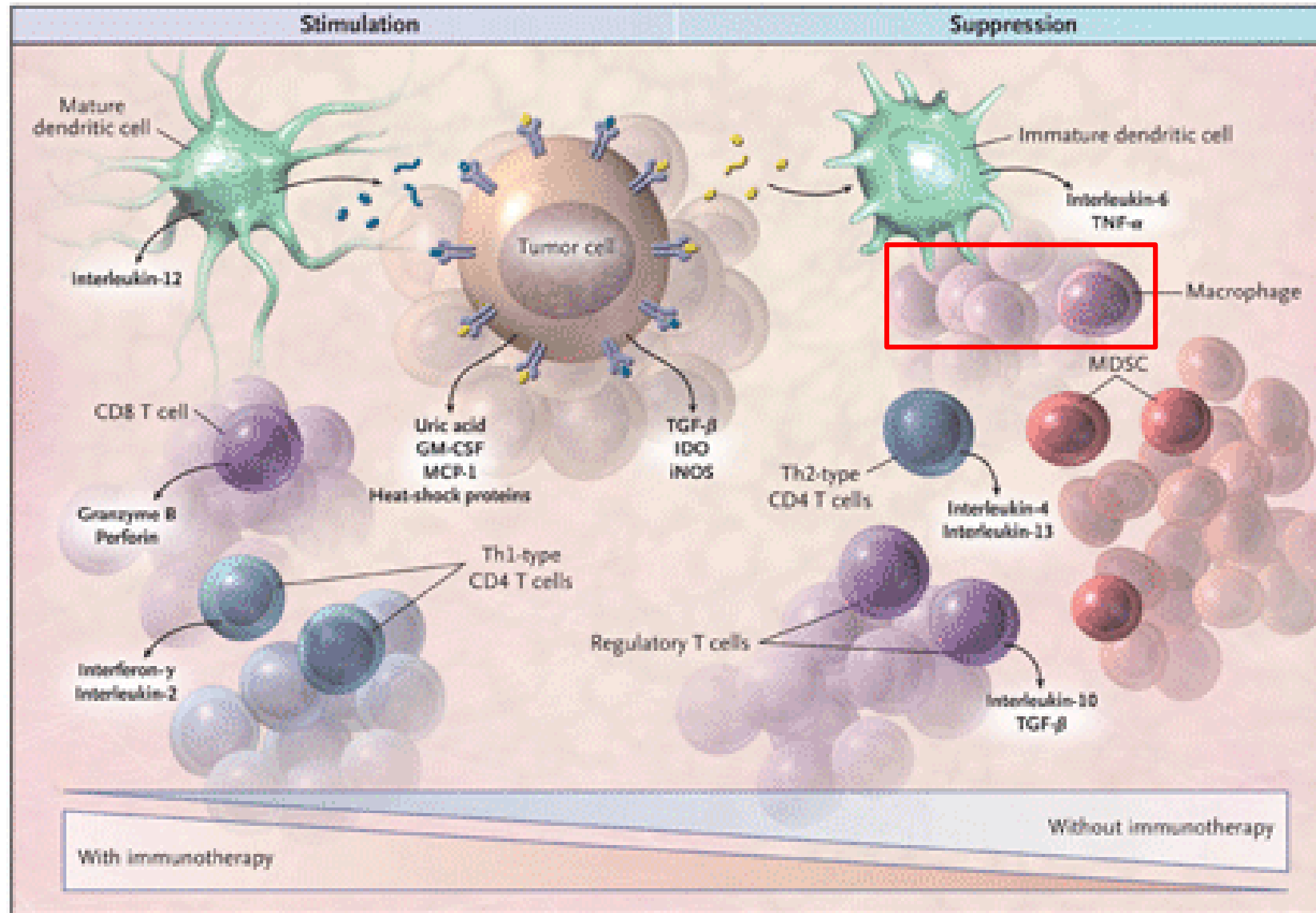
M1 versus M2 macrophages

- M1 macrophages are the standard antigen presenting cell that promotes inflammation

- Tumor-associated macrophages primarily appear to consist of the M2 variety
  - Localize into hypoxic regions of tumors and secrete various immunosuppressive cytokines
  - Promote tumor progression by facilitating angiogenesis and invasion

Tumor Microenvironment
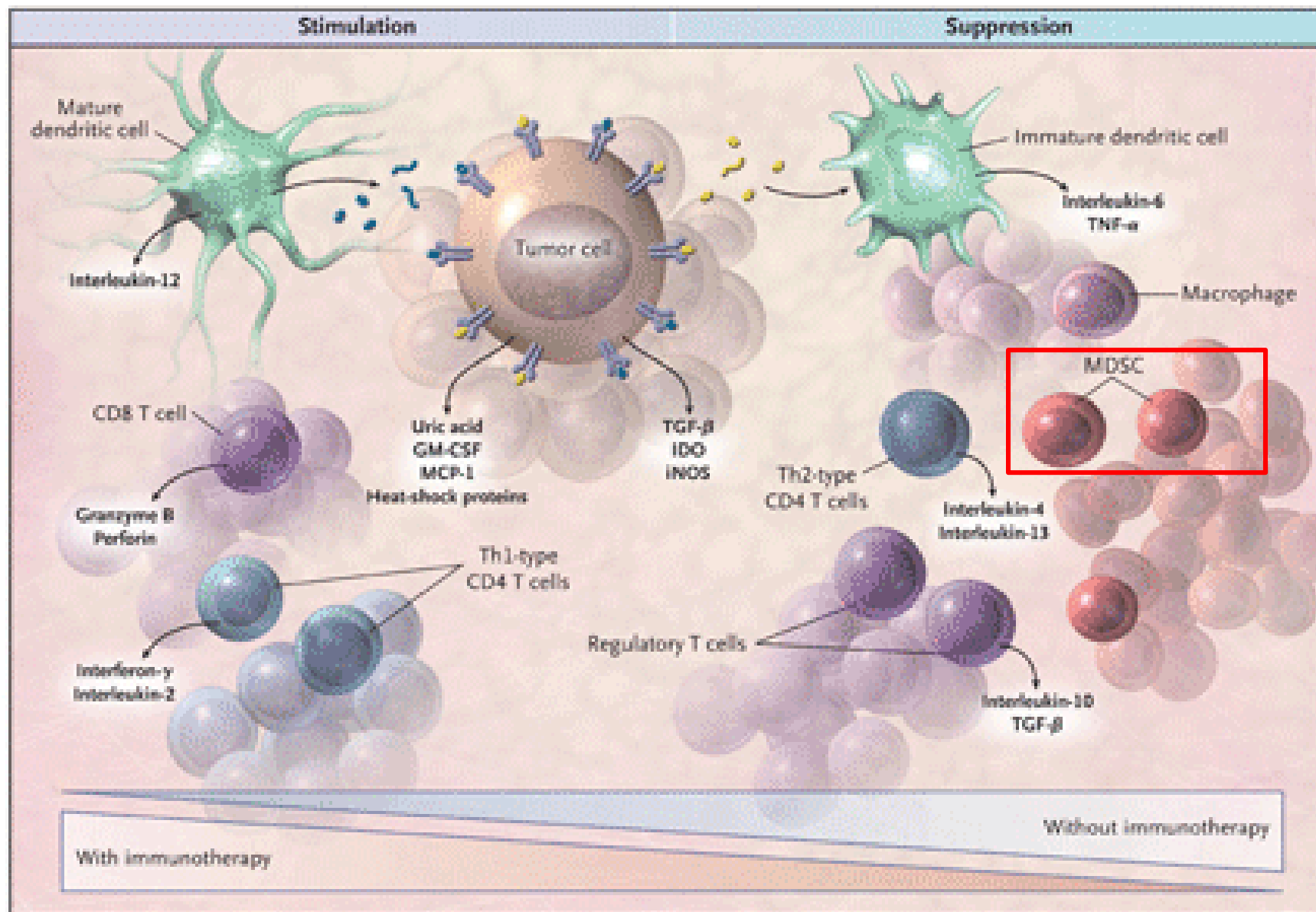
Myeloid-derived suppressor cells

- MDSCs are a collection of granulocytic and monocytic granulocyte precursors that are immunosuppressive

- Tumor growth results in expansion of MDSCs
  - causing a reduction in arginine levels
  - subsequent increase in nitric oxide in tumors
  - inhibits T-cell activation and antigen-specific responses

Tumor Microenvironment
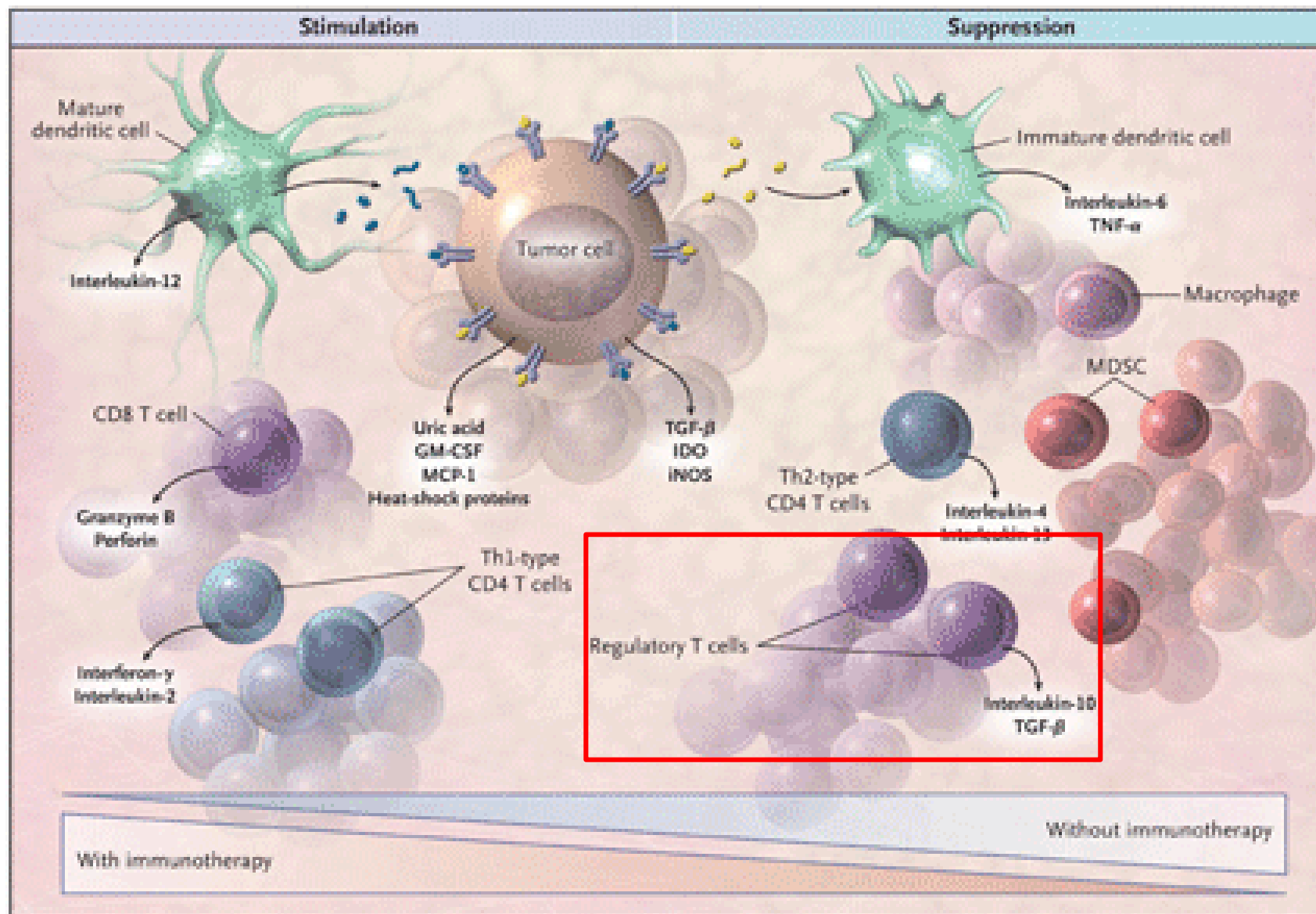
Regulatory T cells (Tregs)

- CD4$^+$ T cells that also express CD25$^+$ Foxp3$^+$

- Produce immunosuppressive cytokines like IL-10 and TGFβ

Lessons and Take Home Messages

- The immune system can be broadly divided into the innate (kills on demand) and adaptive (forms memory) immune arms

- Understanding how immune cells function will improve our understanding of how immunotherapies for cancer work

- Immune cells can also be hijacked by tumors to create an immunosuppressive microenvironment and protect the tumor from elimination

Questions?

Email ccapitini@pediatrics.wisc.edu

Phone (608) 262-2415

Twitter @CapitiniMD