Immunology and Immunotherapy 101 for the non-immunologist

SITC Advances in Immunotherapy

Seattle, WA 2016

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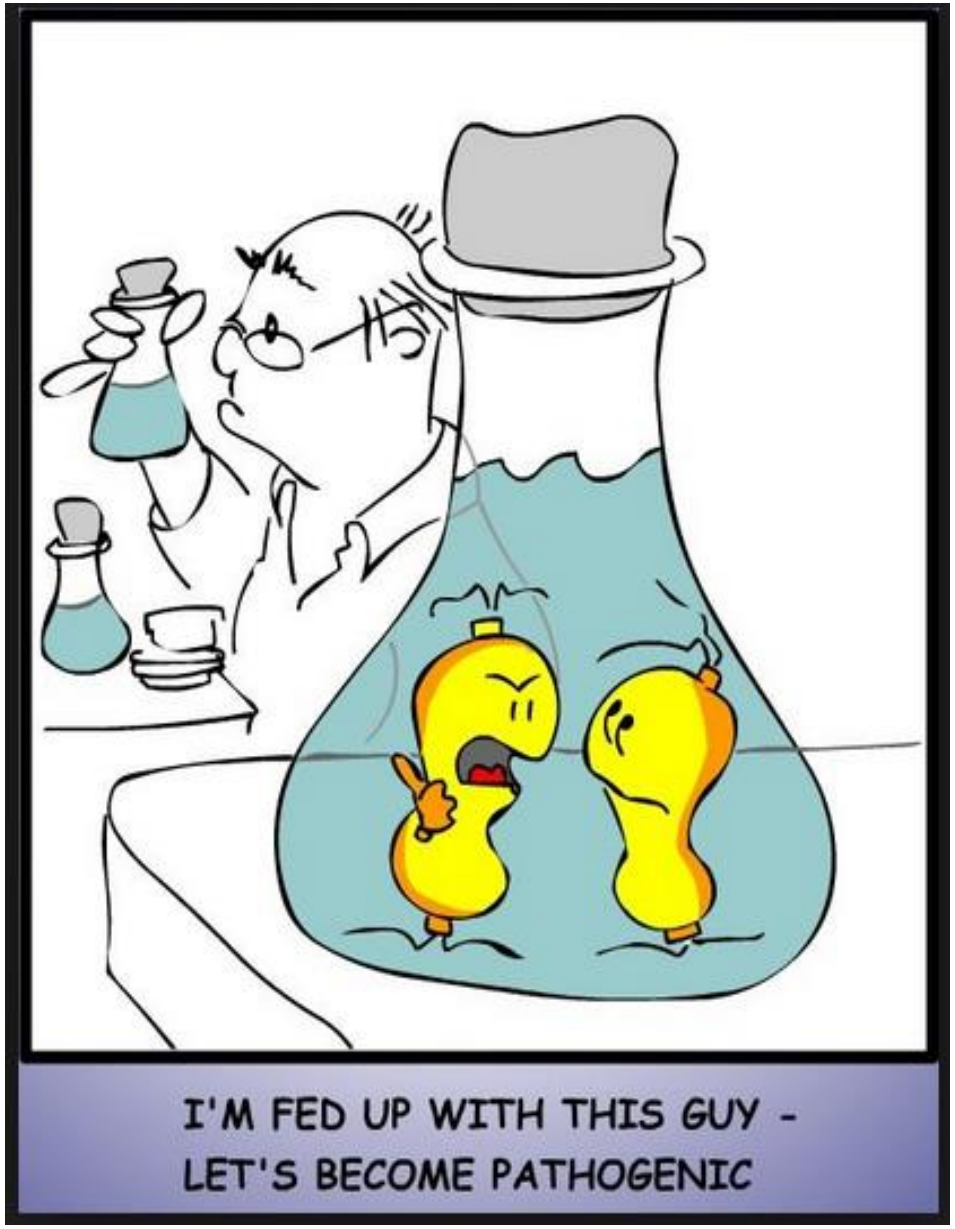
Disclosures

- Advisory Board:
  - Bristol-Myers Squibb, Merck & Co., Inc., Novartis Pharmaceuticals, Pfizer, Sanofi Genzyme, Seattle Genetics
- Consulting fees:
  - Amgen, Astellas
- Contracted research:
  - Medimmune/AstraZeneca, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, ImClone Systems, Inc., Merck & Co. Inc., Novartis Pharmaceuticals, Pfizer, VentiRx Pharmaceuticals

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

Terminology

- **Immunology** – study of host defense systems
- **Immunity** – ability of the host to protect itself against foreign organisms
- **Immune system** – tissues, cells, molecules mounting an ***immune response***



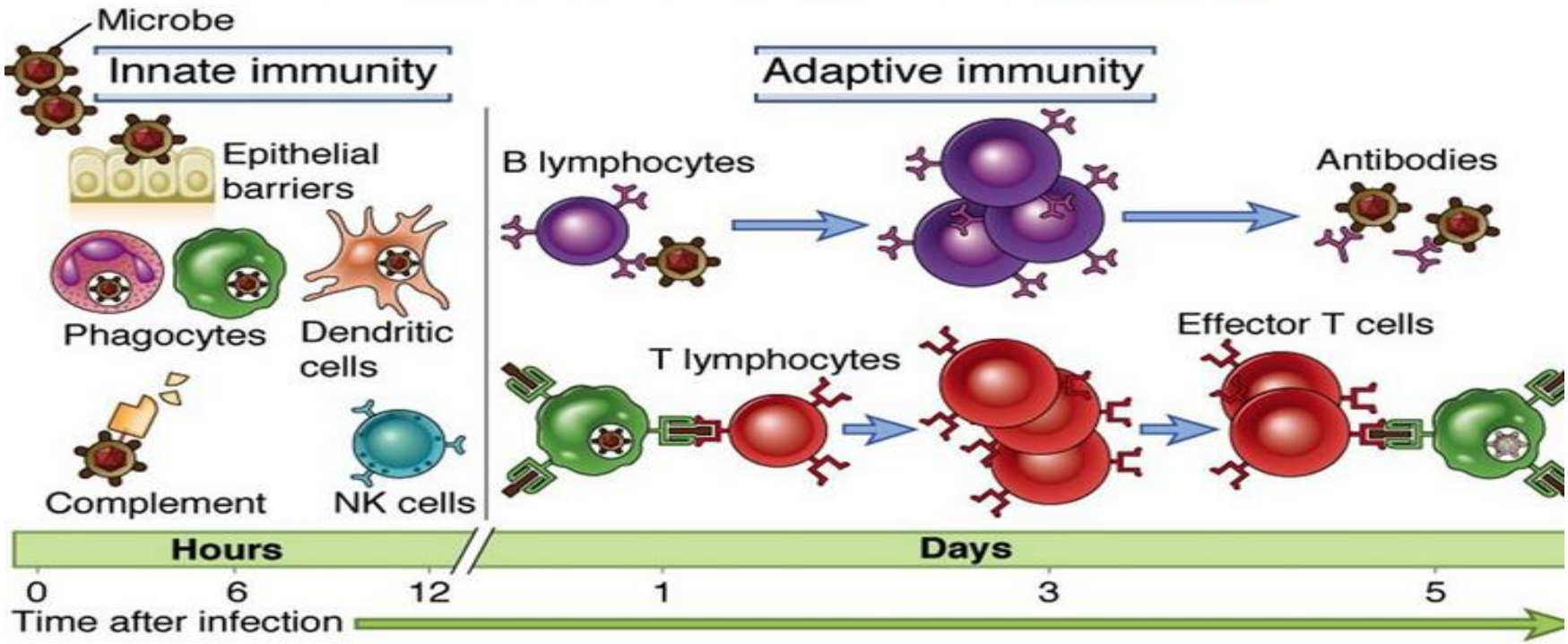
Types of immunity

- **Innate** – aka natural immunity – general protection - external barriers such as skin, always present and ready

- **Passive immunity** – 'borrowed" immunity – short lasting such as antibodies in breast milk

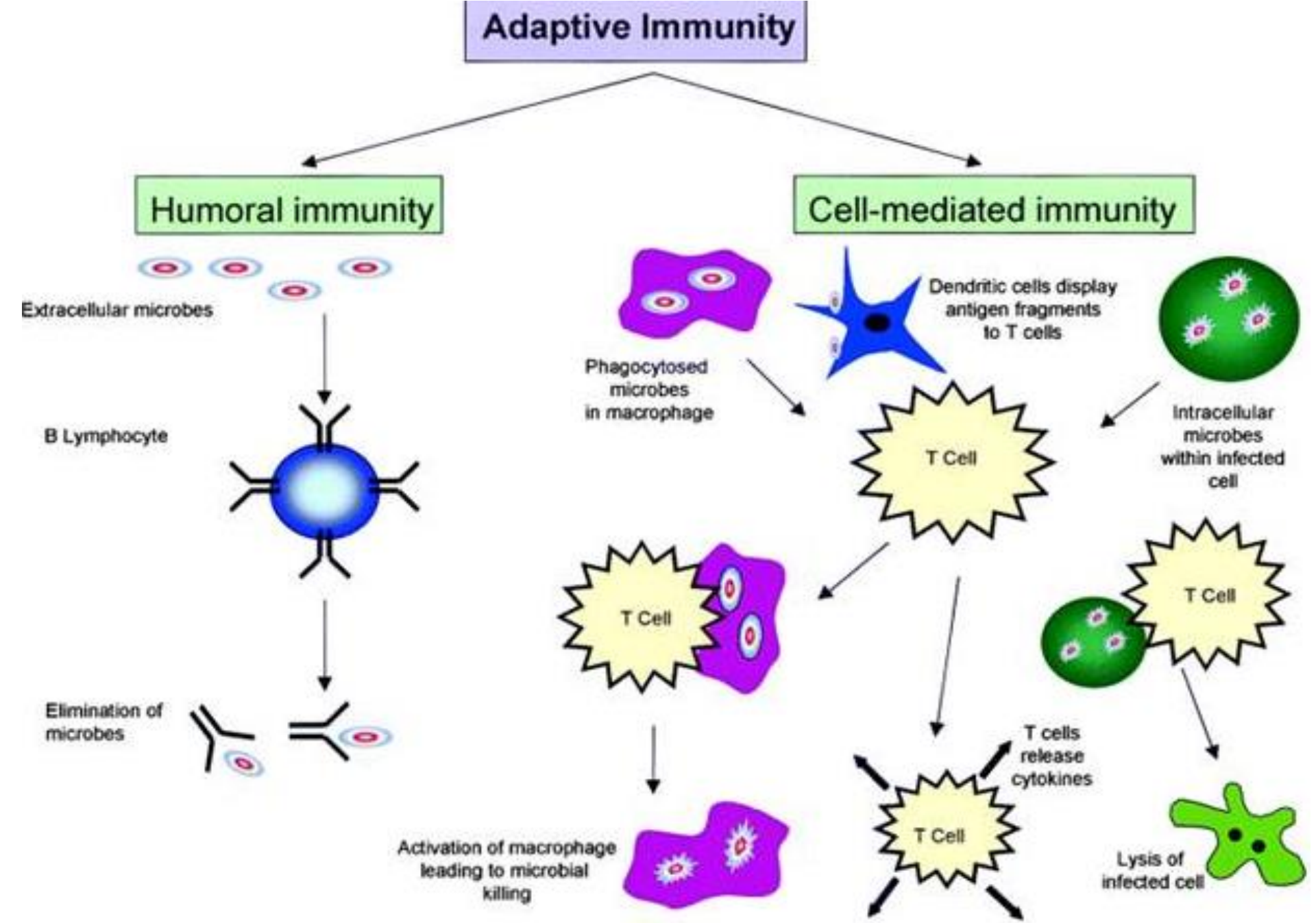
- **Adaptive immunity** – aka active immunity – activated by pathogens - develops through lifetime via exposure to pathogens or vaccination – involves lymphocytes

Innate and adaptive immunity



	Innate	Acquired
	First line of defense, generalized	**Customized and highly specific**
	Barriers – skin, tears, phagocytes, macrophages, NK cells, mast cells, complement	**Antigen presenting cells, T cells, B cells, antibodies and immunity**
Onset rate	**Early, immediate response**	**Late, slow, weeks**
Responses	**Non-specific, antigen independent**	**Very specific, antigen dependent**
Memory	**No**	**Yes**

http://biology-forums.com/index.php?action=gallery;sa=view;id=1488



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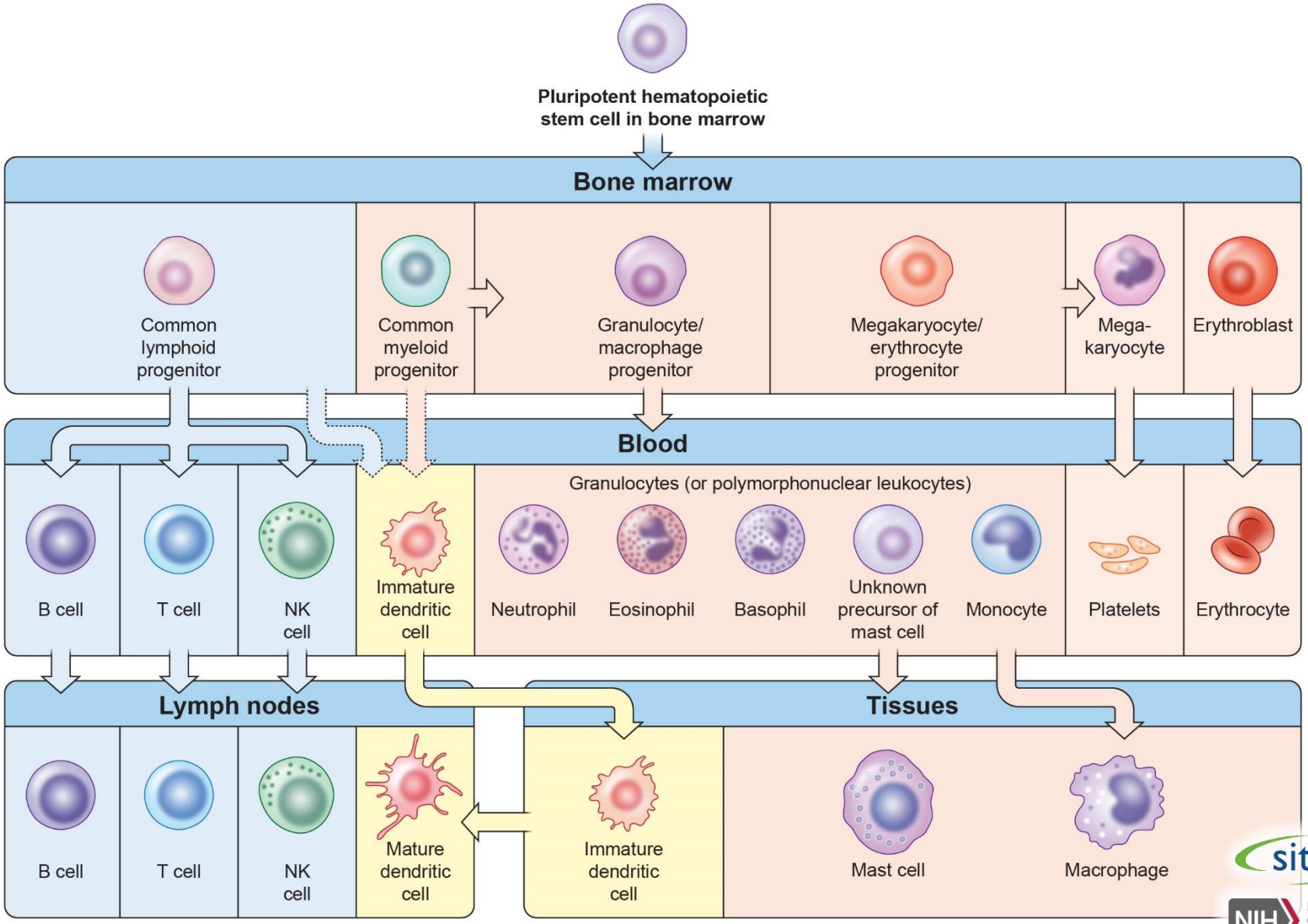
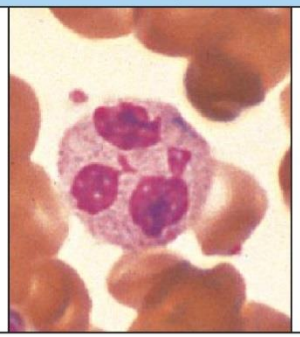
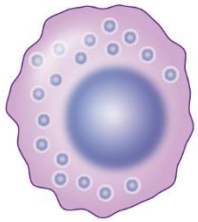
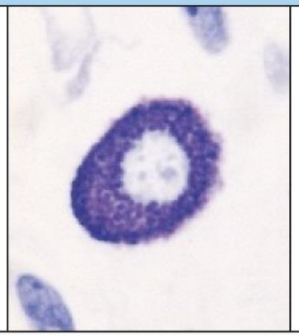
Immune cells are derived from stem cells in the bone marrow

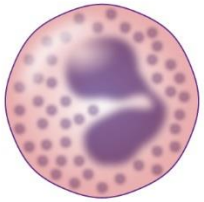
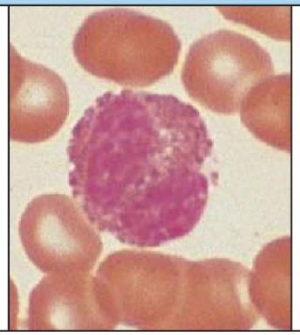


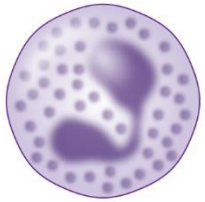
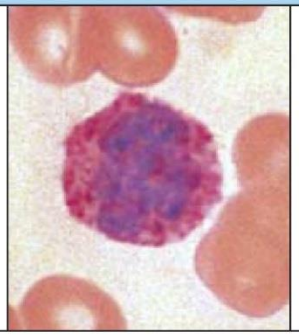
Granulocytes

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

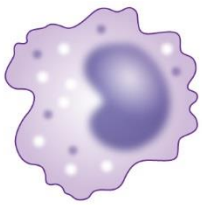
Basophil		
		Promotion of allergic responses and augmentation of anti-parasitic immunity (Blood mast cells)

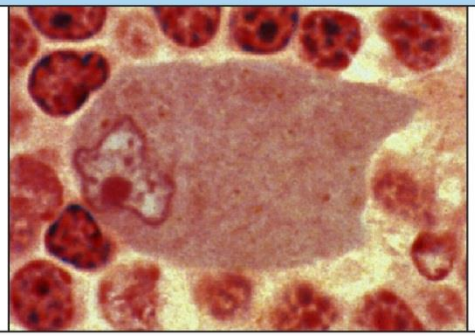
Neutrophils, eosinophils and basophils are sometimes referred to as polymorphonuclear leukoyctes (PMNs)

Phagocytes

Neutrophils, macrophages and dendritic cells

Macrophage



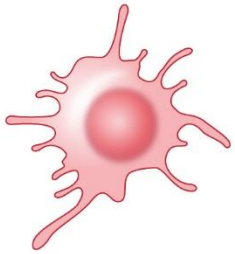


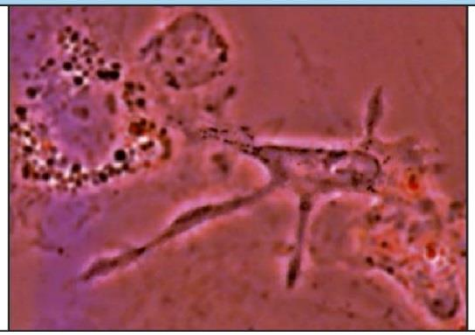
1º Phagocytosis and activation of bactericidal mechanisms

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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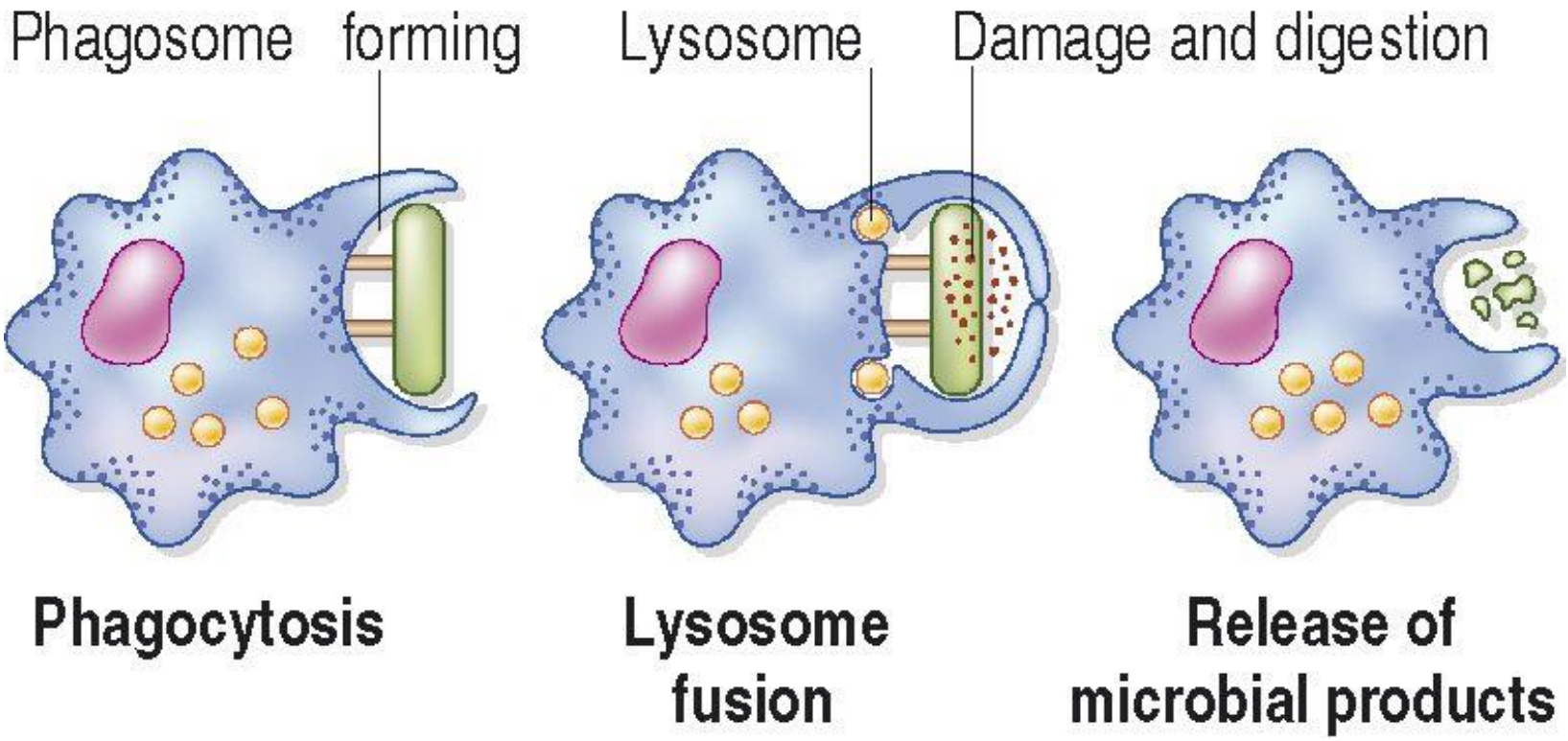
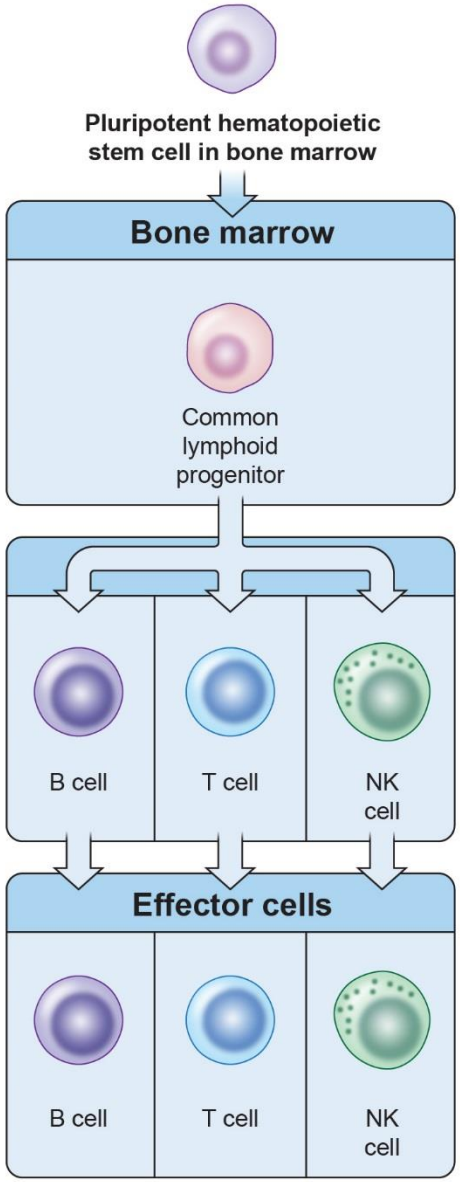
Phagocytosis



Roitt I, Brostoff J, Male D, Immunology, Mosby, 2001

Lymphocytes



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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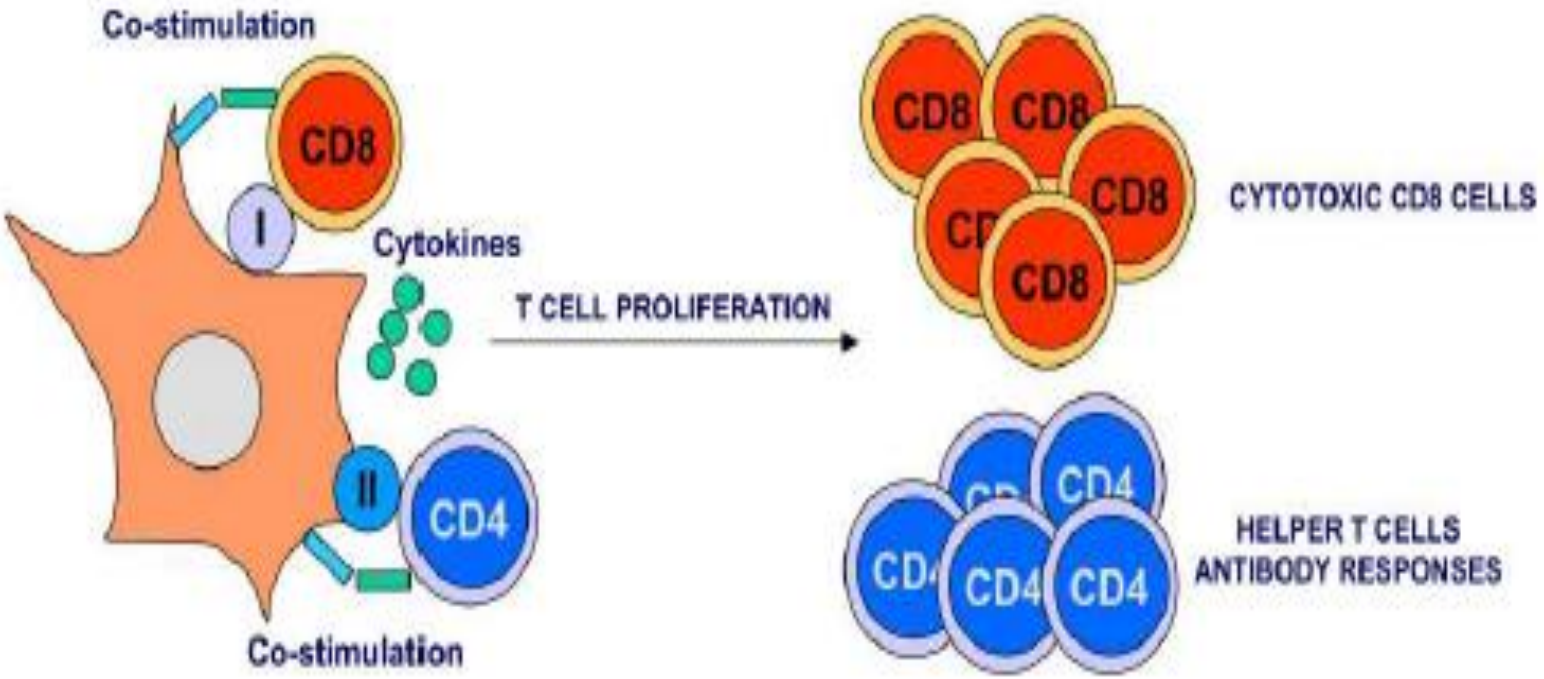
T – lymphocytes

-involved in ***cell mediated immunity***

Mature and migrate to lymphoid organs to await contact with antigens

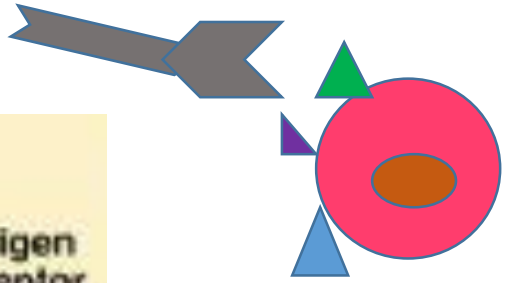
Two Types: CD4 and CD8

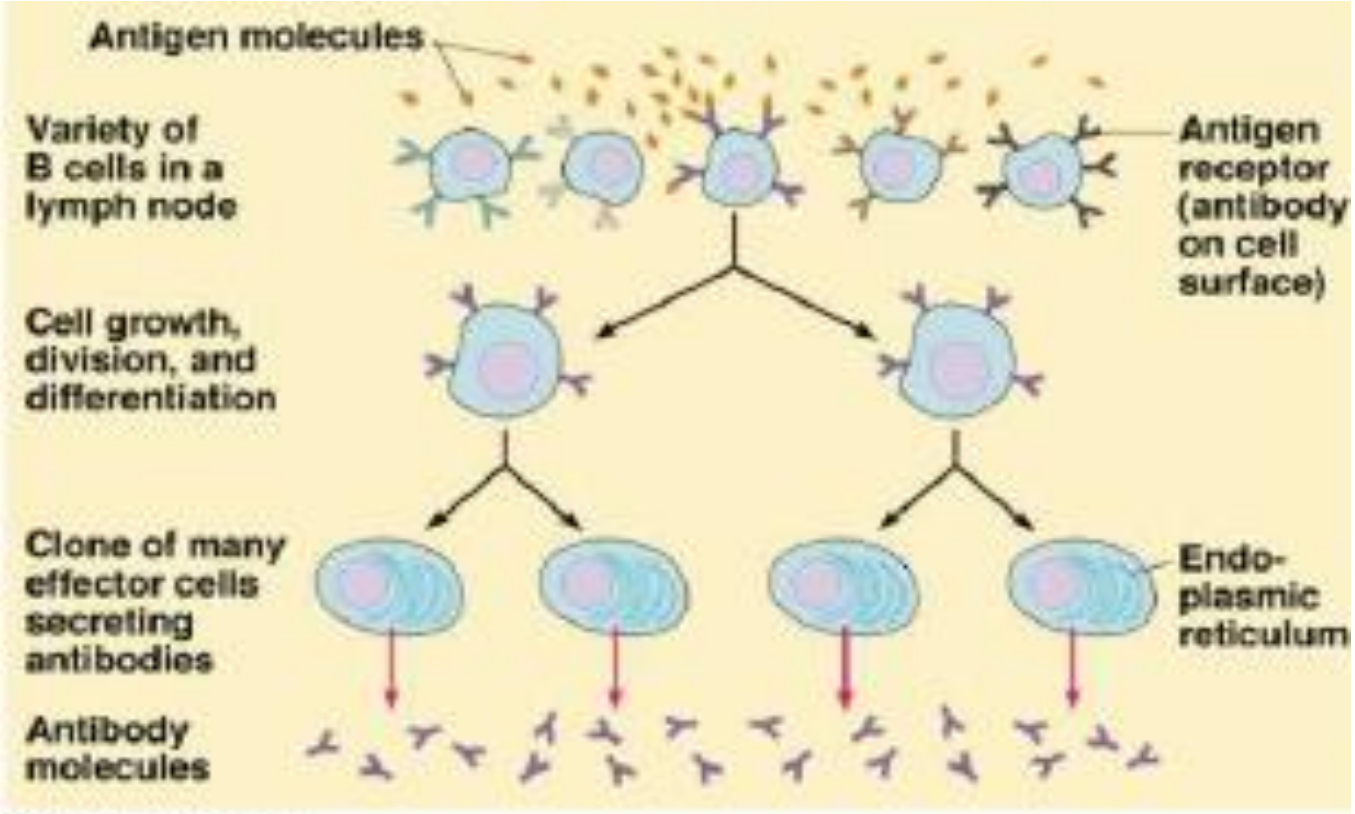


B lymphocytes

– involved in ***humoral immunity***

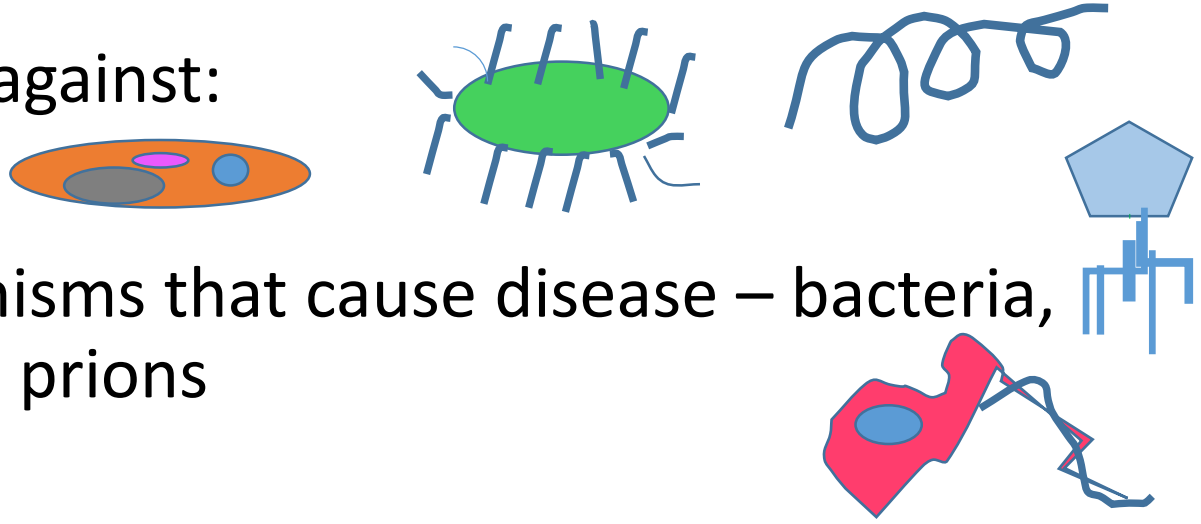
- Respond to antigen stimulation to produce antibodies - antibodies produce immunity





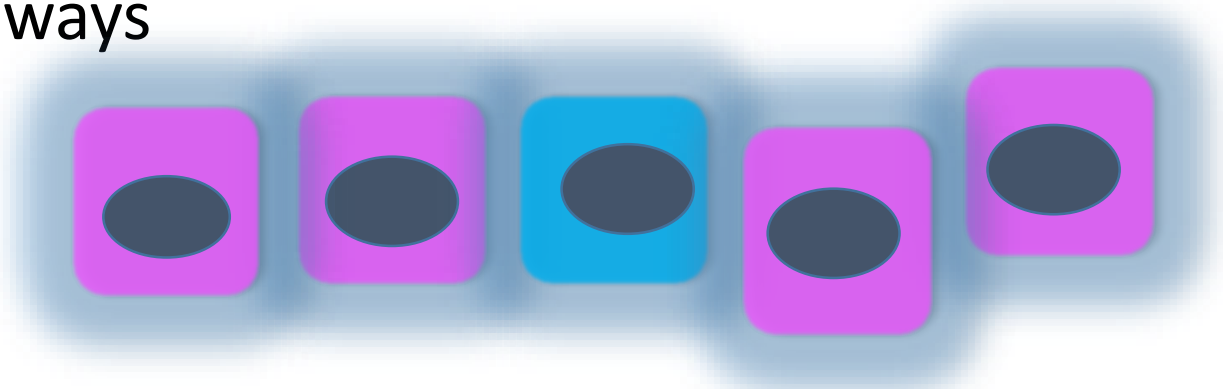
Major roles of the immune system

Fight and protect against:



Pathogens – organisms that cause disease – bacteria, viruses, fungi, and prions

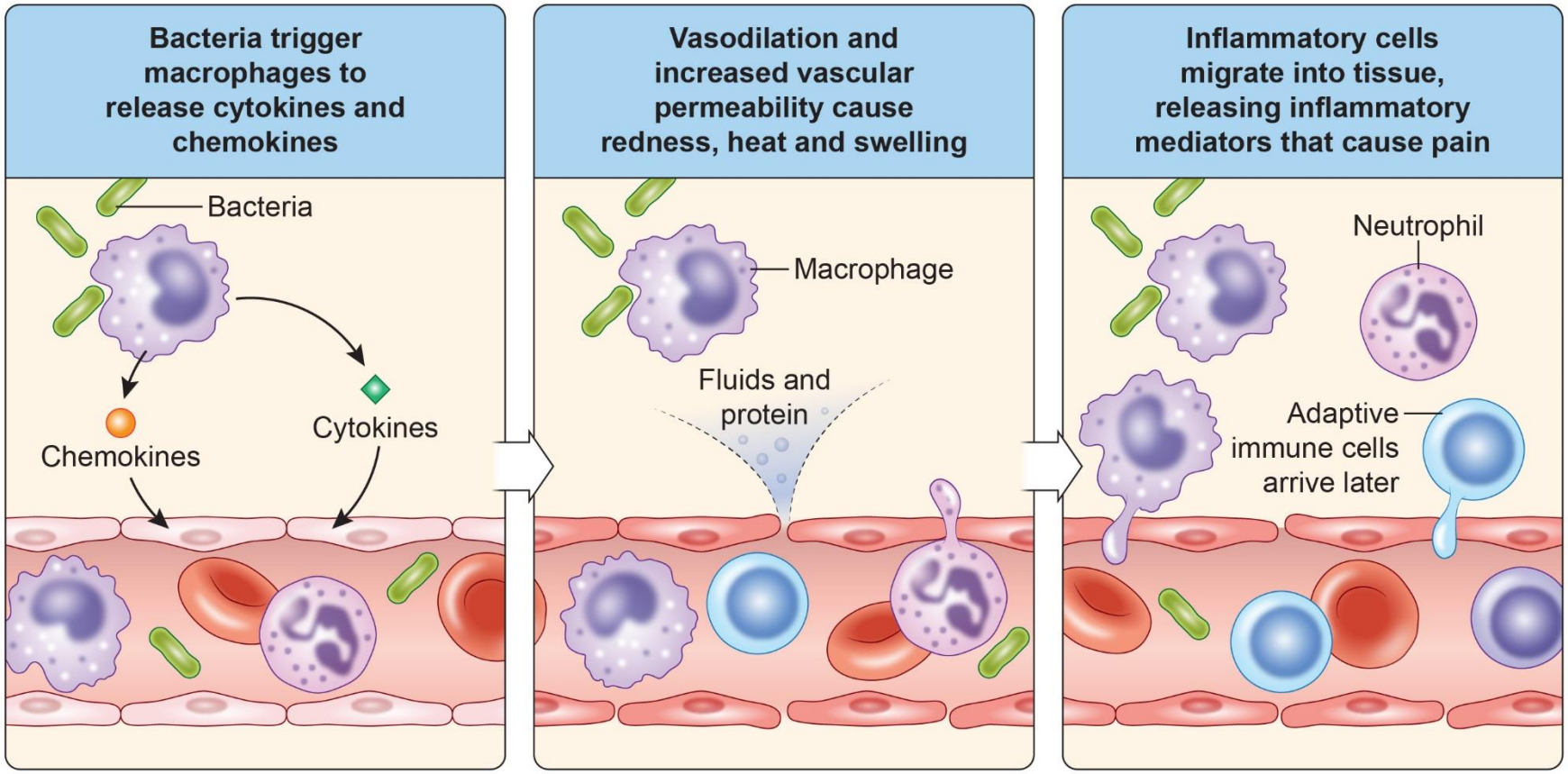
Cancer - aberrant uncontrolled growth and spread of what was originally normal cells with gene mutations, oncogenes and abnormal growth signaling pathways



Immune system challenges

PATHOGEN	CANCER
• Many varieties and types to infect us	• Many or most of our cells in the body can become cancerous
• Usually antigens (identifiers) appear different but – some pathogens (eg viruses) invade normal cells and use them to propagate and grow and take over	• Similar to normal cells and many of the same identifiers as normal cells or tissues
• Possibility of mutating or changing	• Possibility of mutating or changing
• Potential in hiding from the immune system or responses to cause chronic infection	• Potential in hiding from the immune system or responses to continue growth

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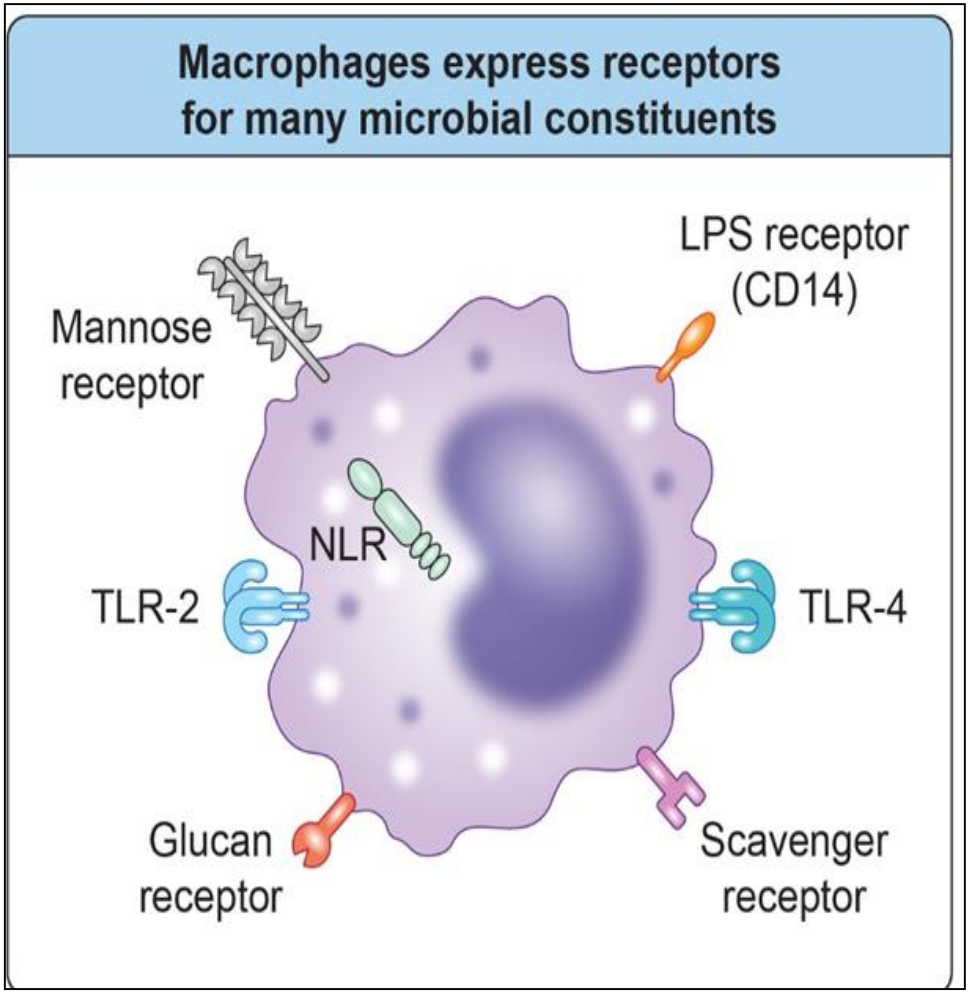
Innate responses are initiated upon recognition of "danger signals" by pattern recognition receptors (PRRs)



"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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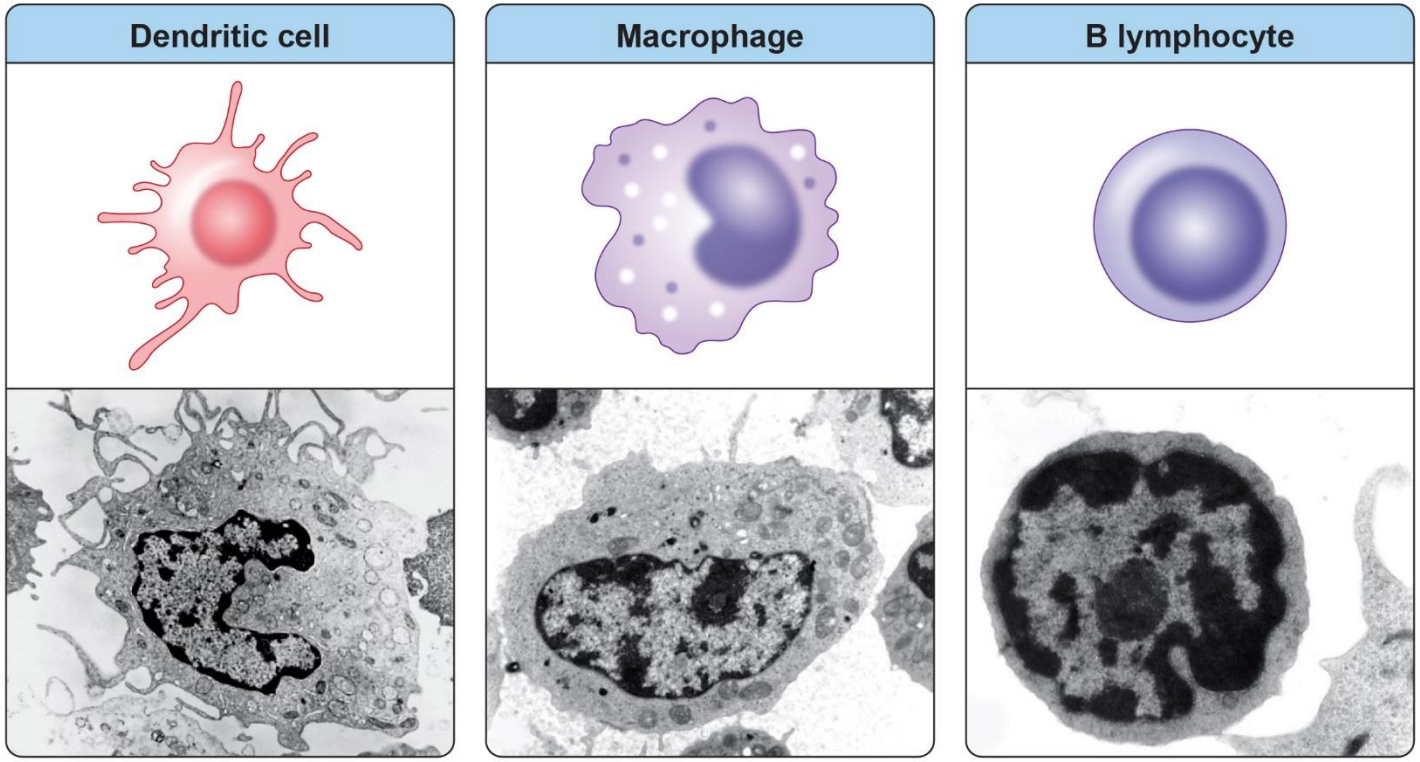
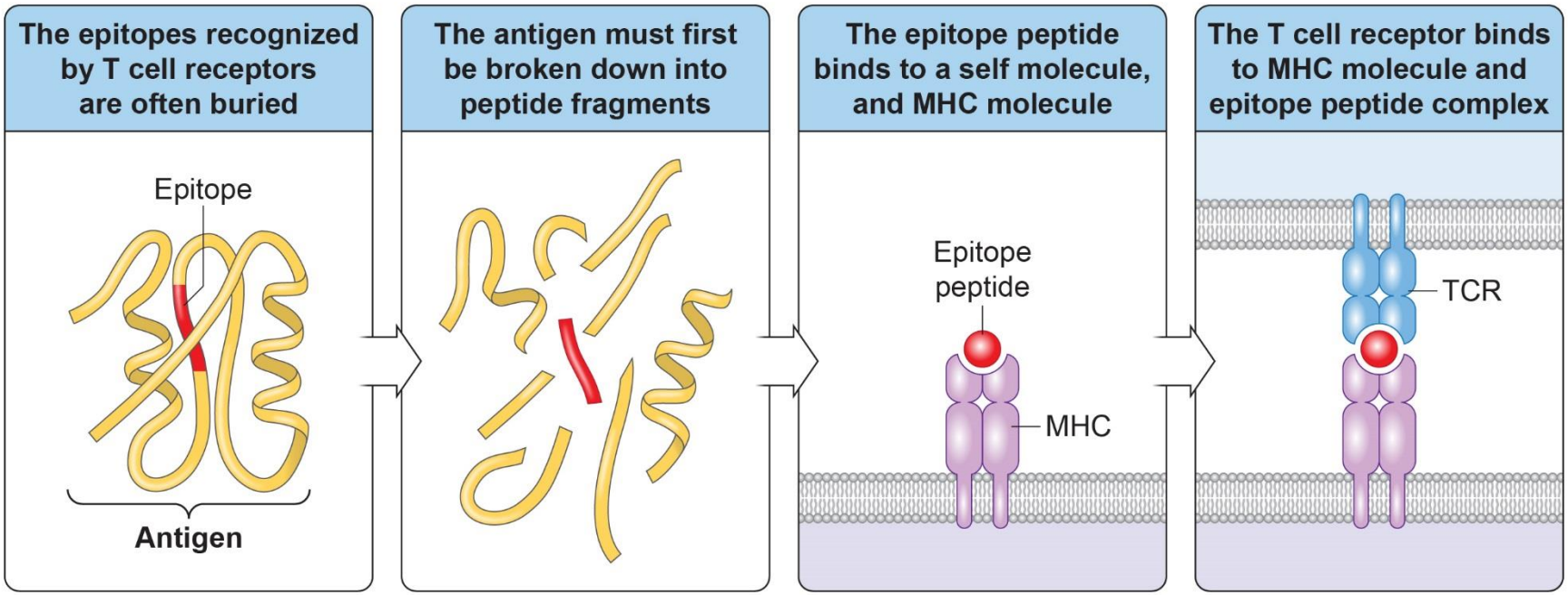
Antigen processing and presentation

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)

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



MHC = Major Histocompatibility Complex

The immune system needs to recognize self versus non-self

- CD8 T cells recognize antigen presented by MHC class I
- CD4 T cells recognize antigen presented by MHC class II

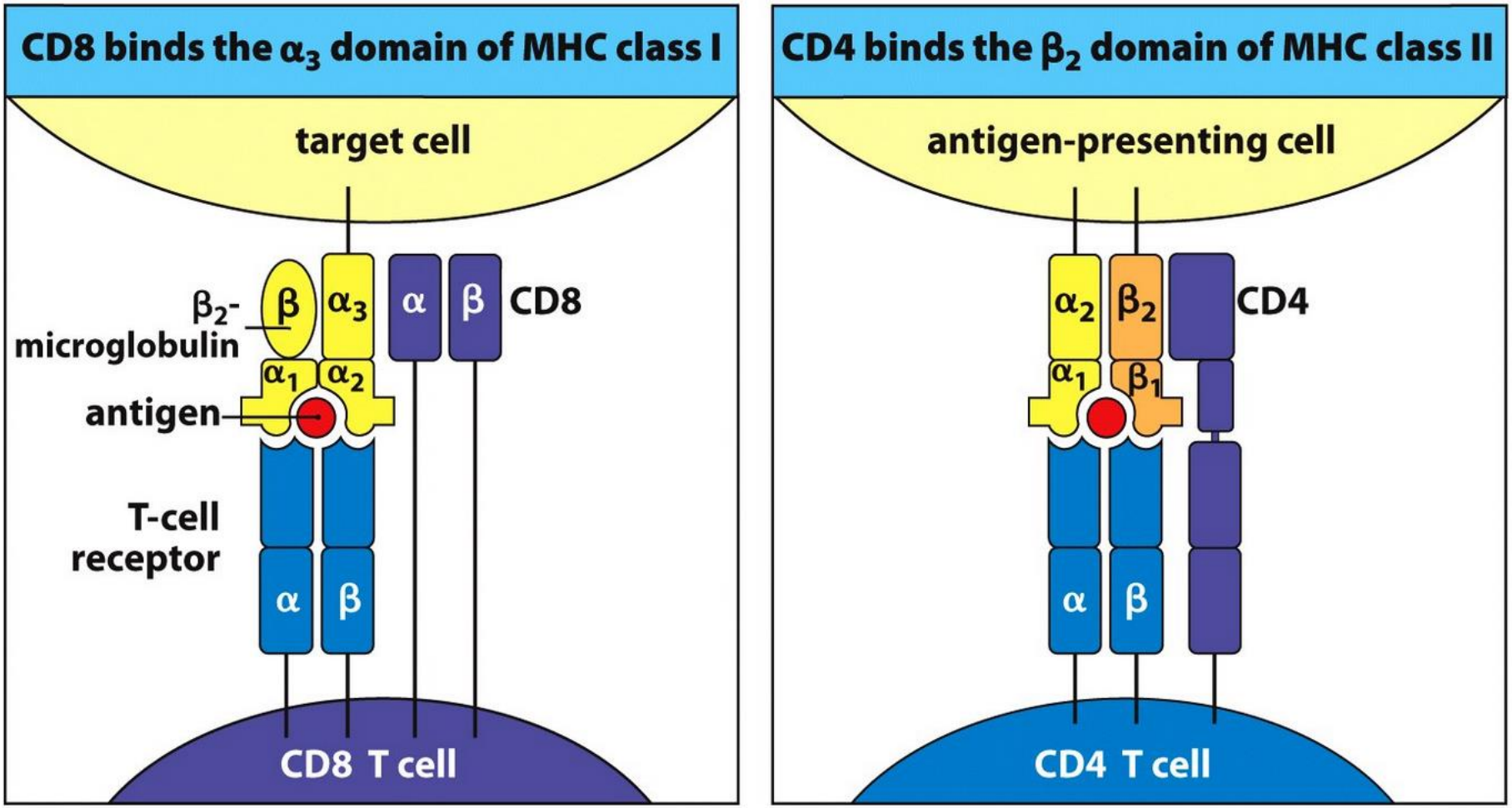
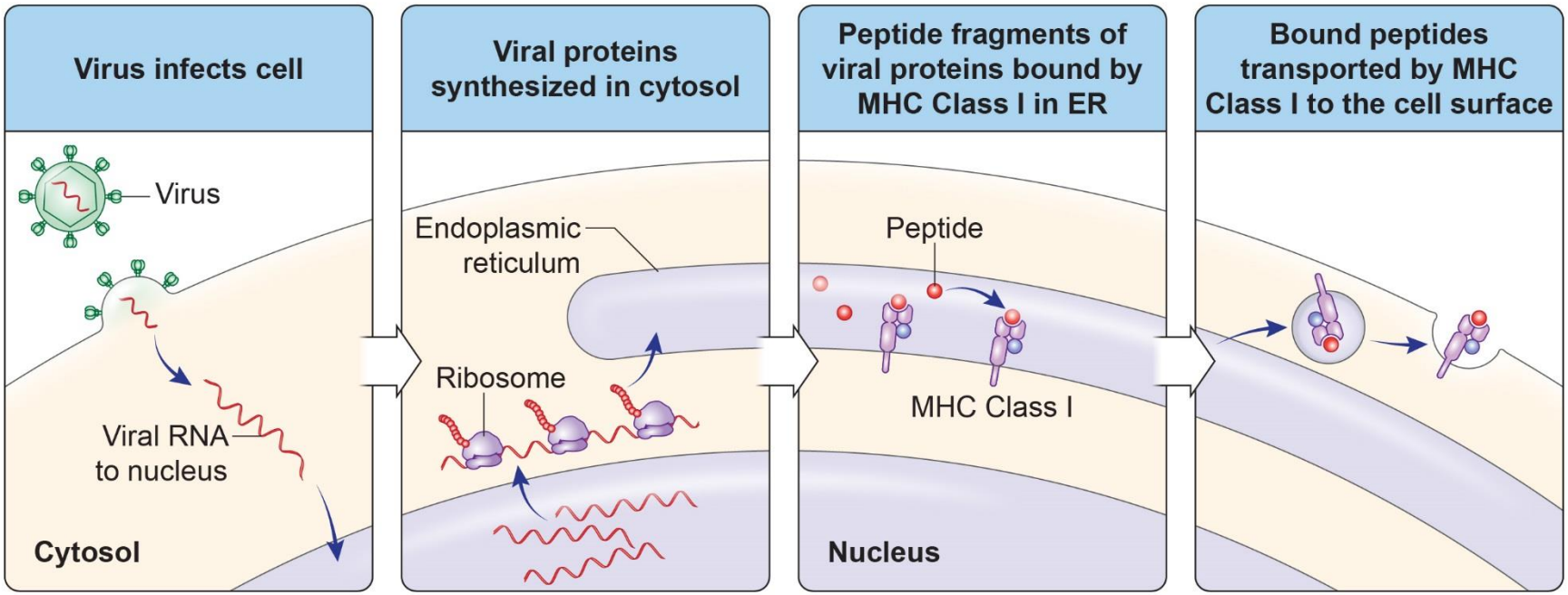


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

http://course1.winona.edu/kbates/Immunology/Chapter5-09.htm

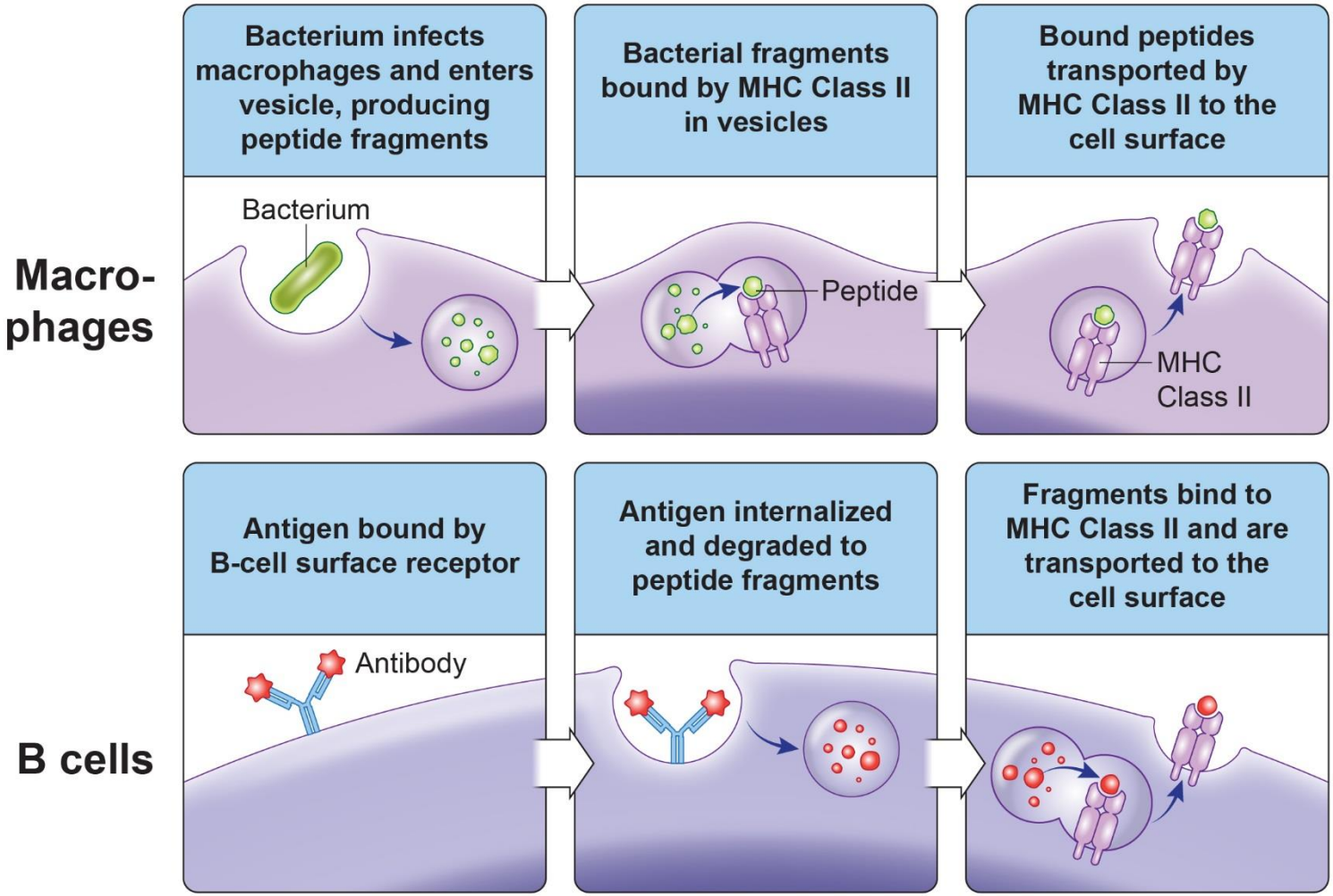
MHC Class I presents peptide antigens to CD8 T cells



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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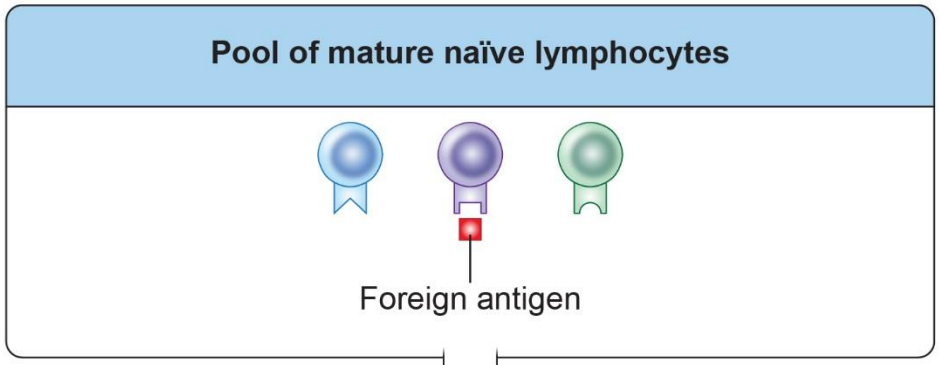
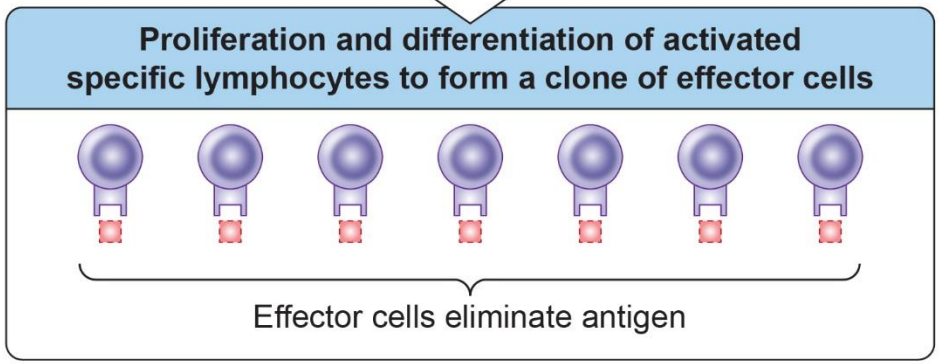
Lymphocyte activation

Naïve



Cells that recognize specific Ag are very rare

Activated or effectors



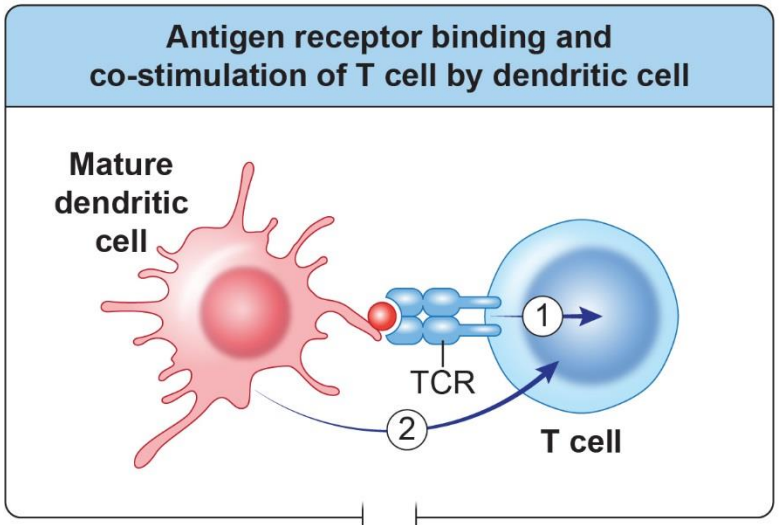
Results in:
- Expansion
- Acquisition of effector functions

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

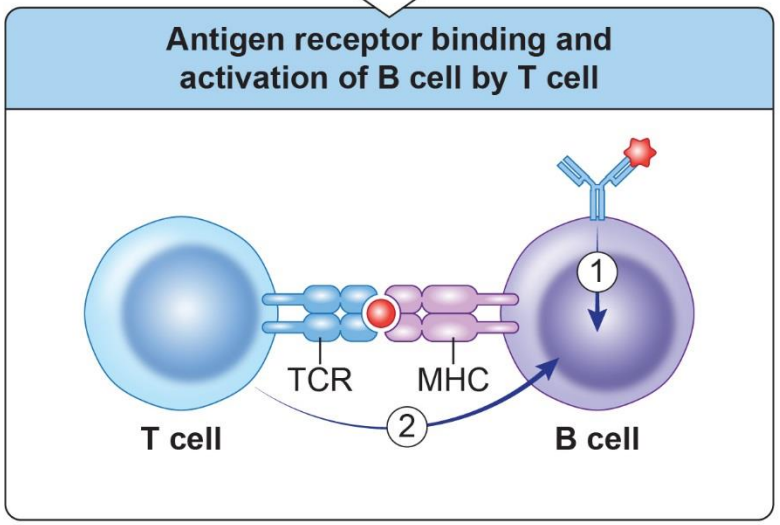
Differentiate into long-lived memory lymphocytes

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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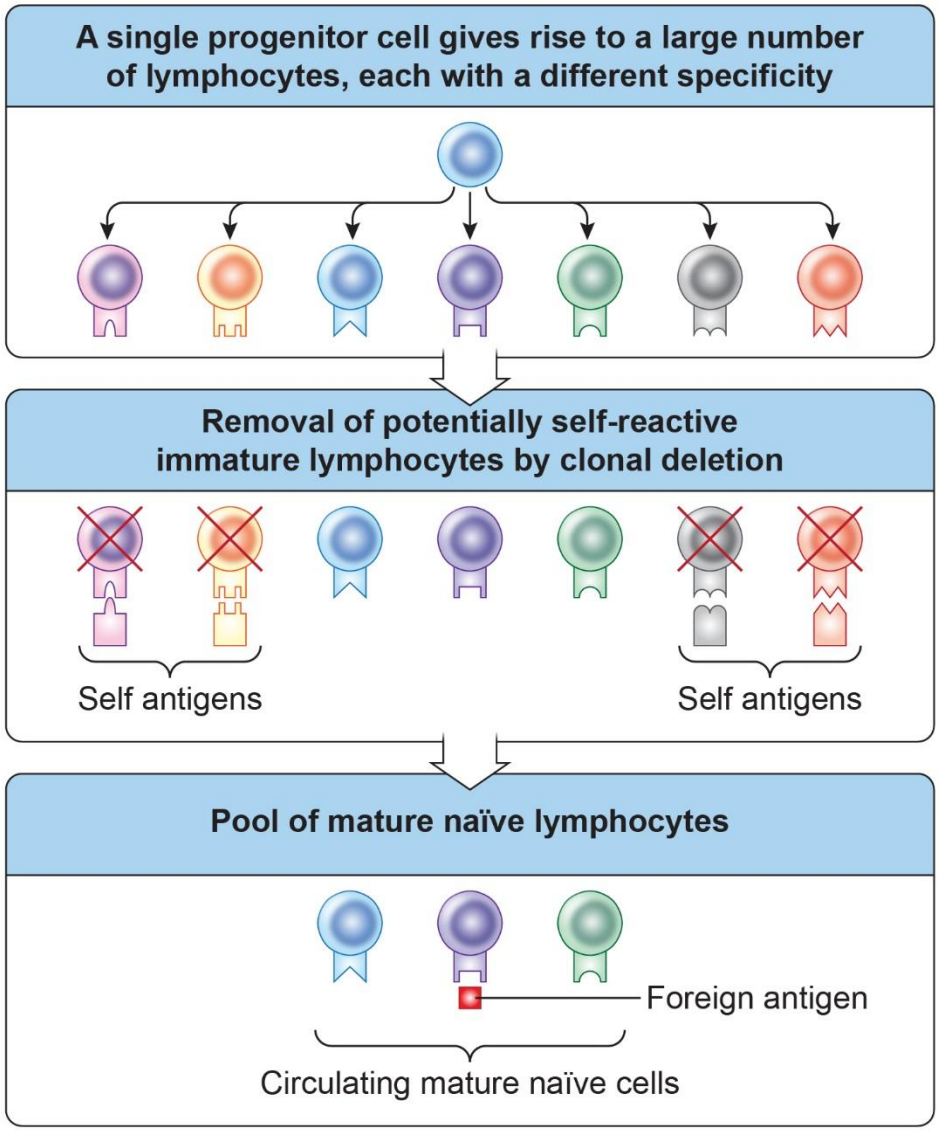
Generating lymphocytes that each have a unique specificity



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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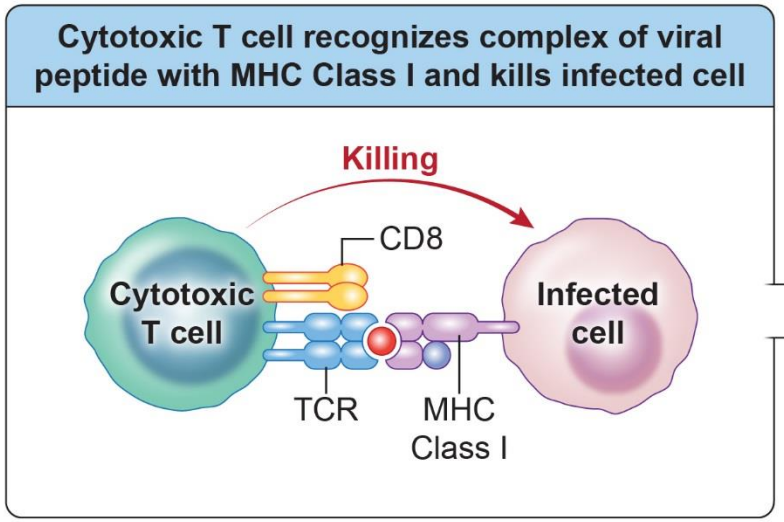
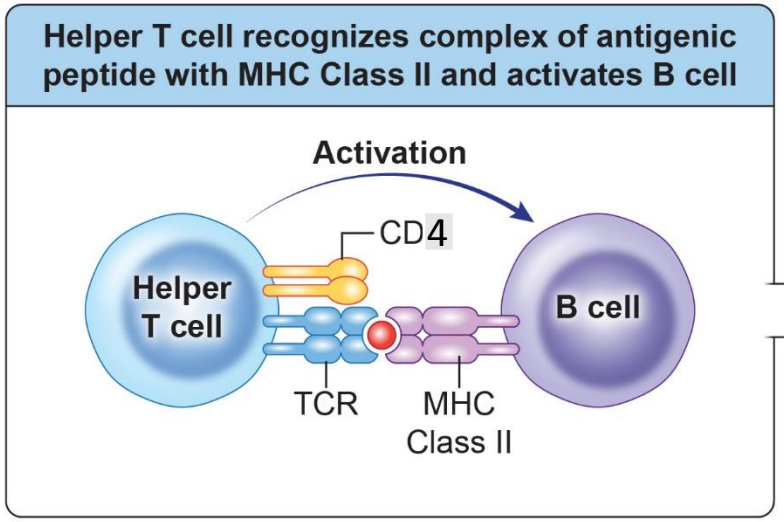
Effector mechanisms of adaptive immunity

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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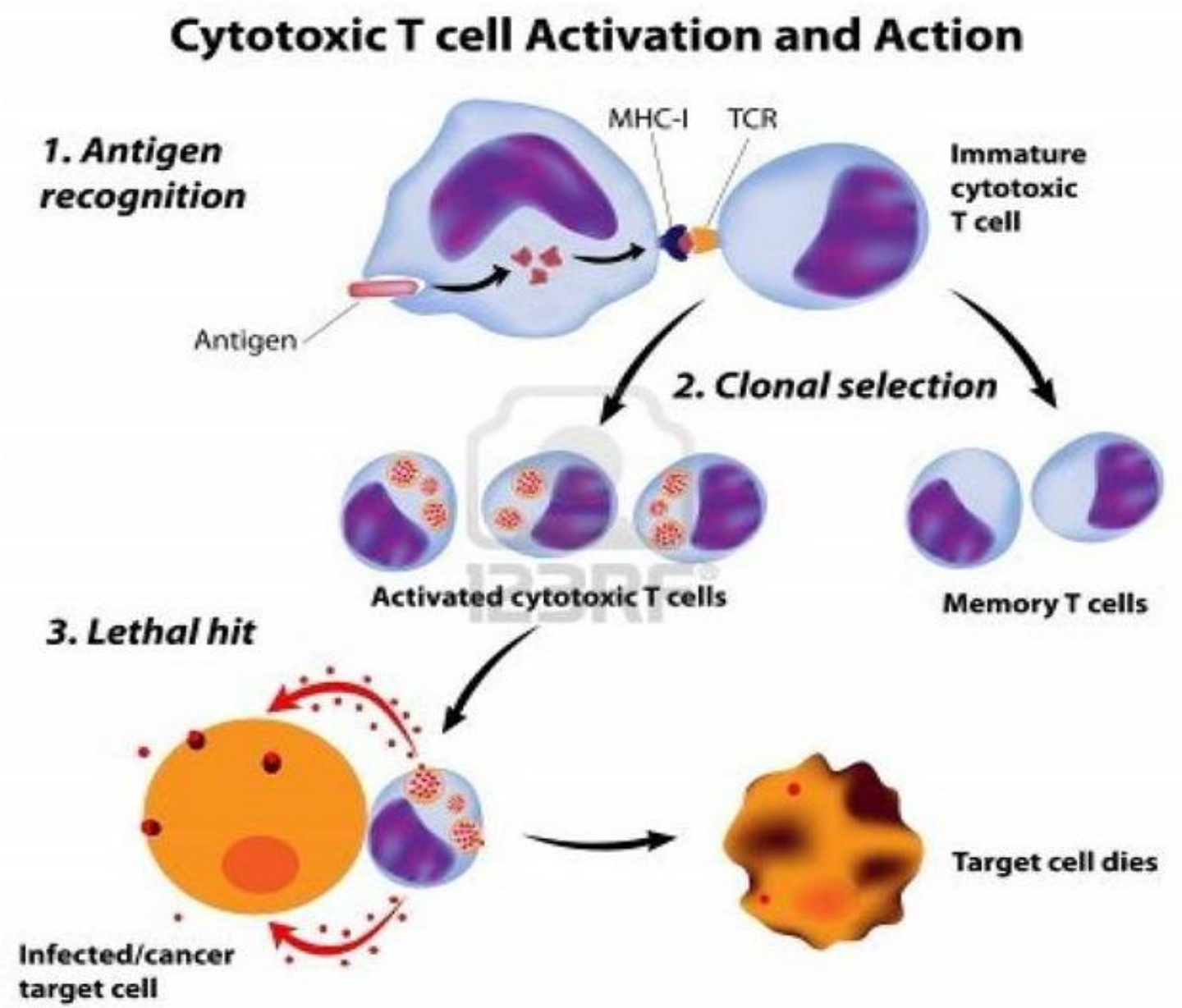
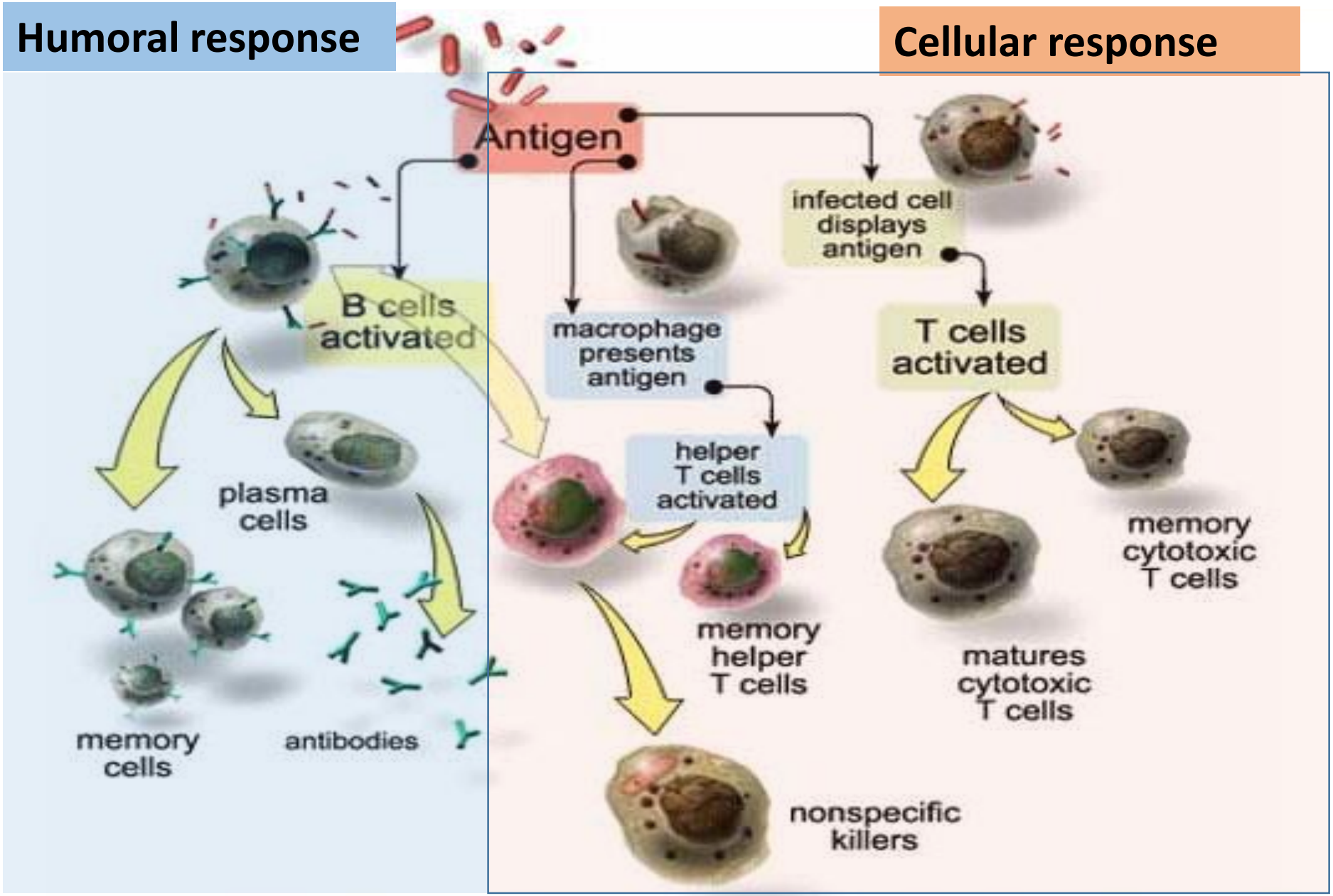


http://intranet.tdmu.edu.ua/data/kafedra/internal/in_mow/classes_stud/uk/med/lik/ptn

ADAPTIVE RESPONSE

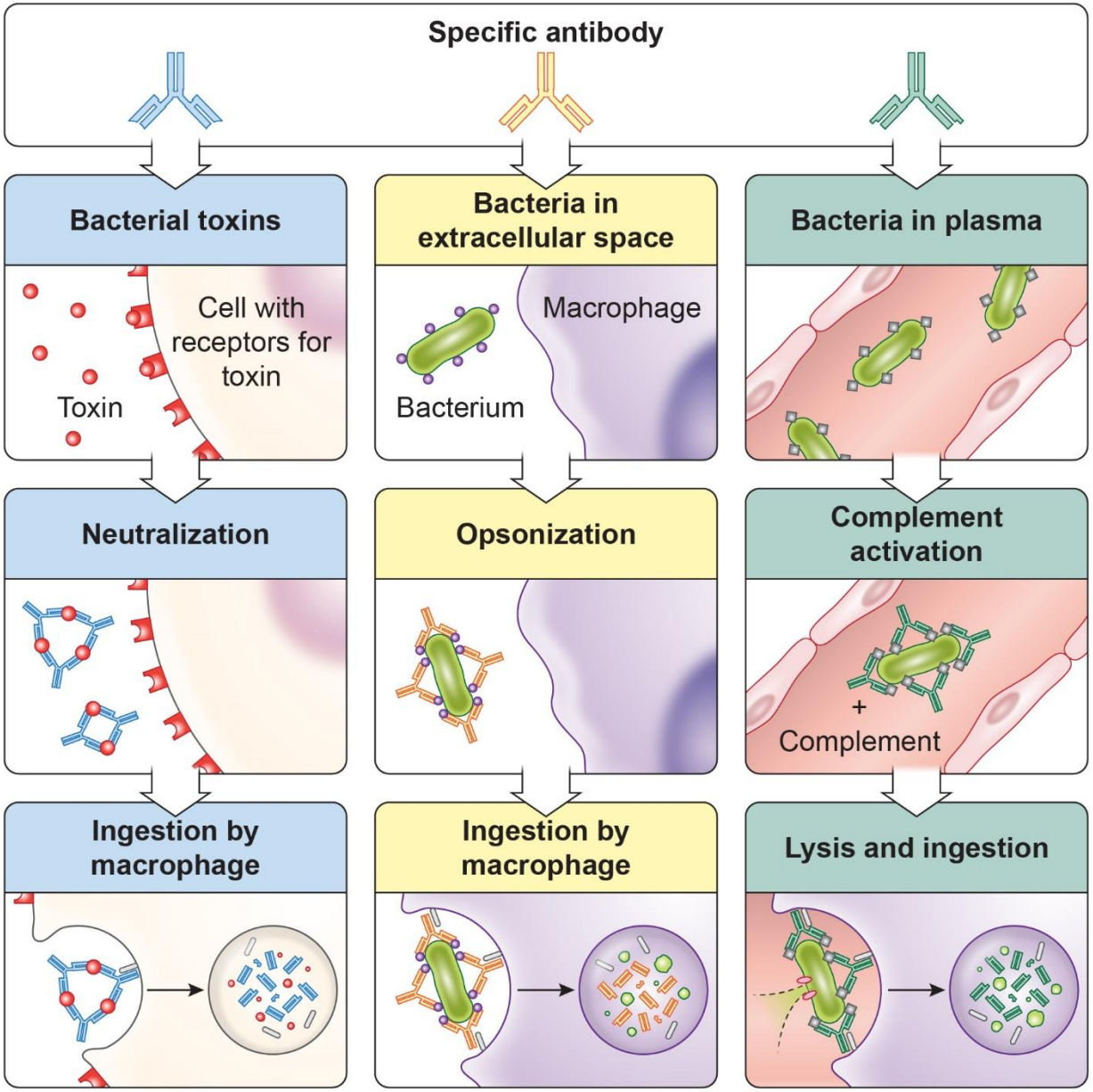
Humoral response

Cellular response



(Source: the Human Immune Response System www.uta.edu/chagas/images/immunSys.jpg)

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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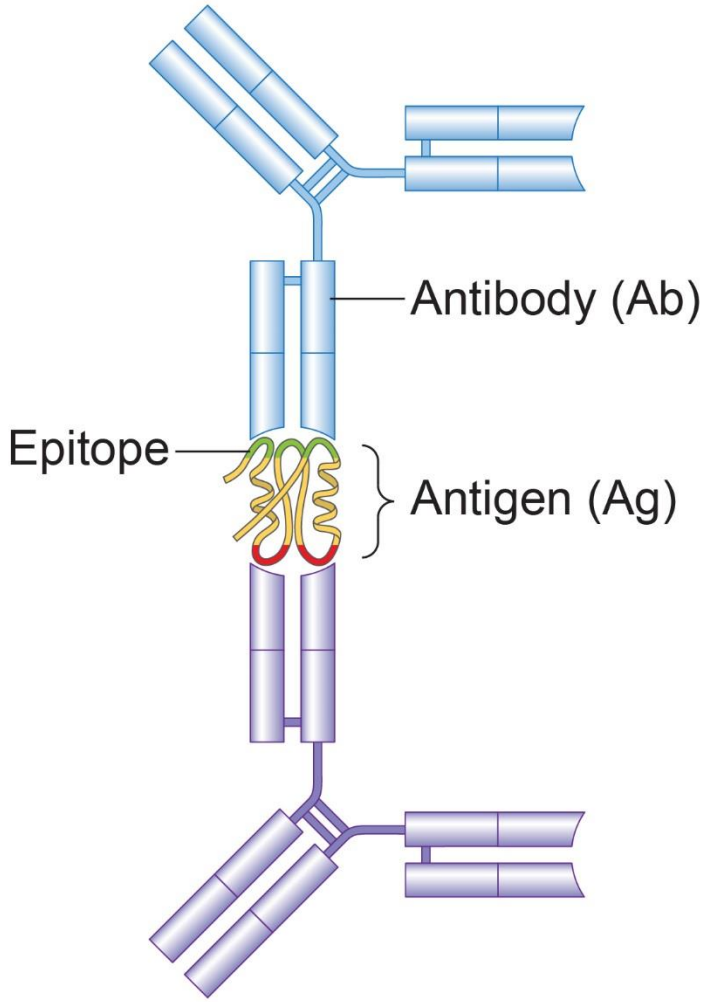
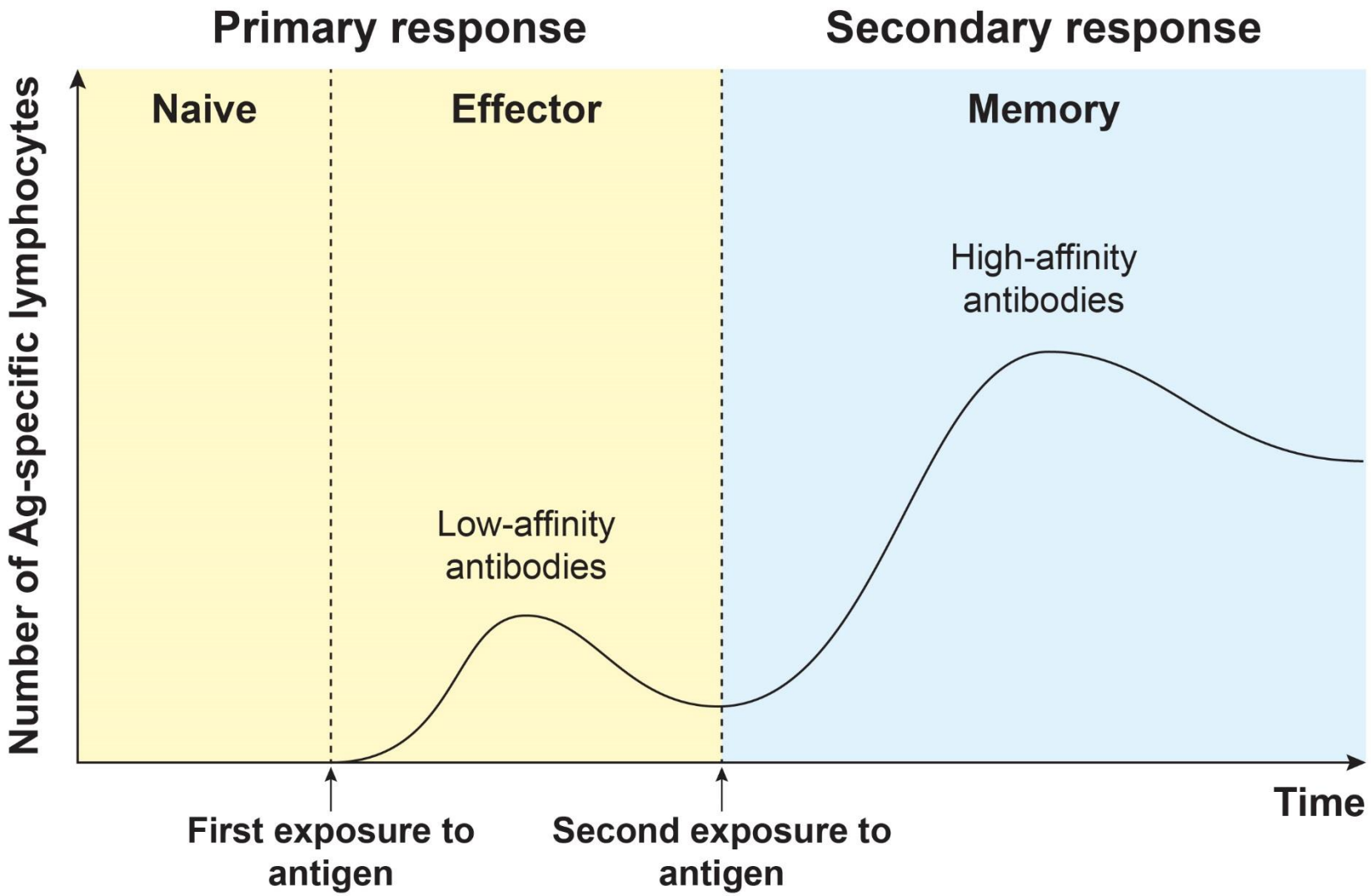
Antigen recognition by antibodies

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



Significance of immunological memory



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

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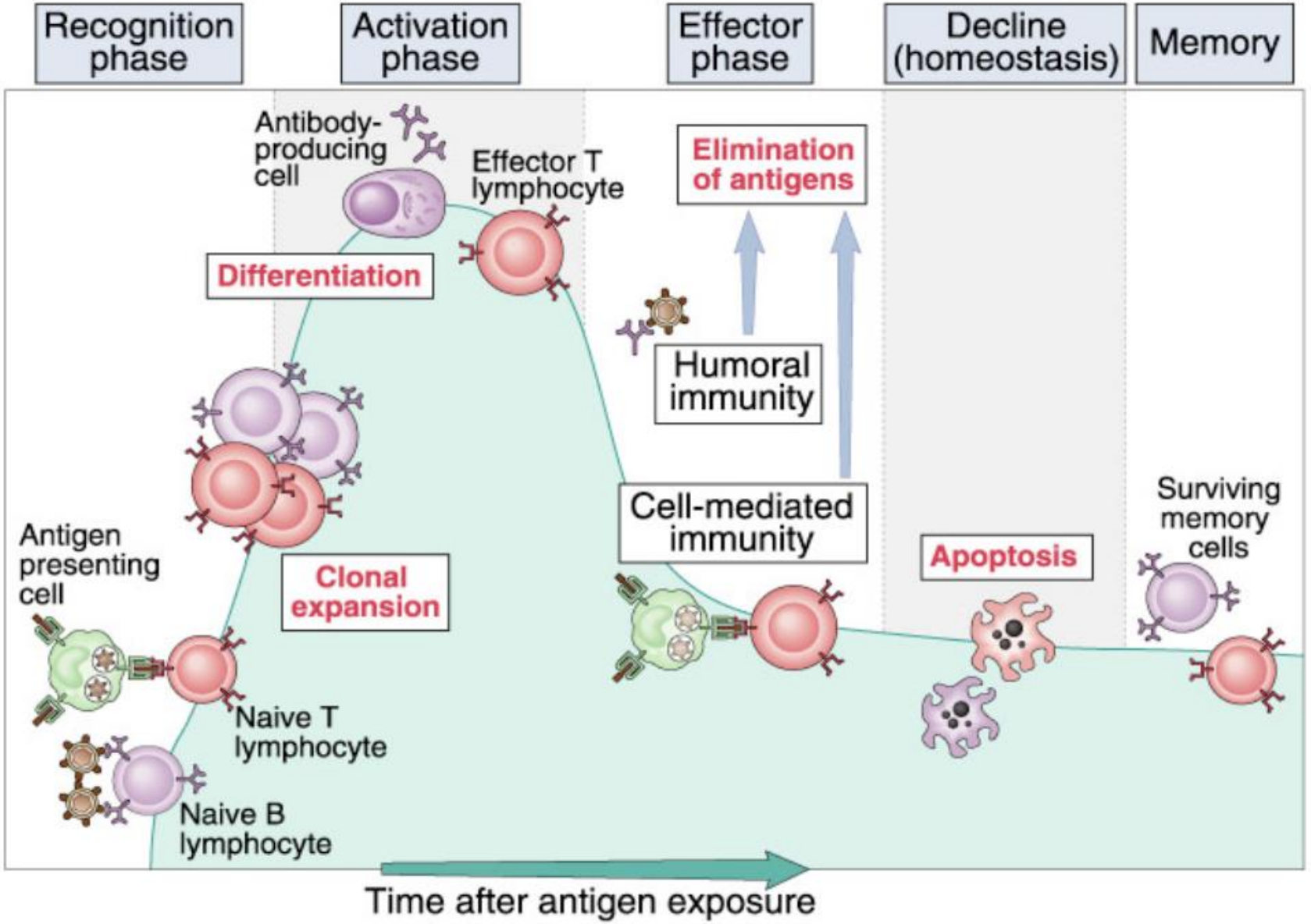
Phases of adaptive immune responses.



Immune responses can be beneficial or harmful

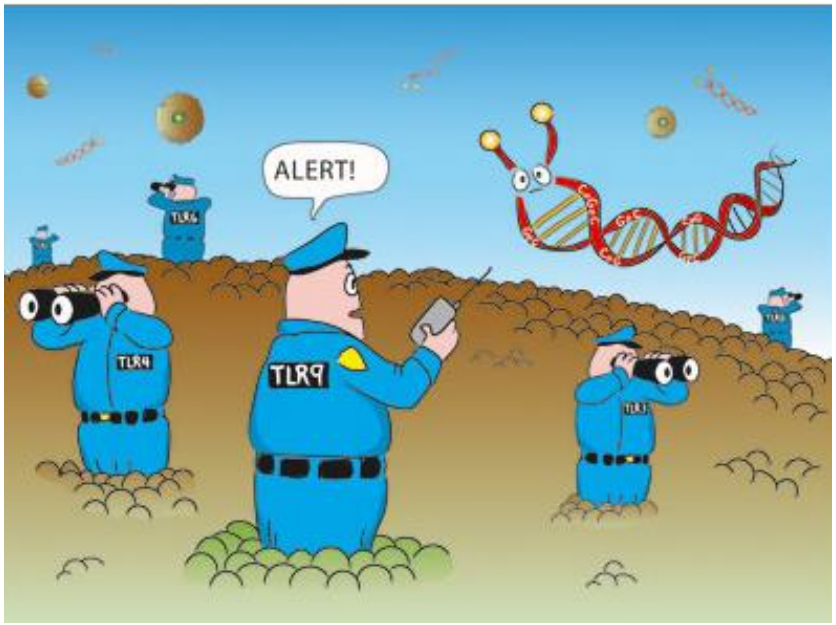
Antigen	Effect of response to antigen	
	Normal response	Deficient response
Infectious agent	Protective immunity	Recurrent infection
Innocuous substance	Allergy	No response
Grafted organ	Rejection	Acceptance
Self organ	Autoimmunity	Self tolerance
Tumor	Tumor immunity	Cancer

Effectiveness of mechanisms mediating immune tolerance and regulation

Immune surveillance and immunoediting

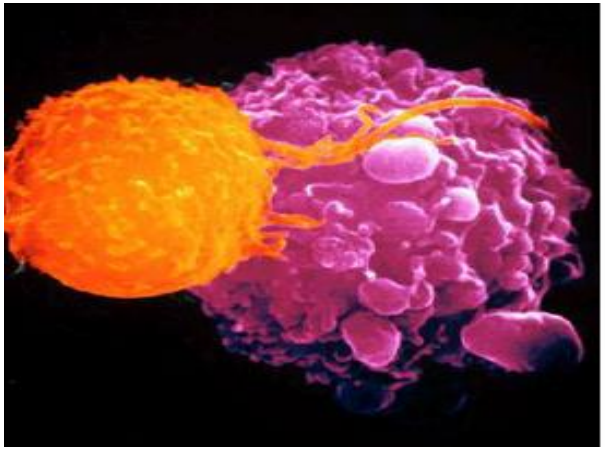
Immune surveillance

- immune system cells – lymphocytes recognize and eliminate transformed cells



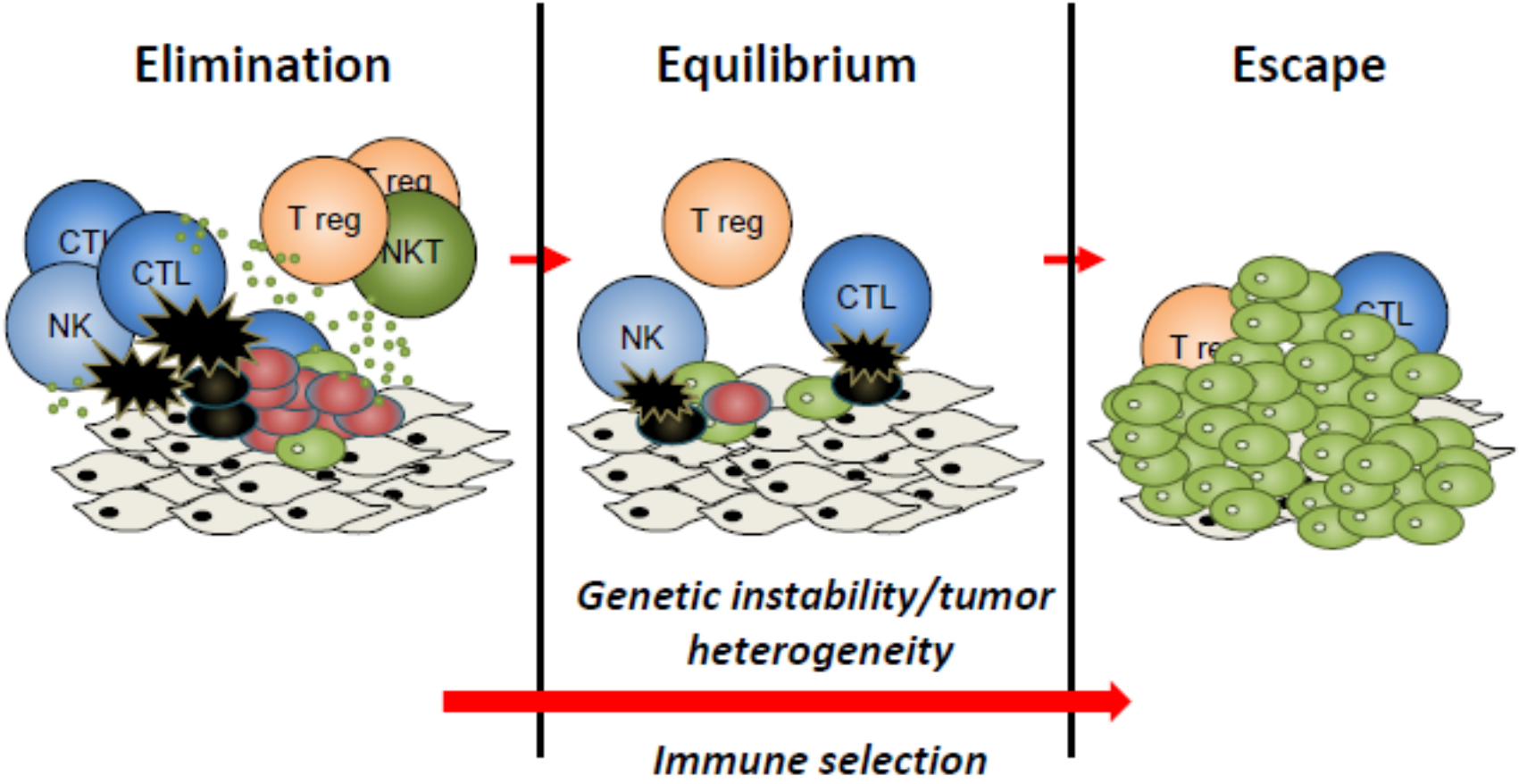
Immunoediting

- tumor cells change immunogenicity to produce immune-resistant variants



The Three 'E's of Immunoediting

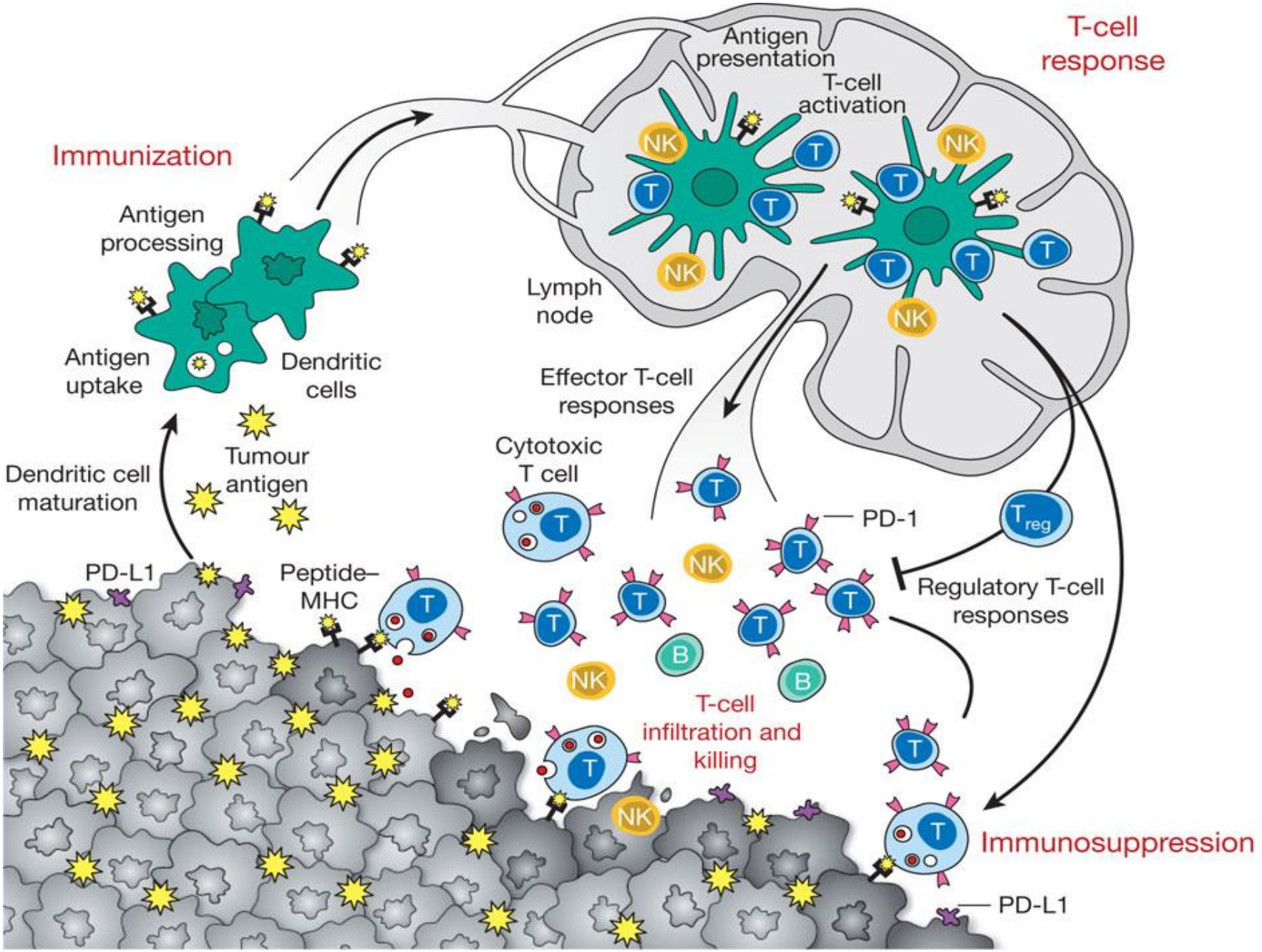
The immune system controls tumor quantity
as well as tumor quality



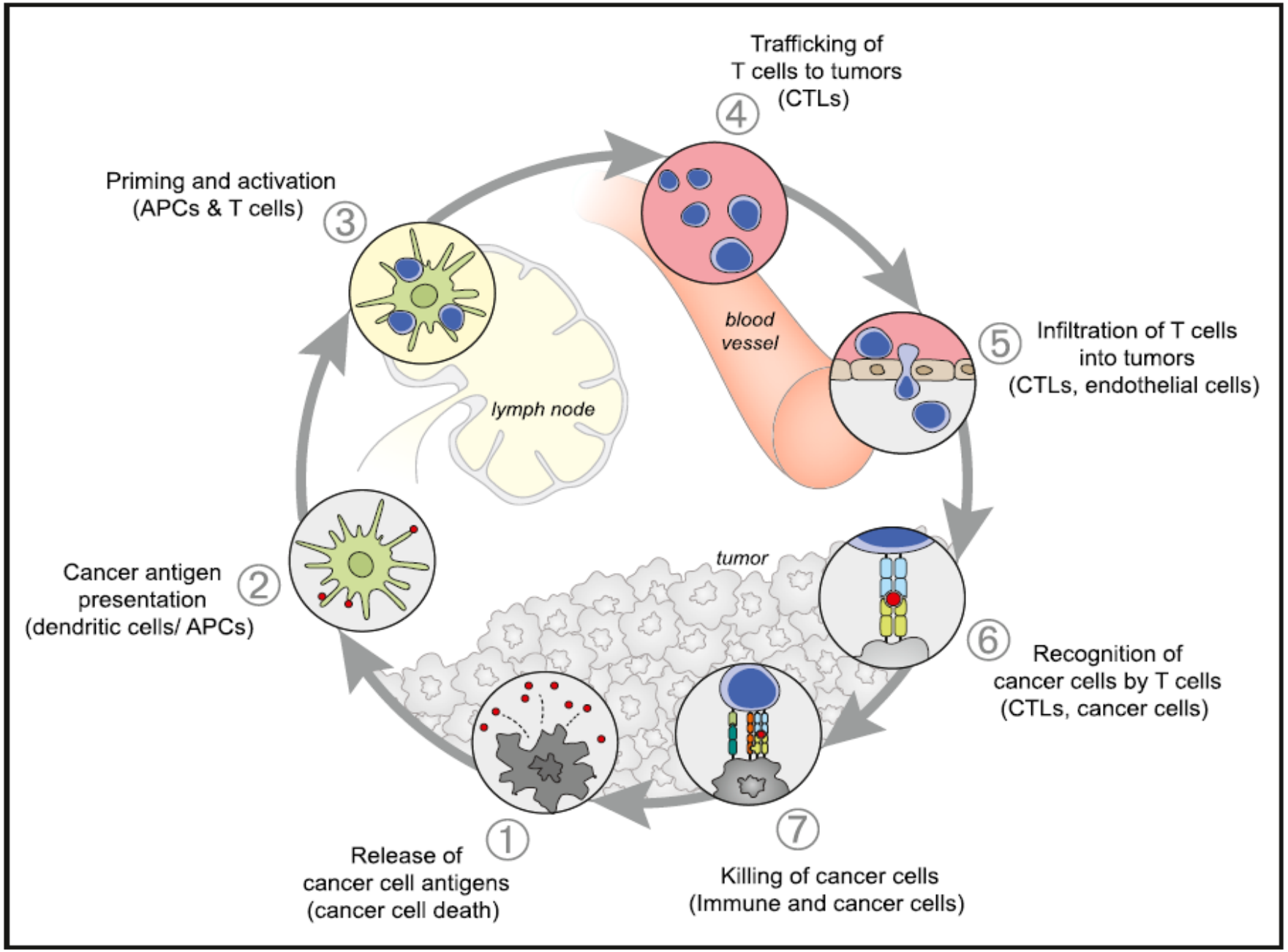
Dunn GP, et al. Nat Immuno. 2002;3:991-998. Schreiber R, et al. Science. 2011;331:1565-1570.
Mittal D, et al. Curr Opin Immunol. 2014;27:16-25.

How does the immune system recognize cancers?

- **Tumor associated antigens** – targets for tumor specific T cell response that rejects the tumor
  - Tumor specific mutated molecules
  - Molecules only in germline cells or differentiation antigens only in particular tissues
  - Abnormal overexpression of antigen with respect to normal cells
  - Abnormal protein modification
  - Oncoviral protein antigen in virus-associated tumor



Mellman et. al. Nature 480, 480-489. 22 December 2011

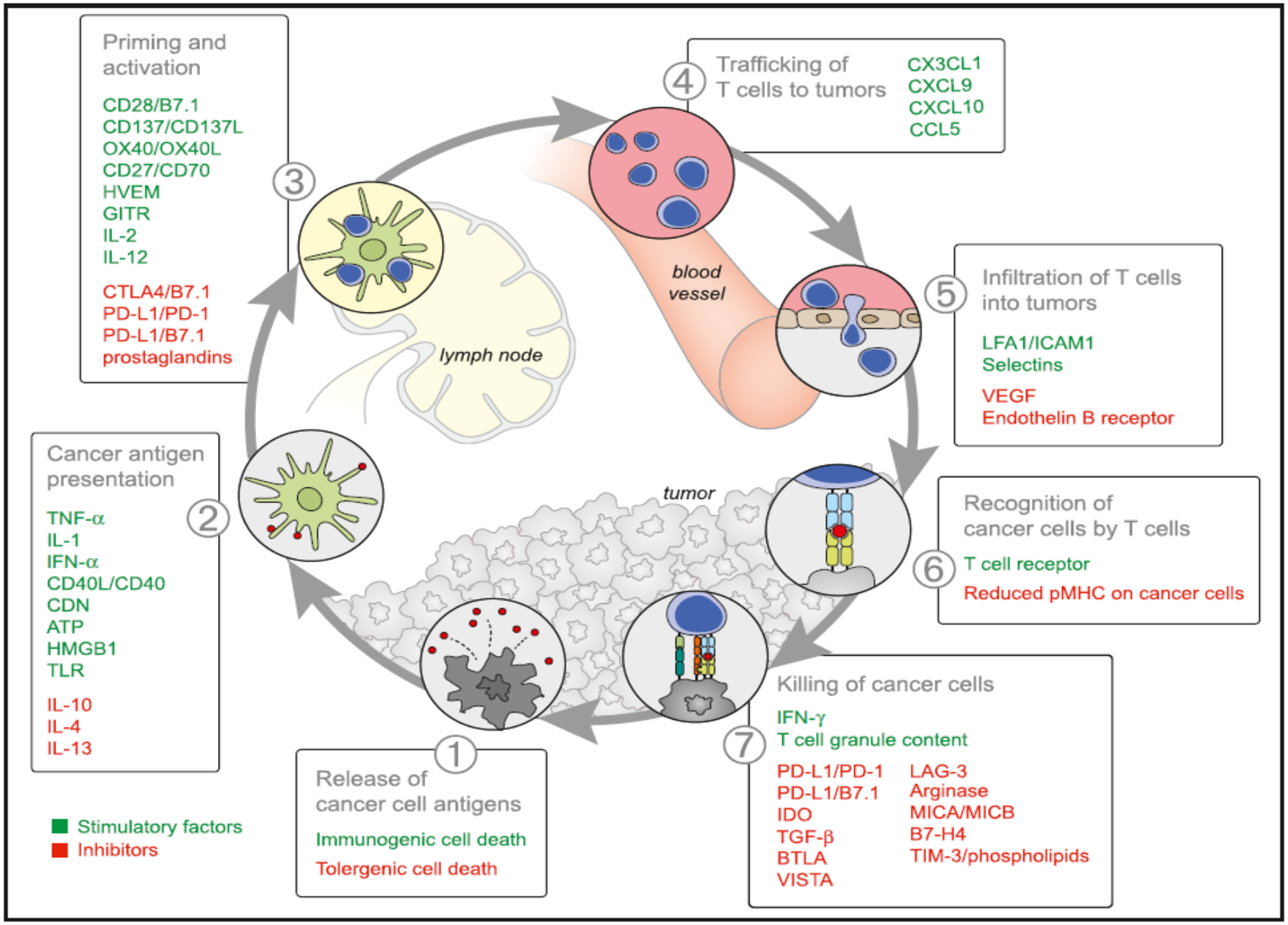


Dan Chen and Ira Mellman. Immunity. 39, July 23, 2013.

Immunotherapy

- Treatment of disease by inducing, enhancing or suppressing an immune response
- Harness and augment anti-tumor responses to treat cancer

- Passive immunotherapy
  - does not engage adaptive response, fast, transient
  - cytokines, antibodies, T cells
- Active immunotherapy
  - Engages adaptive immune response
  - Slow, delayed onset
  - Life-long immunologic memory
  - vaccines



Dan Chen and Ira Mellman. Immunity. 39, July 23, 2013.