Immunity and How Vaccines Work

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Waterford, Aug. 25, 2016

Definitions

Antibody: immunoglobulin (Ig) produced mainly by plasma cells, which identifies and neutralises pathogens

Antigen: Anti(body) gen(erator):substance that can provoke an immune response

Epitope:. the specific piece of the antigen to which an antibody binds.

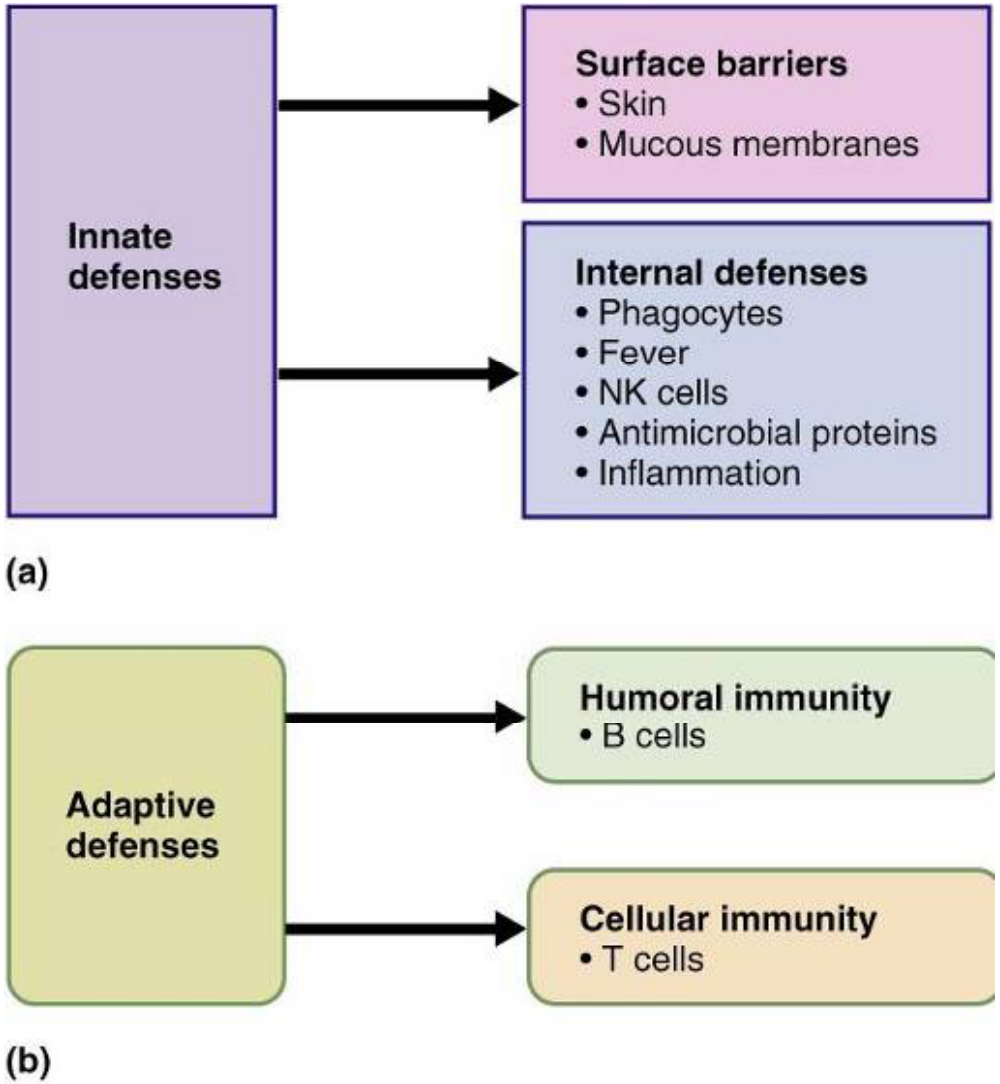
Humoral: relating to fluids

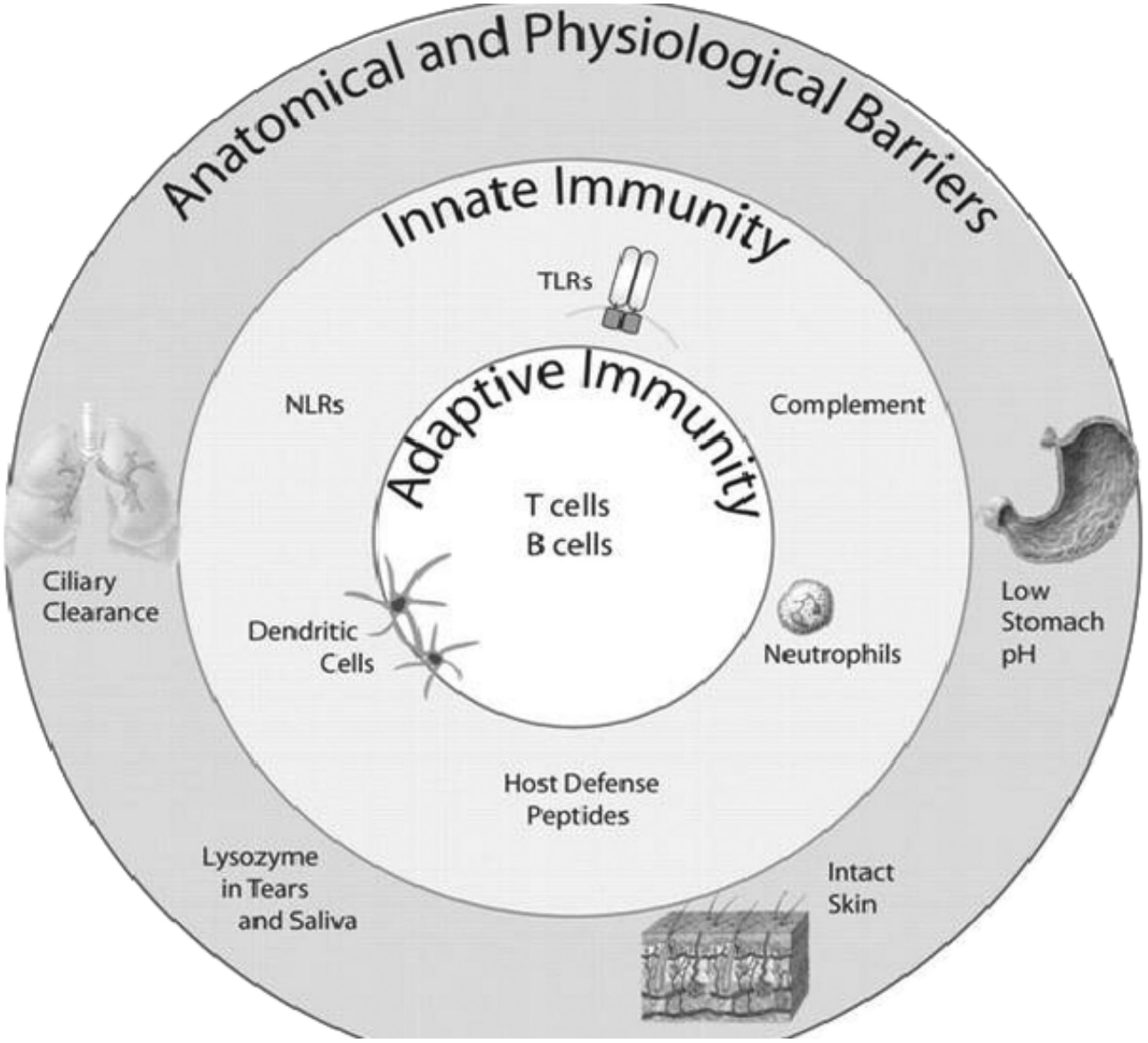
Immunity: resistance to infection (immunis = exempt, protected)

Innate – present from birth

Immune System Overview

- Hematopoietic
- Vasculature
- Lymphatic




Anatomical and Physiological Barriers
Innate Immunity
TLRs
Adaptive Immunity
NLRs
Complement
T cells
B cells
Ciliary
Clearance
Dendritic
Cells
Neutrophils
Low
Stomach
pH
Host Defense
Peptides
Lysozyme
in Tears
and Saliva
Intact
Skin

Innate - Surface Defenses

Skin: physical barrier to microbes

- keratin resistant to bacterial enzymes & toxins
- secretions are acidic

Mucosa: physical barrier

- produces a variety of protective chemicals

Gastric mucosa: physical barrier

- very acidic & produces proteolytic enzymes

Saliva, tears

- contain lysozyme

Mucous

- traps, moves bacteria away from epithelial surface

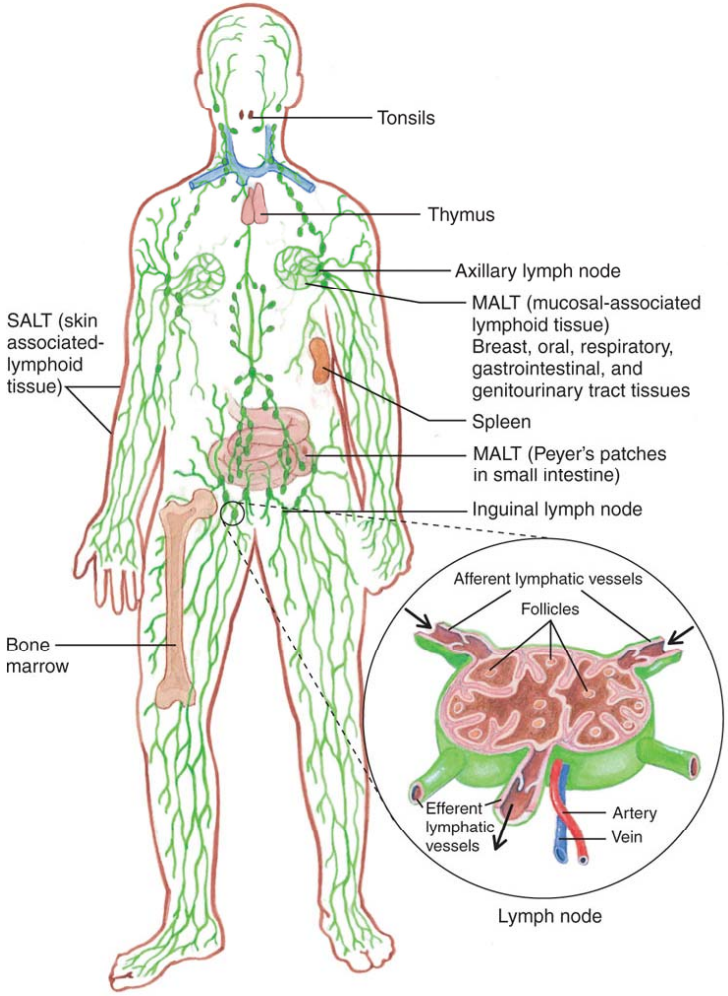
Lymphoid System

Primary lymphoid organs:

Where lymphocytes destined to become B and T cells mature

Bone marrow - B cells mature

Thymus - T cells mature, migrate to secondary lymphoid organs

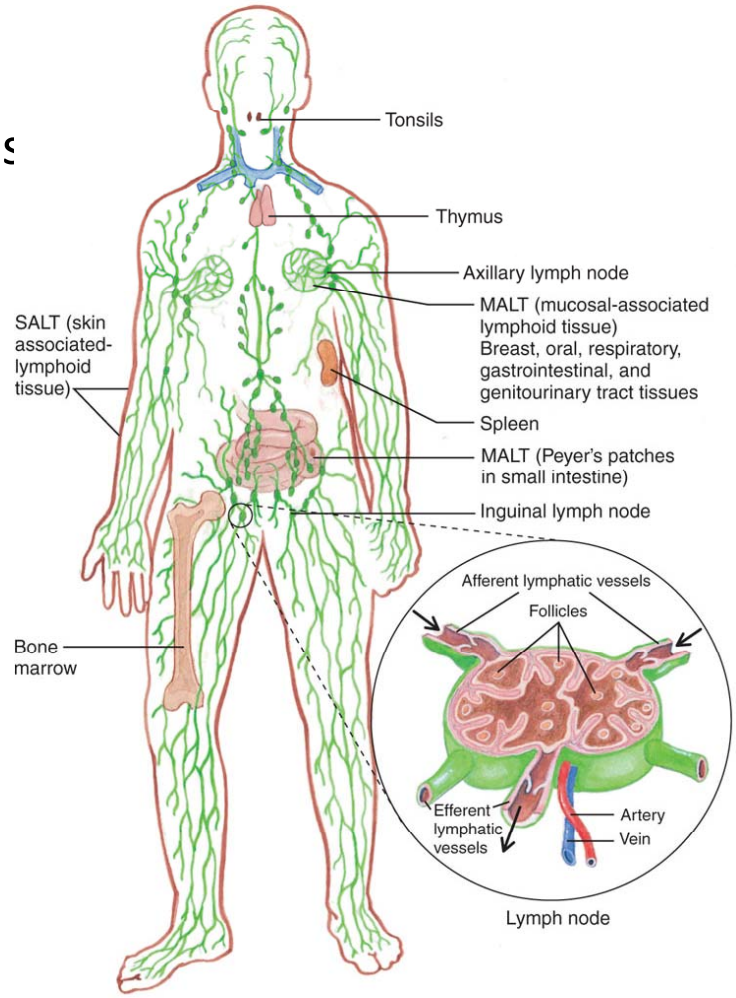


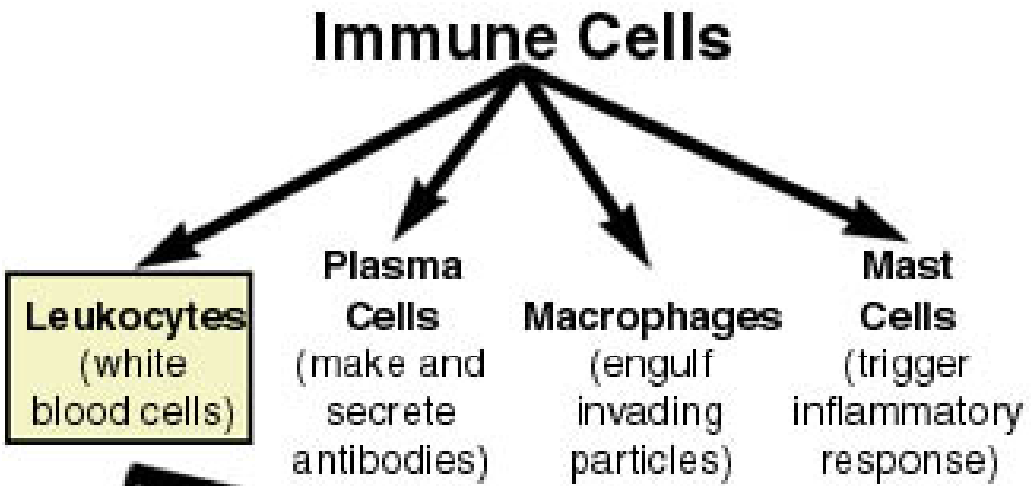
Lymphoid System

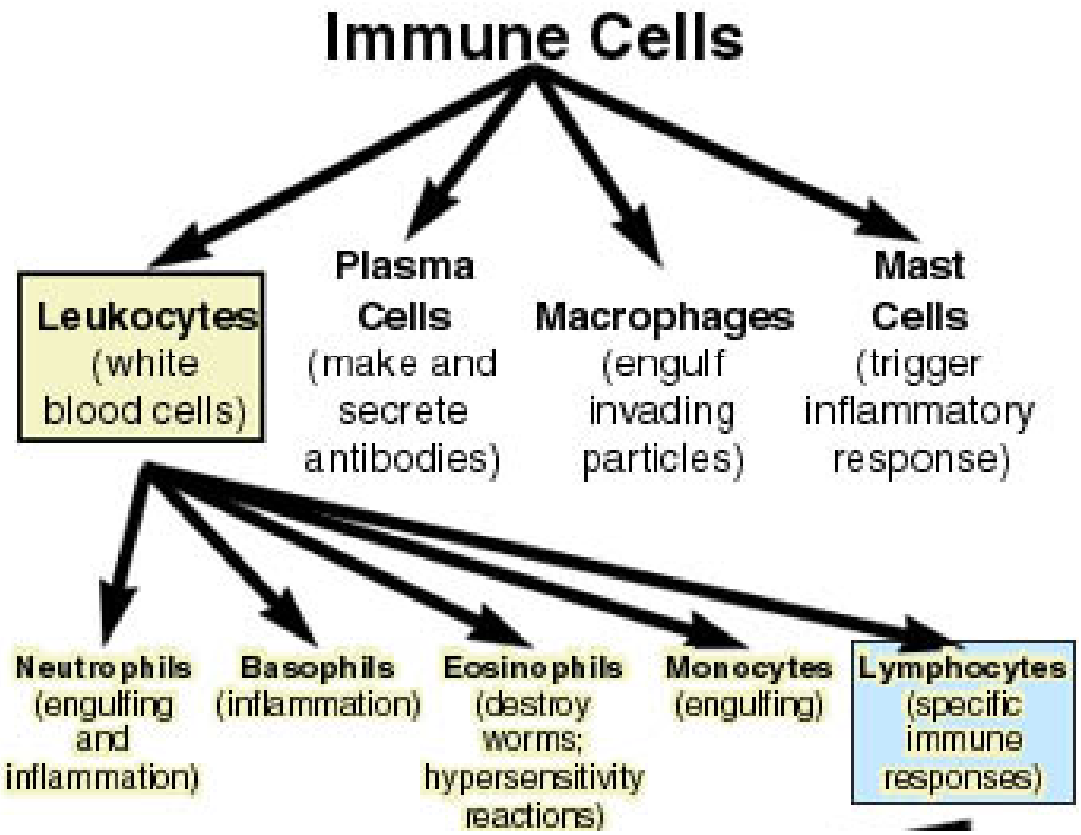
Secondary lymphoid organs: Sites where lymphocytes gather to encounter antigens

Lymph nodes, spleen, tonsils, adenoids
appendix

Situated to allow for initiation of immune response from nearly any place in body




Immune Cells
Leukocytes (white blood cells)
Plasma Cells (make and secrete antibodies)
Macrophages (engulf invading particles)
Mast Cells (trigger inflammatory response)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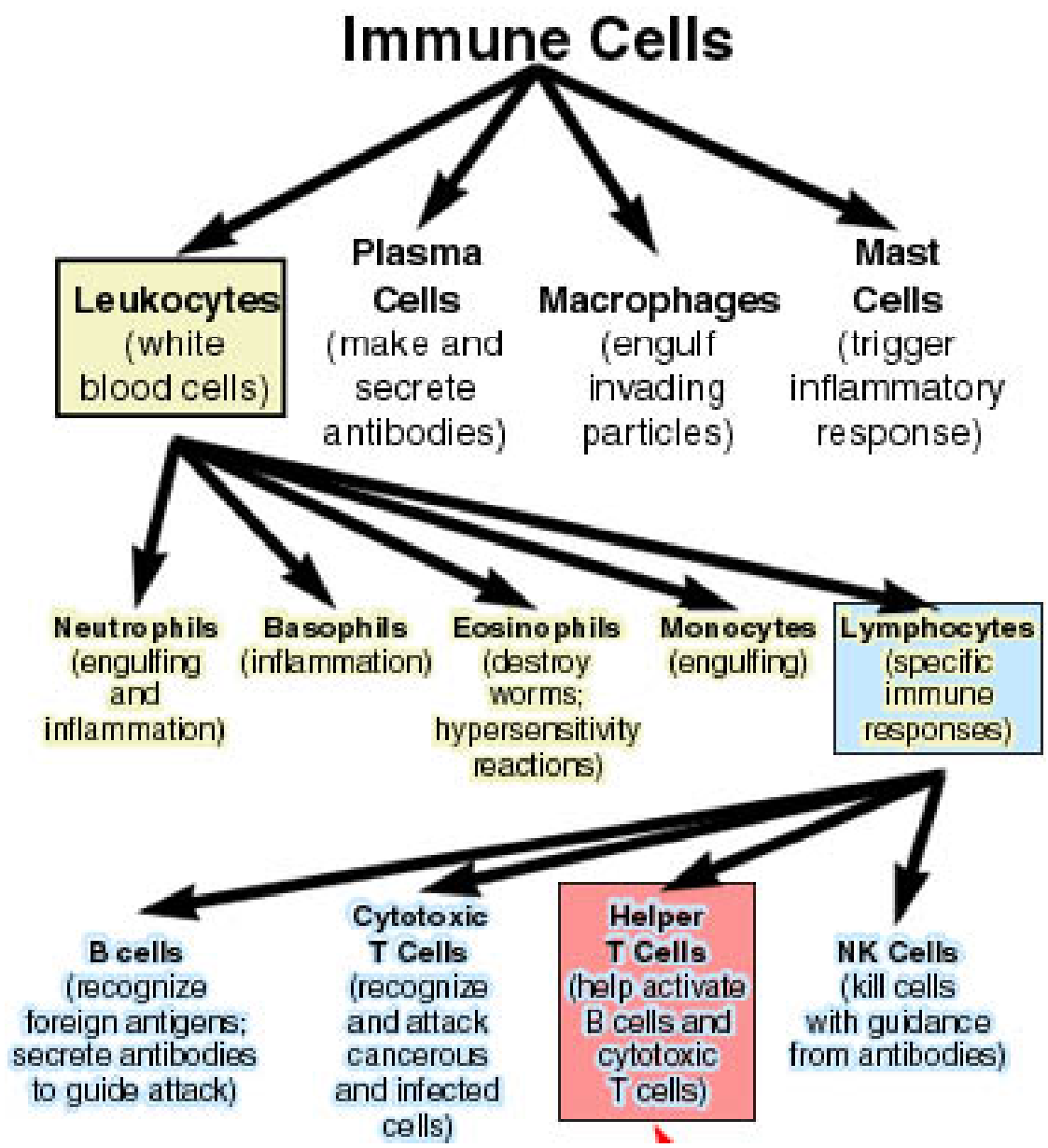
Neutrophils (engulfing and inflammation)
Basophils (inflammation)
Eosinophils (destroy worms; hypersensitivity reactions)
Monocytes (engulfing)
Lymphocytes (specific immune responses)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Monocytes (engulfing)
Lymphocytes (specific immune responses)
B cells (recognize foreign antigens; secrete antibodies to guide attack)
Cytotoxic T Cells (recognize and attack cancerous and infected cells)
Helper T Cells (help activate B cells and cytotoxic T cells)
NK Cells (kill cells with guidance from antibodies)

NK cells

- Large granular lymphocytes, components of innate immunity
- 10-15% of peripheral blood lymphocytes
- Kill virus-infected and tumor cells
- Secrete cytokines and chemokines CCL3, CCL4 & CCL5

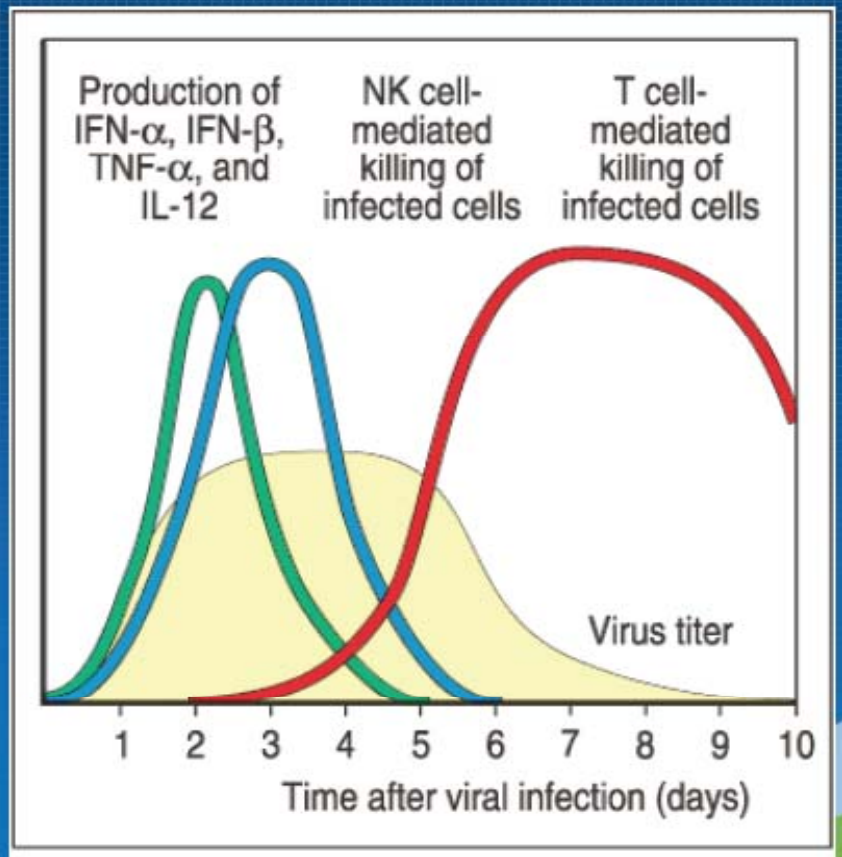


Fig 2.41 © 2001 Garland Science

Inflammation

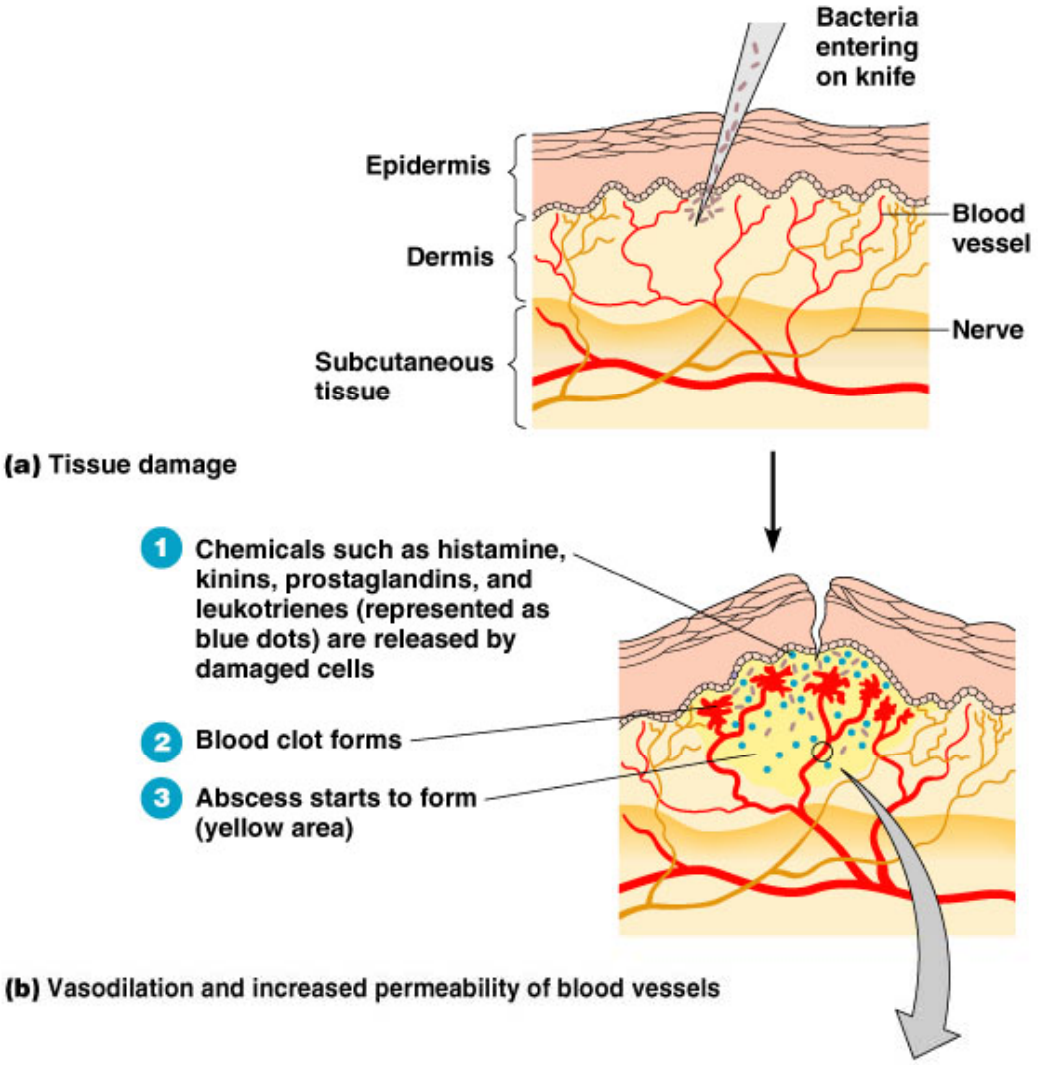


Figure 16.9a, b

Inflammation

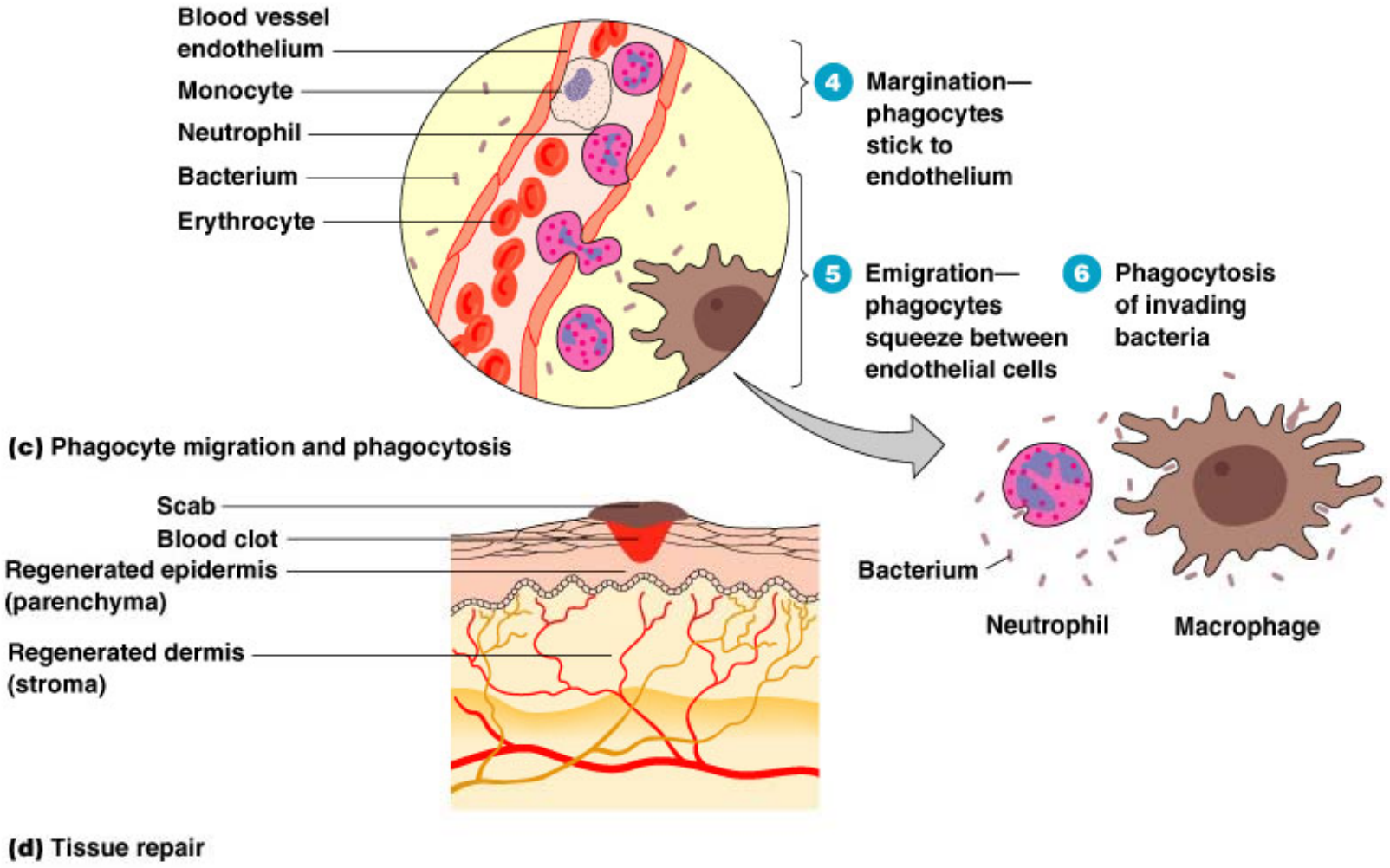
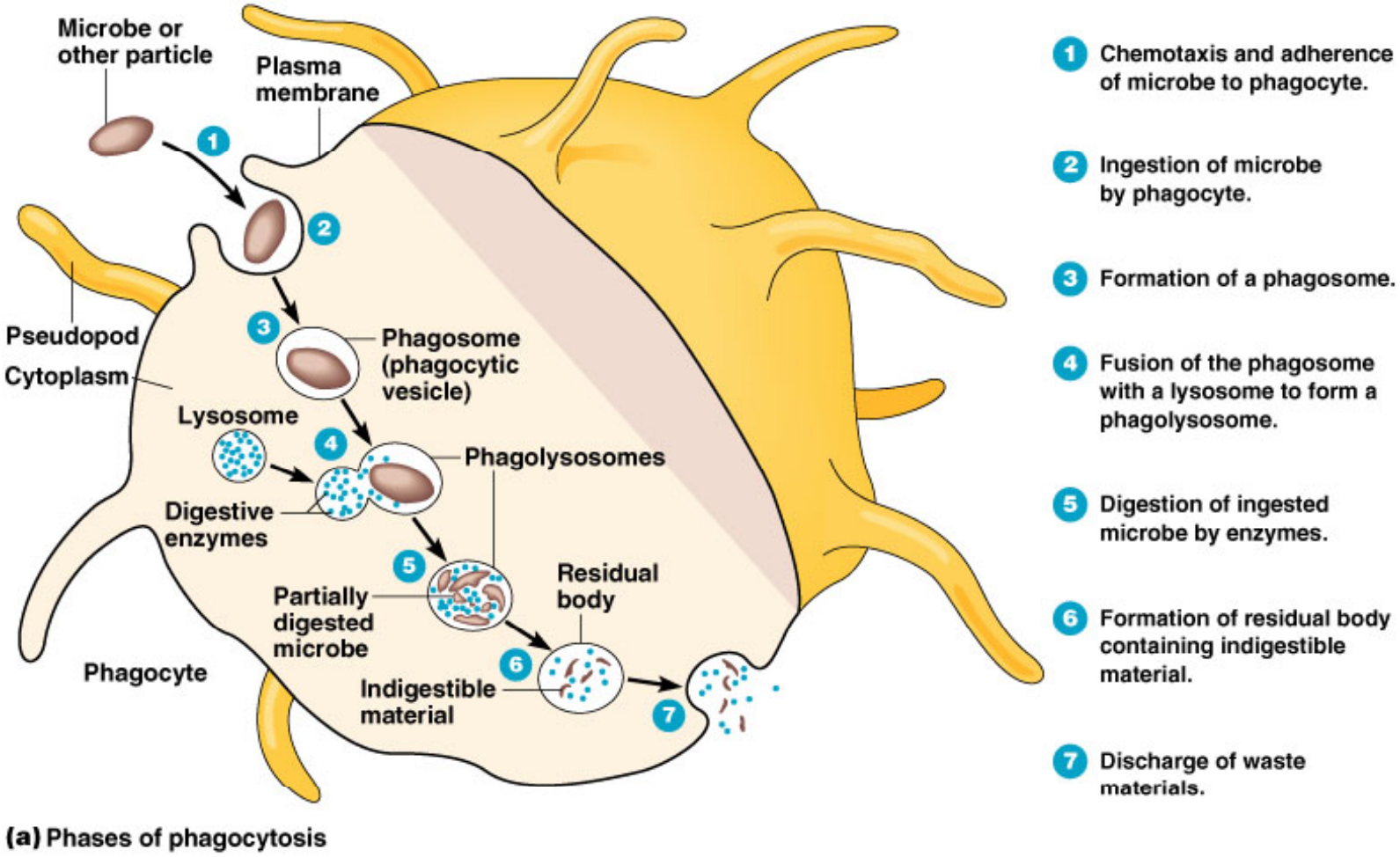


Figure 16.9c, d

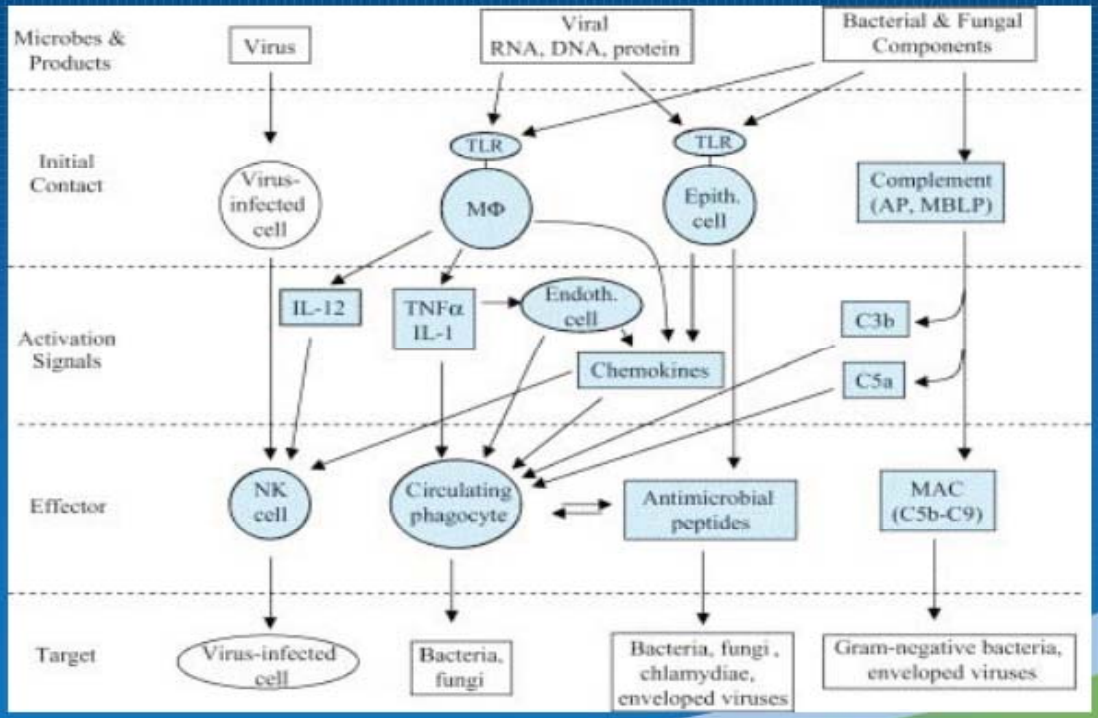
Phagocytosis

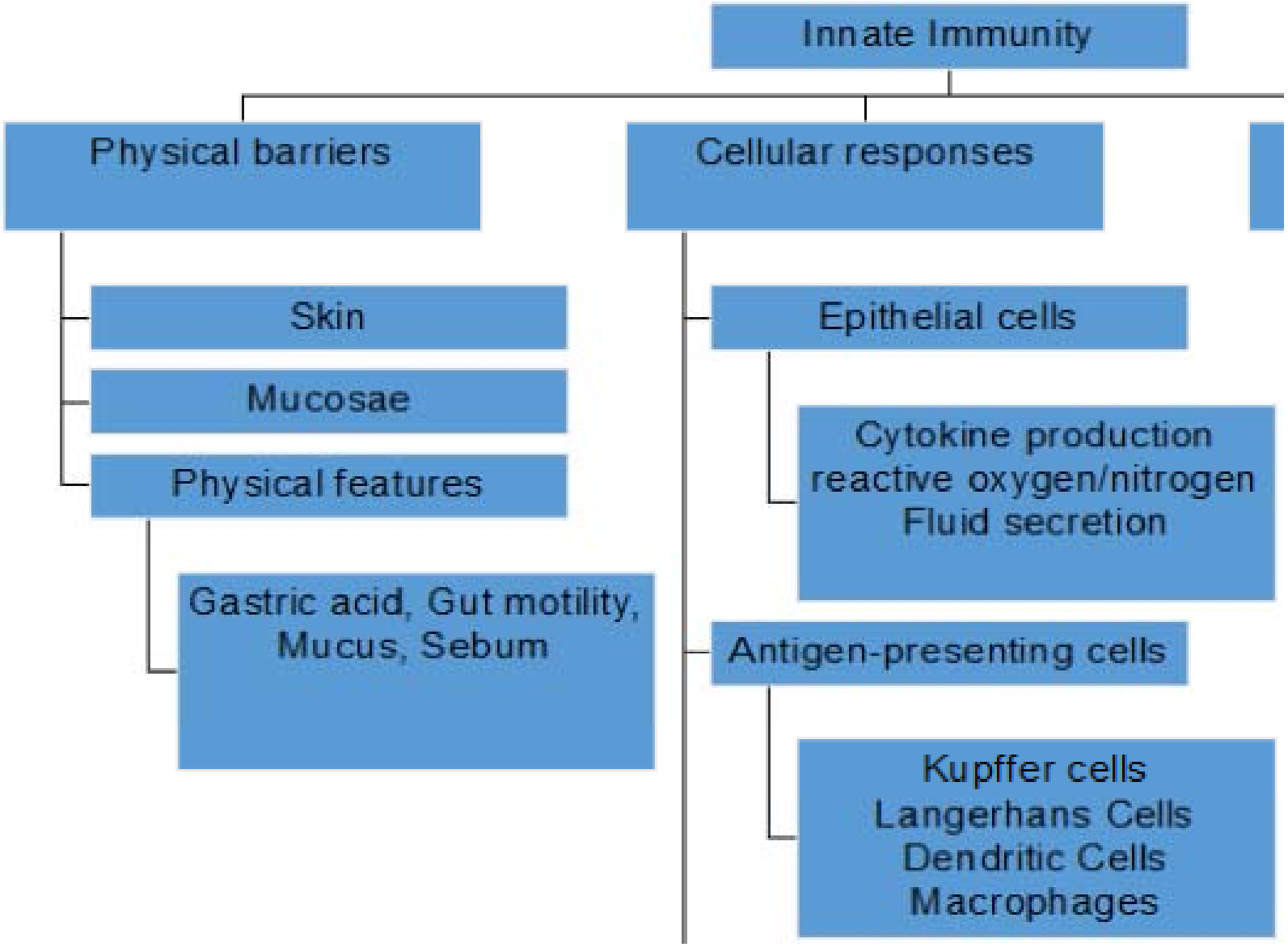


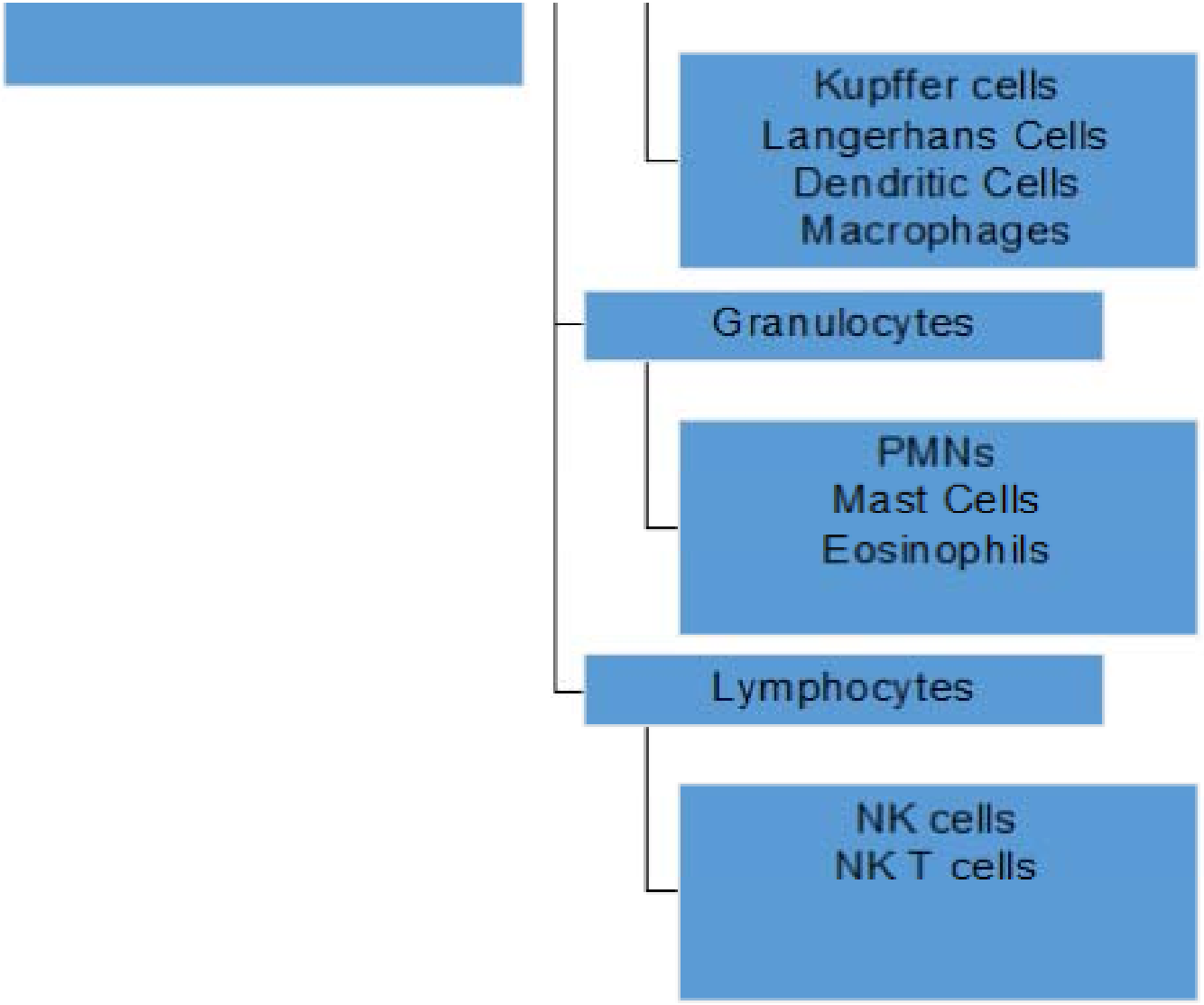
(a) Phases of phagocytosis

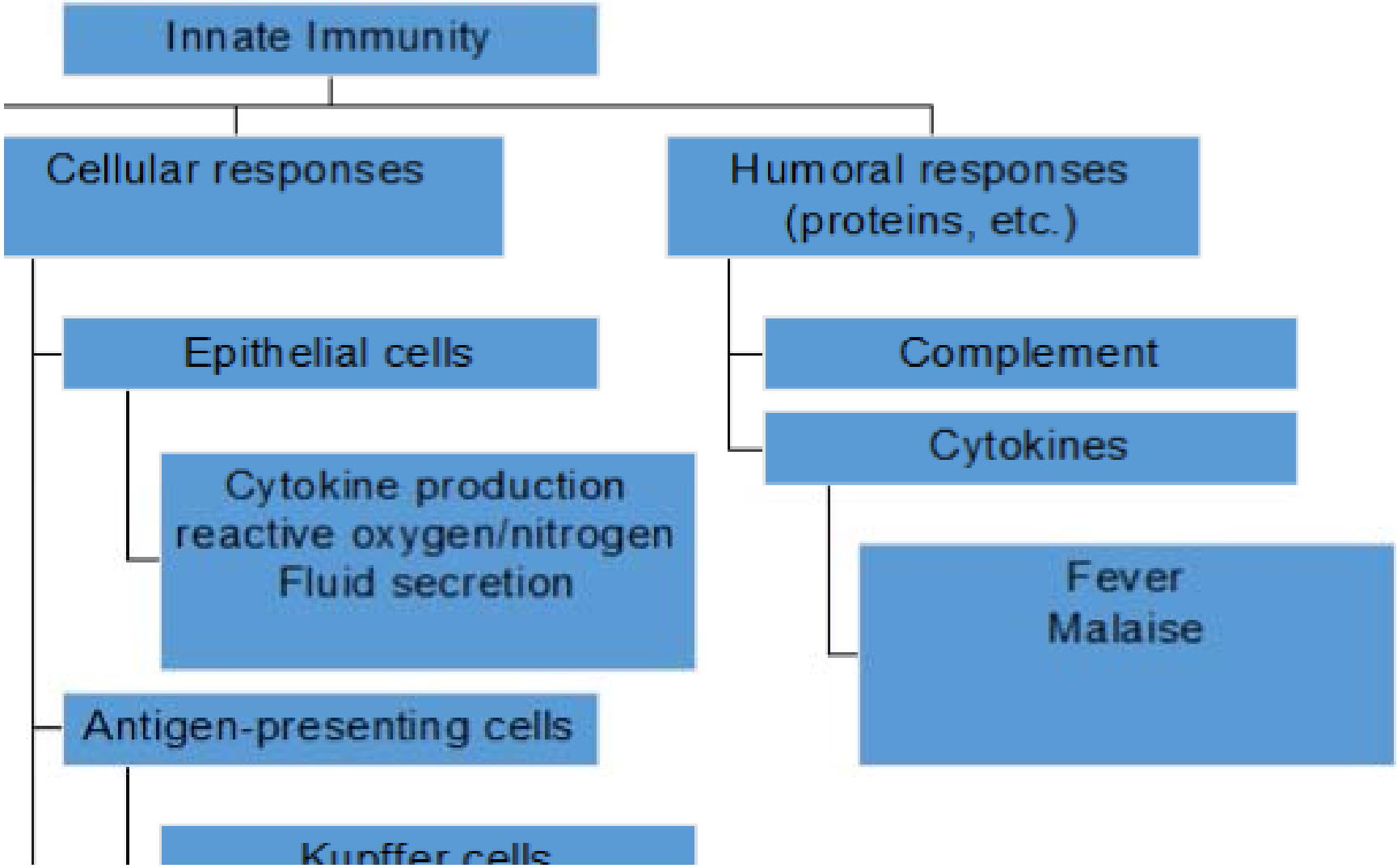
Figure 16.8a

Innate Immunity: A (Very) Broad Overview




Innate Immunity
Physical barriers
Cellular responses
Skin
Mucosae
Physical features
Gastric acid, Gut motility, Mucus, Sebum
Epithelial cells
Cytokine production
reactive oxygen/nitrogen
Fluid secretion
Antigen-presenting cells
Kupffer cells
Langerhans Cells
Dendritic Cells
Macrophages


Kupffer cells
Langerhans Cells
Dendritic Cells
Macrophages
Granulocytes
PMNs
Mast Cells
Eosinophils
Lymphocytes
NK cells
NK T cells


Innate Immunity
Cellular responses
Humoral responses (proteins, etc.)
Epithelial cells
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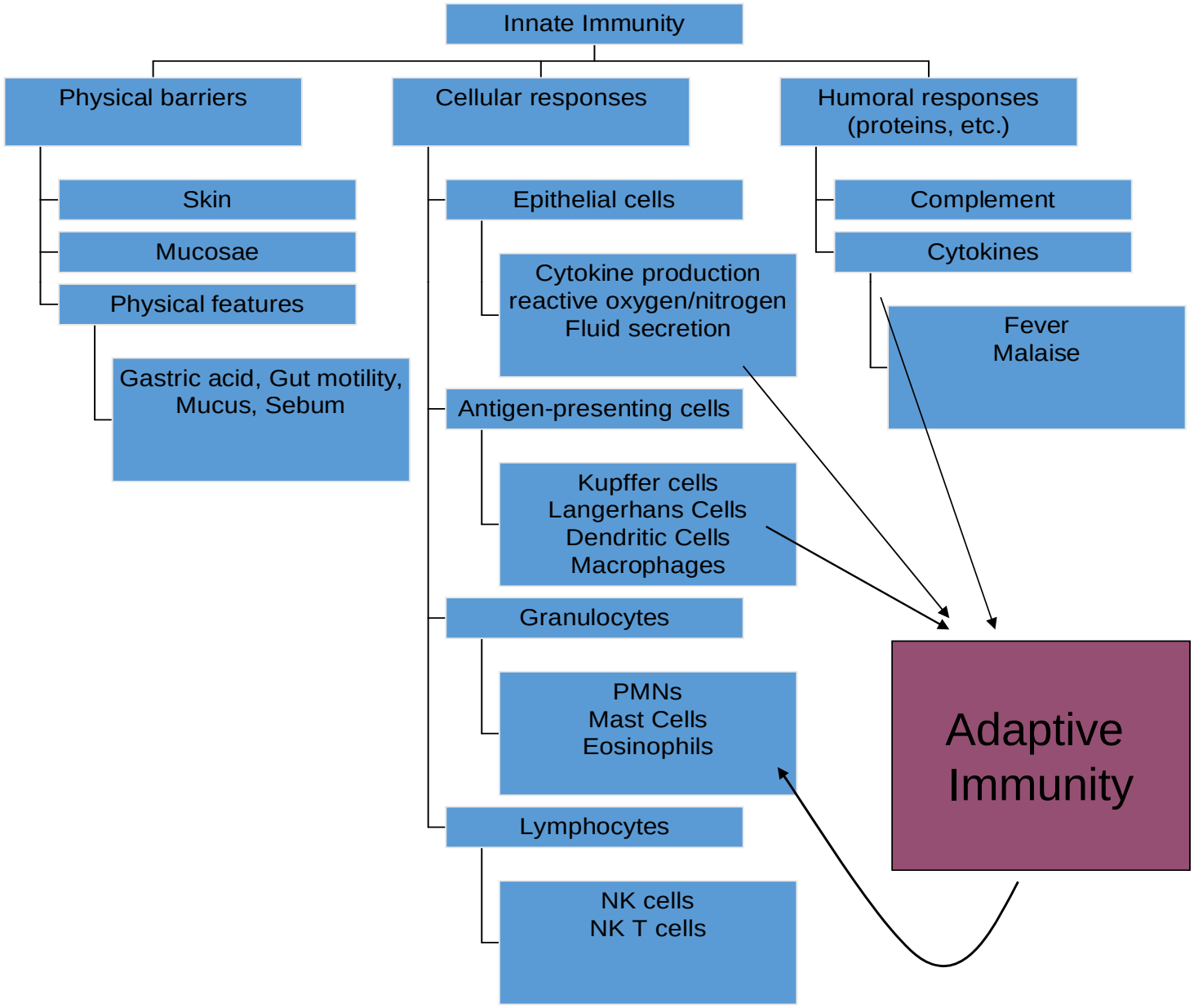
reactive oxygen/nitrogen
Fluid secretion
Antigen-presenting cells
Kupffer cells
Complement
Cytokines
Fever
Malaise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Mast Cells
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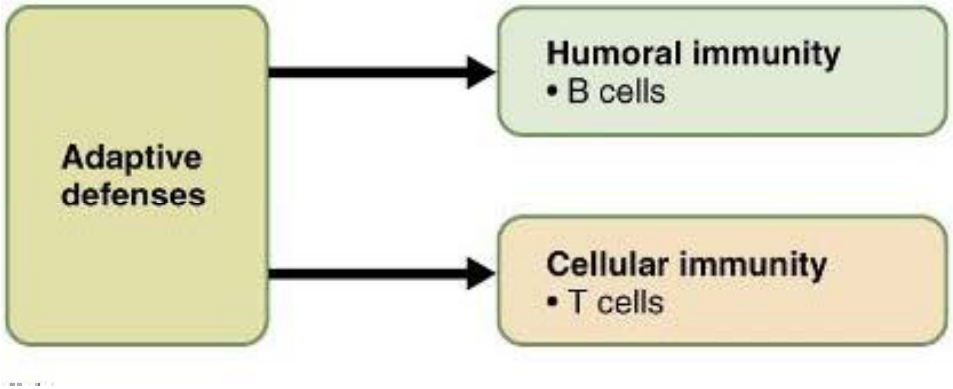
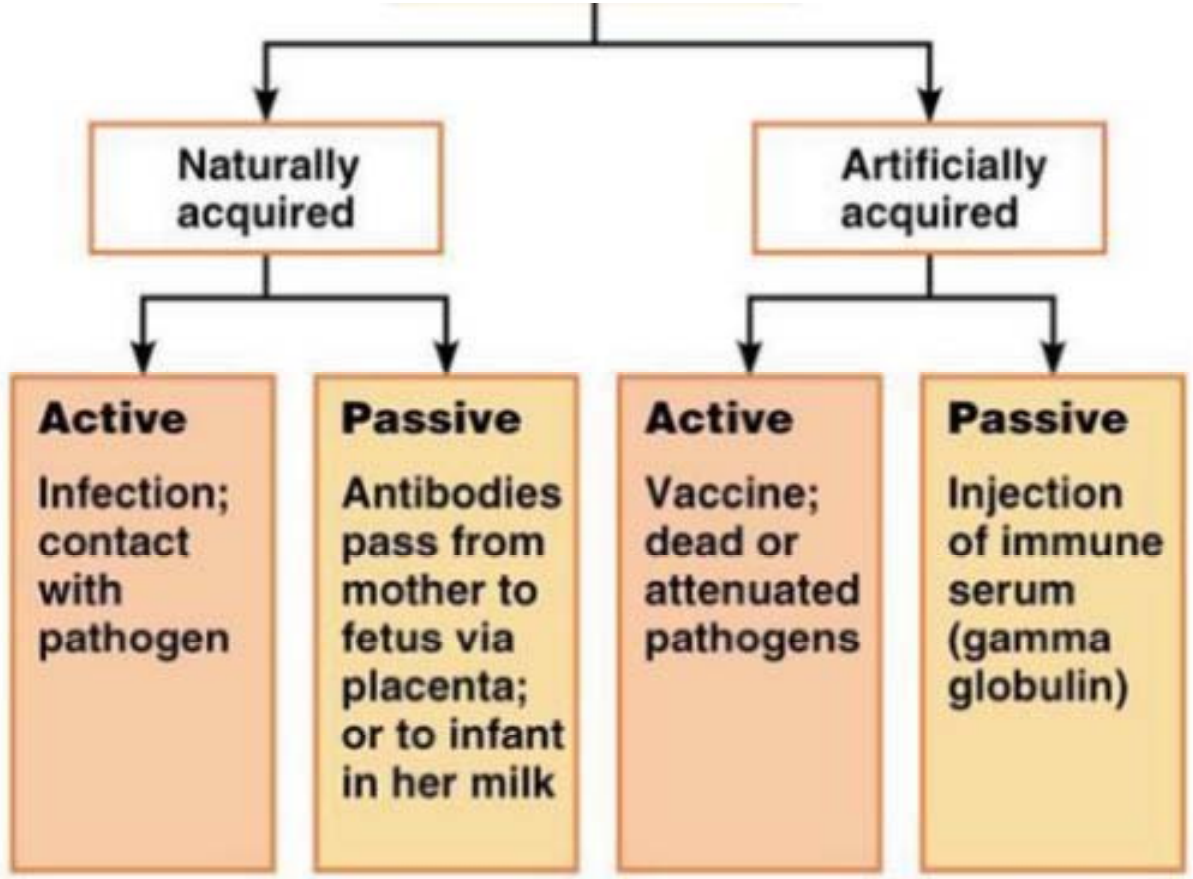
Lymphocytes
NK cells
NK T cells
Complement
Cytokines
Fever
Malaise
Adaptive Immunity

Adaptive Immune System



- Adaptive: responds to specific foreign substances
- Innate and adaptive mechanisms work together

Types of Adaptive Immunity



Adaptive Immunity

Immune system adapts to previously unseen molecules

Induction by infection, vaccination

Immune system mounts response

Immune response must:

Recognise micro-organism as foreign

Respond by producing specific antibodies, lymphocytes

Mediate elimination of organisms

Innate Immunity	Adaptive Immunity
Pathogen recognized by receptors encoded in the germline	Pathogen recognized by receptors generated randomly
Receptors have broad specificity, i.e., recognize many related molecular structures called PAMPs (**p**athogen-**a**ssociated **m**olecular **p**atterns)	Receptors have very narrow specificity; i.e., recognize a particular epitope of antigen
PAMPs are **polysaccharides** and **polynucleotides** that differ little from one pathogen to another but are not found in the host.	Most epitopes are derived from **polypeptides** (proteins) and are specific to each pathogen
Receptors are PRRs (**p**attern **r**ecognition **r**eceptors)	The receptors are B-cell (**BCR**) and T-cell (**TCR**) receptors for antigen
Immediate response	Slow (3–5 days) response (need clones of responding cells to develop
Little or no memory of prior exposure	Memory of prior exposure
Occurs in all multicellular animals	Occurs in vertebrates only

Active Humoral Immunity

Naturally acquired: natural exposure to antigen (i.e. infection)

Ar**tificially acquired**: vaccines

live attenuated, non-live (killed or fragmented pathogen injected to elicit an immune response

Primary response (immunity without disease)

Secondary response (boosters) - intensify response

Specific Memory and Adaptive Response

Adaptive Defenses: Components

Humoral Immunity: provided by antibodies in body fluids

Cell mediated immunity: lymphocytes directly attack specific invaders by lysis or indirectly by initiating inflammation and activating other lymphocytes and macrophages

Adaptive System: Cells

Lymphocytes: initially uncommitted

T-cells: sorted in the Thymus
manage the immune response

B-cells: sorted in the marrow

Antigen Presenting Cells (APCs)

Functions of T_H Cells

Orchestrate immune response

- Recognize antigen presented by APC
- If T_H cell recognizes antigen, cytokines are delivered
- Cytokines activate APC to destroy antigen

Activate B cell

- If T_H cell encounters B cell bearing antigen
- T_H cell produces cytokines
- Cytokines activate B cell
- B cell proliferates
- Drives formation of B memory cells

Adaptive Humoral Response

B-cells: Antigen challenge to naïve B-cell

Antigen binds to B-cell receptors
Antigen ingested by B-cell
B cell presents antigen to T-cell
B cell produces antibody

Adaptive Immune System: Cells

Antigen Presenting Cells (APCs)

Macrophages & B lymphocytes

Ingest foreign material

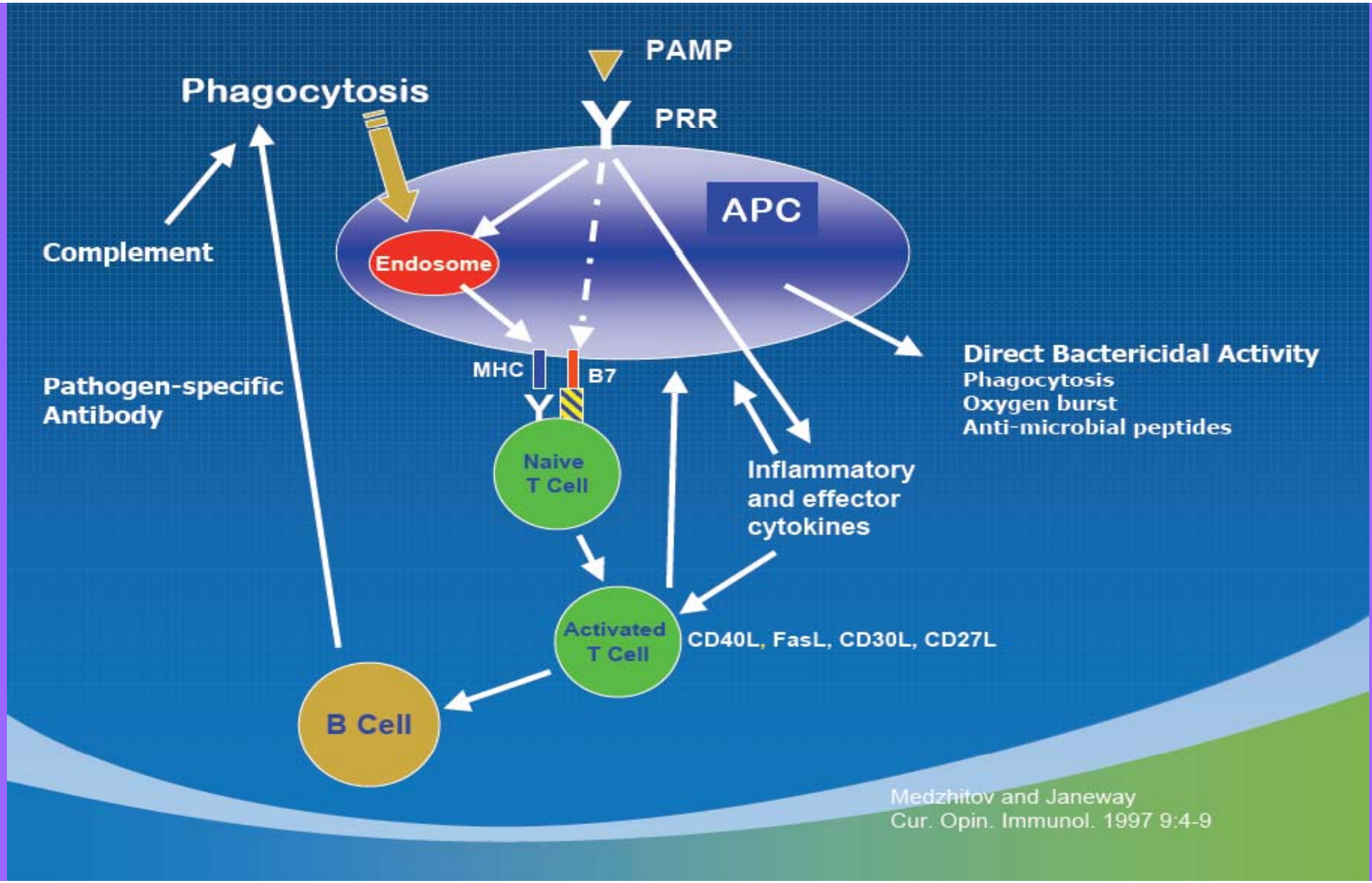
Present antigenic fragments on their cell

Fragments recognised by T-cells.

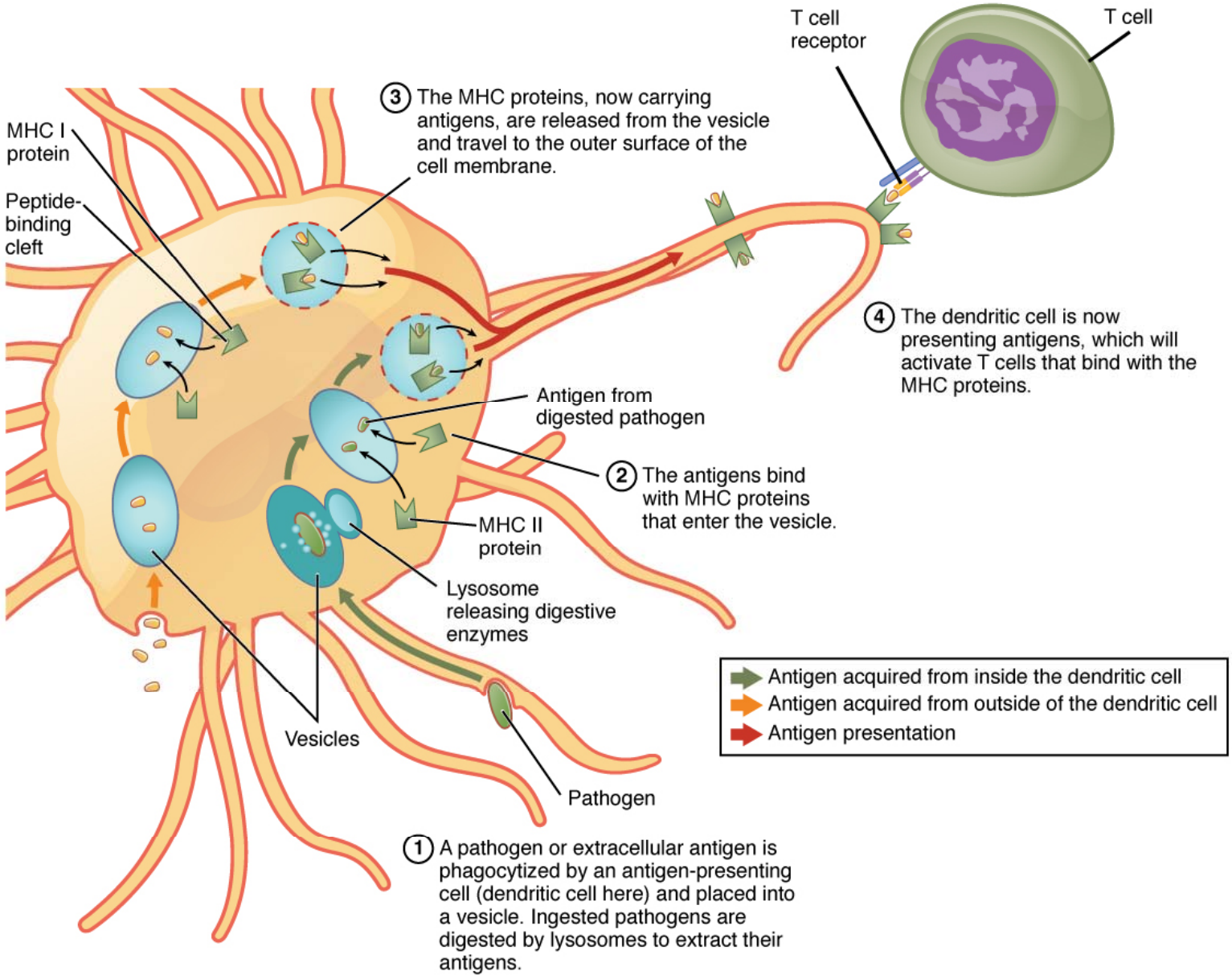
Innate Immunity can Trigger Adaptive Immunity

- Macrophages and dendritic cells "present" antigens to T cells
- This triggers cell- and humoral -mediated adaptive immune responses
- Interaction of PAMPs and TLRs on dendritic cells → secrete cytokines
  → production of T cells
- B cells are also antigen-presenting cells
- Pathogens coated with C3 bind more strongly to B cells → antibody production occurs at doses of antigen far lower than would otherwise be needed

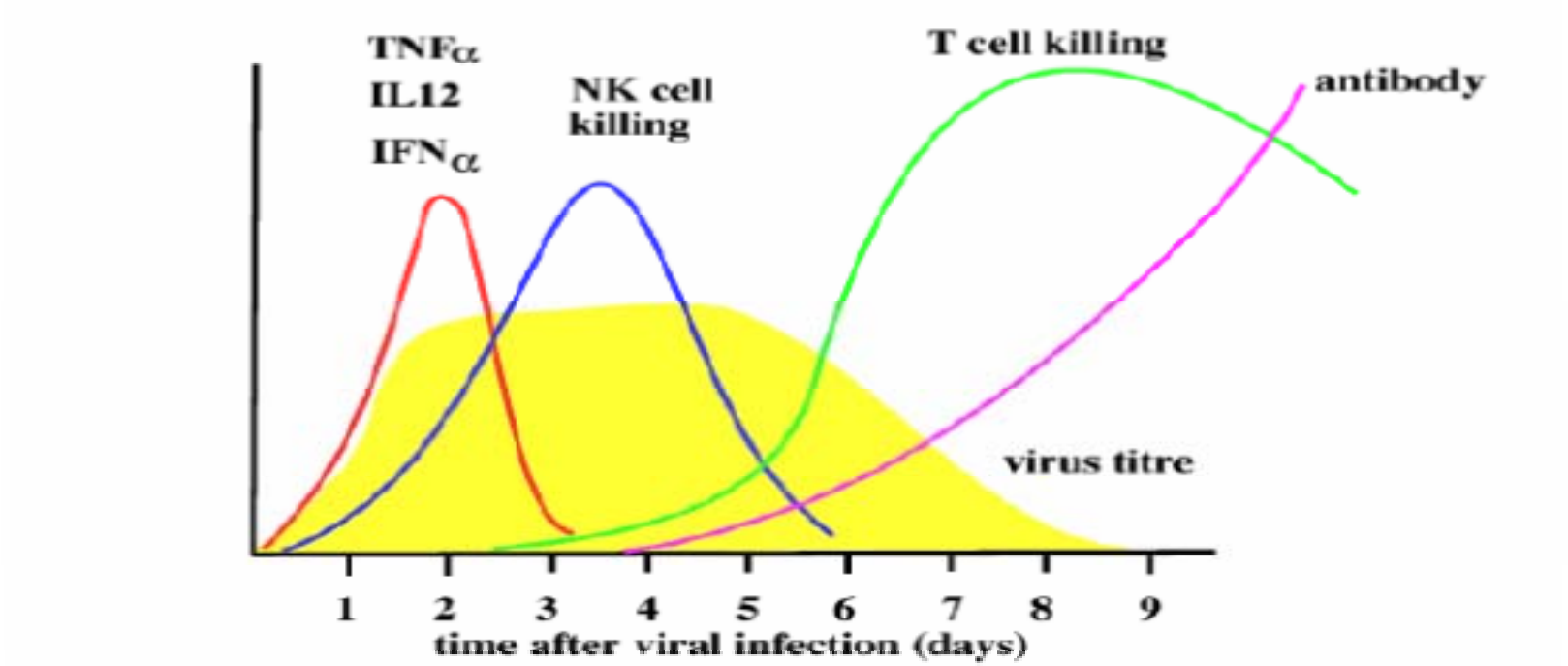
Note: Several vaccine adjuvants contain PAMPs → stimulate innate immune system
→ enhances response of the adaptive immune system to the vaccine


PAMP
PRR
Phagocytosis
Complement
APC
Endosome
MHC
B7
Pathogen-specific
Antibody
Naive
T Cell
Direct Bactericidal Activity
Phagocytosis
Oxygen burst
Anti-microbial peptides
Inflammatory
and effector
cytokines
Activated
T Cell
CD40L, FasL, CD30L, CD27L
B Cell
Medzhitov and Janeway
Cur. Opin. Immunol. 1997 9:4-9

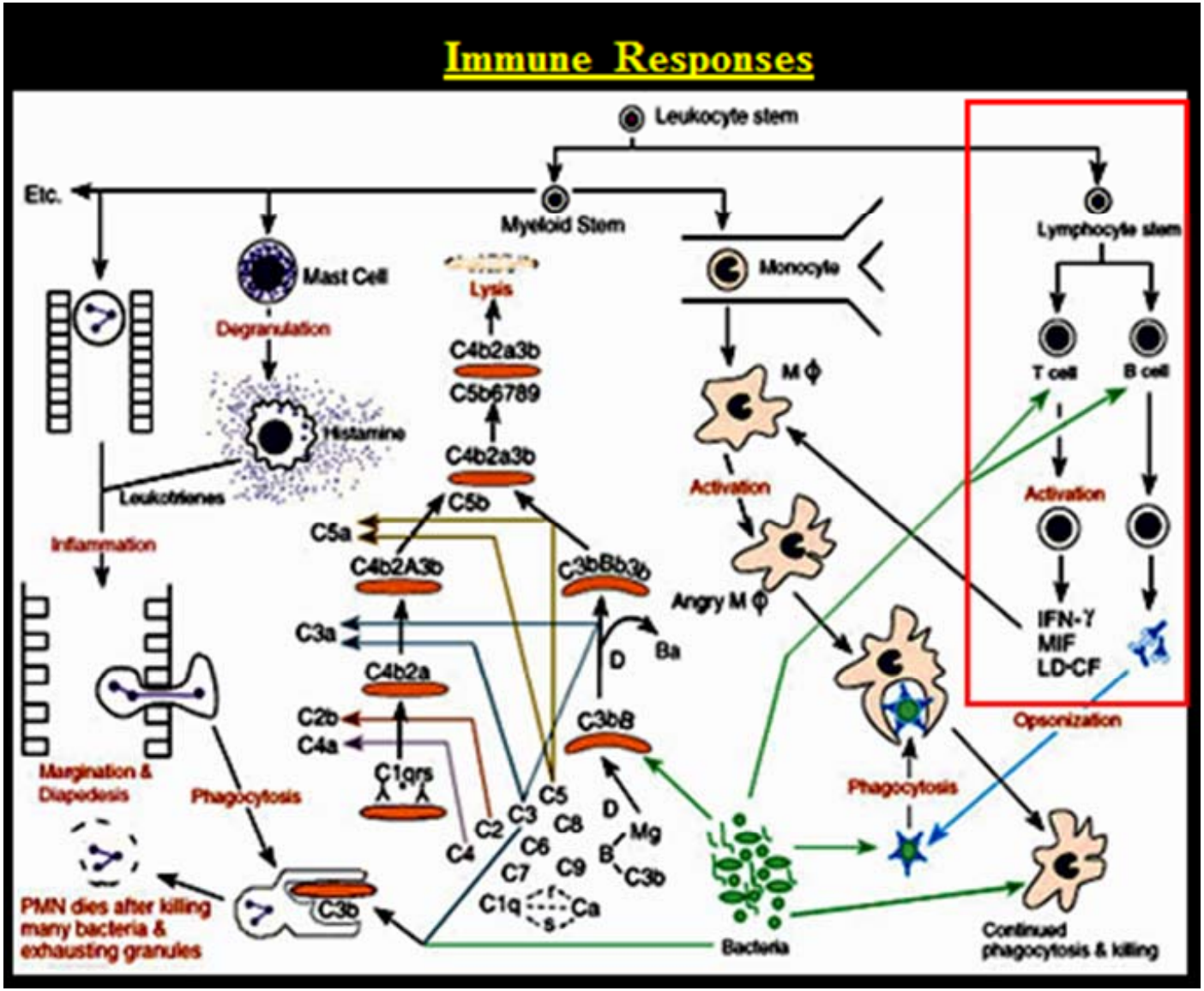
Antigen Presenting Cell



Innate and Adaptive Immunity Work Together



Immune Responses



What is a Vaccine?

- Biological preparation that improves immunity to a particular disease
- Contains antigen(s) that resembles a pathogen
- Stimulates immune system to recognise antigen as foreign,

  destroy it, and "remember" it
- Pathogens later encountered cause memory response

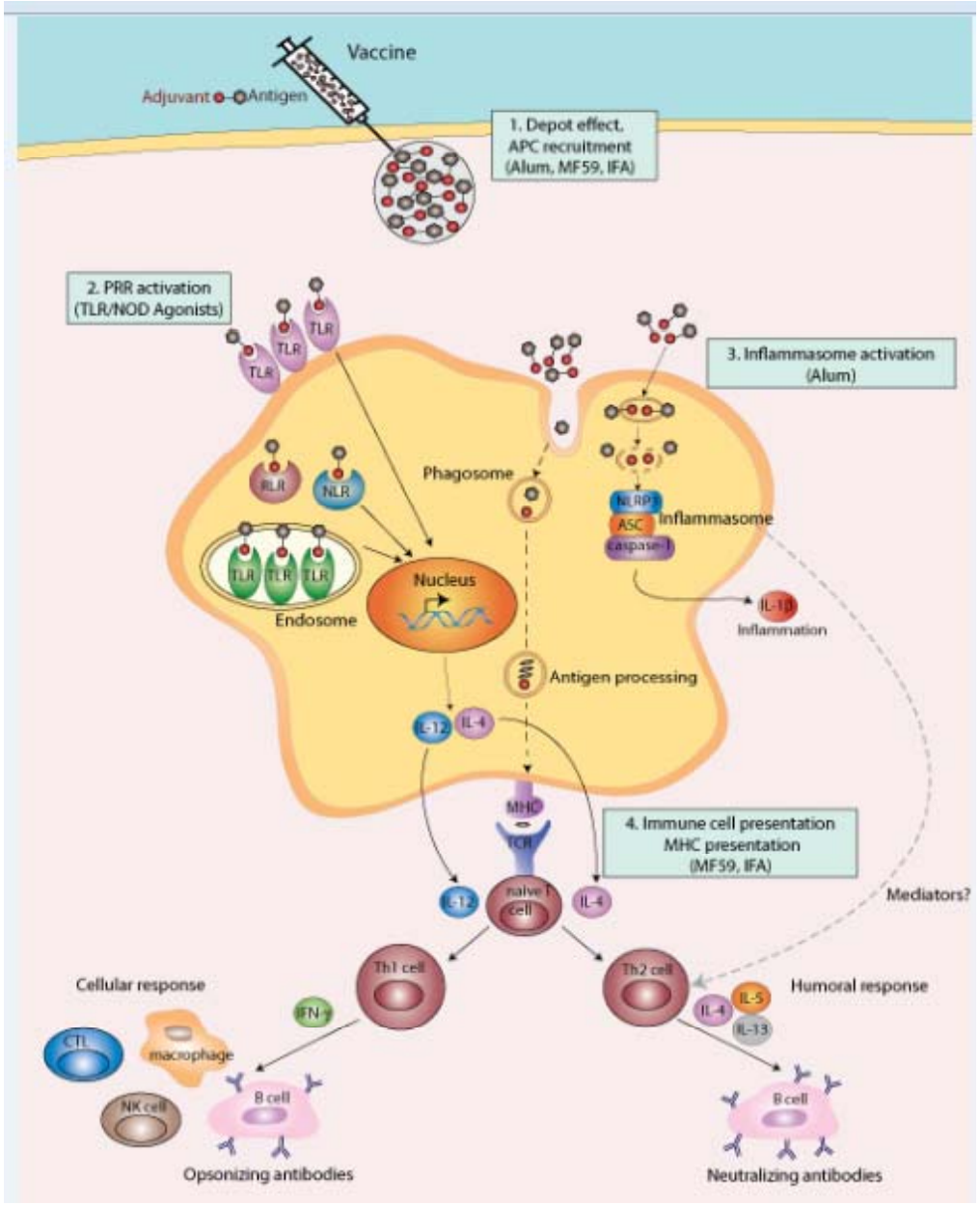
Live Attenuated Vaccines

- Attenuated "wild" virus or bacterium
- Can replicate – immune response is similar to natural infection
- Usually effective with one dose
- Severe reactions possible
- Can revert to a wild-type pathogen
- Fragile – must be stored carefully

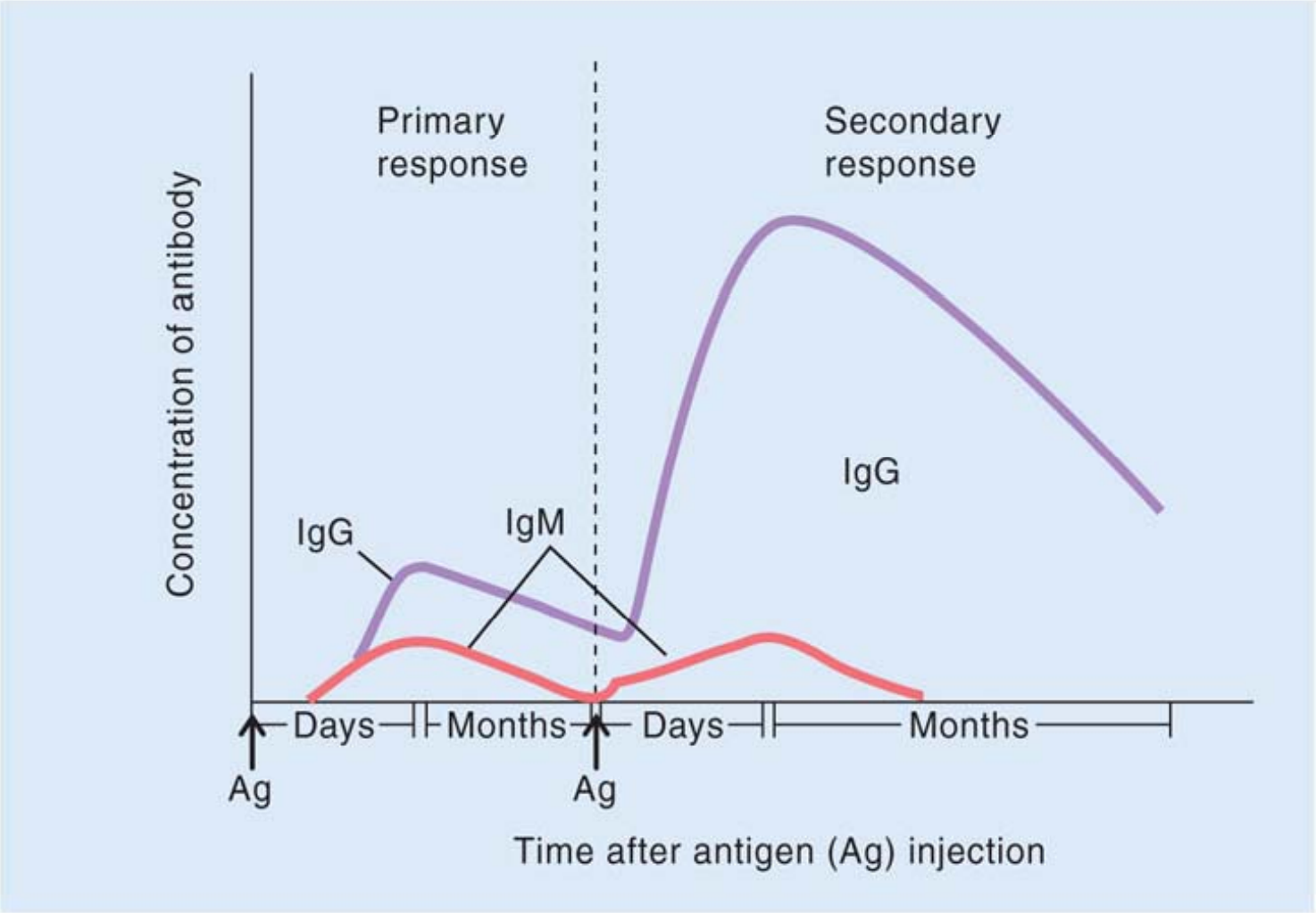
Non-live Vaccines

- No chance of recreating live pathogen
- Less interference from circulating antibody than live vaccines
- Cannot replicate, thus generally not as effective as live vaccines
- Usually require 3-5 doses
- Immune response mostly antibody based

How Vaccines Work



Primary and Memory Response



Reported Cases of VPDs, Europe

	1980	2000	2011	2012	2013
Diphtheria	608	1,585	33	32	32
Measles	851,849	37,421	37,073	26,982	25,375
Mumps	No data	243,344	27,448	38,141	35,075
Pertussis	90,546	53,675	34,432	56,941	27,824
Polio	549	0	0	0	0
Rubella	No data	621,039	9,672	30,509	39,614
Rubella (CRS)	No data	48	7	60	50
Tetanus	1,715	412	197	194	93

Vaccines Work-European Data

Disease	20th Century Annual Morbidity	Cases reported in 2007	Percent decrease
Small pox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	43	>99%
Mumps	162,344	800	>99%
Pertussis	200,752	10,454	95%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	12	>99%
Cong. Rubella Synd.	152	0	100%
Tetanus	580	28	95%
Hib	20,000	22	>99%

JAMA 2007

MMWR Au

Innate Internal Defenses

Inflammatory Response

Macrophages “clean up” pathogens

Activation of the complement cascade occurs and elements of adaptive immunity join the process

Innate Internal Defenses

Antiviral proteins:

Interferon: some cells produce & release interferons (IFNs) when invaded by virus

IFNs stimulate nearby cells to produce proteins that interfere with viral replication

Complement: plasma proteins activated in the presence of foreign substances

Complement activation:

enhances and amplifies inflammation

enhances innate and adaptive defenses

causes lysis of bacteria

Innate Internal Defenses

Complement activation pathways

Classical pathway: requires antibodies

- Antibodies bind to target (antigen)
- Complement protein C1 binds to the antibody-antigen complex (complement fixation)

Alternative pathway: complement factors interact with microorganism surface carbohydrates

- Both lead to a cascade of protein activation, leading to activation of C3

Innate Internal Defenses

Inflammatory Response

Phagocyte mobilisation: infiltration of damaged area by neutrophils and macrophages

Leucocytosis: leukocytosis-inducing factors released by injured cells

promote rapid release of WBCs from marrow

Margination: increased vascular permeability causes decreased fluid in vessels; blood flow slows, neutrophils cling to vessel margins

Innate Defenses

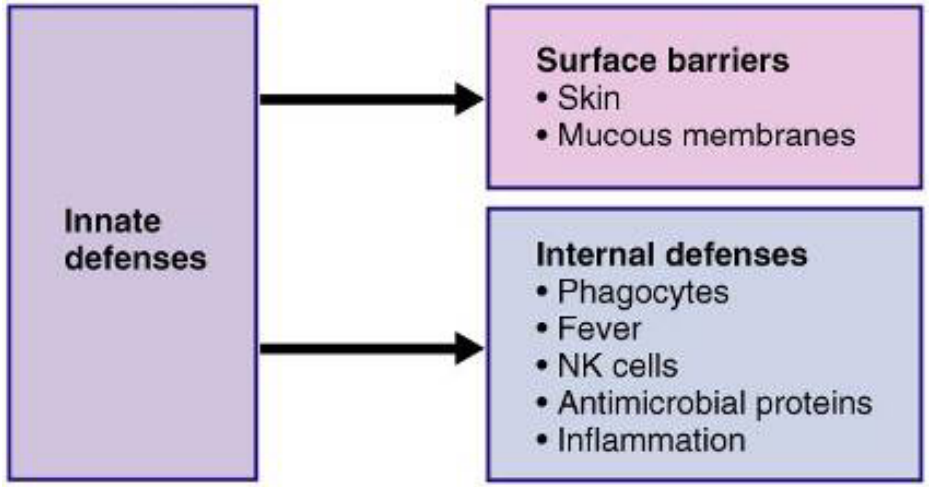
Inflammatory Response

Diapedesis: neutrophils migrate through capillary walls

Chemotaxis: inflammatory chemicals attract neutrophils to move up the chemical concentration gradient

As the process continues, monocytes move into the area and become macrophages.

Innate Defenses



Innate: structural defenses; respond to nonspecific foreign substances

- First line: external surface epithelium and membranes
- Second line: inflammatory processes – antimicrobial proteins, phagocytes, etc.