Innate and adaptive immunity

What is Immunity?

Immunity - derived from *immunitas:*

Latin for exemption from civic duties and prosecution

Immunity

- Protection from disease and especially infectious disease.

- Cells and molecules involved in such protection constitute the **immune system**

The most important physiologic function of the immune system is to prevent infections and to eradicate established infections

Immune system is fundamentally different from other systems

- There are relatively few organs that can be identified with the immune system, and these are small and widely distributed--bone marrow, thymus, lymph nodes, spleen (lymphatic system, blood);
- There are a huge number of immune system cells in humans and they mostly are mobile;
- It makes the immune “system”amorphous, diffuse, and hard to pin down.

Immune response

- The immune system recognizes a substance and identifies it as *foreign*--that is, not a normal component of the organism

- Then the immune cells and organs alter their properties and behavior in order to remove the invader from the body--and it's these changes that we call the immune response.

A network of cells and tissues that:

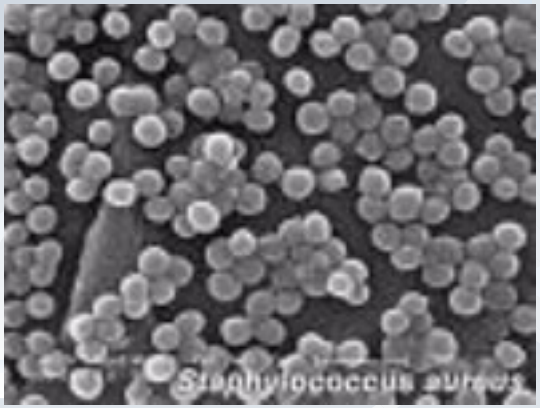
- Defends the body against invading pathogens;
  a) Intracellular (*e.g.* viruses and some bacteria and parasites);
  b) Extracellular (*e.g.* most bacteria, fungi and parasites);
- Removes ‘worn-out’ cells;
- Destroys abnormal/mutant cells within the body (e.g. control of cancer).

Role of the immune system	Implications
Defense against infection	Deficient immunity results in increased susceptibility to infection; exemplified by AIDS
Defense against tumors	Potential for immunotherapy of cancer
The immune system recognize and responds to tissue grafts and newly introduced molecules	Immune responses are barriers to transplantation and gene therapy
The immune system can injure cells and induce pathologic inflammation	Immune response are the cause of allergic, autoimmune and other inflammatory disease

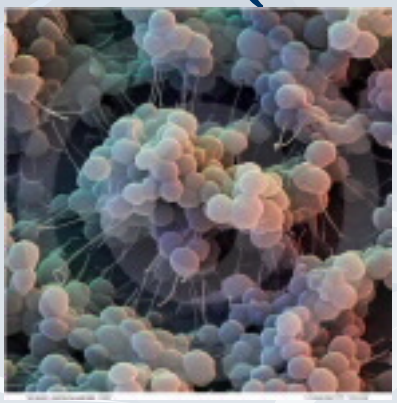
Immune System can also have harmful effects:

- Allergies
- Autoimmune diseases
- Tissue rejection.

Infection-causing organisms (Pathogens)



BACTERIA
Staphylococcus aureus
(causes sepsis)



Staphylococcus epidermis

FUNGUS
Epidermophyton floccosum
(athlete's foot)

VIRUS
HIV (AIDS)

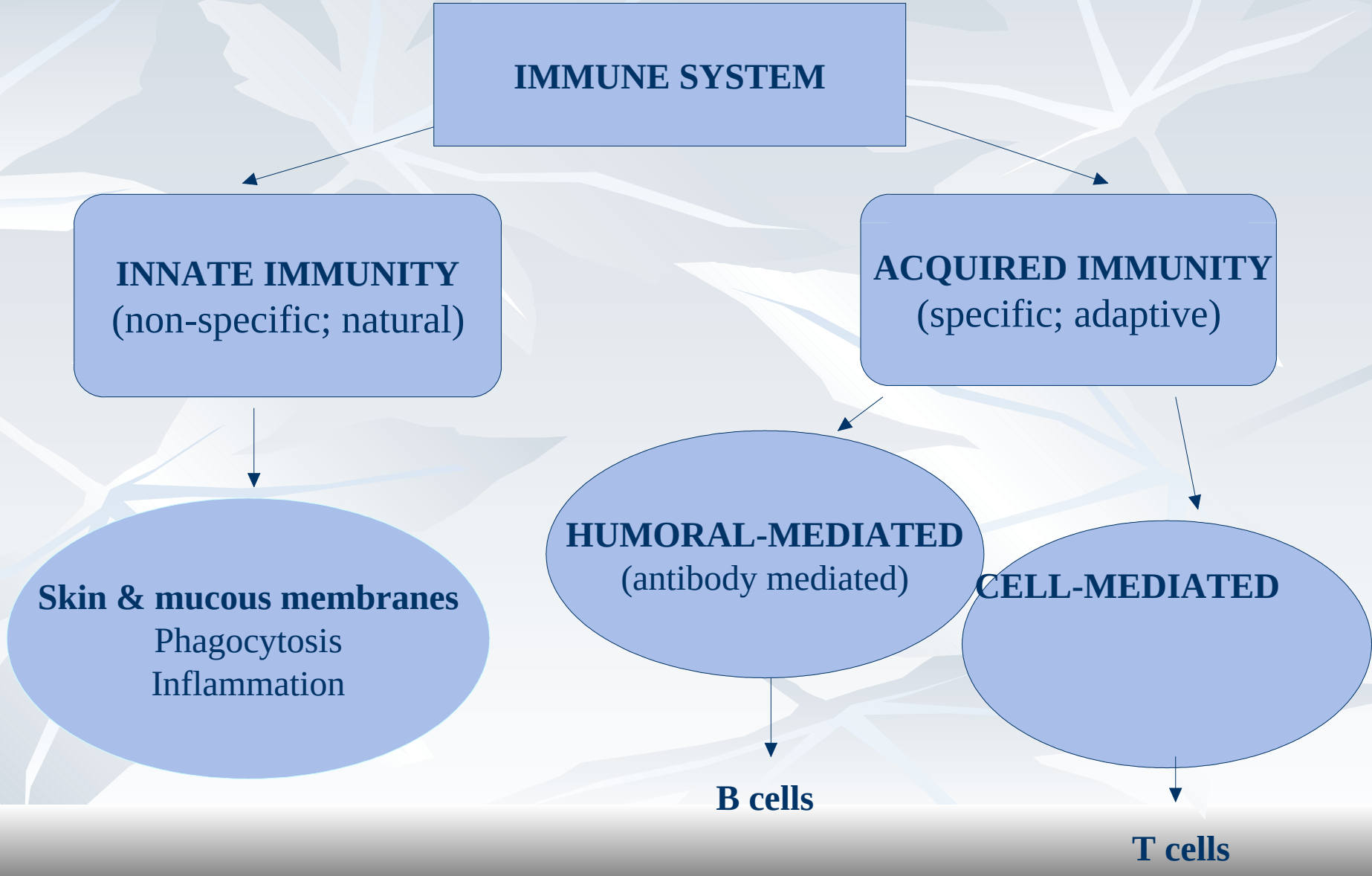
PARASITE
Tapeworm

PROTOZOA
Giardia lamblia

Infection and Immunity Balance

$$\text{Disease} = \frac{\text{Bolus of infection x virulence}}{\text{immunity}}$$

Organisation of the Immune System



Innate and Acquired Immunity

The immune system is split into two functional divisions.

Innate Immunity *is the first line of defense against infectious agents;*

It is present at birth and changes little throughout the life of the individual.

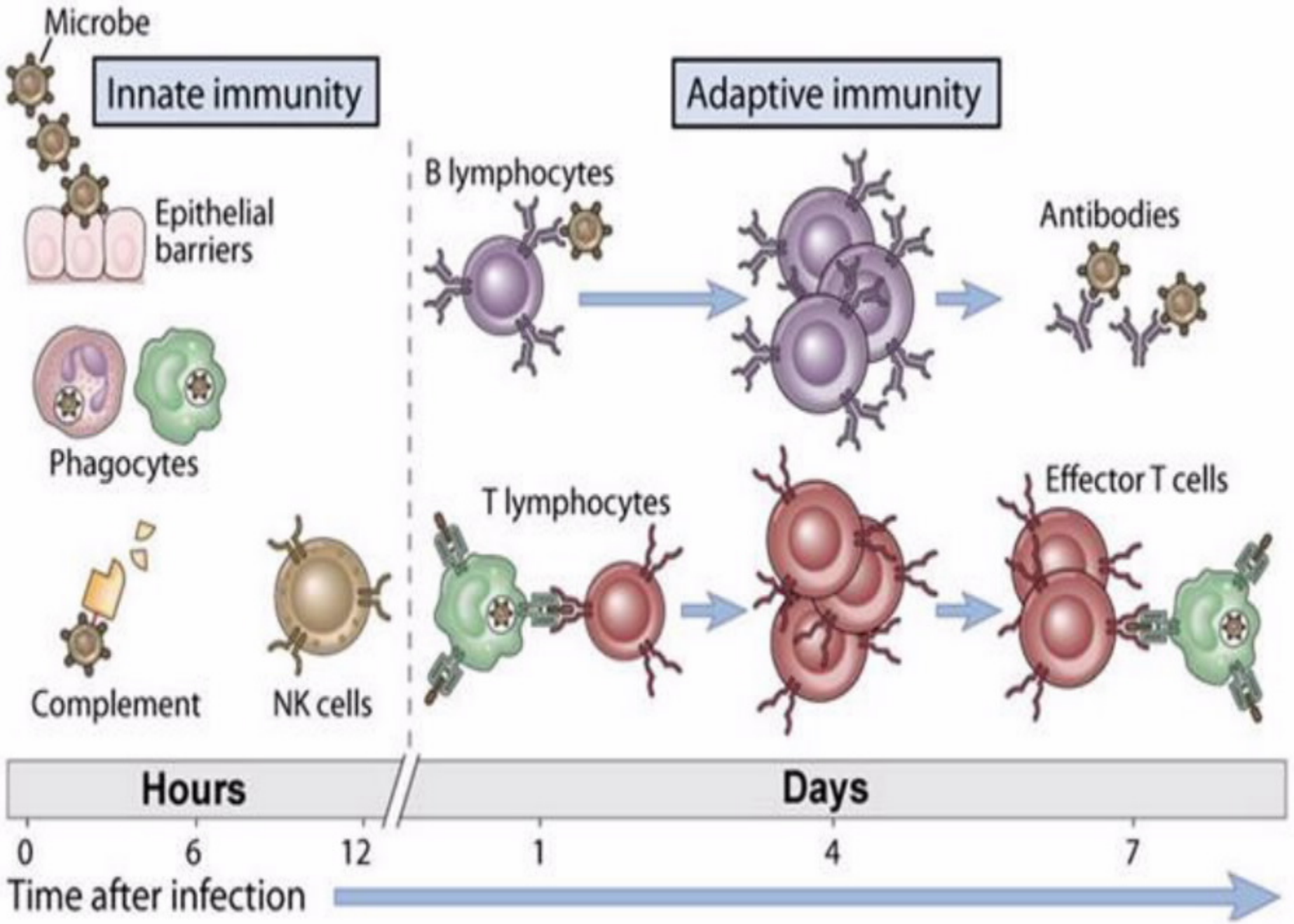
Acquired immunity *produces a specific response to each infectious agent. Furthermore , … remembers the particular infectious agent and can prevent it causing disease later*

Characteristics Innate and Adaptive Immunity

INNATE	ACQUIRED
Humoral	
Acute phase proteins	Antibody
INF	
Lysozyme	
Complement	

Characteristics Innate and Acquired Immunity

INNATE	ACQUIRED
Cell- mediated	
Natural killer cells	T lymphocytes
Phagocytes	B lymphocytes


Microbe
Innate immunity
Adaptive immunity
Epithelial barriers
B lymphocytes
Antibodies
Phagocytes
T lymphocytes
Effector T cells
Complement
NK cells
Hours
Days
0
6
12
1
4
7
Time after infection

How does the Innate IS recognize microbes and damaged cells?

- Inflammation-accumulation and activation of leucocytes and plasma proteins at sites of infection or tissue injury.
- Antiviral defense- NK and type I INF
- Intracellular bacteria- MF

The Innate IS usually responds in the same way to repeat encounters with a microbe, whereas the adaptive IS responds more efficiently to each successive encounter with a microbe

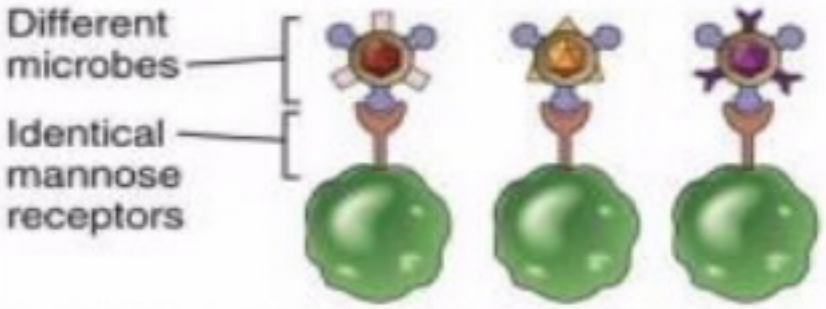
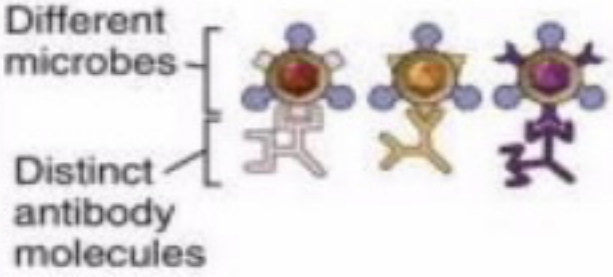
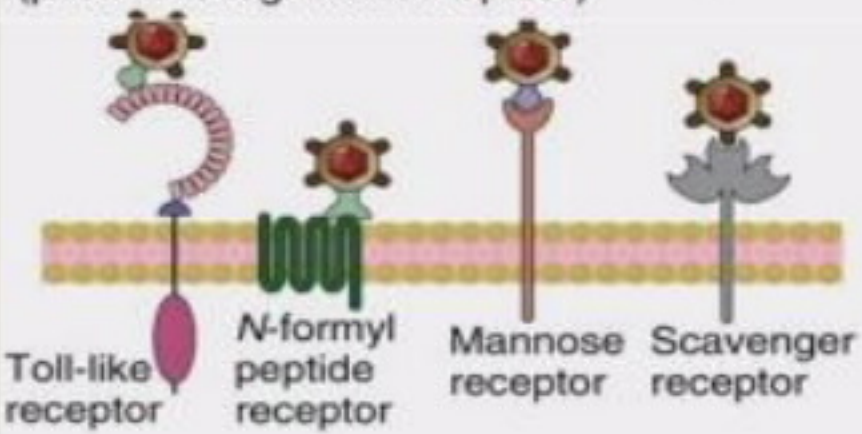
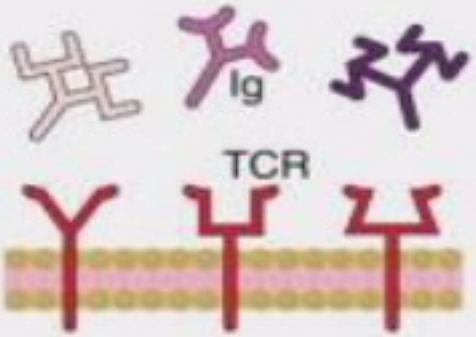
The components of innate immunity have evolved to recognize structures of microbes that are often essential for the survival and infectivity of these microbes

- The receptors of the IIS are encoded in the germline and are not produced by somatic recombination of gene.
- All the receptors of IIS probably recognize less than a thousand microbial patterns.

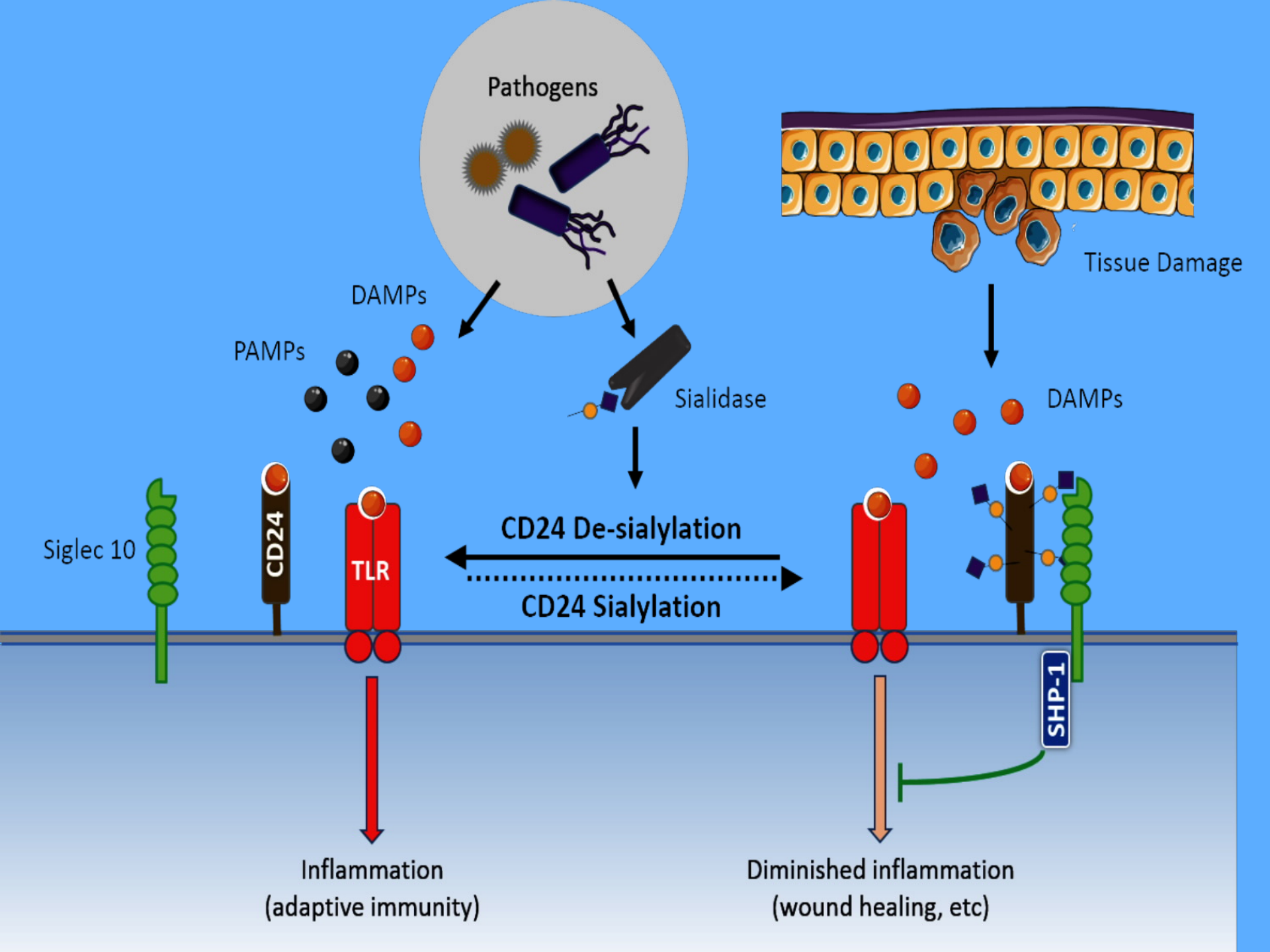
The IIS does not react against the host

IIS recognizes structures that are shared by various classes of microbes and are not present on normal host cell

- MF- LPS R
- Mannose R
- Double stranded ribonucleic acid – dsRNA
- Unmetylated oligonucleotides- CpG
- PAMPs- PRRs

	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns) or damaged cells (damage-associated molecular patterns) 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Receptors	Encoded in germline; limited diversity (pattern recognition receptors) 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of normal self and nonself	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on selection against self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

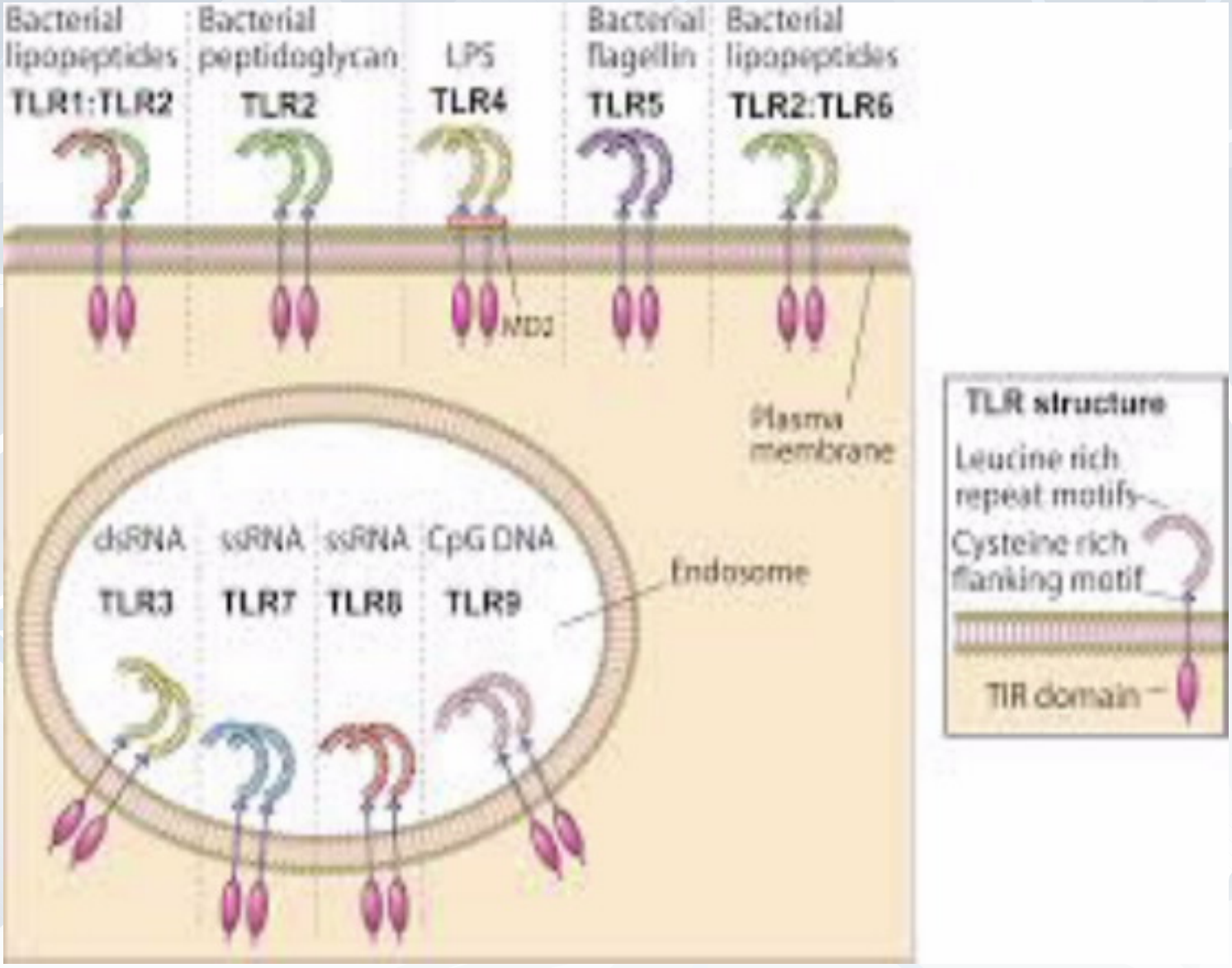
The IIS also recognizes molecules that are released from damaged or necrotic cells. Damage-associated molecular patterns DAMPs


Pathogens
DAMPs
PAMPs
Sialidase
Tissue Damage
DAMPs
Siglec 10
CD24
TLR
CD24 De-sialylation
CD24 Sialylation
SHP-1
Inflammation
(adaptive immunity)
Diminished inflammation
(wound healing, etc)

TLR	Typical Ligands
TLR1	Bacterial lipoproteins
TLR2	lipoteichoic acid (LTA), peptidoglycan (PGN), bacterial lipoproteins, zymosan
TLR3	Double-stranded RNA
TLR4	Lipopolysaccharide (LPS), viral envelope protein MMTV, RSV F protein
TLR5	Flagellin
TLR6	LTA, diacyl lipoproteins, zymosan
TLR7	ssRNA, imidazoquinolines
TLR8	ssRNA, imidazoquinolines
TLR9	Unmethylated CpG DNA
TLR10	Undetermined
TLR11*	Uropathogenic bacteria, profilin-like protein

** a functional gene for TLR11 has only been found in mice.*

Table 1. Toll-like receptors (TLRs) and some of their important ligands. *(Adapted from Akira and Takeda,* Nat. Rev. Immunol. *4, 499, 2004.)*


Bacterial lipopeptides
TLR1:TLR2
Bacterial peptidoglycan
TLR2
LPS
TLR4
Bacterial flagellin
TLR5
Bacterial lipopeptides
TLR2:TLR6
MD2
Plasma membrane
dsRNA
TLR3
ssRNA
TLR7
ssRNA
TLR8
CpG DNA
TLR9
Endosome
TLR structure
Leucine rich repeat motifs
Cysteine rich flanking motif
TIR domain

NOD –like receptors

- NLRP-3 ---NOD like receptor pyrin domain containing 3;

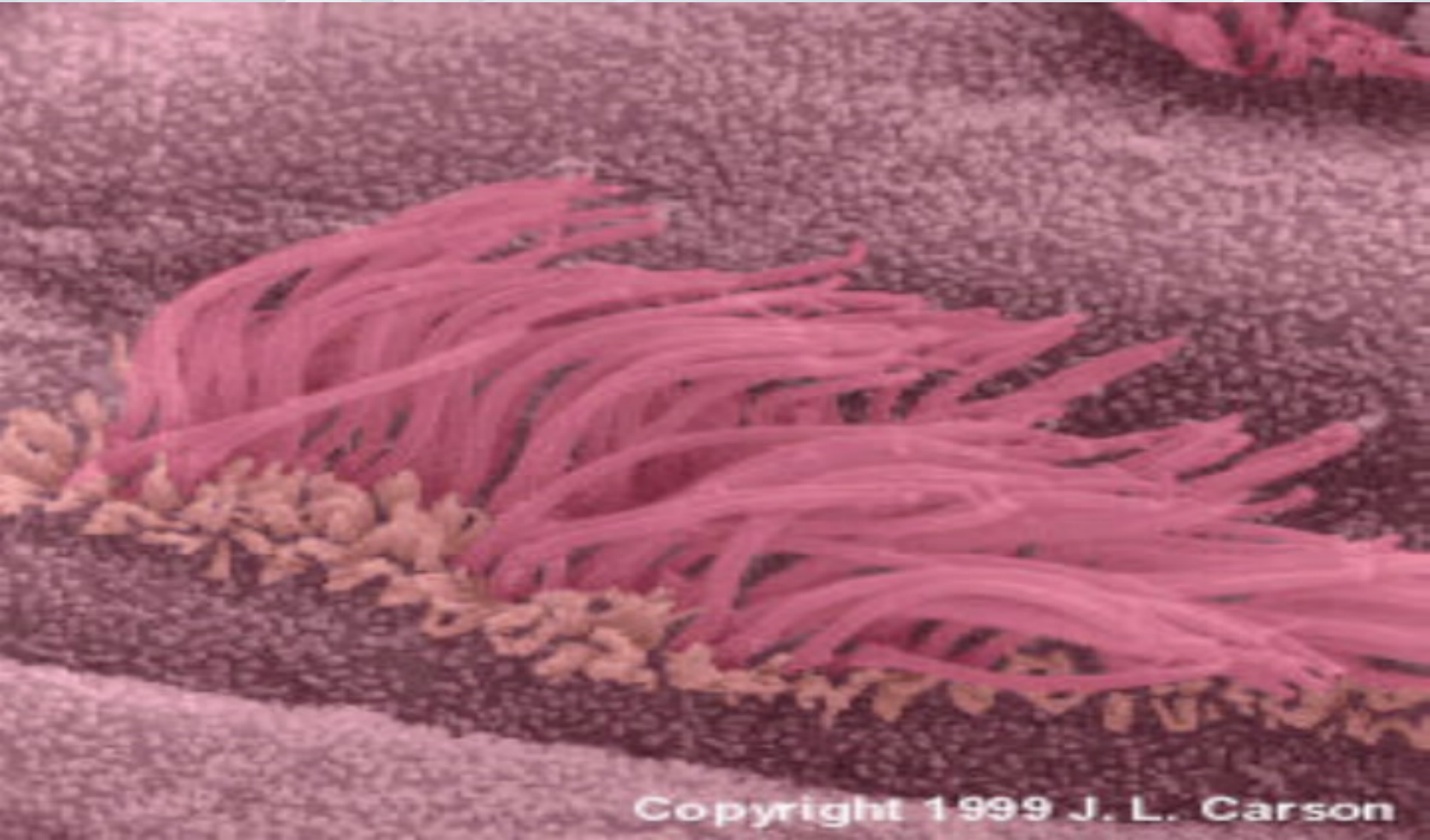
Recognize:

- to microbial products;
- substances that indicate cell damage and death;

Component	Functions
Skin and mucous membranes	
Intact skin	Forms a physical barrier to the entrance of microbes.
Mucous membranes	Inhibit the entrance of many microbes, but not as effective as intact skin.
Mucus	Traps microbes in respiratory and digestive tracts.
Hairs	Filter microbes and dust in nose.
Cilia	Together with mucus, trap and remove microbes and dust from upper respiratory tract.
Tear ducts	Tears dilute and wash away irritating substances and microbes.
Saliva	Washes microbes from surfaces of teeth and mucous membranes of mouth (Lysozyme and phospholipase A).
Epiglottis	Prevents microbes and dust from entering trachea.
Urine	Washes microbes from urethra.

Skin and mucous membranes – chemical factors	
Gastric juice	Destroys bacteria and most toxins in stomach.
Acid pH of skin	Discourages growth of many microbes.
Unsaturated fatty acids.	Antibacterial substance in sebum
Antimicrobial substances	
Interferon (IFN)	Protects uninfected host cells from viral infection.
Complement	Causes lysis of microbes. Promotes phagocytosis, contributes to inflammation attracts white blood cells to site of infection
	Other responses
Phagocytosis	Ingestion and destruction of foreign particles by microphages and macrophages
Inflammation	Confines and destroys microbes and repairs tissues
Fever	Inhibits microbial growth and speeds up body reactions that aid repair.

Cilliary elevator



Normal Commensals

- On Skin
- In the Mouth
- In the UGS
- In the GIS

Gastrointestinal tract contains many billions of bacteria that have a symbiotic relationship with the host;

This bacteria help to prevent pathogens from:

- colonizing the site;
- by preventing attachment;
- competing for essential nutrients;
- releasing antibacterial substances (colicins, short-chain fatty acids);

lactobacilli

Predominant bacteria at various anatomical locations in adults.

- Inhabit Vagina
- pH 4.0-4.5

INNATE IMMUNE SYSTEM

Lysozyme in tears kills Gram-positive bacteria

Removal of particles by turbinates and humidification

Mucus and cilia capture organisms and remove them

Skin: physical barrier

Stomach acid kills ingested pathogens

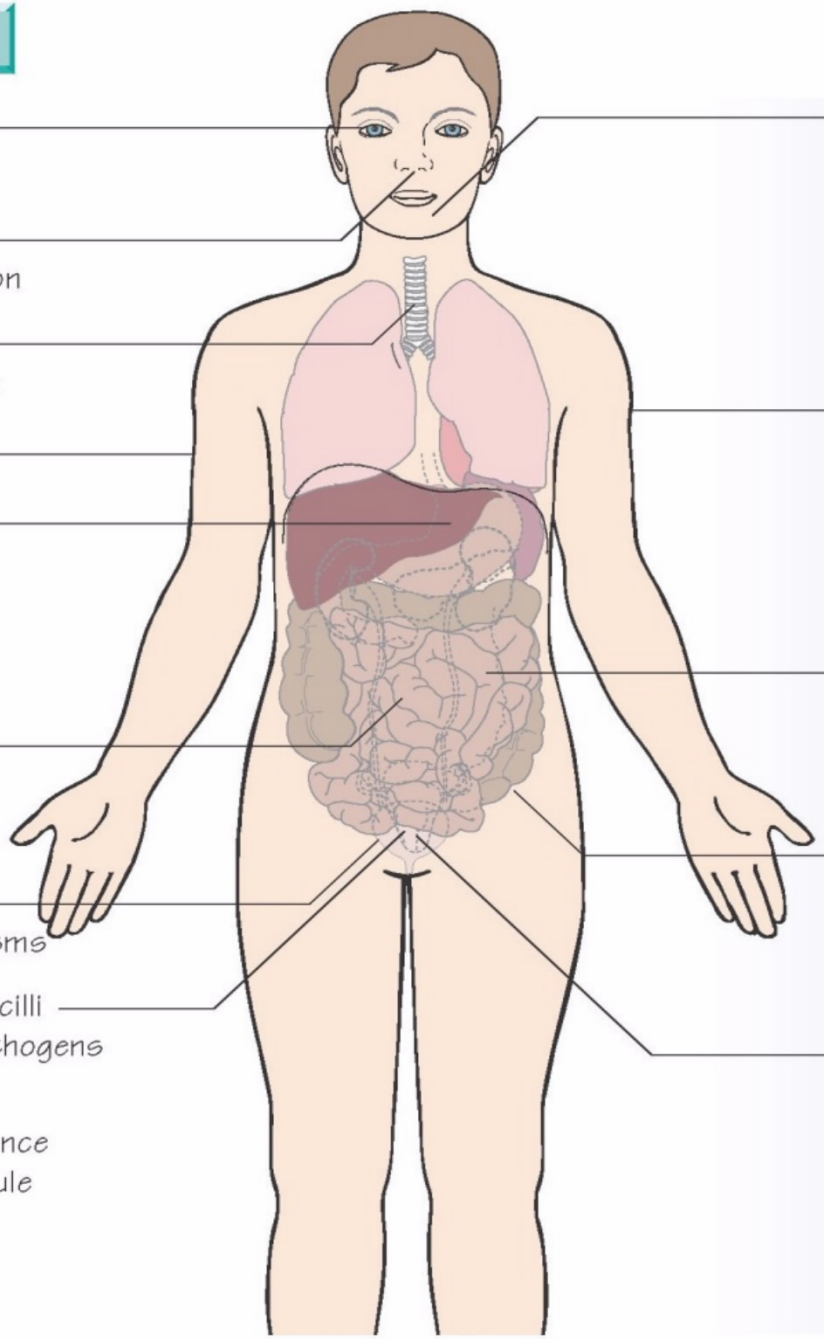
Fatty acids inhibit growth of many bacteria

Competition and toxic products from intestinal flora

Flushing action of urinary flow removes organisms

Low vaginal pH from lactobacilli prevents colonization by pathogens

Whole body:
- Molecular and cellular defence
- Pattern recognition molecule e.g. TLRs
- Neutrophils
- Macrophages



NORMAL FLORA

NASOPHARYNX
- Streptococci
- *Haemophilus*
- *Neisseria*
- Mixed anaerobes
- *Candida*
- *Actinomyces*

SKIN
- Staphylococci
- Streptococci
- Corynebacteria
- Proprionibacteria
- Yeasts

UPPER BOWEL
- Enterobacteriaceae
- Enterococci
- *Candida*

LOWER BOWEL
- *Bacteroides*
- Bifidobacteria
- *Clostridium*
- Peptostreptococci

VAGINA
- Lactobacilli
- Streptococci
- Corynebacteria
- *Candida*
- *Actinomyces*
- *Mycoplasma hominis*

Humoral components of Innate immunity

Complement (C') -- Killing of microbes, opsonization of microbes, actvation leukocytes

Mannose-binding protein--Opsonization of microbes and activation of C'

C-reactive protein -- Opsonization of microbes and activation of C'

Lysozyme-- Bacterial cell wall lysis

Cytokines

TNF, IL-1, 6, 18 -- Inflammation

IFN α, β-- Resistence to viral infection

IFN γ--Macrophage activation

IL-12-- IFNγ production by NK cells

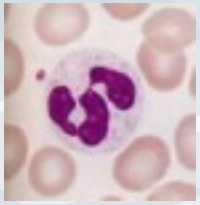
IL-15 -- Proliferation of NK cells, memory T cells

IL-10, TGF β ---Control of Inflammation

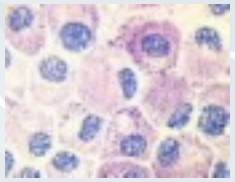
Cellular Components of Innate Immunity

Circulating and Tissue Effector Cells

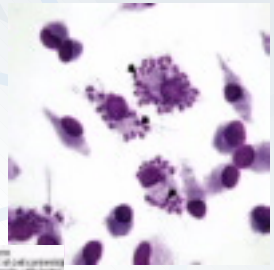
Neutrophils - Early phagocytosis and killing of microbes



Mast Cells - Release of inflammatory granules

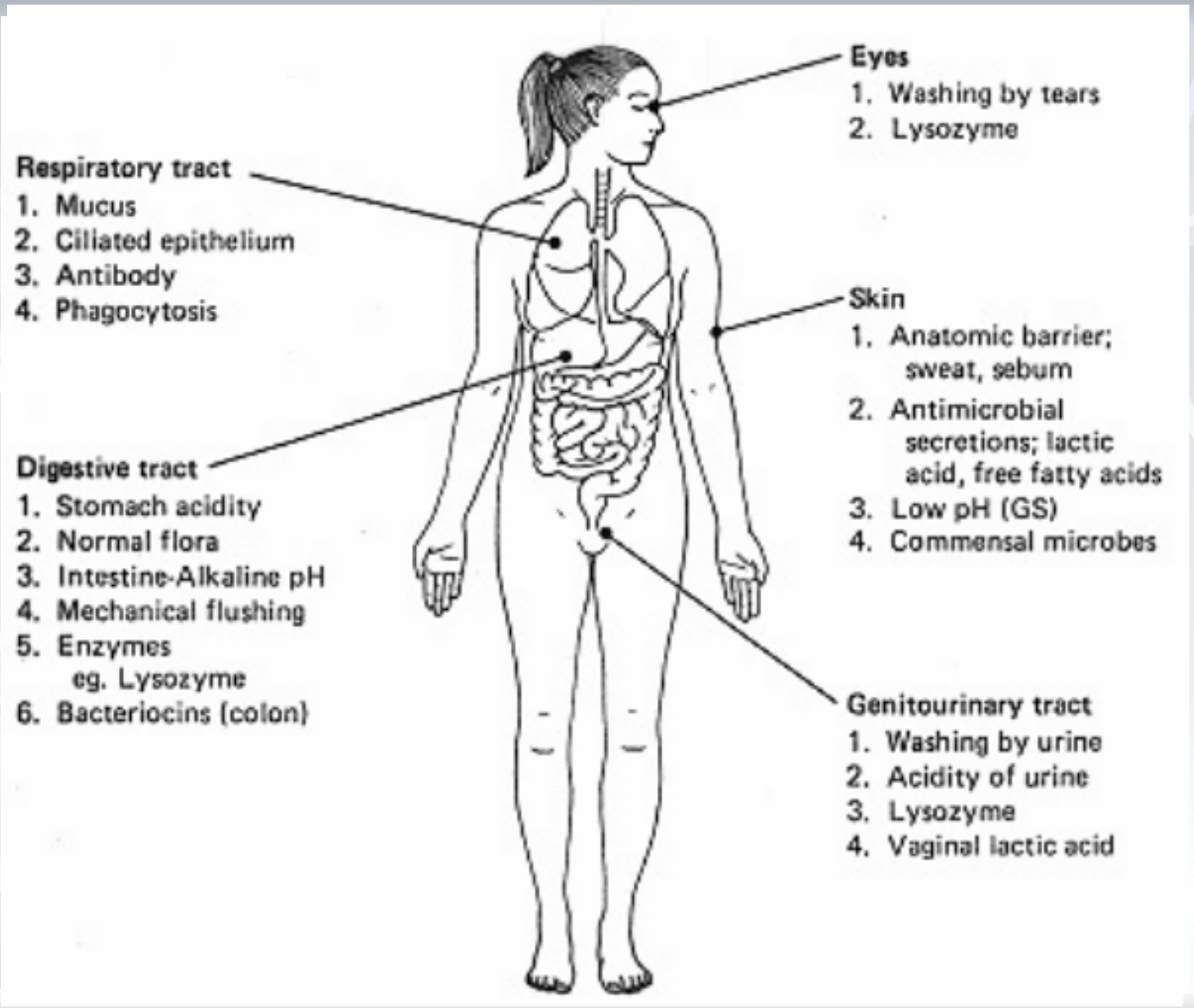


Macrophages - Efficient phagocytosis and killing of microbes: cytokines



Eosinophils - Nasty toxic cells designed to kill helminths (worms)

NK cells - Lysis of infected cells, activation of macrophages


Eyes
1. Washing by tears
2. Lysozyme
Respiratory tract
1. Mucus
2. Ciliated epithelium
3. Antibody
4. Phagocytosis
Skin
1. Anatomic barrier; sweat, sebum
2. Antimicrobial secretions; lactic acid, free fatty acids
3. Low pH (GS)
4. Commensal microbes
Digestive tract
1. Stomach acidity
2. Normal flora
3. Intestine-Alkaline pH
4. Mechanical flushing
5. Enzymes
eg. Lysozyme
6. Bacteriocins (colon)
Genitourinary tract
1. Washing by urine
2. Acidity of urine
3. Lysozyme
4. Vaginal lactic acid

Adaptive Immunity

Specificity

Lymphocytes (B and T cells) bind and respond to foreign molecules known as antigens via antigen receptors

Diversity

The body possesses millions of lymphocytes that can recognize and respond to millions of antigens (one each)

Memory

1st exposure to an antigen generates lymphocytes & long-lived memory cells – next exposure to the same antigen, memory cells react more quickly & stronger response

Self-Tolerance

Lymphocytes can distinguish ‘self’ (our normal antigens) from ‘non-self’ (antigens from foreign material).

Adaptive Immune System

Unlike the **Innate** immune system, the adaptive/acquired Immune system exhibits 2 specific characteristics:

- **SPECIFICITY**
- **DIVERSITY**
- **MEMORY**

“Specificity” is one of the central ideas in immunology,

“specificity”, which means a response tailored to one kind of pathogen rather than an indiscriminate protection against many different pathogens.

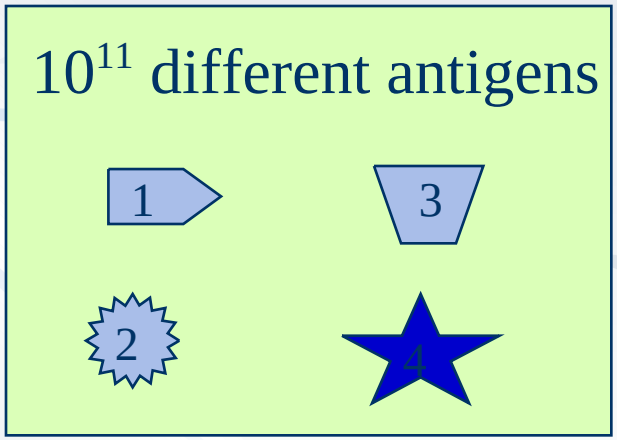
When the body detects a foreign substance, it mounts an immune response against that substance and no other.

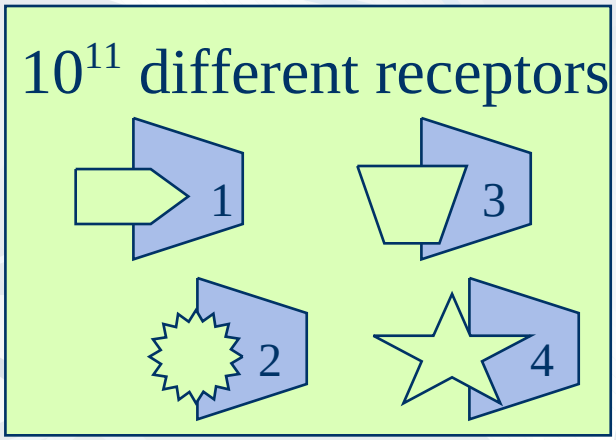
So, the immune system only responds to one pathogen at a time, not to all possible pathogens.

In other words, it is specific.

SPECIFIC IMMUNITY

For each different antigen there is a specific receptor





MEMORY

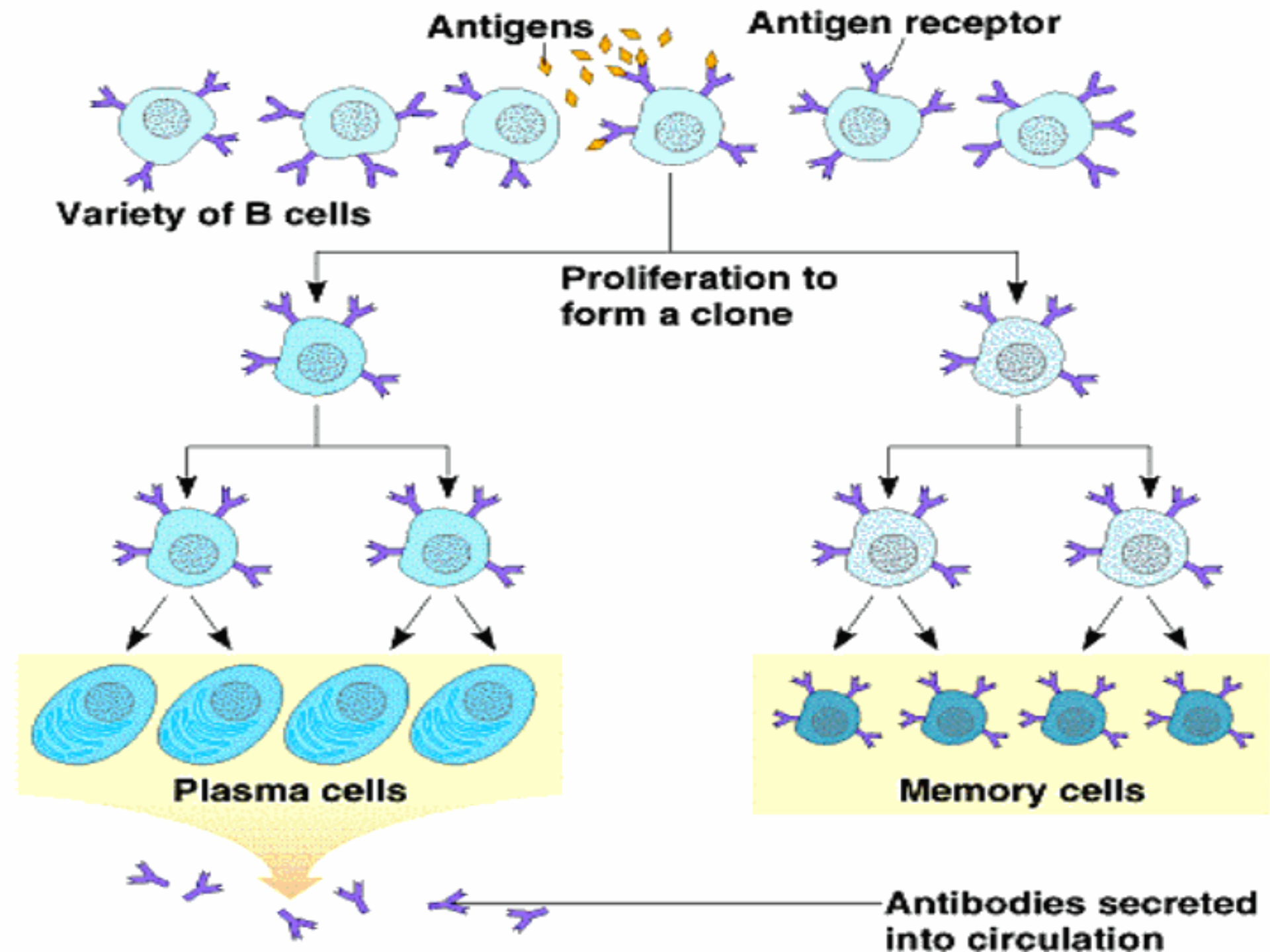
This is the basis of vaccination.

The Acquired Immunity will respond more effectively, and more vigorously to a secondary exposure of any given antigen.

Normally, this results in a protective response.

Memory cells

- Some kinds of T lymphocytes and some B lymphocytes don’t become effector cells after they’re exposed to antigen;
- Instead they differentiate into specialized cells called ***memory*** B or T lymphocytes.


Antigens
Antigen receptor
Variety of B cells
Proliferation to form a clone
Plasma cells
Memory cells
Antibodies secreted into circulation

These "memory cells" have two properties:

- First- there are lots of them (far more than the original number of cells with a particular antigen receptor), that have specific receptors for that antigen.
- Second - memory cells can be stimulated to divide by antigen more easily and more rapidly than unexposed (“naive”) lymphocytes.

The adaptive immune system can be subdivided into

- antibody-based (**humoral)** immunity
- cell based (**cellular)** immunity

Humoral Immunity

- Humoral immunity is generated by ANTIBODY RESPONSES.

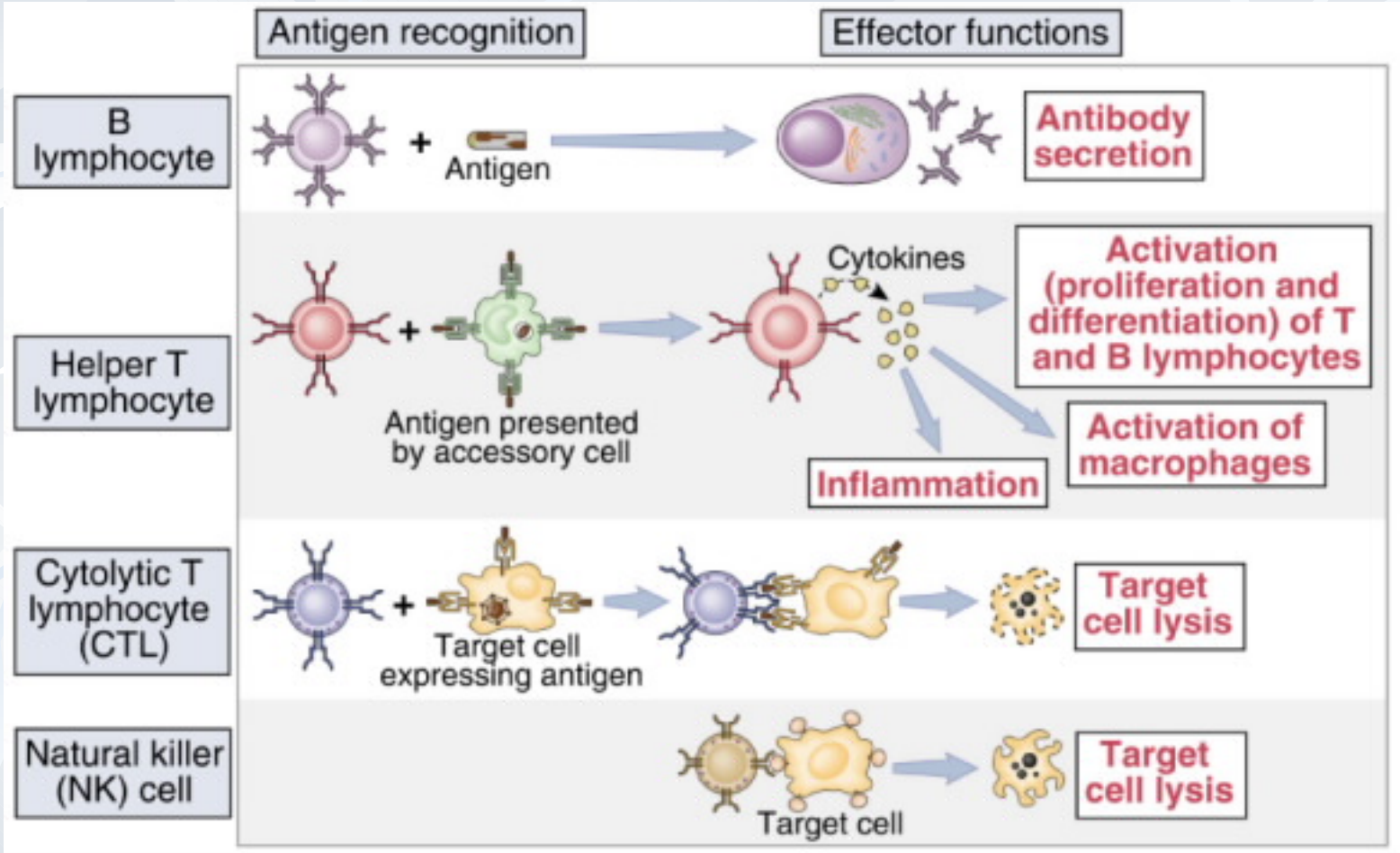
- Humoral immunity targets **extracellular** antigens, including bacteria, protozoa, parasites.

Cellular Immunity

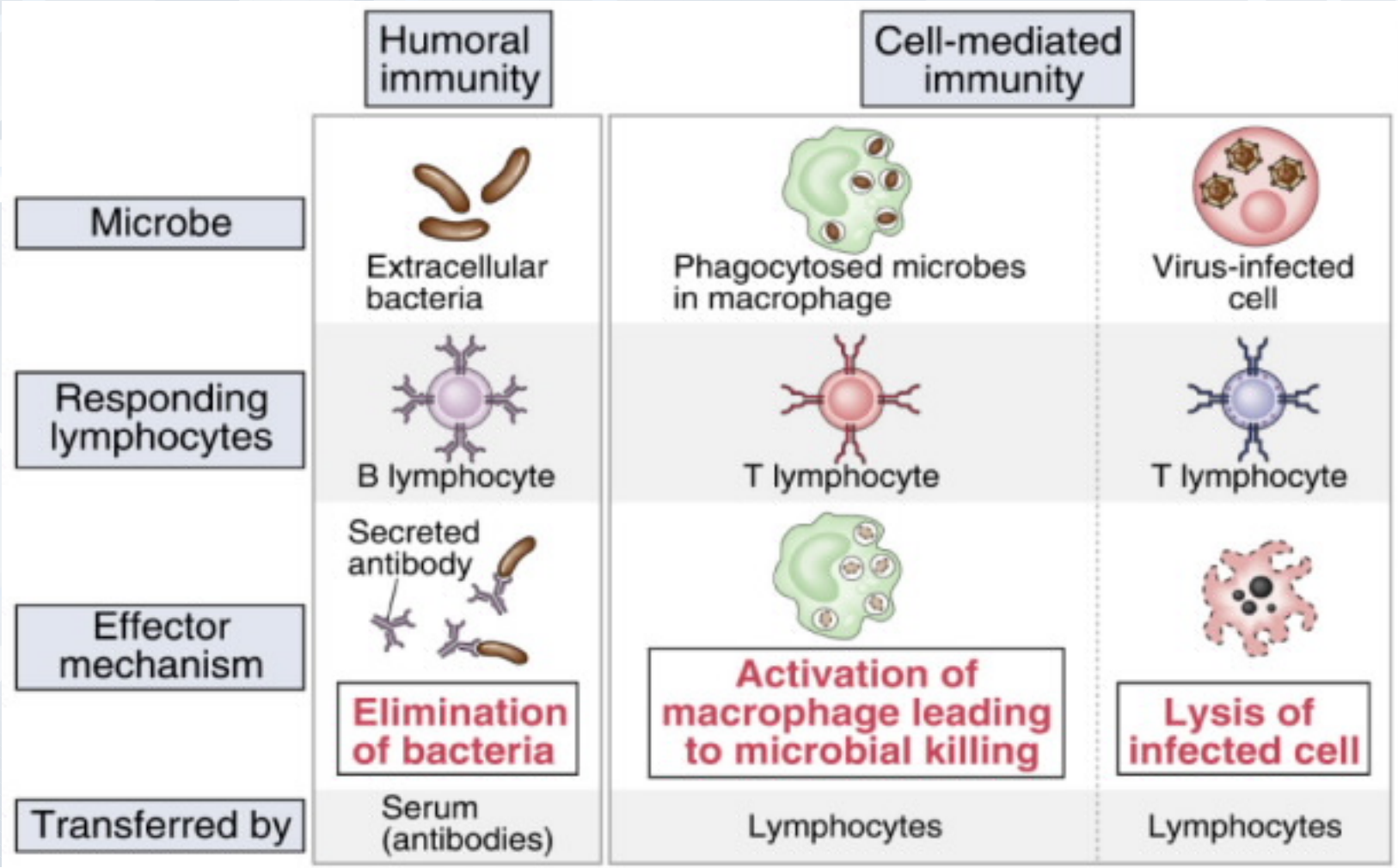
Cellular Immunity serves 2(3) basic purposes:

- *To assist the humoral response by secretion of cytokines*
- *To kill foreign eukaryotic cells, or altered self cells.*
  - Virally infected cells
  - Organ grafts
  - Cancer
- *(To suppress specific immune responses)*

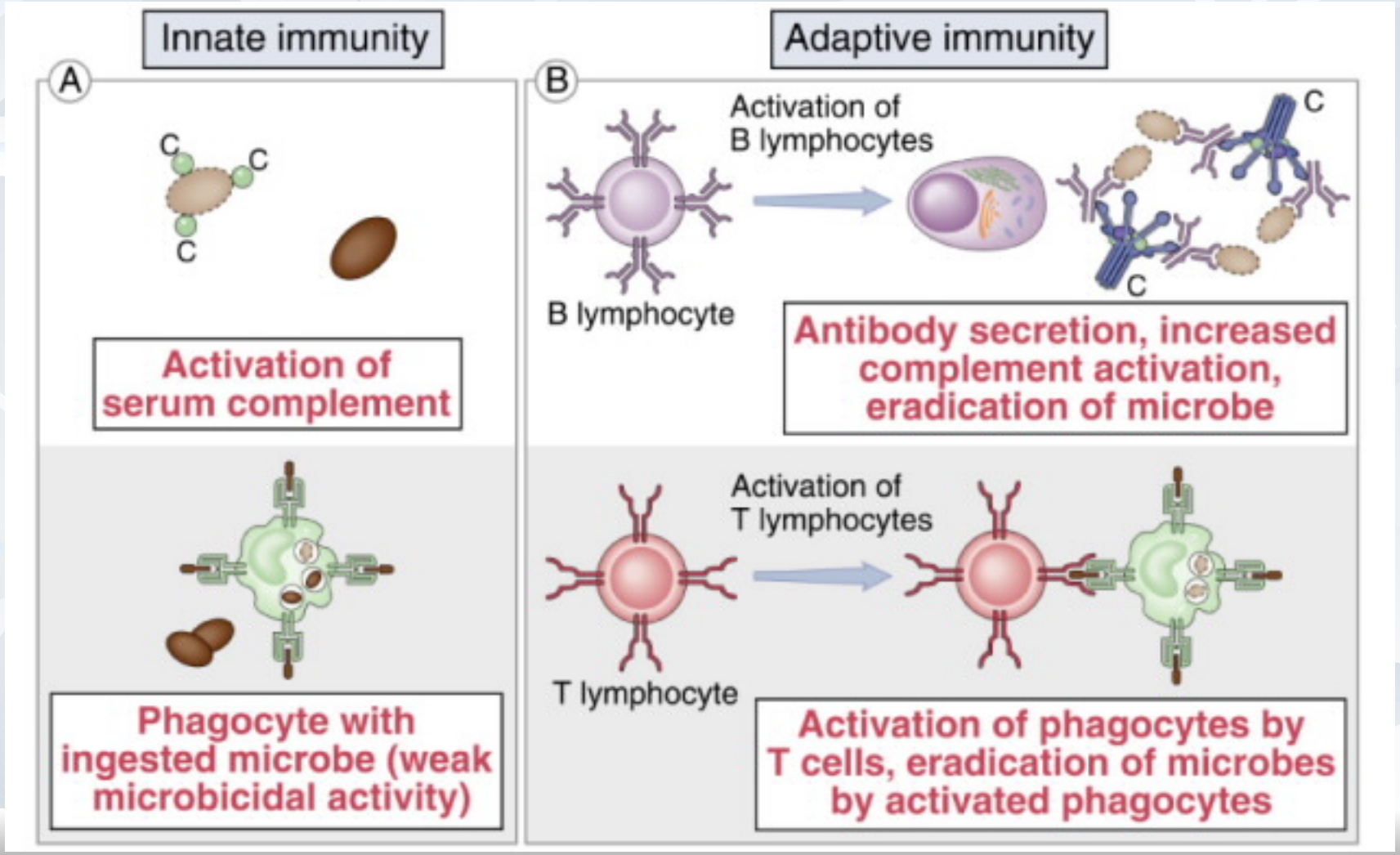
Classes of lymphocytes



Humoral vs. Cell-mediated immunity



Adaptive immunity enhances innate immunity



Innate vs Adaptive Immunity

Innate
(Phagocytosis, Inflammation)

Nonspecific

– Defends against any pathogen upon first exposure
– Responds to infectious agents, chemical irritants, tissue injury, burns
- No memory

Adaptive
(Lymphocytes)

Specific

– Responds to specific pathogens on 2nd or later exposure
– Comes into play after nonspecific responses have begun.
- Memory

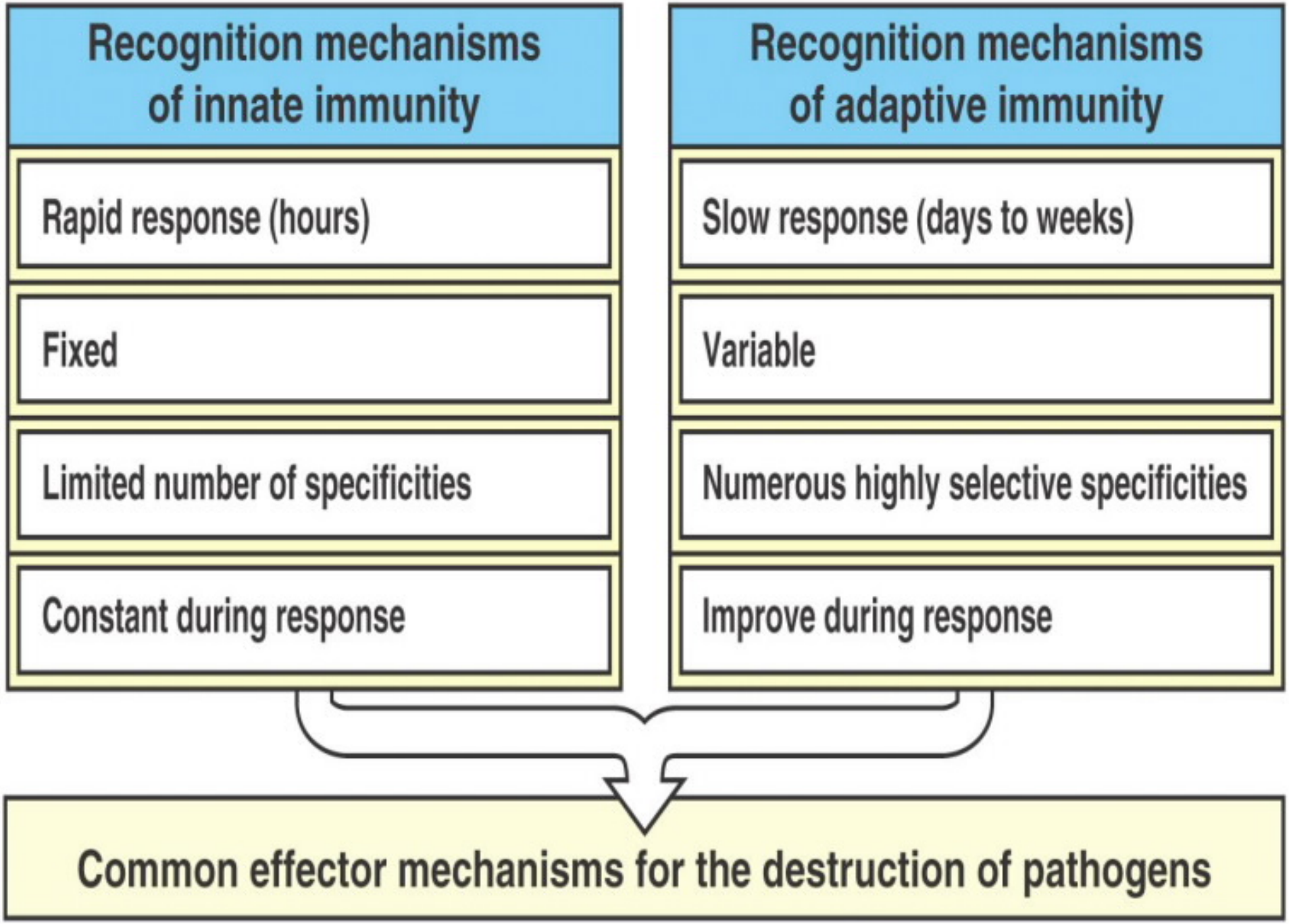
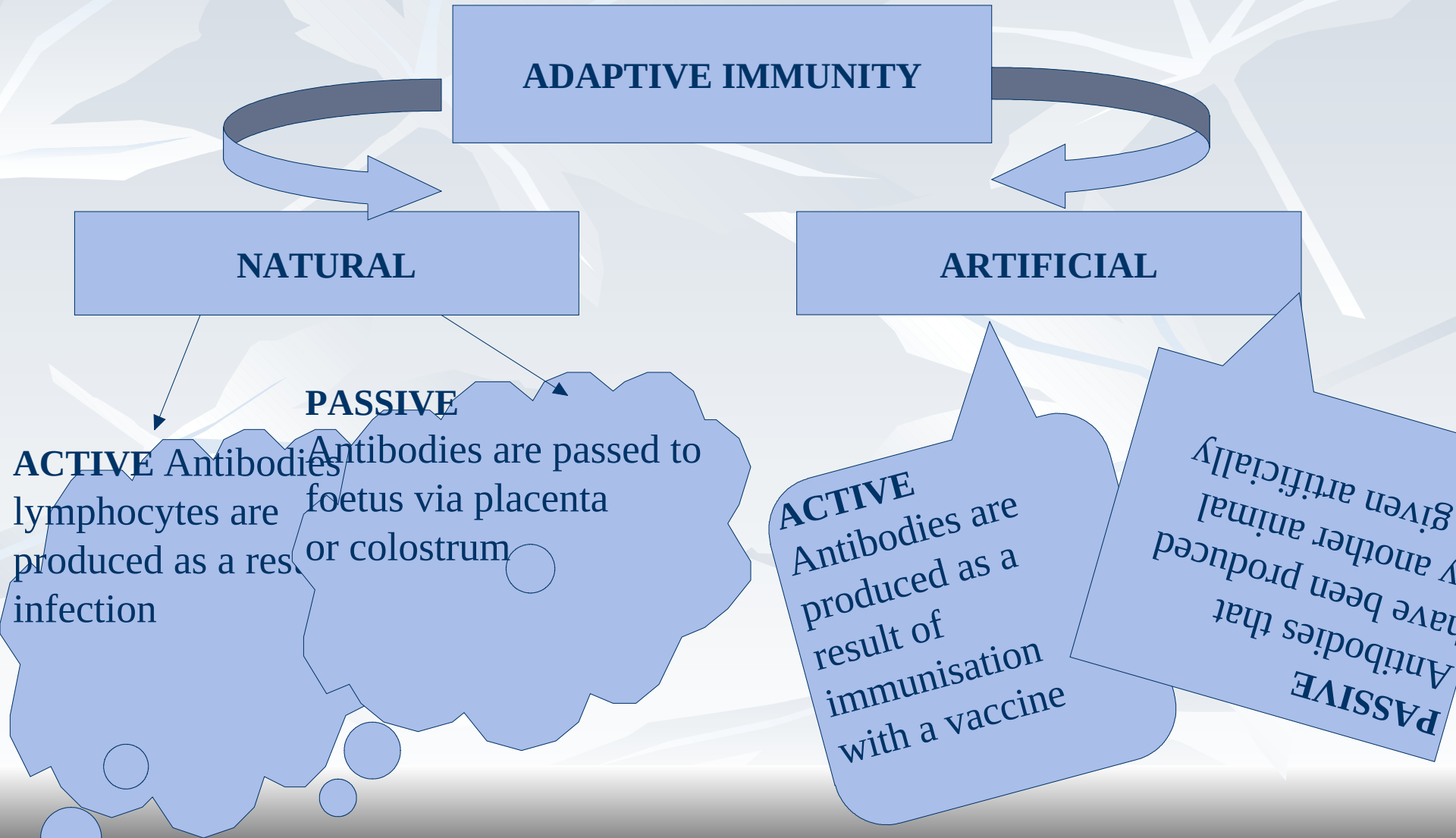


Figure 1-7 The Immune System, 2/e (© Garland Science 2005)

Adaptive Immunity can be NATURAL or ARTIFICIAL



Naturally acquired, Artificially acquired

- **Naturally** occurs without human intervention.
- **Artificially** occurs when antigens or antibodies are given to a person by artificial means, e.g. by injection.

Active, Passive

- When immunity arrives from a response of the immune system, it is called ***active immunity***. This involves producing the antibodies / or lymphocytes yourself;
- ***Passive immunity*** is provided by antibodies that have not been produced in the person's own immune system as a result of an immune response to a pathogen.

Natural Active

- This occurs by a person contracting a disease which is referred to as ***naturally acquired active*** immunity.
- Whenever T-Cells and B-Cells are activated, some become "memory" cells.
- The next time that an individual encounters that same antigen, the immune system is primed to destroy it quickly.
- Long-term Immunity

AB protect organisms by a variety of mechanisms

- Neutralization of toxins
- Lysis of bacteria in presence of C
- Opsonization of bacteria to facilitate phagocytosis
- Interference of with adherence of bacteria and viruses to cell surface

T cells mediate a variety of reactions

- Cytotoxic destruction of virus infected cells and bacteria;
- Activation of MF
- Help B cells


wiseGEEK

Artificial Active

This occurs via an injection of weakened (attenuated) or dead antigens. In this case an immune response is activated resulting in the production of antibodies and memory cells. This latter form of immunity is called ***artificially acquired active*** immunity.

The principle of immunization is based on this.

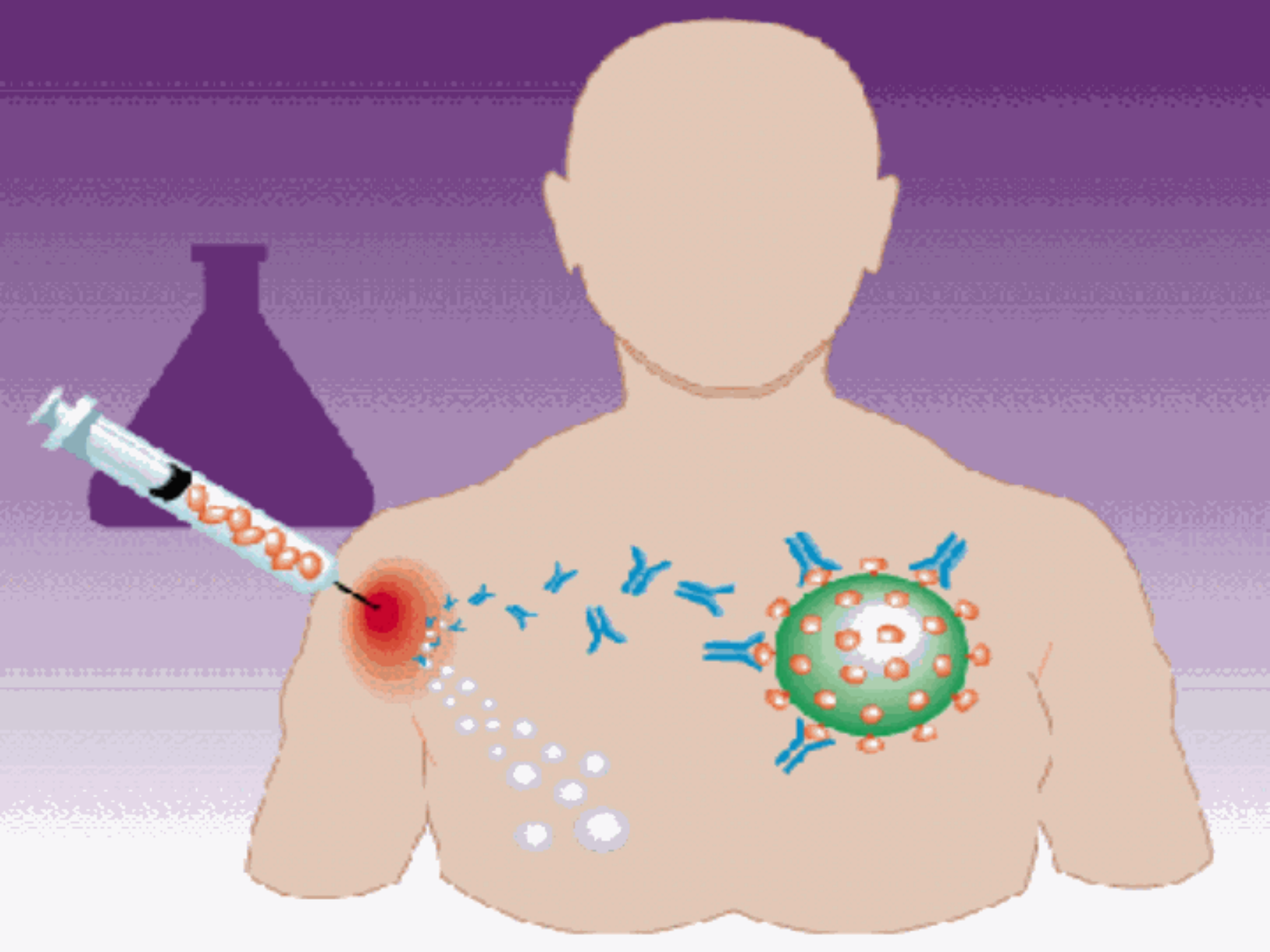
Natural Passive

- This could happen ***naturally*** when a mother passes her own antibodies to her baby, either through her placenta or her breast milk.
- Infants are protected by antibodies they receive from their mothers (primarily before birth).

Short-term Immunity

Artificial Passive

Another method of gaining ***passive*** immunity is ***artificially***, for example when a person is given an injection of antibodies if they suspect that they have been exposed to a disease such as tetanus or diphtheria.

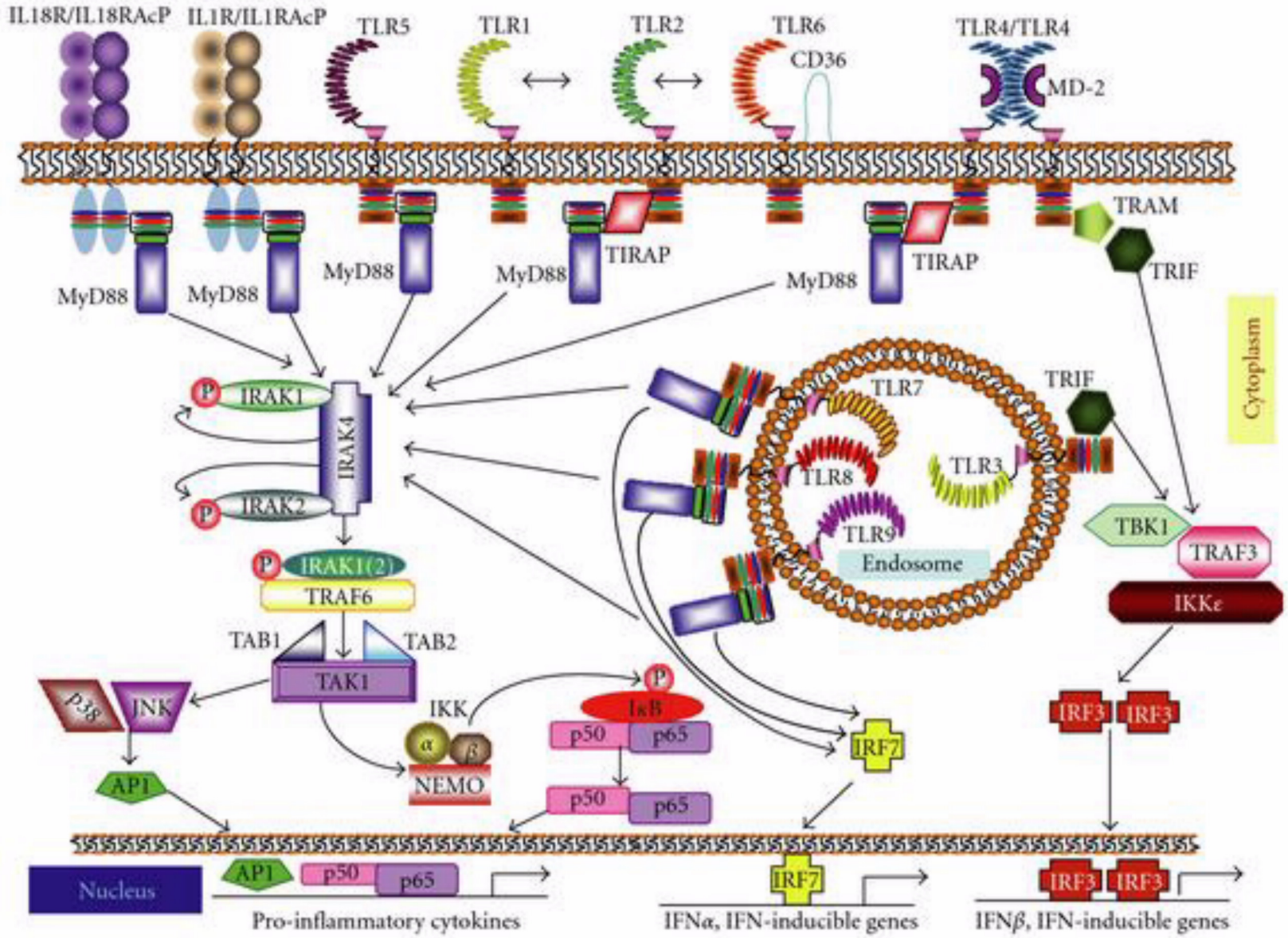


Questions

- After Frank takes the cold pill, what kind of immunity was protecting himself? Explain. Passive or active?
- Describes at least three characteristics of the innate and adaptive immune response systems?
- Describes at least three characteristics of the innate and adaptive immune response systems? The primary and secondary immune response to antigen?

Questions

- What clue in the history of patient with recurrent pneumococcal or staphylococcal infections would favor a possible diagnosis of IRAK 4 deficiency?
- Why might IRAK deficient patients fail to respond to immunization with polysaccharide antigens?


IL18R/IL18RAcP
IL1R/IL1RAcP
TLR5
TLR1
TLR2
TLR6
CD36
TLR4/TLR4
MD-2
TRAM
TRIF
MyD88
MyD88
MyD88
MyD88
TIRAP
MyD88
TIRAP
Cytoplasm
P
IRAK1
IRAK4
P
IRAK2
TLR7
TRIF
TLR8
TLR3
TLR9
Endosome
TBK1
TRAF3
IKKε
P
IRAK1(2)
TRAF6
TAB1
TAB2
TAK1
p38
JNK
AP1
IKK
α
β
NEMO
P
IκB
p50
p65
p50
p65
IRF7
IRF3
IRF3
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Pro-inflammatory cytokines
IRF7
IFNα, IFN-inducible genes
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IFNβ, IFN-inducible genes

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