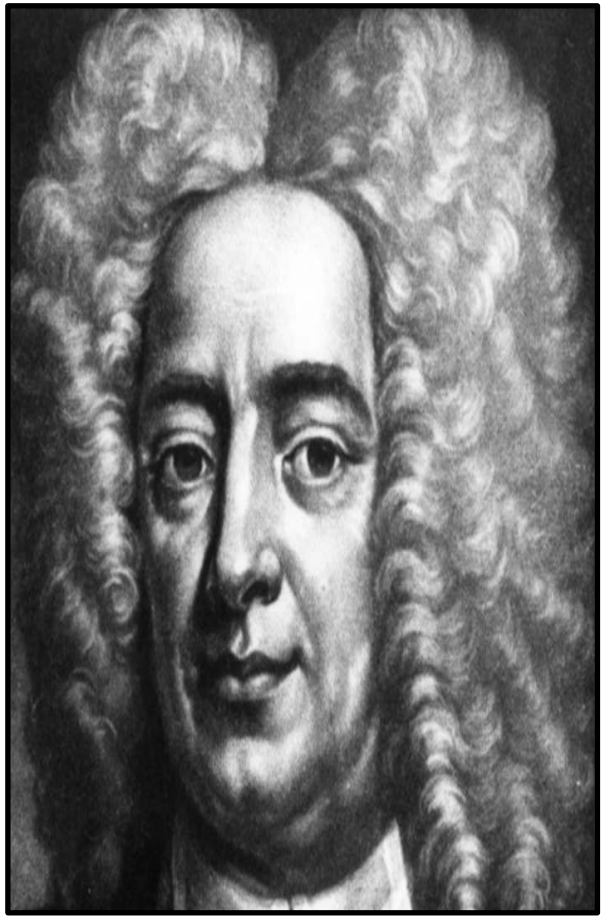
Immunity: Pioneers in Vaccines

Lady Worltey Montague

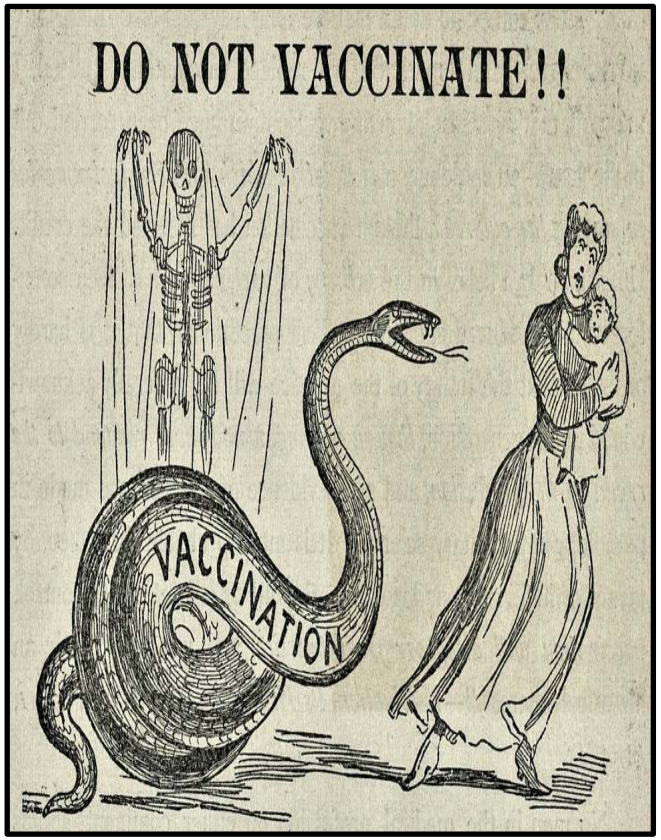


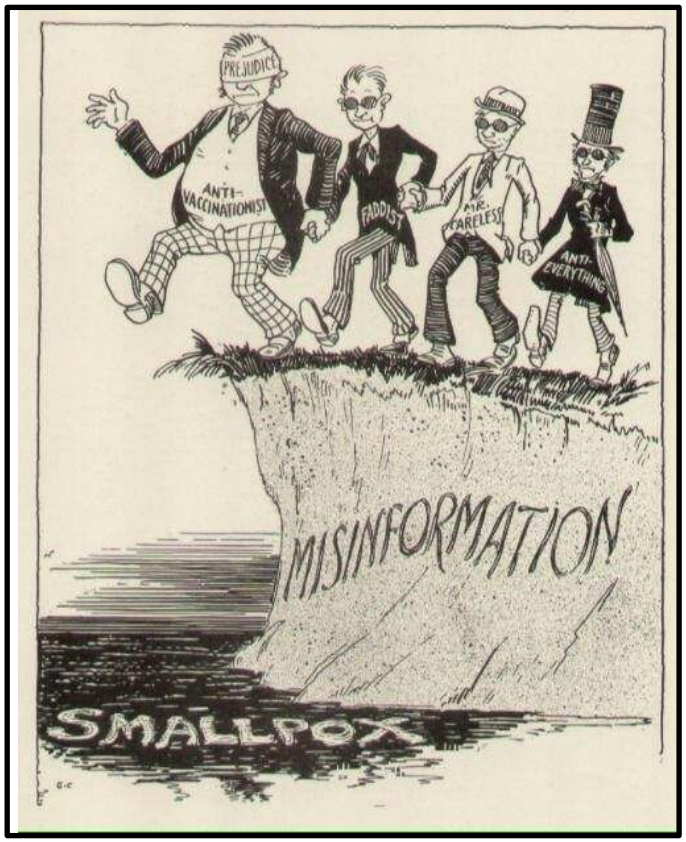
Cotton Mather
(1663-1728)

Edward Jenner
(1749-1823)
Father of vaccinology

An Indian Variolation vial with smallpox virus

Unfounded Fear of vaccination among people





www.pinterest.com

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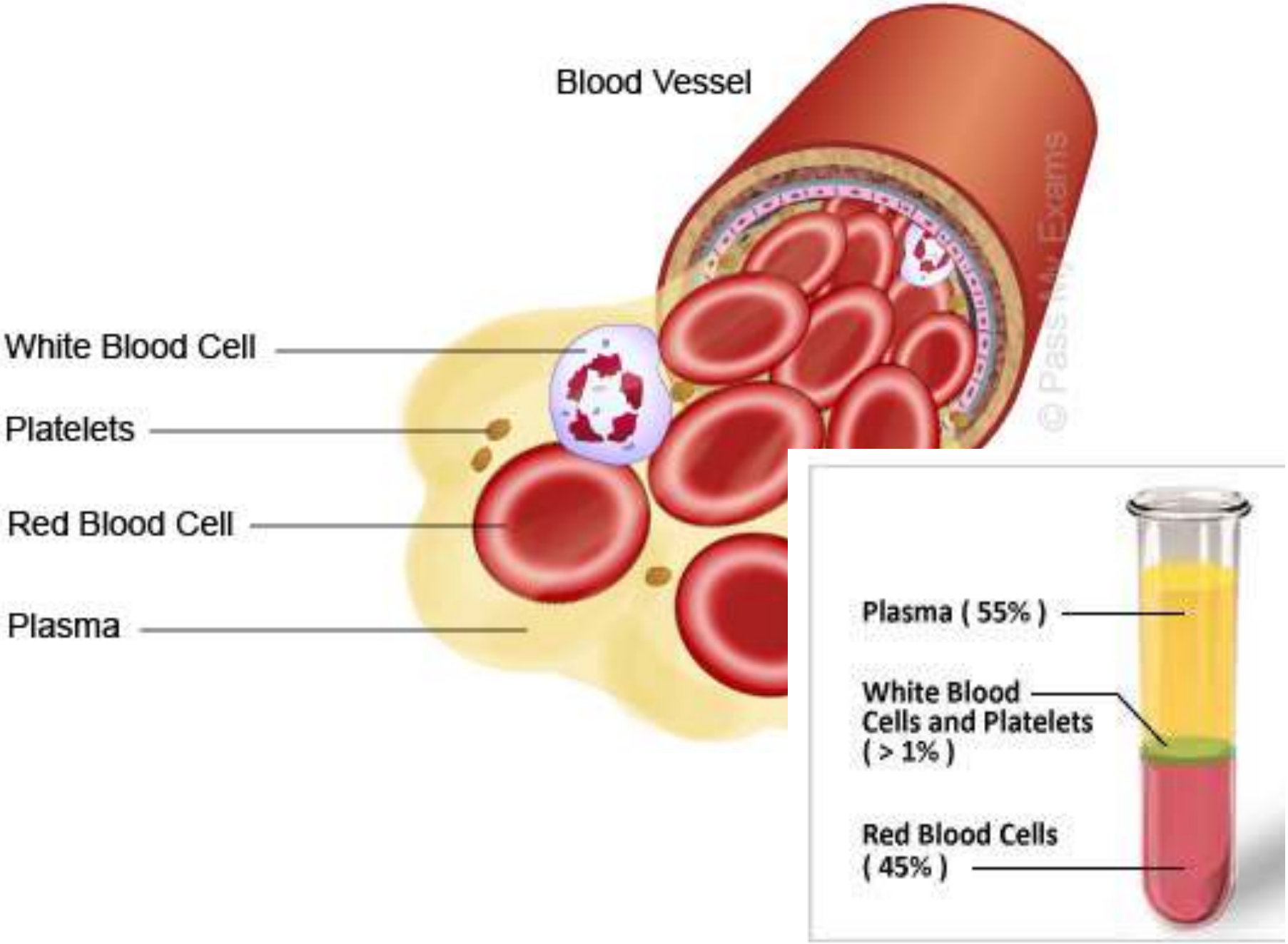
Misconceptions

- Many vaccine shots weaken immune system
  - Century ago =1 shot of small Pox
    (200 different proteins)
  - Currently = 11 vaccines with 20 shots in one year
    (120 different proteins/entities)
  - Theoretically infants can respond to 10,000 vaccines at a time

- Unexplained ill effects is more likely in 0-5 years
  - Attribute to vaccination is coincidental

- Make them susceptible to neurological diseases
- A great violation of the bodily freedoms of the individual
  - Following vaccination, their children might "low and…browse in the fields like oxen.

- Passage of materials between individuals→ spread infection, change in skin color
  - Some religions in several countries have recently denounced vaccination campaigns as "western" and "anti-religion."


Blood Vessel
White Blood Cell
Platelets
Red Blood Cell
Plasma
Plasma (55%)
White Blood Cells and Platelets (> 1%)
Red Blood Cells (45%)

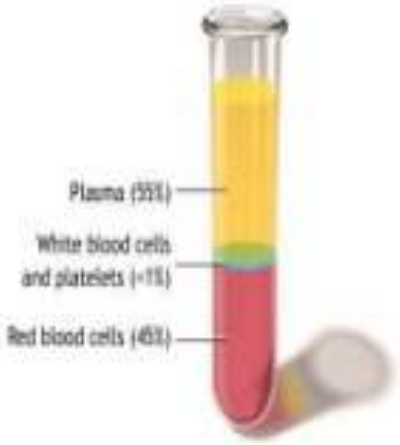
2. Plasma vs. serum

•**Plasma** is the liquid, cell-free part of blood, that has been **treated with anti-coagulants**.

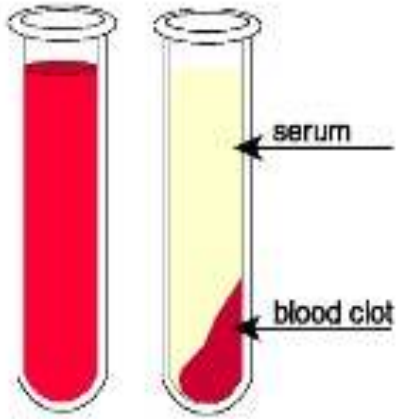
Serum is the liquid part of blood **AFTER coagulation**, therfore devoid of clotting factors as fibrinogen.

Anticoagulated

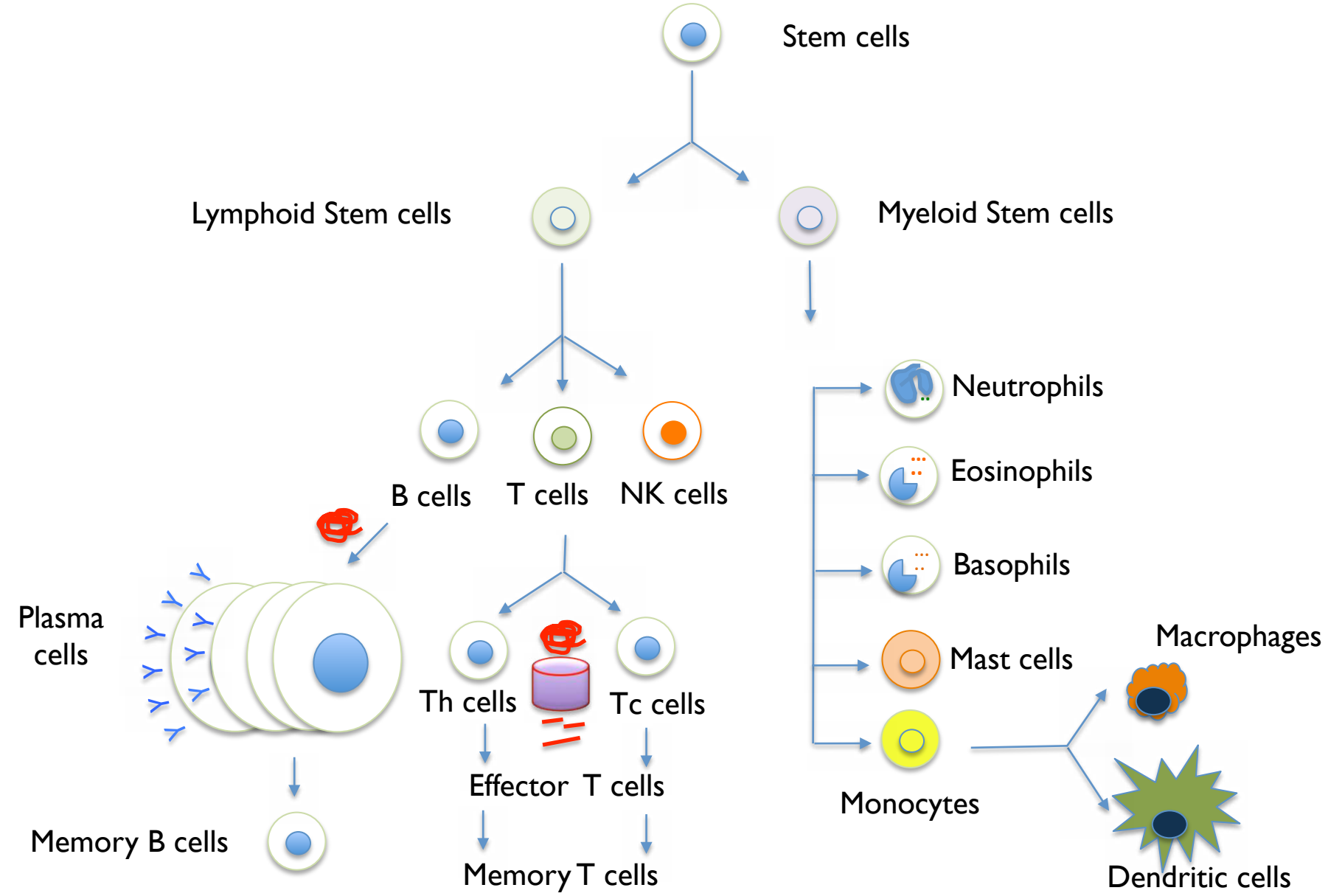
Clotted



•serum= plasma - fibrinogen

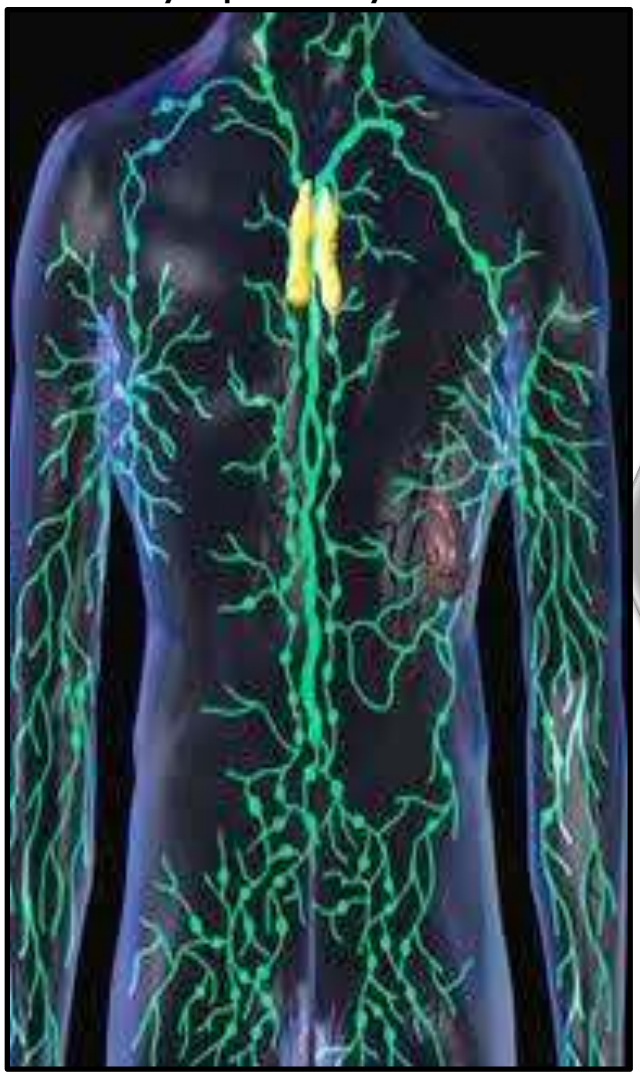


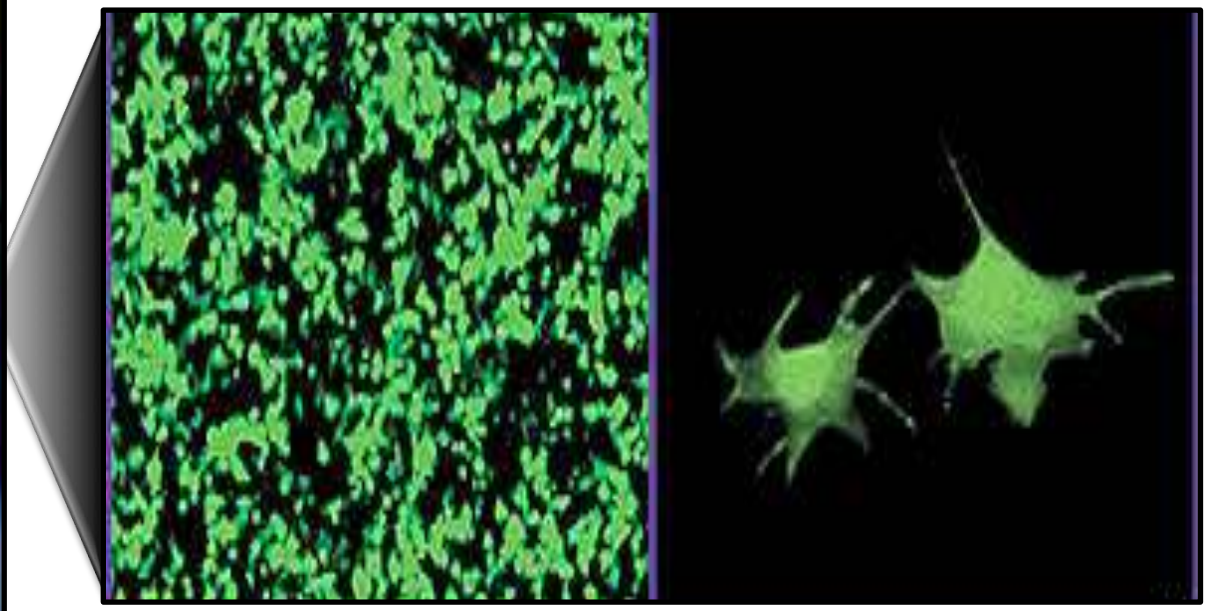
Cells of the Immune System



How the presence of pathogens is sensed ?

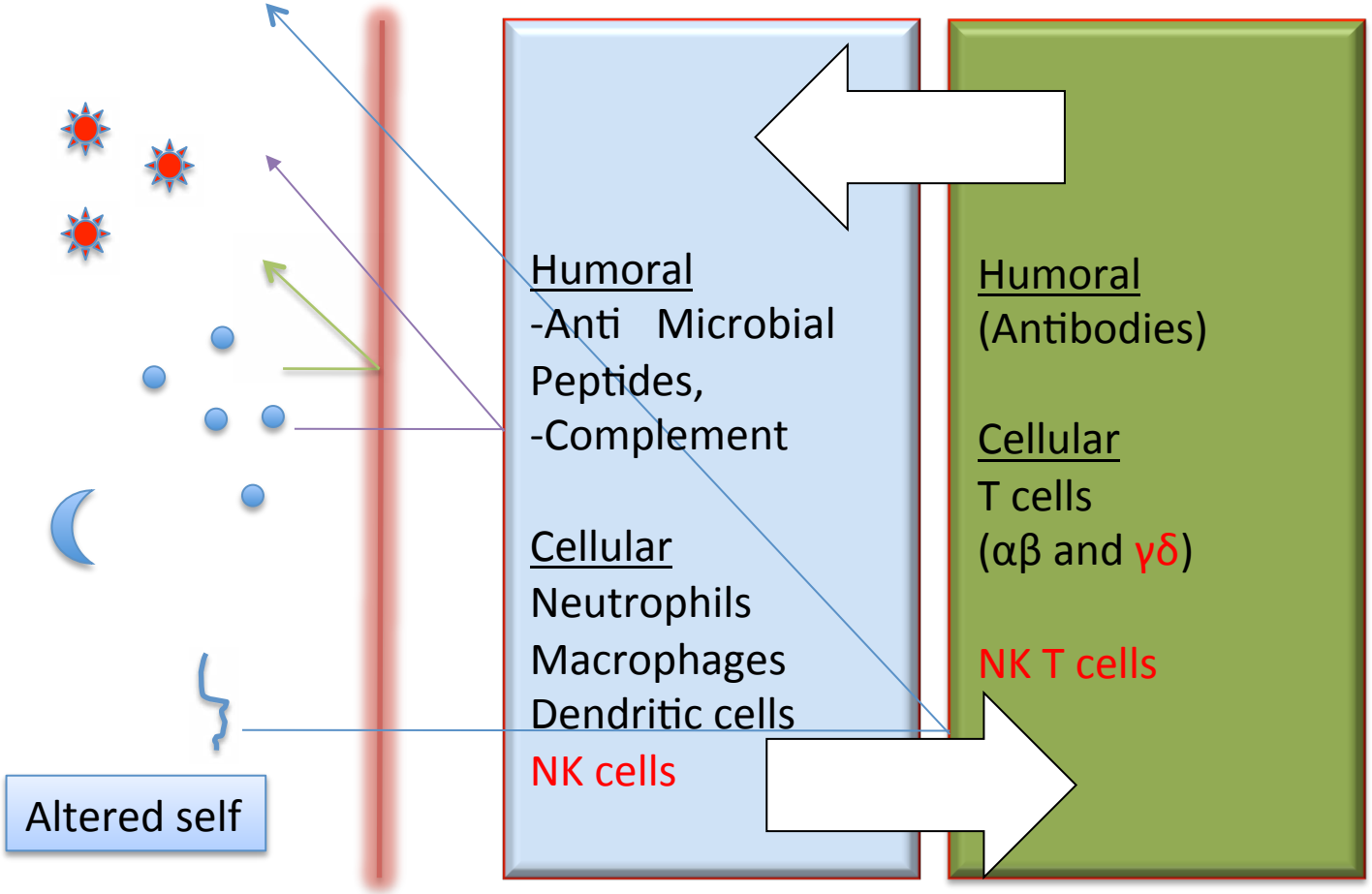
Lymphatic system





Dendritic cells (anti-CD11c)

Types of Immune defenses



Line of defense 1 2 3

Mechanical and chemical
Anatomical and Physiological Barriers
(Intact skin, Mucous membrane, Temperature, pH)

Innate
Phagocytic Barriers
Inflammatory Barriers and fever
Protein factors such as Interferons

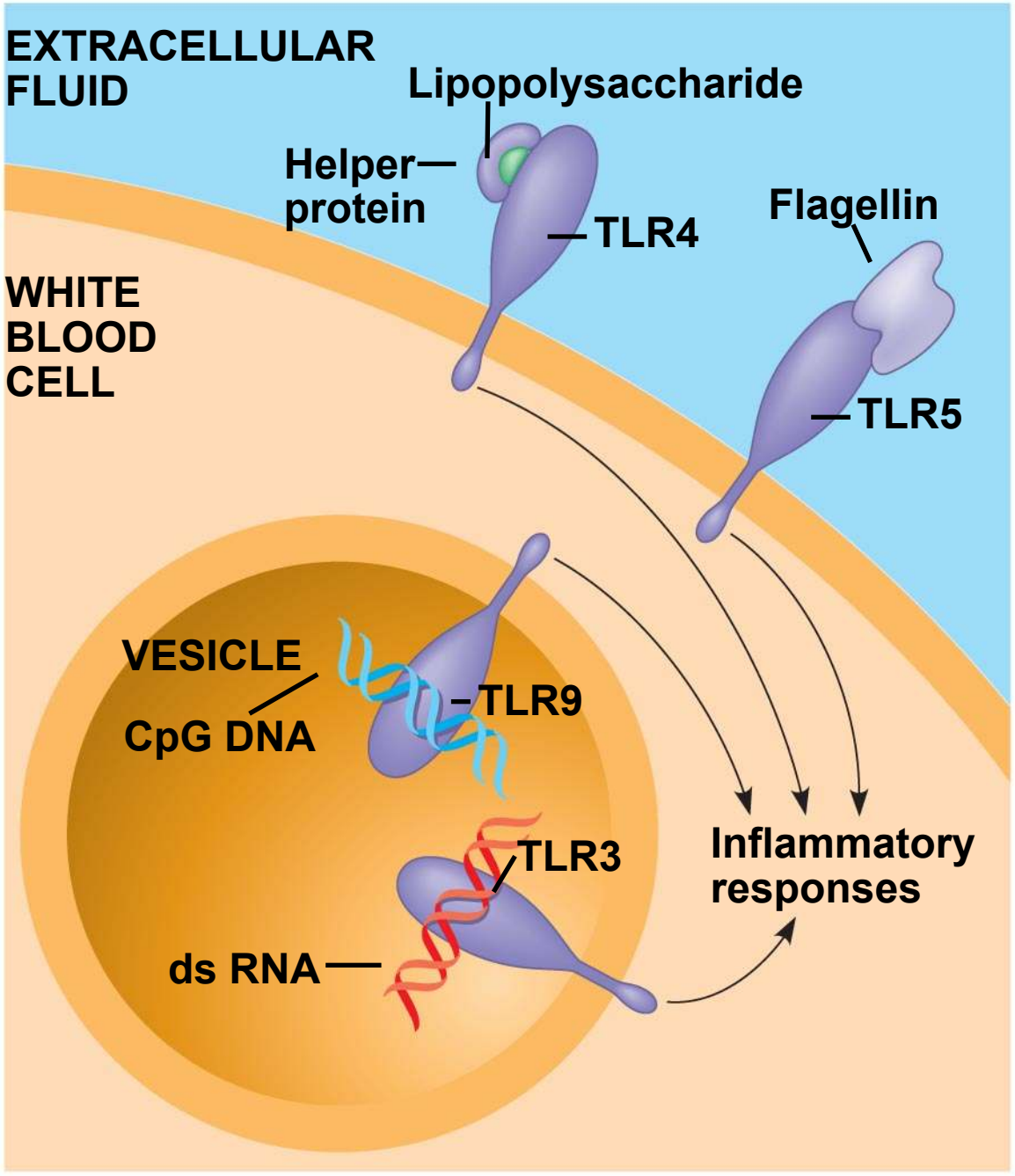
Adaptive

Types of immune defenses against microbes:

Three types of defense mechanisms provide antimicrobial immunity. The first line of defense comprise of mechanical and chemical barriers that are intact skin, mucosal surfaces laden with mucocilliary expulsion system and anti-microbials. Second line of defense includes innate immune responses that comprise of both humoral and cellular components. The humoral components are complement proteins, defensins, lysozymes in various secretions and cellular components consist of innate immune cells such as neutrophils, basophils, eosinophils, macrophages, dendritic cells, NK cells etc. The third line of defense also includes both humoral (antibodies) and cellular components (T cells and B cells). *NK cells, NKT cells and γδ T cells may be categorized to be working at the interface* of innate and adaptive immune responses. There is cross regulation of innate and adaptive immune mechanisms as is shown by forward and reverse arrows. There is a sequential deployment of each of the defense mechanism to fend off any pathogenic insults.

INNATE

TLR signaling



- A *white blood cell engulfs* a microbe, then fuses with a *lysosome* to destroy the microbe.
- There are different types of *phagocytic cells*:
  - **Neutrophils** engulf and destroy microbes.
  - **Macrophages** are part of the *lymphatic system* and are found throughout the body.
  - **Eosinophils** discharge *destructive enzymes*.
  - **Dendritic cells** stimulate development of *acquired immunity*.

Antimicrobial Peptides and Proteins

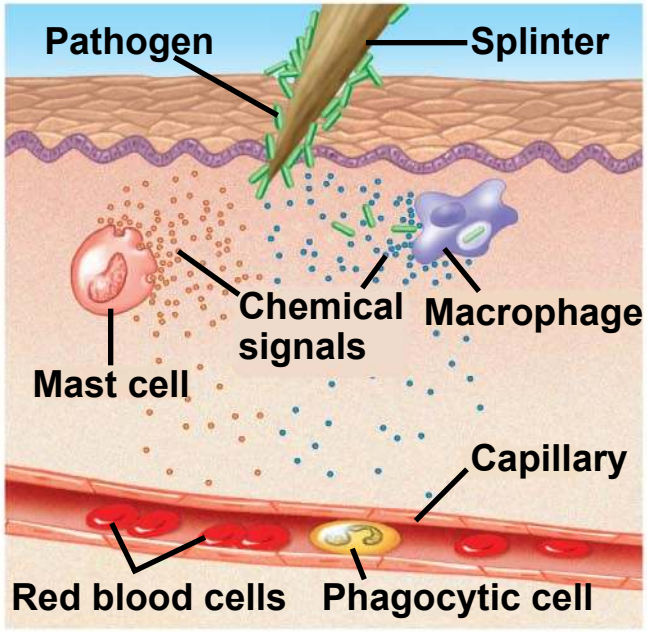
- Peptides and proteins function in innate defense by attacking microbes directly or impeding their reproduction. Eg., **Defensins**
- **Interferon** proteins provide innate defense against viruses and help activate macrophages.
- About 30 proteins make up the **complement system**, which causes lysis of invading cells and helps trigger inflammation.

Inflammatory Responses

- **Cardinal Signs: Rubor (red), Calor (Heat), dolor (pain), Tumor (swelling), Functiolasia (loss of function)**
- Following an injury, ***mast cells*** release ***histamine***, which promotes changes in *blood vessels*; this is part of the **inflammatory response.**
- These changes *increase local blood supply* and allow more phagocytes and antimicrobial proteins to enter tissues.
- *Pus* = a fluid rich in white blood cells, dead microbes, and cell debris, accumulates at the site of inflammation.

Major events in a local Inflammatory Response

1.



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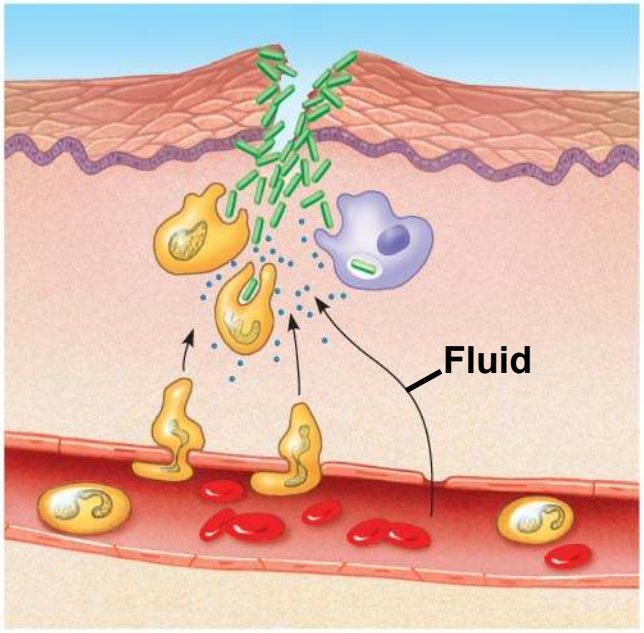

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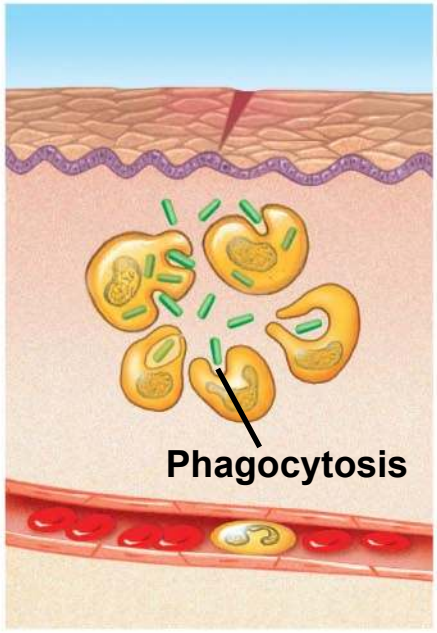
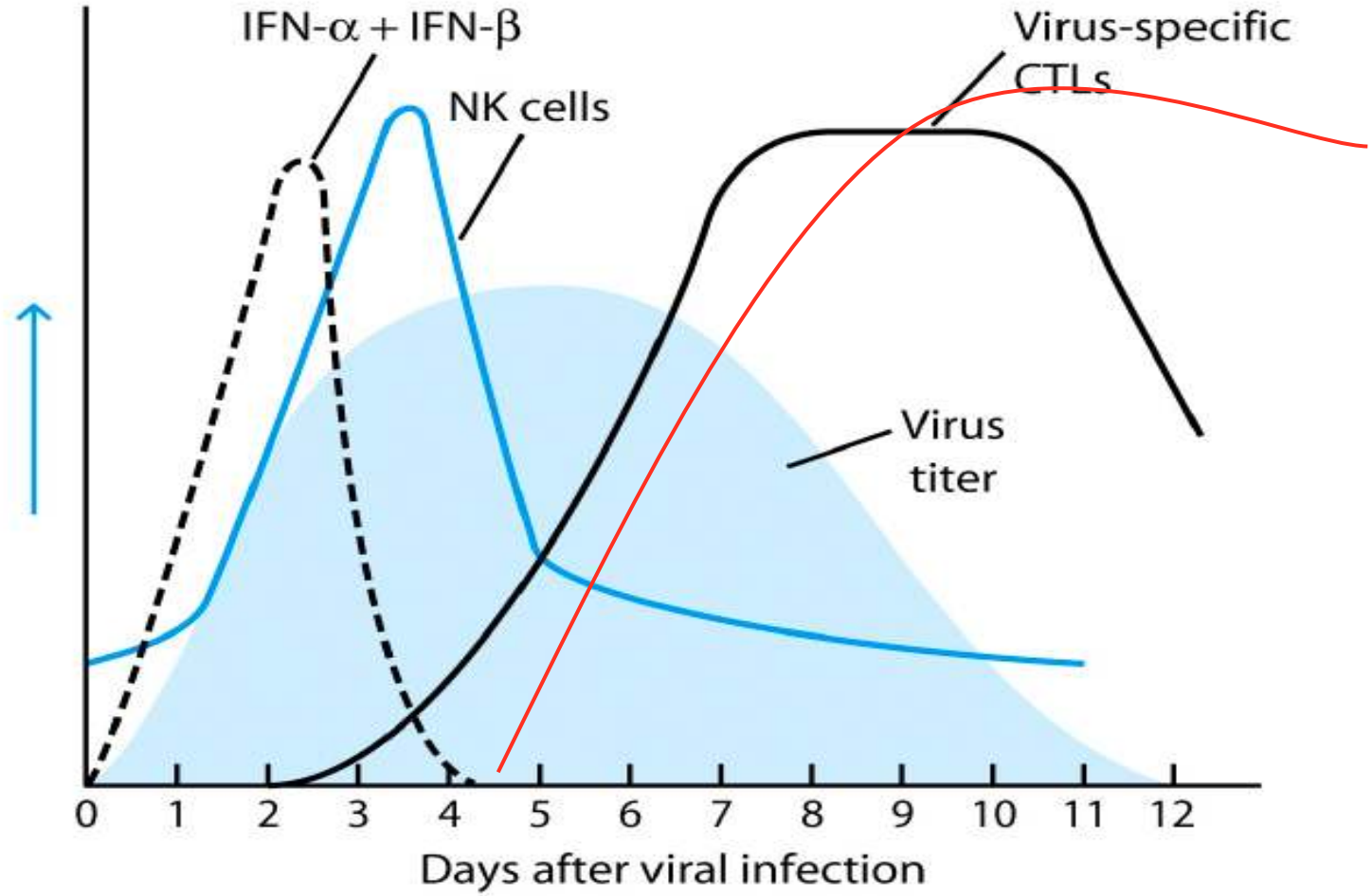


- Inflammation can be either local or systemic (throughout the body).
- Fever is a systemic inflammatory response triggered by pyrogens released by macrophages, and toxins from pathogens.
- *Septic shock* is a life-threatening condition caused by an *overwhelming inflammatory response*.

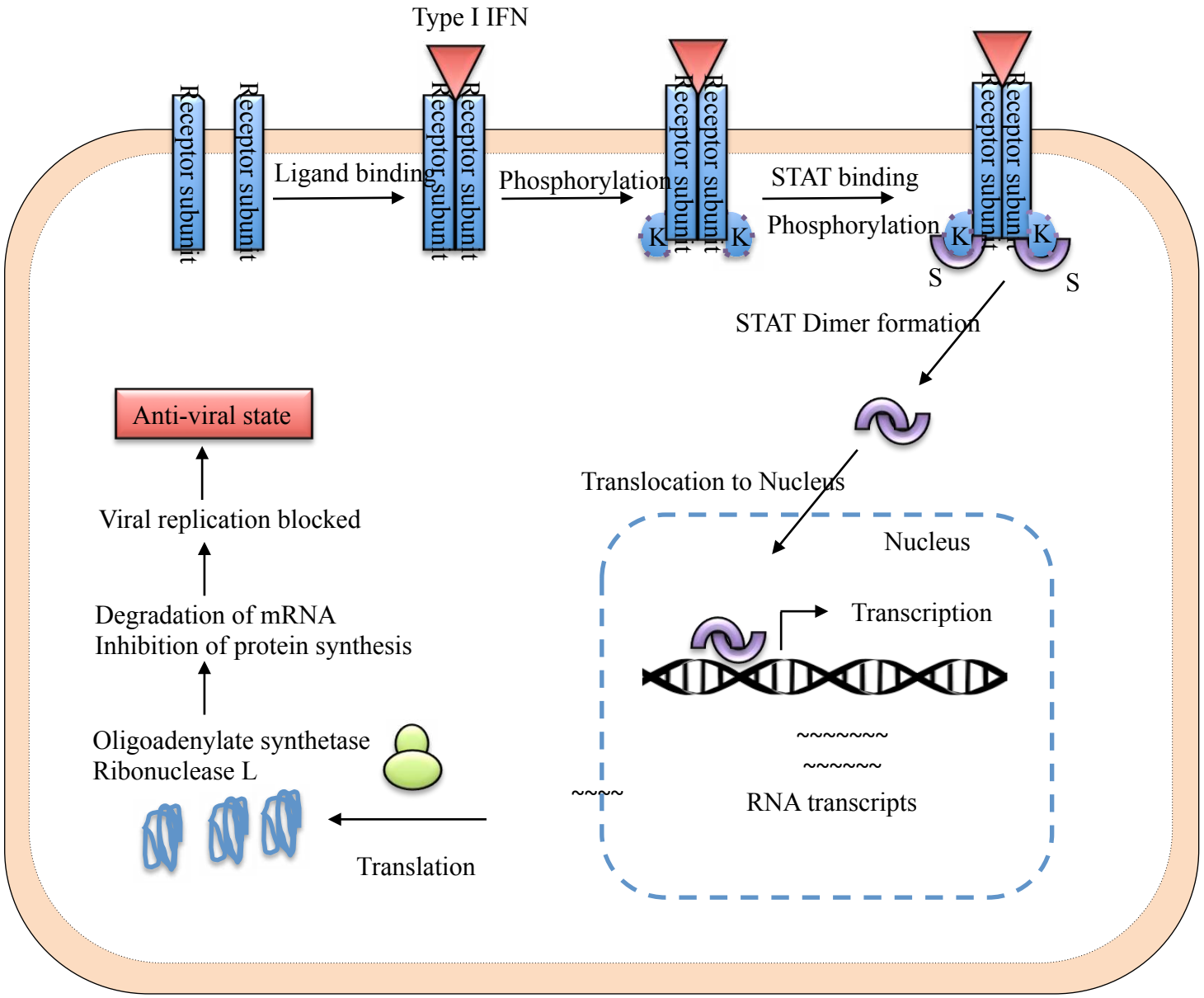
Natural Killer Cells

- All body cells (except red blood cells) have a class I MHC protein on their surface.
- **MHC = Major Histocompatibility Complex** , part of the extracellular matrix.
- Class II MHC protein molecules are found on specialized cells(macrophage, Dendritic cells, B cells)
- Cancerous or infected cells no longer express this MHC protein; **natural killer (NK) cells** attack these damaged cells.

What happens in your body once a viral infection sets in



Cell Signaling: Type I IFN as an example



G protein-coupled receptors, Receptor tyrosine kinases, Ion channel receptors

Activation of JAK/STAT pathways by interferon signaling in target cells to confer anti-viral immunity. The binding of type I IFN to receptors induces dimerization of the receptor. This leads to the activation of already bound Janus kinase (JAK). Kinases (K) autophosphorylate and phosphorylates the receptor and create docking sites for Signal Transducer and Activator of Transcription (STAT) protein (S) binding. Upon binding to the receptor STAT molecules are tyrosine-phosphorylated by the activity of JAKs, the STATs form active dimers that translocate into the nucleus to regulate transcription and translation of many genes including those required for the degradation of mRNA and inhibition of protein translation to create an anti-viral state in the cell.

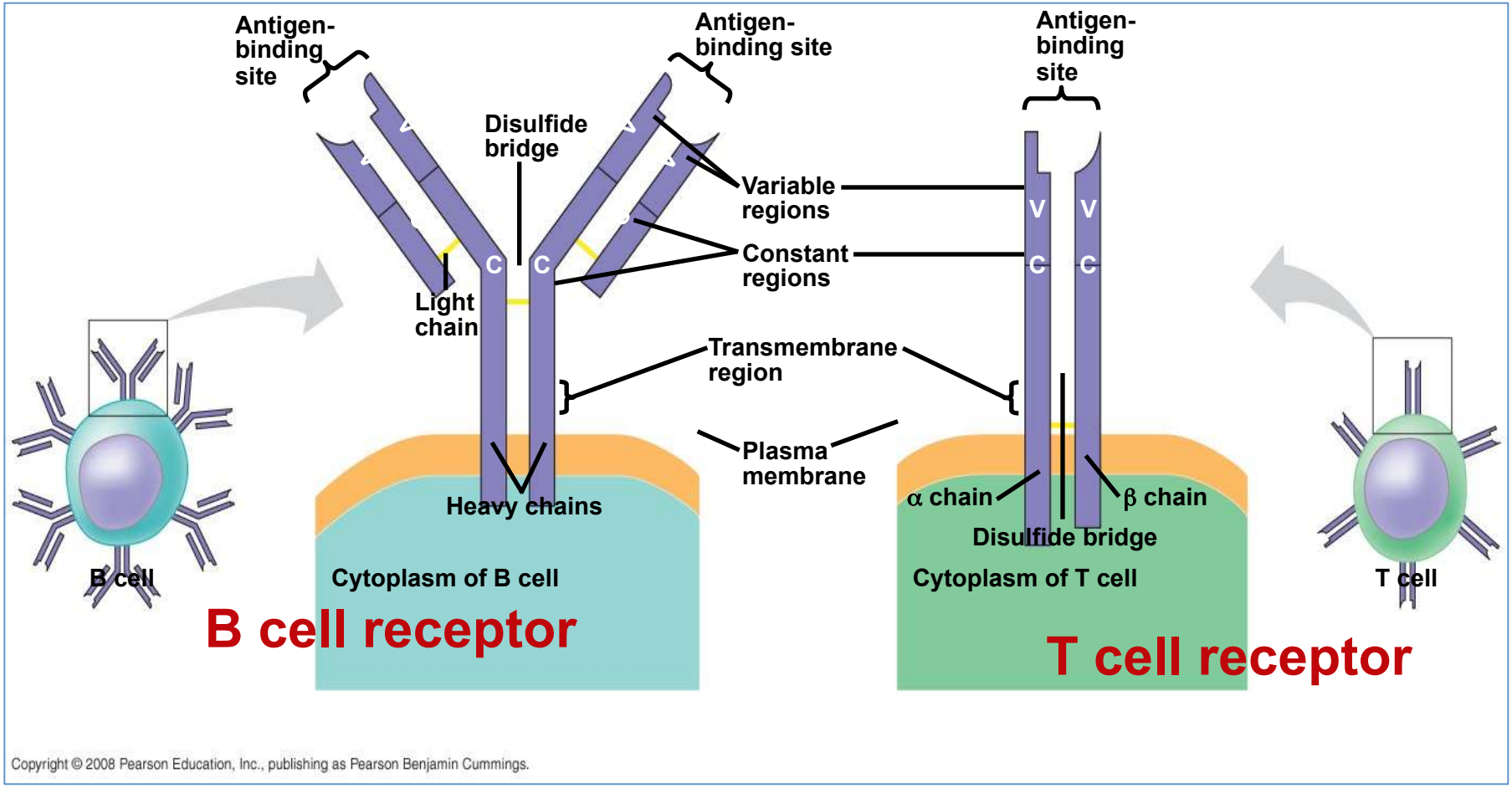
In Acquired Immunity, lymphocyte receptors provide pathogen-specific recognition

- White blood cells called ***lymphocytes*** recognize and respond to antigens, foreign molecules.
- Lymphocytes that *mature in* the *thymus* above the heart are called ***T cells***, and those that *mature in bone marrow* are called ***B cells*****.**
- Lymphocytes contribute to immunological memory, an enhanced response to a foreign molecule encountered previously.
- **Cytokines** are secreted by macrophages and dendritic cells to recruit and activate lymphocytes.

Acquired Immunity = Active Immunity: *Specific*

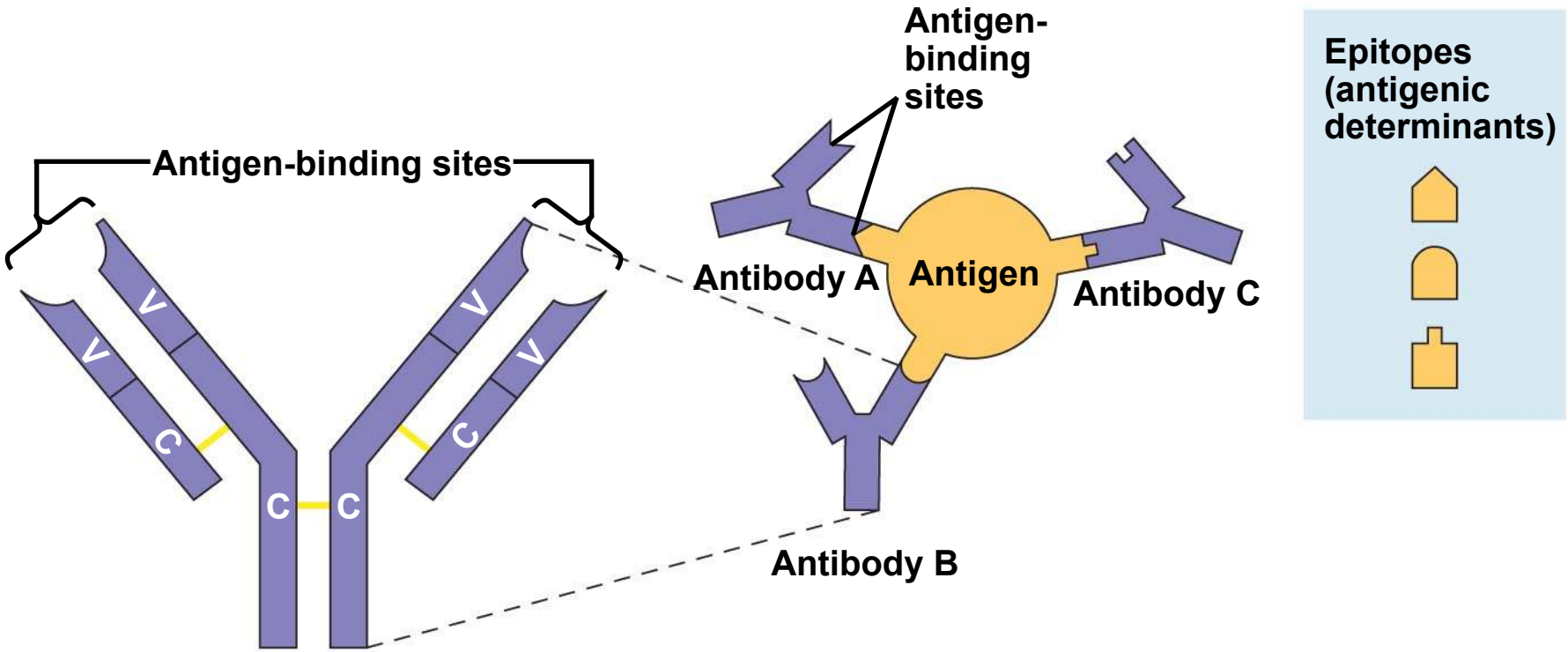
- B cells and T cells have receptor proteins that can bind to foreign molecules.
- Each individual lymphocyte is specialized to recognize a **specific** type of molecule.
- An **antigen** is any foreign molecule to which a lymphocyte responds.
- A single B cell or T cell has about 100,000 identical **antigen receptors**.

Antigen receptors on lymphocytes



- All antigen receptors on a single lymphocyte recognize the same ***epitope*****,** or *antigenic determinant,* on an antigen.
- B cells give rise to **plasma cells**, which secrete proteins called **antibodies** or **immunoglobulins.**

Epitopes = antigen determinants



The Antigen Receptors of B Cells and T Cells

- **B cell receptors** bind to **specific**, intact antigens.
- The B cell receptor consists of two identical **heavy chains** and two identical **light chains.**
- The tips of the chains form a *constant (C) region*, and each chain contains a *variable (V) region*, so named because its amino acid sequence varies extensively from one B cell to another.
- *Secreted **antibodies**, or **immunoglobulins**, are structurally similar to B cell receptors* but lack transmembrane regions that anchor receptors in the plasma membrane.

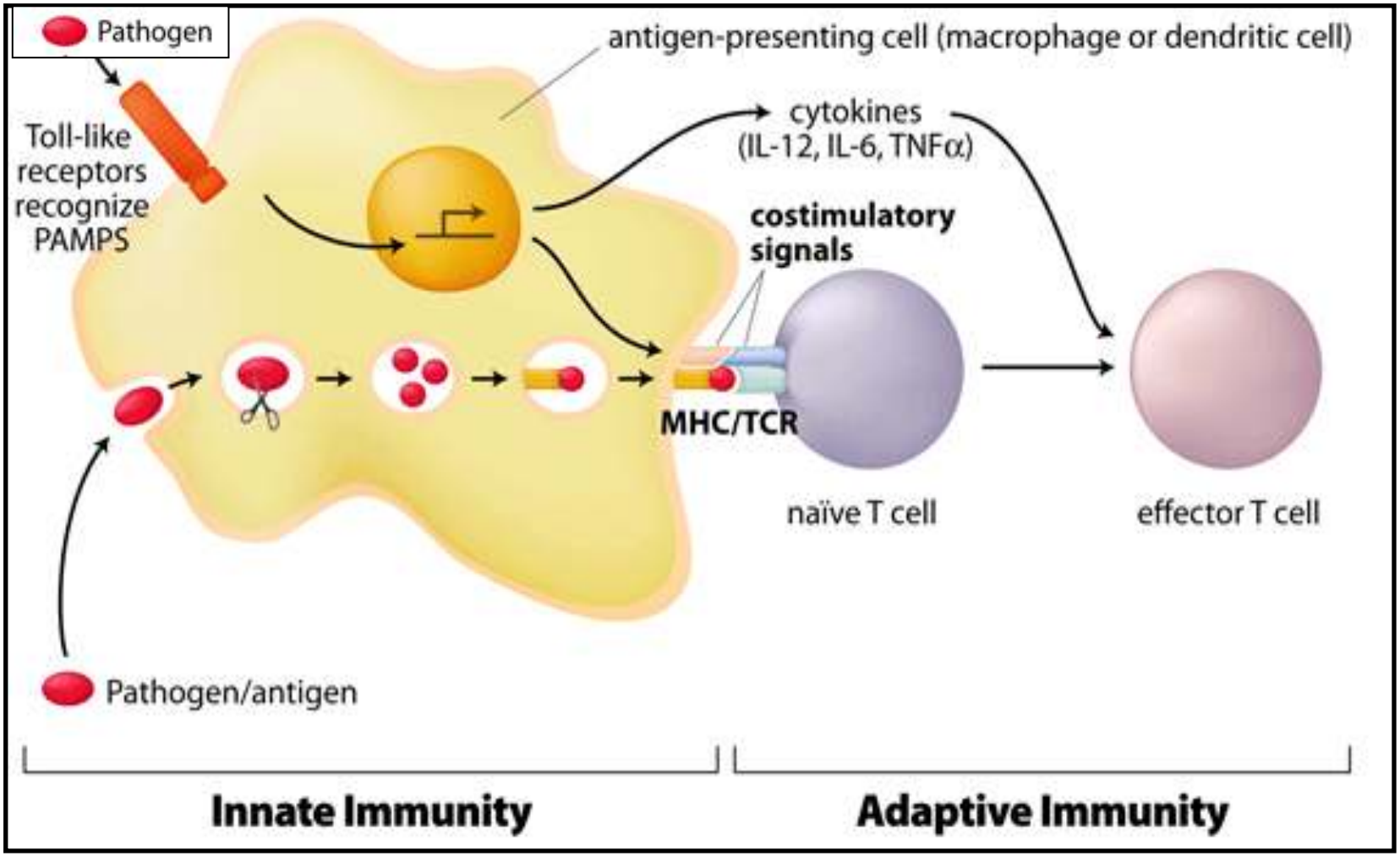
- Each **T cell receptor** consists of two different polypeptide chains. The tips of the chain form a variable (V) region; the rest is a constant (C) region.
- *T cells can bind to an antigen that is free or on the surface of a pathogen*.
- T cells bind to *antigen fragments presented on a host cell*. These antigen fragments are *bound to cell-surface proteins called MHC* molecules.
- **MHC** molecules are so named because they are encoded by a family of genes (many unique / specific) called the **Major Histocompatibility Complex.**

The Role of the MHC

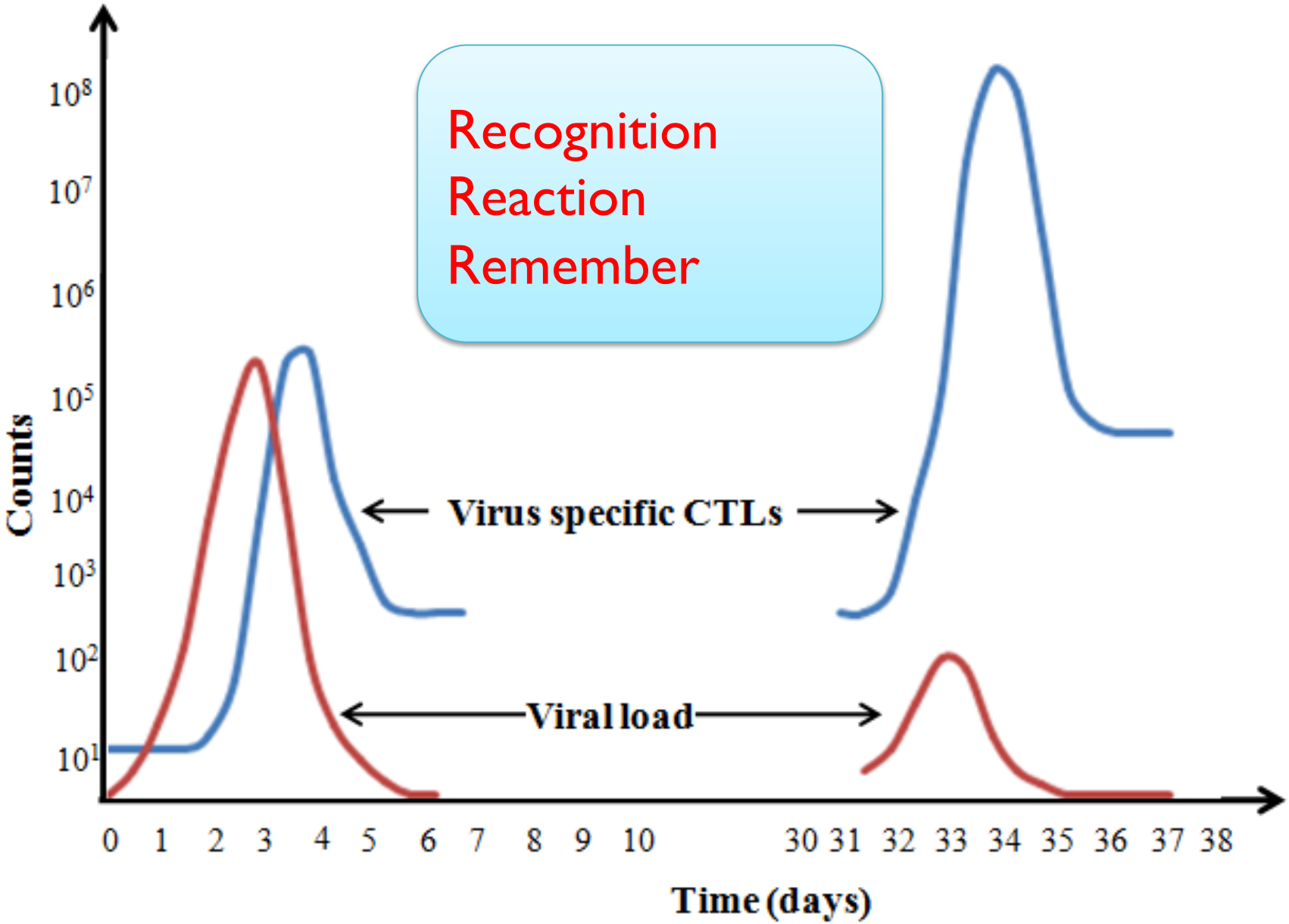
- In infected cells, *MHC molecules* bind and transport antigen fragments to the cell surface, a process called ***antigen presentation*.**
- A nearby *T cell can then detect* the antigen fragment displayed on the cell's surface.
- Depending on their source, peptide antigens are handled by different classes of MHC molecules.

Induction of T cells response upon infection

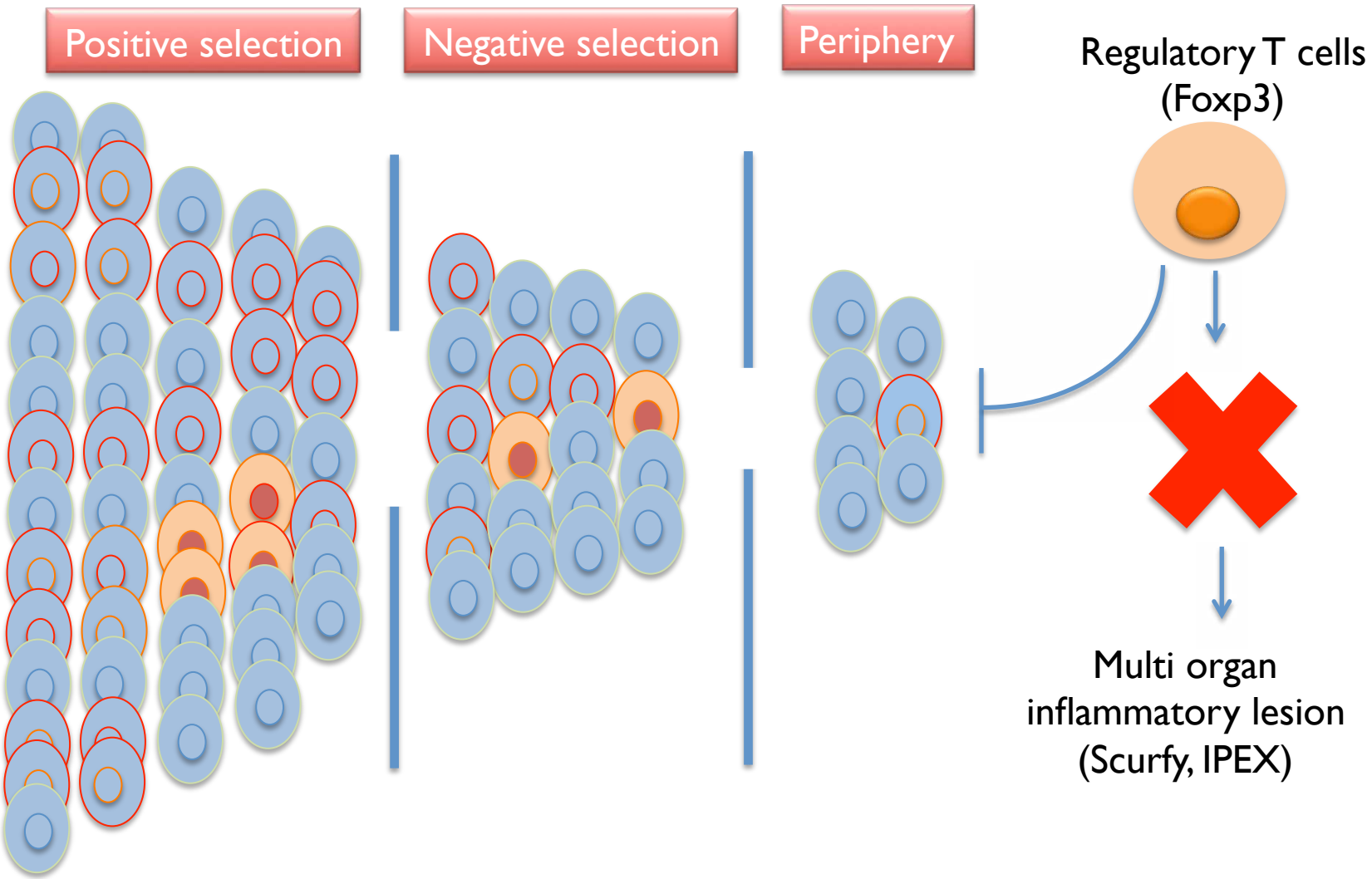
Signal 1,2,3 : set the lymphocytes free



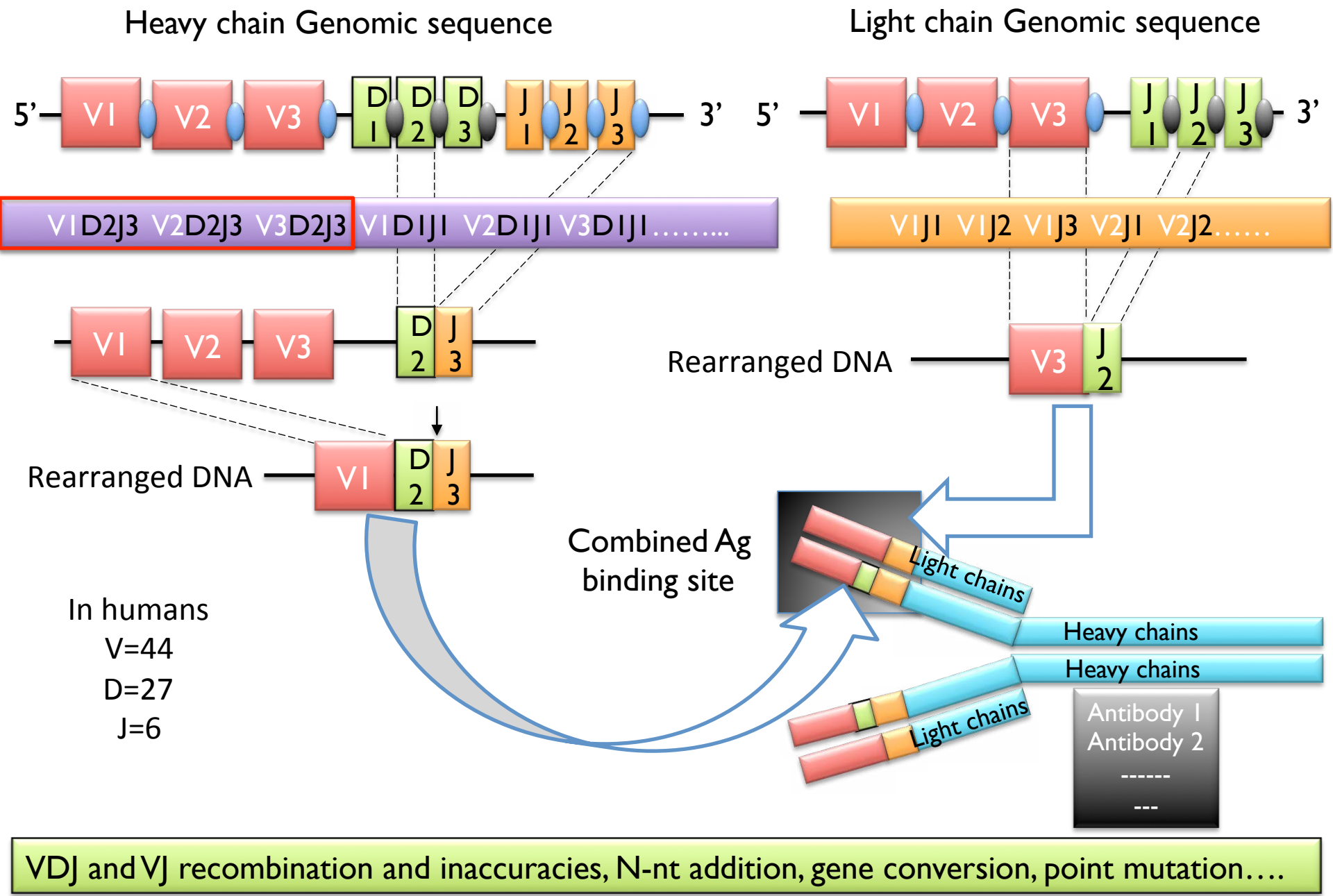
Halmarks of Adaptive Immunity



How do T cells of appropriate specificity selected ?

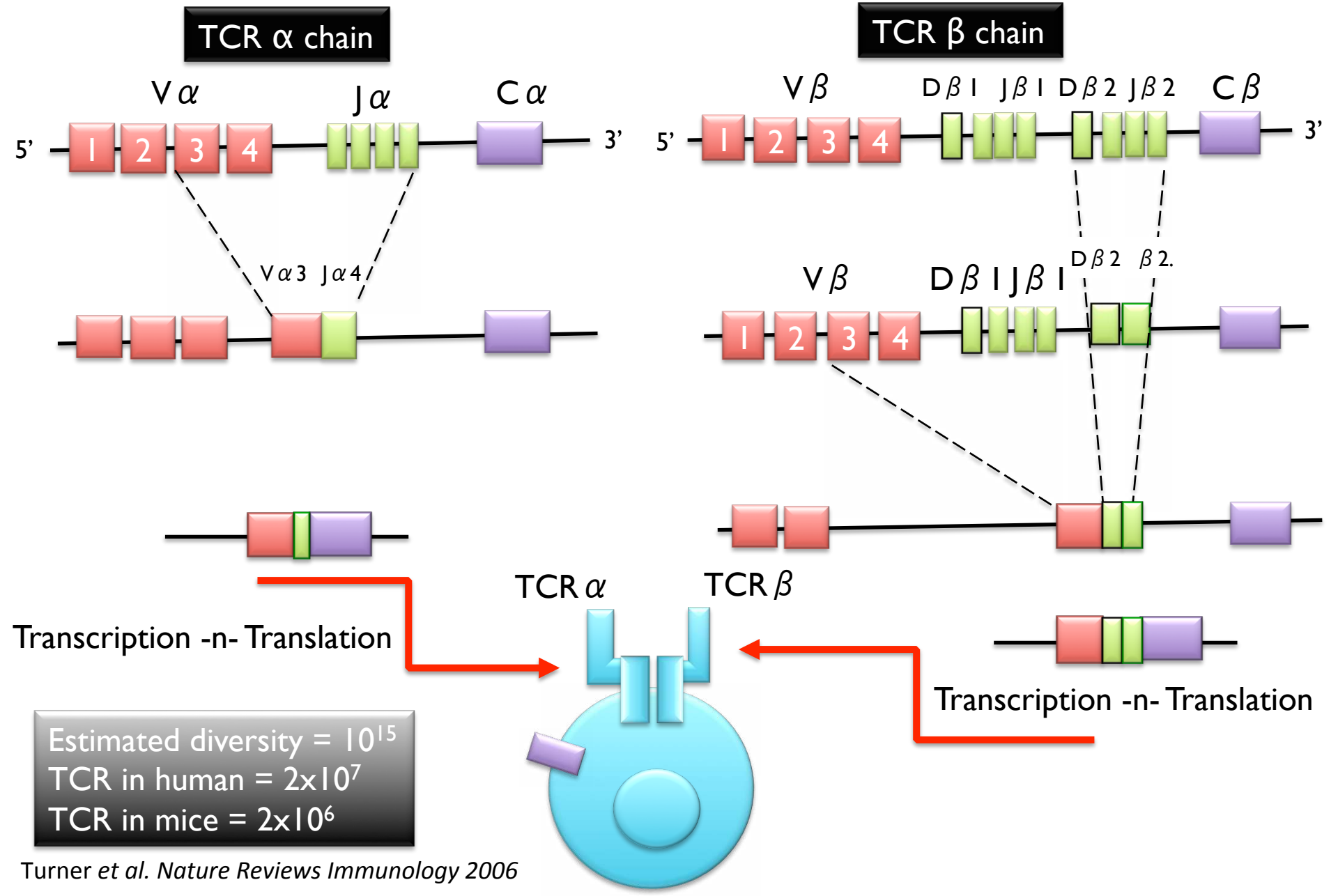


Recombination of BCR: GoD



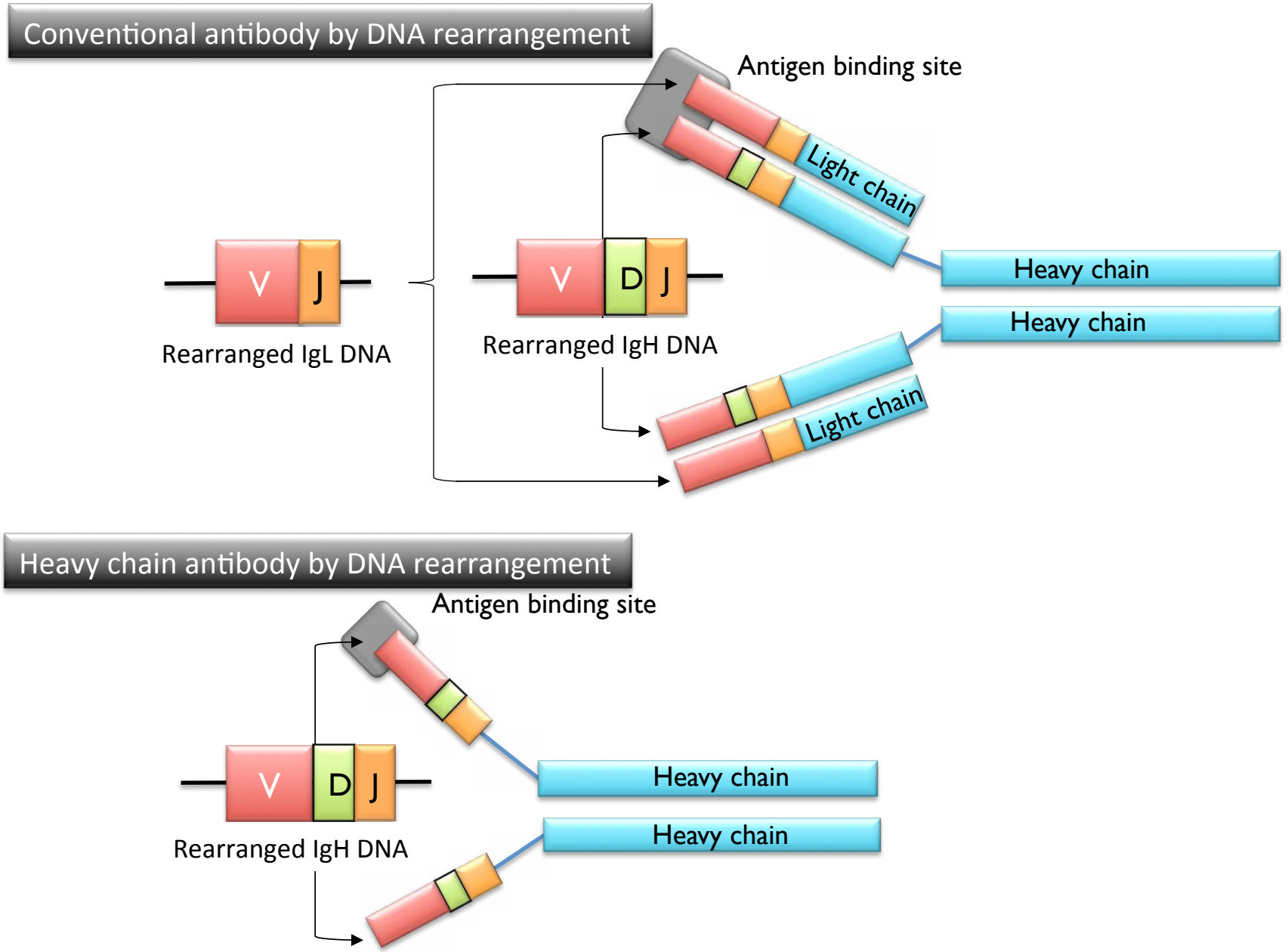
VDJ and VJ recombination and inaccuracies, N-nt addition, gene conversion, point mutation….

Recombination of TCR

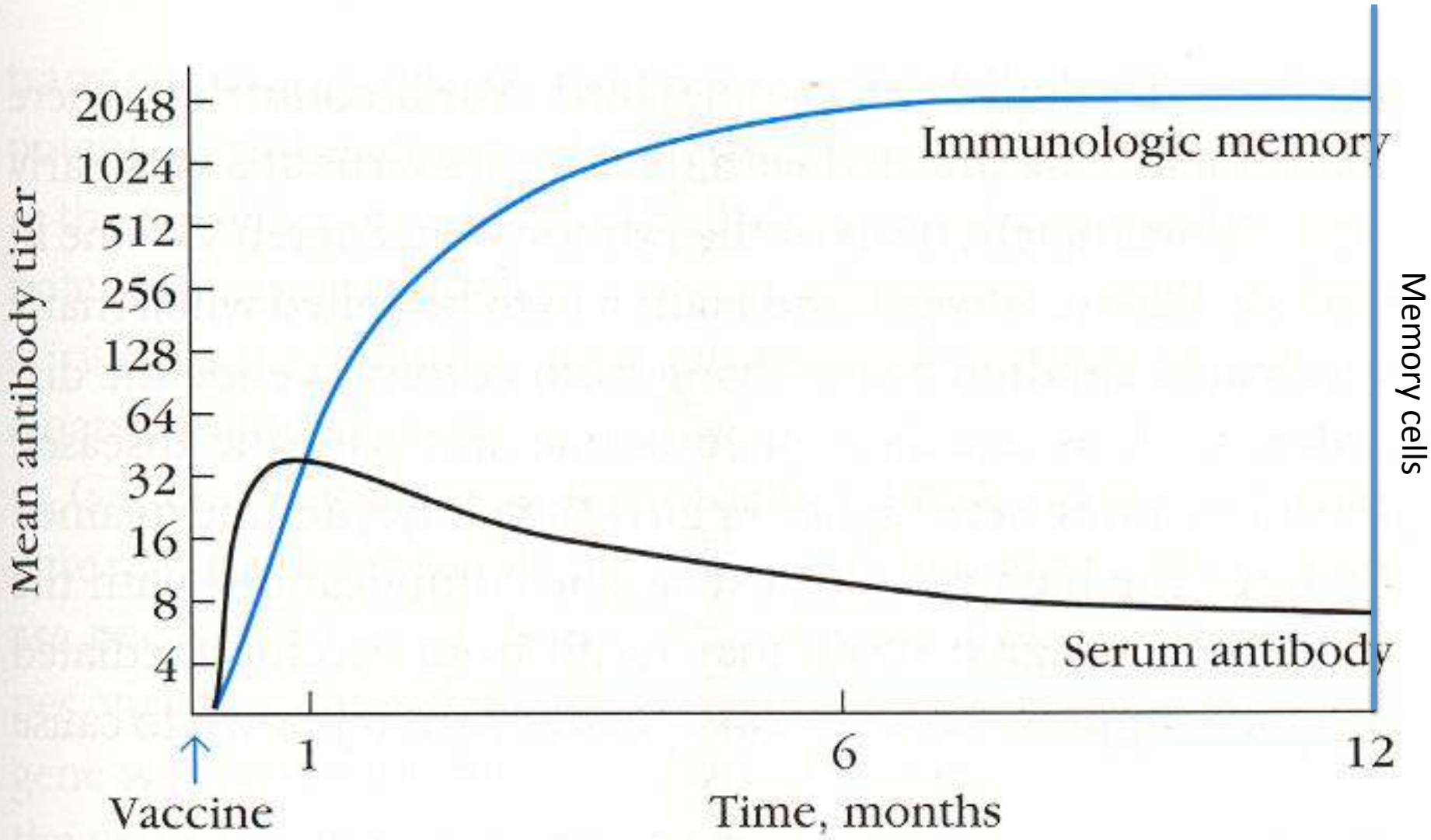


Turner *et al. Nature Reviews Immunology 2006*

A curious case of a unique antibody



Immune memory vs antibody titers



Vaccine: Types of Immunization

- Passive Immunization
  - Methods of acquisition include natural maternal antibodies,
    - anti-toxins and immune globulins
  - Ig pooled from immune humans or animals → Protection transferrable
  - For a quick protection (Acute infections), Immunodeficient individuals, Disease is already present
  - No Memory would be generated
  - Problems associated:-Anaphylaxis and hypersensitivity,

(Examples: Hepatitis A and B , Rabies, Measles, Tetanus, Ebola virus, Envenoming)

- Active Immunization
  - Methods of acquisition include natural infection, vaccines (many types) or toxoids
  - Adjuvants are used along with to induce enhanced responses
  - Supposedly induce a long lasting protection

(Examples: Polio virus, hepatitis B virus, yellow fever vaccine, BCG)