

Biomedical Engineering for Global Health

Pathogens and the immune system

Lecture 8

Review of lecture 7

- Science
 - "Science is the human activity of seeking natural explanations for what we observe in the world around us."
- Engineering
 - Systematic design, production and operation of technical systems to meet practical human needs under specified constraints
 - Six steps of the engineering design method

How can technology help?

Science

1. Understanding biology: pathogens & disease immune system

Engineering

2. Developing vaccines: from idea to product
 - vaccine design
 - production
 - testing safety & effectiveness
3. Addressing challenges for vaccine development:
 - Developed vs. developing countries
 - The AIDS vaccine challenge

Lecture map

1. The players: Types of pathogens
Cells of the Immune system

2. Types of Immunity

2A. Physical barriers

2B. Innate Immunity

Macrophages

Neutrophils

Complement proteins

Splinter example

2C. Adaptive Immunity

B-lymphocytes: ANTIBODIES

T-lymphocytes: Cell-mediated

Immunologic MEMORY

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Immunologic MEMORY

Types of pathogens

Mycobacterium tuberculosis
Staphylococcus aureus
Escherichia coli O147:H7
Vibrio cholera
Bordetella pertussis (whooping cough)

Bacteria

SARS- Severe Acute Respiratory Syndrome
Influenza (Flu)
HIV (AIDS)
Hepatitis C virus
Ebola/ Marburg viruses

Viruses

Plasmodium sp. (Malaria)
Cryptosporidium

Parasites

Candida albicans

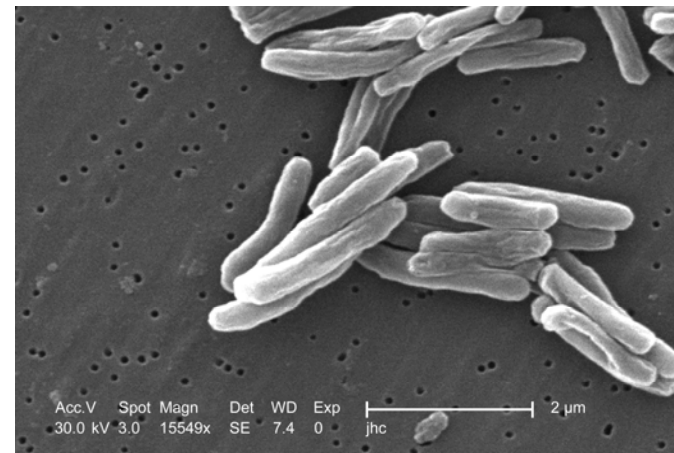
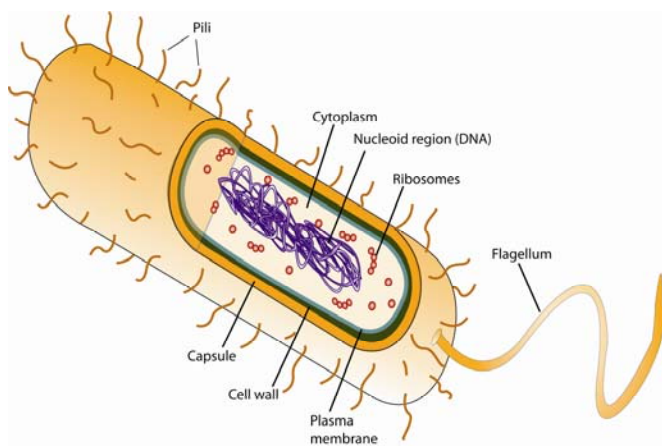
Fungi

Bacteria

- Cells with membrane and cell wall (usually)
- Can survive & reproduce outside host
- Can be killed or inhibited by antibiotics
- Responsible for >90% of hospital infections

How do bacteria cause disease?

- Invade host
- Reproduce
- Produce toxins which disturb function of normal cells

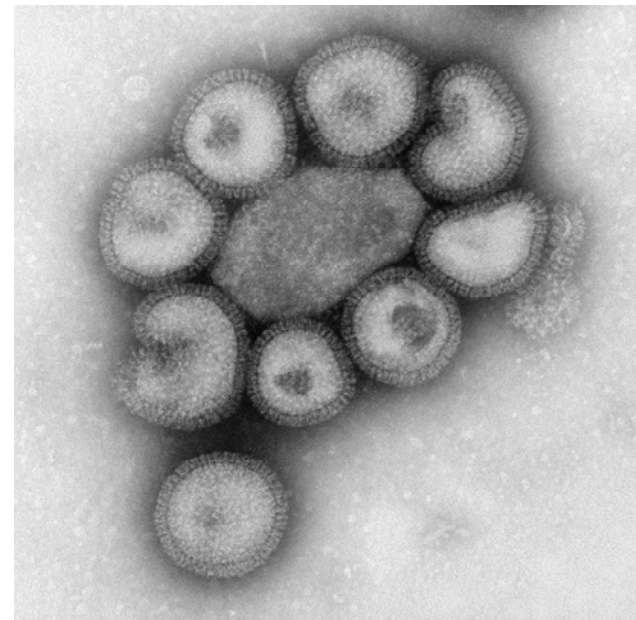
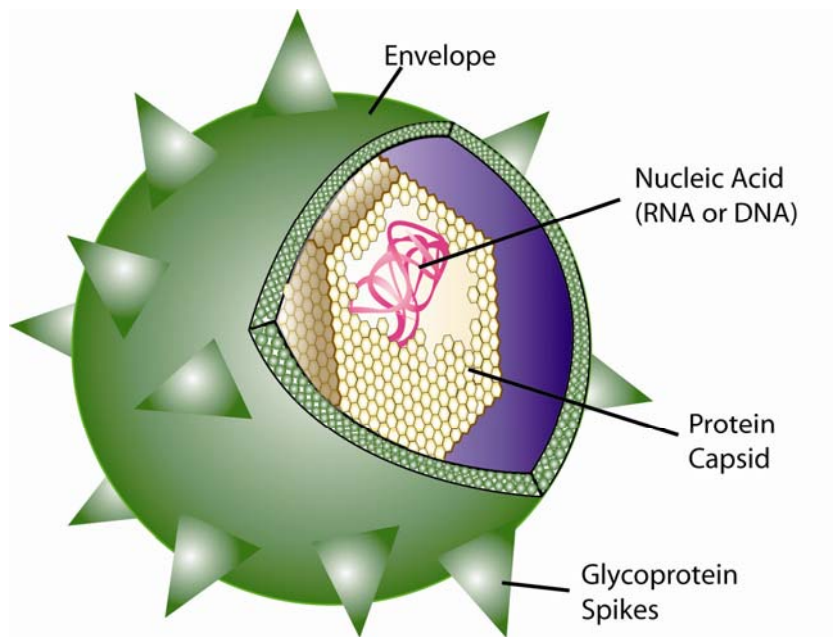


Size ~ 1 μm

www.cdc.gov

Viruses

- Nucleic acid core surrounded by protein capsid, and for some viruses an envelope
- Use host intracellular machinery to reproduce
- They cannot be killed with antibiotics, but antivirals may inhibit different stages of their life cycle in the host
- >50 viruses that can infect humans



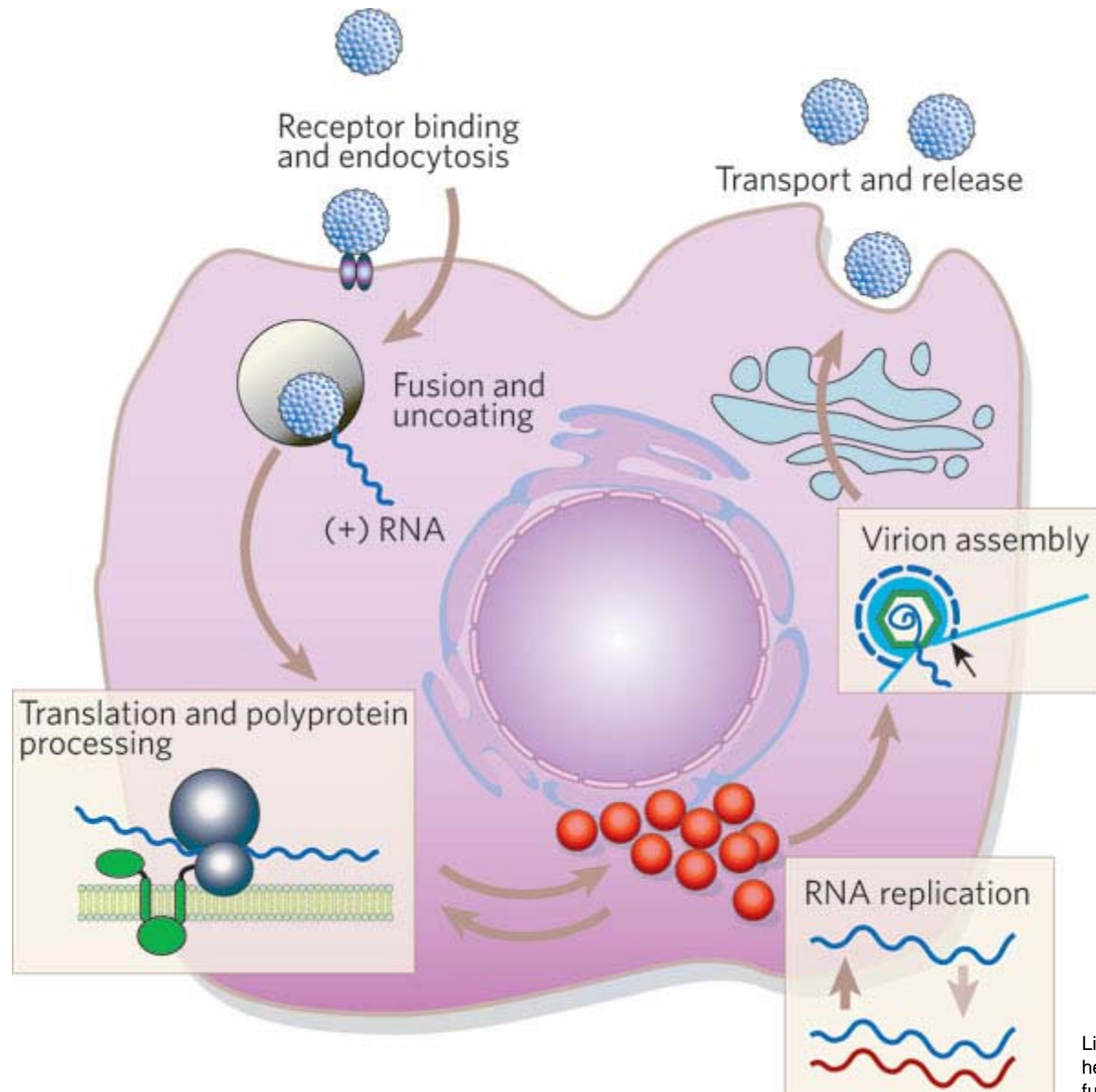
www.cdc.gov

Size ~ 0.1 μm = 100nm

How do viruses cause disease?

1. Virus invades host cell
 - Binds to cell membrane receptors
 - Endocytosis brings virus into cell
2. Virus takes over cell
 - Use viral nucleic acid and host cell resources to make new viral nucleic acid and proteins
3. More virus is released from host cell
 - Virus causes host cell to lyse OR
 - Viral particles bud from host cell surface

How do viruses cause disease?

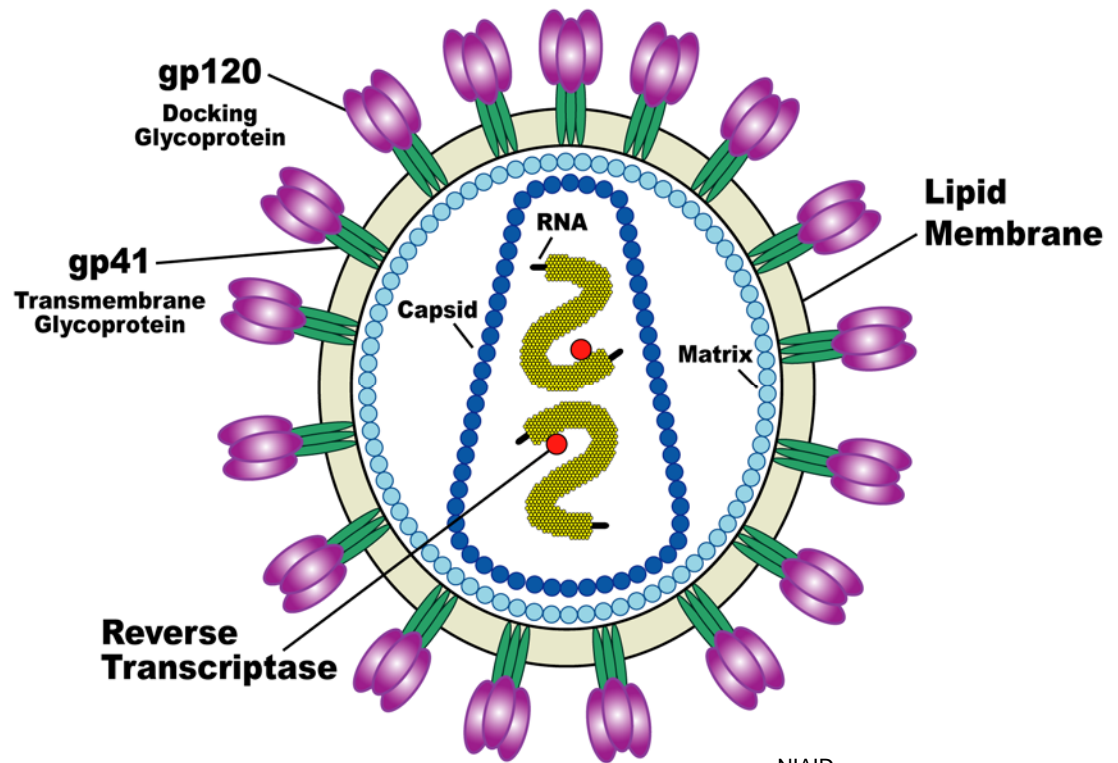


Lindenback: Charles M. Rice. Unraveling hepatitis C virus replication from genome to function. Nature Publishing Group. 2005. 436(7053): 9333-938.

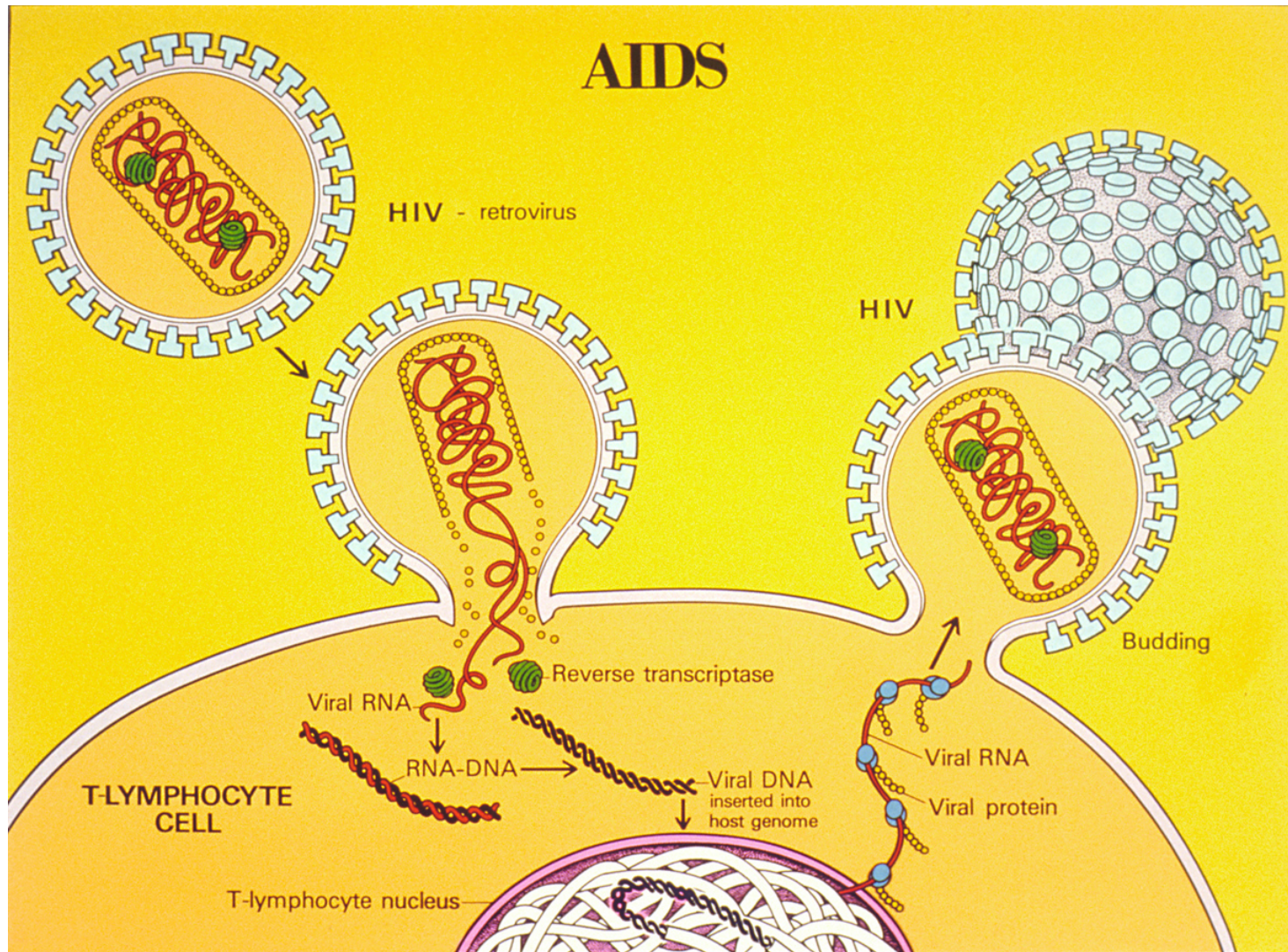
The Human Immunodeficiency virus (HIV)

Viral components:

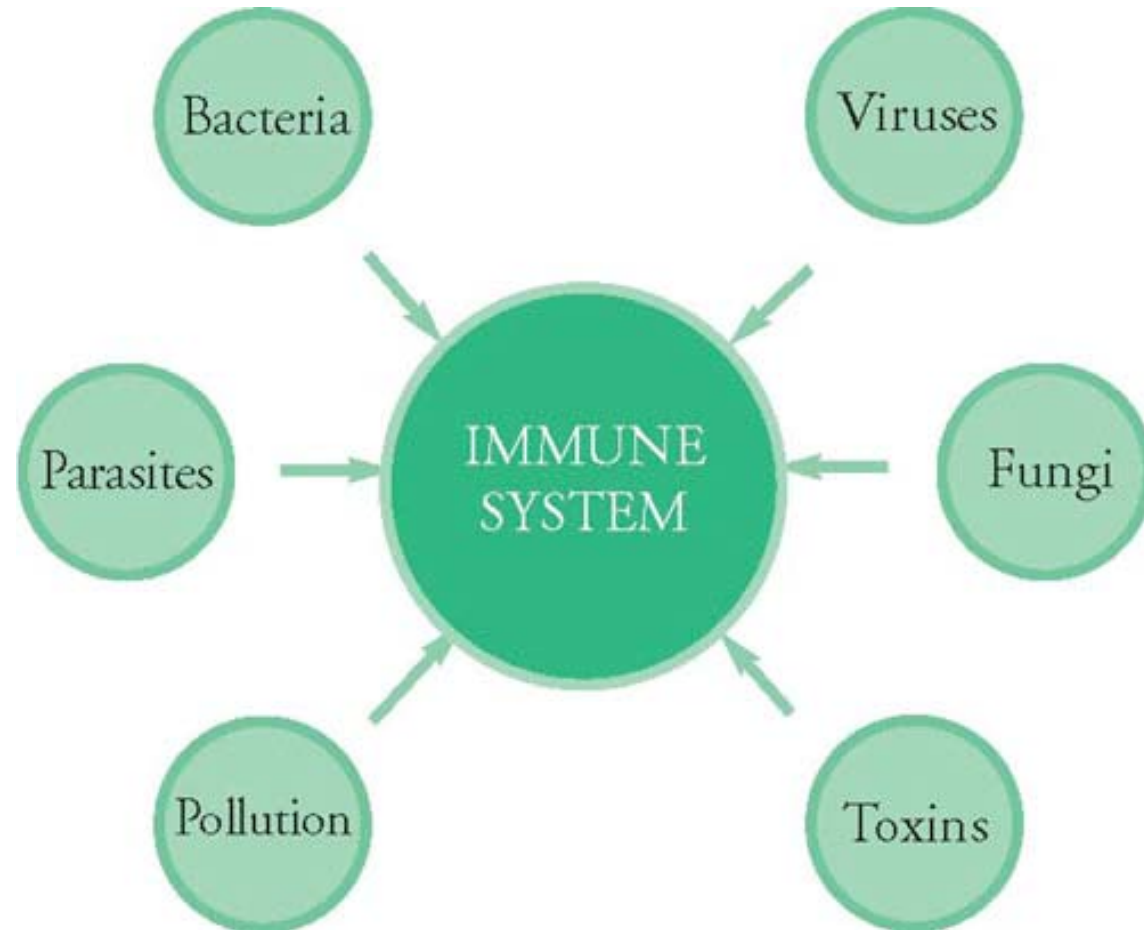
- nucleic acid core (DNA/RNA)
- protein capsid
- envelope
- Glycoproteins



The Human Immunodeficiency virus (HIV)



How are we protected against pathogens?



Lecture map

1. **The players:** Types of pathogens

Cells of the Immune system

2. Types of Immunity

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2B. Innate Immunity

Macrophages

Neutrophils

Complement proteins

Splinter example

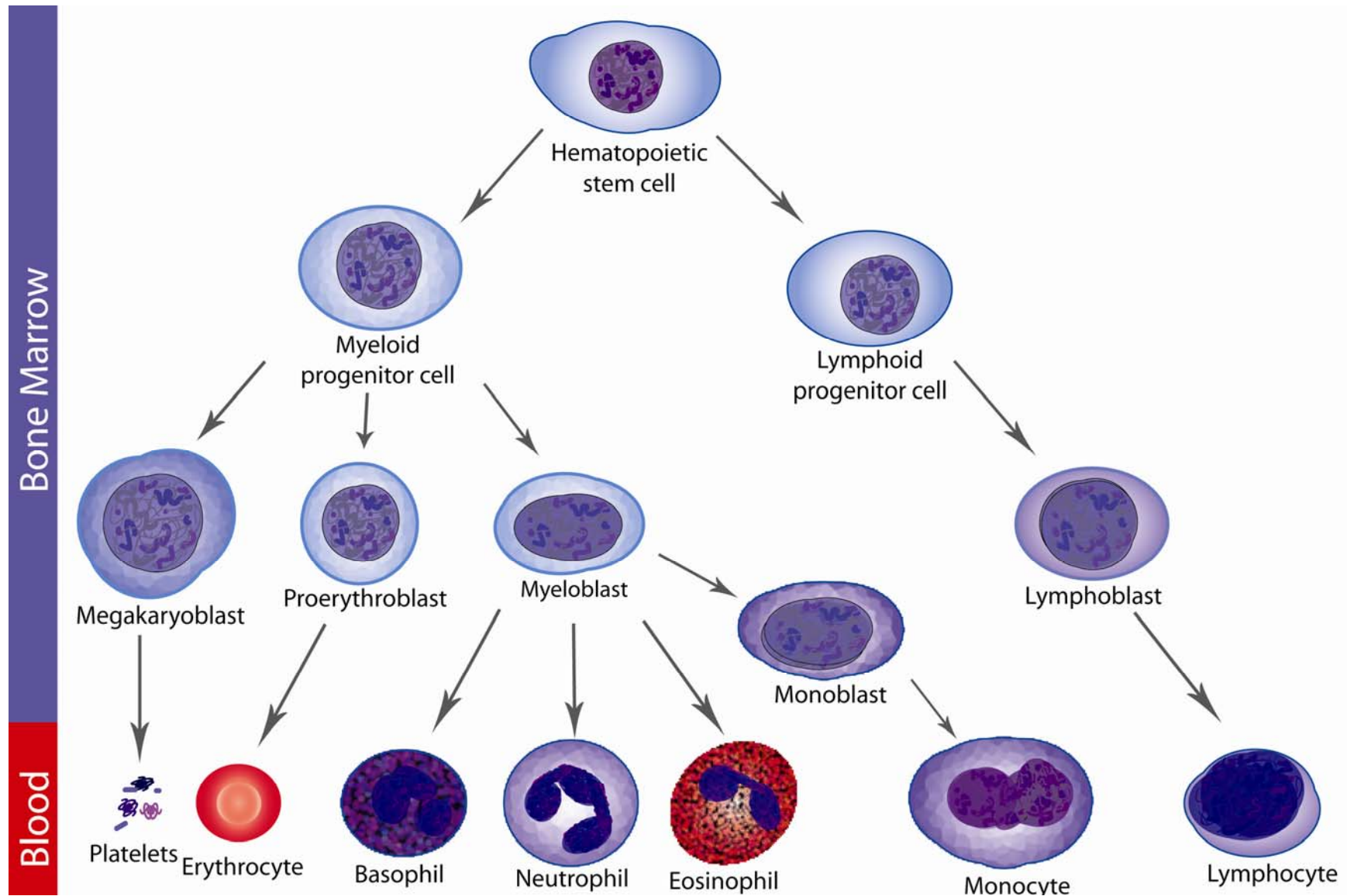
2C. Adaptive Immunity

B-lymphocytes: ANTIBODIES

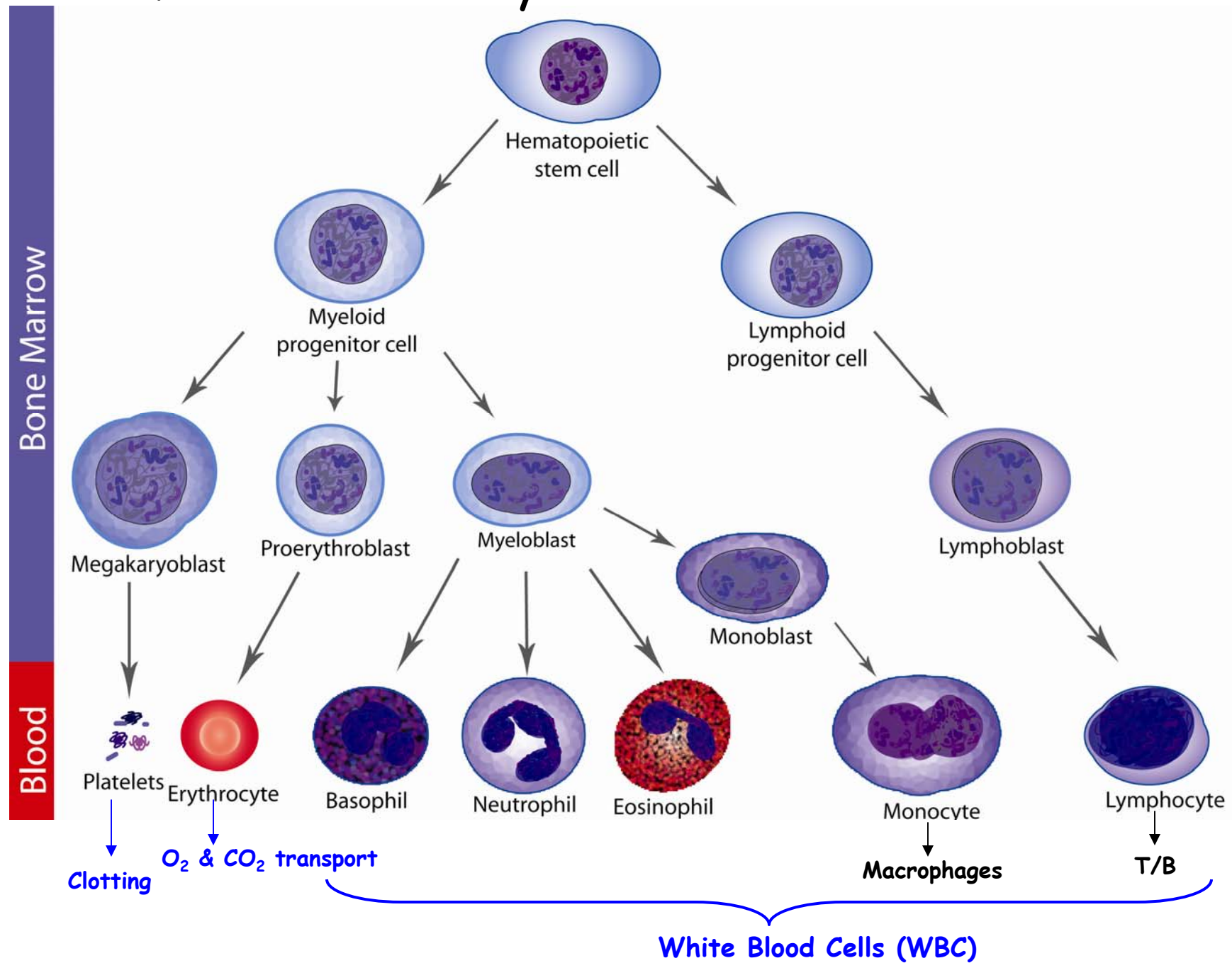
T-lymphocytes: Cell-mediated

Immunologic MEMORY

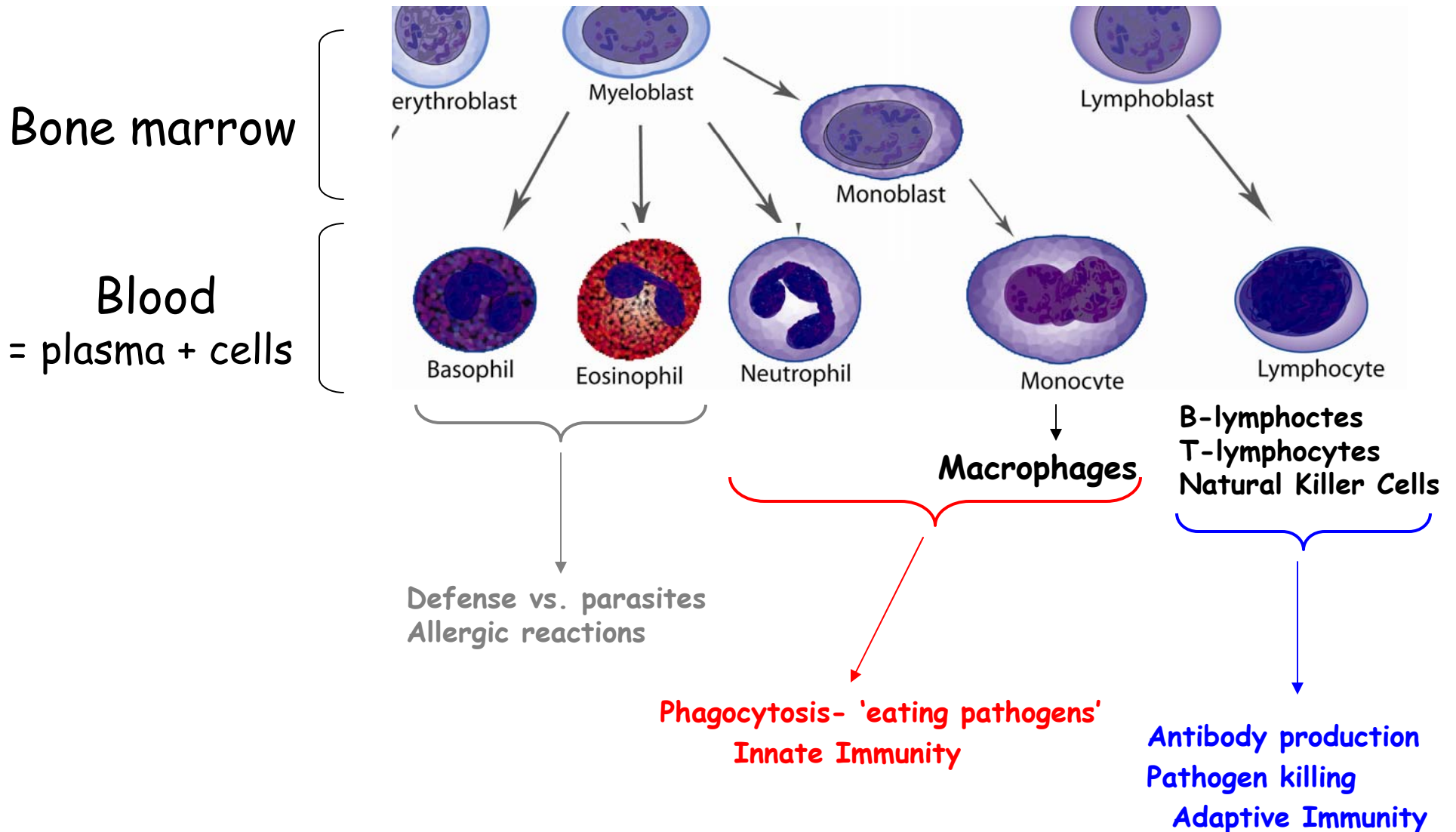
Cells of the immune system



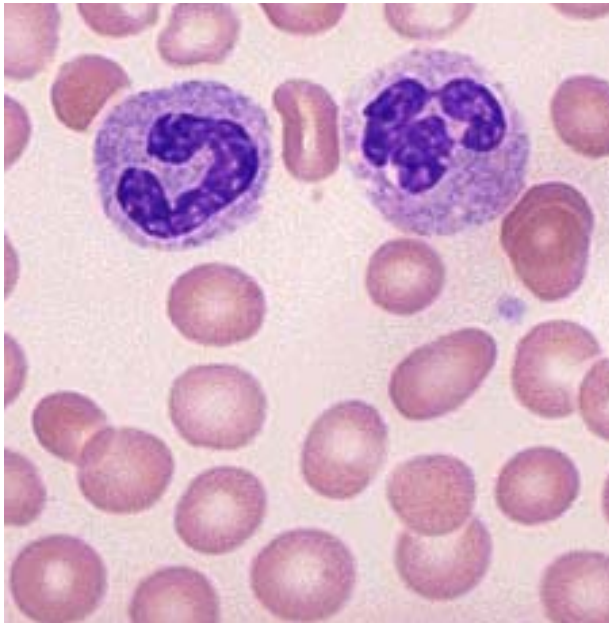
Cells of the immune system



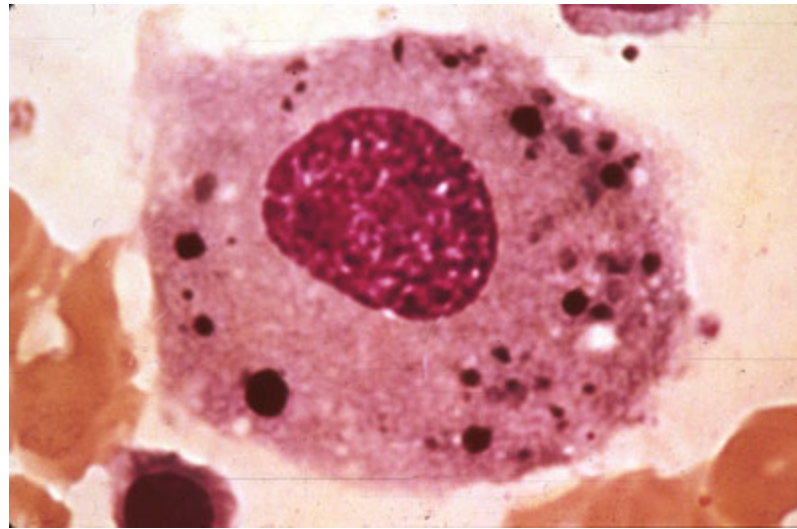
Cells of the immune system



Cells of the immune system



Neutrophil



Macrophage



Lymphocyte

Phagocytosis- killing

B-lymphocytes
T lymphocytes
NK cells

Question:

- Based on your understanding of the characteristics of bacteria, viruses, and blood cells, identify which item best represents a bacterium, a virus and a blood cell and be able to explain why you chose each.

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Immunologic MEMORY

Types of Immunity

Physical Barriers

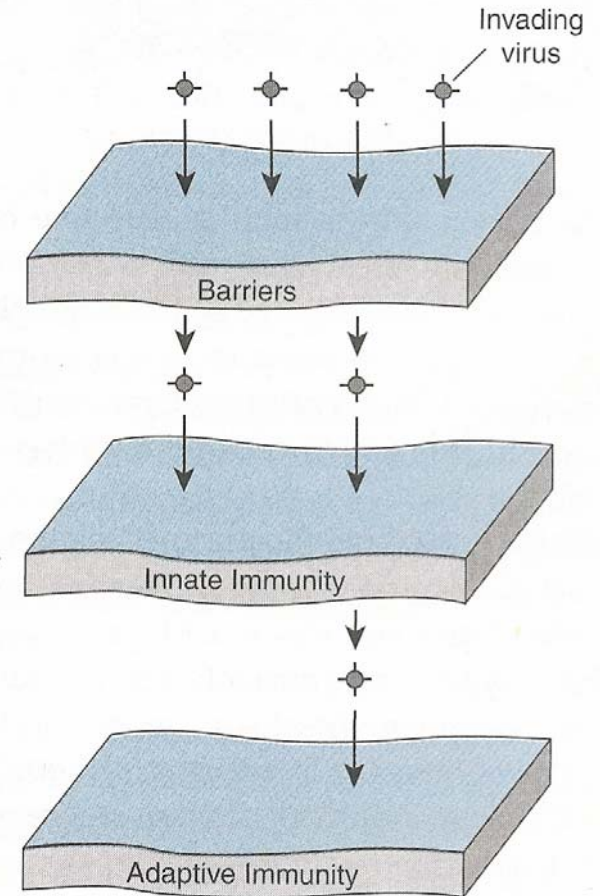
- skin (2 square meters!)
- mucose membranes (400 square meters!)

Innate Immune System

- General inflammatory response against pathogens outside of the cell

Adaptive Immune System

- Can adapt to defend against any specific invader inside or outside of the cell
- Important when innate immunity cannot defend against the attack
- Provides 'Immune Memory'



What happens when you get a splinter?

What happens when you get a splinter?

- Pathogen makes it past a physical barrier
- Symptoms?
 - Red, swollen, hot, pus
- What causes these symptoms?
 - **The Innate immune system** is kicking into gear!
- Usually innate immune system can take care of it

The Innate Immune System: 3 main weapons

-Activated Macrophages

Phagocyte ('eat') invading pathogens

Produce chemicals that:

- increase blood flow (redness & heat)
- cause 'fluid leaking' (swelling)
- recruit neutrophils (pus)

Present antigen to adaptive immune system

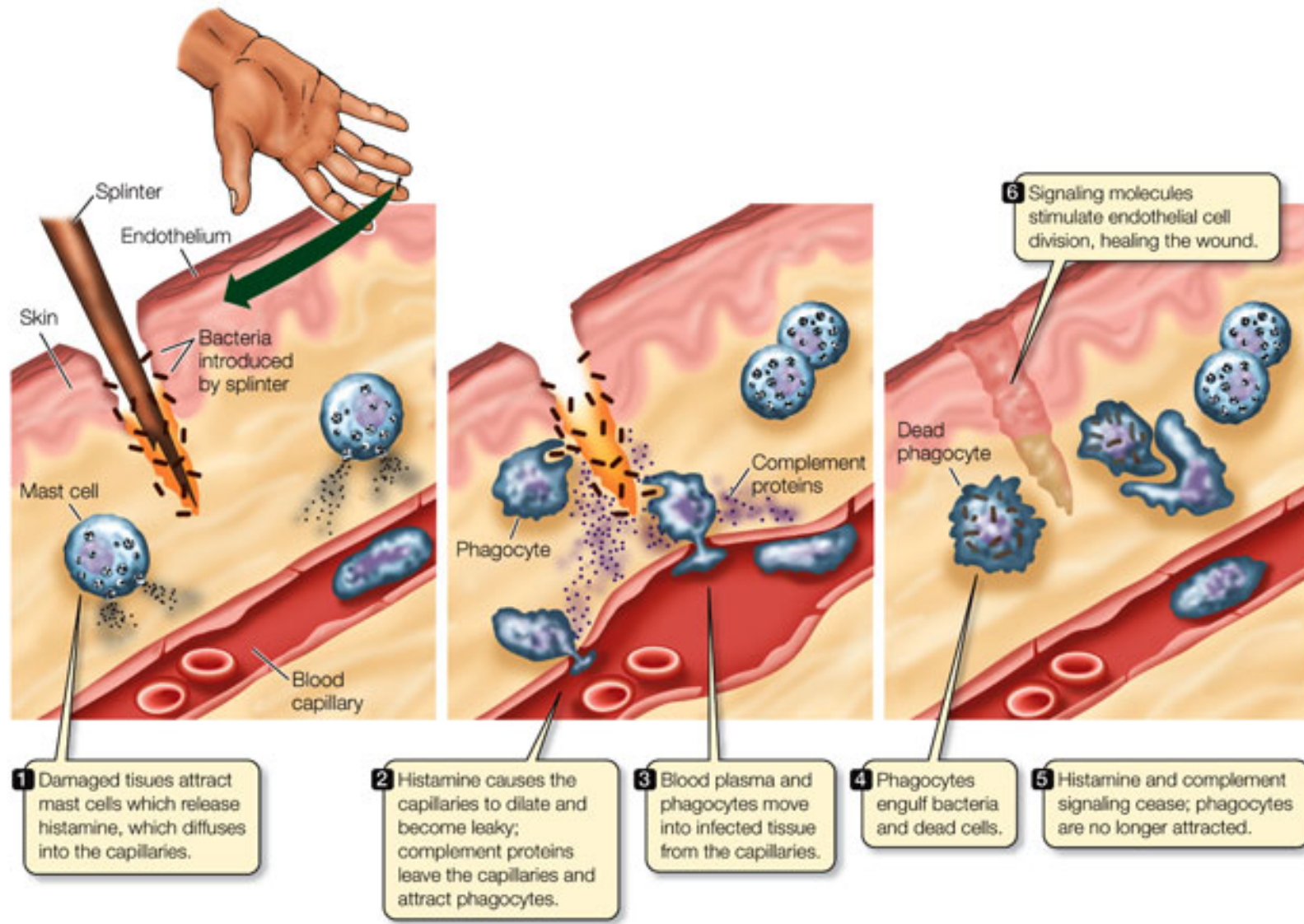
-Complement proteins

Present in tissue and blood

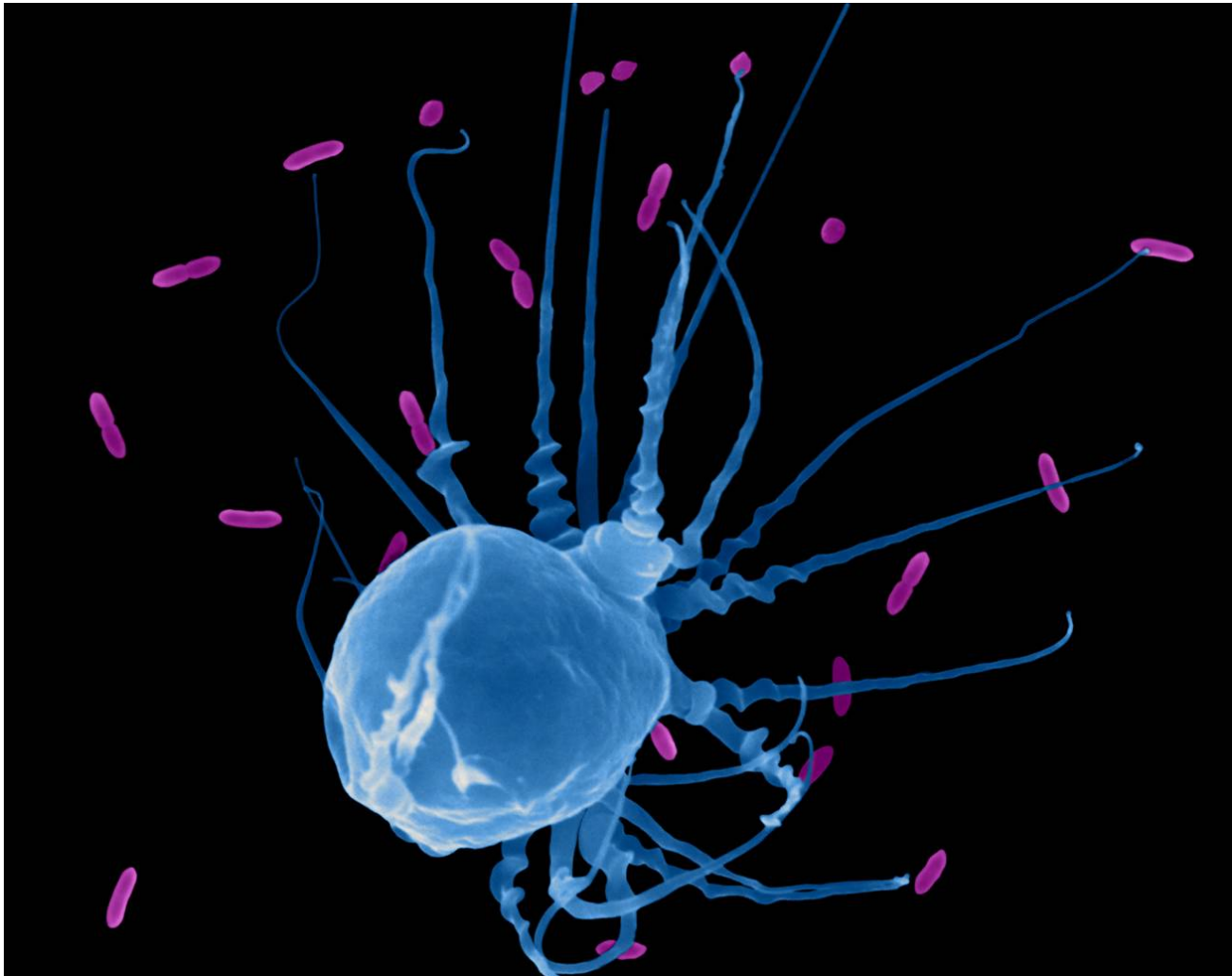
Attach to surface of bacteria and viruses targeting them for phagocytosis

Recruit other immune cells from blood

What happens when you get a splinter?



LIFE 8e, Figure 18.4



Macrophage attacking *E.coli*

©Denis Kunkel

Question:

- Based on your understanding of the innate immune system, represent a macrophage during phagocytosis

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**T-lymphocytes: Cell-mediated
Immunologic MEMORY**

The Adaptive Immune System

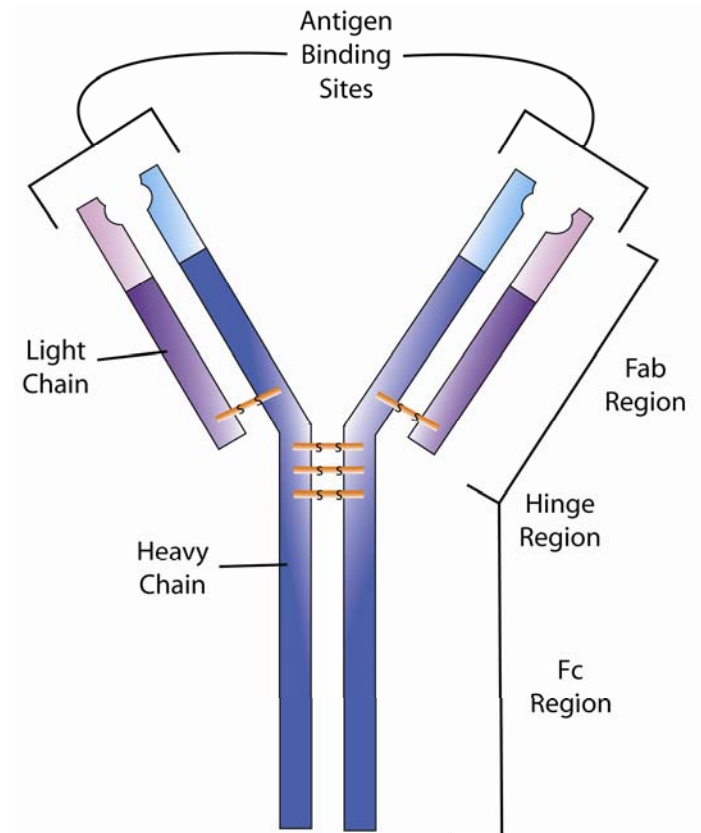
- Recognizes antigens (molecular signatures) specific for each pathogen
- Effective against both intra- and extracellular pathogens
- Two main components: **Humoral immunity**
 - Relies on Antibodies produced by B-lymphocytes
 - Fights pathogens outside of cells

Cell-mediated Immunity

- Relies on specific receptors on the surface of T-lymphocytes
- Fights pathogens inside of cells

What is an antibody?

- Bridge between:
 - Pathogen
 - Tool to kill it
- Antibodies have two important regions:
 - Fab region:
 - Binds antigen
 - Binds surface of virus infected cell
 - Fc region:
 - Binds macrophages and neutrophils, induces phagocytosis
 - Binds natural killer cell, induces killing

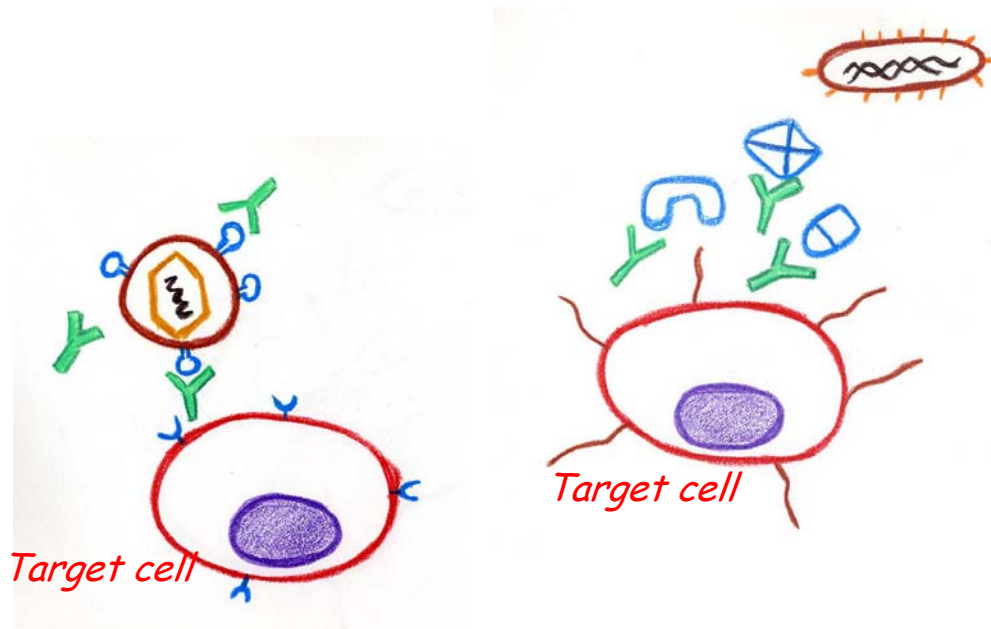


The Adaptive Immune response: humoral immunity

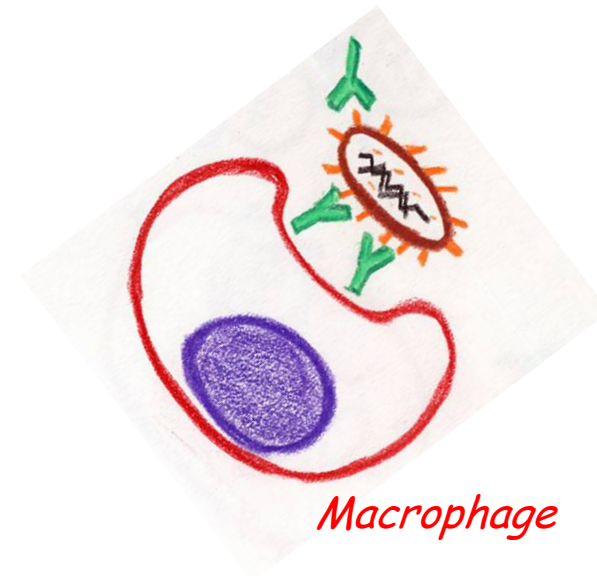
How do antibodies work?

1. **Neutralization:** Blocking the biological activity of toxin or pathogen *ie. Blocking access*
2. **Bridge:** Bringing together pathogens and phagocytes

The Adaptive Immune response: humoral immunity



1. Neutralization



2. Bridge: pathogen-phagocyte

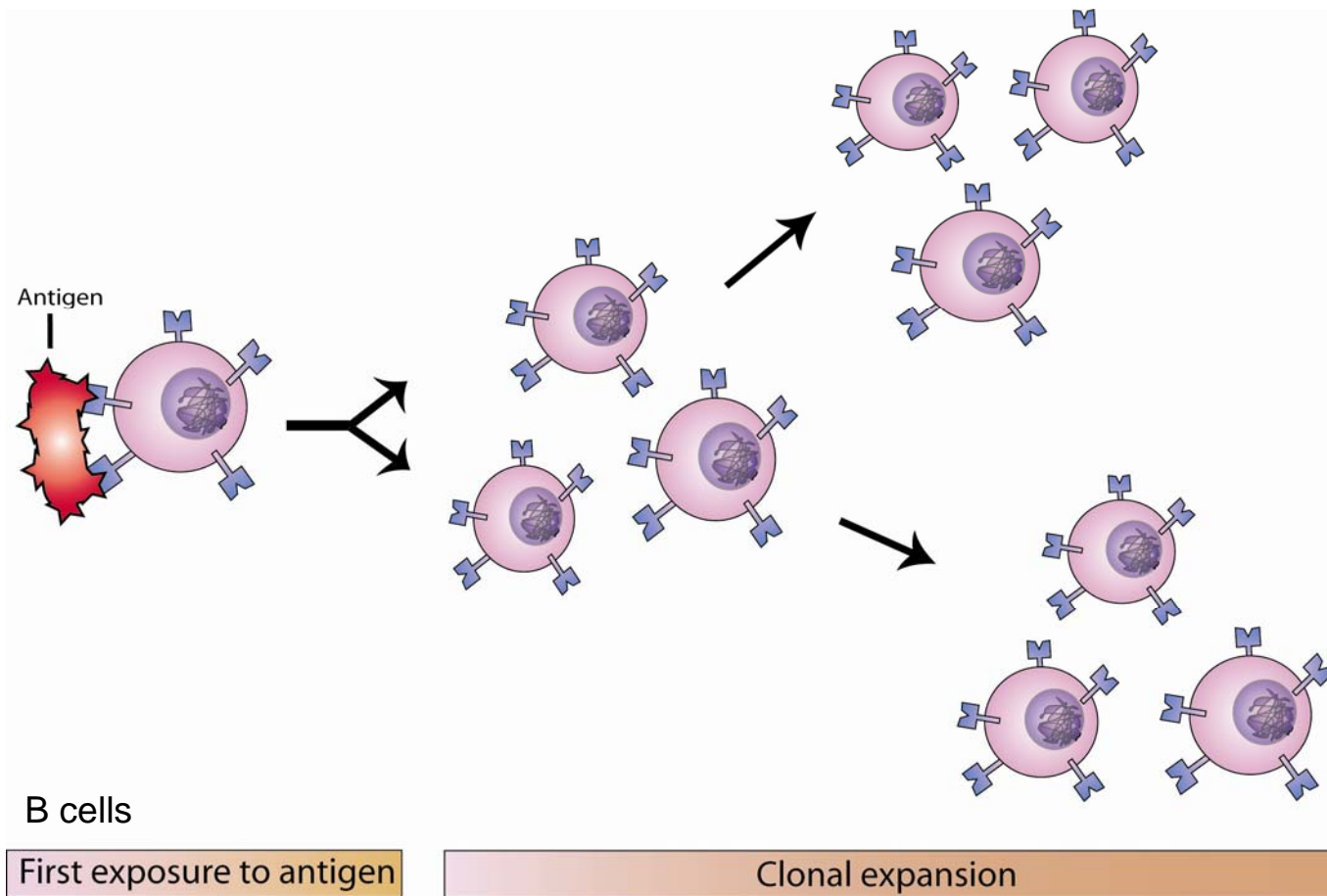
Question:

- Which components of your kit are most like antibodies?
- Arrange the components of the kit to demonstrate how these antibodies “bridge” a pathogen and the tool to kill it?

The Adaptive Immune response: humoral immunity

- How are antibodies made?
 - B cells
 - Lymphocytes that make antibodies
 - Have B cell receptors on surface
 - 100 million different types of B cells, each with different surface receptors
 - B cell receptors are so diverse they can recognize every organic molecule
 - When a B cell binds antigen:
 - Proliferates - In one week, clone of 20,000 identical B cells
 - Secretes antibody

Clonal selection and proliferation



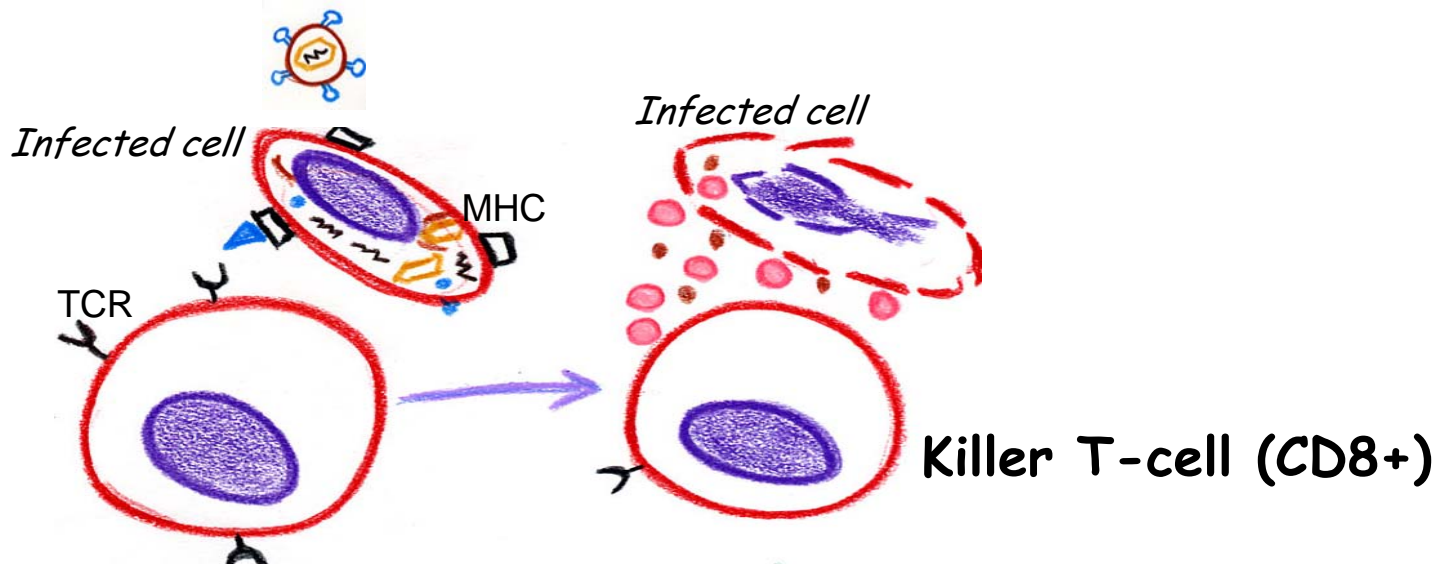
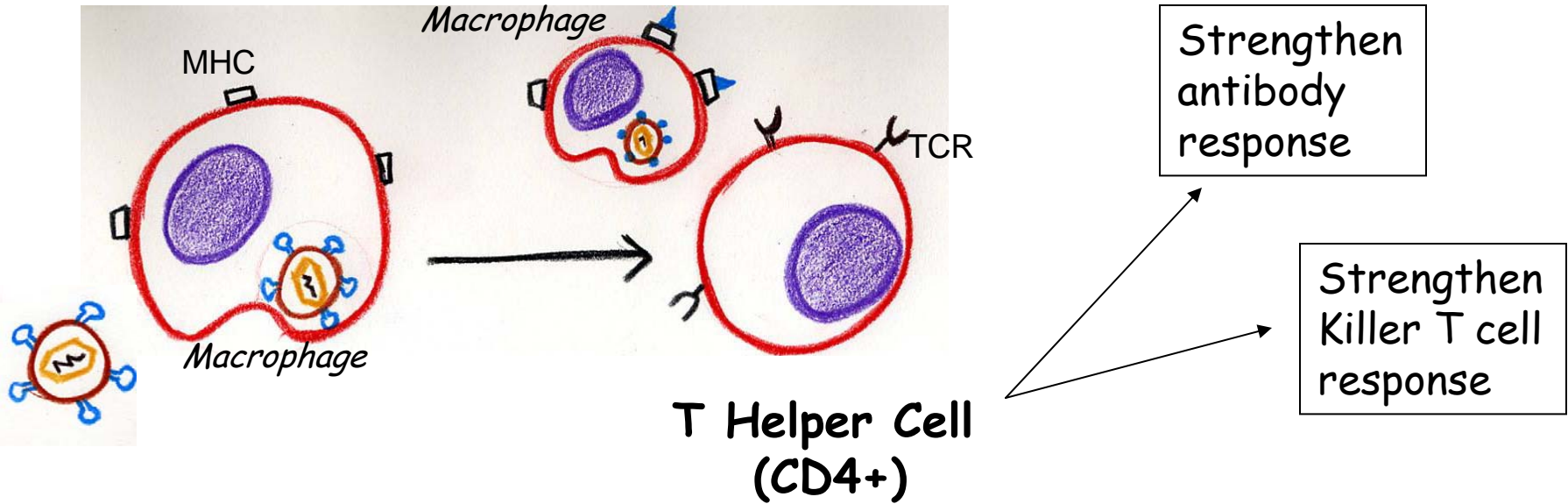
The Adaptive Immune response: cell-mediated immunity

- How do we kill virus once inside the cell?
 - Antibodies cannot get to it
 - Need T cells
- T Cells
 - Recognize protein antigens
 - When bind antigen, undergo clonal selection
 - Three types of T Cells:
 - Killer T Cells (Cytotoxic T Lymphocytes - CTLs)
 - Helper T Cells (orchestrate adaptive immune response)
 - Regulatory T Cells

How do T Cells recognize Virus-Infected Cells?

- All cells have **Major Histocompatibility Complex (MHC)** molecules on surface
- T Cells inspect MHC proteins and use this as a signal to identify infected cells
- **Antigens (bits of pathogens) get loaded into MHC molecules:**
 - When virus invades target cell, fragments of viral protein are loaded onto MHC proteins
 - 'Professional' Antigen Presentation Cells (APCs= phagocytes of innate immunity)

Antigen presentation and cellular immunity



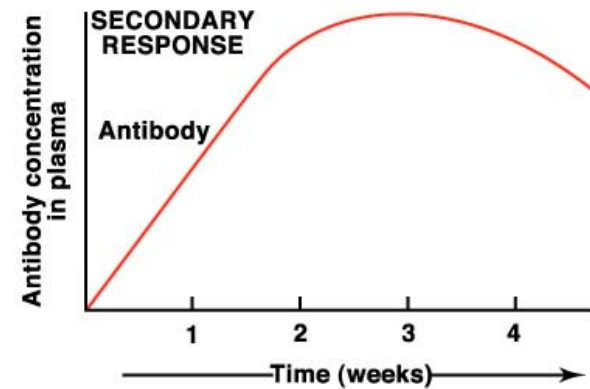
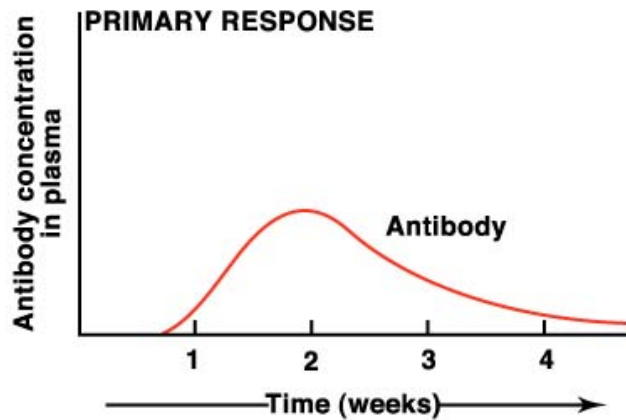
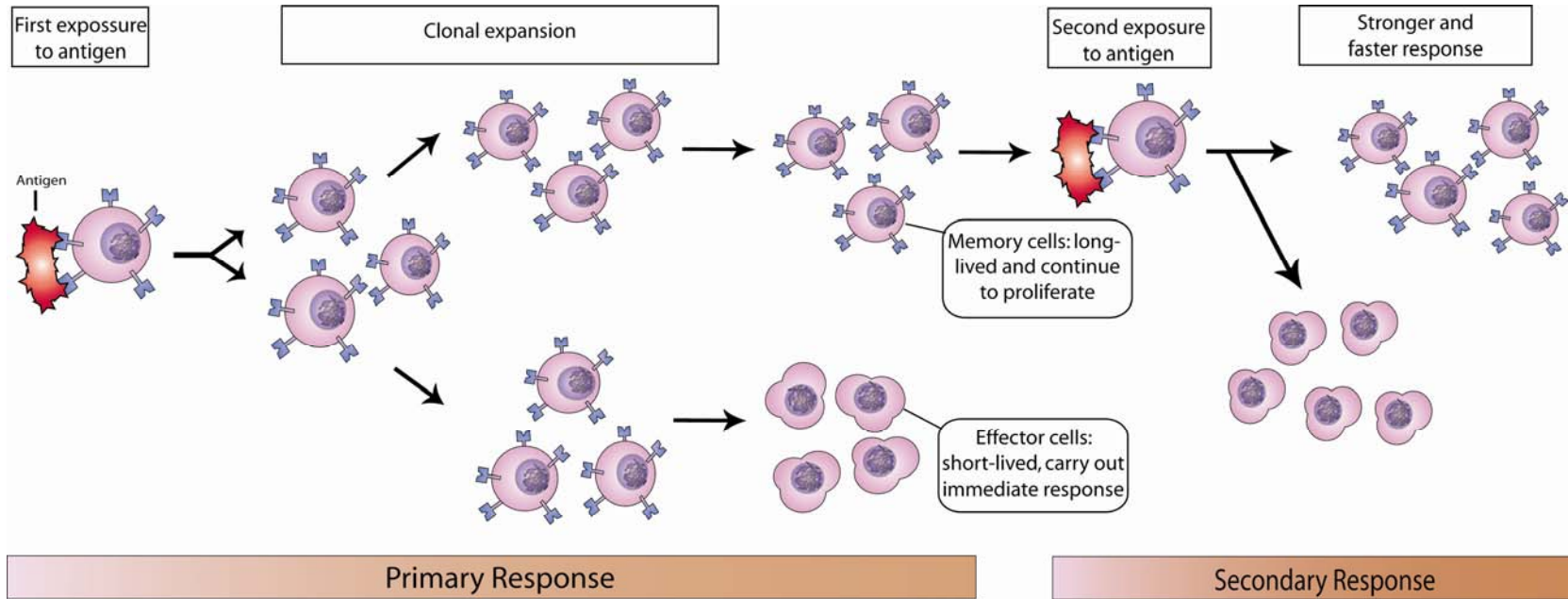
Question:

- Demonstrate how the T cell can identify a virus infected cell: antigen presentation
- Why is this component of the adaptive immune system a significant advance over the innate immune system?

Immunologic Memory

- First time adaptive immune system is activated by an antigen:
 - Build up a clone of B cells and T cells
 - Takes about a week
 - After infection is over, most die off
 - Some remain - memory cells
- Second time adaptive immune system is activated by that antigen:
 - Memory cells are easier to activate
 - Response is much faster - no symptoms

Immunologic Memory



The adaptive Immune Response

Putting it together...

Summary of lecture 8

- Pathogens: Bacteria and Virus
- Levels of Immunity:
 - Barriers → First line of defense
 - Innate → Inflammation
 - Phagocytes
 - Complement
 - Adaptive → Immunologic memory
 - Antibody mediated immunity
 - Cell mediated immunity → Pathogens within cells
 - Diversity to recognize 100 million antigens

Next time

- How do vaccines work?
- Vaccine development:
 - Design
 - Production
 - Testing safety & efficacy
- Challenges of vaccine development