Biomedical Engineering for Global Health

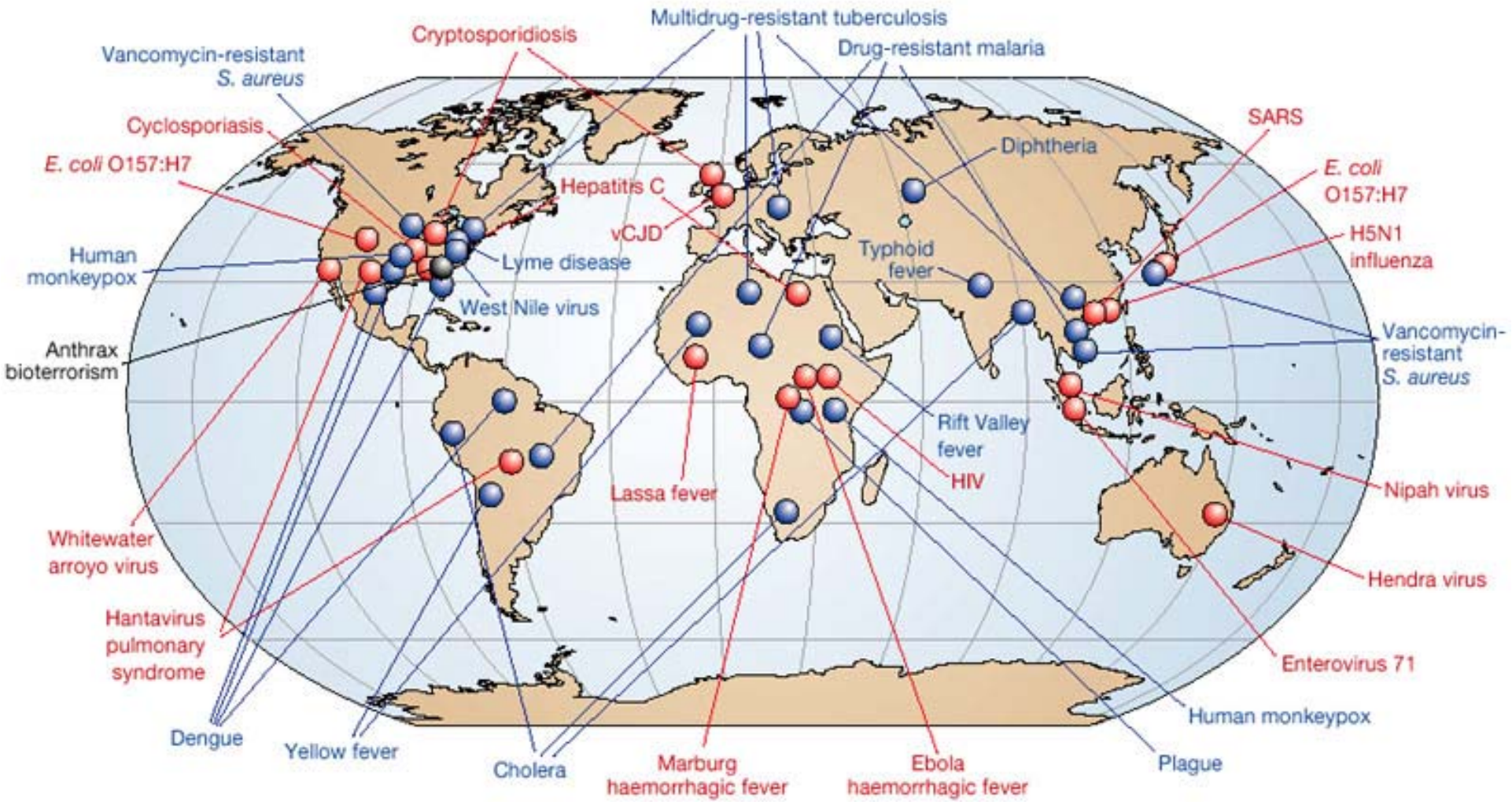
Pathogens and the immune system

Lecture 8

Review of lecture 7

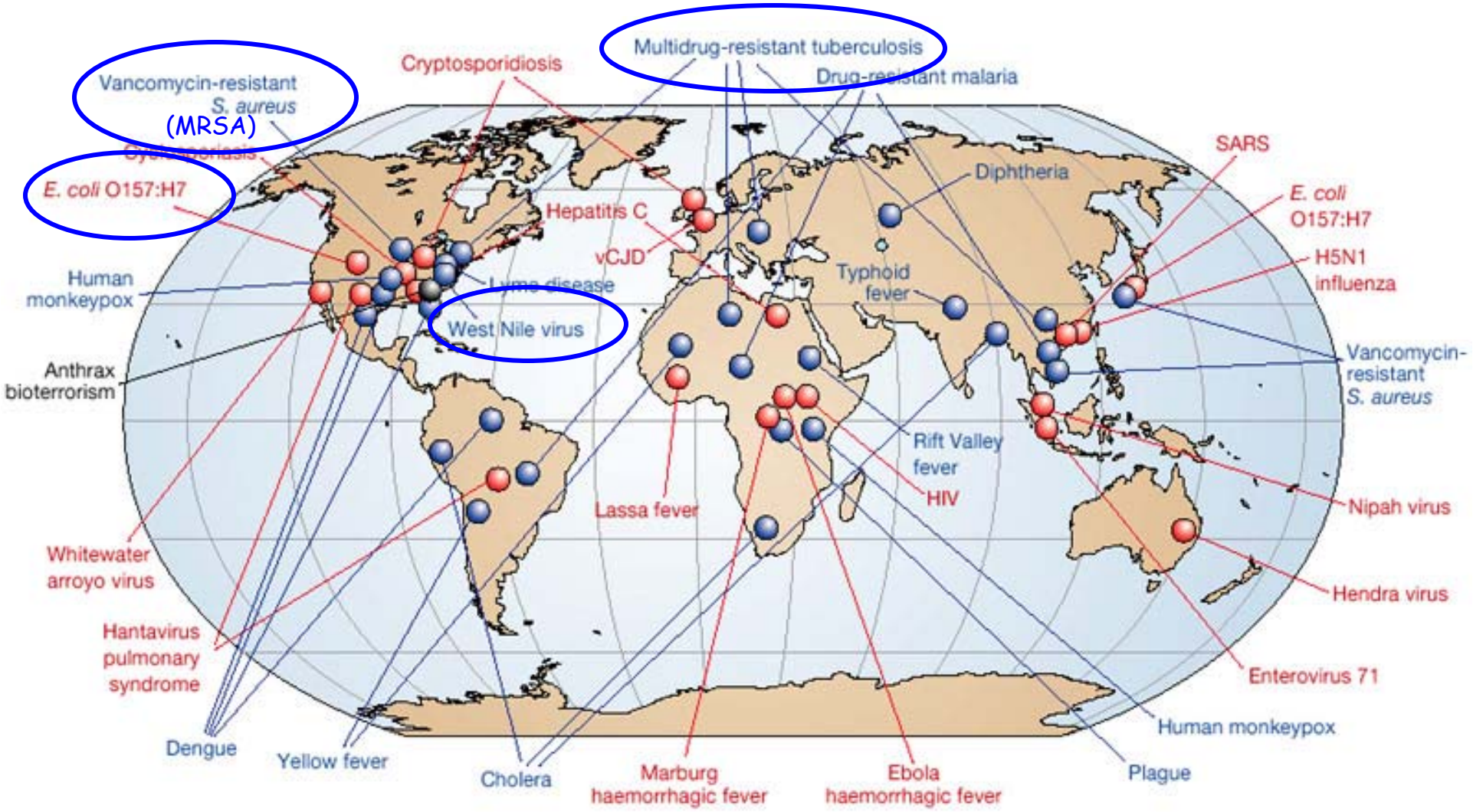
- Science
  - "**Science** is the human activity of seeking natural explanations for what we observe in the world around us."
- Engineering
  - Systematic design, production and operation of technical systems to meet practical human needs under specified constraints
  - Six steps of the engineering design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

Infectious diseases: a global health problem

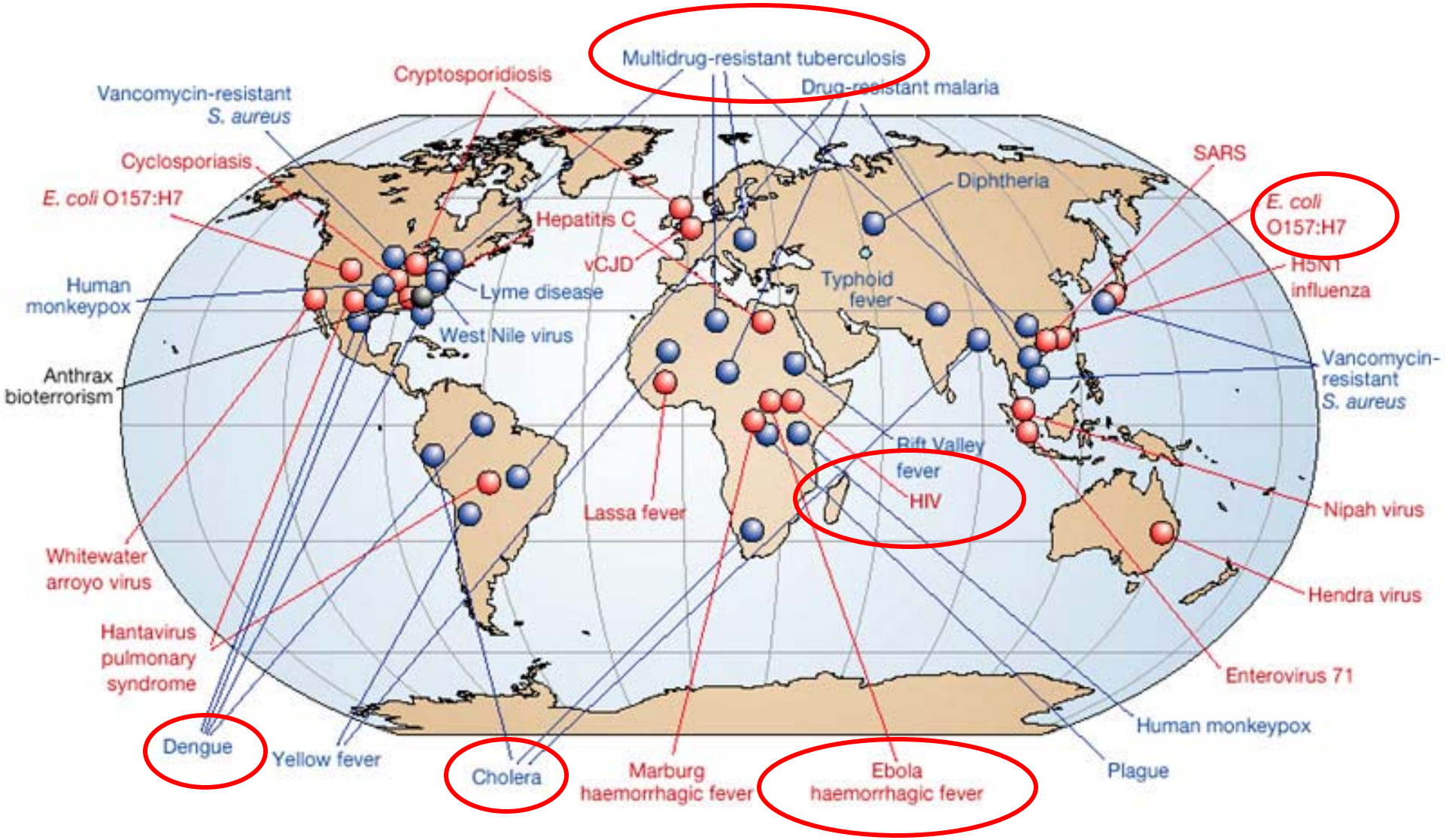


(From Morens, D., et al , 2004)

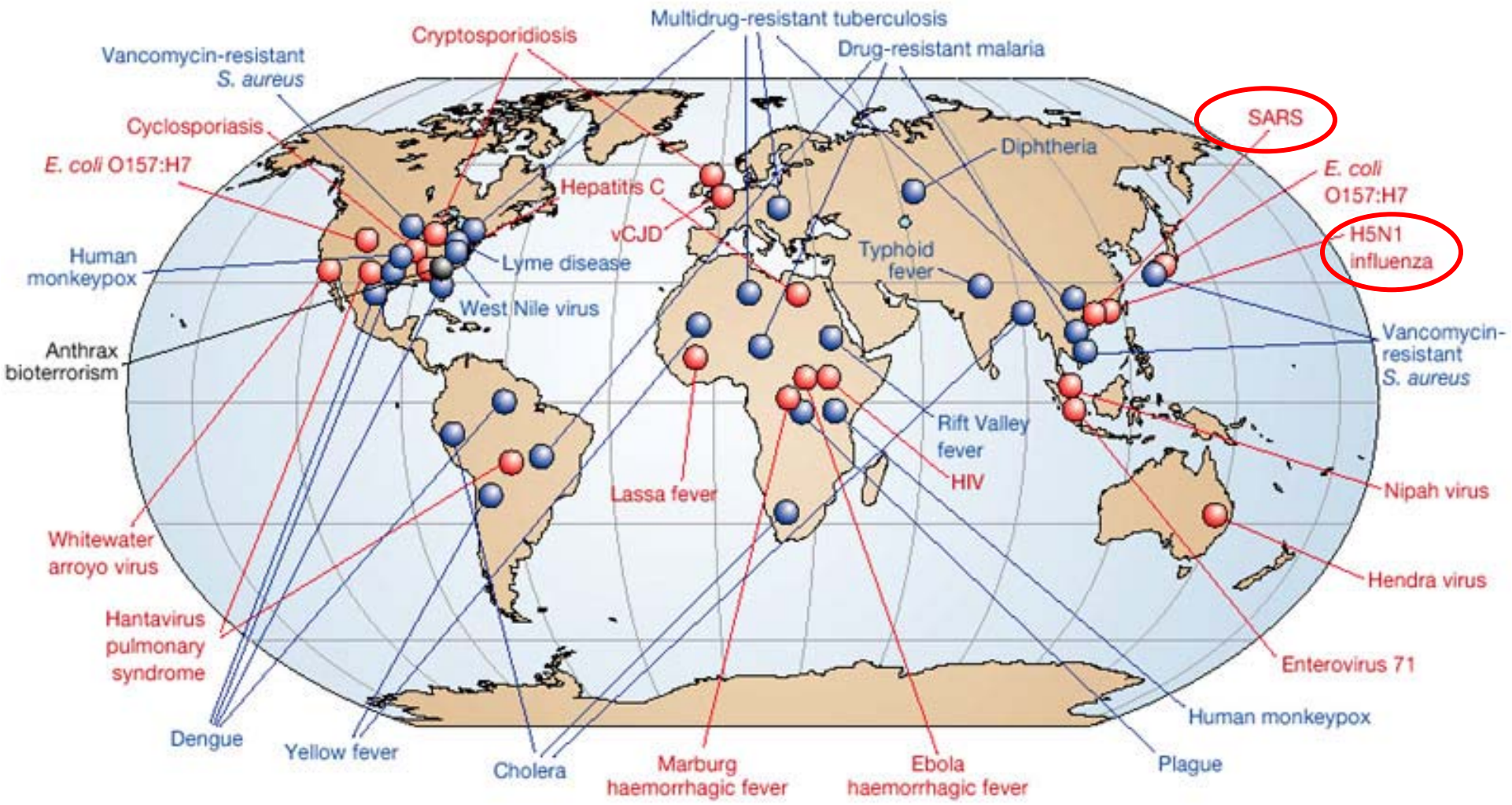
Infectious diseases: a global health problem



Infectious diseases: a global health problem



Infectious diseases: a global health problem



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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Types of pathogens

Mycobacterium tuberculosis
Staphylococus 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)
Cryptospridium

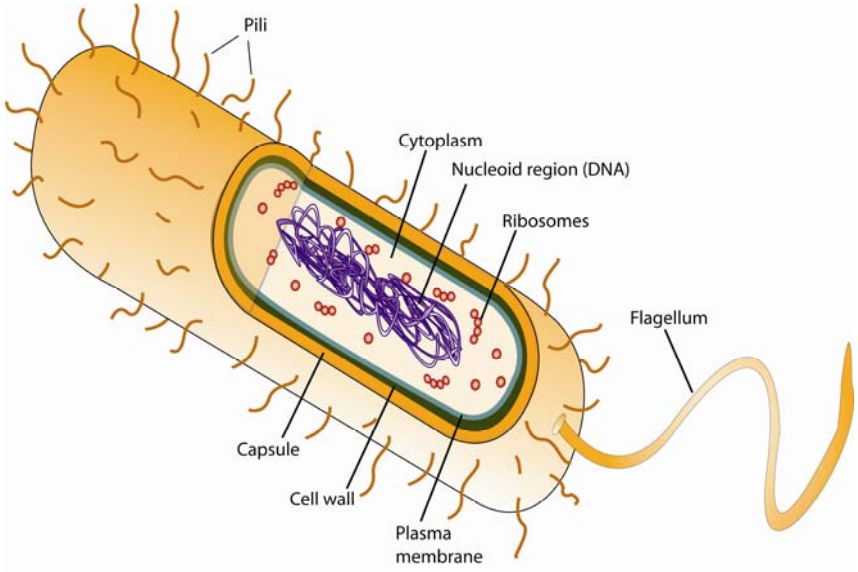
Parasites

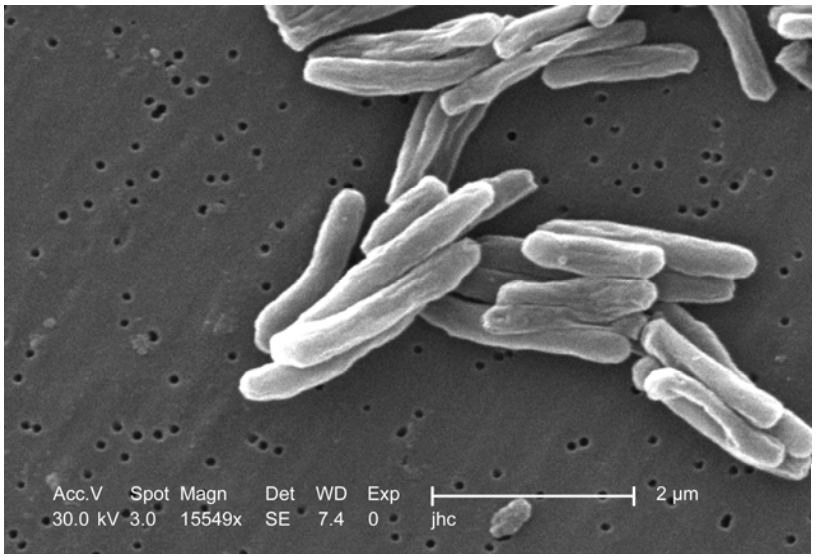
Candida albicans

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

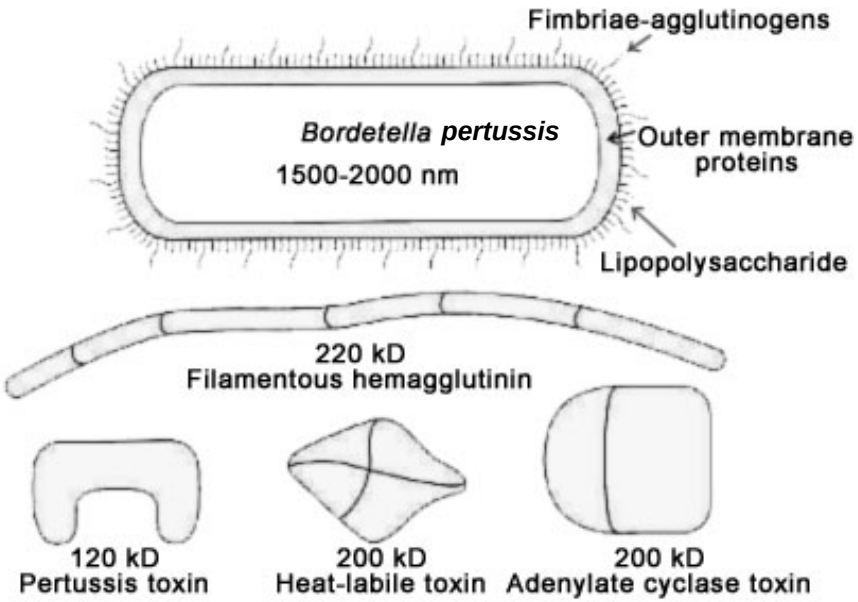


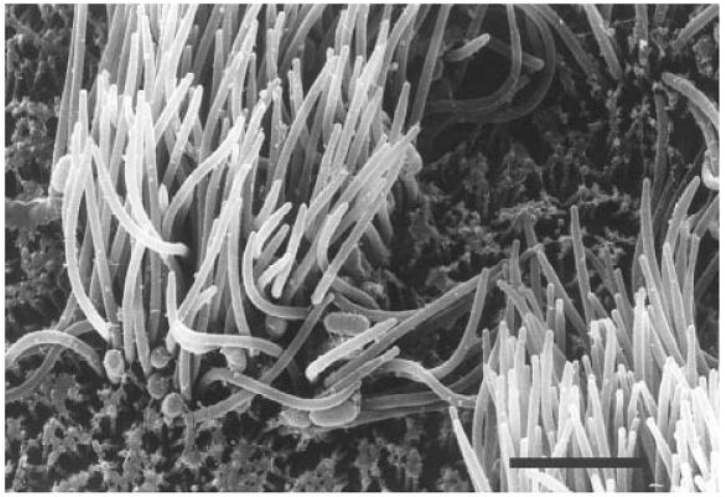


Size ~ 1 µm

How do bacteria cause disease?

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

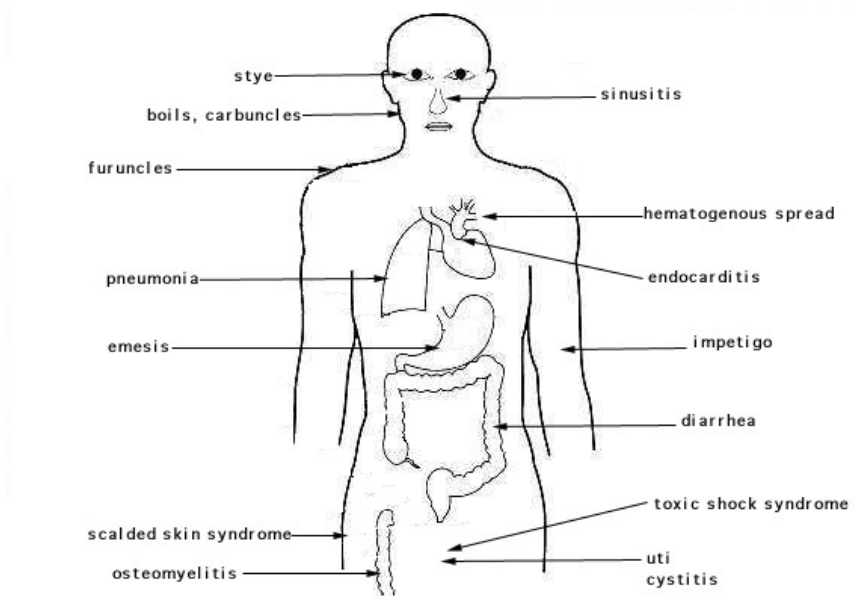


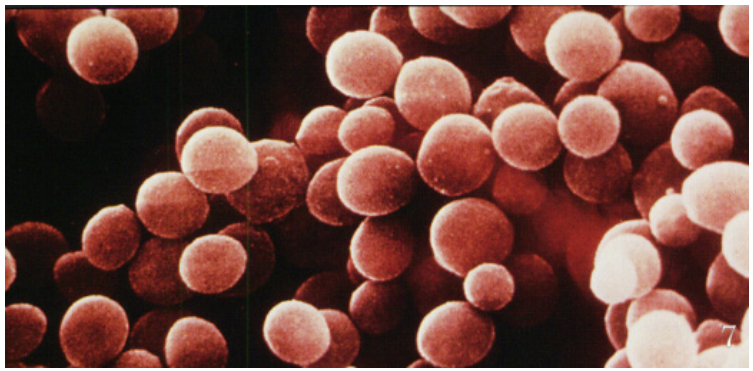


Paralyze cilia & inhibit clearance of respiratory secretions
= whooping cough

How do bacteria cause disease?

MRSA: Methycillin Resistant Staphylococcus aureus

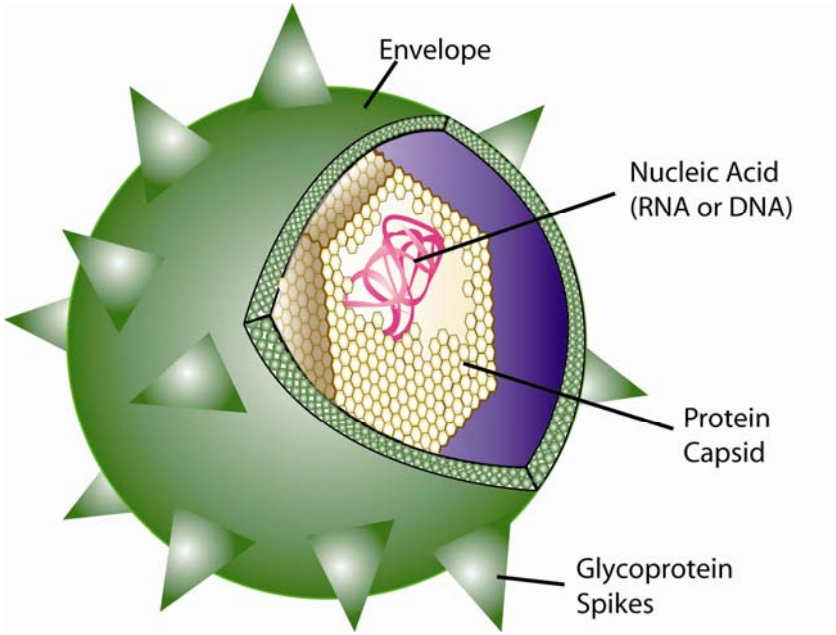


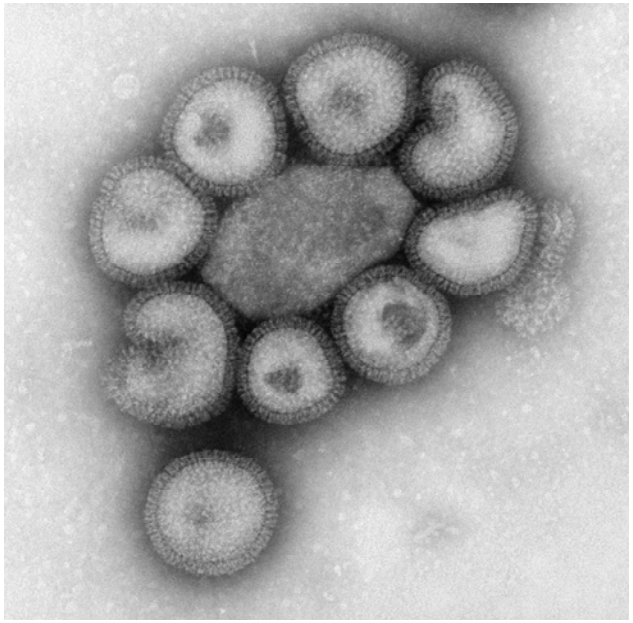


http://www.npr.org/templates/story/story.php?storyId=15453093

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





Size ~ 0.1 μm = 100nm

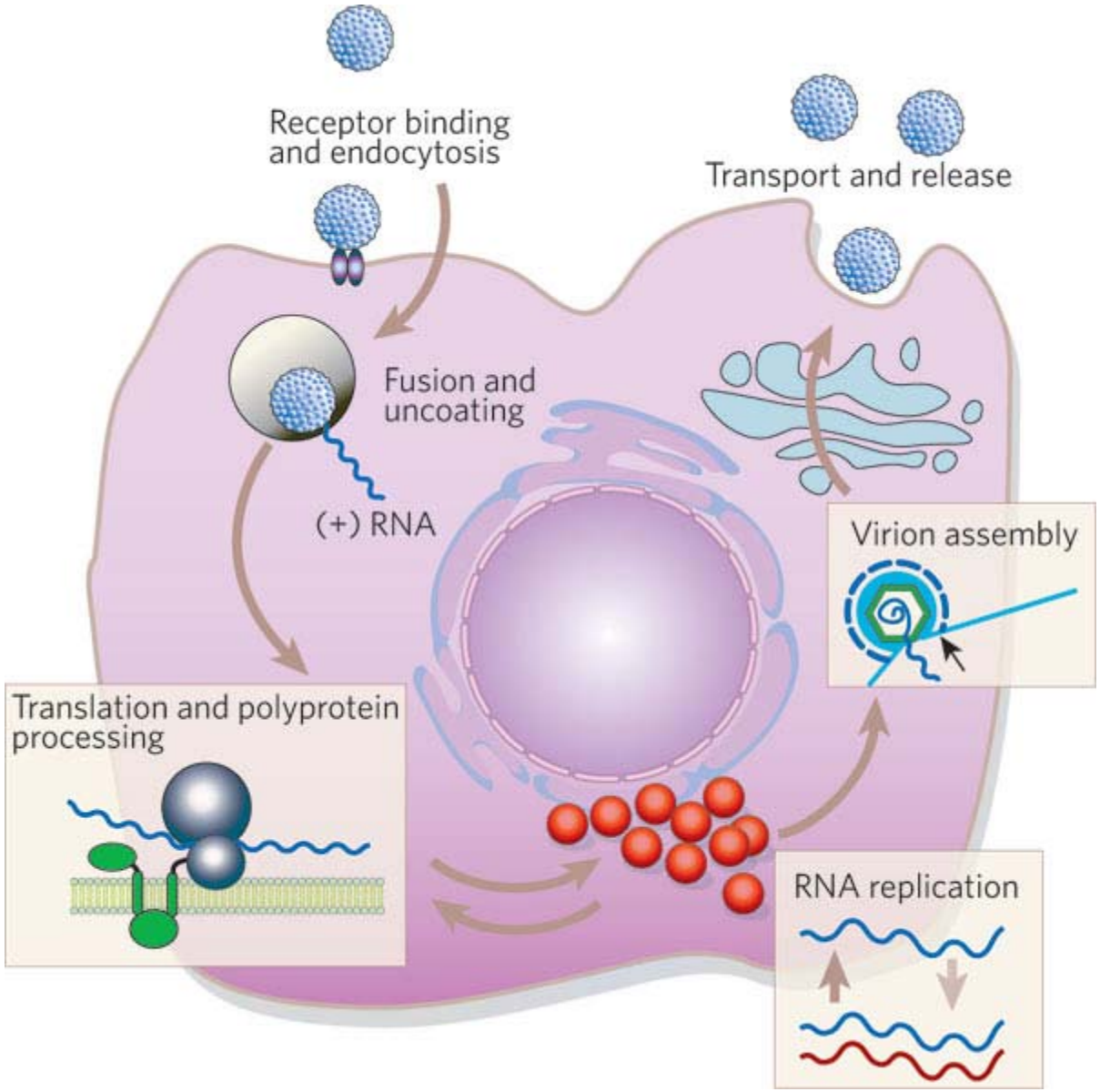
How do viruses cause disease?

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

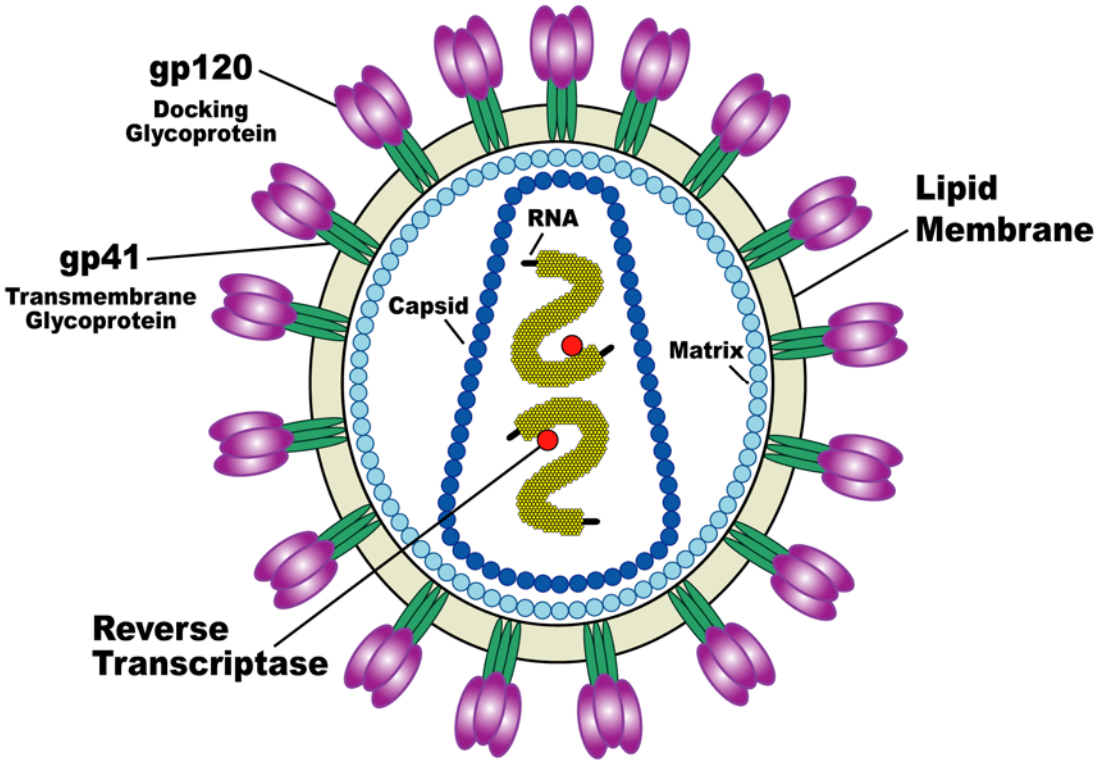
How do viruses cause disease?



The Human Immunodeficiency virus (HIV)

Viral components:

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



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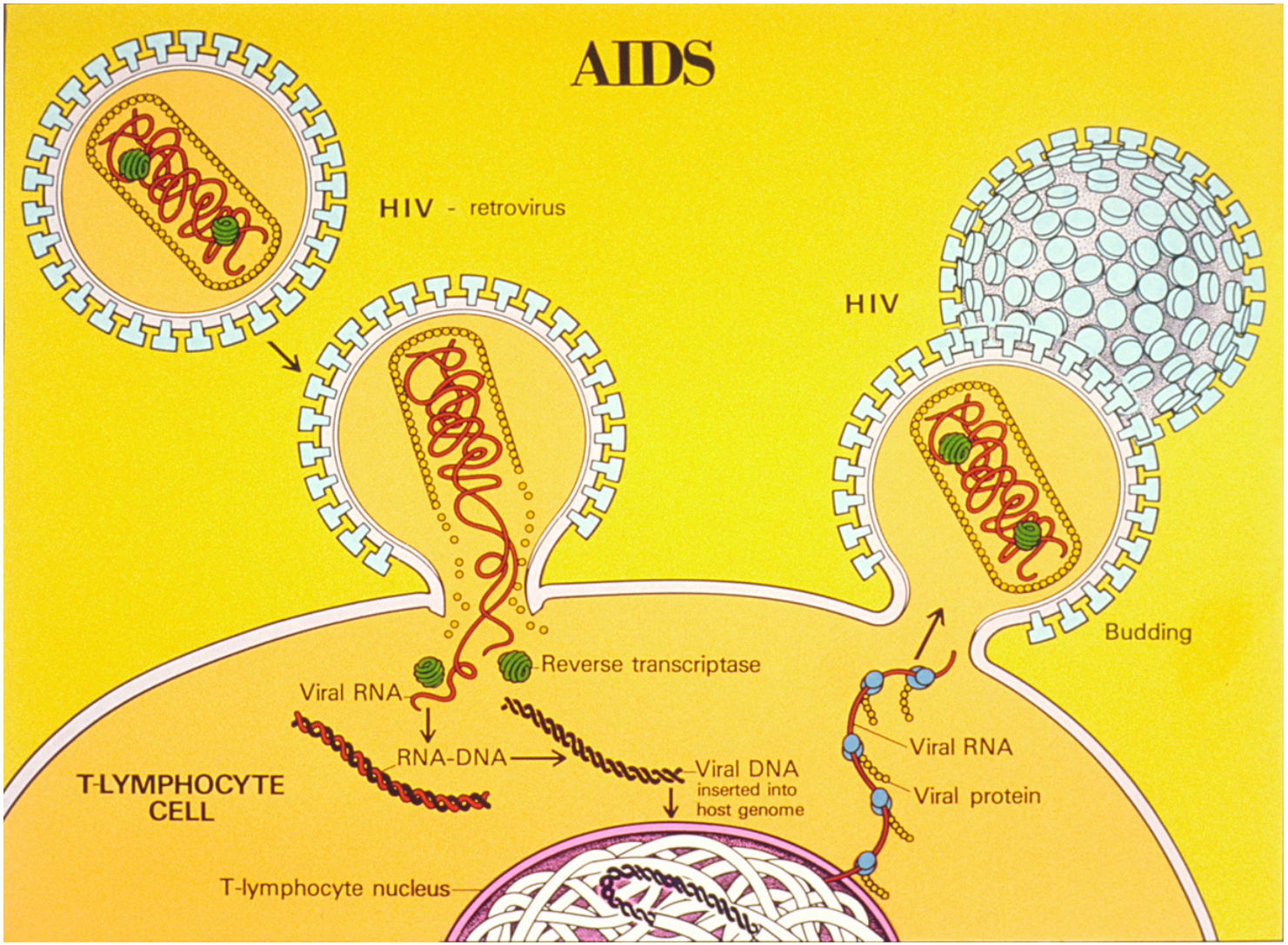
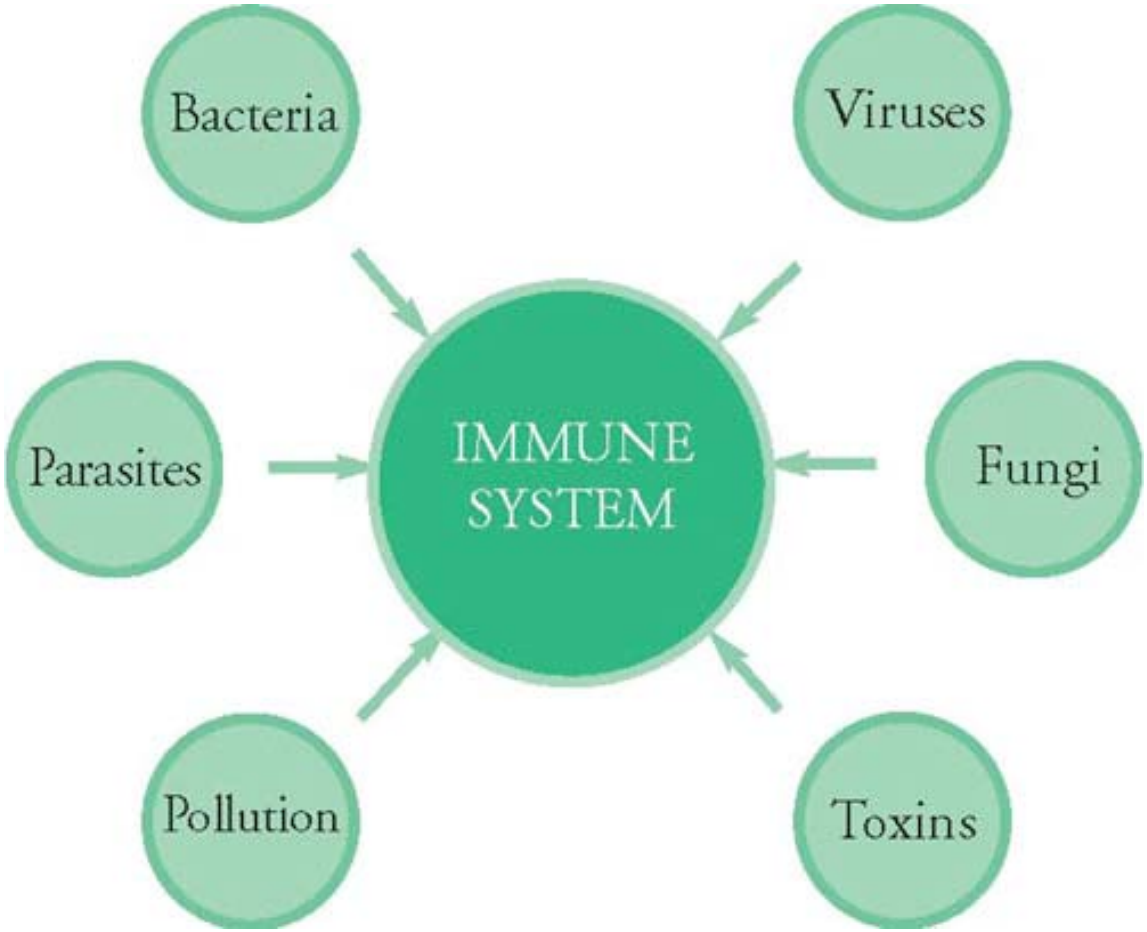


NCI/Trudy Nicholson

How are we protected against pathogens?



Lecture map

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

   Cells of the Immune system

2. Types of Immunity

   2A. Physical barriers

   2B. Innate Immunity

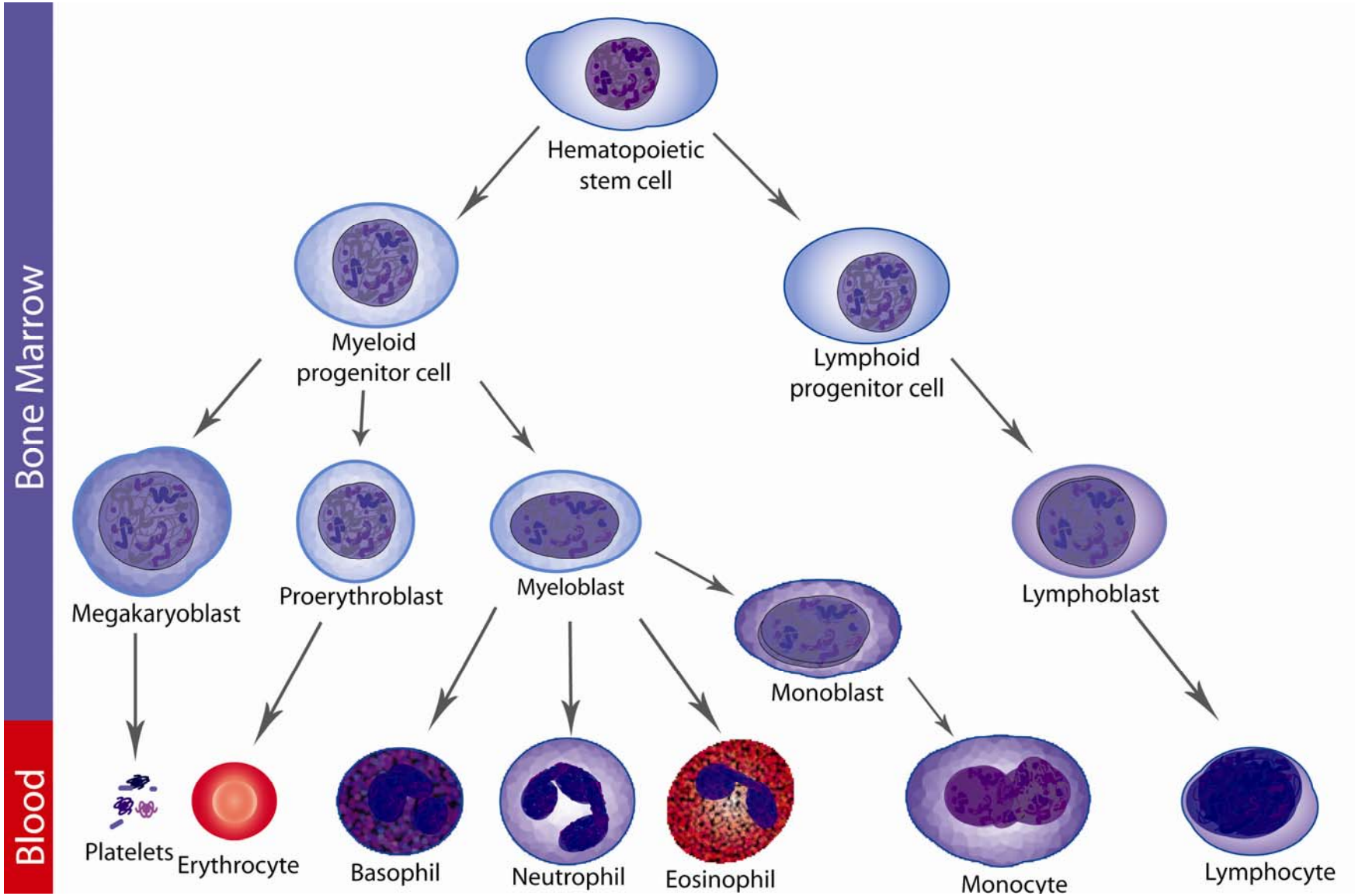
   Macrophages
   Neutrophils
   Complement proteins

   Splinter example

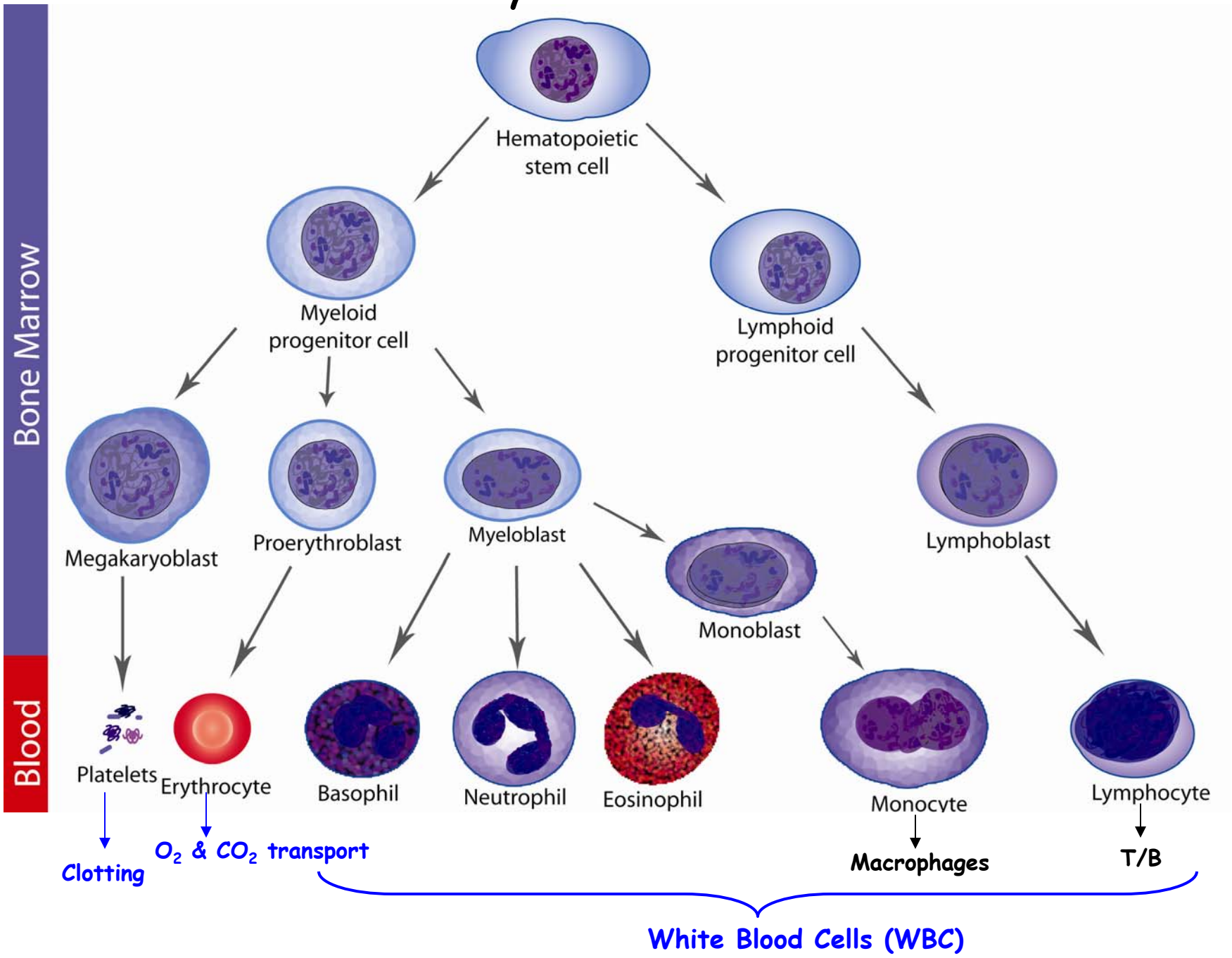
   2C. Adaptive Immunity

   B-lymphocytes: ANTIBODIES
   T-lymphocytes: Cell-mediated
   Immunologic MEMORY

Cells of the immune system



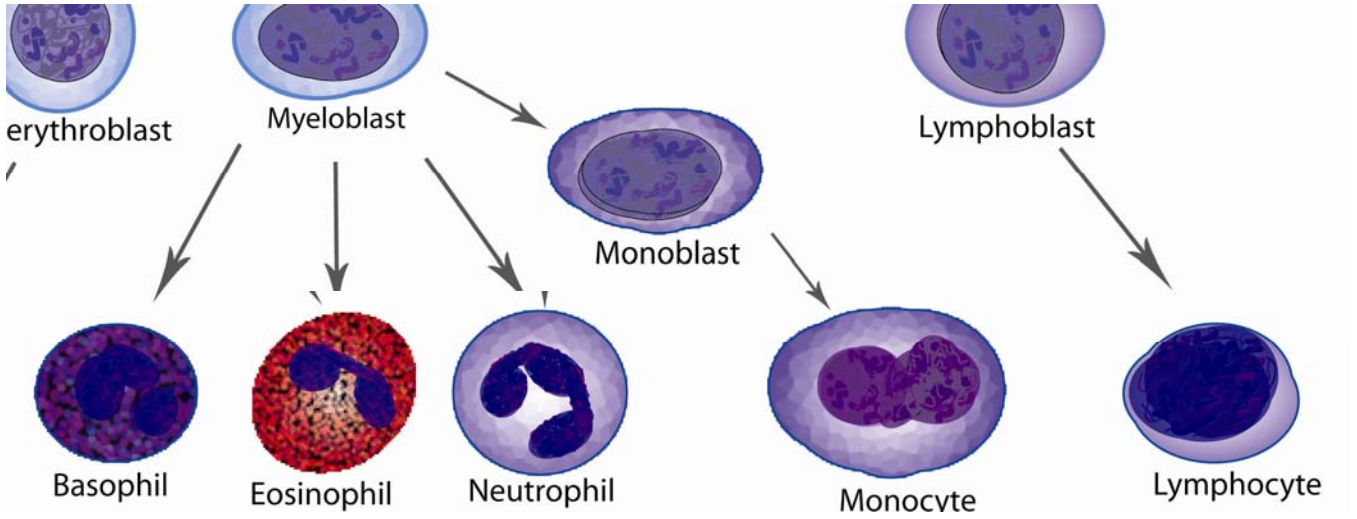
Cells of the immune system



Cells of the immune system

Bone marrow

Blood
= plasma + cells



Defense vs. parasites
Allergic reactions

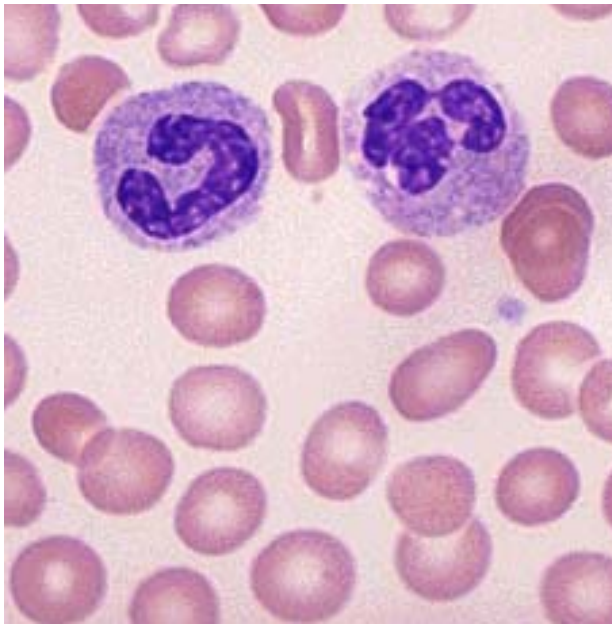
Macrophages

Phagocytosis- 'eating pathogens'
Innate Immunity

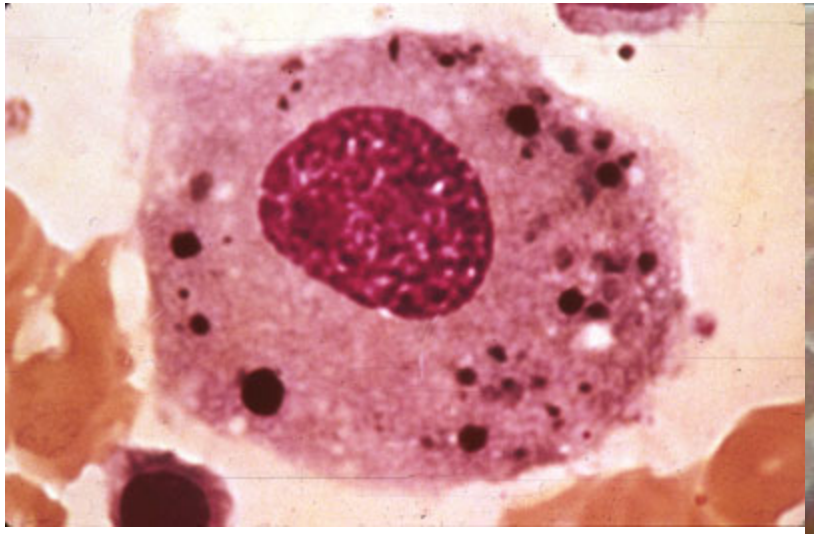
B-lymphoctes
T-lymphocytes
Natural Killer Cells

Antibody production
Pathogen killing
Adaptive Immunity

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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Complement proteins

Splinter example

2C. Adaptive Immunity

B-lymphocytes: ANTIBODIES
T-lymphocytes: Cell-mediated
Immunologic MEMORY

Types of Immunity

Physical Barriers

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

Innate Immune System

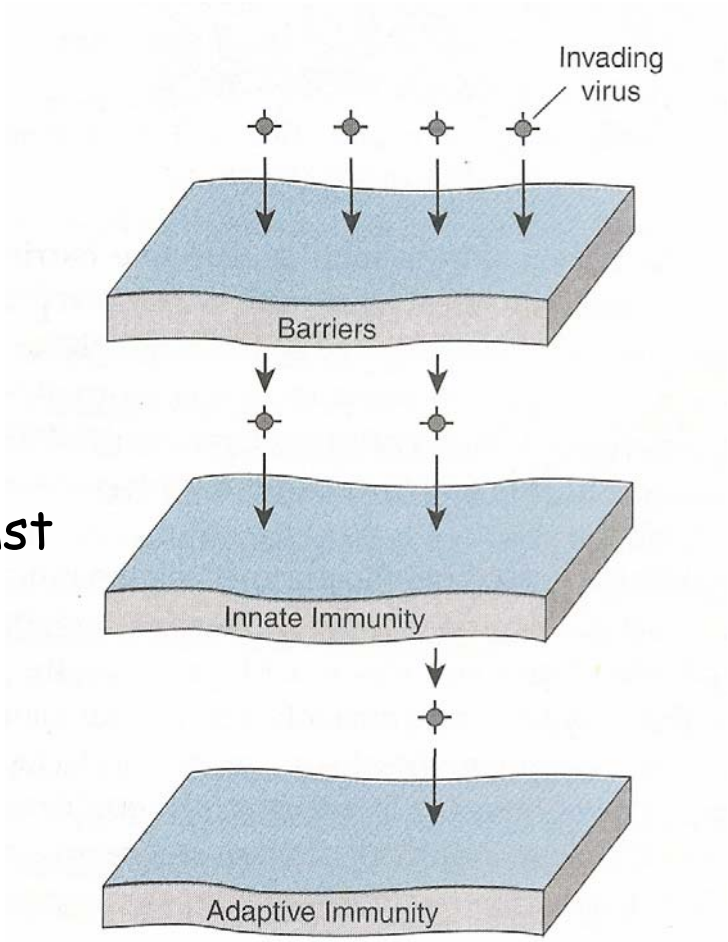
- General inflammatory response against pathogens outside of the cell

Adaptive Immune System

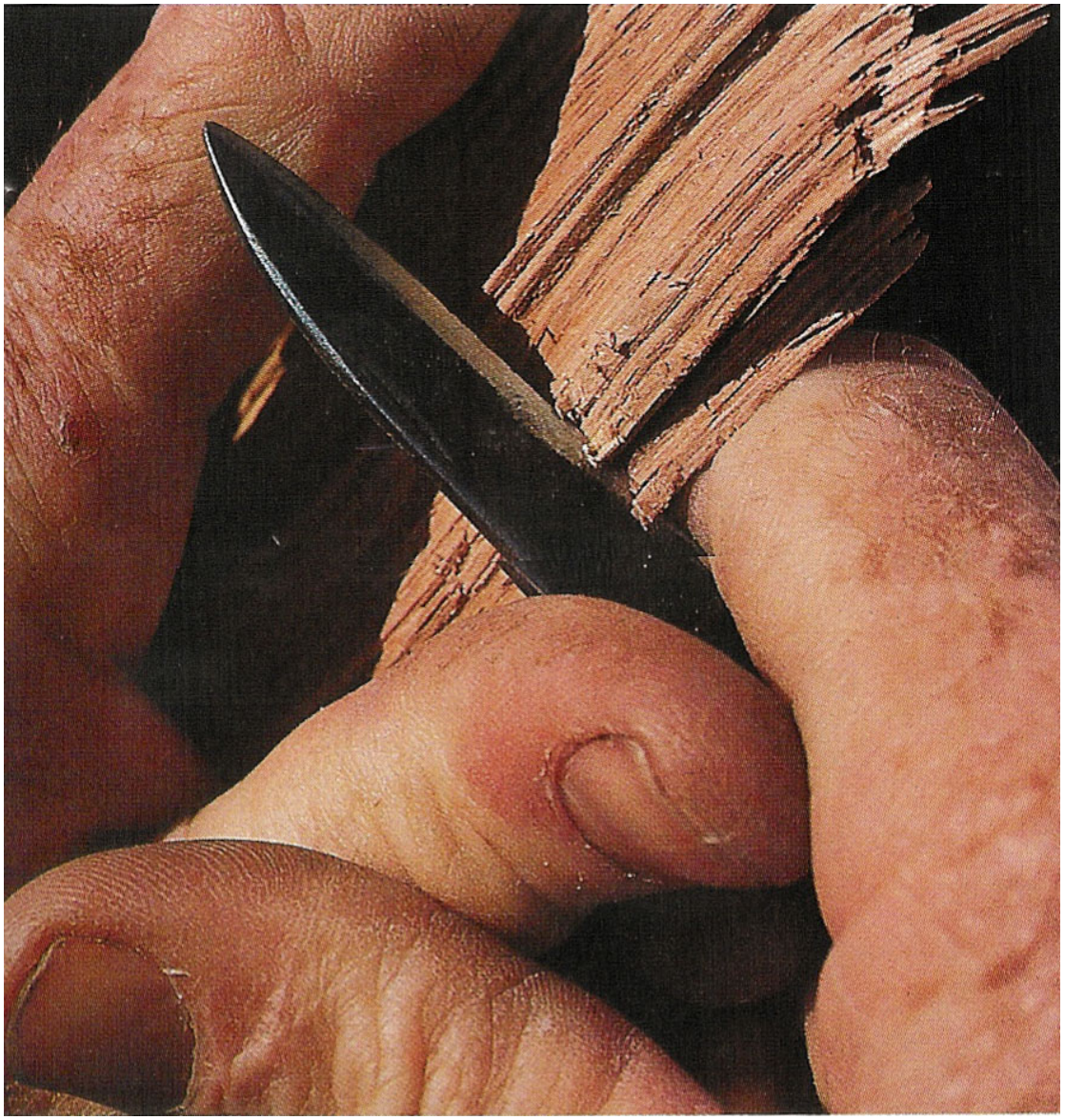
- Can adapt to defend against any specific invader inside or outside of the cell

- 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

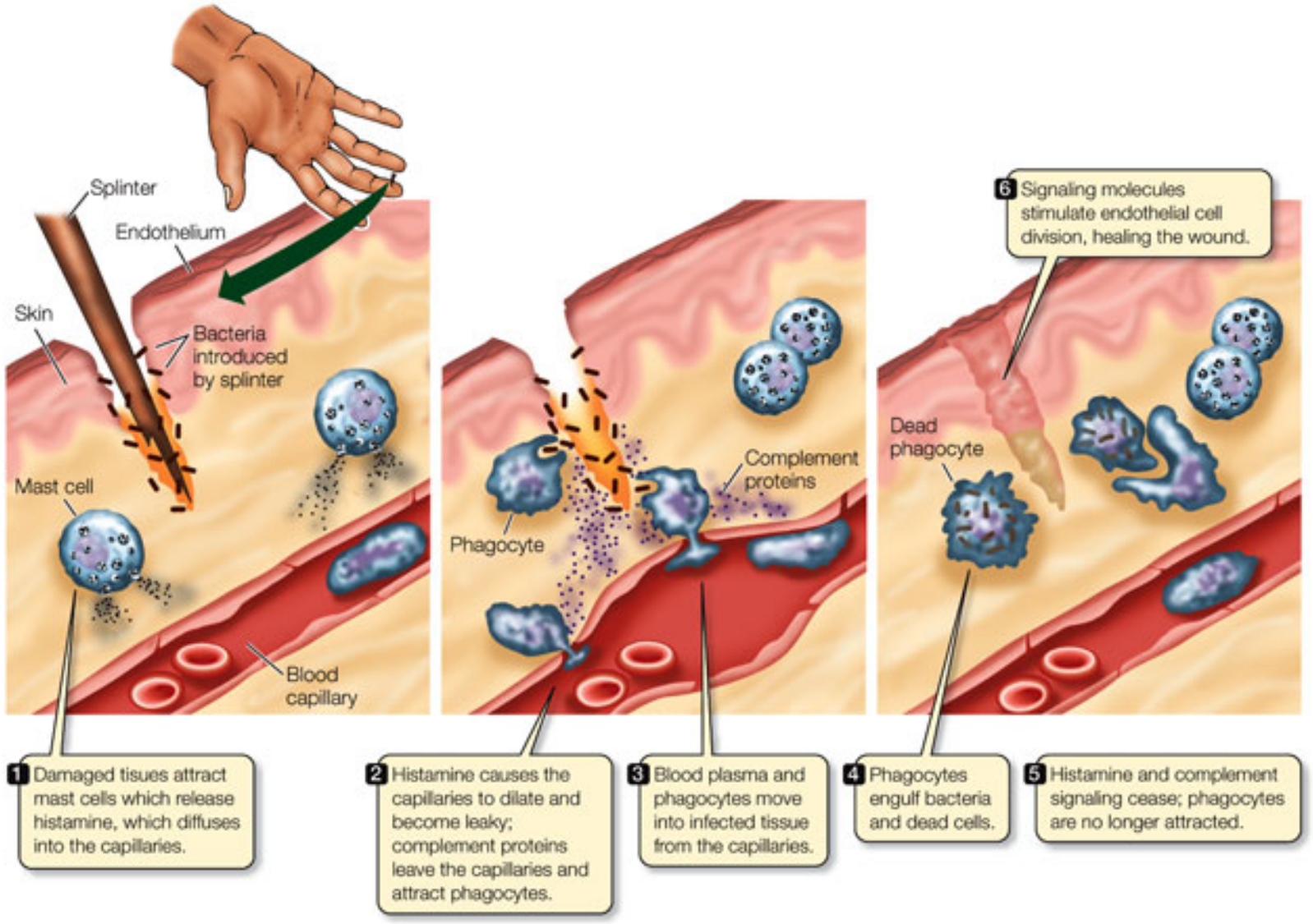
-Activated Macrophages

- Phagocyte ('eat') invading pathogens
- Produce chemicals that:
  - increase blood flow (redness & heat)
  - cause 'fuild leaking' (swelling)
  - recruit neutrophils (pus)
- Present antigen to adaptive immune system

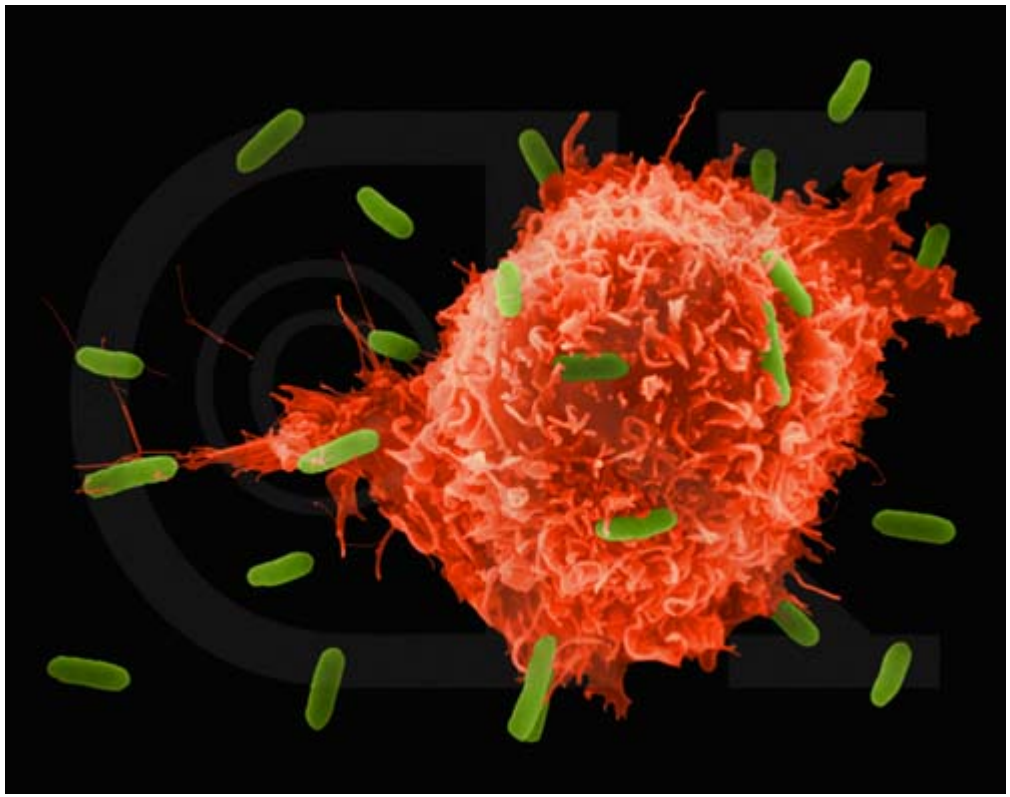
-Complement proteins

- 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* SEM x 8,800 ©Denis Kunkel

Question:

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

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   B-lymphocytes: ANTIBODIES
   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

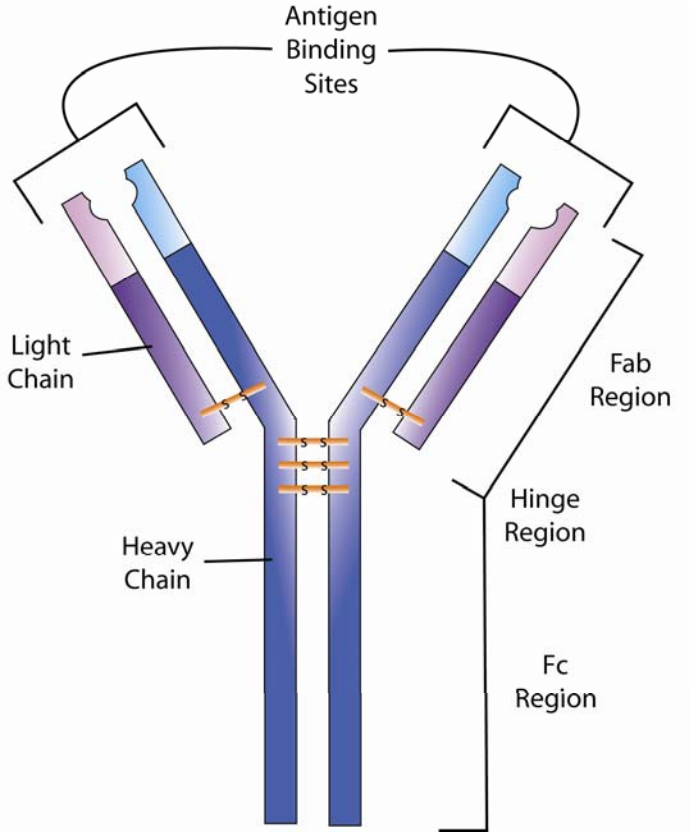
- Relies on Antibodies produced by **B**-lymphocytes
- Fights pathogens outside of cells

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



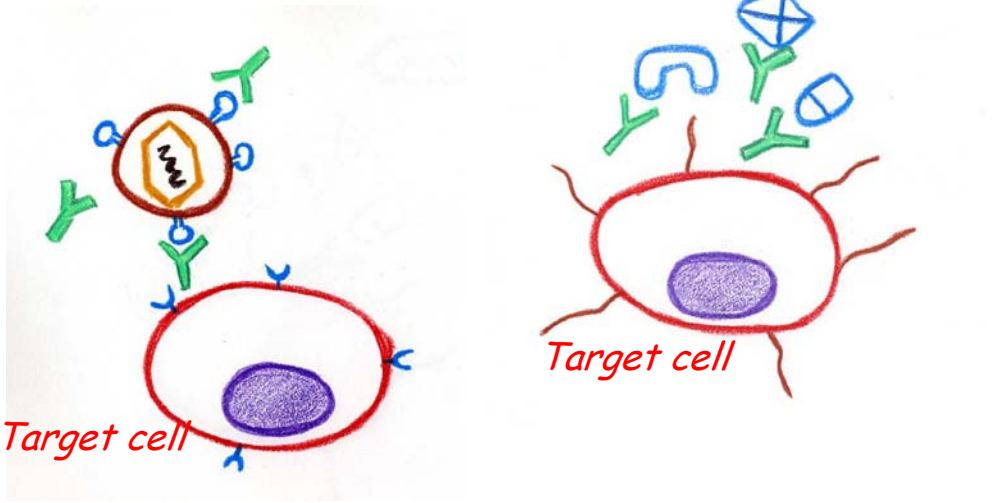
The Adaptive Immune response: humoral immunity

How do antibodies work?

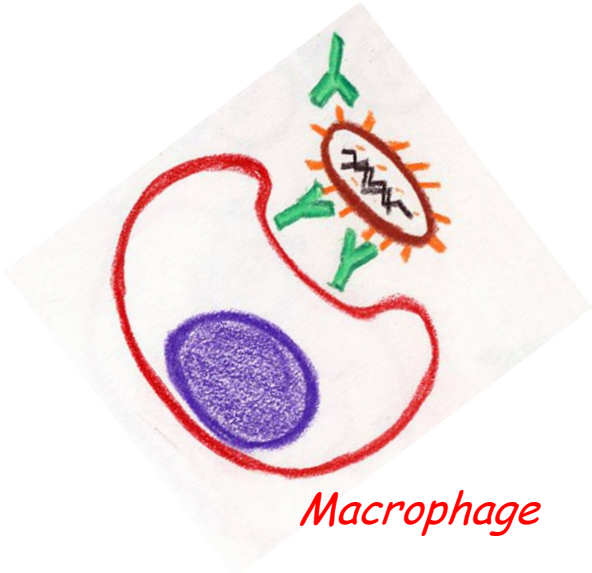
1. **Neutralization**: Blocking the biological activity of toxin or pathogen *ie. Blocking access*

2. **Bridge:** Bringing together pathogens and phagocytes

The Adaptive Immune response: humoral immunity



1. Neutralization



2. Bridge: pathogen-phagocyte

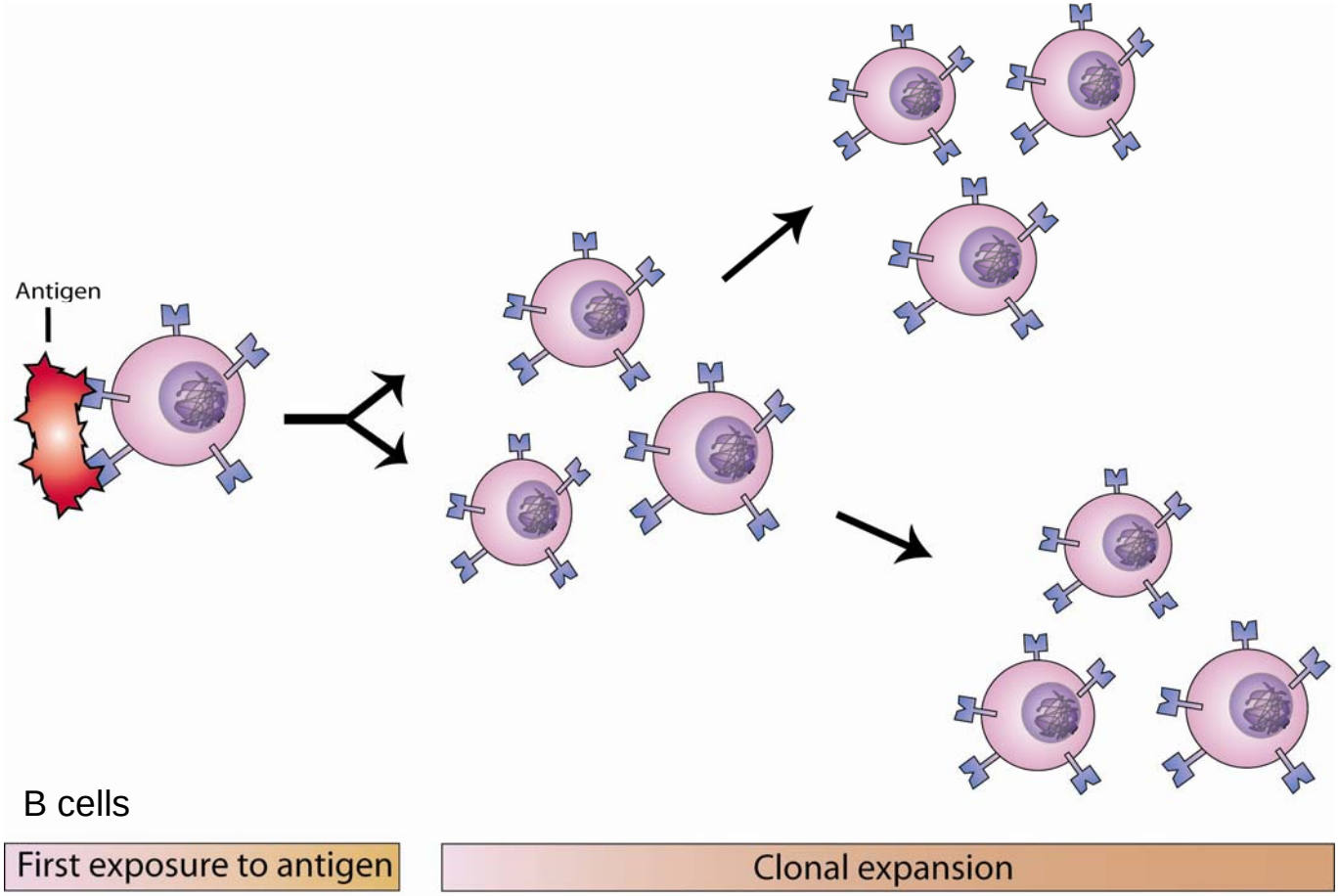
Question:

- 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?

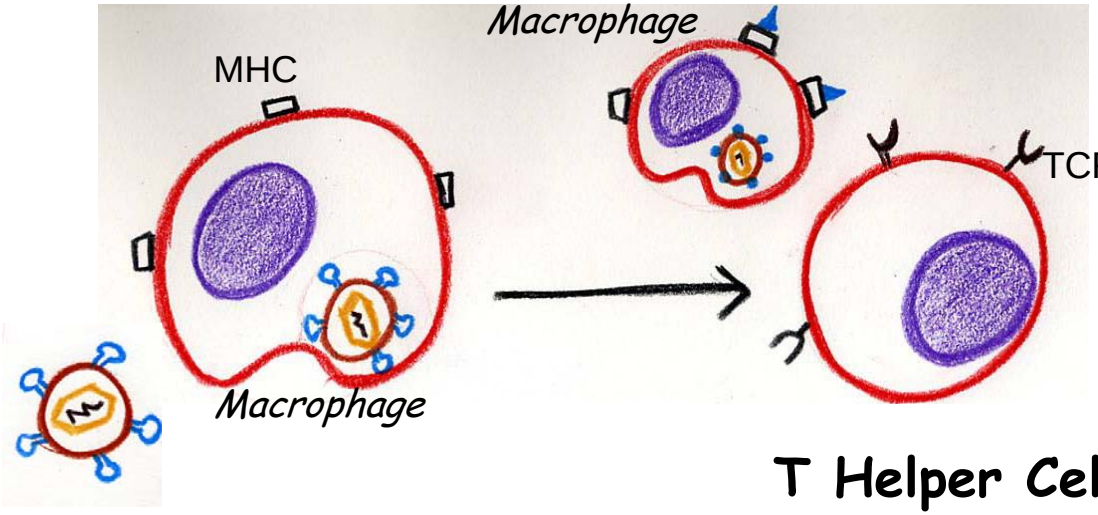
- All cells have **M**ajor **H**istocompatibility **C**omplex (MHC) molecules on surface

- 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
  - 'Profesional' Antigen Presentation Cells (APCs= phagocytes of innate immunity)

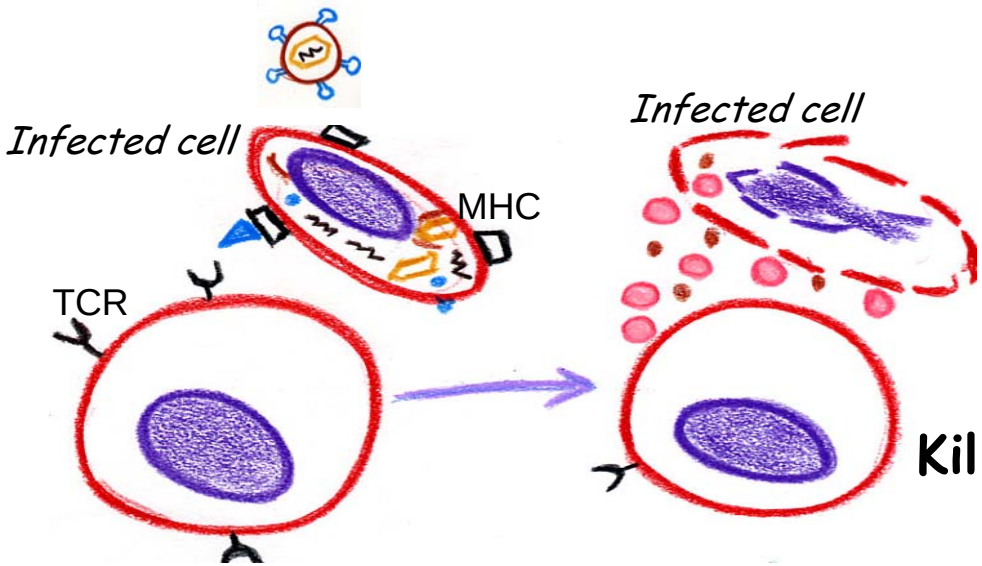
Antigen presentation and cellular immunity



Strengthen antibody response

Strengthen Killer T cell response

T Helper Cell (CD4+)



Killer T-cell (CD8+)

Question:

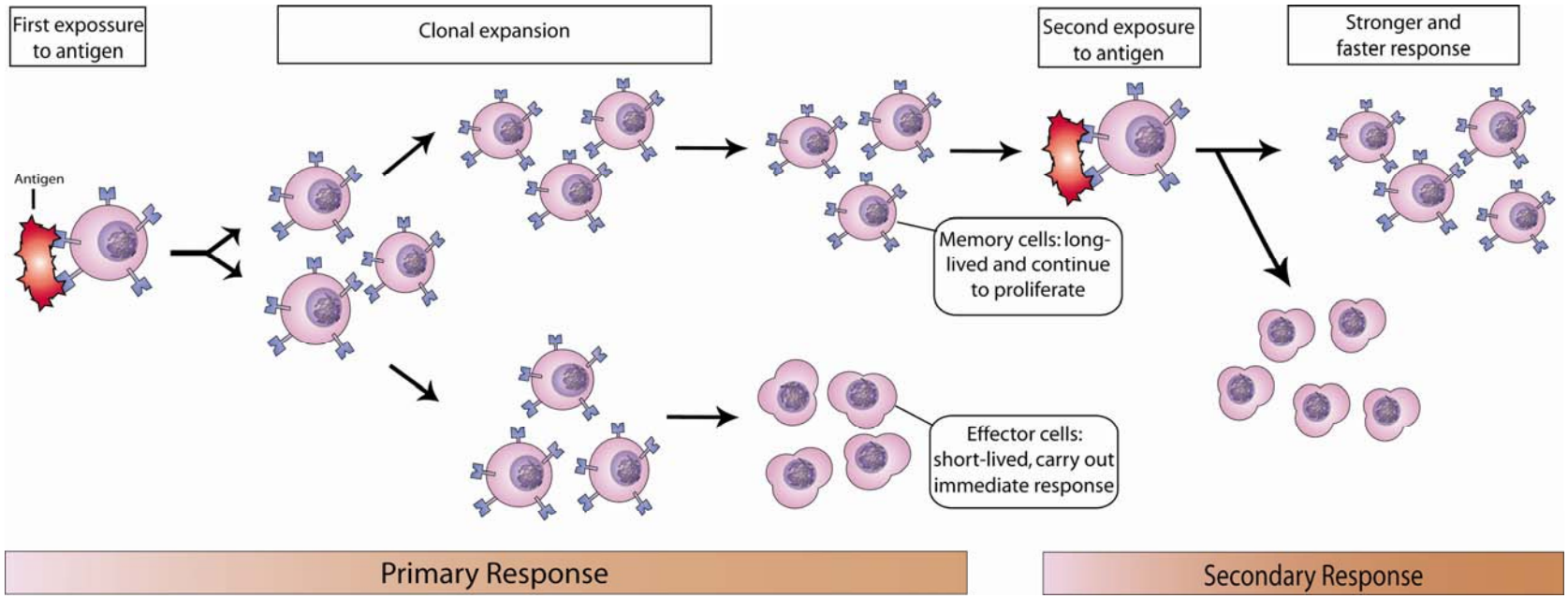
- Demonstrate how the T cell can identify a virus infected cell: antigen presentation

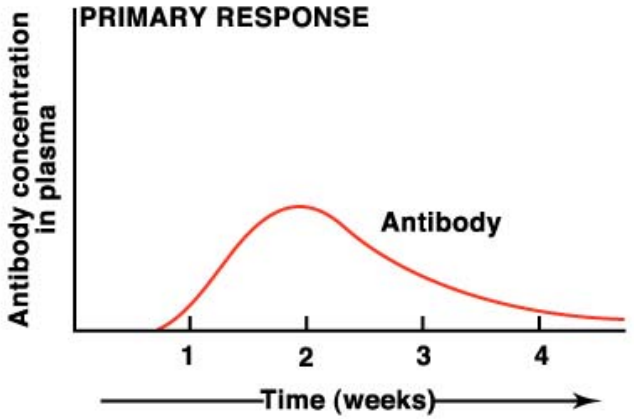
- Why is this component of the adaptive immune system a significant advance over the innate immune system?

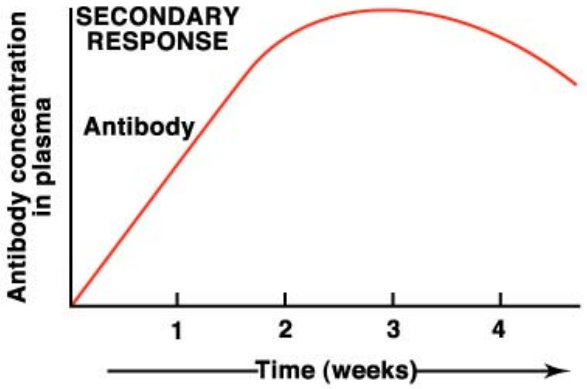
Immunologic Memory

- **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







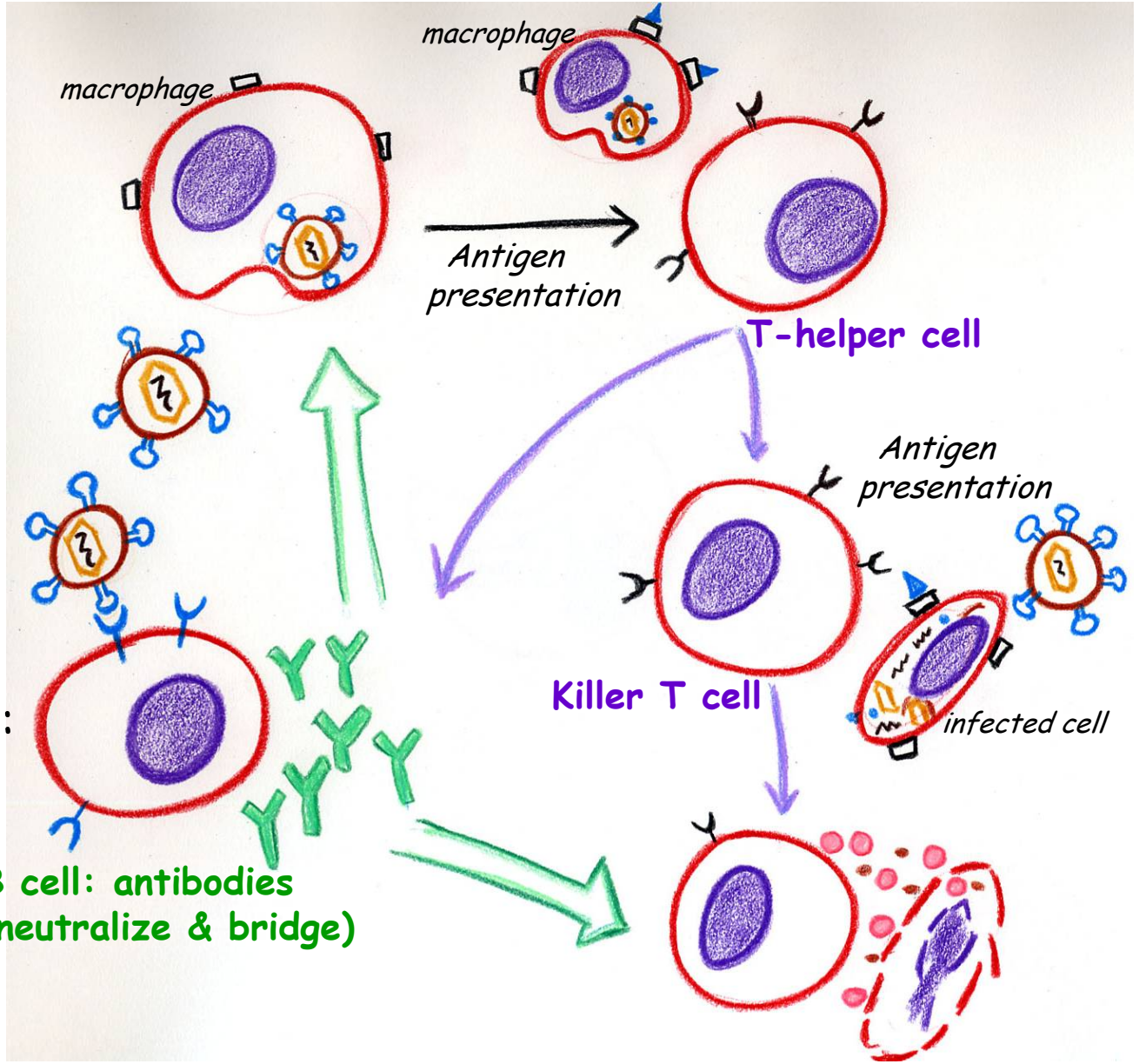
The adaptive Immune Response

Putting it together…

The Adaptive immune response

1. Cellular Immunity:

2. Humoral Immunity:



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