Basic Immune System and Immunology of HIV

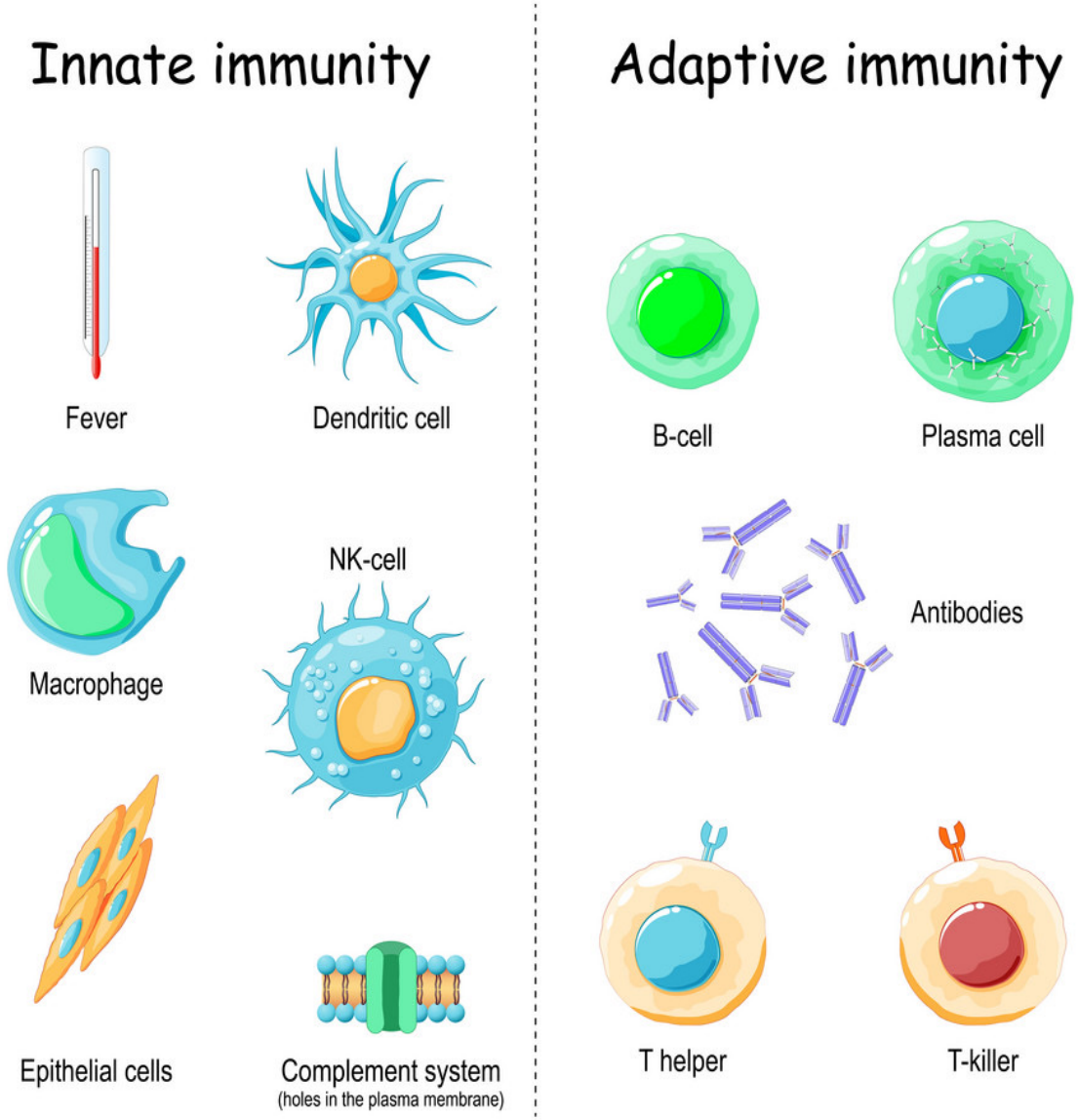
Introduction – Immune system

- The immune system is a collection of:
  - cells,
  - chemicals and
  - processes
- Function: to protect the skin, respiratory passages, intestinal tract, and other areas from foreign antigens

Innate and adaptive immunity

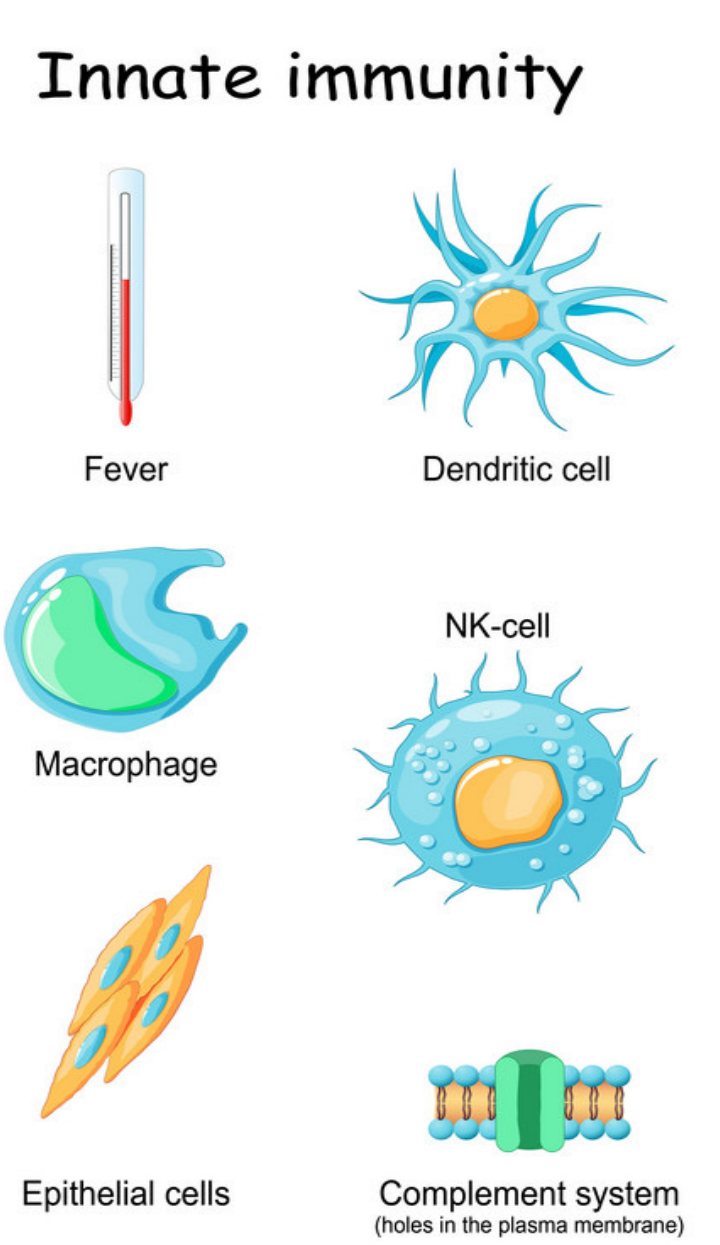
The immune system can be viewed as having two “lines of defence”:

1. innate immunity and
2. adaptive immunity



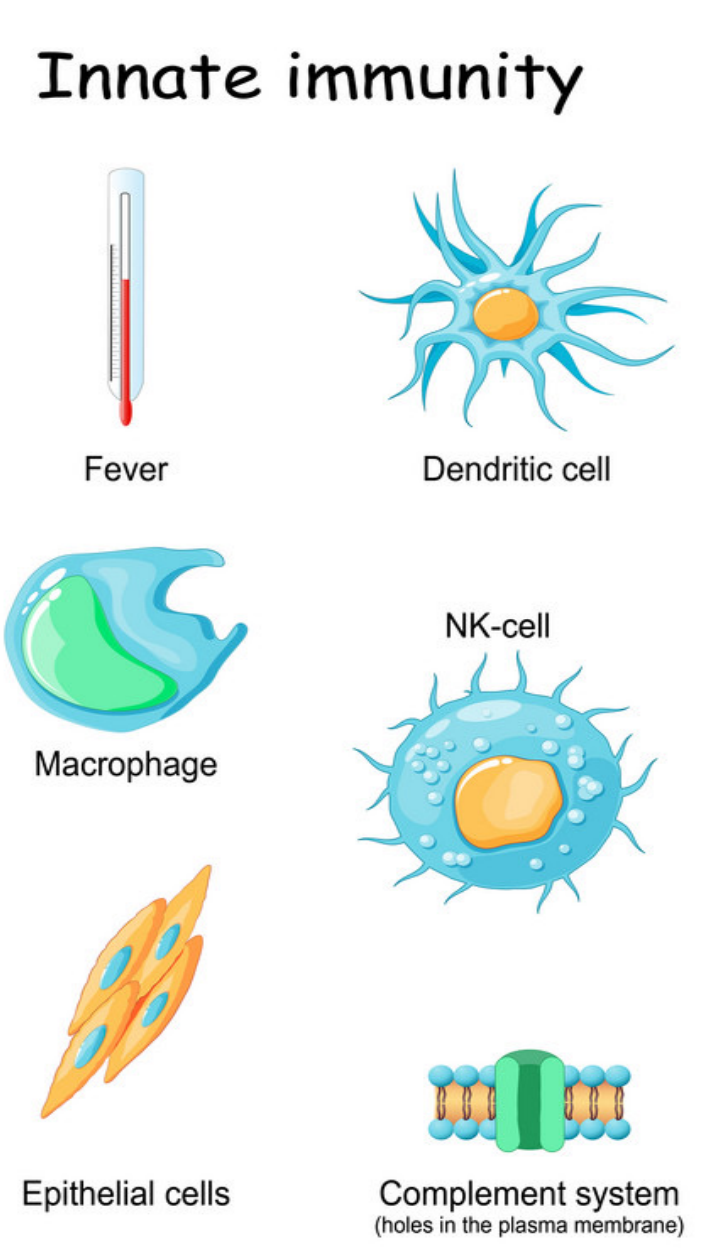
Innate immunity

- First line of defence
- It's an antigen-independent
- Immediately or within hours response
- Has no immunologic memory
- Its unable to recognize or “memorize” the same pathogen in future

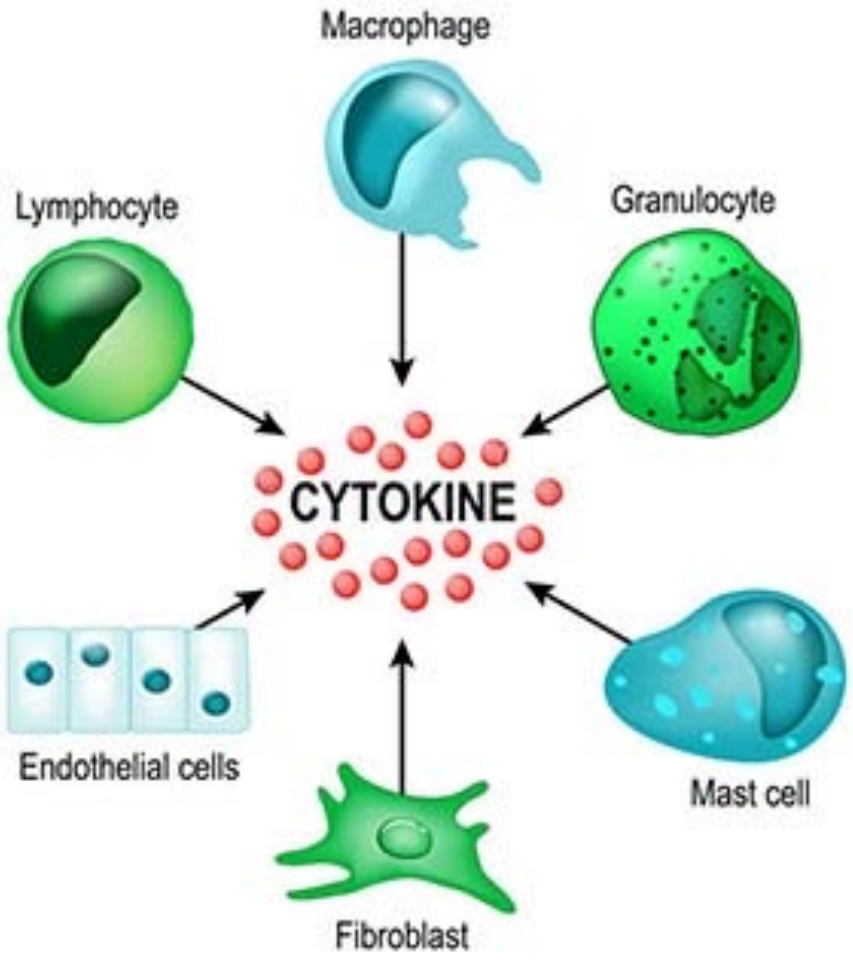


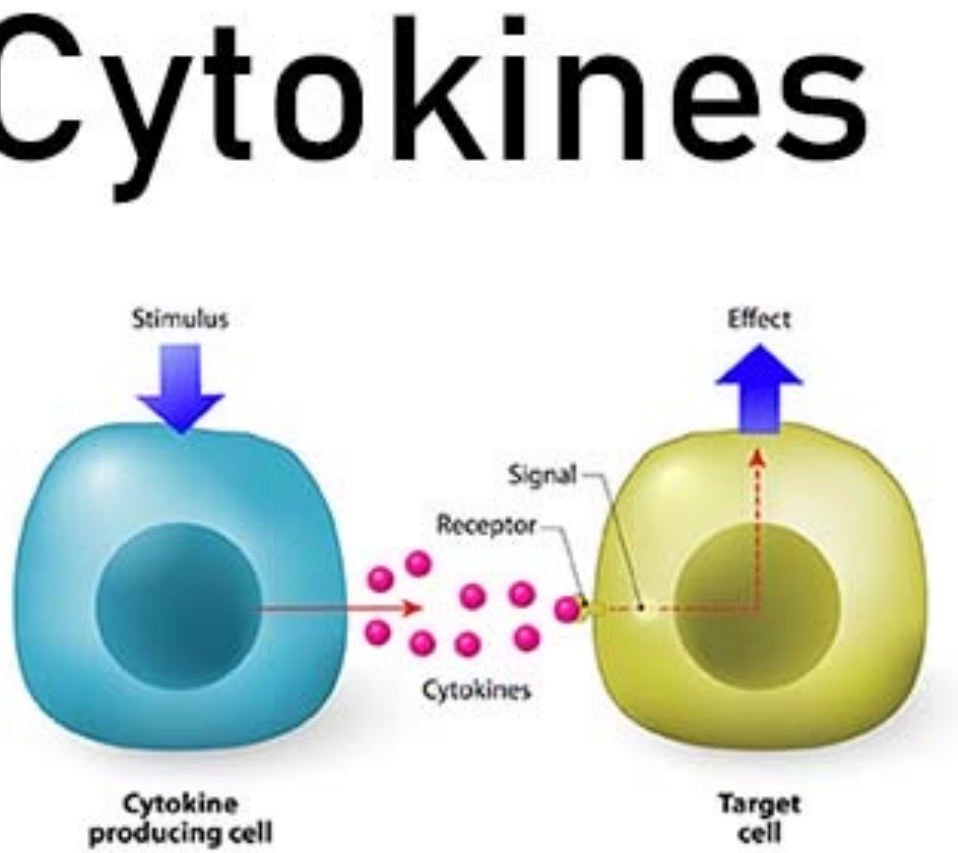
Innate immunity

- Cells involved:
  - phagocytes (macrophages and neutrophils),
  - dendritic cells,
  - mast cells,
  - basophils,
  - eosinophils,
  - natural killer (NK) cells and
  - innate lymphoid cells

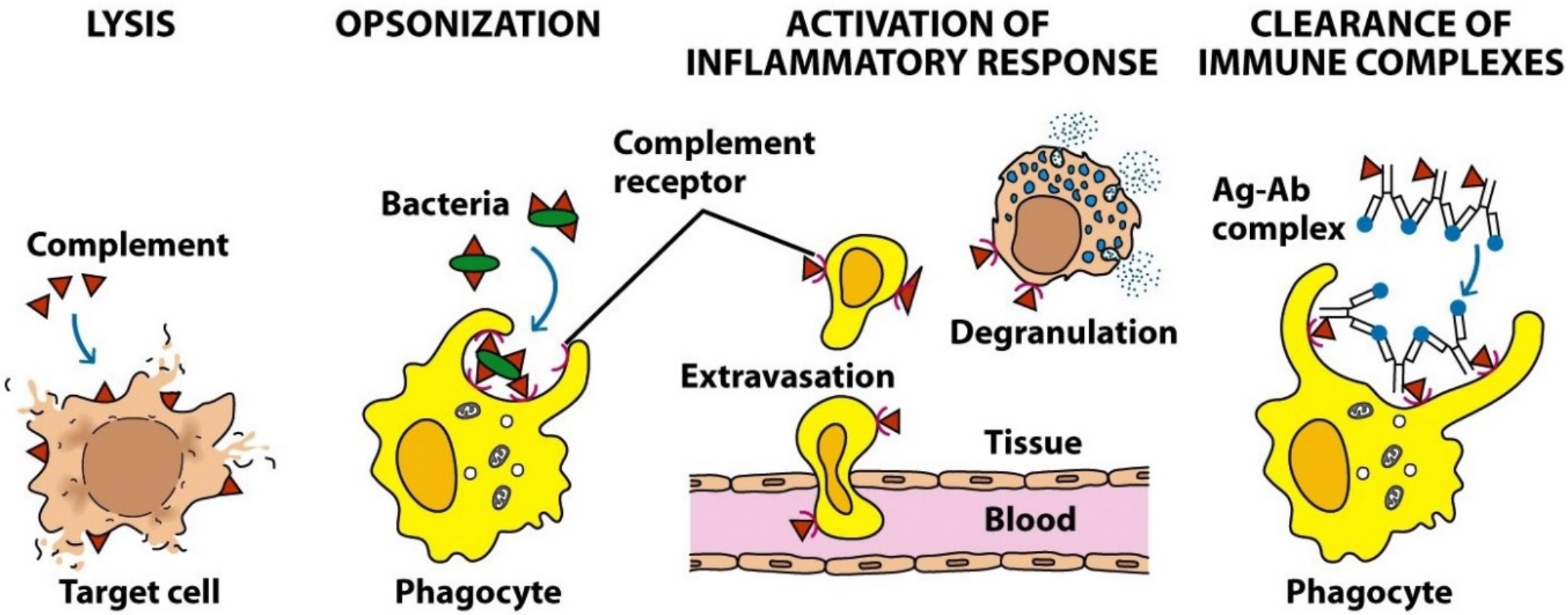


Innate immunity



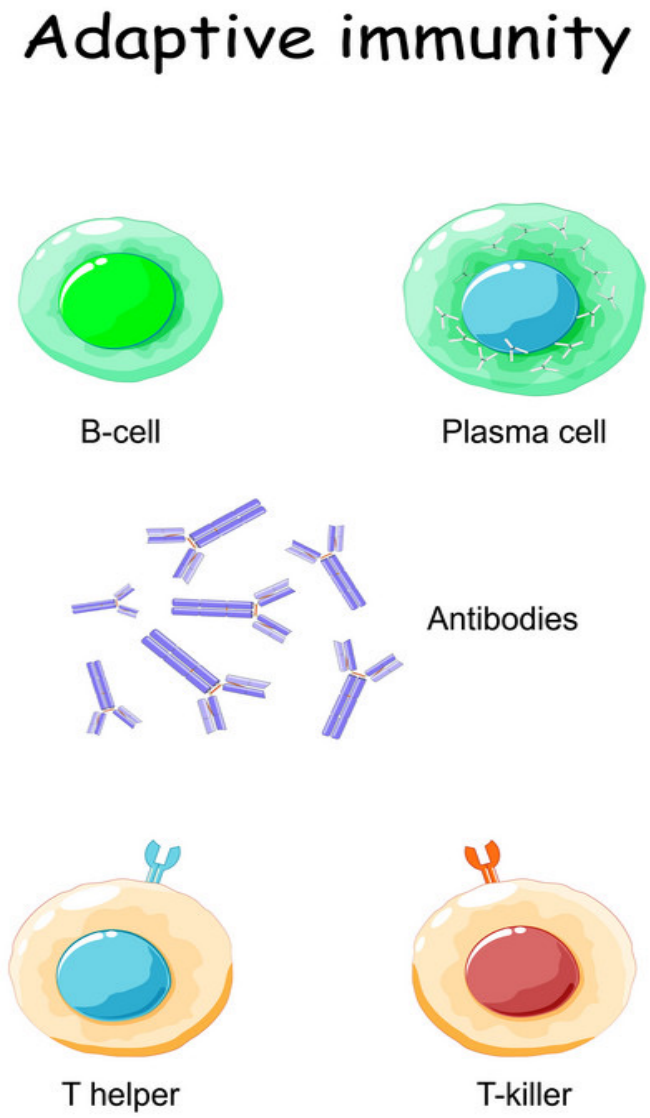


Innate Immune System: Complement system



Adaptive Immunity

- Critical when innate immunity is ineffective in eliminating pathogens
- Primary functions are:
  a) Recognise specific ”nonself” antigens
  b) Generate pathogen-specific immunologic response
  c) Develop an immunologic memory – deals with subsequent infection

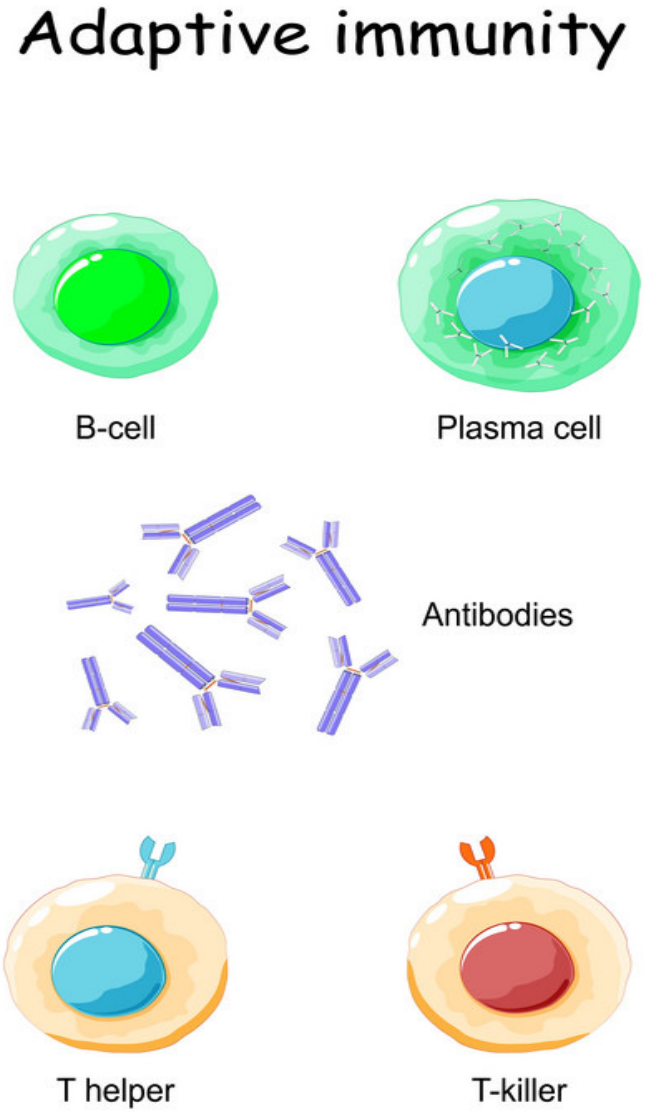


Adaptive Immunity

- Cells:

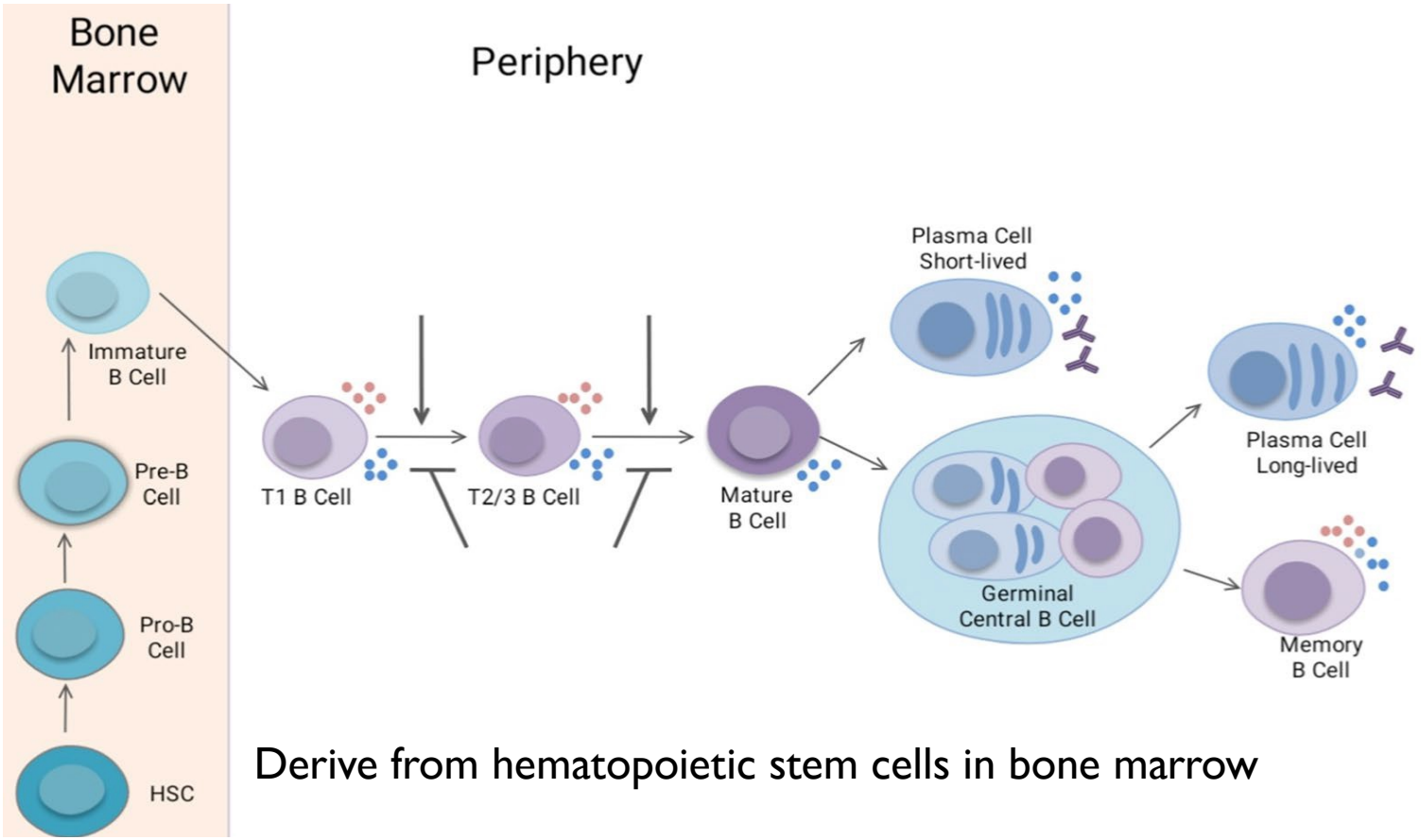
1. B cells
   - which differentiate into plasma cells to produce antibodies

1. Antigen-specific T cells,
   - which are activated to proliferate through the action of APCs

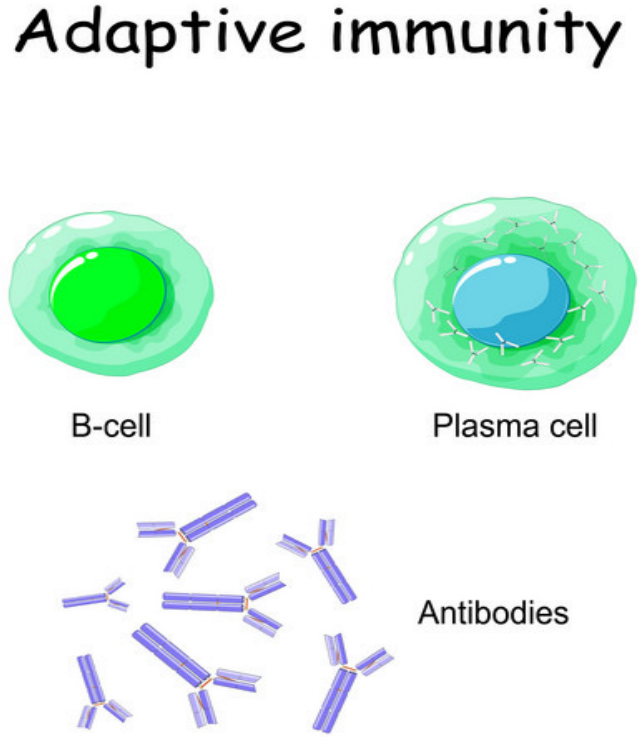


Adaptive Immunity

- B Cells:

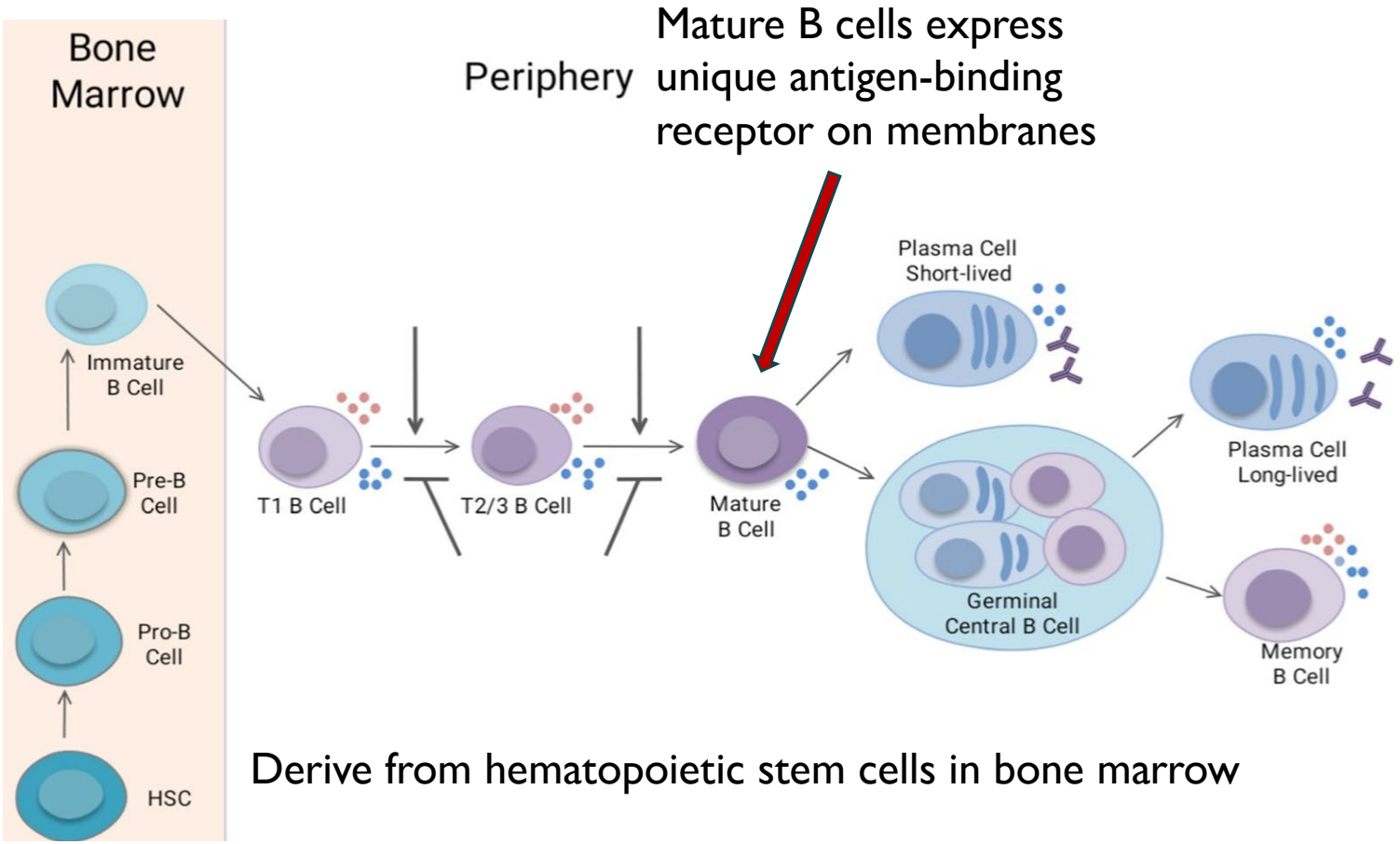


Derive from hematopoietic stem cells in bone marrow

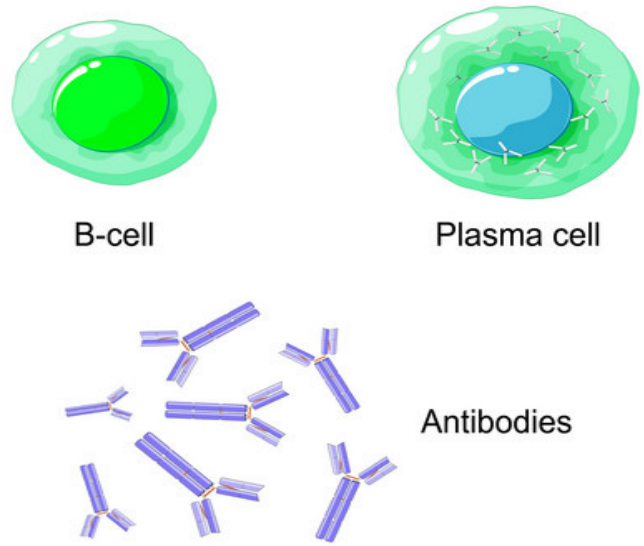


Adaptive Immunity

- B Cells:

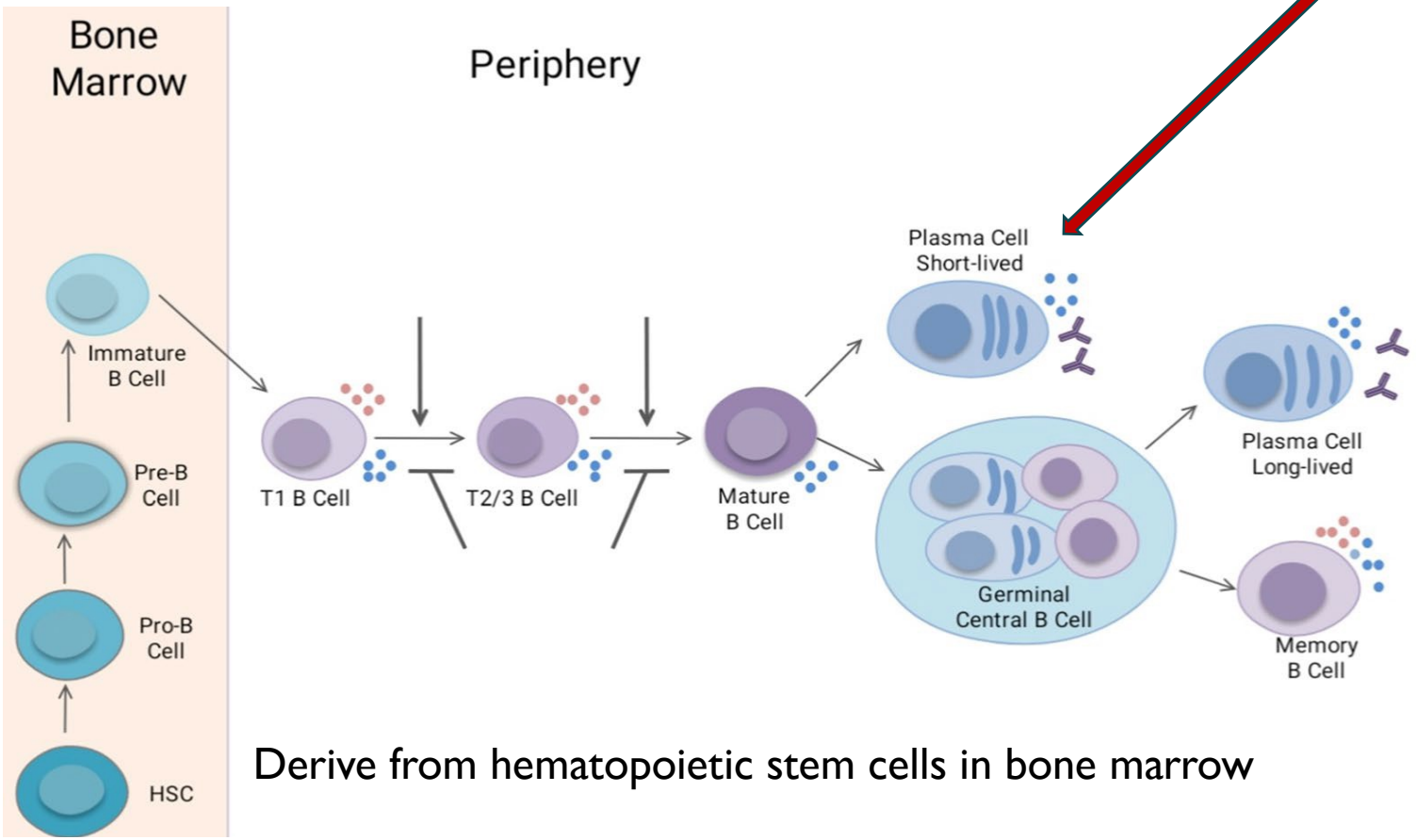


Derive from hematopoietic stem cells in bone marrow



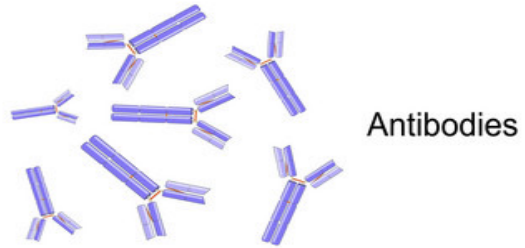
Adaptive Immunity

- B Cells:



Derive from hematopoietic stem cells in bone marrow

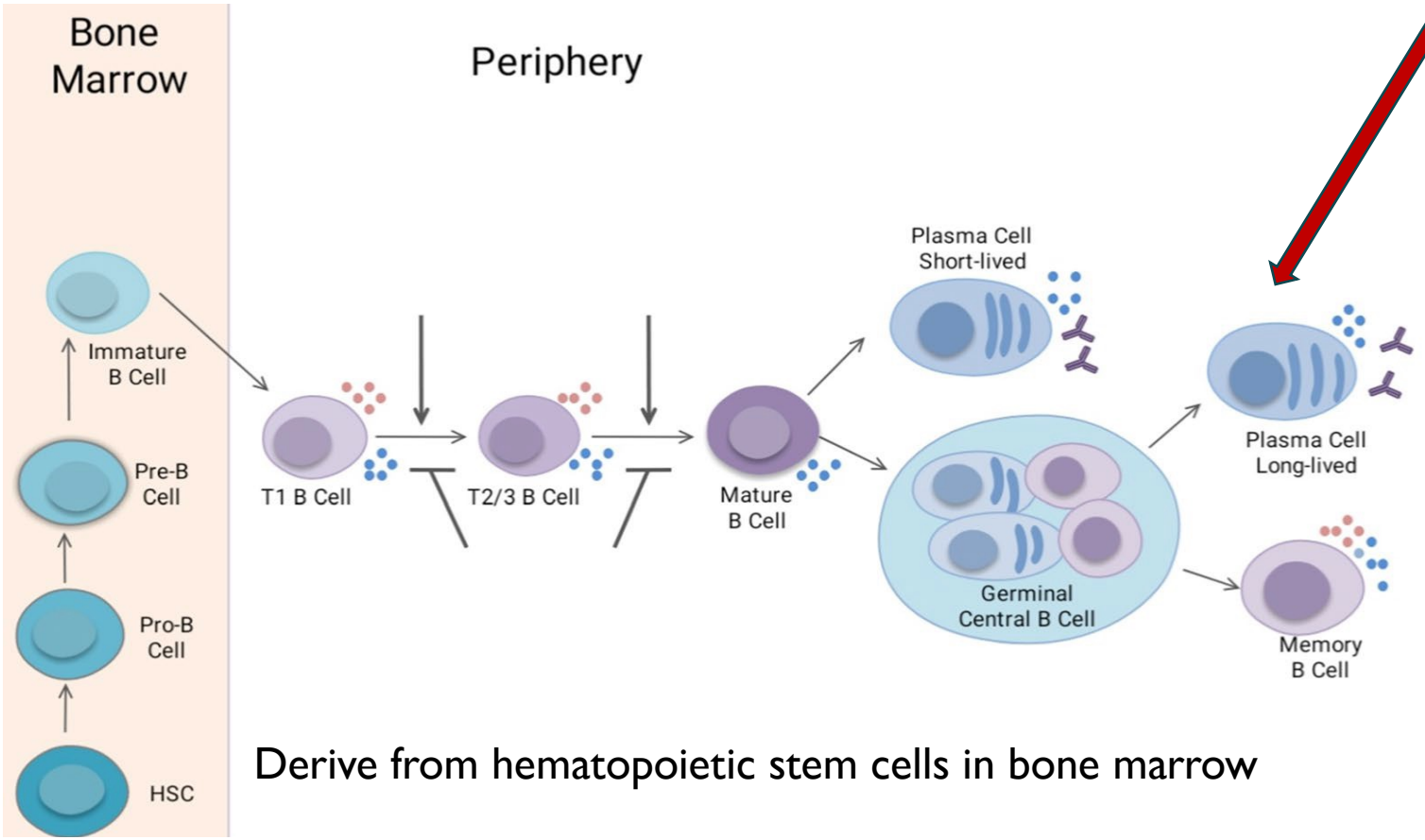
Upon activation, B cells proliferate and transform into either antibody-secreting plasma cells or long-lasting memory B cells.

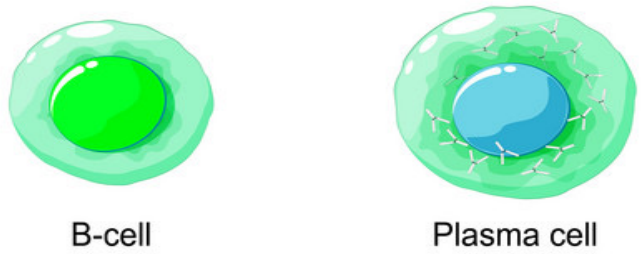


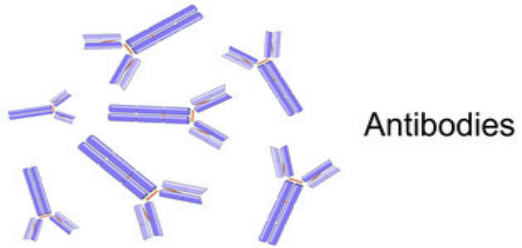
Adaptive Immunity

Main function is to produce antibodies against foreign antigens

- B Cells:



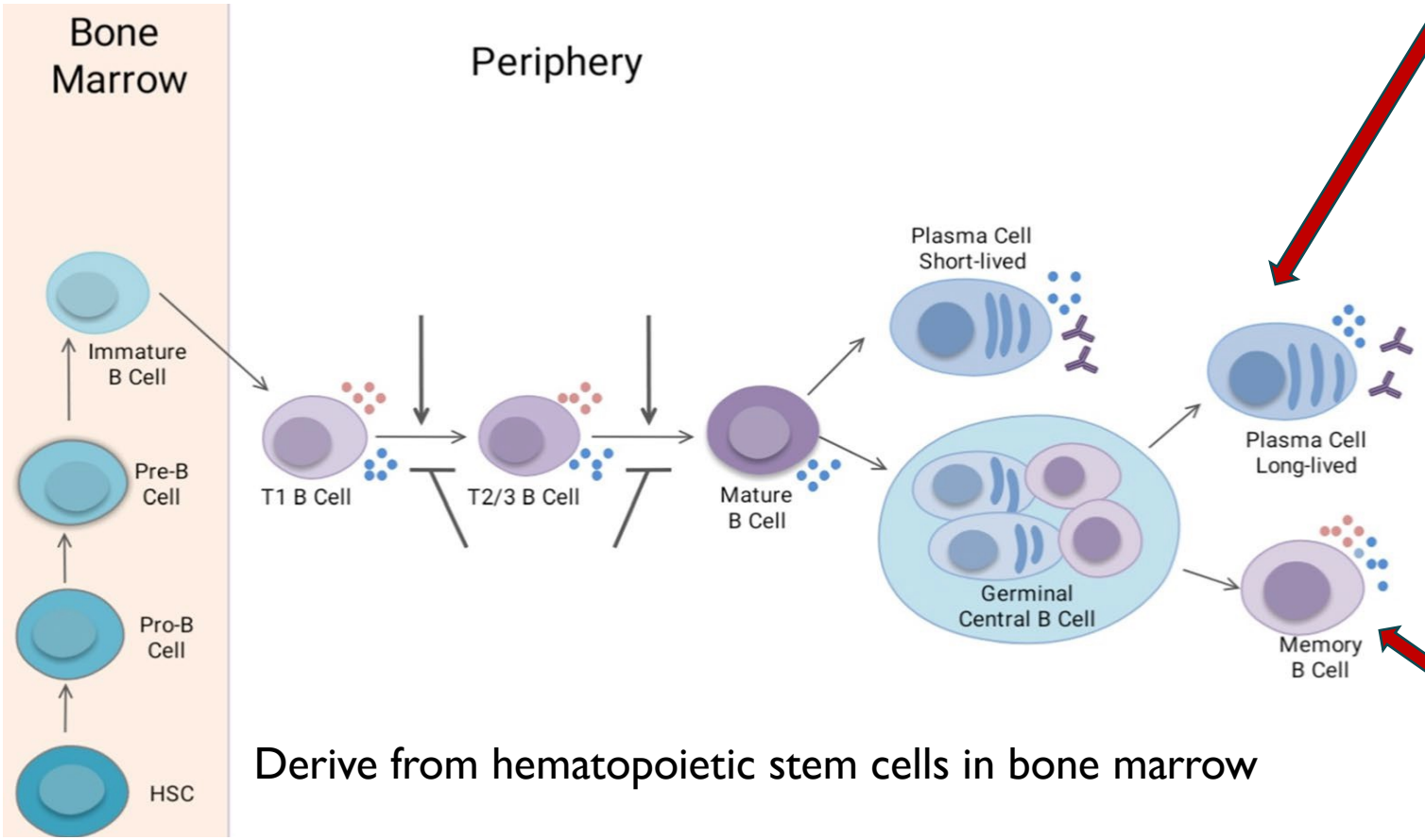




Derive from hematopoietic stem cells in bone marrow

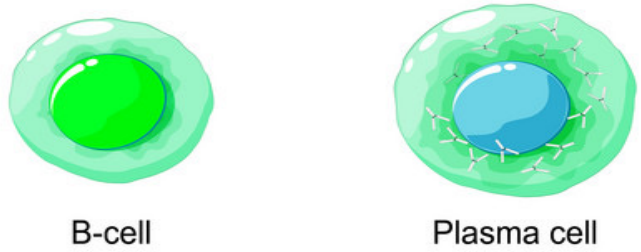
Adaptive Immunity

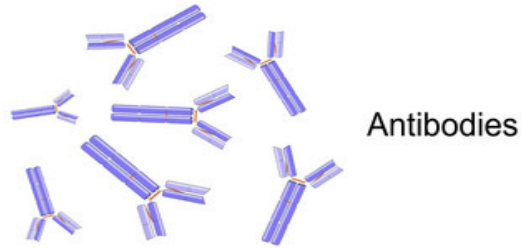
- B Cells:



Derive from hematopoietic stem cells in bone marrow

Main function is to produce antibodies against foreign antigens



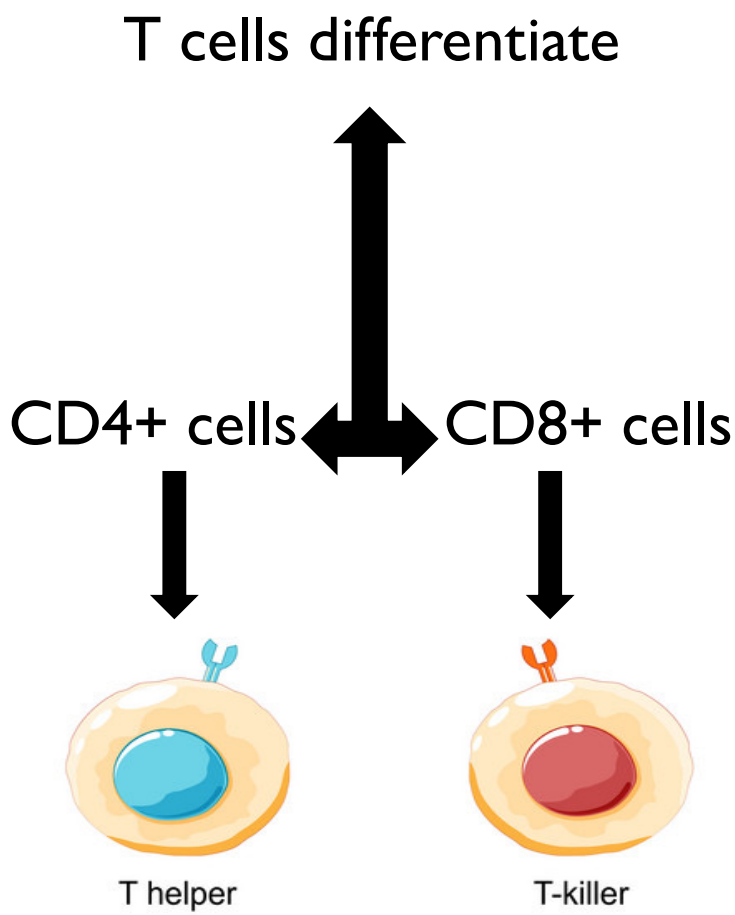


Memory B cells, persistently express antigen-binding receptors and contribute to immune response readiness

Adaptive Immunity

- CD8+ cytotoxic T cells: destroy cells infected by foreign agents and tumour cells expressing appropriate antigens.
- CD4+ Th cells: do not directly kill infected cells or clear pathogens, but they mediate the immune response and regulate the type of immune response that develops.
- Memory cells are retained after infection.

T Cells and APCs



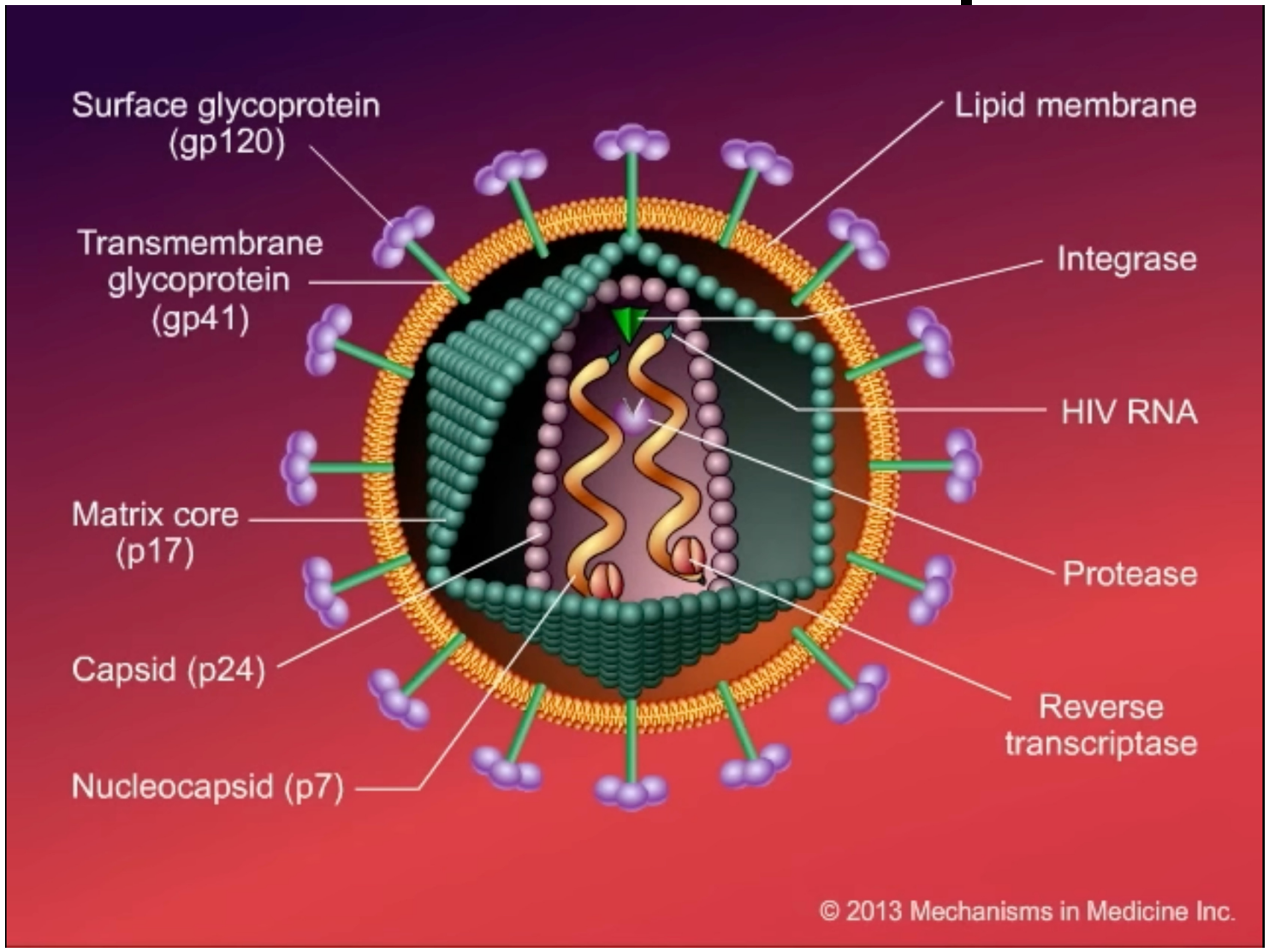
Antibody- vs. cell-mediated immunity

- Antibody-mediated immunity – B cell antibody production
- B cell antigen-binding receptor recognizes and binds to antigen
- Local Th cells secrete cytokines that help B cells multiply and direct antibody type
- IL-6 helps B cells to mature
- Secreted antibodies bind to antigen and opsonizing them for phagocytosis

Antibody- vs. cell-mediated immunity

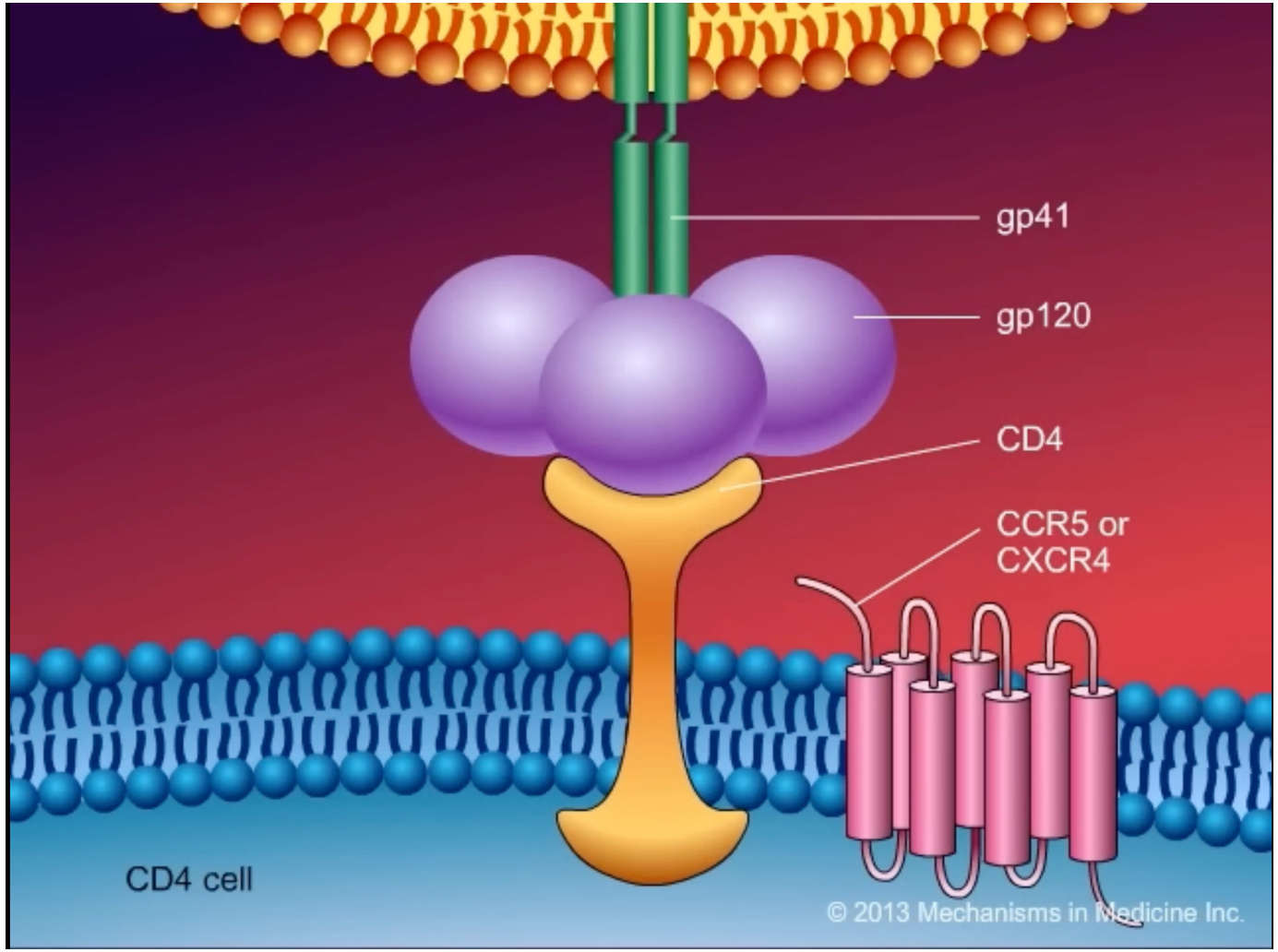
- Cell-mediated immunity is T-cell dependent
- Antigen-specific cytotoxic T cells induce apoptosis of cells displaying foreign antigens
- There is activation of macrophages and NK cells, enabling them to destroy intracellular pathogens
- They stimulate cytokine (such as IFNγ) production that further mediates the effective immune response.

Innate Immune response to HIV



- Structure of HIV

Innate Immune response to HIV



- Upon infection, it encounters the innate immune system
- Cells, cytokines & chemokines respond
- Leading to T-cell proliferation

Adaptive Immune Response to HIV

Cellular Immune Response

- This response is induced when HIV enters target cells (e.g., T cells) and starts synthesizing viral proteins
- These activated CD8+ T cells then lyse HIV-infected cells and secrete antiviral cytokines and chemokines that:
  - Inhibit virus replication
  - Block viral entry into CD4+ T cells
- Development of robust CD8+ T cell responses is crucial for controlling HIV replication and results in declining viral load after primary infection.

Adaptive Immune Response to HIV

Humoral Response

- The humoral response occurs later in infection
- The first antibodies to appear are non-neutralizing antibodies targeting structural proteins (e.g., P17 and P24) and generally do not persist.
- Later, the body generates neutralizing antibodies specific to proteins involved in viral entry
- These potent NAbs play a major role in controlling HIV infection in elite controllers

Insights into HIV Cure Efforts

- Reservoirs - CD4+
- The “shock-and-kill” paradigm proposes to combine a latency-reversing agent (LRA) with immune effectors, such as a CD8+ T-cells or NK cells,
  - to selectively eliminate infected cells from the reservoir.
- There are limitations to the Current Shock and Kill Strategies

Insights into HIV vaccine design efforts

- Only the RV144 trial showed reduced HIV-1 transmission, suggesting a potential link between V2-binding antibodies and IgA levels.
- Subsequent trials based on RV144 findings failed to demonstrate significant efficacy
- A current phase III trial explores the potential of inducing high levels of non-neutralizing antibodies.
- Broadly neutralizing antibodies remain a primary goal for an effective HIV-1 vaccine.

Bibliography

1. Ward AR, Mota TM, Jones RB. Immunological approaches to HIV cure. InSeminars in immunology 2021 Jan 1 (Vol. 51, p. 101412). Academic Press
2. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy, Asthma & Clinical Immunology. 2018 Sep;14(2):1-0.
3. Bhardwaj N, Hladik F, Moir S. The immune response to HIV. Nat Rev Immunol. 2013;13:1-2.