Failures of Host Defense Mechanisms

13

RUB

Based on Janeway's Immunobiology Book (9th Edition), by Kenneth Murphy, Casey Weaver - Chapter 13

Students: Salsabil Nouasria & M.Adib Weis

18.06.2025

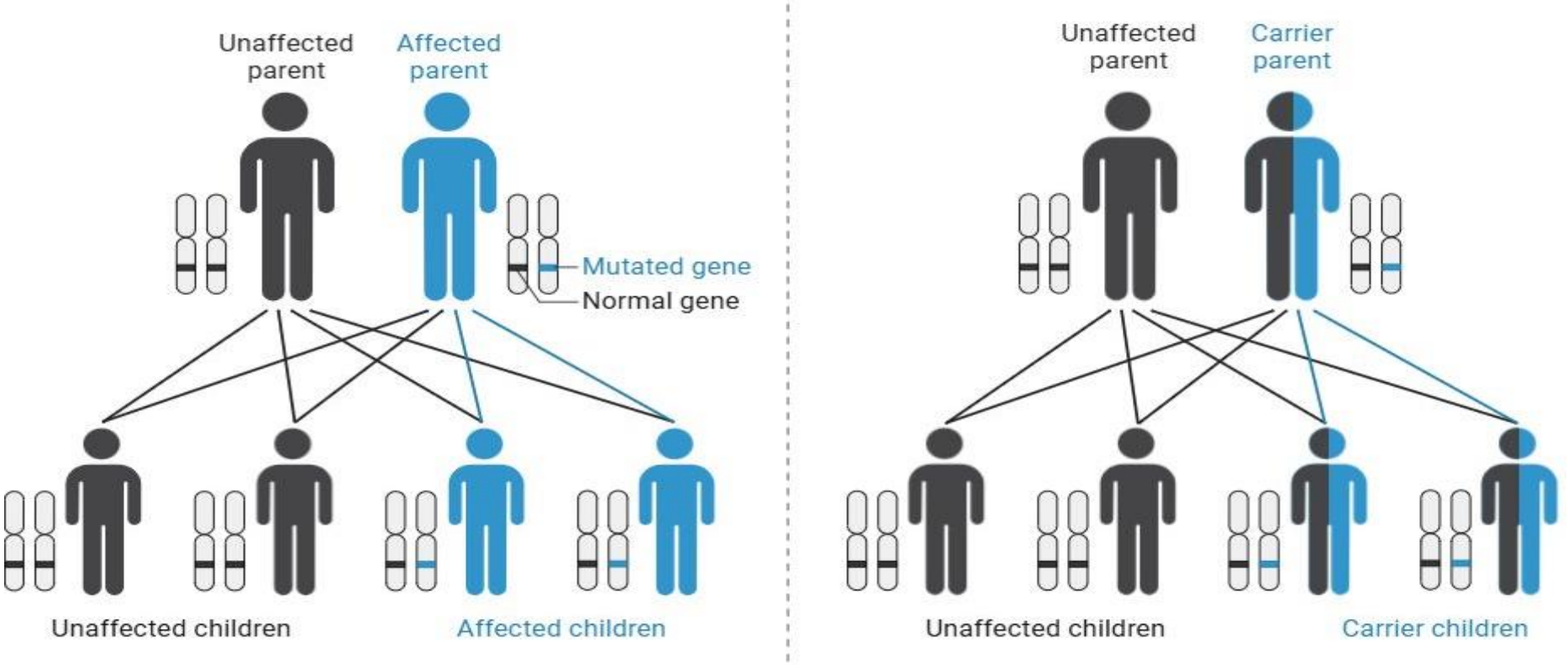
MOLECULAR IMMUNOLOGY

I. **Immunodeficiency diseases**

II. Evasion and subversion of immune defenses

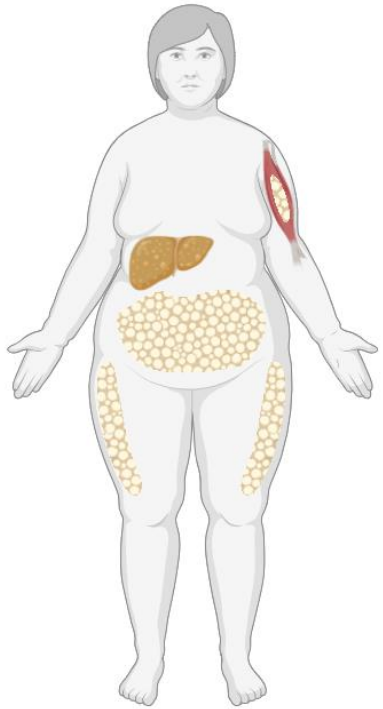
III. Acquired immune deficiency syndrome

What Are Immunodeficiencies?

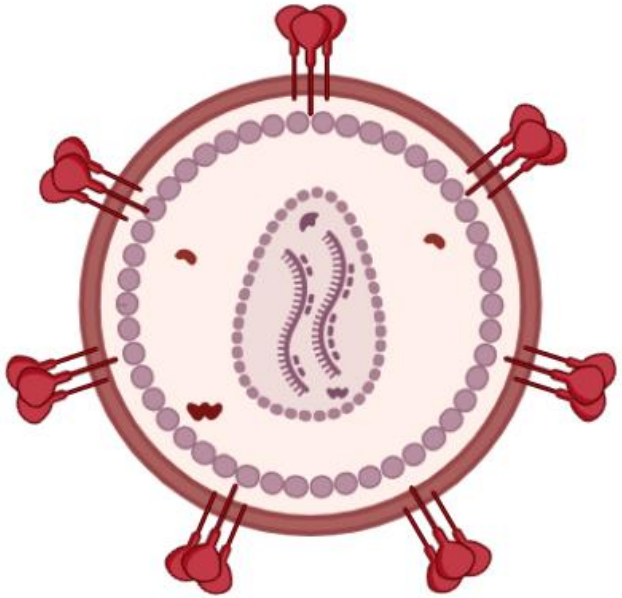


Primary: Inherited genetic defects (approx.150 syndromes)

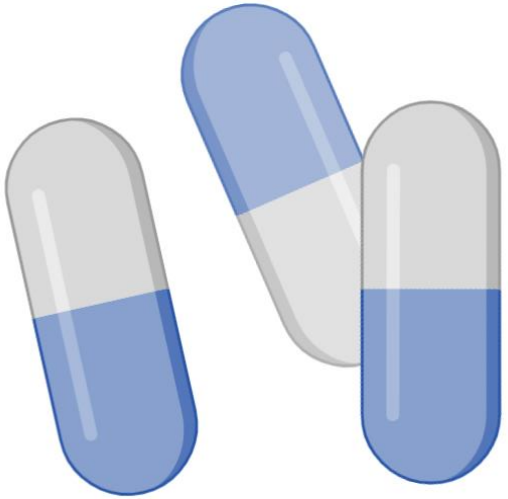
What Are Immunodeficiencies?



malnutrition



HIV

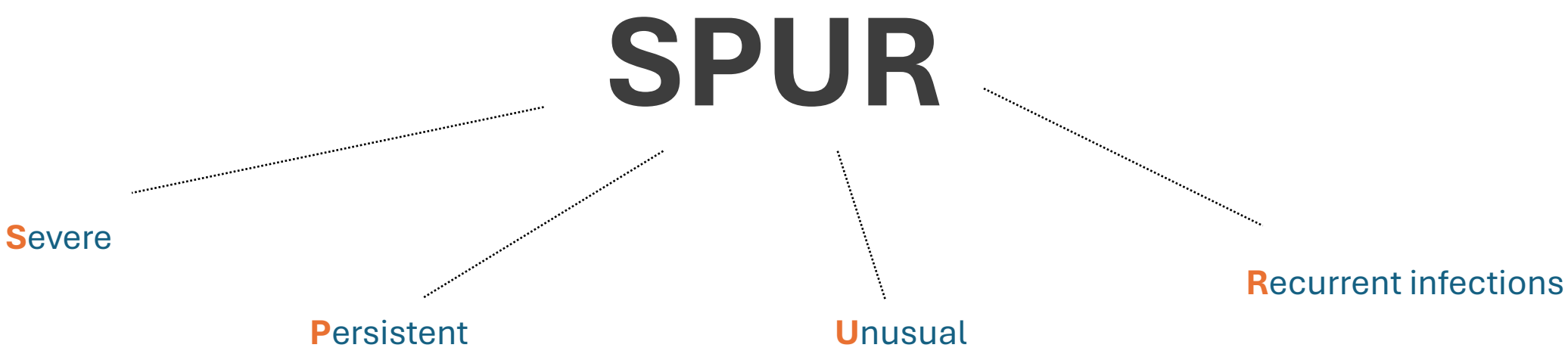


drugs

Secondary: Acquired

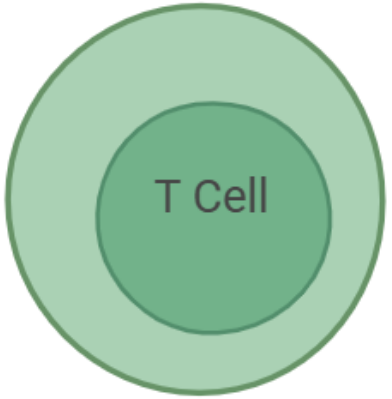
What Are Immunodeficiencies?

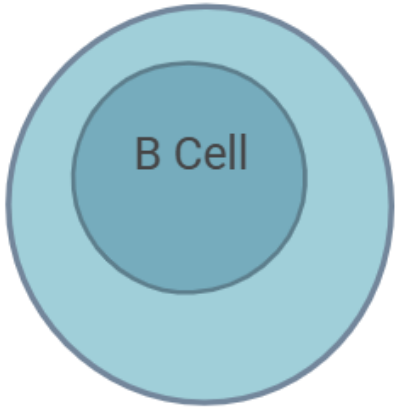
Clinical Recognition :



Immunodeficiencies Categories

- T-cell defects (SCID)
- B-cell/antibody defects
- Cytokine pathway defects
- Lymphoproliferative disorders
- Dendritic cell & innate immunity defects
- Autoinflammatory diseases
- Treatment





SEVERE COMBINED IMMUNODEFICIENCY (SCID)

Most Severe Immunodeficiency

- **Combined** = T-cell & B-cell immunity affected
- **Fatal without treatment** - "Bubble boy disease"

https://time.com/5573015/gene-therapy-bubble-boy-treatment

https://www.researchgate.net/figure/Photograph-of-a-4-month-old-patient-with-SCID-complicated-by-systemic-disseminated-BCG_fig1_383281865

X-linked SCID

https://link.springer.com/article/10.1007/s10875-022-01337-y

ADA deficiency

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

X-linked SCID

- **Mechanism**

Gene: IL2RG (γc chain of IL-2 receptor)

Problem: T-cells can't develop in thymus

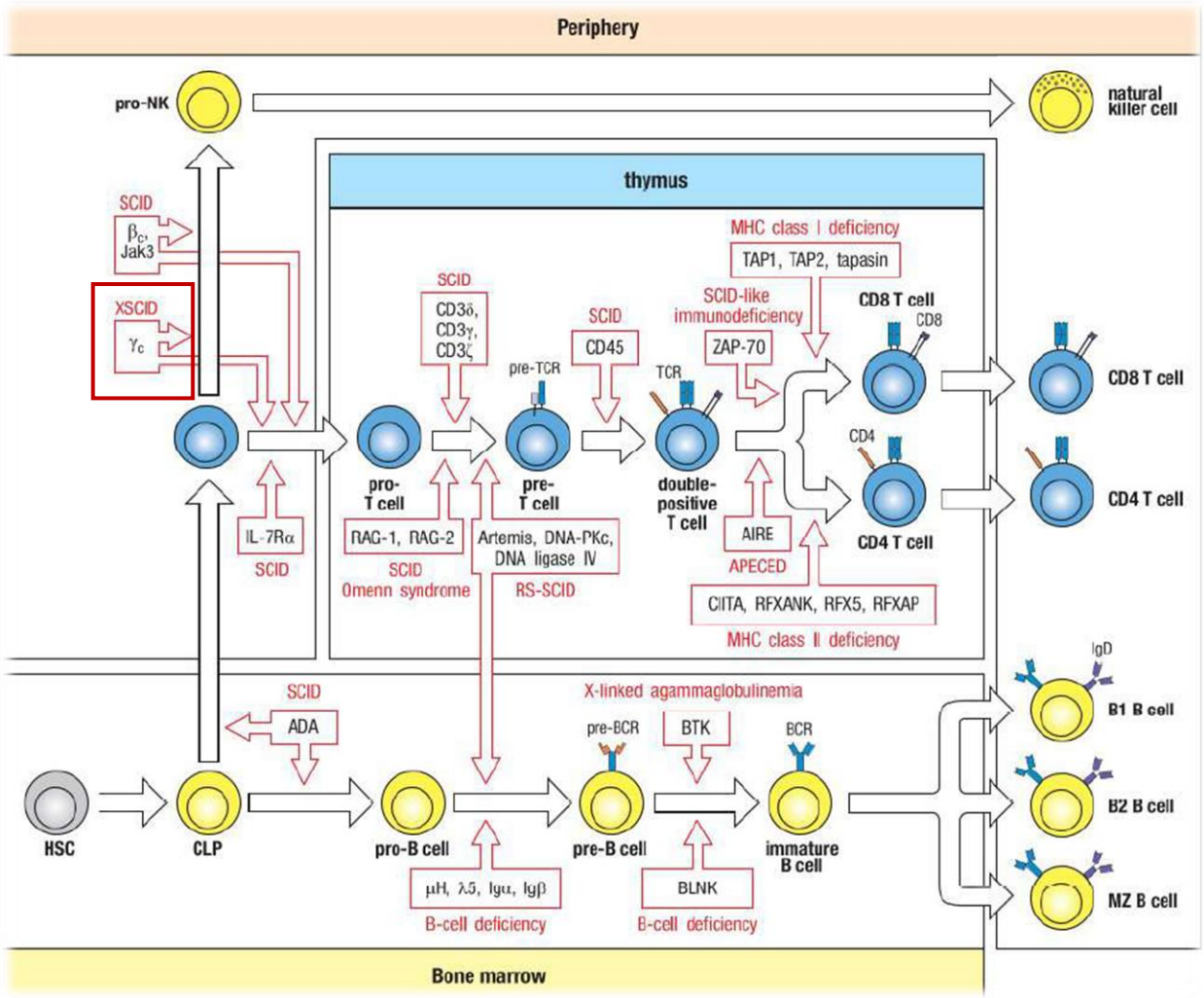
Pattern: T^- B^+ NK^- (no T-cells, no NK cells)

- **Clinical Presentation**

Male infants (X-linked inheritance)

Symptoms after 6 months

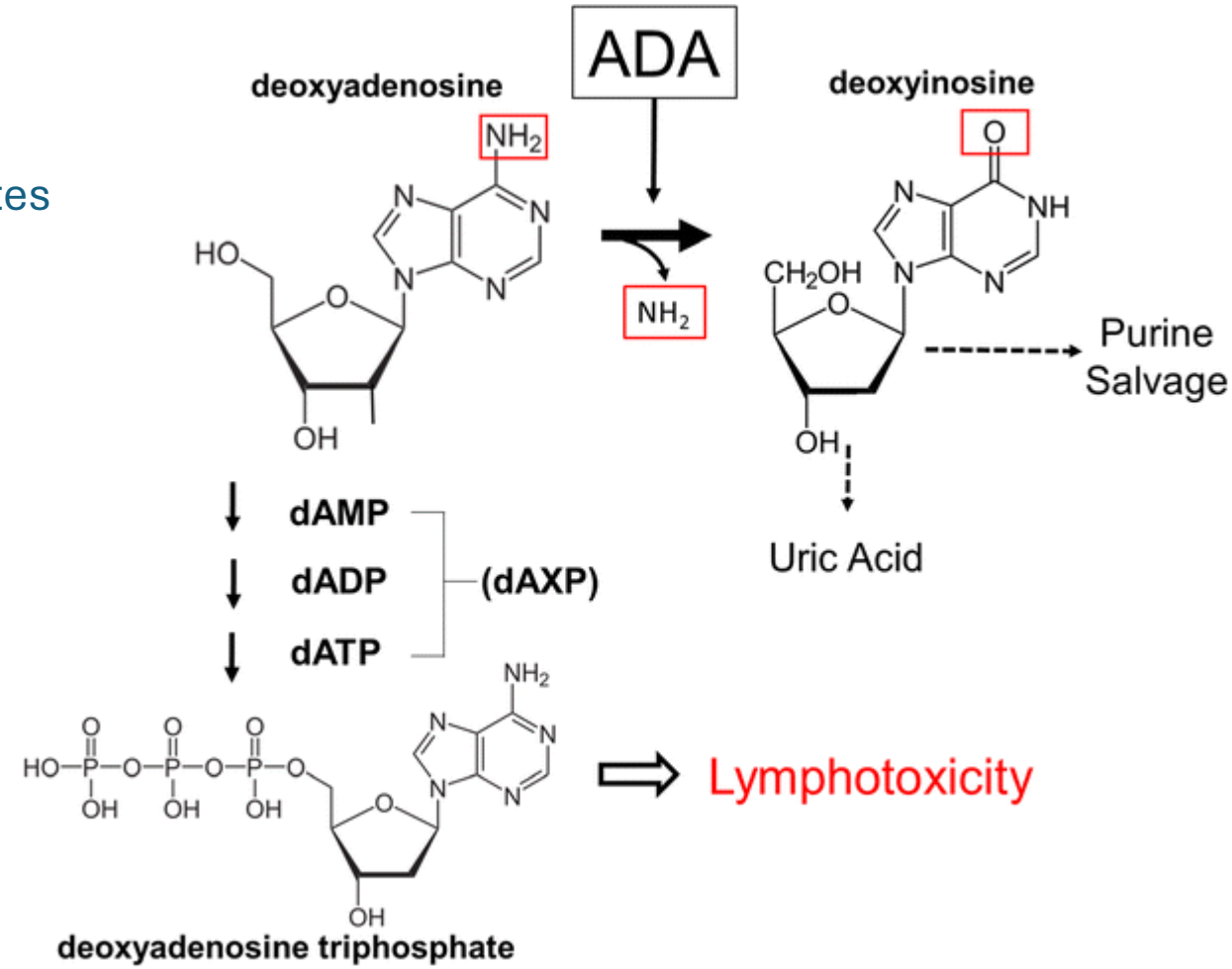
Chronic diarrhea + persistent thrush



SEVERE COMBINED IMMUNODEFICIENCY (SCID)

ADA Deficiency

- **Mechanism:** Toxic adenosine metabolites kill lymphocytes
- **Pattern:** Affects ALL lymphocytes (T^- B^- NK^-)



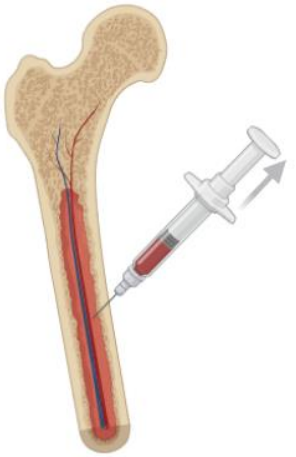
SCID Treatment Strategy

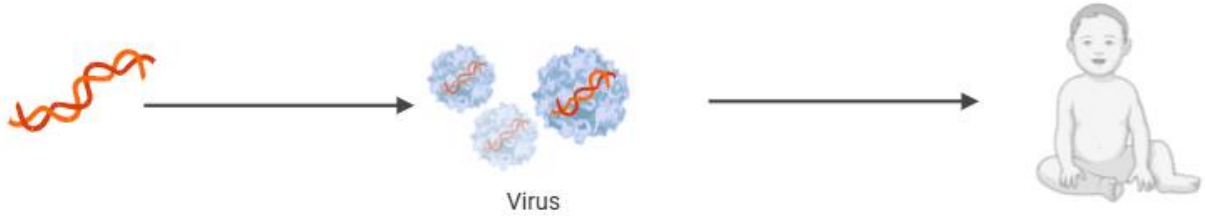
- **Curative Treatments**

Bone marrow transplant: Near 100% cure if done early

Gene therapy: Fix genetic defect directly

Key Message: Early diagnosis + treatment = Normal life expectancy





B-CELL & ANTIBODY DEFECTS

- **B-Cell Defects Overview**

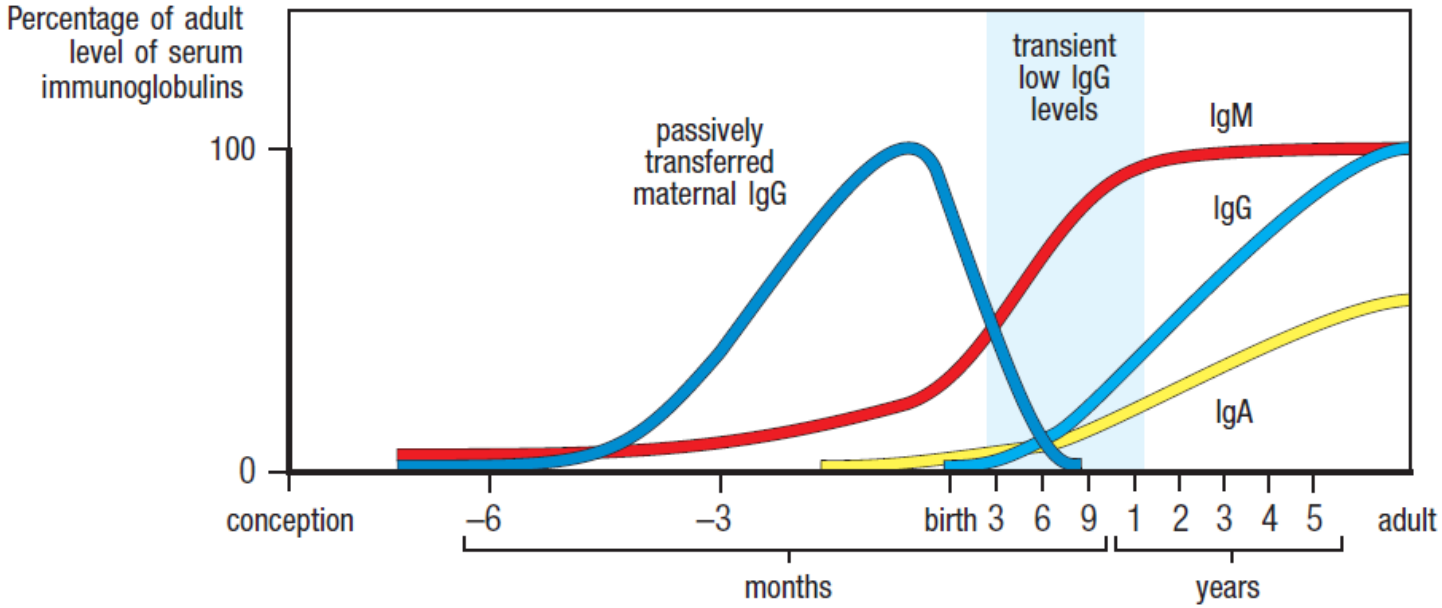
Antibody Production Failures

Most common primary immunodeficiencies

Pattern: Recurrent respiratory tract infections

Maternal IgG protects first 6 months

Symptoms when maternal protection wanes



B-CELL & ANTIBODY DEFECTS

- **X-linked Agammaglobulinemia (XLA)**

Gene: BTK (Bruton's tyrosine kinase)

Problem: B-cell development stops at pre-stage

Result: No mature B-cells, no antibodies

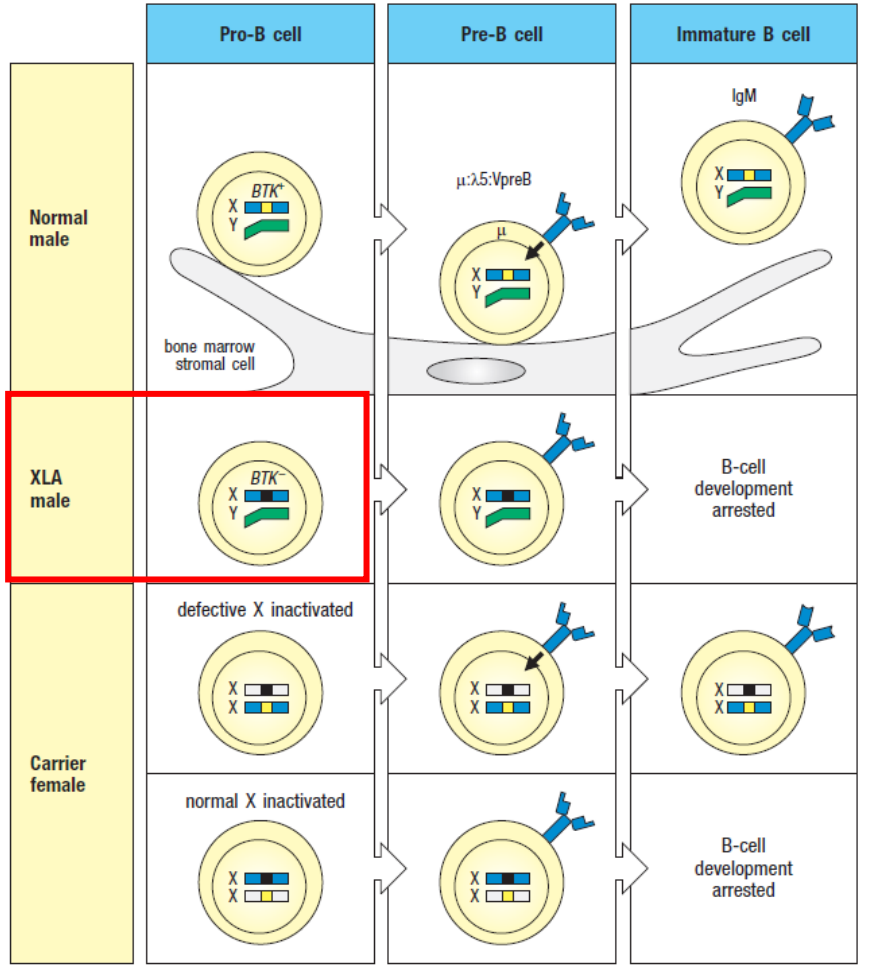
- **Clinical Features**

Male patients (X-linked)

Absent/tiny tonsils (no B-cells to populate them)

Recurrent sinopulmonary infections

Normal viral immunity initially (T-cells work)



B-CELL & ANTIBODY DEFECTS

- **X-linked Agammaglobulinemia (XLA)**

Gene: BTK (Bruton's tyrosine kinase)

Problem: B-cell development stops at pre-B cell stage

Result: No mature B-cells, no antibodies

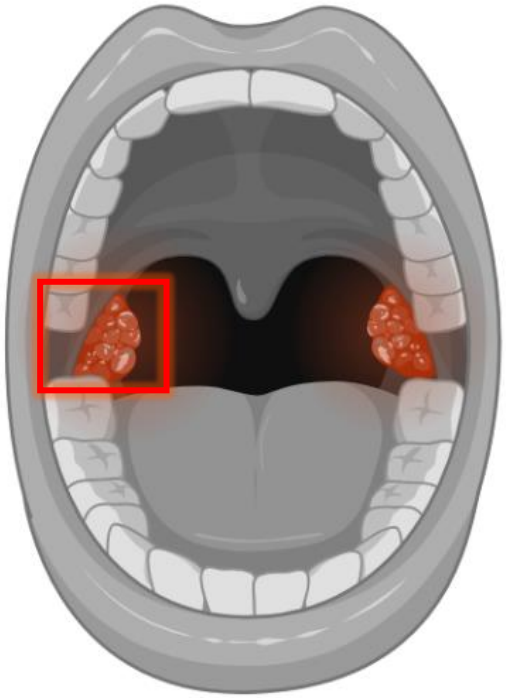
- **Clinical Features**

Male patients (X-linked)

Absent/tiny tonsils (no B-cells to populate them)

Recurrent sinopulmonary infections

Normal viral immunity initially (T-cells work)



B-CELL & ANTIBODY DEFECTS

- **Hyper-IgM Syndromes**

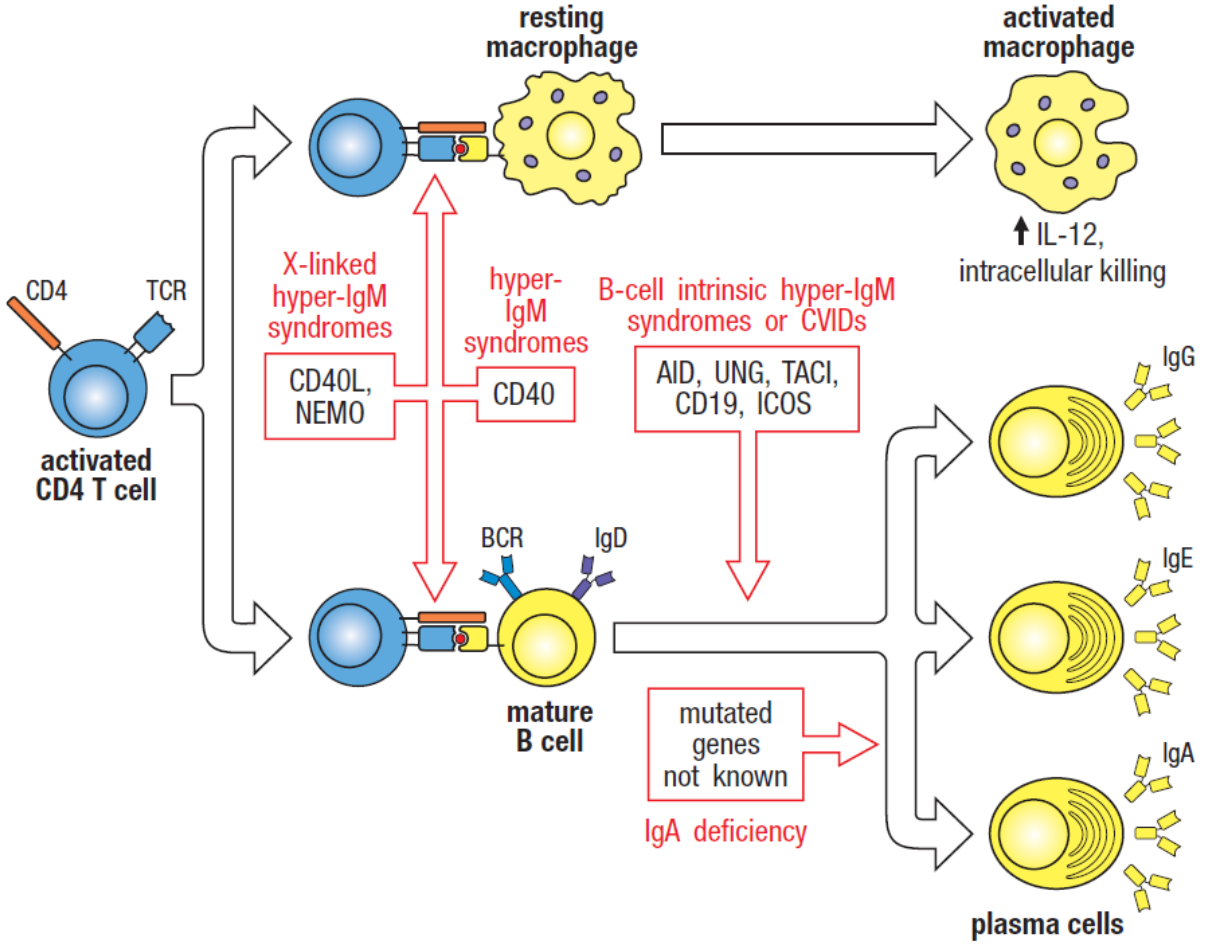
  Most common: CD40 ligand deficiency (X-linked)

  Problem: Can't switch from IgM to IgG/IgA/IgE

  Pattern: High IgM, low other antibodies

- **Clinical Features**

Opportunistic infections (Pneumocystis)

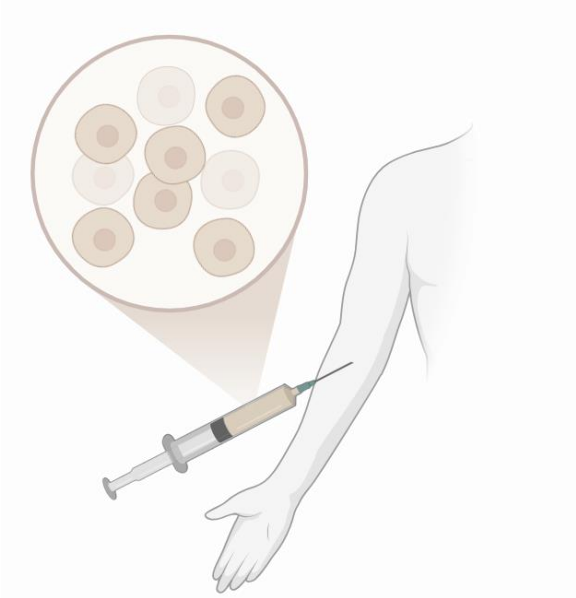


TREATMENT & GLOBAL IMPACT

Hematopoietic Stem Cell Transplantation

Replace defective immune system

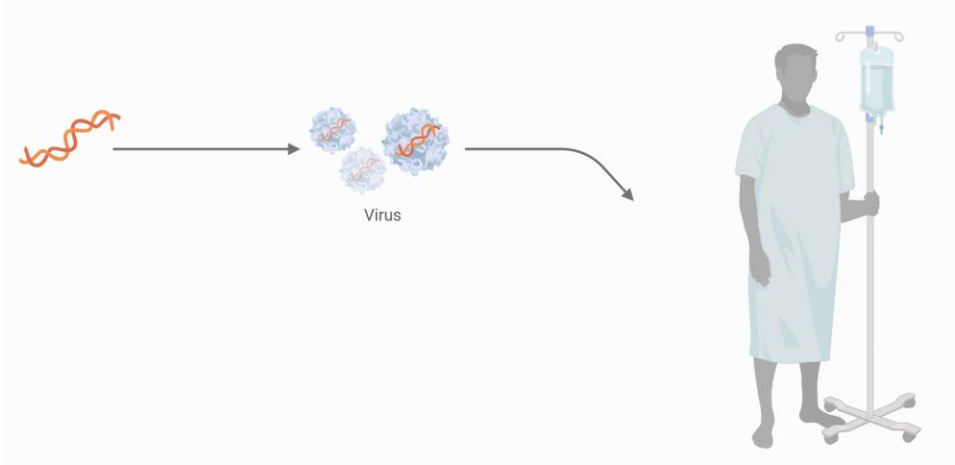
Near 100% cure for SCID if done early



Gene Therapy Breakthroughs

ADA-SCID

Patient's own cells, no rejection



Key Takeaways

Scientific Insights

- **T-cells are central** to all adaptive immunity - when they fail, everything collapses
- **Infection patterns are diagnostic** - bacterial vs viral susceptibility reveals defect type
- **Timing matters** - maternal antibodies protect first 6 months, then vulnerability begins

Clinical Pearls

- **SCID**: "Combined" immunodeficiency, fatal without treatment, but 100% curable if caught early
- **B-cell defects**: Most common primary immunodeficiencies
- **X-linked diseases** are predominant in male infants

Treatment Revolution

- **Early intervention saves lives** - outcomes depend on timing
- **Bone marrow transplant**: Curative for severe immunodeficiencies
- **Gene therapy**: Breakthrough using patient's own cells (ADA-SCID success)

I. Immunodeficiency diseases

II. Evasion and subversion of immune defenses

III. Acquired immune deficiency syndrome

How Pathogens Outsmart the Immune System

Immune evasion

the ability of pathogens to avoid recognition, neutralization or destruction by the host immune system

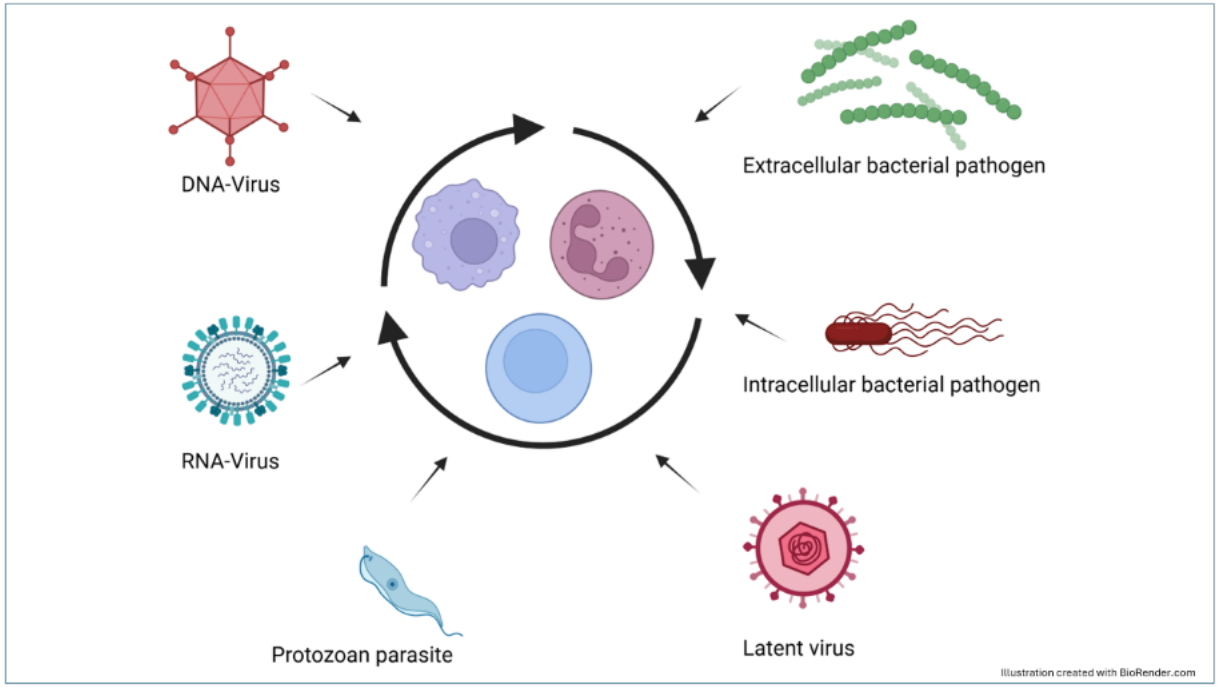
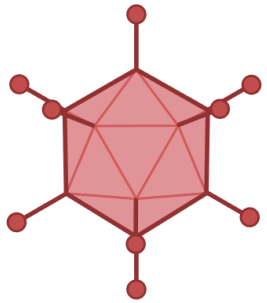
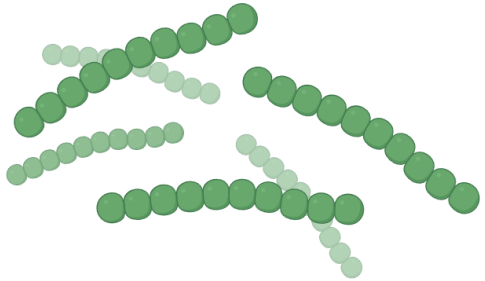


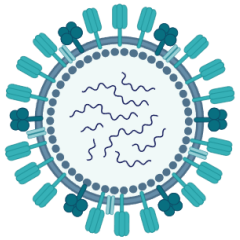
Illustration created with BioRender.com



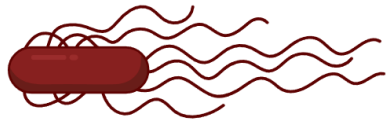
DNA-Virus



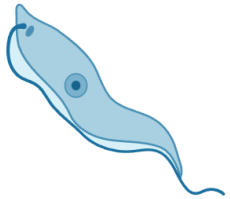
Extracellular bacterial pathogen



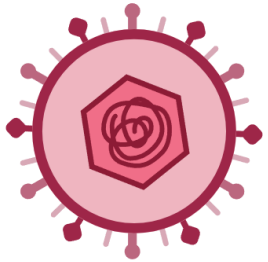
RNA-Virus



Intracellular bacterial pathogen

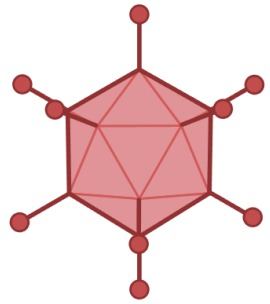


Protozoan parasite

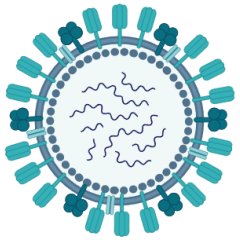


Latent virus

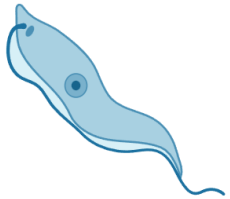
Illustration created with BioRender.com



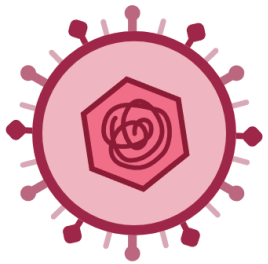
DNA-Virus



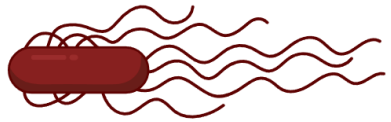
RNA-Virus



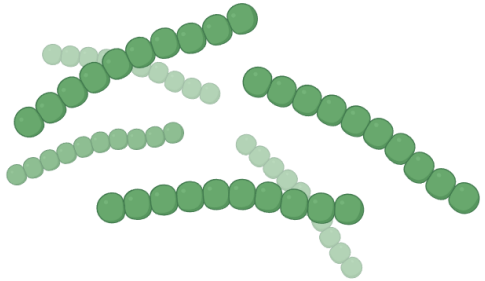
Protozoan parasite



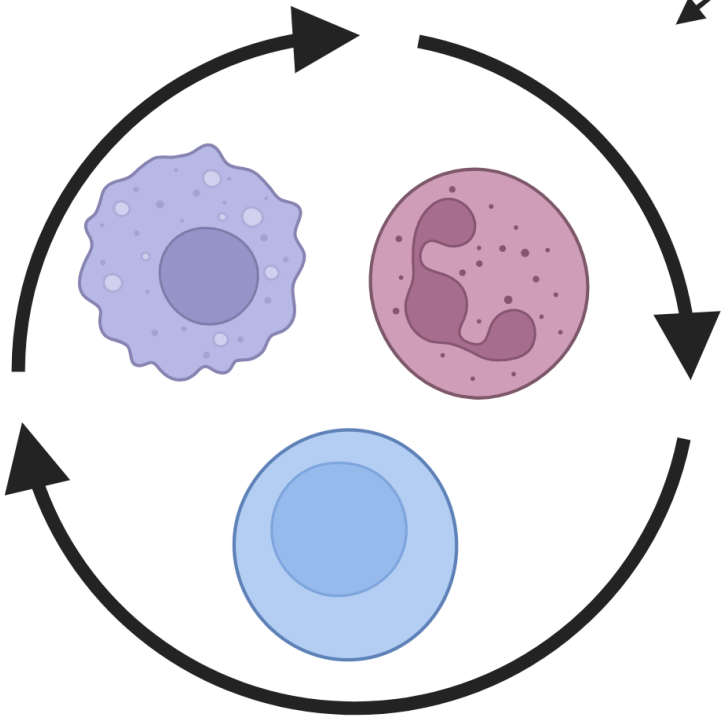
Latent virus



Intracellular bacterial pathogen



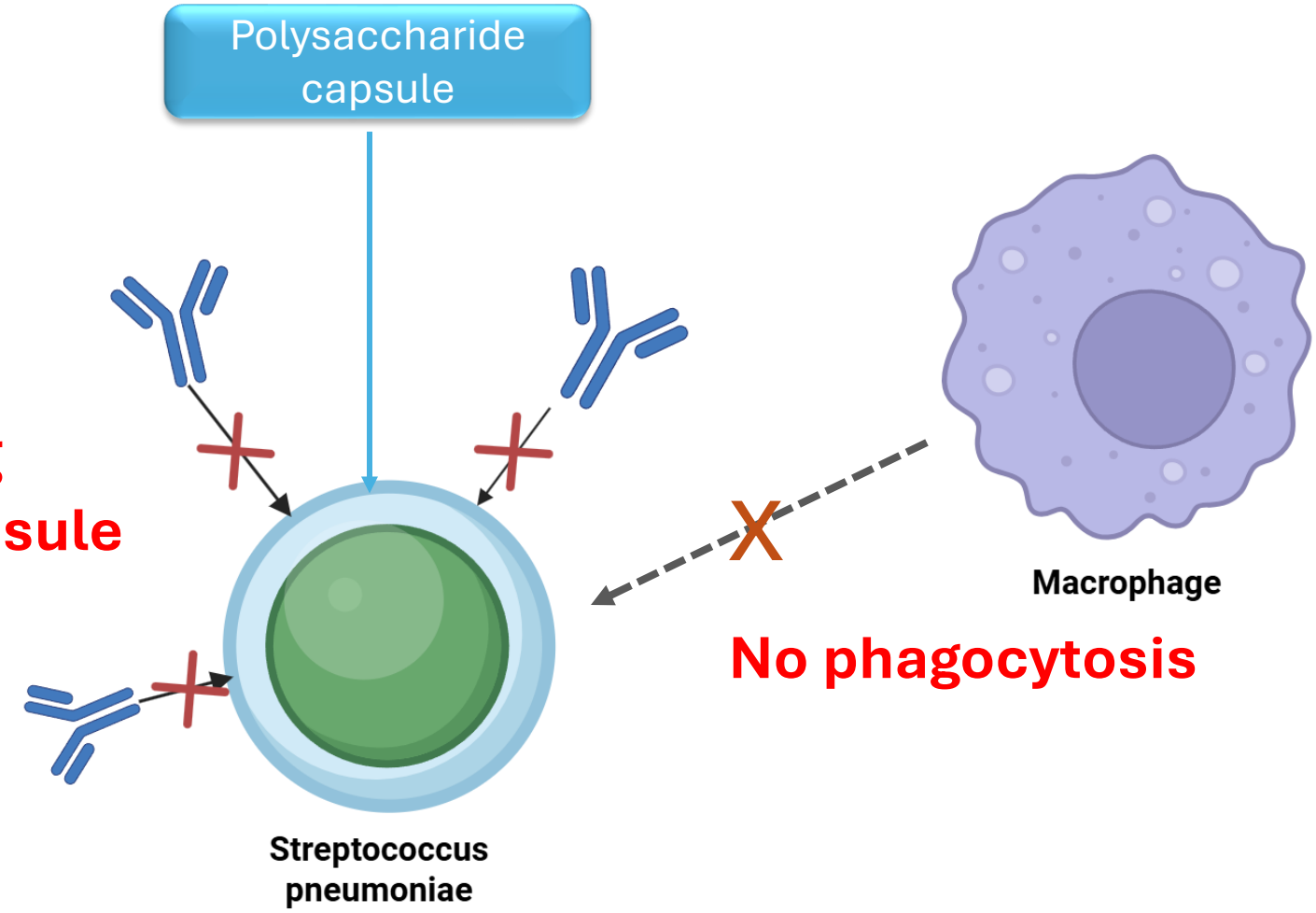
Extracellular bacterial pathogen



Extracellular Bacterial Pathogens

- Capsule formation blocks complement and phagocytosis (S. pneumoniae)
- Protein A binds IgG Fc region and disrupts opsonization (*S. aureus*)
- Antigenic variation of pili avoids antibody detection (Neisseria gonorrhoeae)
- Modified PAMPs prevent recognition by PRRs
- Production of enzymes to degrade antimicrobial peptides

Capsule formation blocks complement and phagocytosis (S. pneumoniae)

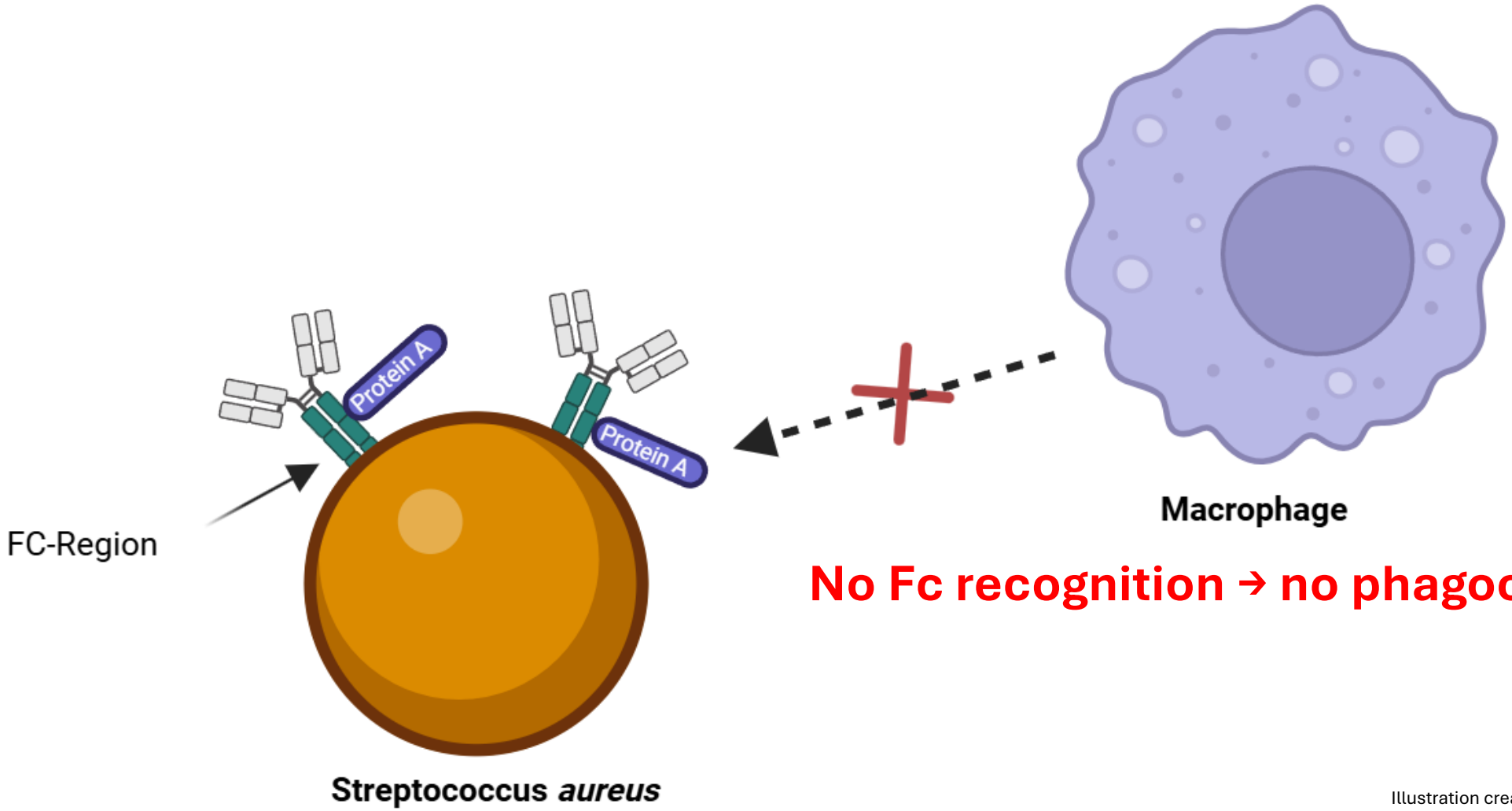


No binding
blocked by capsule

No phagocytosis

Illustration created with BioRender.com

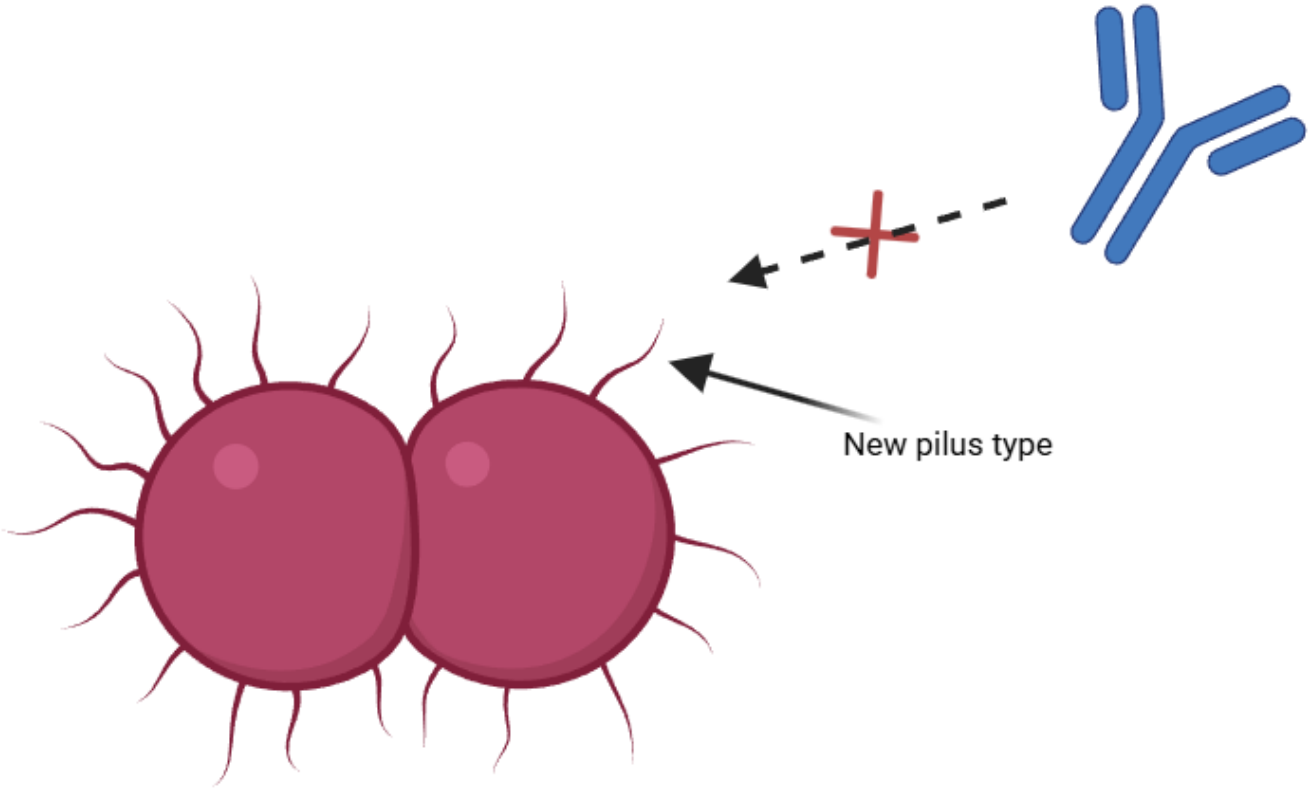
Protein A binds IgG Fc region and disrupts opsonization (*S. aureus*)



No Fc recognition → no phagocytosis

Illustration created with BioRender.com

Antigenic variation of pili avoids antibody detection (Neisseria gonorrhoeae)

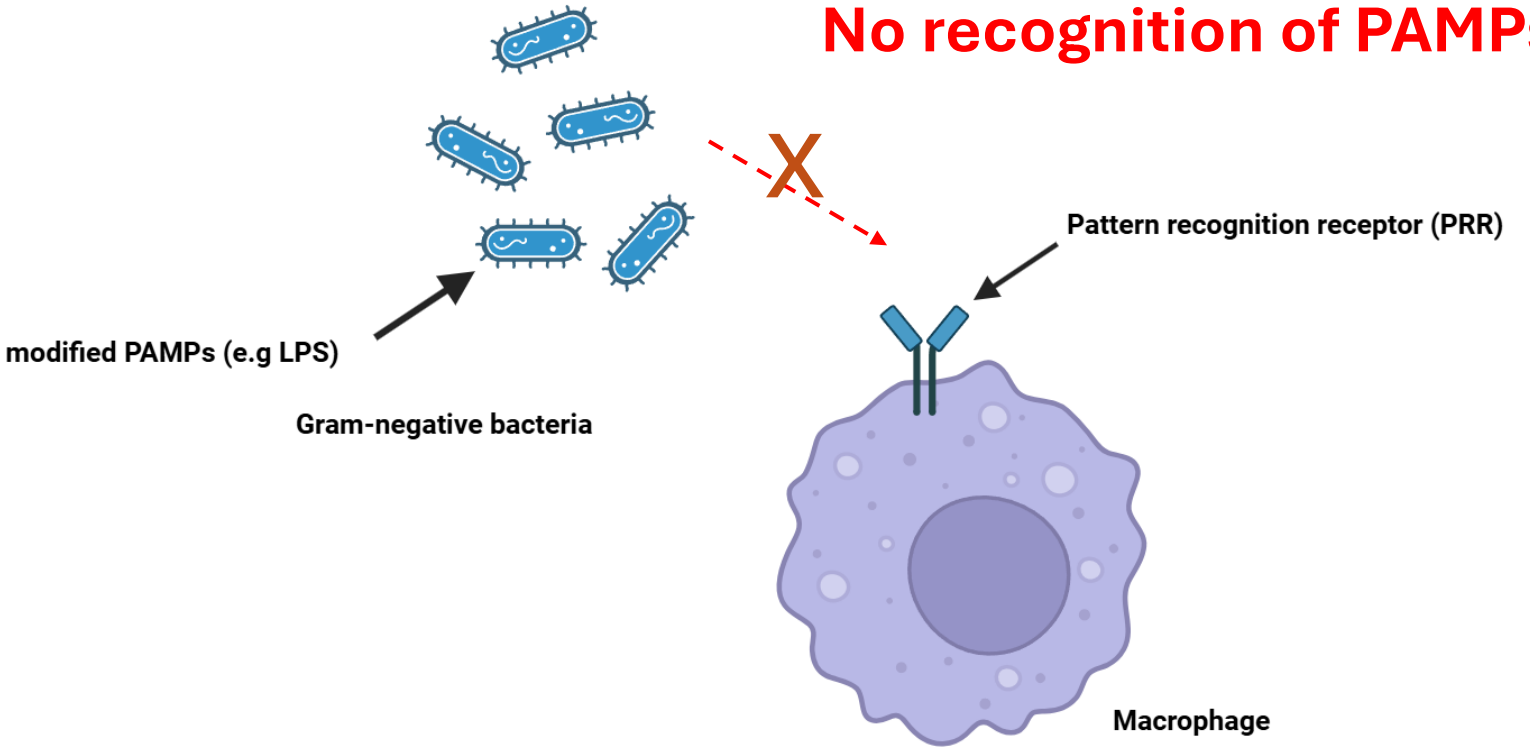


Neisseria gonorrhoeae

- The bacterium changes pili structure via antigenic variation
- Gene conversion creates new pilus types
- Result: Old antibodies can’t bind → immune escape
- The immune system must start a new response

Illustration created with BioRender.com

Modified PAMPs prevent recognition by PRRs



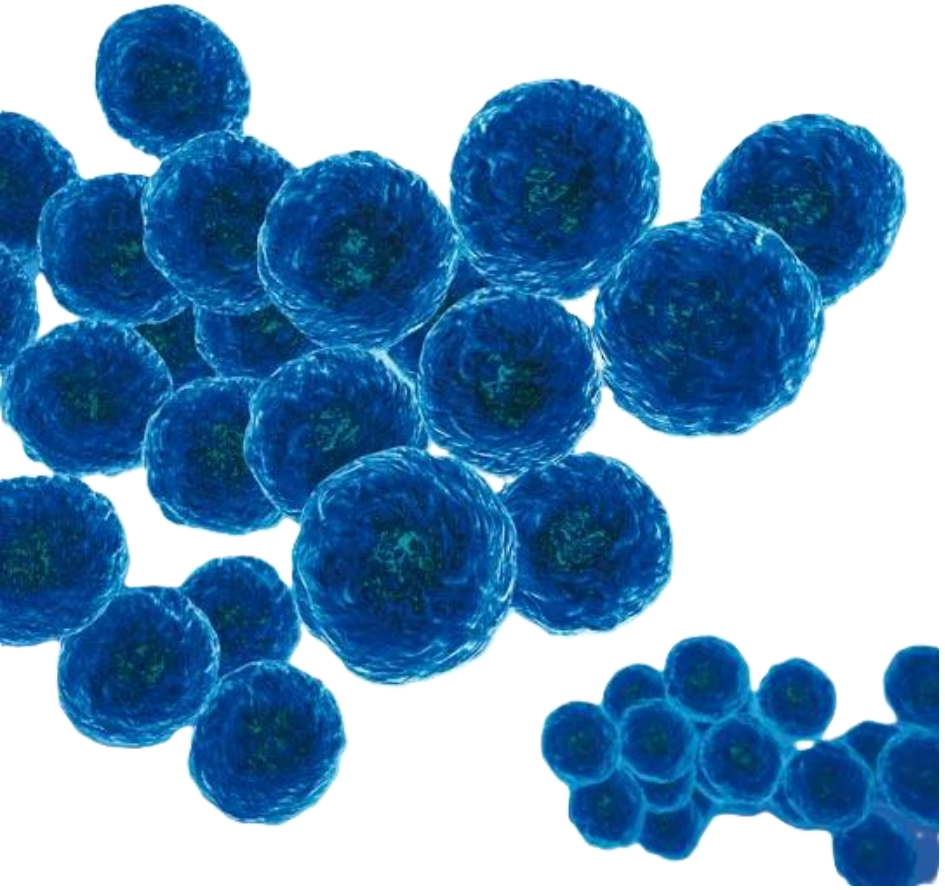
- PRRs recognize PAMPs
- Some pathogens modify their PAMPs to avoid detection
- Modified PAMPs → reduced or no PRR activation

→no innate immune response: allowing the bacteria to survive longer inside the host

PRRs= Pattern Recognition Receptors
PAMPs= Pathogen-Associated Molecular Patterns

Illustration created with BioRender.com

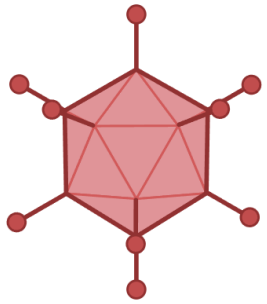
Production of enzymes to degrade antimicrobial peptides



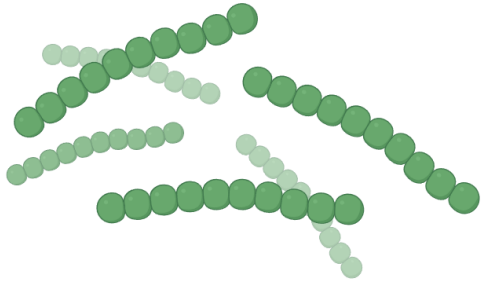
Staphylococcus aureus

https://www.hartmann-science-center.com/de-de/hygienewissen/erregersuche-von-a-z/pathogens-19/staphylococcus-aureus

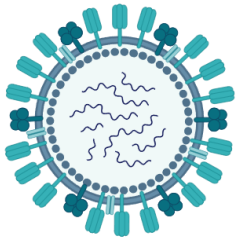
- Antimicrobial Peptides disrupt bacterial membranes
- Some bacteria produce proteases that degrade AMPs
- This neutralizes the antimicrobial effect
- Result → survival in host tissues
- Examples: Staphylococcus aureus, Pseudomonas aeruginosa



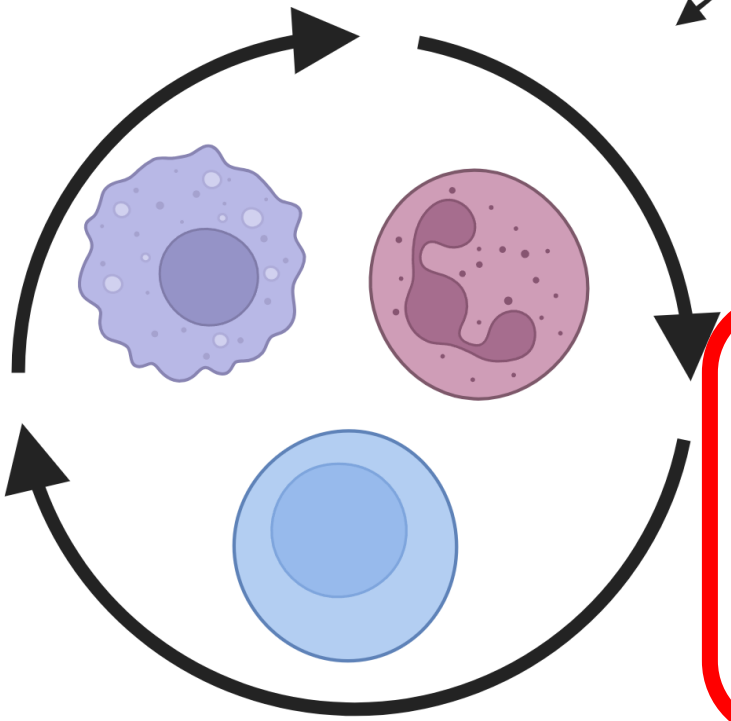
DNA-Virus

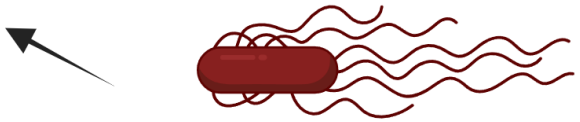


Extracellular bacterial pathogen

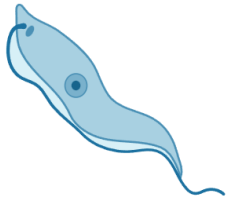


RNA-Virus

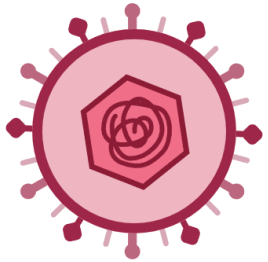




Intracellular bacterial pathogen



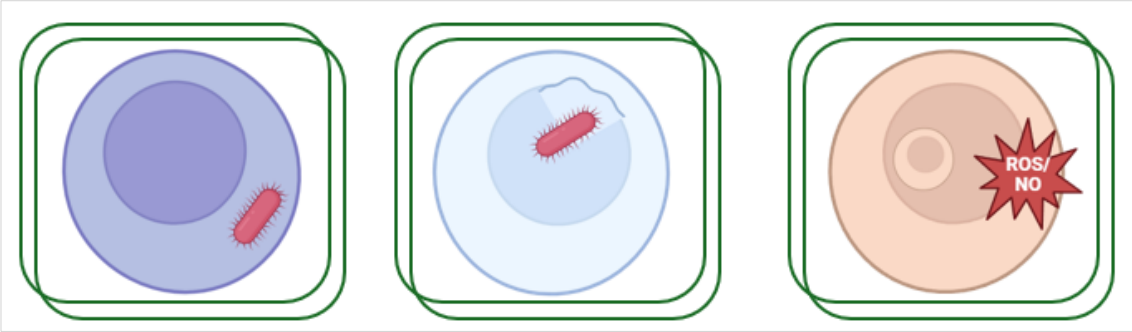
Protozoan parasite



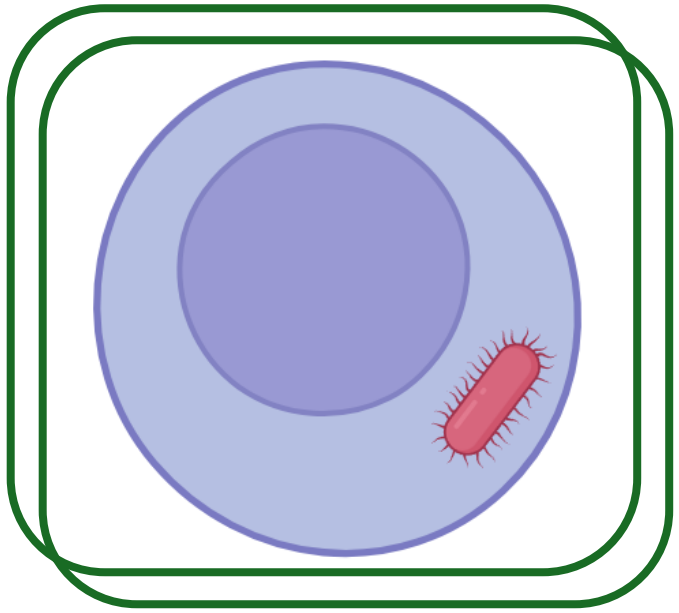
Latent virus

Intracellular bacterial pathogen

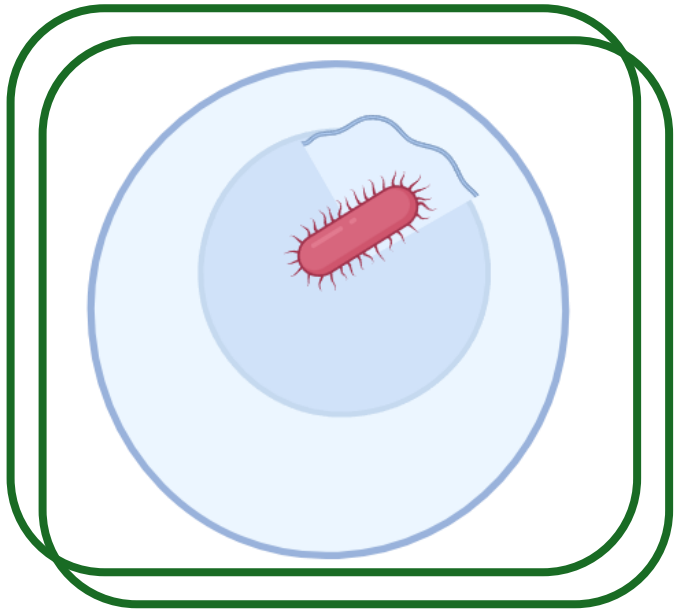
- some bacterial pathogens survive inside host cells
- Avoid antibodies and complement
- Intracellular lifestyle provides immune protection



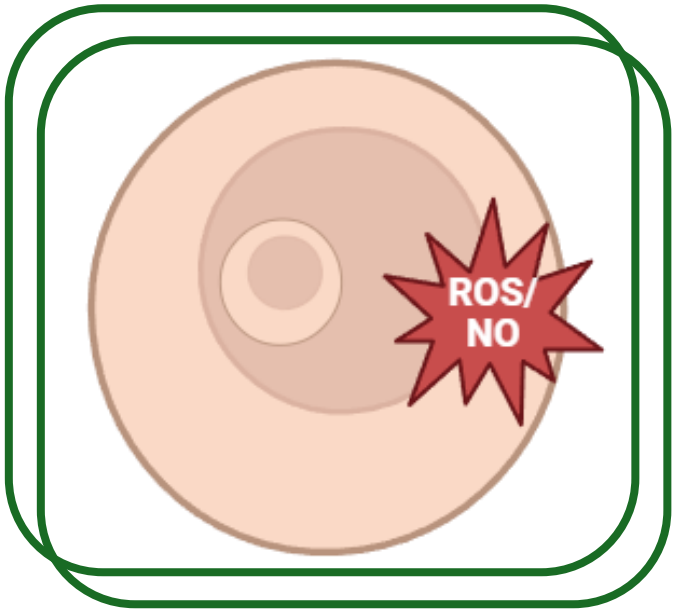
Mechanisms of survival



M. tuberculosis:
blocks phagolysosome fusion

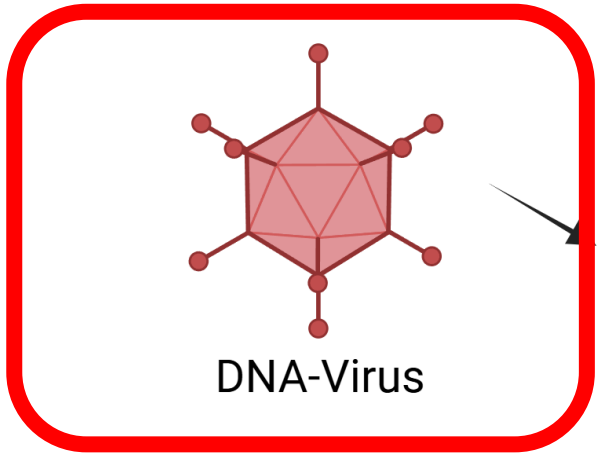


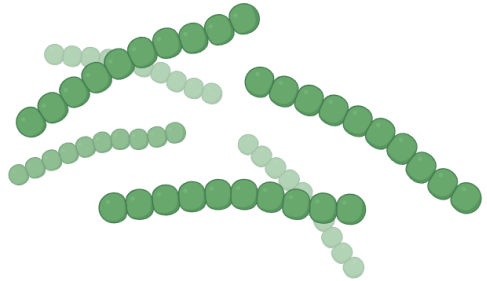
Listeria monocytogenes:
escapes from phagosome into cytosol



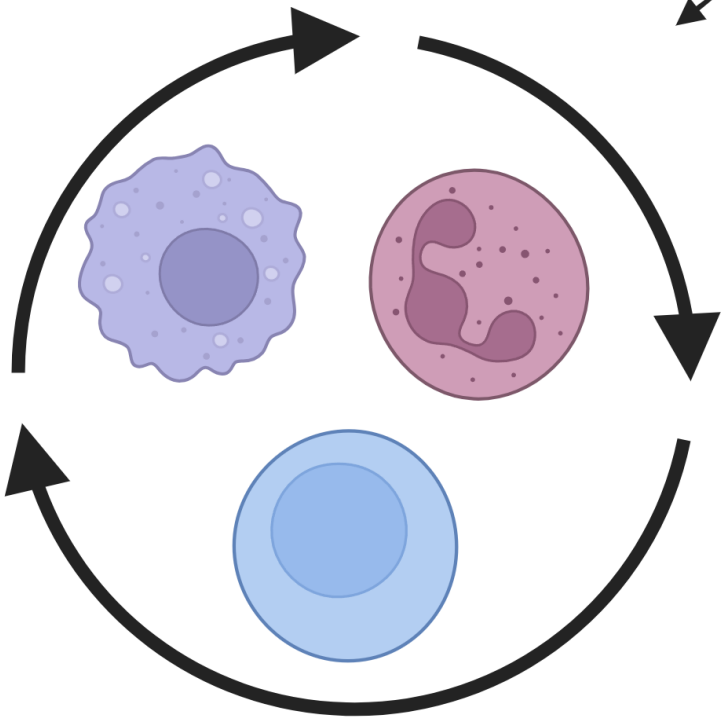
Toxoplasma gondii:
forms protective vacuole, resists ROS/NO

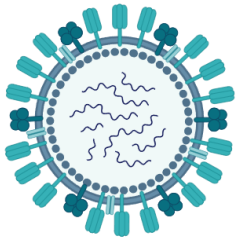
Illustration created with BioRender.com



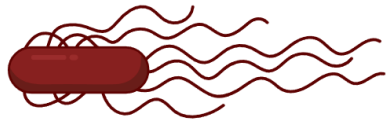


Extracellular bacterial pathogen

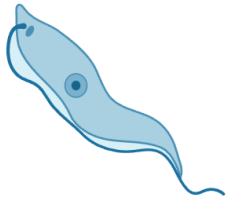




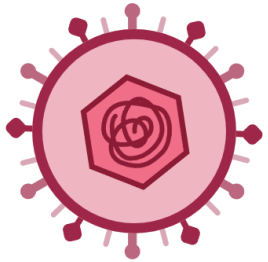
RNA-Virus



Intracellular bacterial pathogen



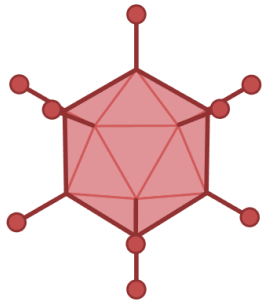
Protozoan parasite



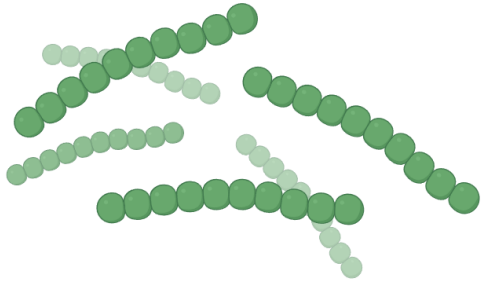
Latent virus

DNA Viruses

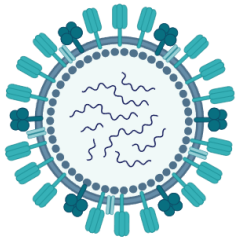
- Block MHC I expression → $CD8^+$ T cells can't detect infected cells
- Produce cytokine inhibitors
- Inhibit apoptosis to keep host cell alive
- Evade Natural Killer cells activation
- Examples: Cytomegalovirus, Epstein-Barr Virus



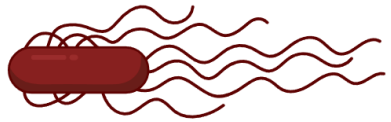
DNA-Virus



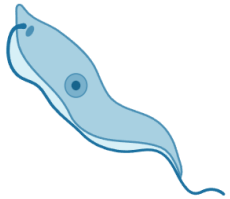
Extracellular bacterial pathogen



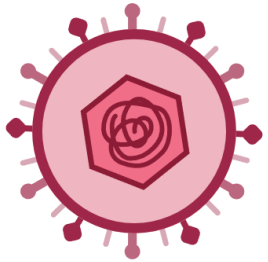
RNA-Virus



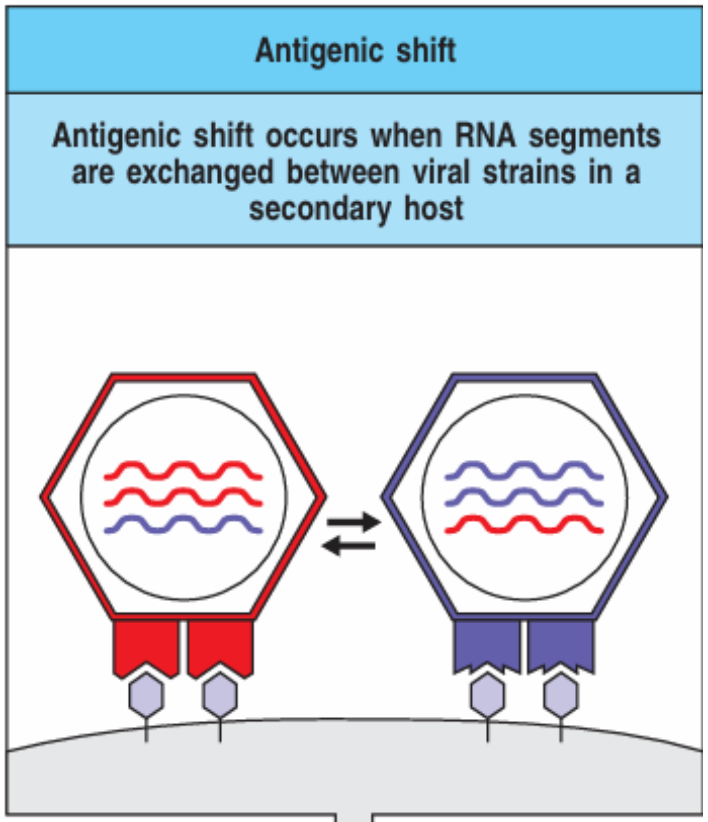
Intracellular bacterial pathogen

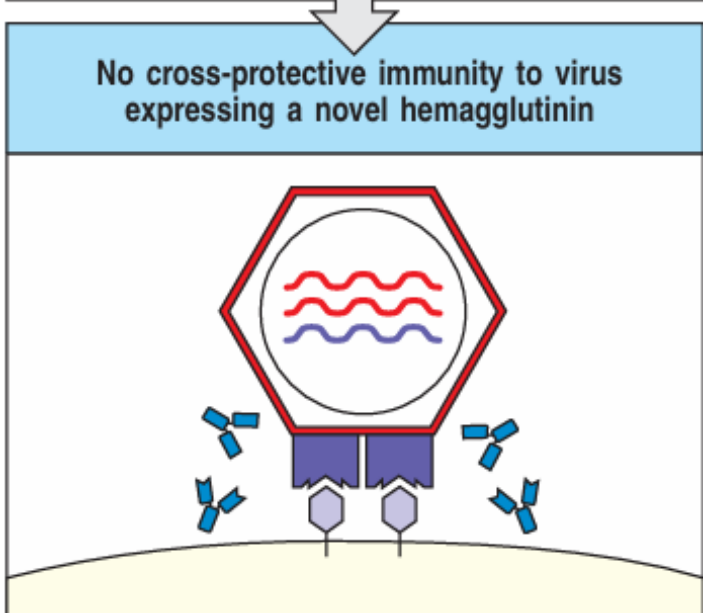


Protozoan parasite



Latent virus

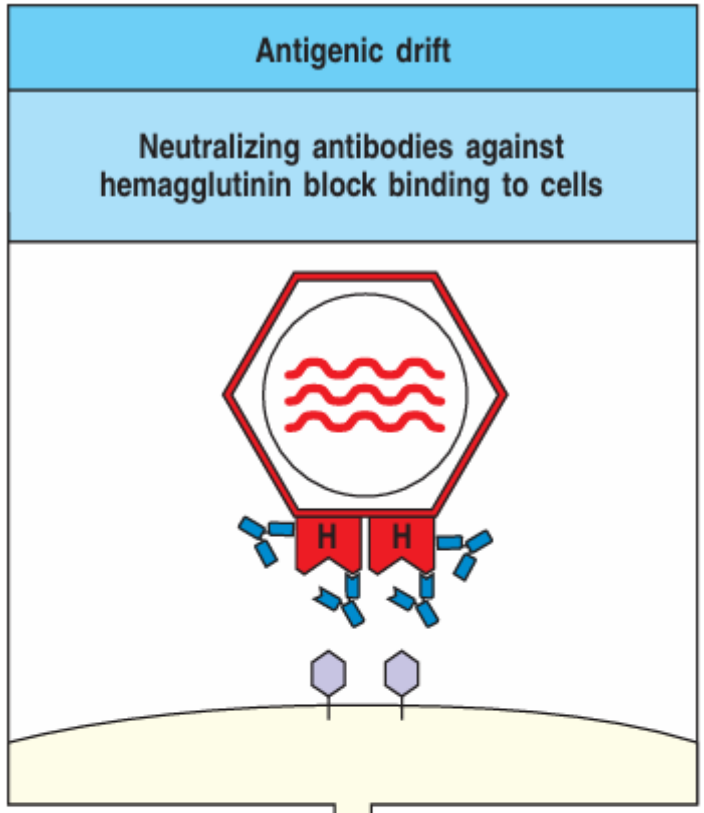


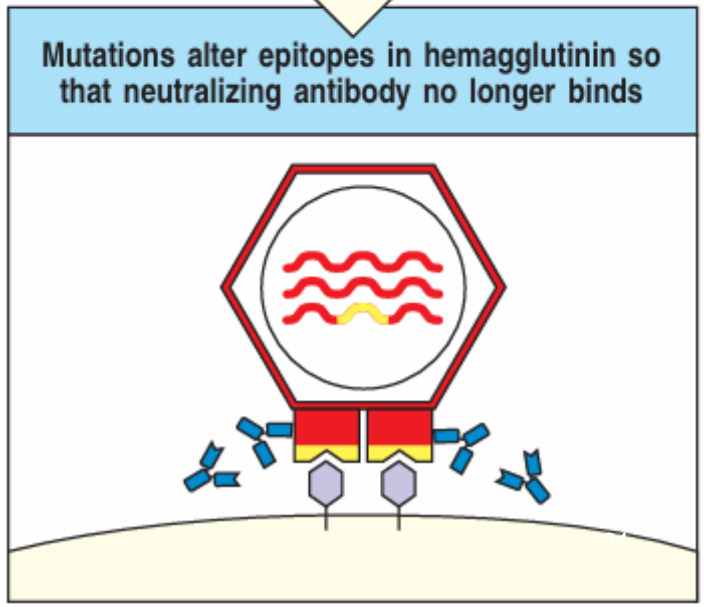


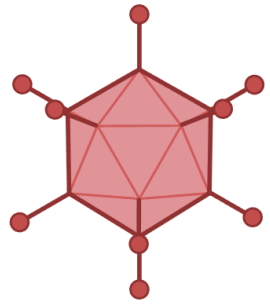
RNA Viruses

Antigenic shift and drift

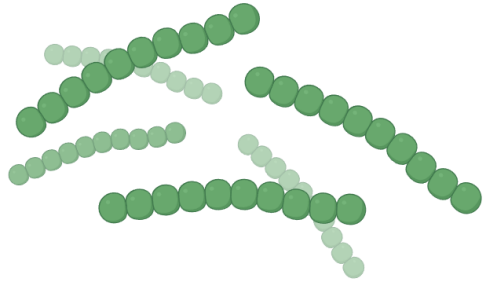
Example: Influenza Virus



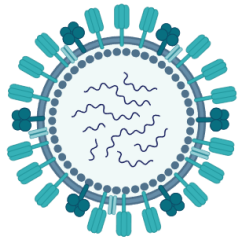




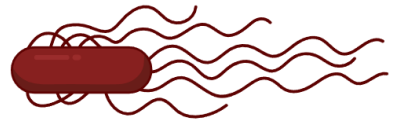
DNA-Virus



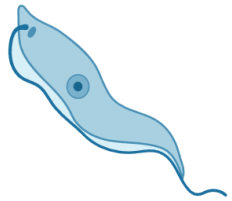
Extracellular bacterial pathogen



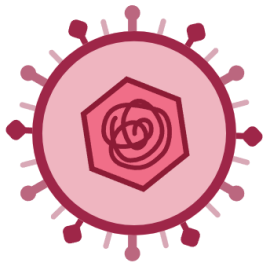
RNA-Virus



Intracellular bacterial pathogen



Protozoan parasite



Latent virus

Long-term immune evasion: Parasites and latent viruses

	Protozoan Parasites	Latent Viruses
Examples	*Trypanosoma*, *Plasmodium*	*Herpes Simplex Virus, Epstein-Barr Virus*
Main Strategy	Antigenic variation	No antigen expression
Immune Evasion	Escape from antibodies	Escape from T cell detection

Key Takeaways

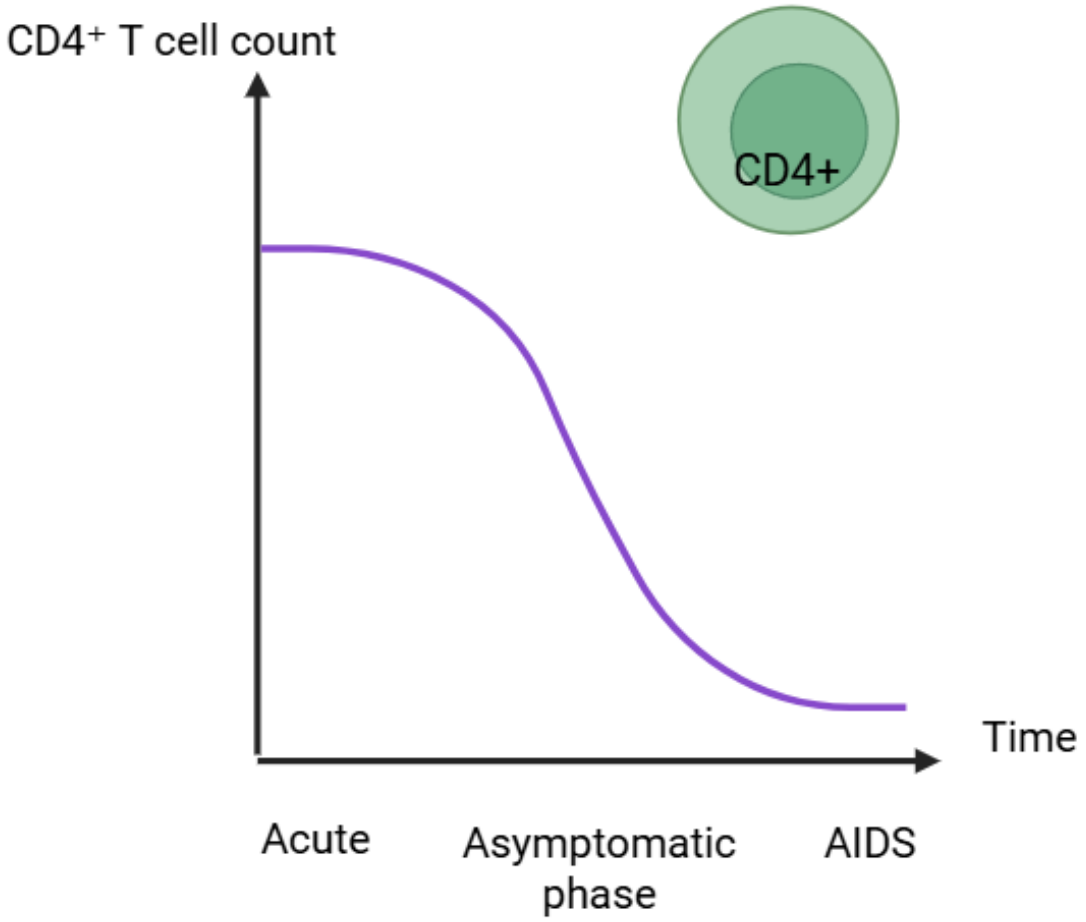
- Pathogens use diverse strategies to evade the immune system
- Extracelullar Bacteria: capsules, antigenic variation, enzyme secretion
- Intracellular pathogens: hide in host cells, block degradation
- RNA Viruses: antigenic drift and shift
- DNA Viruses: Interfere with MHC-I, cytokines, apoptosis, and NK cells
- Parasites & latent viruses: escape through antigen switching or latency

I. Immunodeficiency diseases

II. Evasion and subversion of immune defenses

III. Acquired immune deficiency syndrome

What is AIDS (Acquired immune deficiency syndrome)?

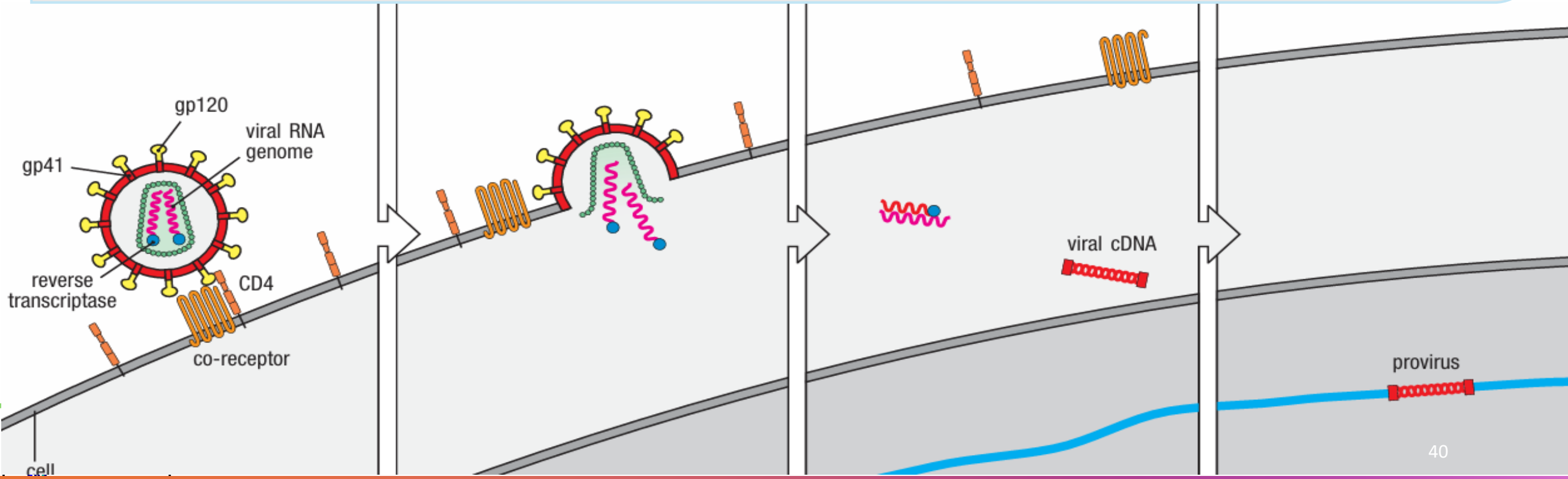


- AIDS = final stage of HIV infection
- Severe loss of immune function
- Mainly affects $CD4^+$ T cells
- Patients can easily get infections and some types of cancer.

Illustration created with BioRender.com

HIV structure and target cells

- HIV is a retrovirus with an RNA genome
- Infects $CD4^+$ T cells, macrophages, and dendritic cells
- Envelope protein gp120 binds to CD4 receptor and CCR5/CXCR4 co-receptor
- Virus fuses with host membrane and releases RNA
- Reverse transcriptase converts RNA into DNA (cDNA)
- Viral DNA integrates into host genome as a provirus



Immune Evasion by HIV

- Antigenic variation: constant mutation of envelope proteins (e.g. gp120) → to escape antibody recognition
- Latency: HIV integrates into host DNA and hides as provirus → is invisible to immune cells
- The Nef protein from HIV hides infected cells by lowering MHC-I, which prevents recognition by $CD8^+$ T cells
- Fewer $CD4^+$ T cells lead to a weaker and failing immune system.

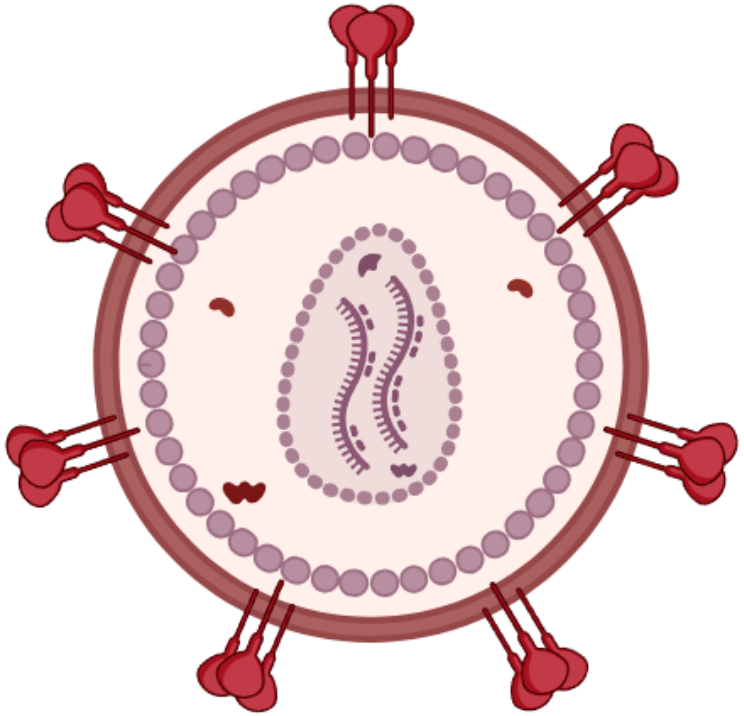


Illustration created with BioRender.com

Key Takeaways

- HIV is a retrovirus that targets $CD4^+$ T cells
- It evades immunity through mutation, latency, and MHC-I downregulation
- Progressive $CD4^+$ T cell loss leads to immune collapse
- AIDS patients suffer from opportunistic infections and cancers


THANKS
FOR YOUR ATTENTION
memegen.es