Class 8

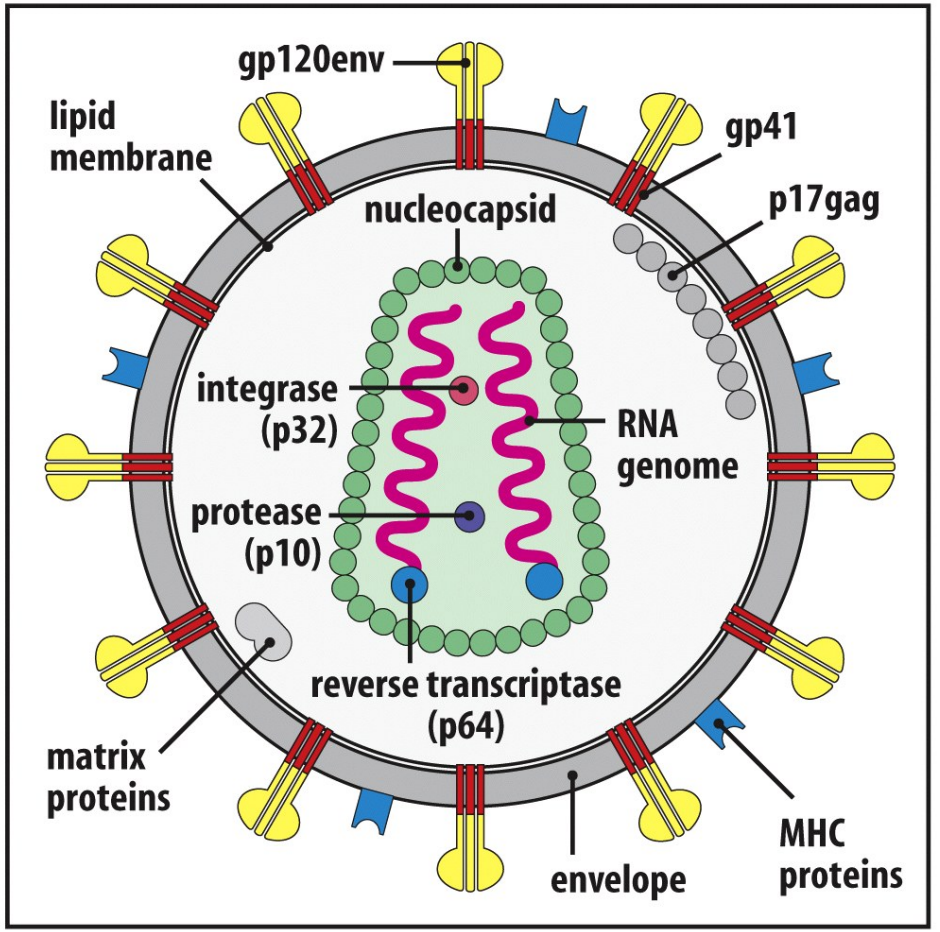
HIV & AIDS

Stem cells & relevance in therapeutics

Reference: Information available in the slides sufficient for the syllabus
If you need additional information/clarification, please consult the instructor/TAs

HIV: Introduction & How it infects human?

- Belongs to group of retrovirus: lentivirus
- Two copies of RNA genome
- Numerous copies of essential enzymes
- Enters cells by envelop proteins:
    - Gp120: binds to CD4 and CCR5/ CXCR4
    - Gp41: helps in fusion with PM
    - Fusion inhibitors:T20
    - How HIV escape the host immune response: “escape mutants”
    - After acute phase, HIV mutates rapidly, gives rise to <u>many variants in a single infection</u>
- infects immune cells (CD4 T cells, dendritic cells, and macrophages)



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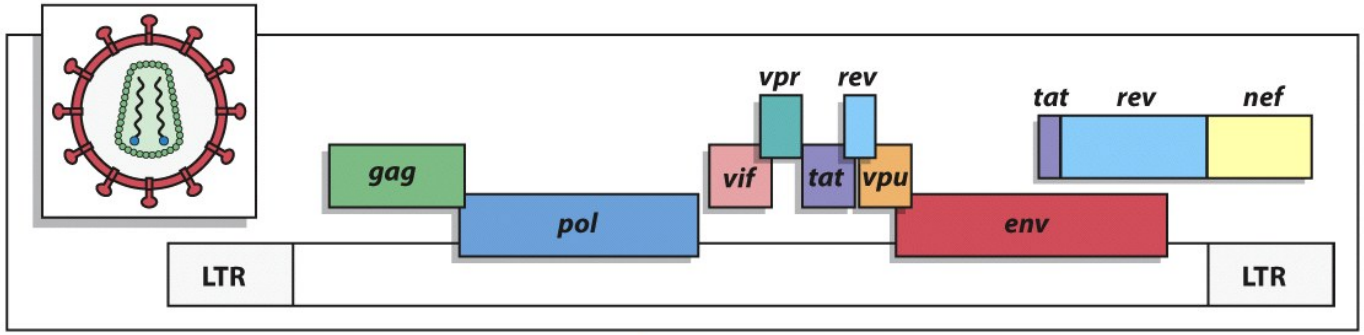
Genomic organization of HIV



Gene		Gene product/function
gag	Group-specific antigen	Core proteins and matrix proteins
pol	Polymerase	Reverse transcriptase, protease, and integrase enzymes
env	Envelope	Transmembrane glycoproteins. gp120 binds CD4 and CCR5; gp41 is required for virus fusion and internalization
tat	Transactivator	Positive regulator of transcription
rev	Regulator of viral expression	Allows export of unspliced and partially spliced transcripts from nucleus
vif	Viral infectivity	Affects particle infectivity
vpr	Viral protein R	Transport of DNA to nucleus. Augments virion production. Cell-cycle arrest
vpu	Viral protein U	Promotes intracellular degradation of CD4 and enhances release of virus from cell membrane
nef	Negative-regulation factor	Augments viral replication *in vivo* and *in vitro*. Decreases CD4, MHC class I and II expression

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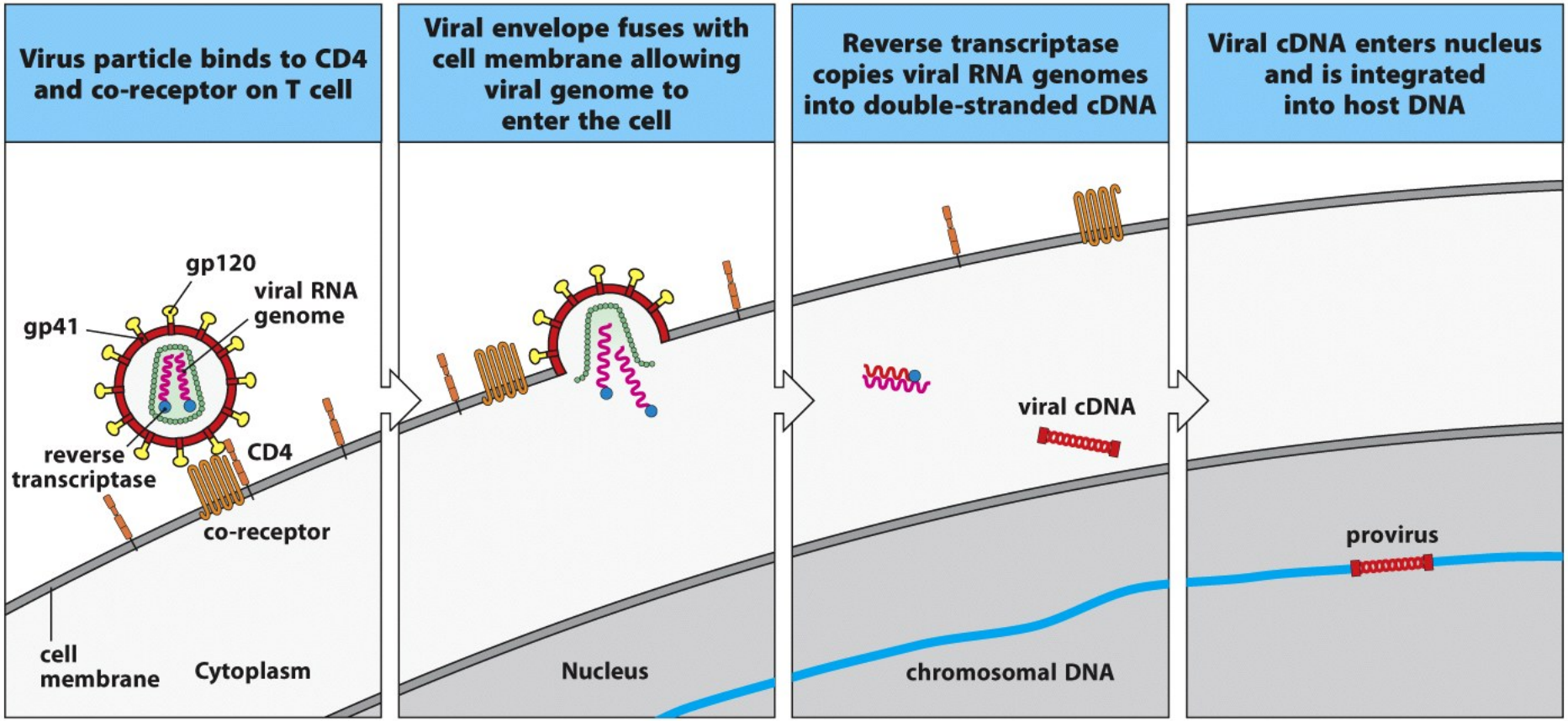
Life cycle of virus

HIV RNA is transcribed by viral reverse transcriptase into DNA that integrates into the host-cell genome.



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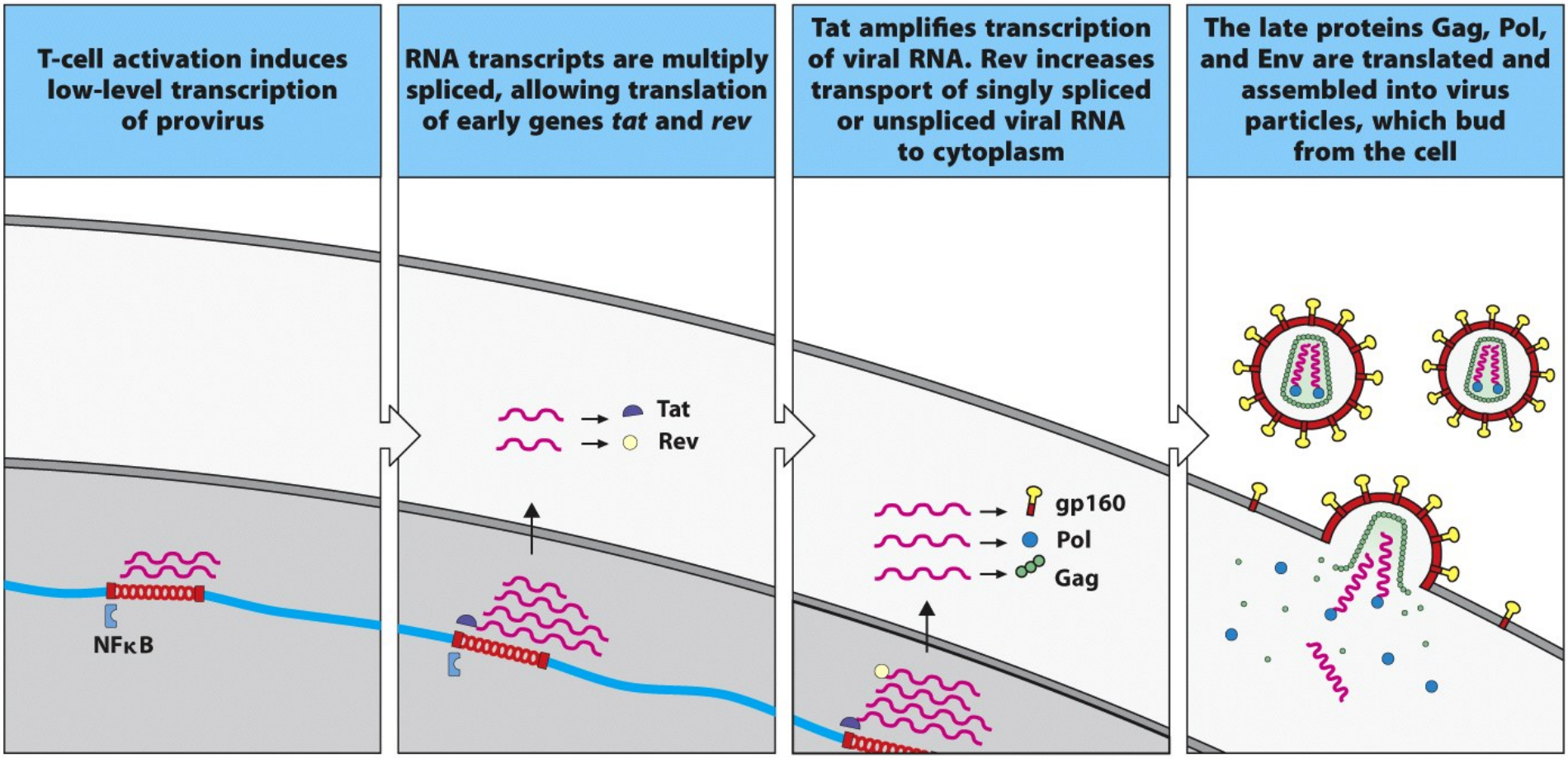
Life cycle of virus



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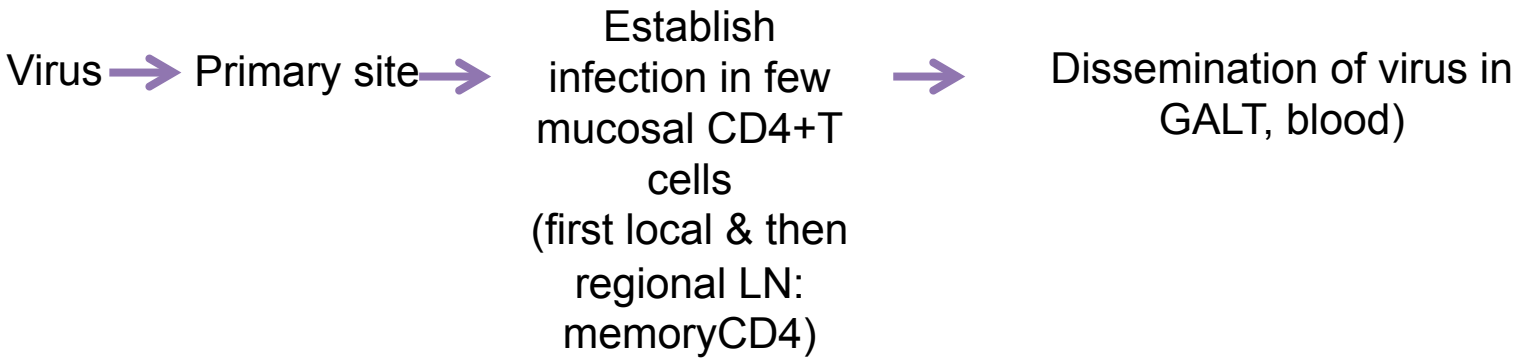
Route of HIV infection and disease progression after HIV entry

- HIV spread by transfer of body fluids (blood, mucosal fluid): pregnant mother to her baby
- HIV (retrovirus) mainly infect cells that express CD4 (receptor) along with CCR5/CXCR4 (co-receptor): "cellular tropism"
- Free virus: blood, semen ,vaginal fluid, mother's milk
- Unlike other viral infection, HIV infection seems rarely to lead to an protective immune response
- Initial acute infection is somewhat controled, but HIV continues to replicate



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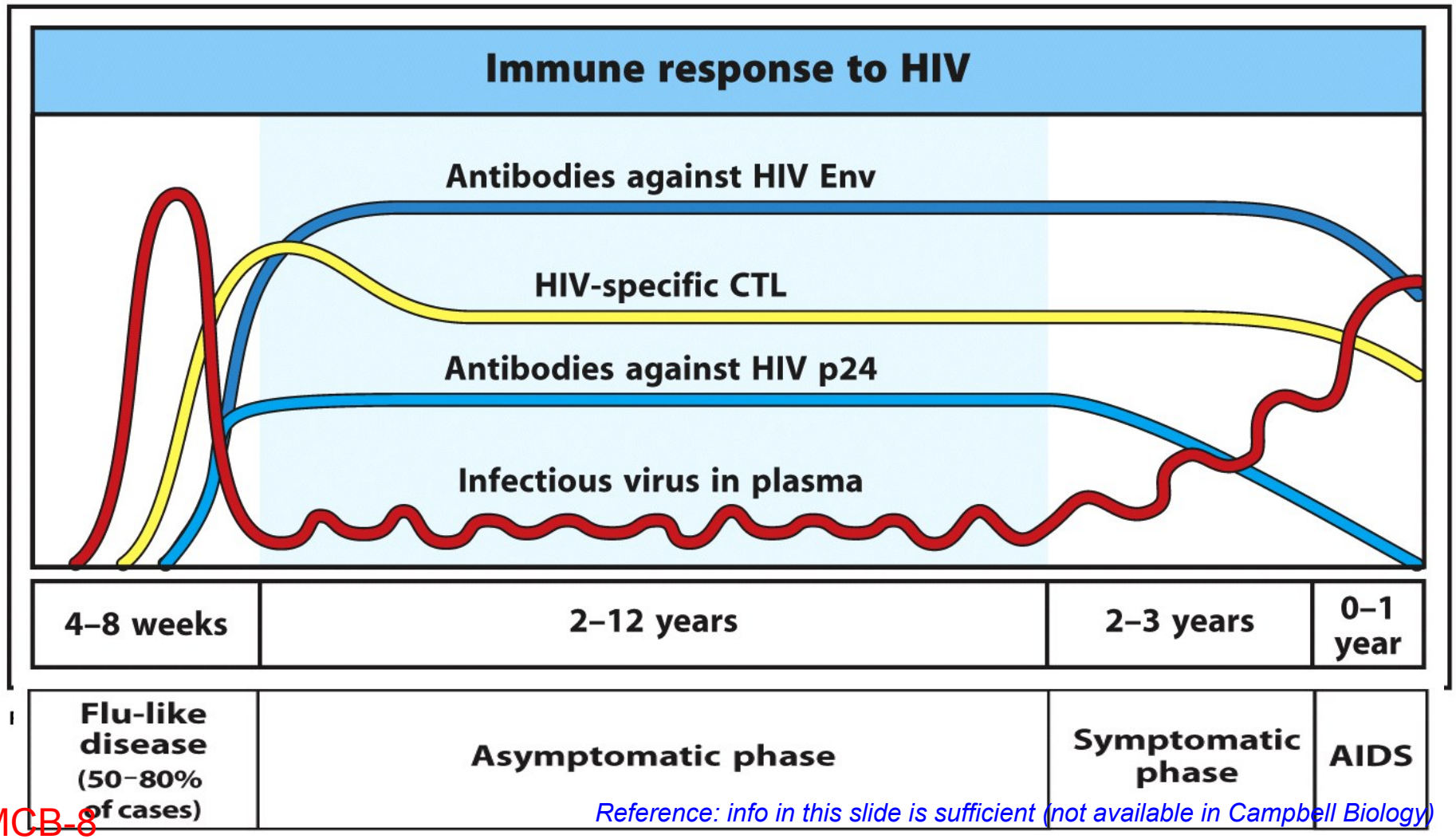
Most individuals infected with HIV progress over time to AIDS.

Course of infection

- Immune system unable to eliminate virus



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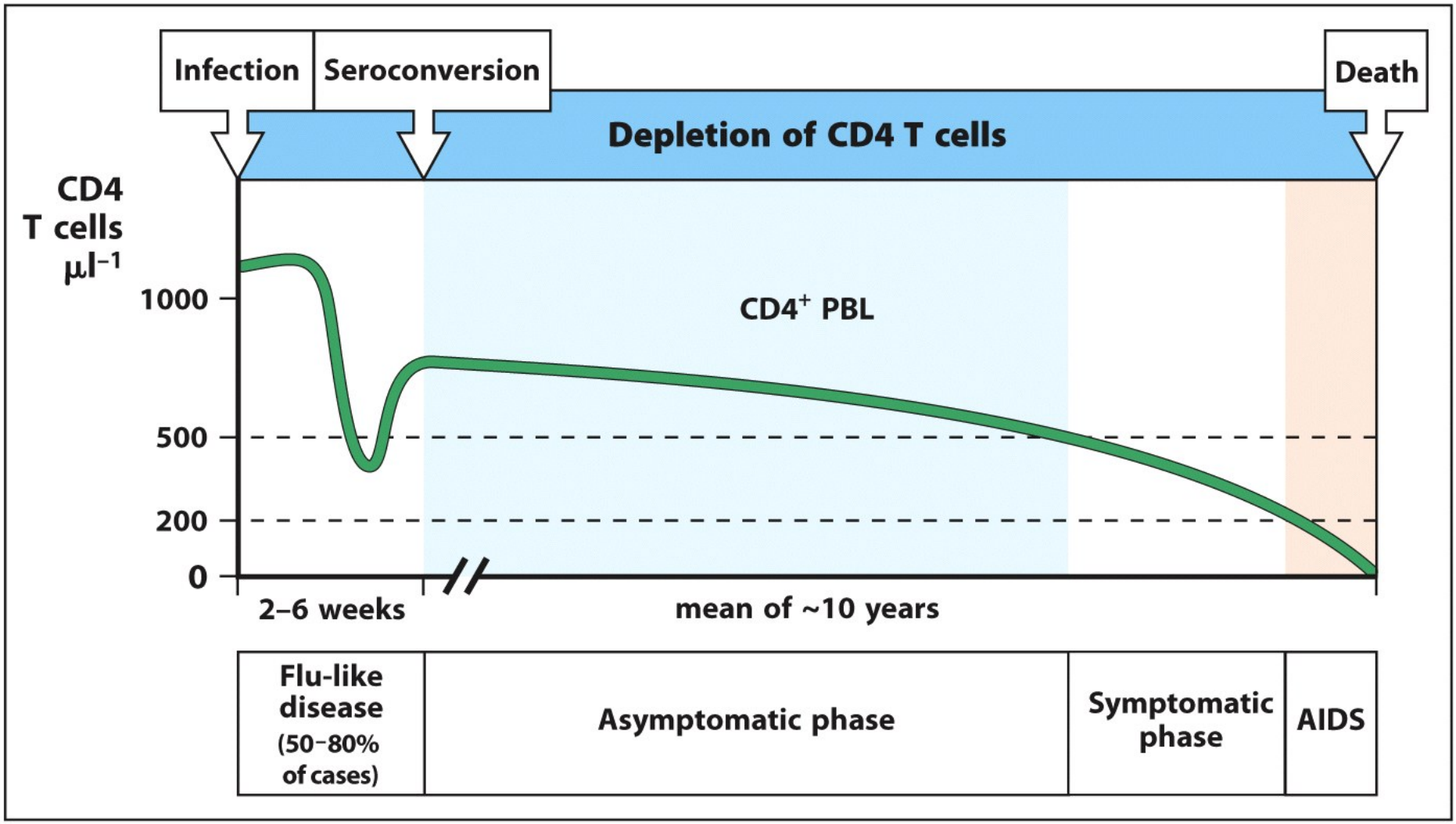
How HIV causes AIDS

Mechanisms of CD4+T cell killing



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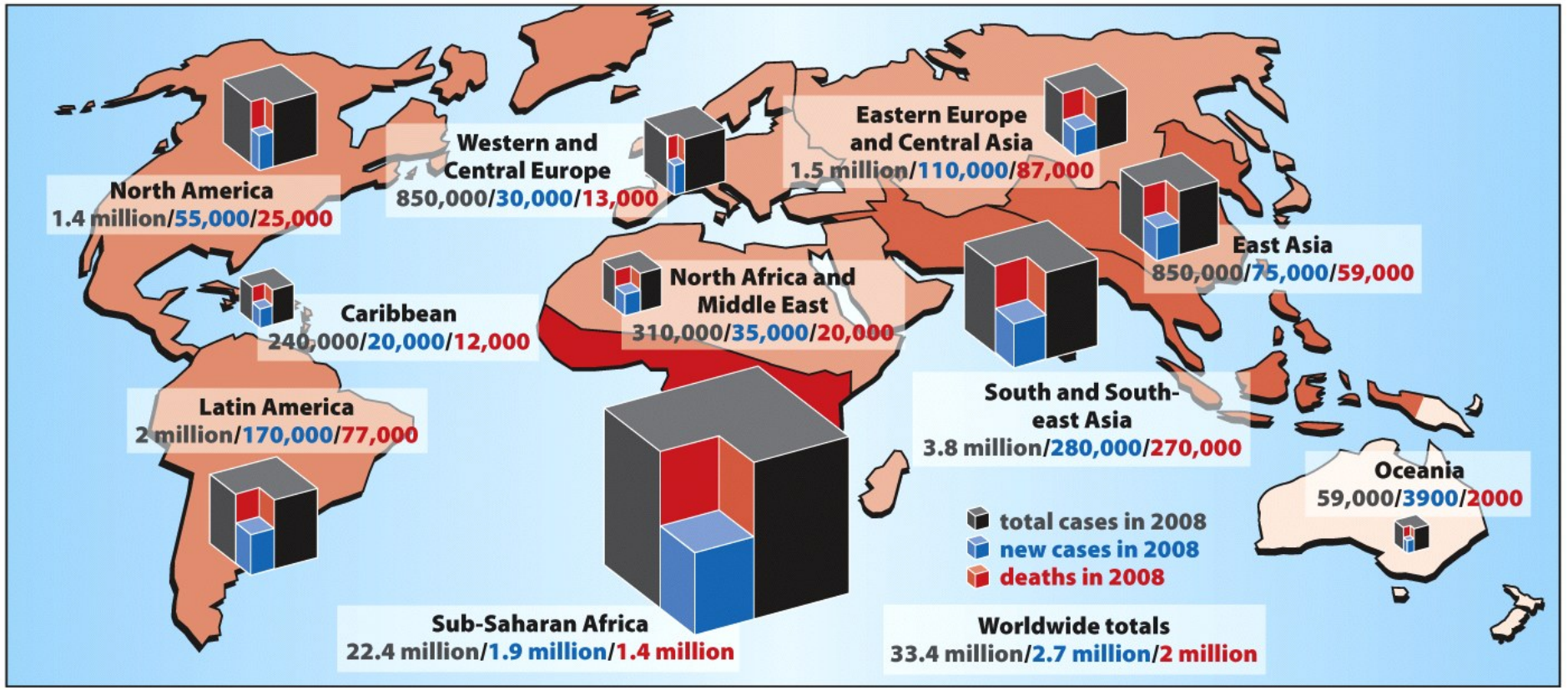
AIDS: General features & demography

- First documentation: sample of serum from Kinhasa (Republic of Congo) stored in 1959
- Official report of first case -1981, HIV discovered on 1983
- Susceptibility to infection with opportunistic pathogen
- Two types of HIV: HIV-1 (highly virulent) & HIV-2



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How genetics play a role in sensitivity to HIV infection?

Genetic variation in the host can alter the rate of progression of disease.

Genes that influence progression to AIDS				
Gene	**Allele**	**Mode**	**Effect**	**Mechanism of action**
HIV entry				
CCR5	Δ32	Recessive	Prevents infection	Knockout of CCR5 expression
		Dominant	Prevents lymphoma (L)	Decreases available CCR5
			Delays AIDS	
	P1	Recessive	Accelerates AIDS (E)	Increases CCR5 expression
CCR2	I64	Dominant	Delays AIDS	Interacts with and reduces CXCR4
CCL5	In1.1c	Dominant	Accelerates AIDS	Decreases CCL5 expression
CXCL12	3′A	Recessive	Delays AIDS (L)	Impedes CCR5–CXCR4 transition (?)
CXCR6	E3K	Dominant	Accelerates *P. carinii* pneumonia (L)	Alters T-cell activations (?)
CCL2-CCL7-CCL11	H7	Dominant	Enhances infection	Stimulates immune response (?)

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Reference: info in this slide is sufficient (not available in Campbell Biology)

How genetics play role in sensitivity to HIV infection?

Genes influences progression of AIDS

Genes that influence progression to AIDS				
Gene	**Allele**	**Mode**	**Effect**	**Mechanism of action**
Cytokine anti-HIV				
IL10	5′A	Dominant	Limits infection	Decreases IL-10 expression
			Accelerates AIDS	
IFNG	−179T	Dominant	Accelerates AIDS (E)	
Acquired immunity, cell mediated				
HLA	A, B, C	Homozygous	Accelerates AIDS	Decreases breadth of HLA class I epitope recognition
	*B*27*	Codominant	Delays AIDS	Delays HIV-1 escape
	*B*57*			
	*B*35-Px*		Accelerates AIDS	Deflects CD8-mediated T-cell clearance of HIV-1
Acquired immunity, innate				
KIR3DS1	3DS1	Epistatic with HLA-Bw4	Delays AIDS	Clears HIV^+, HLA^- cells (?)

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How HIV infection cause AIDS?

The destruction of immune function increases the susceptibility to opportunistic infection and eventually to death.

Infections	
Parasites	*Toxoplasma* spp. *Cryptosporidium* spp. *Leishmania* spp. *Microsporidium* spp.
Intracellular bacteria	*Mycobacterium tuberculosis* *Mycobacterium avium intracellulare* *Salmonella* spp.
Fungi	*Pneumocystis jirovecii* *Cryptococcus neoformans* *Candida* spp. *Histoplasma capsulatum* *Coccidioides immitis*
Viruses	Herpes simplex Cytomegalovirus Herpes zoster

Malignancies
Kaposi's sarcoma – (HHV8) Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma Primary lymphoma of the brain

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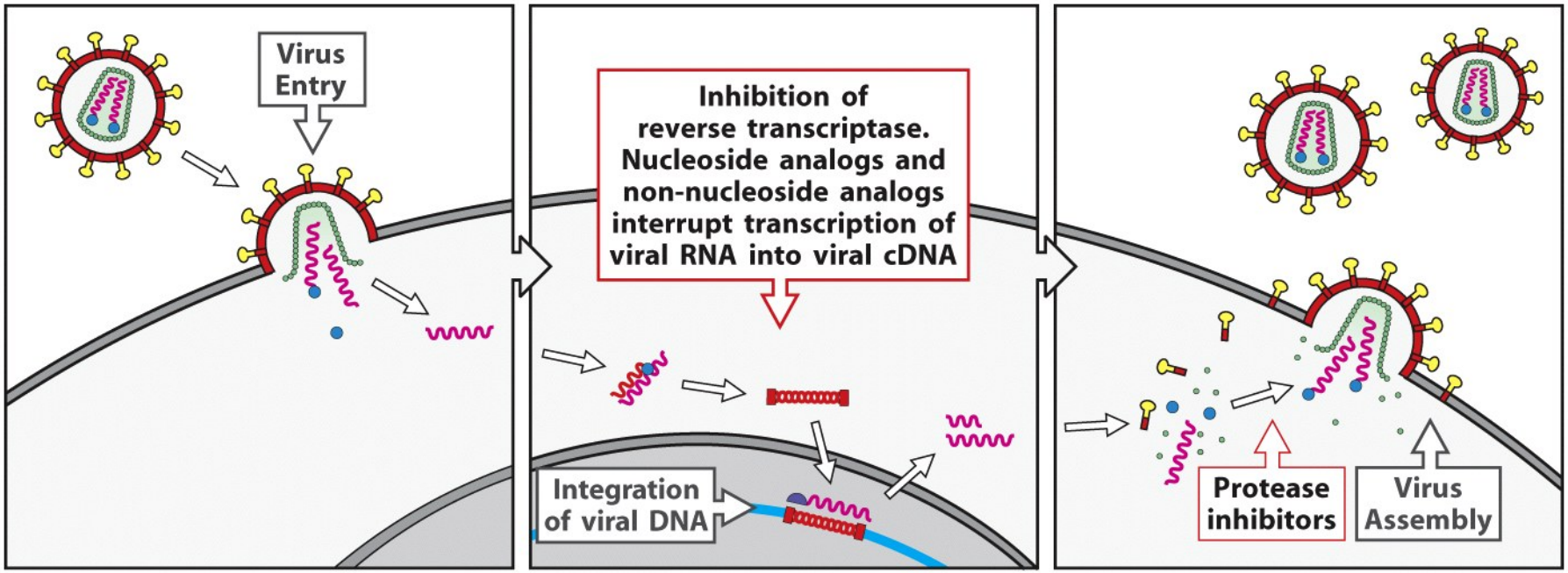
How HIV infection (AIDS patients) are treated?

- **Potential drug targets for HIV**
  - Drugs that block HIV replication lead to a rapid decrease in virus titer

    Nucleoside analogs (zidovudine (AZT)

    - Target: Reverse transcriptase
    - Mechanism of action: prevents establishment of virus into new cells



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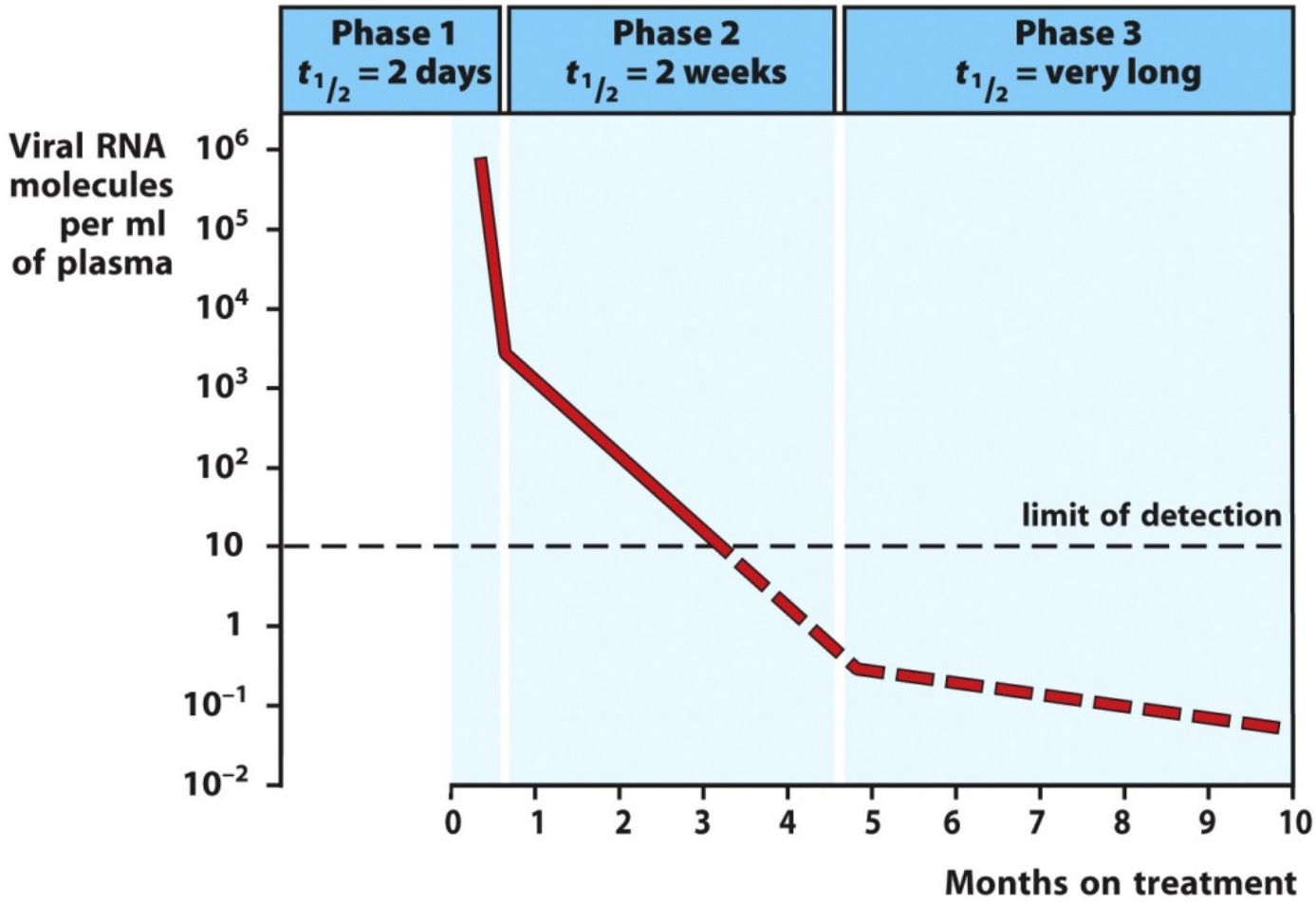
How AIDS patients are treated?

Combination therapy (HAART therapy): cocktails of protease inhibitors & nucleoside analogs



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How to control HIV infection?

Besides therapeutics, Prevention and education are one way in which the spread of HIV and AIDS can be controlled.

Challenges in HIV treatment?

HIV accumulates many mutations in the course of infection, and drug treatment is soon followed by the outgrowth of drug-resistant variants.

Reference: info in this slide is sufficient (not available in Campbell Biology)

How bacteria and virus able to cause various diseases in humans?

Two possibilities:

- Either pathogen evolve ways to evade host defense mechanisms or host has a weak immune system

1. **Pathogen (bacteria and virus) mediated mechanisms that help them evading human immune system**
   - Antigen variation
   - Immunosuppression
   - Inappropriate immune activation
   - Latency

2. **Host related immune deficiency**
   - Primary immunodeficiency
   - Acquired immunodeficiency

Reference: info in this slide is sufficient (not available in Campbell Biology)

How do we know/identify that an individual has weak immune system

- A history of repeated infections suggests a diagnosis of immunodeficiency.
- Another reasons for failure of host immune response.
- Primary immunodeficiency and secondary immunodeficiency

Reference: info in this slide is sufficient (not available in Campbell Biology)

How primary immunodeficiency occurs in human?

Primary immunodeficiency diseases are caused by inherited gene defects

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency			General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General

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How to fix the genetic defects in human?

Blood Brothers for Life: A Family's Story

When Julie and Jonathan Henderson found out that their two-year old son Nicolas had T-cell lymphoma they were devastated. They had just found out that Julie was pregnant, and what was supposed to be an exciting time preparing for the new baby, turned into months of doctor visits, hospital stays and chemotherapy. After Nicolas' chemotherapy failed to work, the Henderson's doctor tried a relatively new transplant procedure using stem cells taken from the umbilical cord blood of their newborn baby, Nathaniel.

They worked with Cryo-Cell International, Inc., the world's first private cord blood bank and fastest growing Umbilical Cord Blood Stem Cell banking company, to process, test and store Nathaniel's umbilical cord blood. Today, Nicolas is a happy, energetic four-year-old who is in remission. He and his baby brother Nathaniel share a special bond.

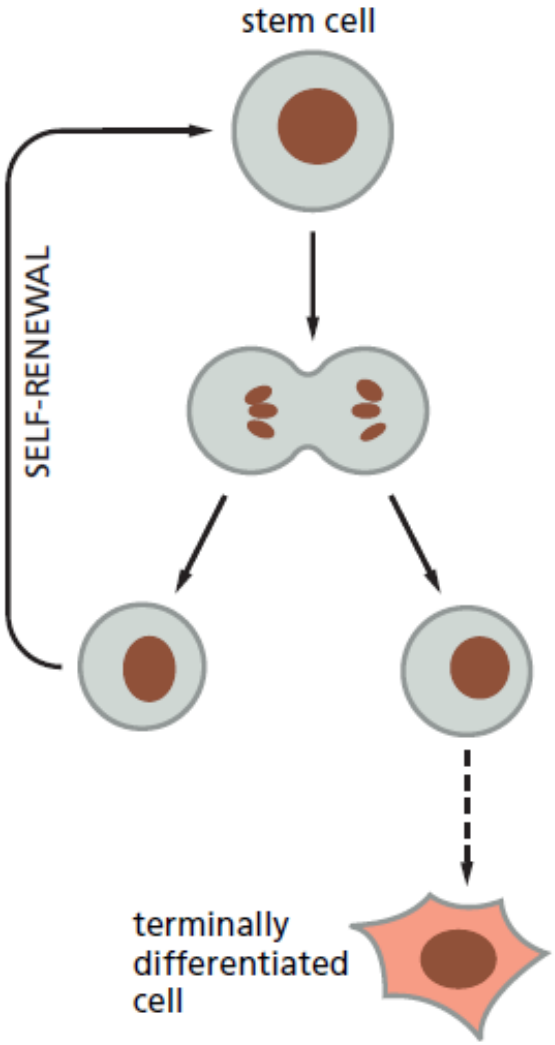
HOW CAN UMBILICAL CORD CELLS BE USED TO CURE DISEASE?

Stem Cells

Definition:

- Able to divide
- Capable of differentiation
- Not terminally differentiated
- Daughter cells can remain in undifferentiated state or differentiate

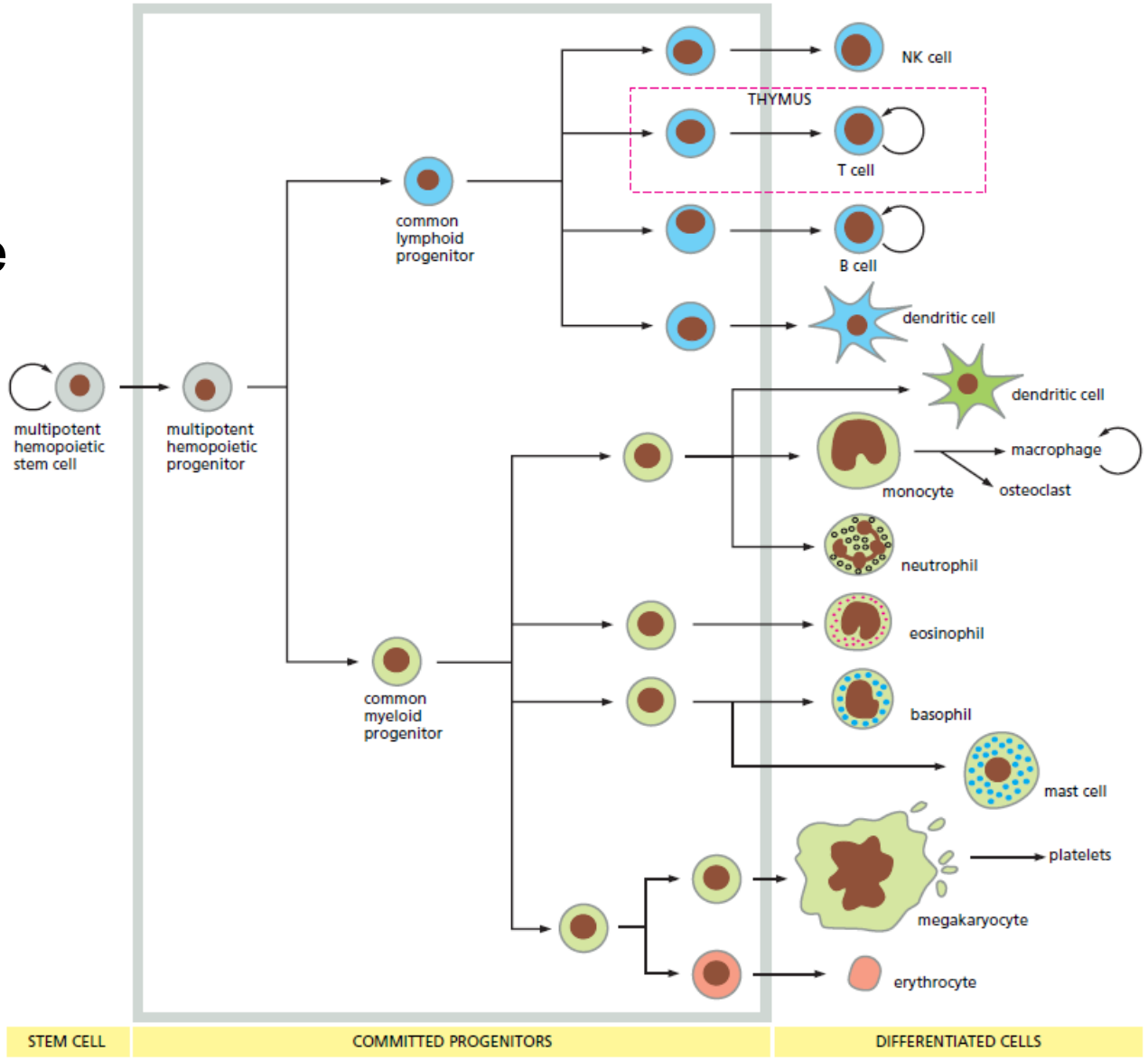
Examples: Epidermal stem cells, hematopoietic stem cells etc.



Hematopoiesis

- Stem cells are multipotent, can give rise to the complete range of blood cell types

- Commitment is a stepwise process followed by terminal differentiation

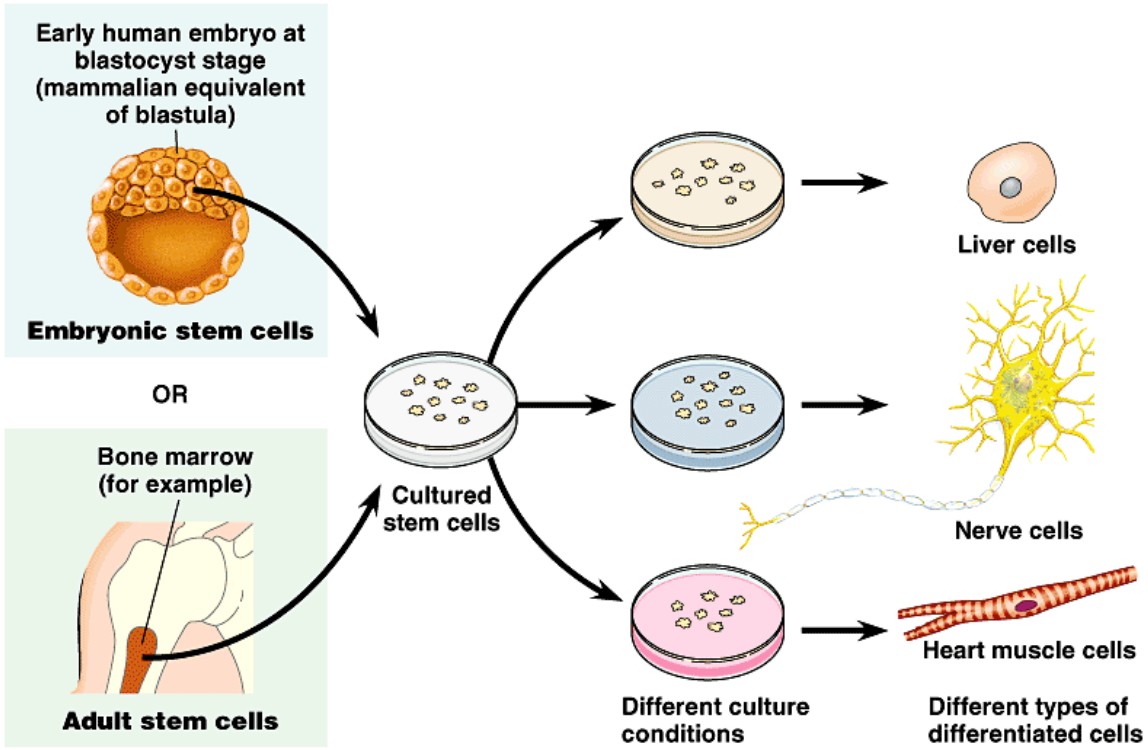


Embryonic Stem Cell

- Stem Cells in the adult body are tissue-specific

Each type of specialized cell has a memory of its developmental history and seems fixed in its specialized fate

- Patient-specific ES cells could solve the problem of immune rejection
- ES cells can make any part of the body



Embryonic Stem Cell

• ES cells can be derived from early human embryos and from human fetal germ cells

• ES cells can be induced to differentiate into a wide variety of cell types in culture, by treatment with appropriate combinations of signal proteins and growth factors

• Ethical objections to use of human embryos as stem cell reservoir

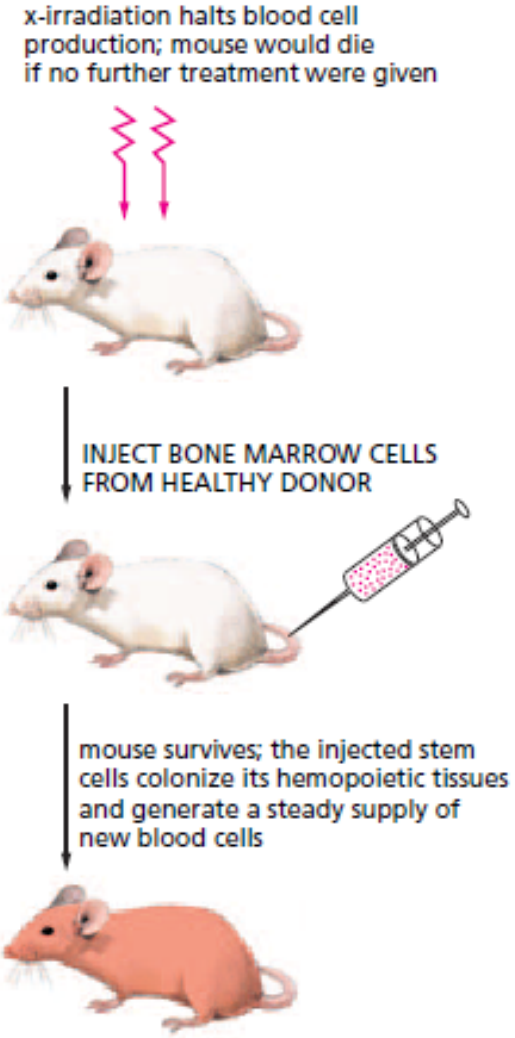
• Conversion of somatic cell to ES cell by manipulating gene expression

How stem cell transplantation work: Experiment

- X-ray irradiated mouse can be saved by transfusion of cells taken from the bone marrow of a healthy, immunologically compatible donor

- Hematopoietic stem cells can be isolated from bone marrow using Fluorescence Activated Cell Sorter (FACS)

- Stem cell population in bone marrow is rather low (~ 1 in 10000)



How to fix the primary immunodeficiency in human?

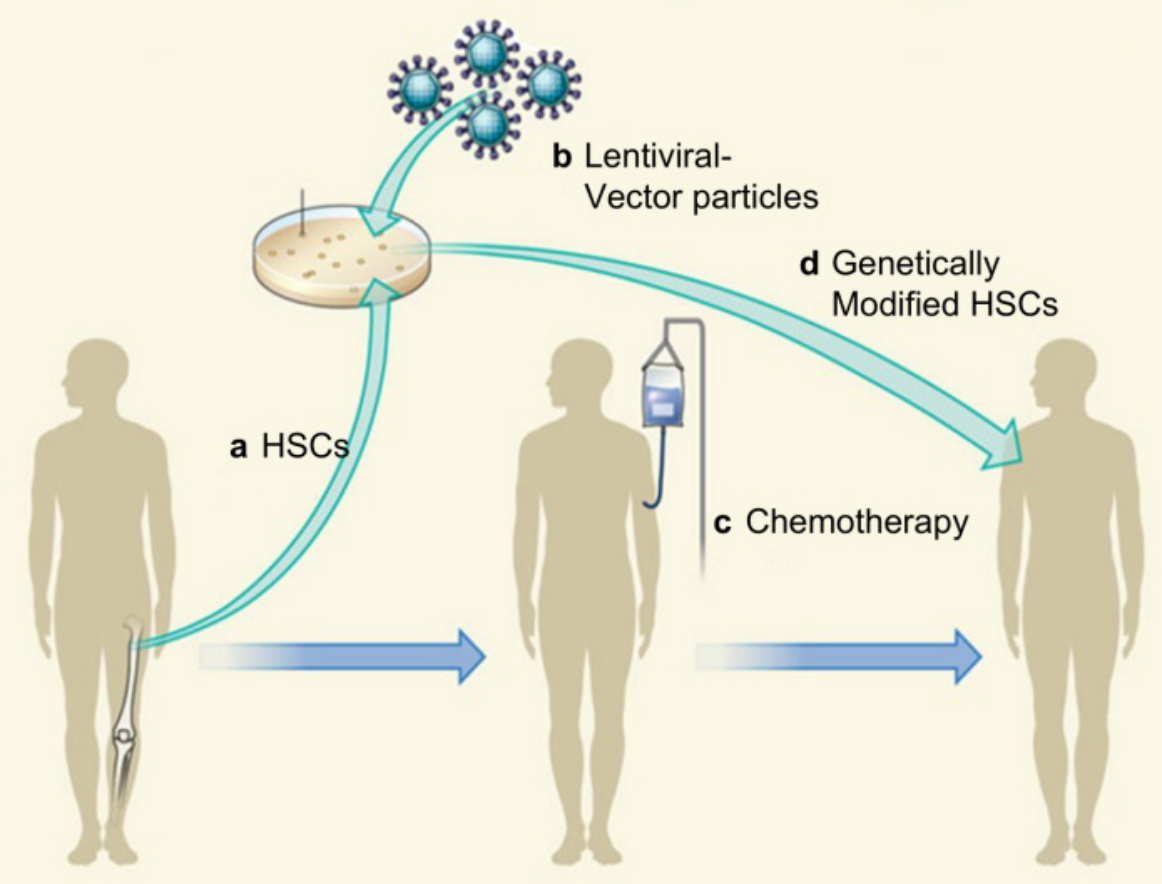
Somatic gene therapy

Principle:

- Correct the defective copy of gene by replacing with correct gene using retroviral vector

Severe complication: malignancy (5/10 patient treated for X-SCID developed leukemia)

Alternate solution: induced pluripotent cells (iPS)



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