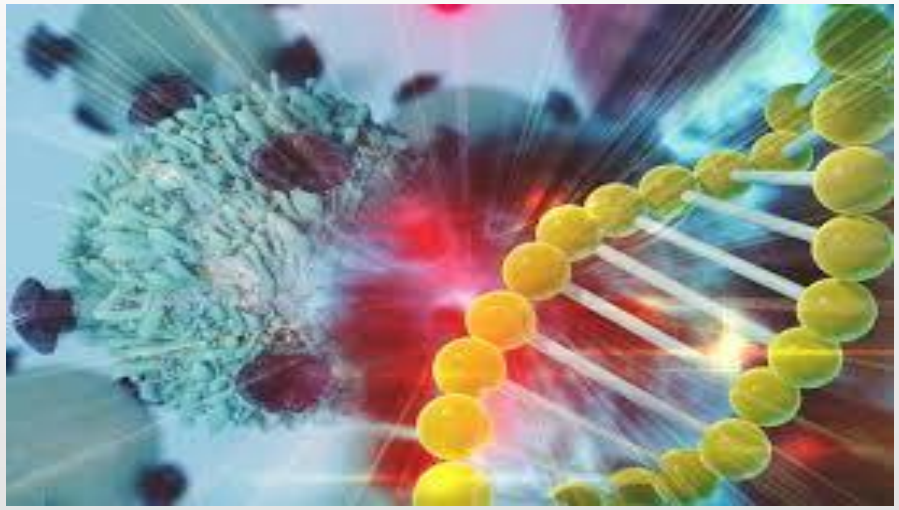


PSMU
DEPARTMENT OF MICROBIOLOGY, VIROLOGY AND IMMUNOLOGY

Lecture:

Retroviruses, general characteristics.

Oncoviruses. HIV.

For two-way communication

between the lecturer and students during the lecture,
please contact the following e-mail address:

v.fedorchenko@pdmu.edu.ua

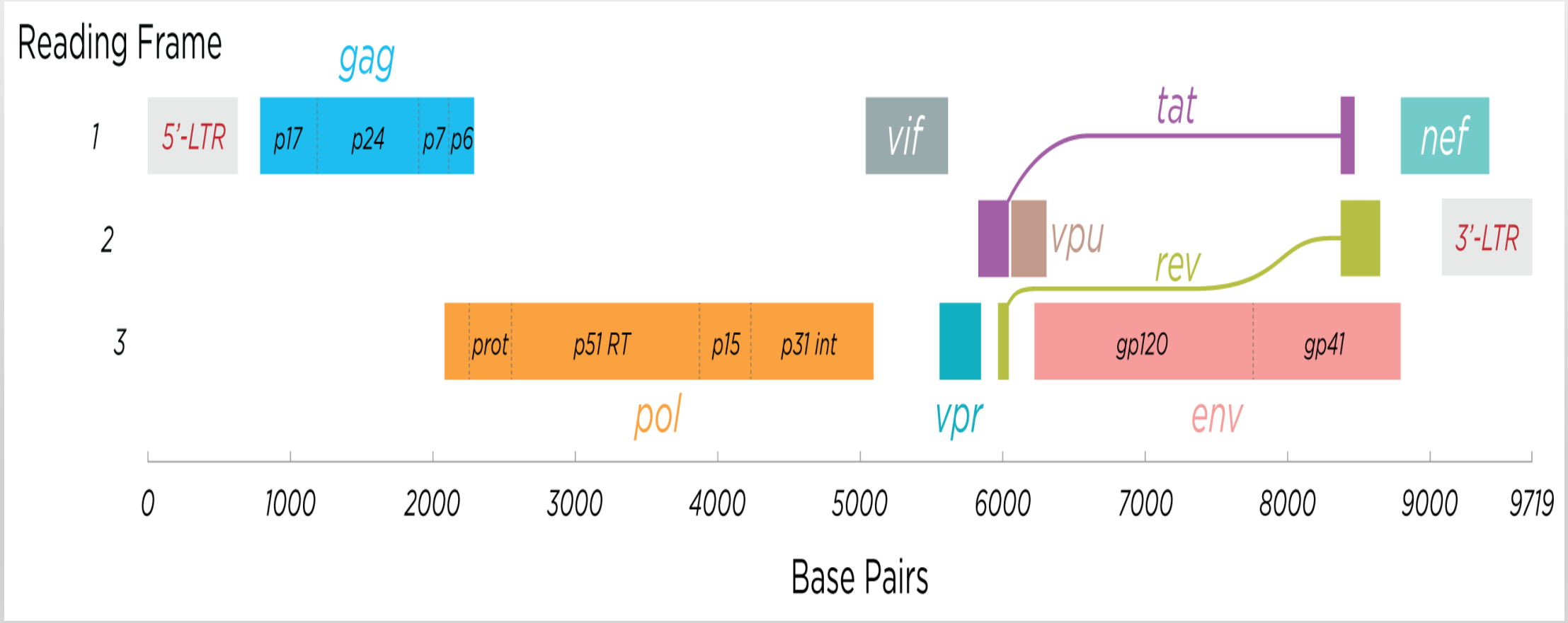
HISTORICAL PERSPECTIVES OF AIDS

1981	Recognition of Pneumocystis carinii pneumonia (PCP) and Kaposi's sarcoma (KS) in young healthy men in NYC and Los Angeles
1982	GRID to AIDS by CDC
1983	Isolation of Lymphadenopathy-Associated Virus (LAV) by Pasteur Institute (Luc Montagnier)
1984	Isolation of Human T-Lymphotrophic Virus , Type III (HTLV-III) by NCI/NIH (Robert Gallo)
1986	Recommendation of the name Human Immunodeficiency Virus (HIV) by an international subcommittee on virus taxonomy

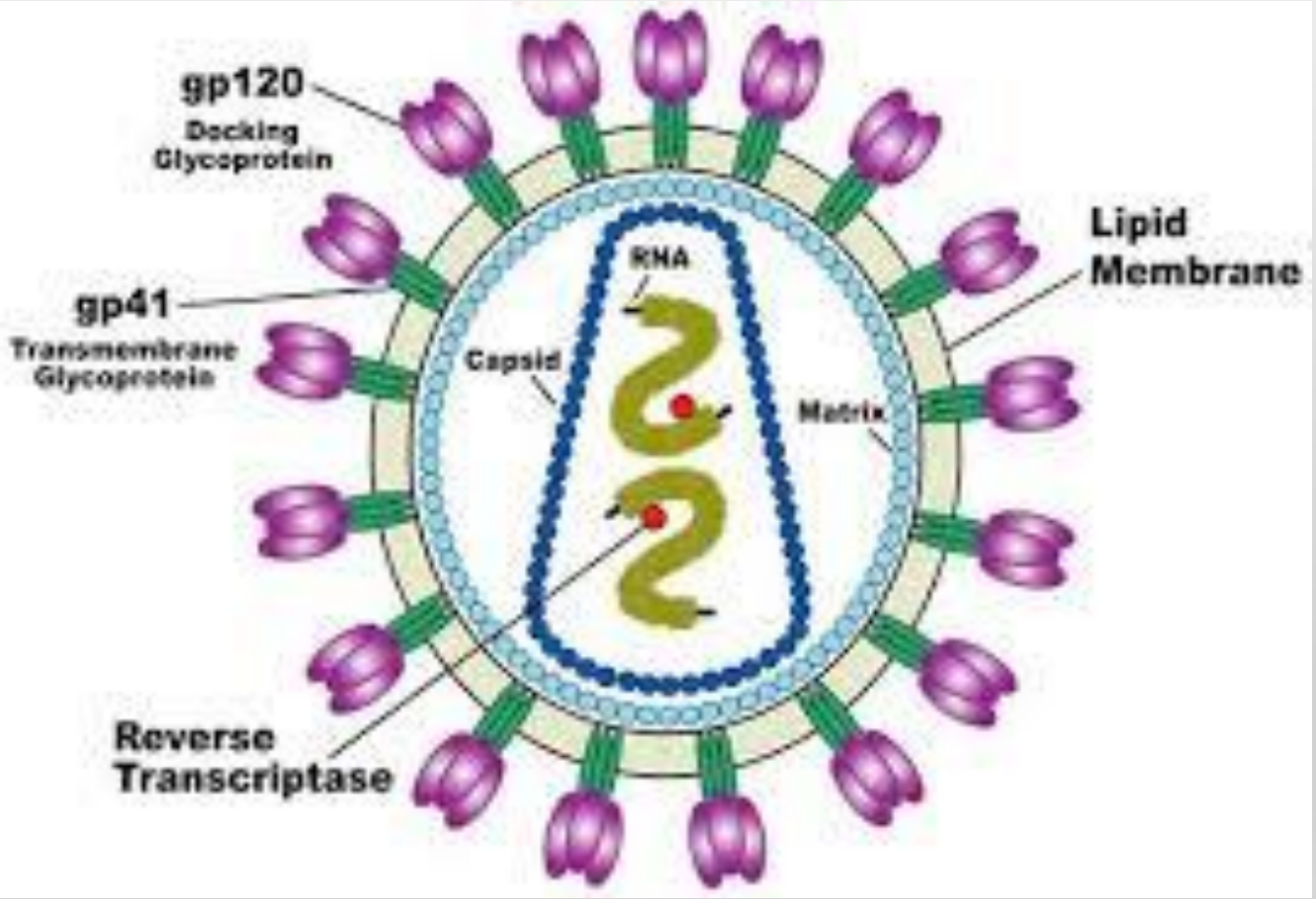
What Is HIV/AIDS?

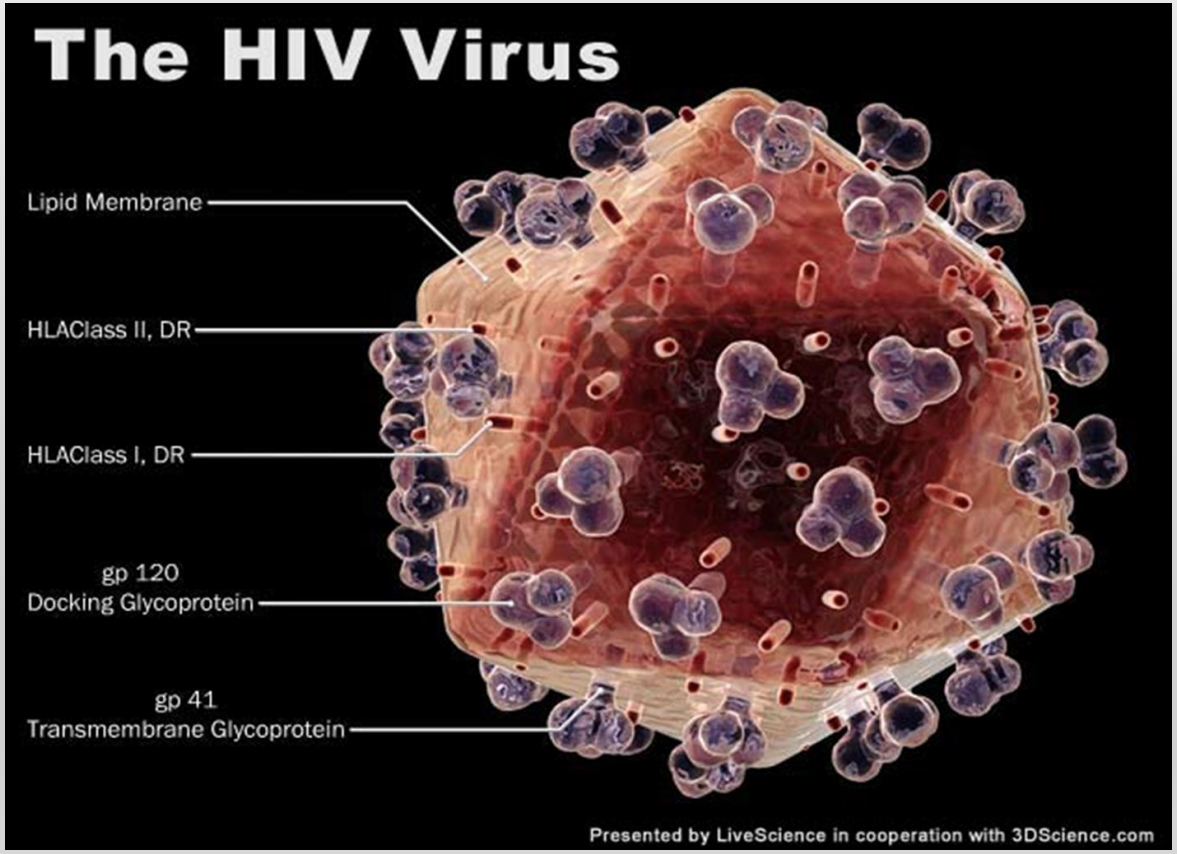
- Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV).
- HIV attacks and destroys white blood cells, causing a defect in the body's immune system.

Genome

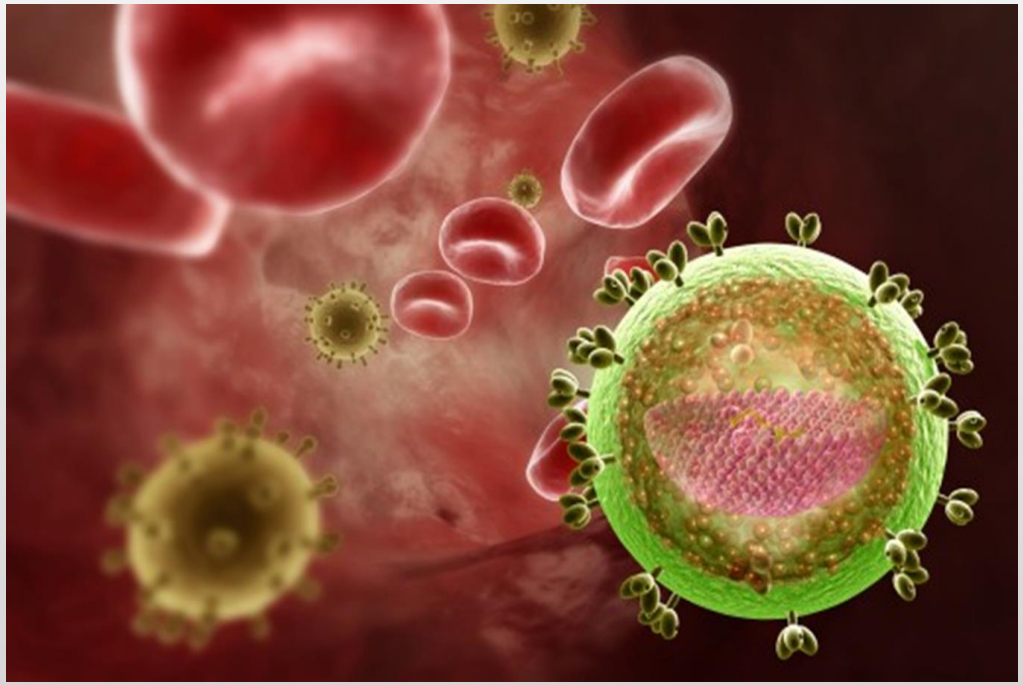

Reading Frame
gag
1
5'-LTR
p17
p24
p7
p6
vif
tat
nef
2
vpu
rev
3'-LTR
3
prot
p51 RT
p15
p31 int
gp120
gp41
pol
vpr
env
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
9719
Base Pairs

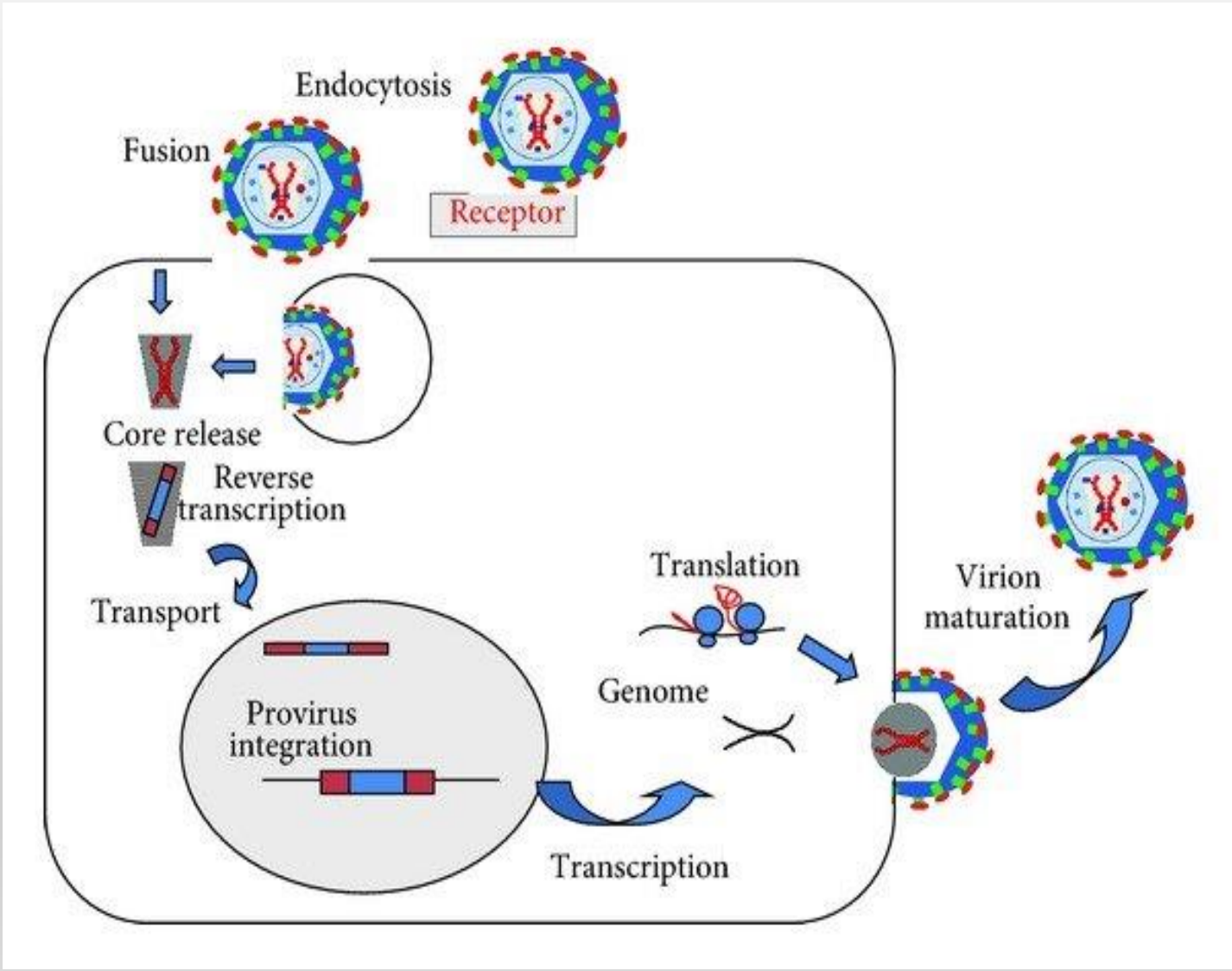
Structure


gp120
Docking
Glycoprotein
gp41
Transmembrane
Glycoprotein
Lipid
Membrane
RNA
Capsid
Matrix
Reverse
Transcriptase


The HIV Virus
Lipid Membrane
HLAClass II, DR
HLAClass I, DR
gp 120
Docking Glycoprotein
gp 41
Transmembrane Glycoprotein
Presented by LiveScience in cooperation with 3DScience.com

Life cicle




Endocytosis
Fusion
Receptor
Core release
Reverse transcription
Transport
Translation
Virion maturation
Genome
Provirus integration
Transcription

Epidemiology

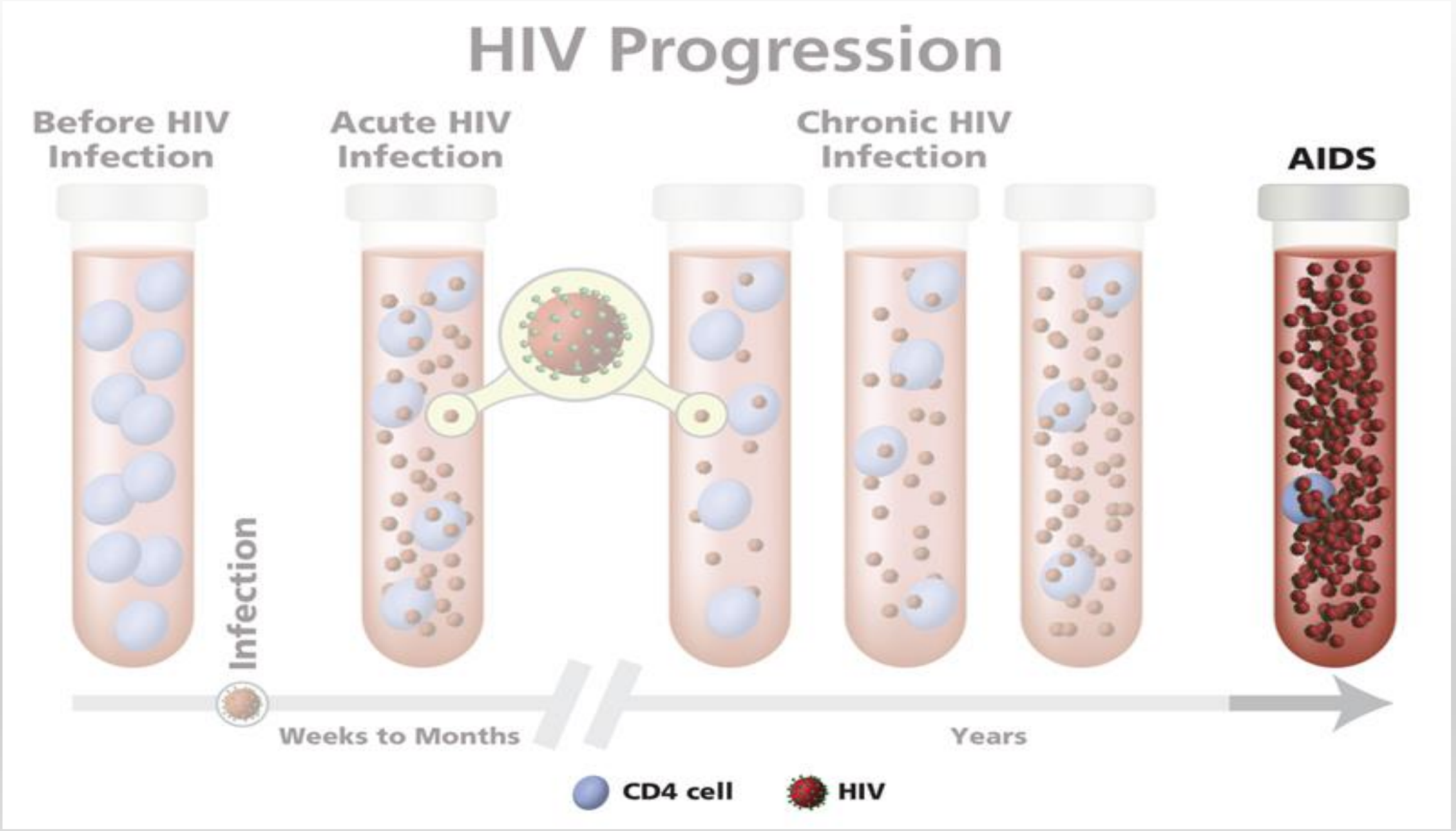
Unprotected sexual intercourse with an infected partner

Vertical transmission
(from mother to child)

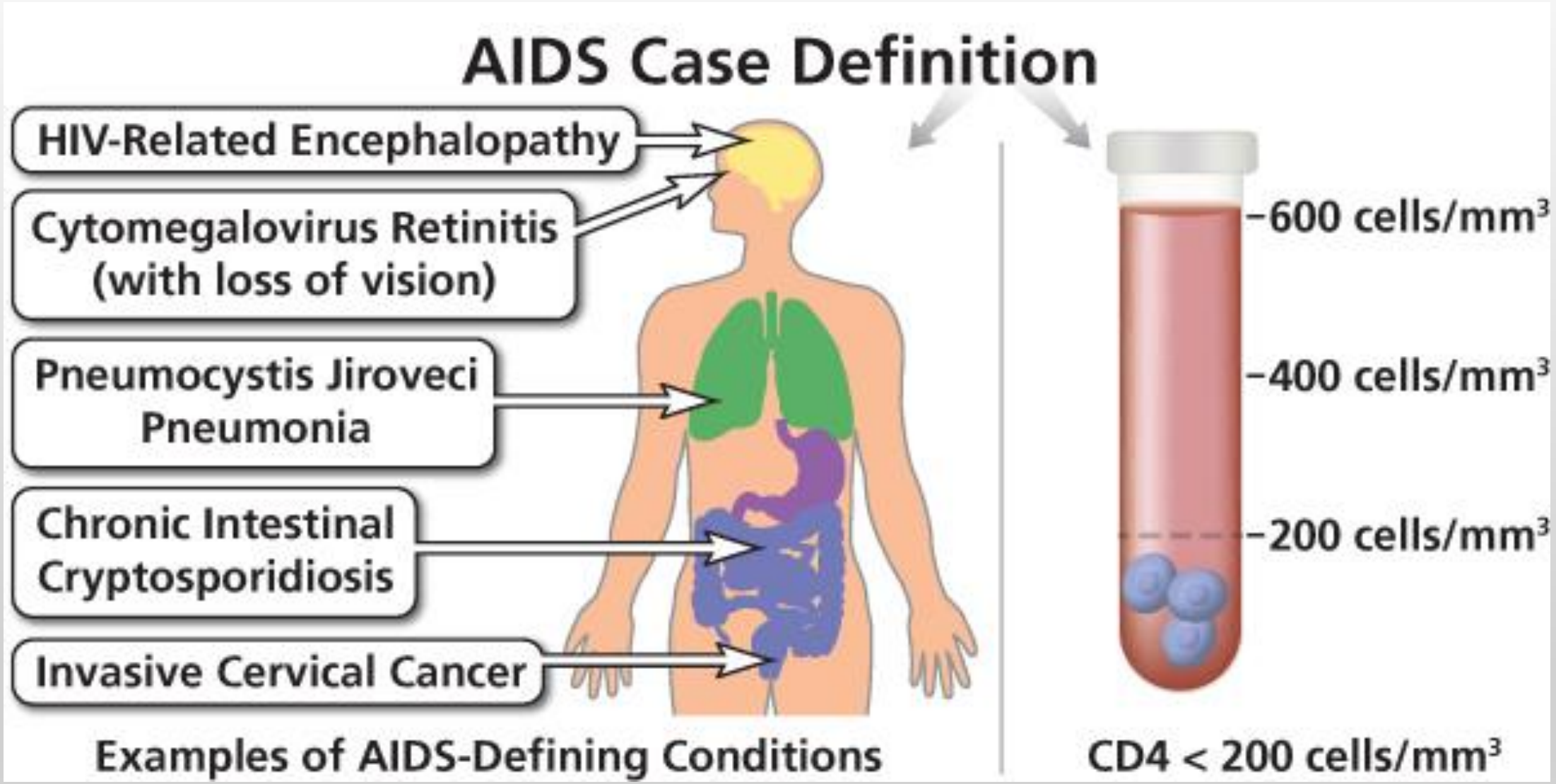
- in utero
- during delivery
- breastmilk

Injection drug use
(rare: infected blood/blood products)

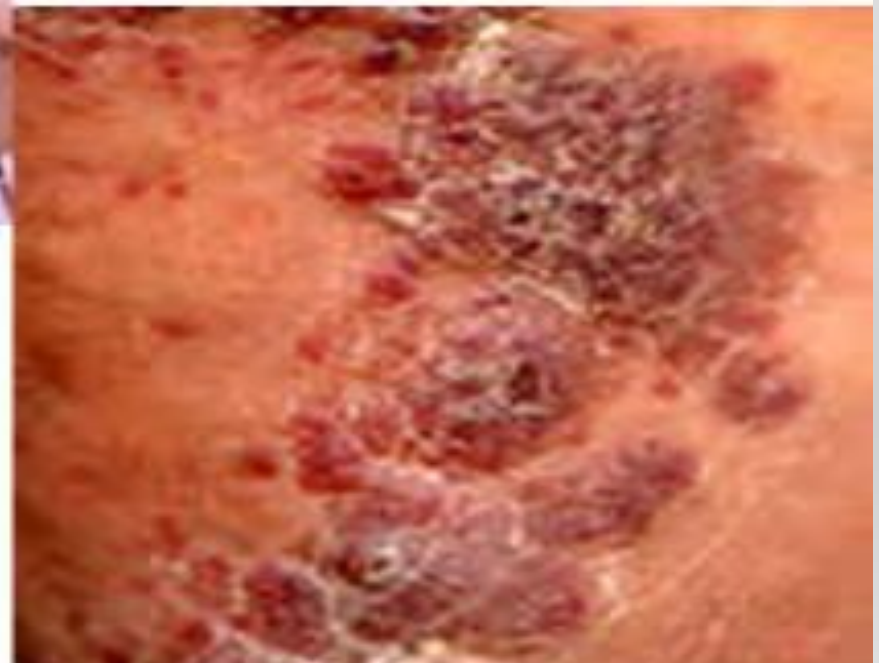
HIV infection


HIV Progression
Before HIV Infection
Acute HIV Infection
Chronic HIV Infection
AIDS
Infection
Weeks to Months
Years
CD4 cell
HIV

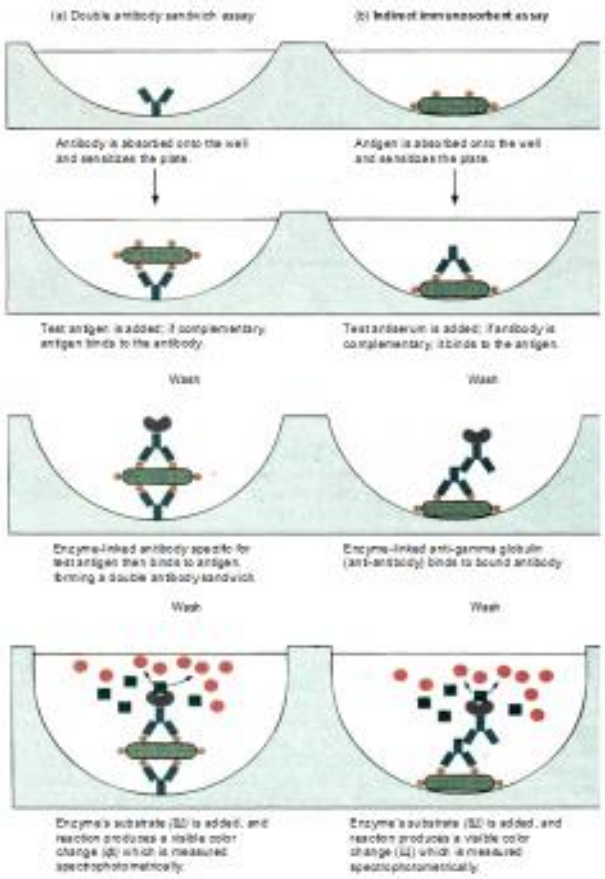
AIDS Case Definition

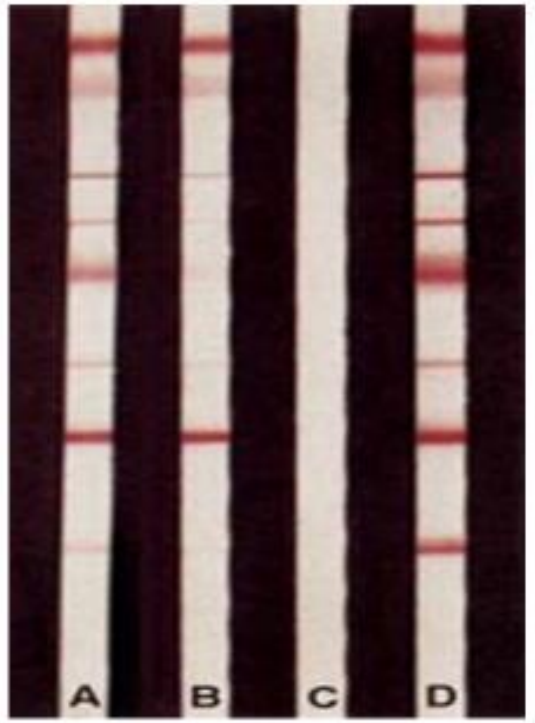


Kaposi sarcoma

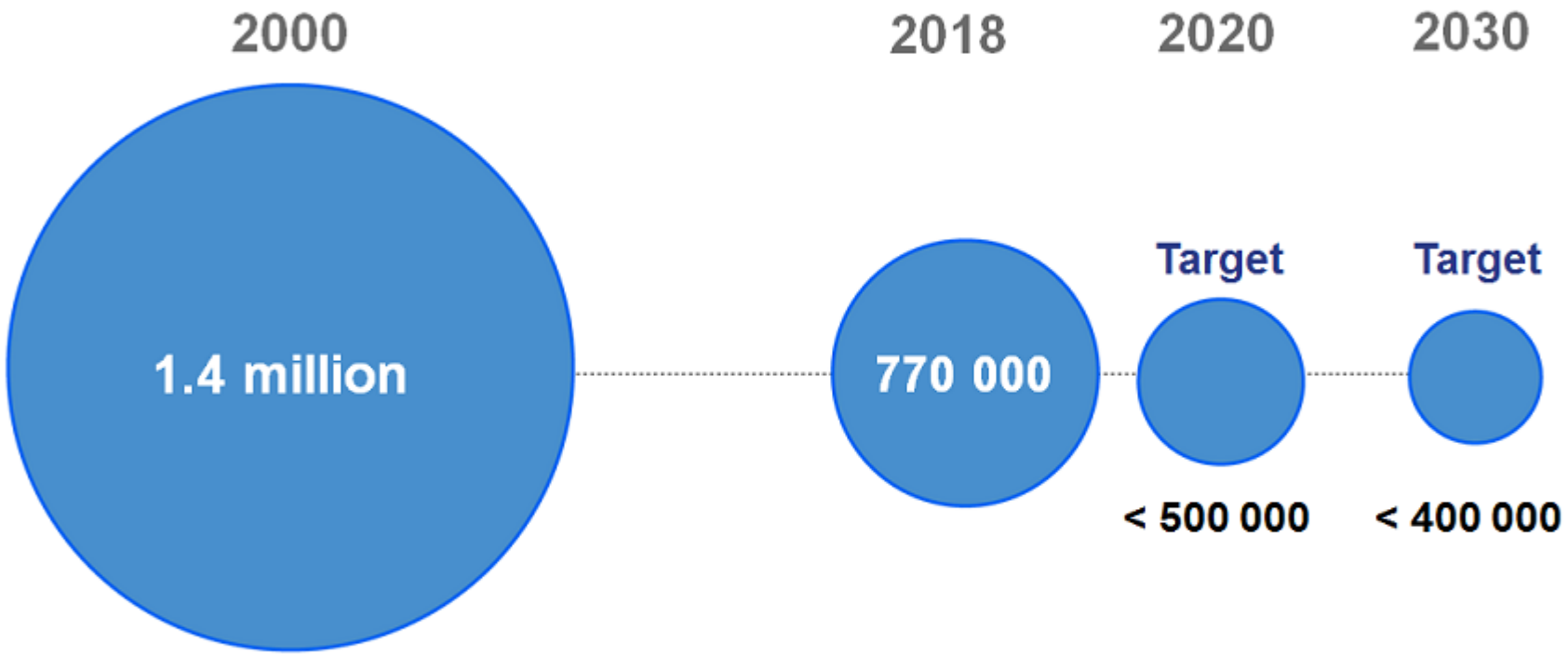


Laboratory diagnostics





Number of HIV-related deaths



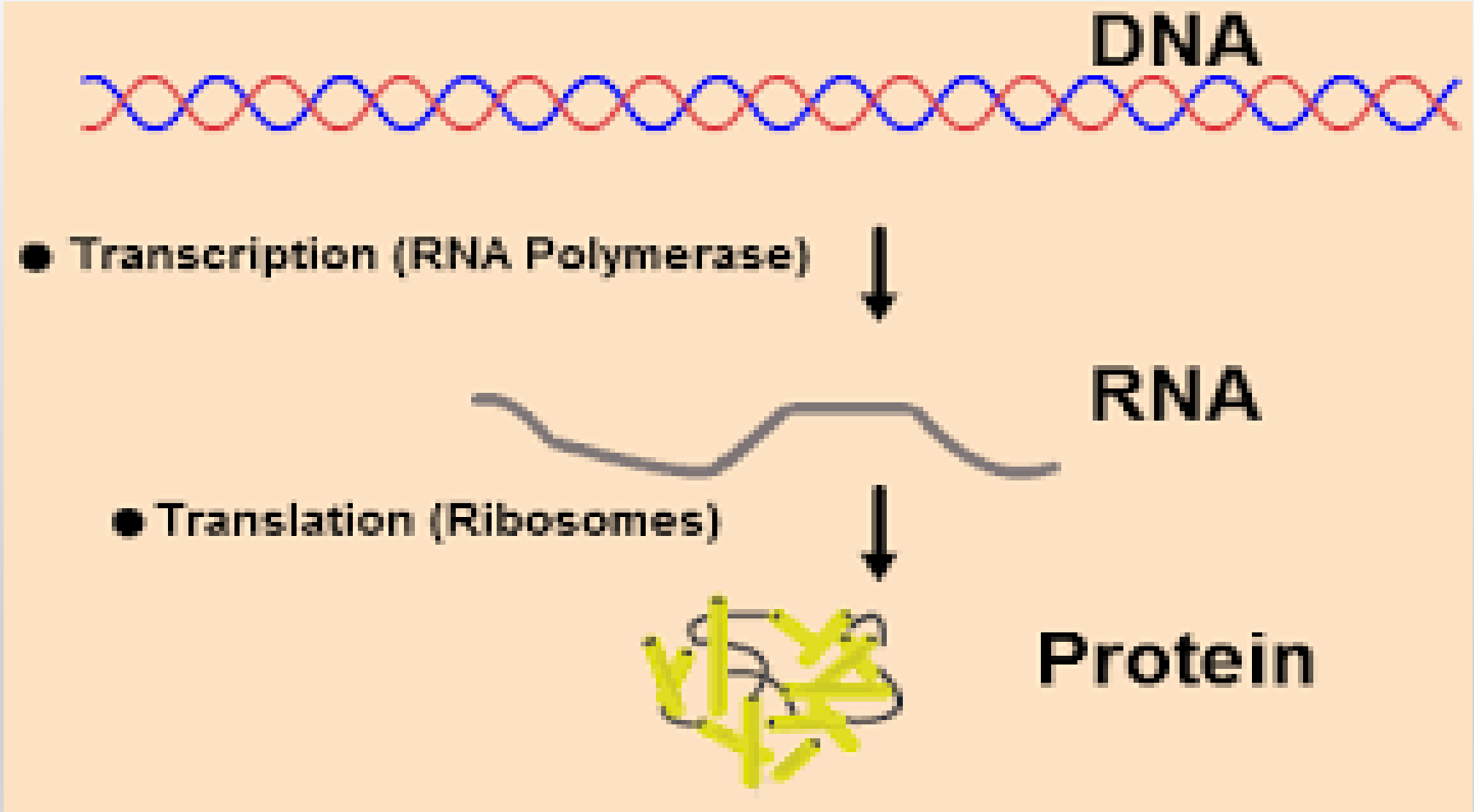
Source: UNAIDS/WHO estimates

World Health Organization

DEFINITION :-

- Transcription is synthesis of single stranded RNA from a double stranded DNA template. Its produces messenger RNA (mRNA).

- Translation is the 1st stage of protein biosynthesis from RNA. In this process formation of a polypeptide by using mRNA as a template. It occurs in ribosomes.
- Transcription and Translation both process are the part of gene expression.


DNA
Transcription (RNA Polymerase)
RNA
Translation (Ribosomes)
Protein

Definition

Gene promoters are DNA sequences located upstream of gene coding regions and contain multiple cis-acting elements, which are specific binding sites for proteins involved in the initiation and regulation of transcription

In most transcription units, the promoters is located next to transcription start site but is not itself transcribed

Apoptosis - Definition

- A pathway of cell death induced by a tightly regulated suicidal program, in which the cells destined to die activate enzymes that degrade cells own nuclear DNA and nuclear, cytoplasmic proteins.

DEFINITION

- Willis, definition of neoplasm
- A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and persist in the same excessive manner after cessation of the stimuli which evoke the change.

Classification of Anti-Retroviral drugs (Anti-HIV drugs):

- The Anti-HIV drugs can be classified into

1. **Nucleoside reverse transcriptase inhibitors (NRTIs):** Zidovudine, Stavudine, Lamivudine, Abacavir, Zalcitabine, Emtricitabine, Didanosine.

2. **Non nucleoside reverse transcriptase inhibitors (NNRTIs):** Efavirenz, Nevirapine, Delaviridine.

3. **Nucleotide reverse transcriptase inhibitors (NTRTIs):** Tenofovir

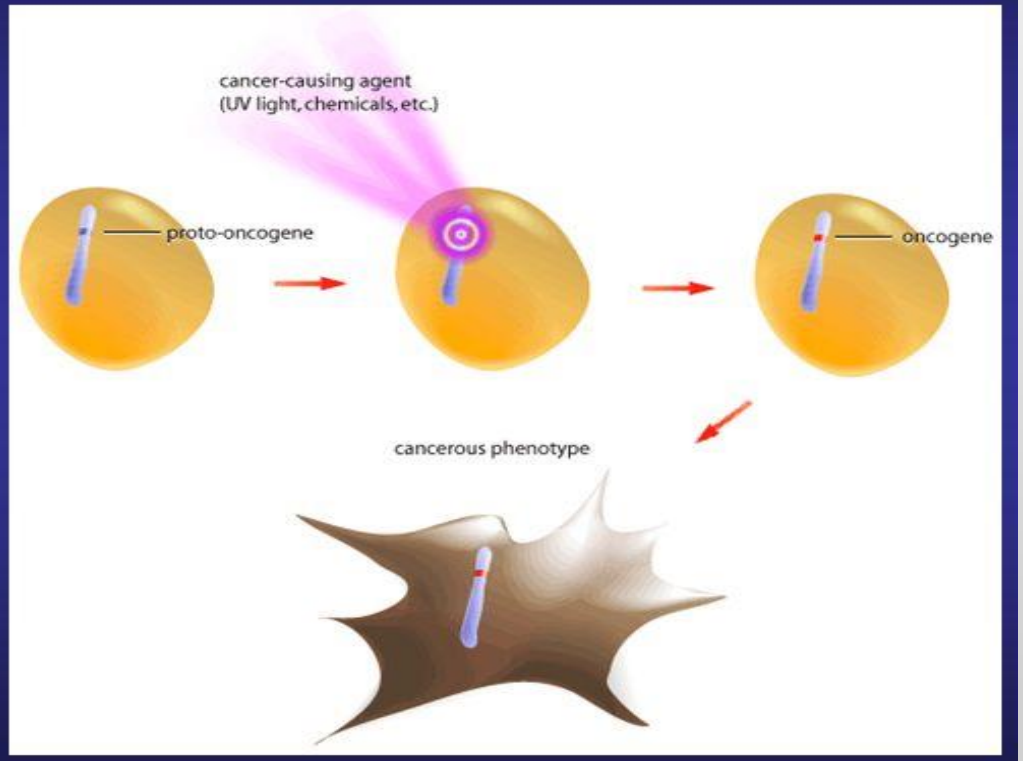
4. **Protease inhibitors (PIs):** Saquinavir, Indinavir, Nelfinavir, Amprenavir, Fosamprenavir, Ritonavir, Lopinavir, Atazanavir.

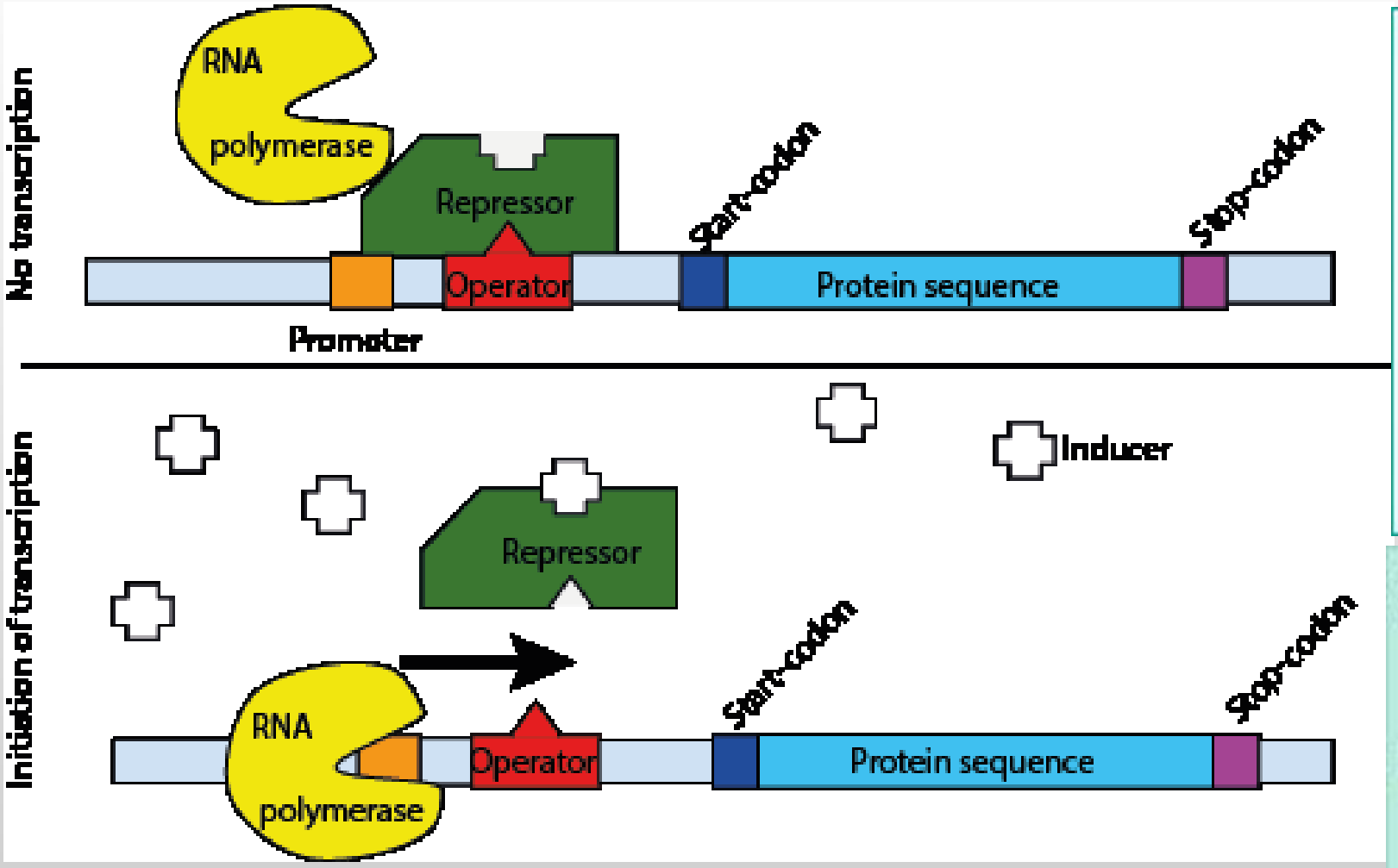
5. **Entry/Fusion inhibitors:** Enfuvirtide

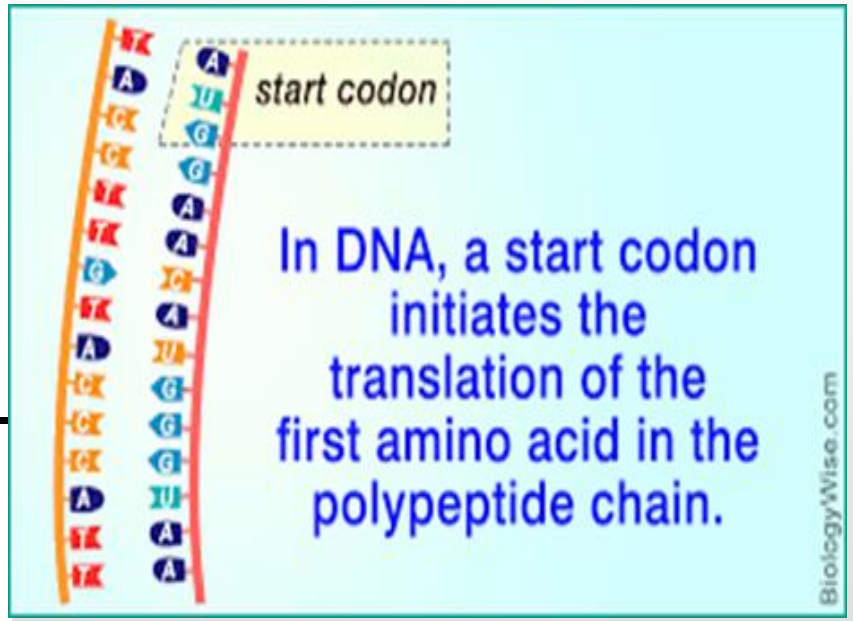
Oncogenes

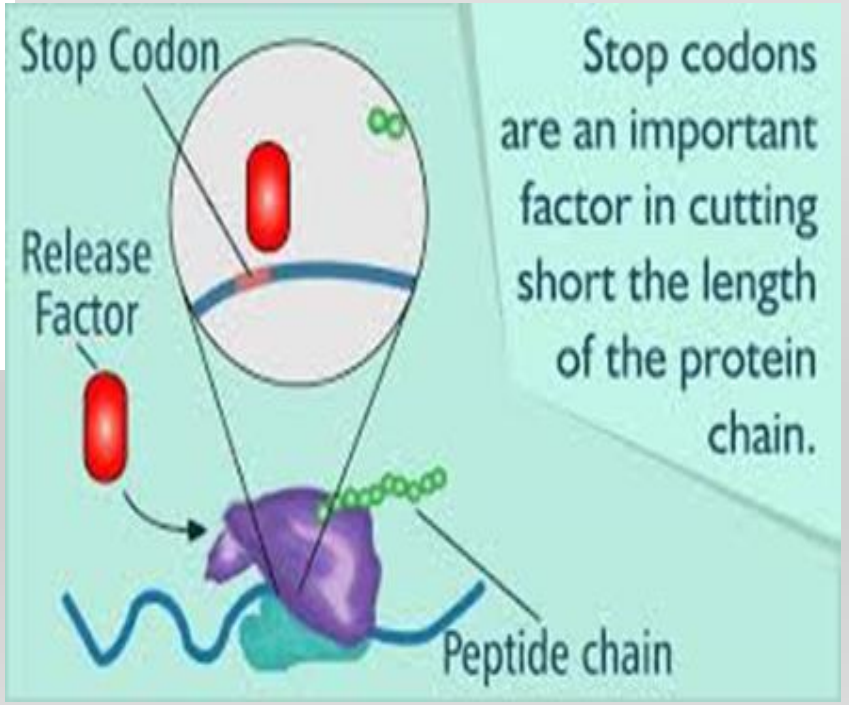
Definition: Oncogenes are genes whose expression causes cells to become cancerous.

Tumorigenic mechanism: The normal version of the gene (termed a proto-oncogene) becomes mutated so that it is overactive. Because of their overactivity, oncogenes are genetically dominant over proto-oncogenes, that is only one copy of an oncogene is sufficient to cause a change in the cell's behavior.




No transcription
RNA
polymerase
Repressor
Start-codon
Stop-codon
Operator
Protein sequence
Promoter
Initiation of transcription
Inducer
Repressor
RNA
polymerase
Operator
Start-codon
Stop-codon
Protein sequence

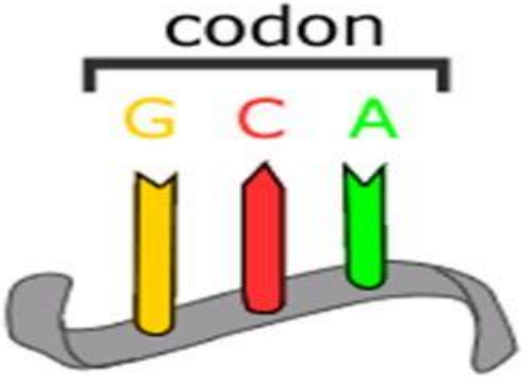

start codon
In DNA, a start codon initiates the translation of the first amino acid in the polypeptide chain.
BiologyWise.com


Stop Codon
Release Factor
Stop codons are an important factor in cutting short the length of the protein chain.
Peptide chain

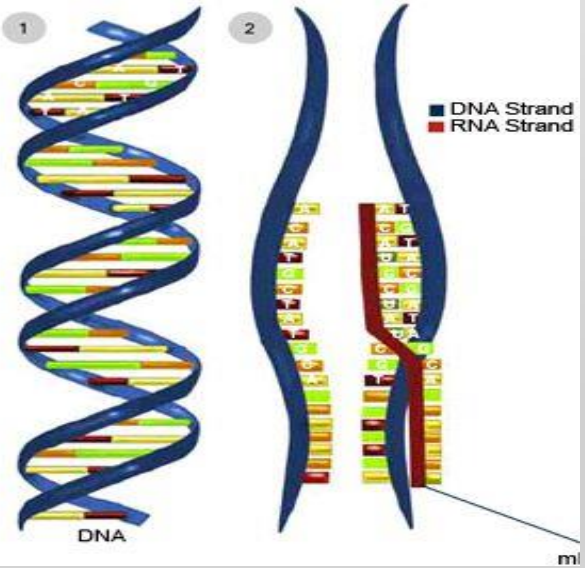
Definitions…

- **CODON** – triplet of bases on an mRNA strand 3.5.3

- **RNA polymerase** – forms an mRNA strand complementary to the ANTI-SENSE strand of DNA (the strand acting as the template) 3.5.2



1 codon = 1 amino acid



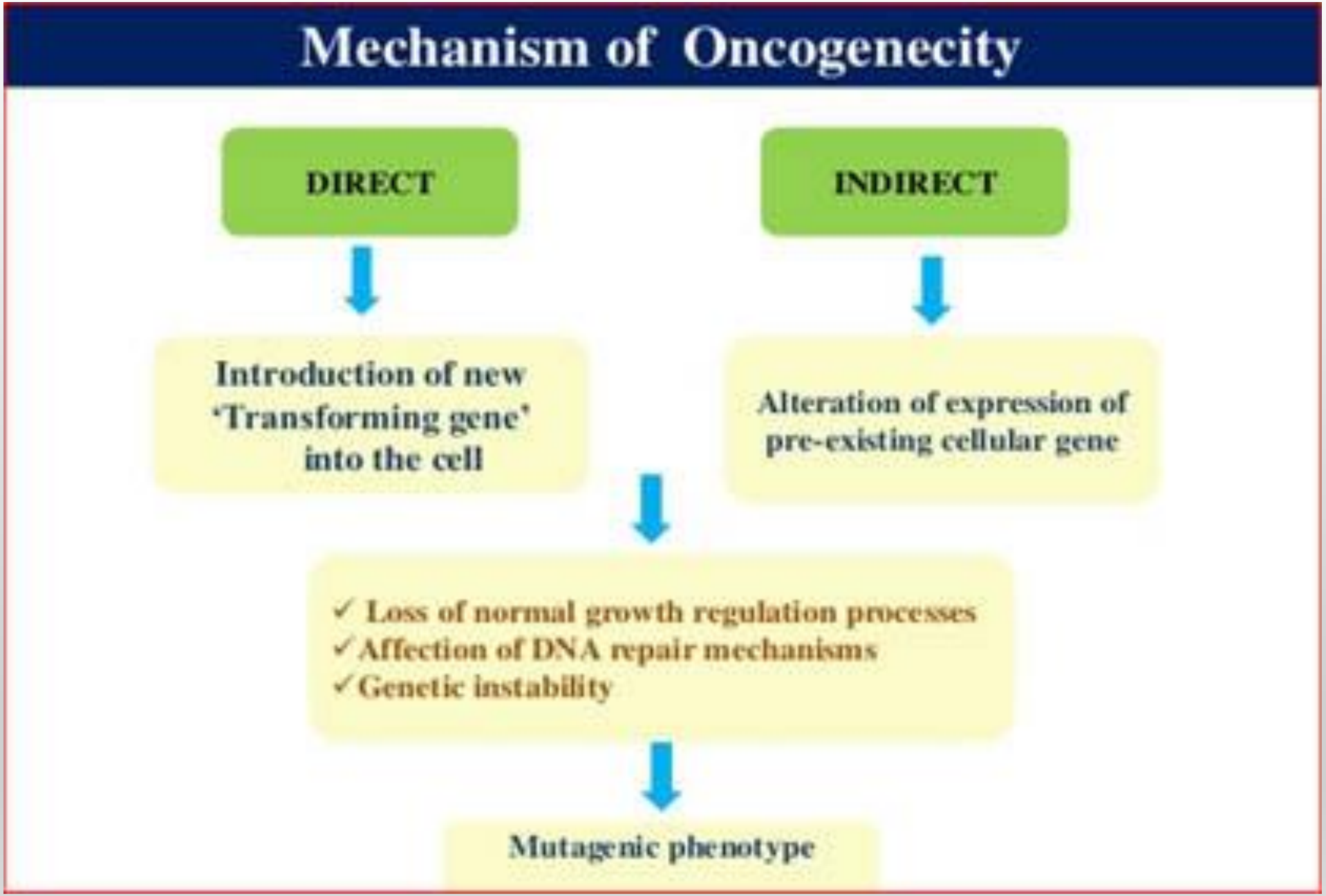
Define proto-oncogenes oncogene,and growth factors

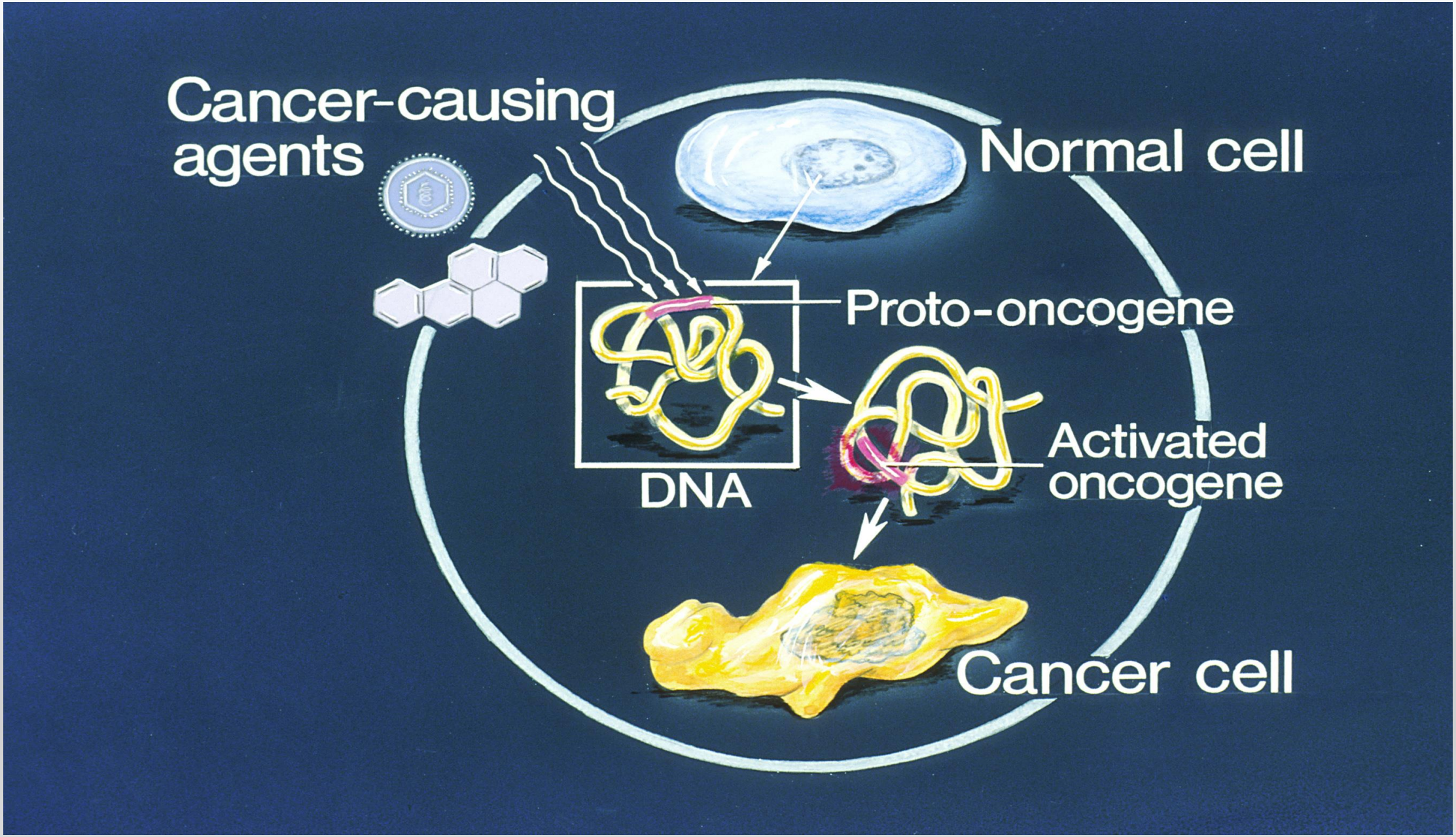
* A **proto-oncogene** is a normal gene that can become an oncogene due to mutations or increased expression. The proto-onncogenes converted to ocogenes and develop cancer.

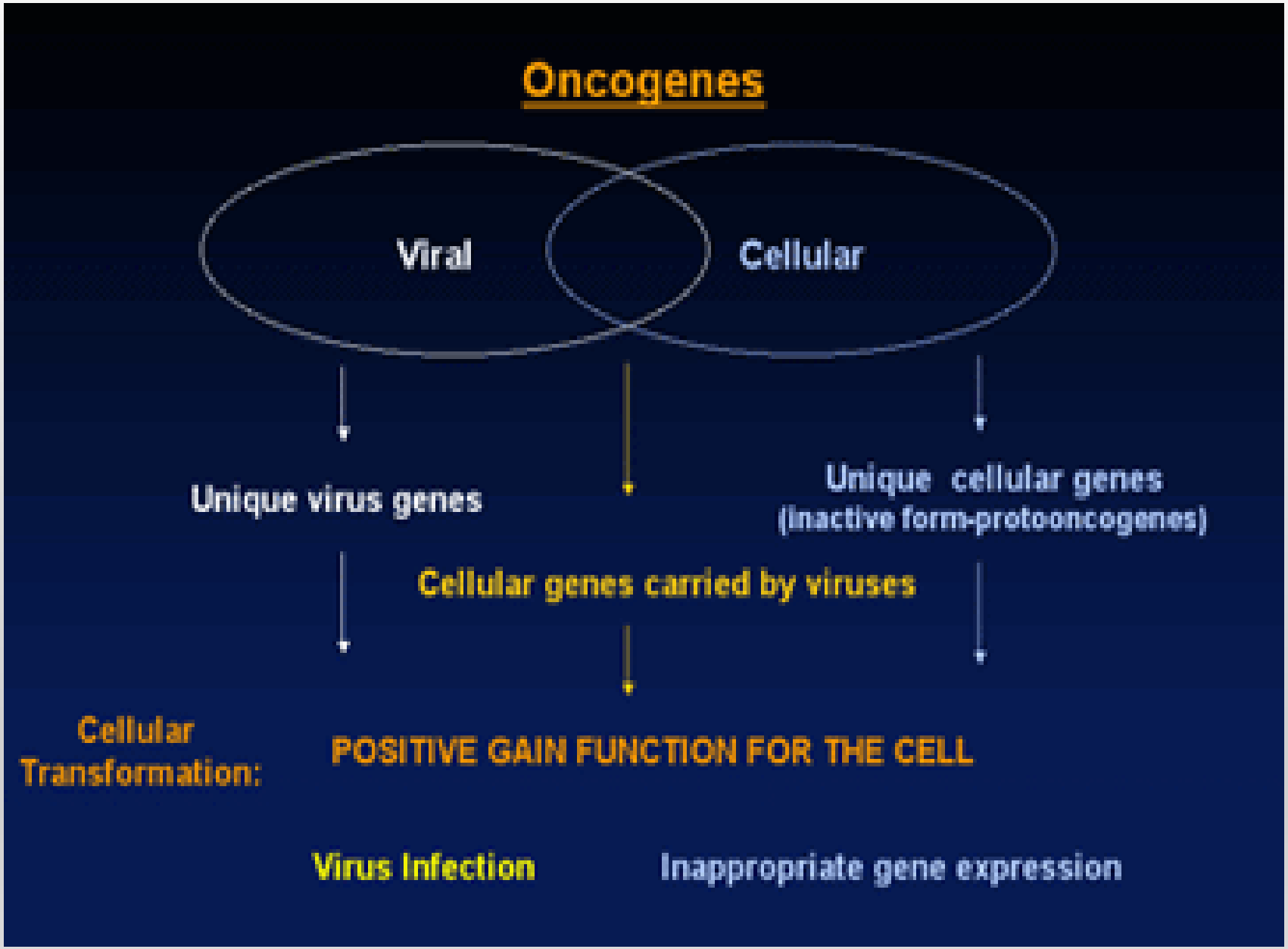
* A mutant proto-oncogene whose protien product is involved in the transformation of normal cell to cancer cell.

* An **oncogene** can be defined as an altered gene whose product acts in a dominant manner to accelerate cell growth or cell division.

Mechanism of Oncogenecity

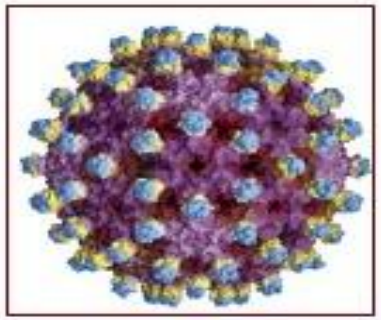



Cancer-causing agents
Normal cell
Proto-oncogene
DNA
Activated oncogene
Cancer cell


Oncogenes
Viral
Cellular
Unique virus genes
Unique cellular genes
(inactive form-protooncogenes)
Cellular genes carried by viruses
Cellular
Transformation:
POSITIVE GAIN FUNCTION FOR THE CELL
Virus Infection
Inappropriate gene expression

Major human Oncogenic Viruses

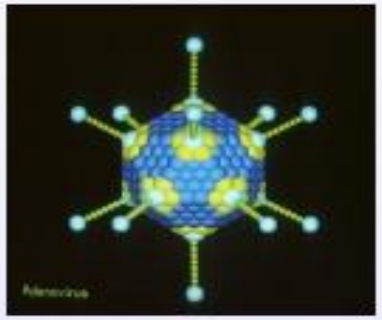
- At least 6 viruses are thought to contribute to cancers (15 – 20%):
- DNA Viruses
  - Small DNA tumor viruses
    - Human Papilloma virus (HPV)
    - SV40
    - Adenovirus
  - Herpesviruses (large)
    - Epstein Barr virus (EBV)
    - Kaposi's Sarcoma Herpesvirus (KSHV)
  - Other
    - Hepatitis virus B



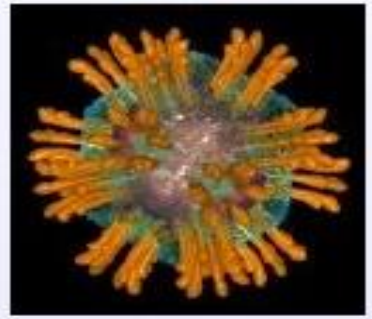
Hepatitis B virus HBV
www.hivandhepatitis.com/.../hbv_virus4..jpg

Human Papillomavirus
www.hyscience.com/hpv_380.jpg

- RNA Viruses
  - Human T-cell Leukemia Virus 1 (HTLV1)
  - Hepatitis virus C
- 80% of viral-associated cancers
  - Cervical cancer (HPV)
  - Liver cancer (HBV and HCV)



Adeno virus
commons.wikimedia.org/wiki/File:Adenovirus.jpg



Hepatitis virus C
kenoath.wordpress.com/2009/04/

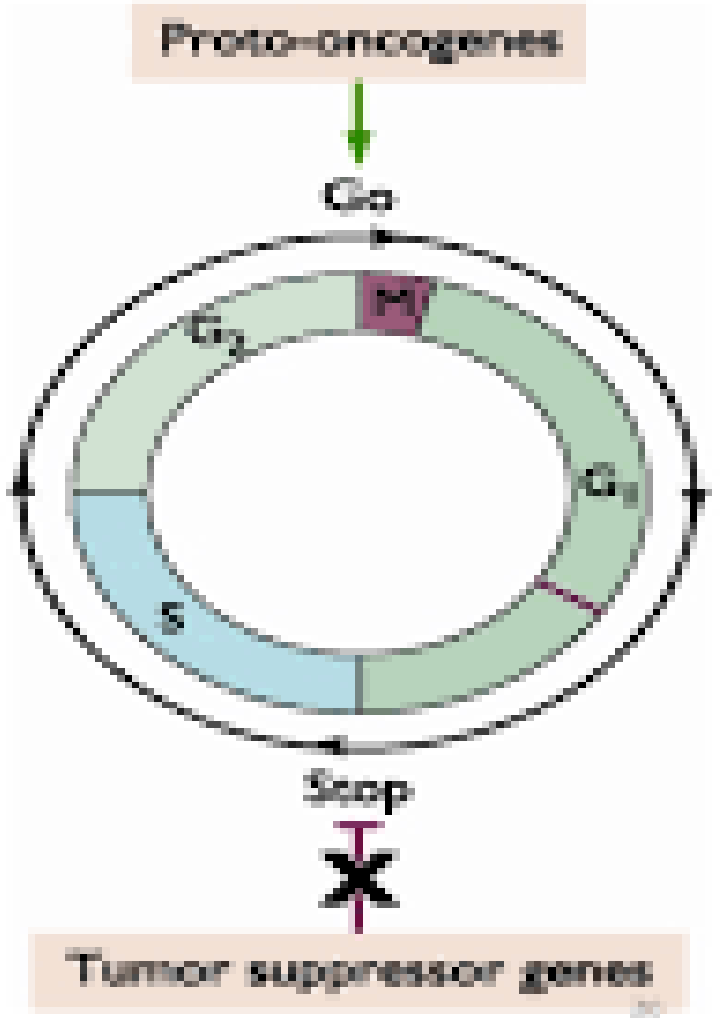
Oncogenic viruses

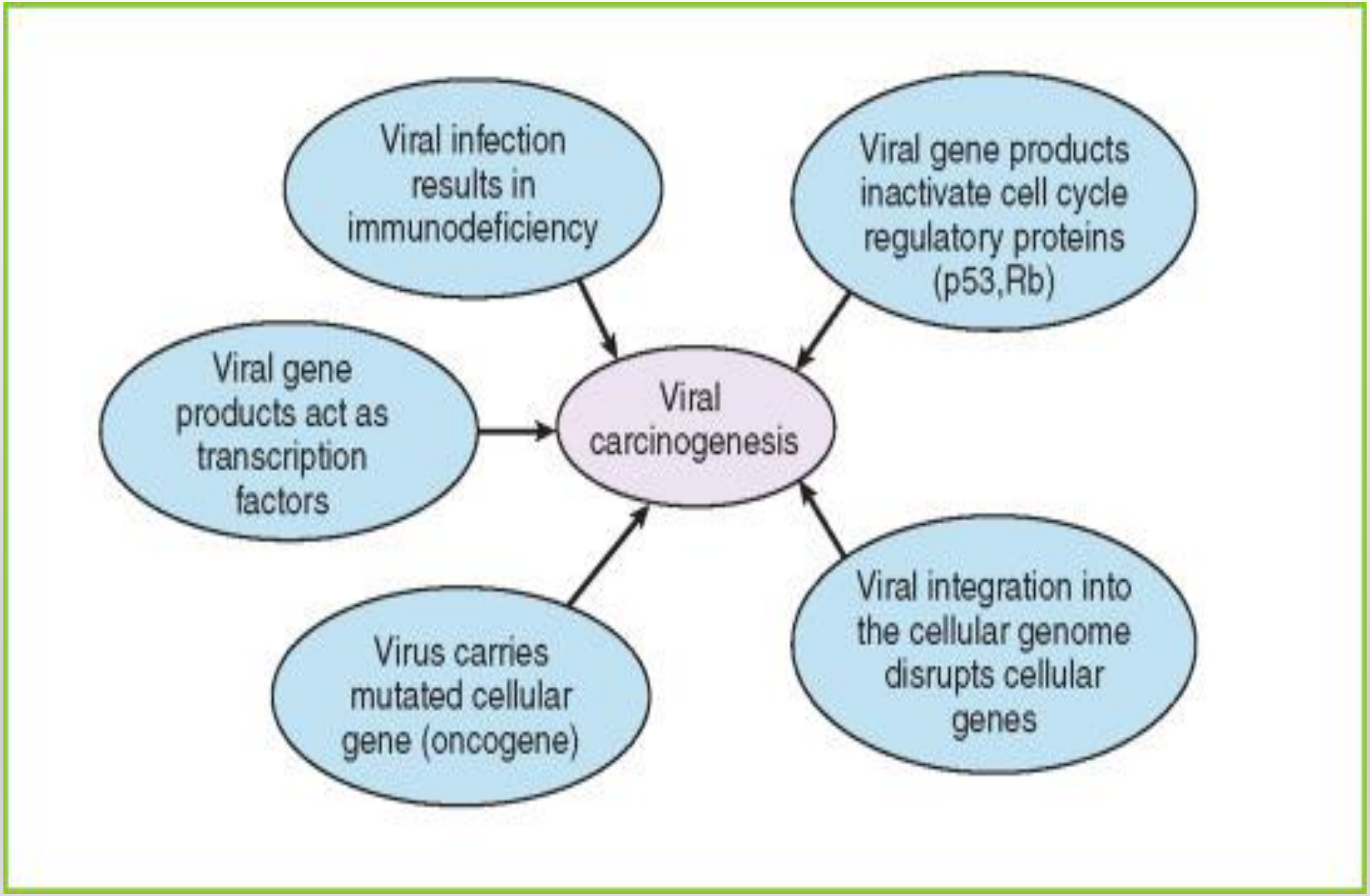
Key Concepts

- Normal cells infected with certain viruses can be transformed into cancer cells due to expression or activation of viral oncogenes
- Transformation can result in integration of viral genes or genomes into the host genome

Oncogenic viruses

- Oncogenesis is the result of genetic changes that alter the expression or function of proteins that play critical roles in the control of cell growth and division
- •Oncogenic viruses cause cancer by inducing changes that affect cell growth and division




Viral infection results in immunodeficiency
Viral gene products inactivate cell cycle regulatory proteins (p53,Rb)
Viral gene products act as transcription factors
Viral carcinogenesis
Virus carries mutated cellular gene (oncogene)
Viral integration into the cellular genome disrupts cellular genes

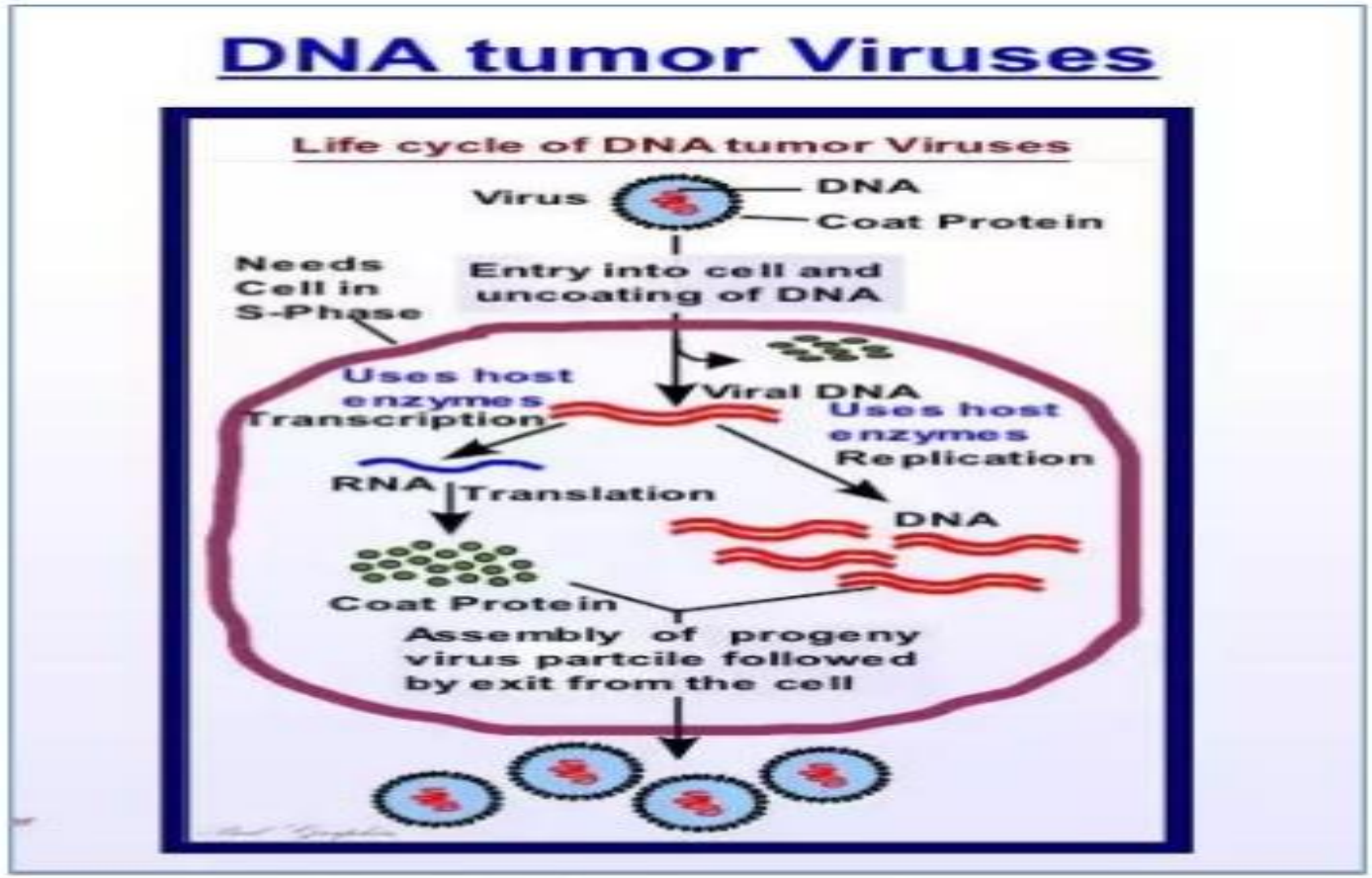
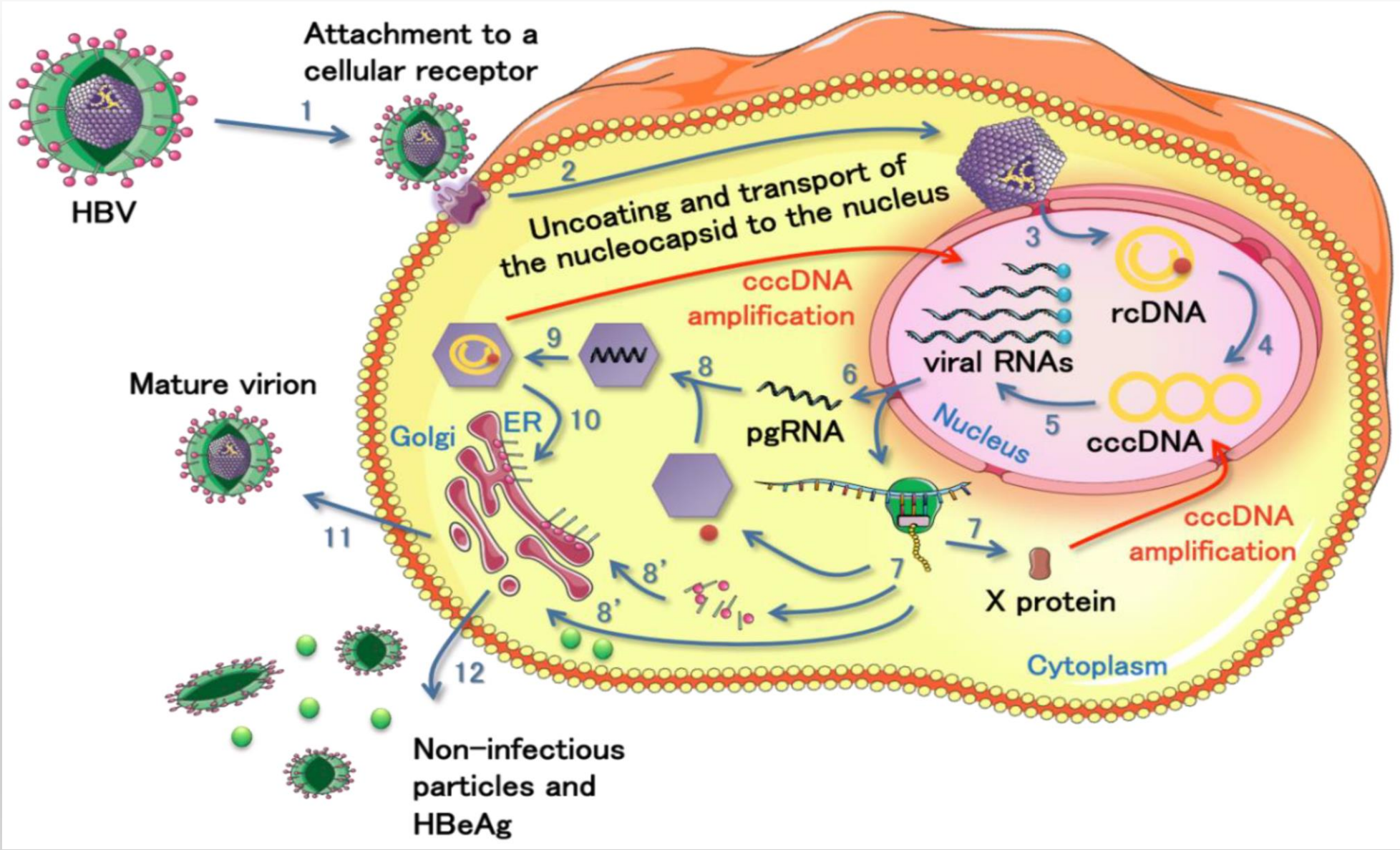
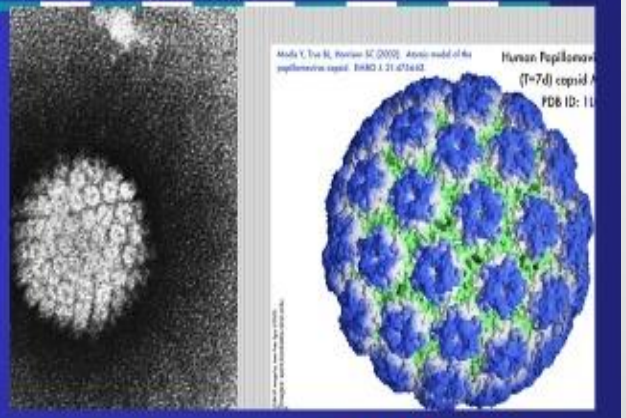


Fig: Cell cycle of DNA tumor viruses


HBV
Attachment to a cellular receptor
1
2
Uncoating and transport of the nucleocapsid to the nucleus
3
rcDNA
4
viral RNAs
5
cccDNA
Nucleus
6
pgRNA
cccDNA amplification
7
X protein
cccDNA amplification
7
8
8'
8'
9
10
Golgi
ER
11
Mature virion
12
Non-infectious particles and HBeAg
Cytoplasm

HUMAN PAPILLOMAVIRUSES

- *Papovavirus*
  - dsDNA,
  - icosahedral in shape
  - Naked (non-enveloped)
  - Resistant to drying, freezing, and solvents



- Human papillomaviruses include at least 200 types that infect the skin and mucosa
- Most types cause specific types of warts and favor certain anatomic locations
- Infections are described as clinical, subclinical & latent

Replication of Viruses

Papova Virus Replication

General Steps in Viral Replication Cycle

A- Attachment

B- Penetration

C- Uncoating

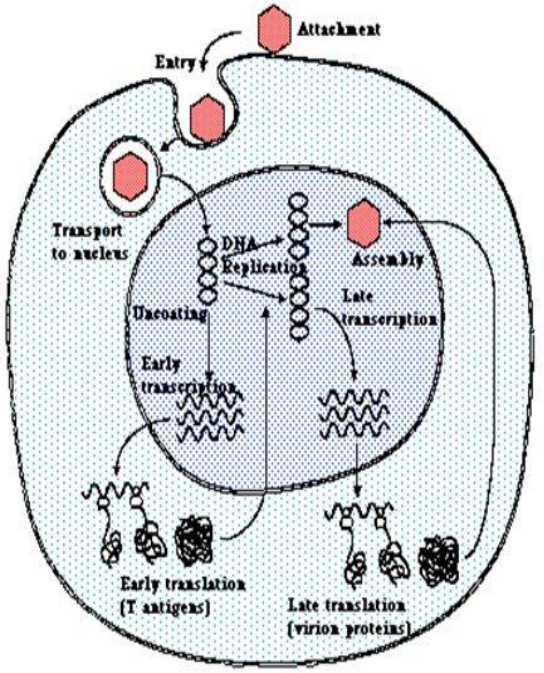
D- Early transcription

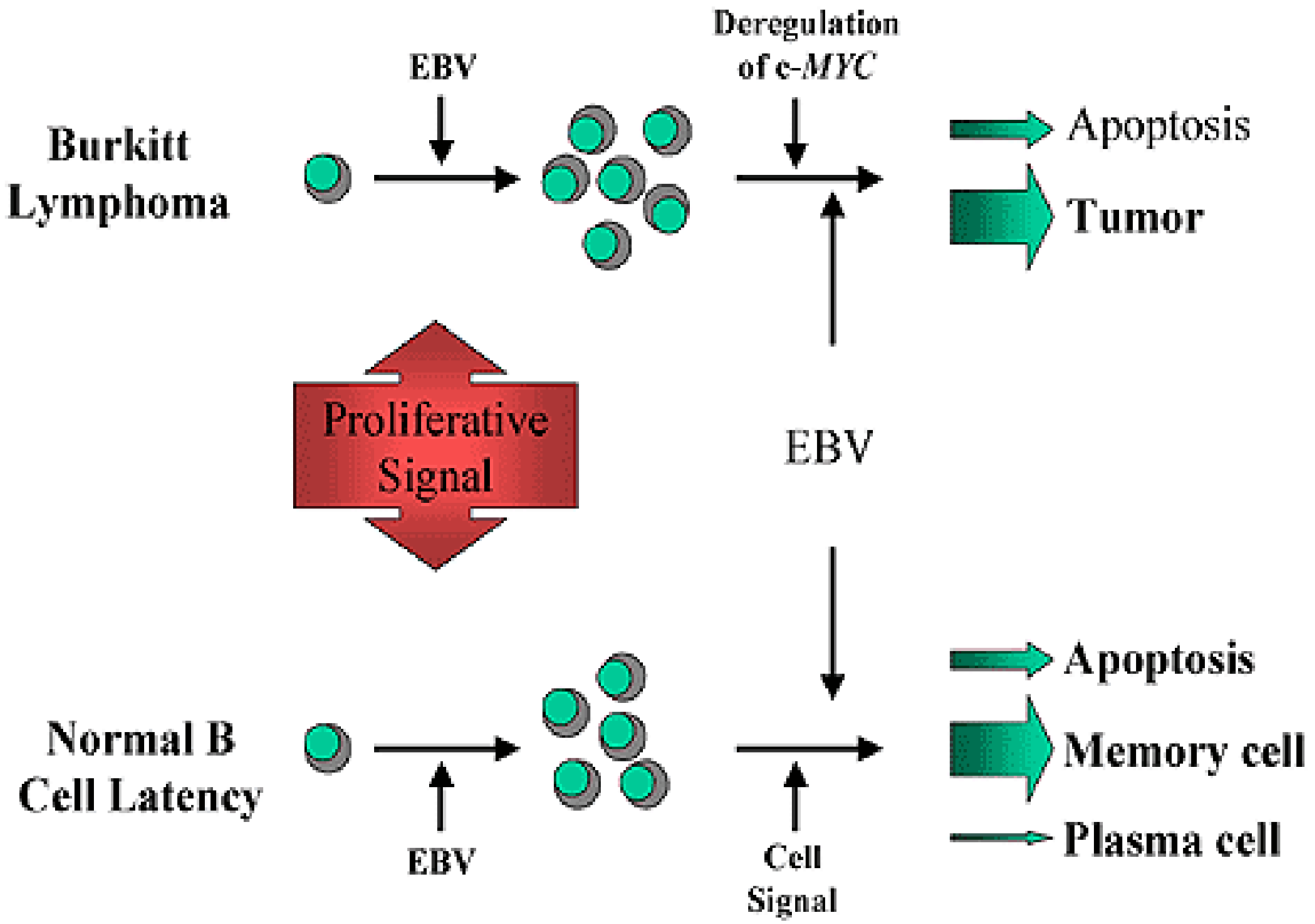
E- Early Translation

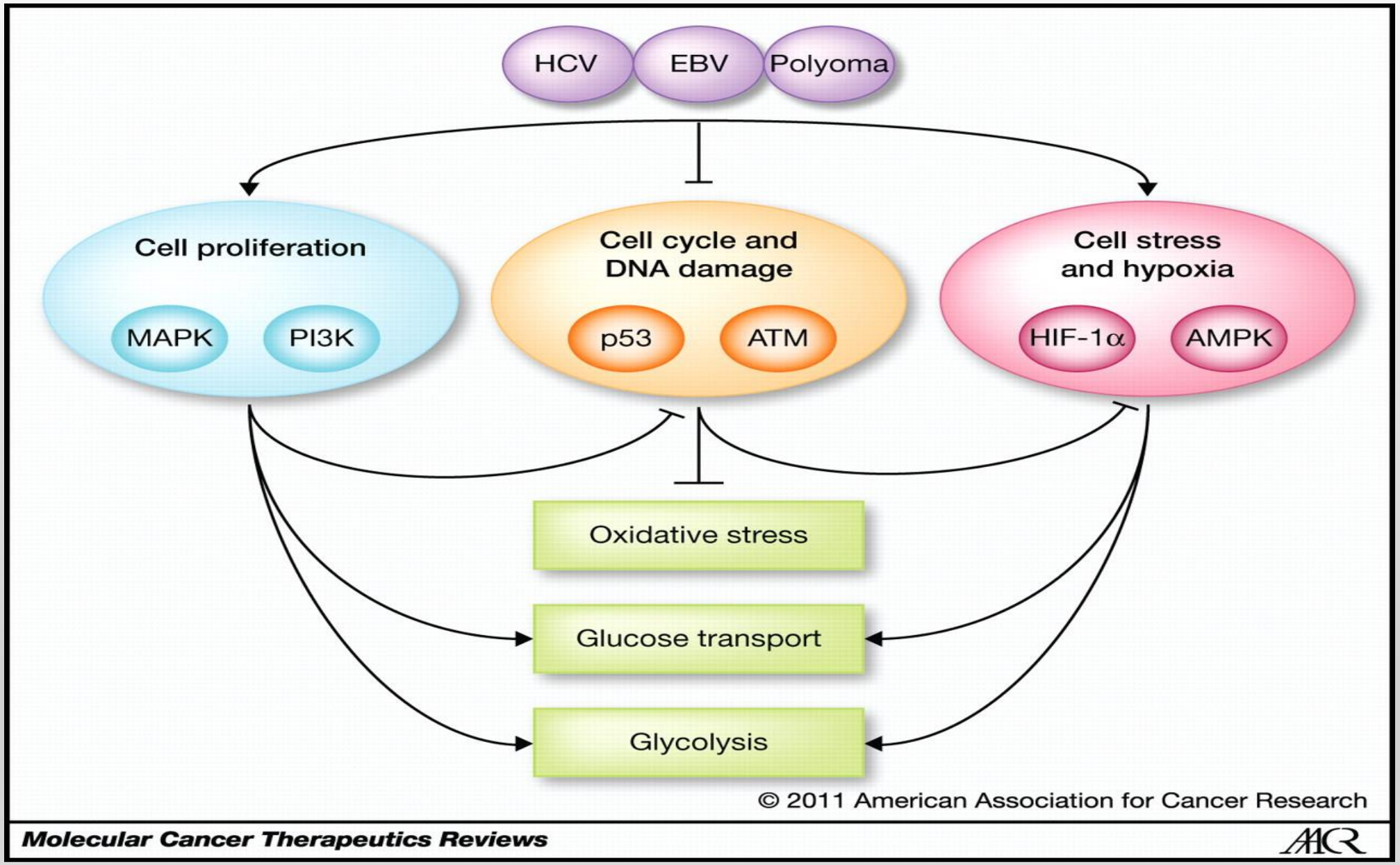
F- Nucleic acid synthesis

G- Late transcription and translation

H- Assembly and release




Deregulation
of c-MYC
EBV
Burkitt
Lymphoma
Apoptosis
Tumor
Proliferative
Signal
EBV
Normal B
Cell Latency
Apoptosis
Memory cell
Plasma cell
EBV
Cell
Signal


HCV
EBV
Polyoma
Cell proliferation
MAPK
PI3K
Cell cycle and DNA damage
p53
ATM
Cell stress and hypoxia
HIF-1α
AMPK
Oxidative stress
Glucose transport
Glycolysis
© 2011 American Association for Cancer Research
Molecular Cancer Therapeutics Reviews
AACR

RNA oncogenic viruses

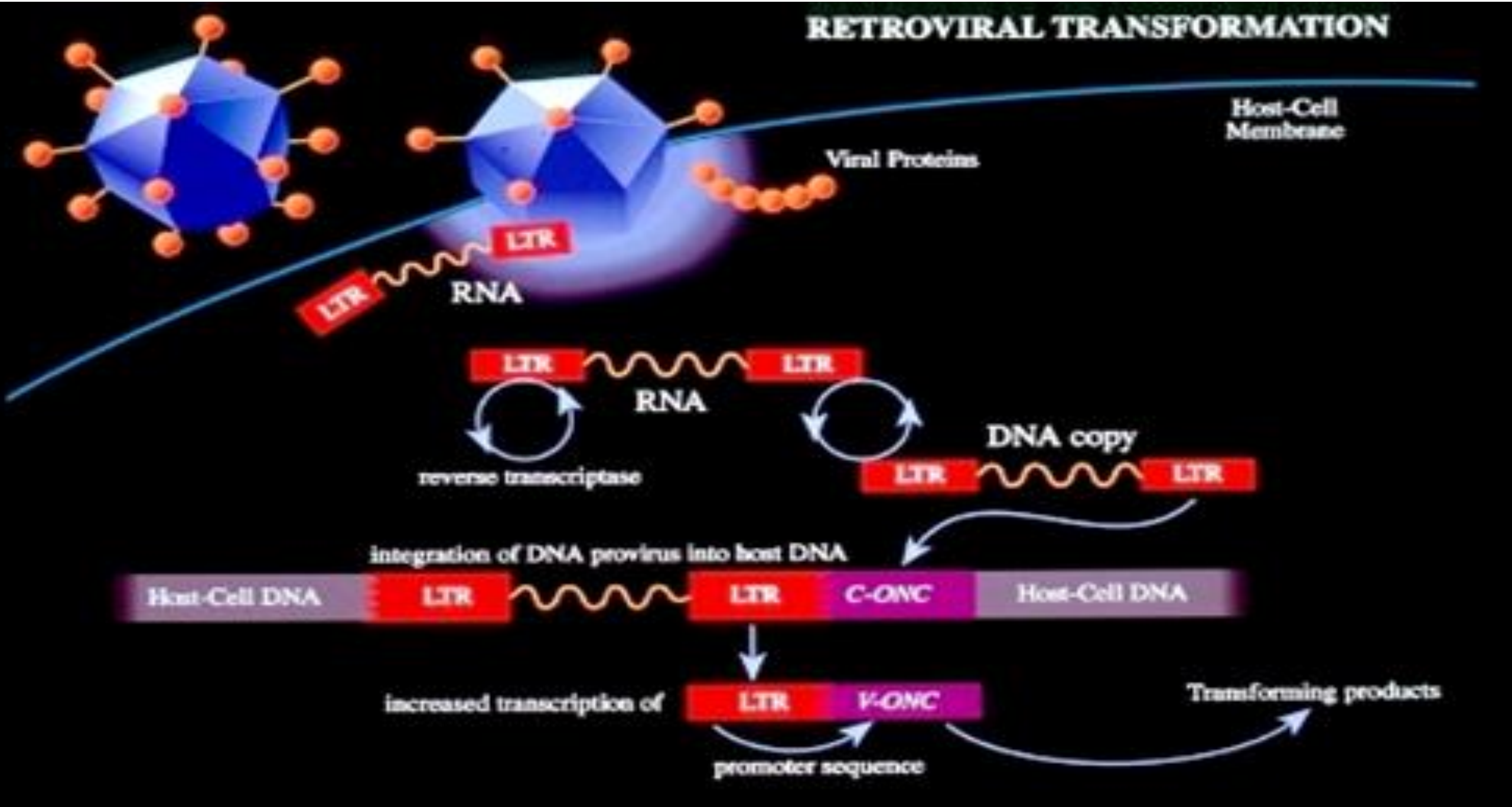
- **Retroviridae**
  - Human T cell leukemia viruses
    - (HTLV-1 and HTLV-2)
      - Causes
        - » Adult T – cell leukemia
        - » Lymphoma
  - Feline leukemia virus (FeLV)
    - Contagious
    - Causes leukemia and lymphoma in cats
  - Related to presence of reverse transcriptase
  - Some contain promoters that turn on other oncogenes

Retroviral oncogene

- Viral oncogene was first defined by Peyton Rous In 1911 in rous sarcoma virus (rsv) that transforms chicken embryo fibroblast in culture and induces large sarcomas.

- Its RNA genome is reverse transcribed into DNA which gets incorporated into the host cell genome.

- It contains specific genetic information responsible for transformation of infected cells.


RETROVIRAL TRANSFORMATION
Host-Cell Membrane
Viral Proteins
LTR
LTR
RNA
LTR
LTR
RNA
reverse transcriptase
DNA copy
LTR
LTR
integration of DNA provirus into host DNA
Host-Cell DNA
LTR
LTR
C-ONC
Host-Cell DNA
increased transcription of
LTR
V-ONC
promoter sequence
Transforming products