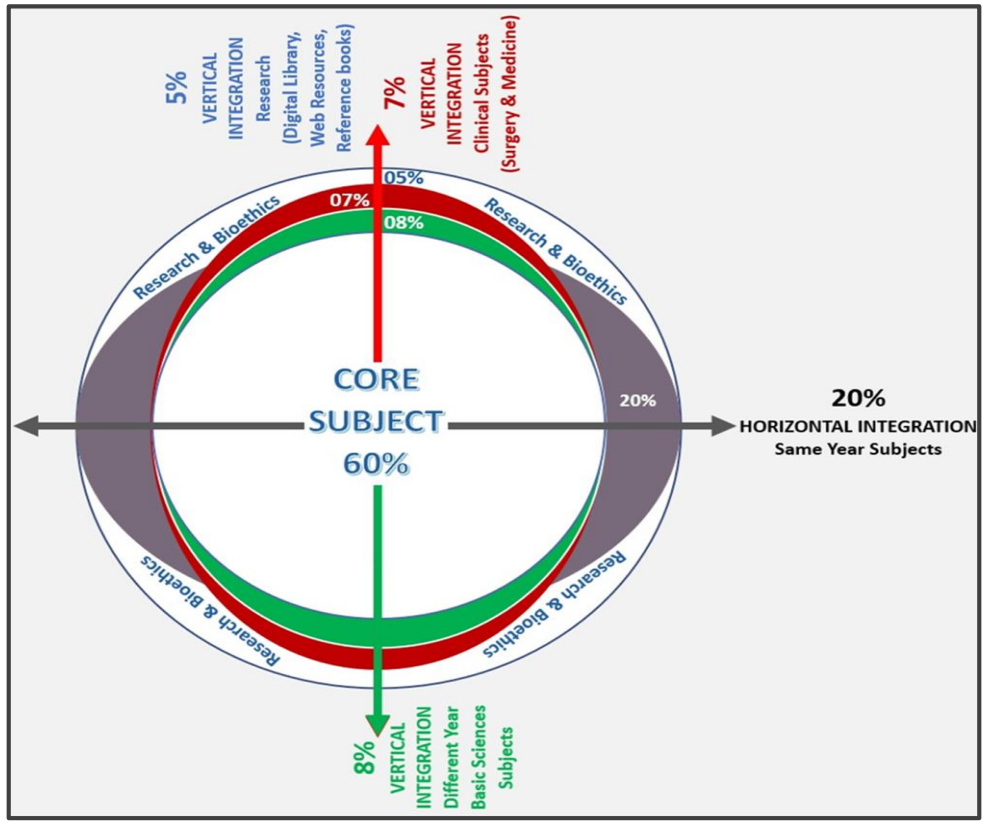
DRUGS USED IN TREATMENT OF VIRAL HEPATITIS (HBV)

Dr. Zunera Hakim

- Katzung's Basic & Clinical Pharmacology, 15th Edition
- Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

SCHEME OF LECTURE



3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	

LEARNING OBJECTIVES

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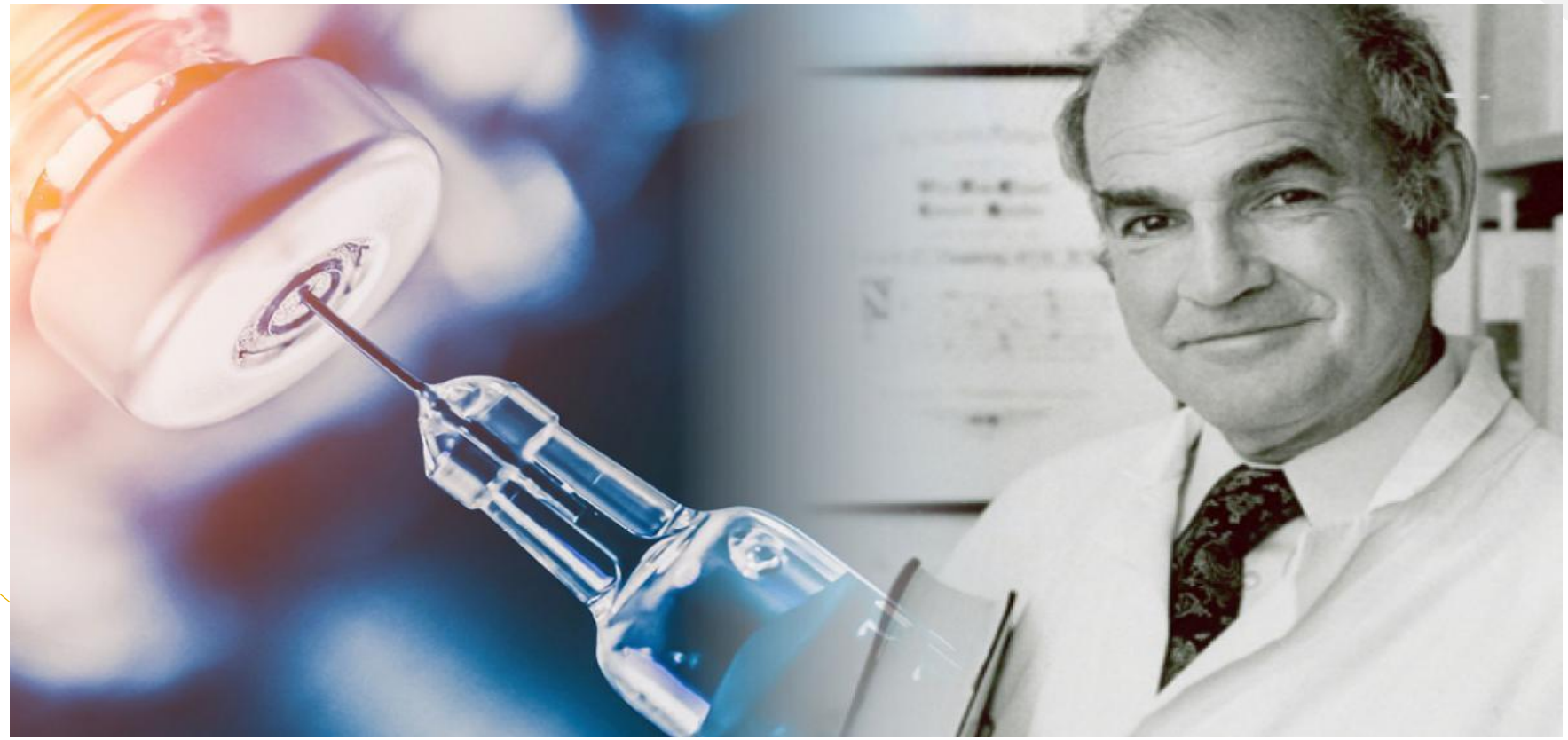
At the end of the lecture, students will be able to:

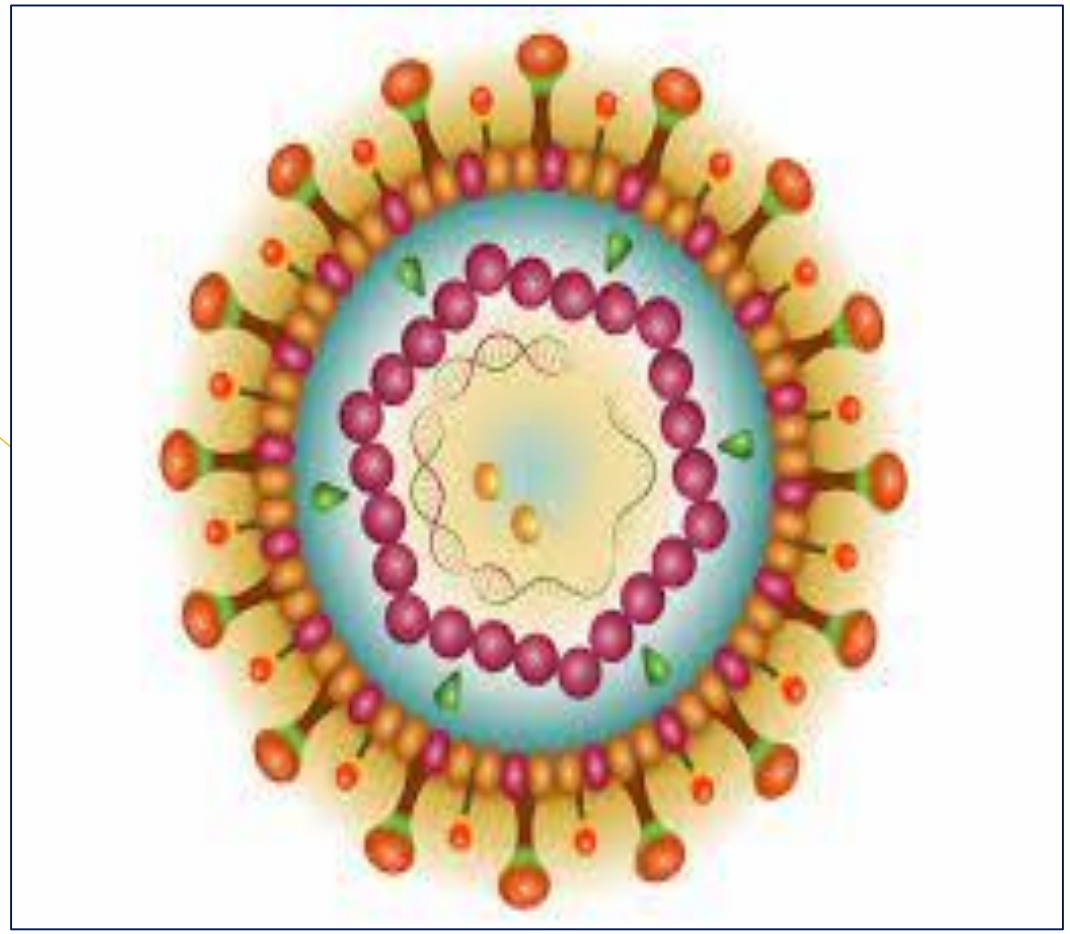
- Classify antiviral drugs used in the treatment of hepatitis B
- Discuss the mechanism of action , adverse effects and contra indications of interferons
- Describe the salient pharmacokinetic & pharmacodynamic features of directly acting anti viral drugs
- Outline the advantages and disadvantages of interferon therapy over directly acting anti-virals

HEPATITIS B VIRUS



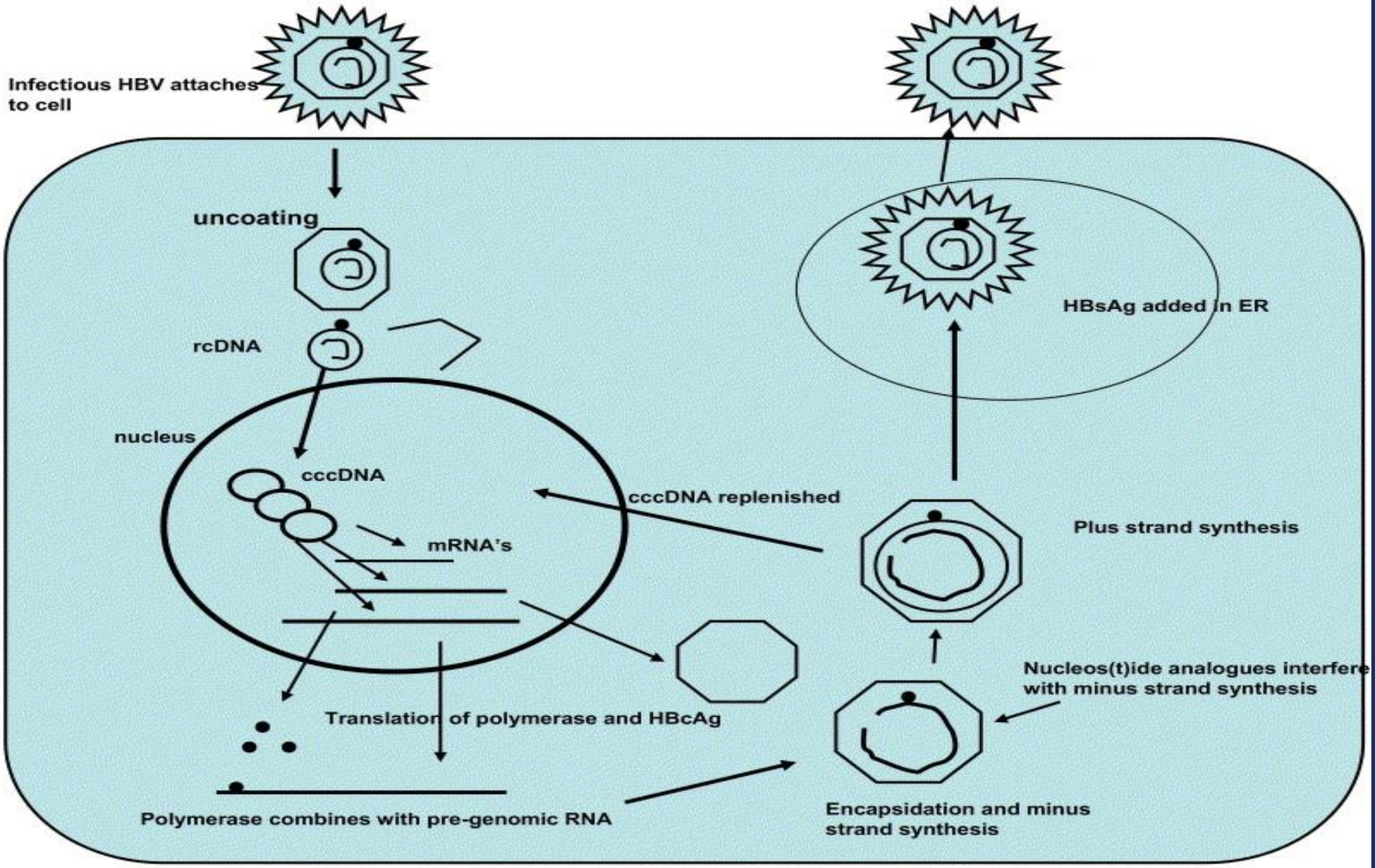
Australian antigen (AuAg)- Dr. Baruch Blumberg 1967

HEPATITIS B VIRUS

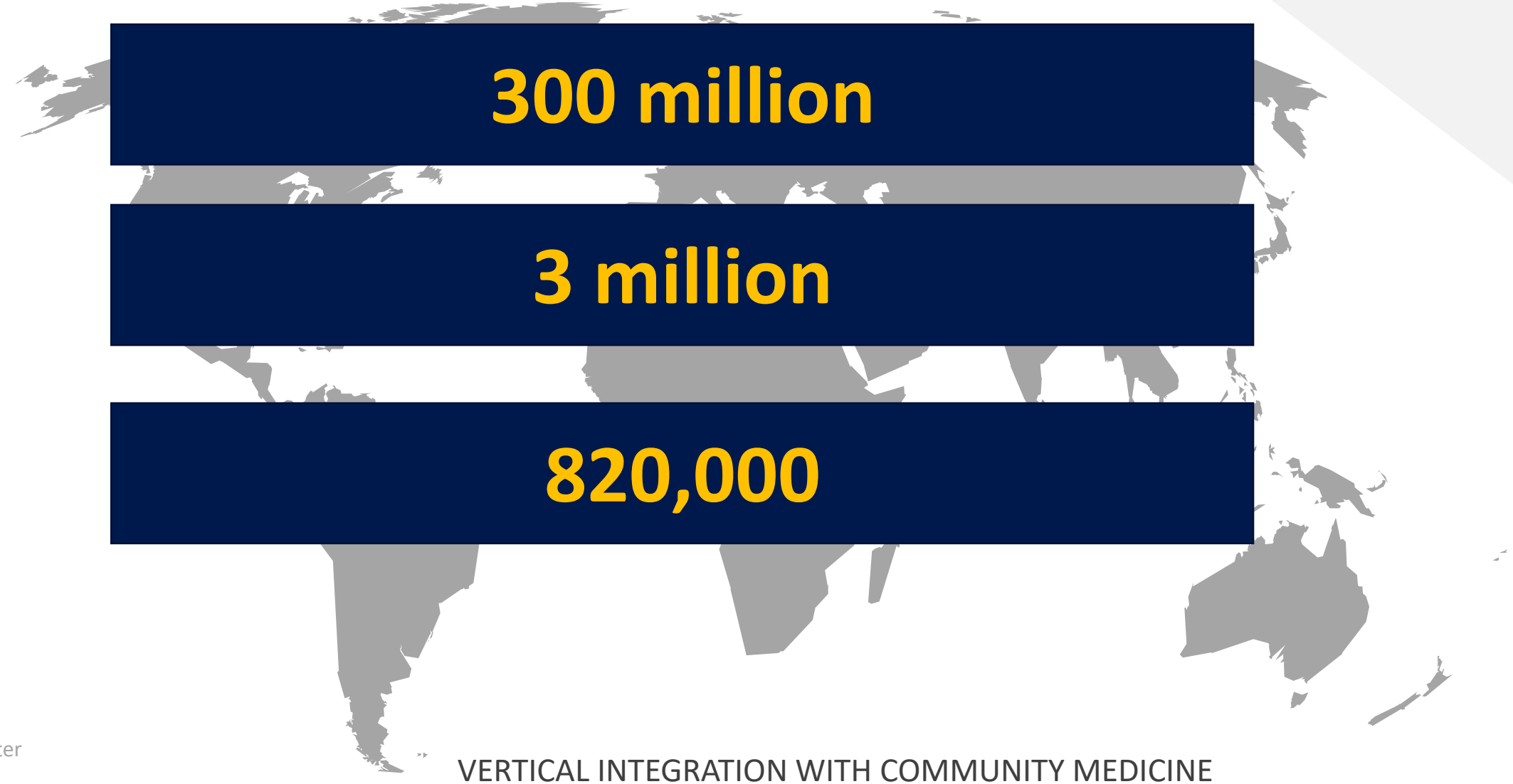


- Enveloped with three types of surface proteins
- Single copy of double stranded relaxed circular DNA (rcDNA)
- Different genotypes (A-J) respond differently to therapy
- Transmitted through contaminated instruments, needles, exchange of body fluids and secretions and perinatal transmission

HBV REPLICATION CYCLE



PREVALENCE OF HEPATITIS B

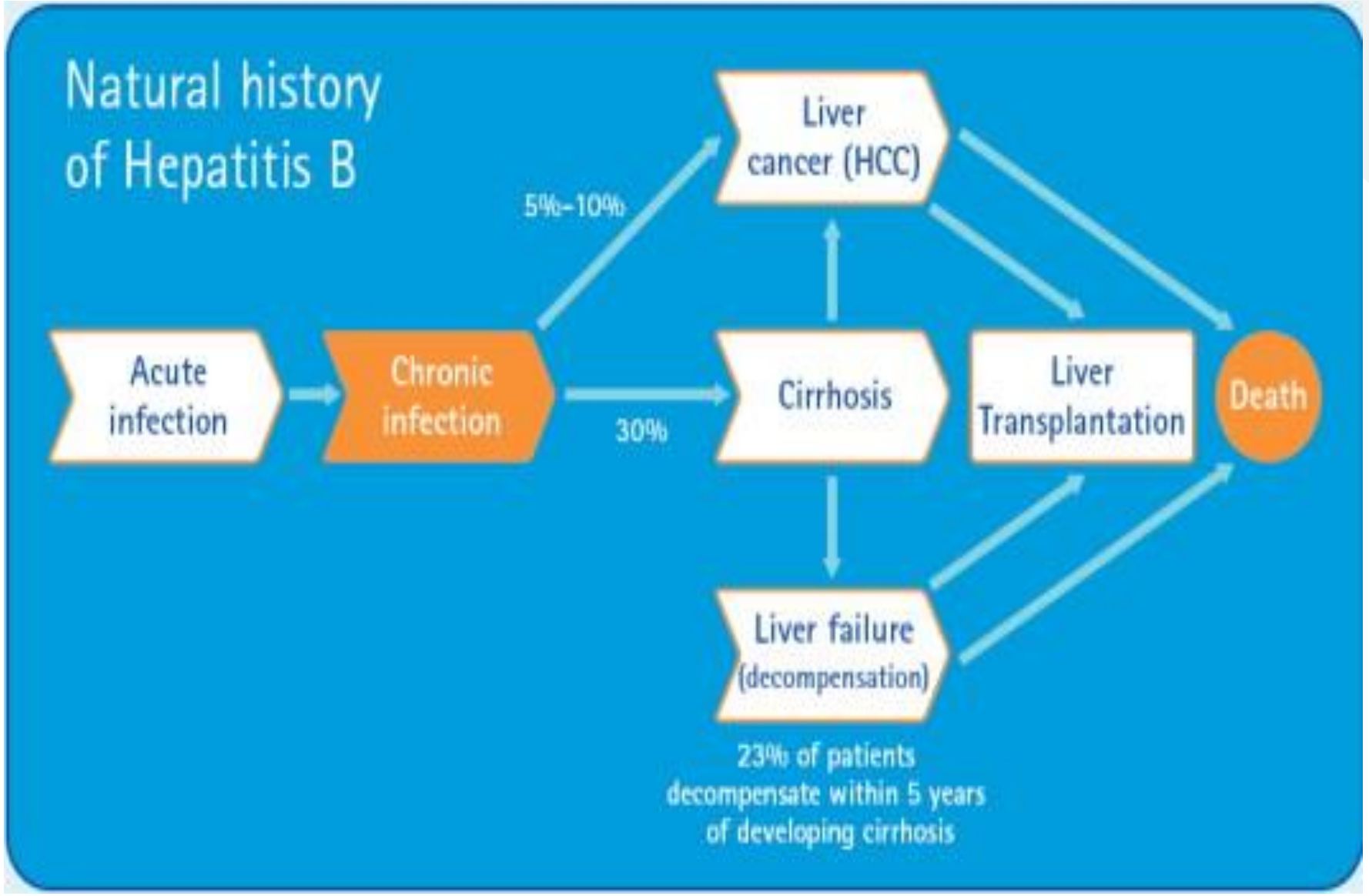


300 million

3 million

820,000

NATURAL COURSE OF DISEASE



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HEPATITIS B VIRUS TREATMENT

The goals of chronic HBV treatment are:

- Suppression of HBV DNA levels to undetectable levels
- Seroconversion from positive to negative
- Reduction in elevated serum amino transaminase levels
- Reduce the risk of disease progression and complications

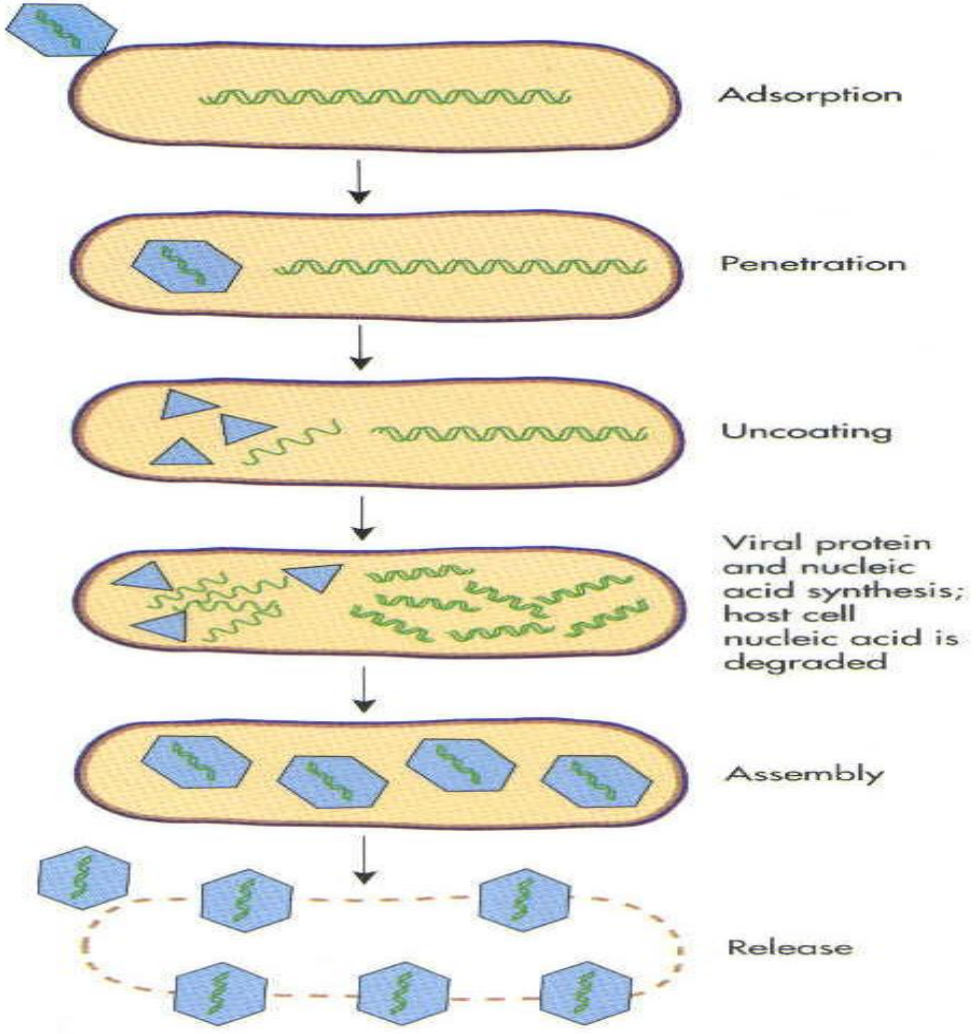
ANTIVIRAL DRUGS

GENERAL PROPERTIES

- Ability to enter virus infected cells
- Antiviral drugs target an essential viral enzyme or protein to inhibit a pathway unique to the virus but not the cell (selective toxicity for viruses is difficult to achieve)
- Many antiviral drugs are *Purine or Pyrimidine analogs*
- Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active
- Anti-viral agents inhibits active replication and do not eliminate non-replicating or latent virus
- Clinical efficacy depends on achieving inhibitory conc. at the site of infection within the infected cells
- Effective host immune response remains essential for the recovery from the viral infection

VIRAL REPLICATION & DRUG TARGETS

- Cell entry
  - Attachment
  - Penetration
- Uncoating/dismantling
- Viral nucleic acid and protein synthesis
- Post-translational modifications
- Assembly of virion components
- Release of virions



DRUGS USED IN HEPATITIS B

- **IMMUNO-MODULATORS**
  - Interferon α-2b
  - Pegylated interferon α-2a

- **DIRECTLY ACTING ANTIVIRALS (nucleos(t)ide analogues HBV polymerase inhibitors)**
  - Adefovir dipivoxil (nucleotide)
  - Lamuvudine
  - Tenofovir Alafenamide/Tenofovir disoproxil fumarate (nucleotide)
  - Telbuvudine
  - Entecavir

INTERFERON

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Natural proteins (glycoprotein cytokines) produced by the cells of the immune systems in response to various inducers such as viruses, bacteria, parasites & tumor cells.

Antiviral, anti-proliferative & immuno-modulator properties

1. Interferon type I
   - Alpha (α) –synthesized by leukocytes
   - Beta (β) –synthesized by epithelial cells

   Interferon alpha & beta have potent anti-viral activity (α > β)

2. Interferon type II
   - Gamma (γ)- synthesized by NK cells and T lymphocytes

   Interferon γ has strong immunomodulatory effect

INTERFERON

- Synthesized through DNA recombinant technology
- Commercially available preparations are:
  - Interferon alfa- 2a
  - Interferon alfa-2b
- Polyethylene glycol covalently attached to interferon for improvement of pharmacokinetic profile
  - Peg interferon alfa-2a (40,000 Da)
  - Peg interferon alfa- 2b (12,000 Da)

INTERFERON

PHARMACOKINETICS

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Orally not active

- IM or S/C

Half life 2-5 hours

PEG longer terminal $t_{1/2}$

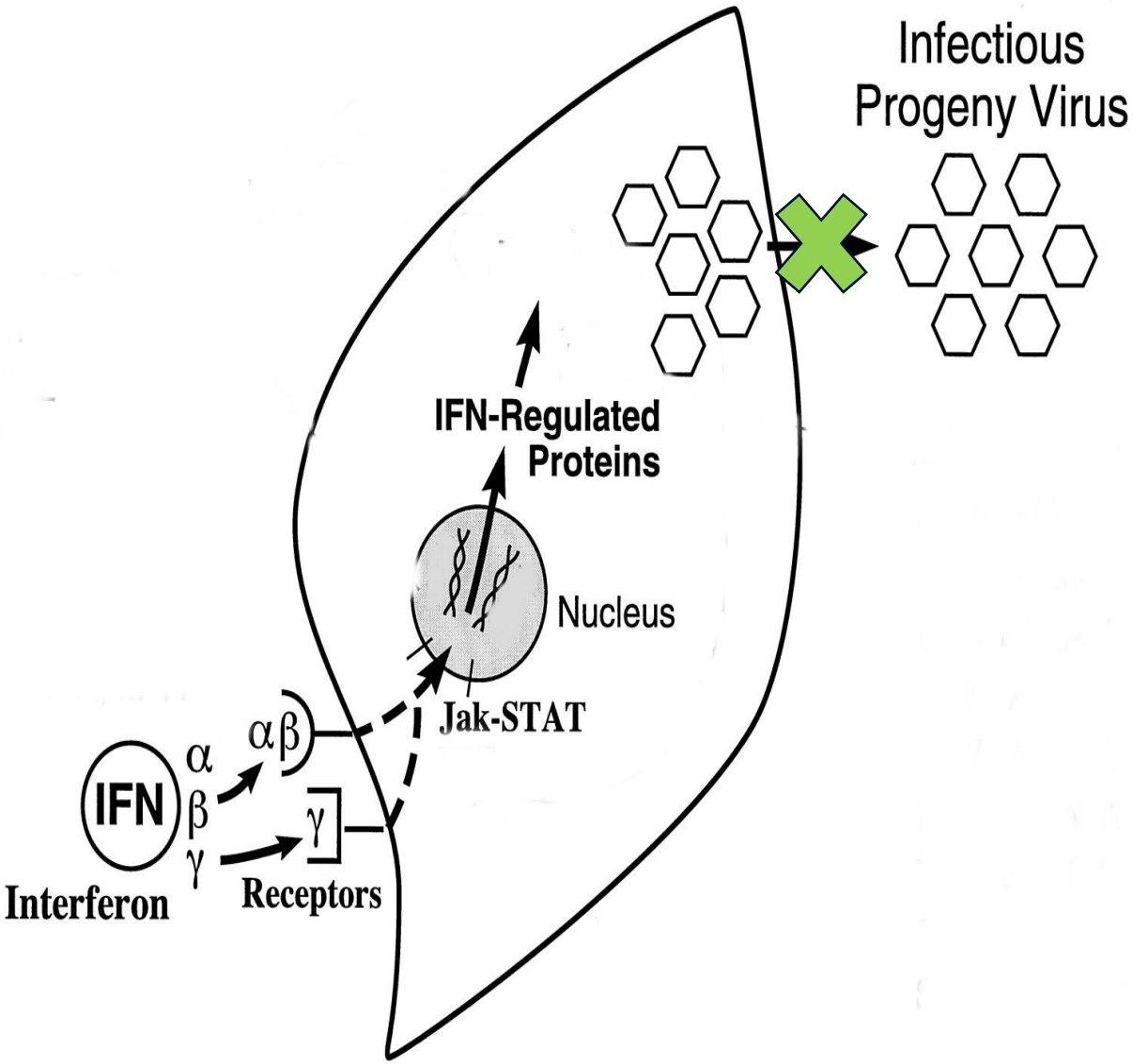
(PegINF-α2A : 80-90 h , PegINF- α2b: 30-54h)

- Renal clearance with minor hepatic pathway

- Peg IFN renal elimination (30%),rest is hepatic and cellular degradation of IFN-receptor complexes

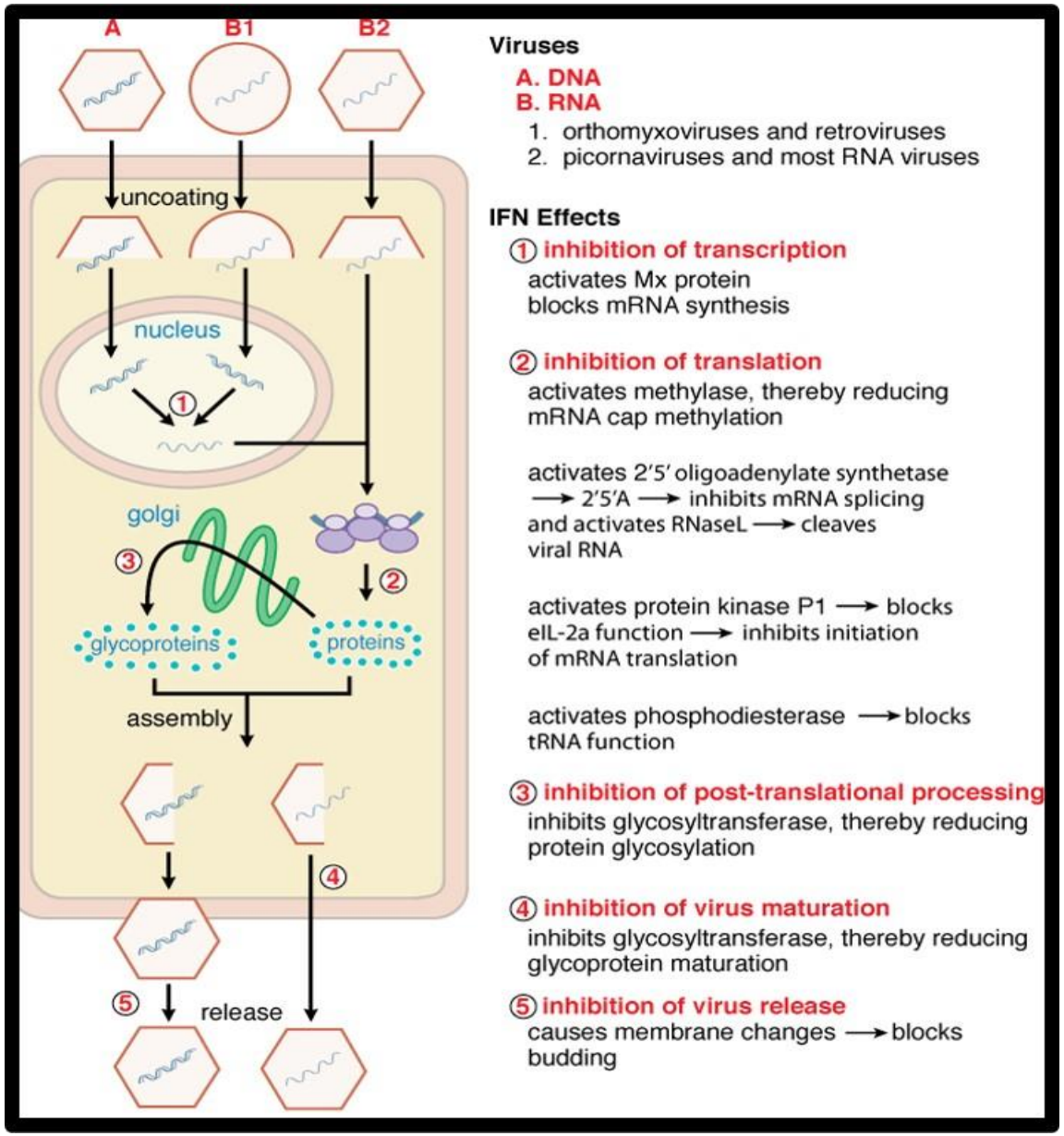
CORE-PHARMACOLOGY

MECHANISM OF ACTION



- Exert a complex range of effects on virus infected cells that result in the inhibition of viral penetration, mRNA synthesis, translation, virion assembly & release.
- IFN binds to cell surface receptors & initiate JAK-STAT signal transduction pathway
- Transcription of IFN-response element leads to synthesis of numerous proteins mediating effects at different stages of viral cycle

MECHANISM OF ACTION



- **Inhibition of protein synthesis is the major inhibitory effect**
  - ❖ 2-5 adenylate synthetase (mRNA cleavage)
  - ❖ Protein kinase (inhibits translation and induce apoptosis)
  - ❖ Phosphodiesterase (cleaves tRNA and prevent peptide elongation)

- Increased expression of major histocompatibility complex antigen
- Increased phagocytic activity of macrophages
- Increased proliferation and survival of cytotoxic T-cells

IFN type	Indications in the clinic
IFN-α	Hairy cell leukemia Multiple myeloma Chronic myeloid leukemia Follicular lymphoma Cutaneous T lymphoma Kaposi sarcoma Melanoma Renal cell carcinoma Hepatocellular carcinoma Condyloma accuminata Hepatitis B Hepatitis C
IFN-β	Multiple sclerosis
IFN-γ	Chronic granulomatous disease

INTERFERON

ADVERSE EFFECTS

- Flu like/influenza syndrome (headache,fever,chills, myalgias & malaise)
- Elevated of hepatic enzymes (increase with didanosine)
- Neuropsychiatric (mood disorder,depression, somnolence,confusion,seizures)
- Myelosuppression (granulocytopenia & thrombocytopenia) (increase with zidovudine)
- Autoimmune disorders(thyroiditis & hypothyroidism)
- Cardiovascular effects (tachycardia & hypotension)
- Renal(proteinuria, azotemia & interstitial nephritis)
- Hearing loss, tinnitus
- Retinopathy
- Pneumonitis
- Alopecia
- Profound weight loss
- Fatigue
- Rash
- Myalgia

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CORE-PHARMACOLOGY

CONTRAINDICATIONS

- Hepatic decompensation
- Autoimmune disease
- Cardiac dysfunction
- Psychiatric diseases
- Epilepsy
- Thyroid disease
- Renal insufficiency
- Hematological disturbances
- **Pregnancy**

DIRECTLY ACTING ANTIVIRALS

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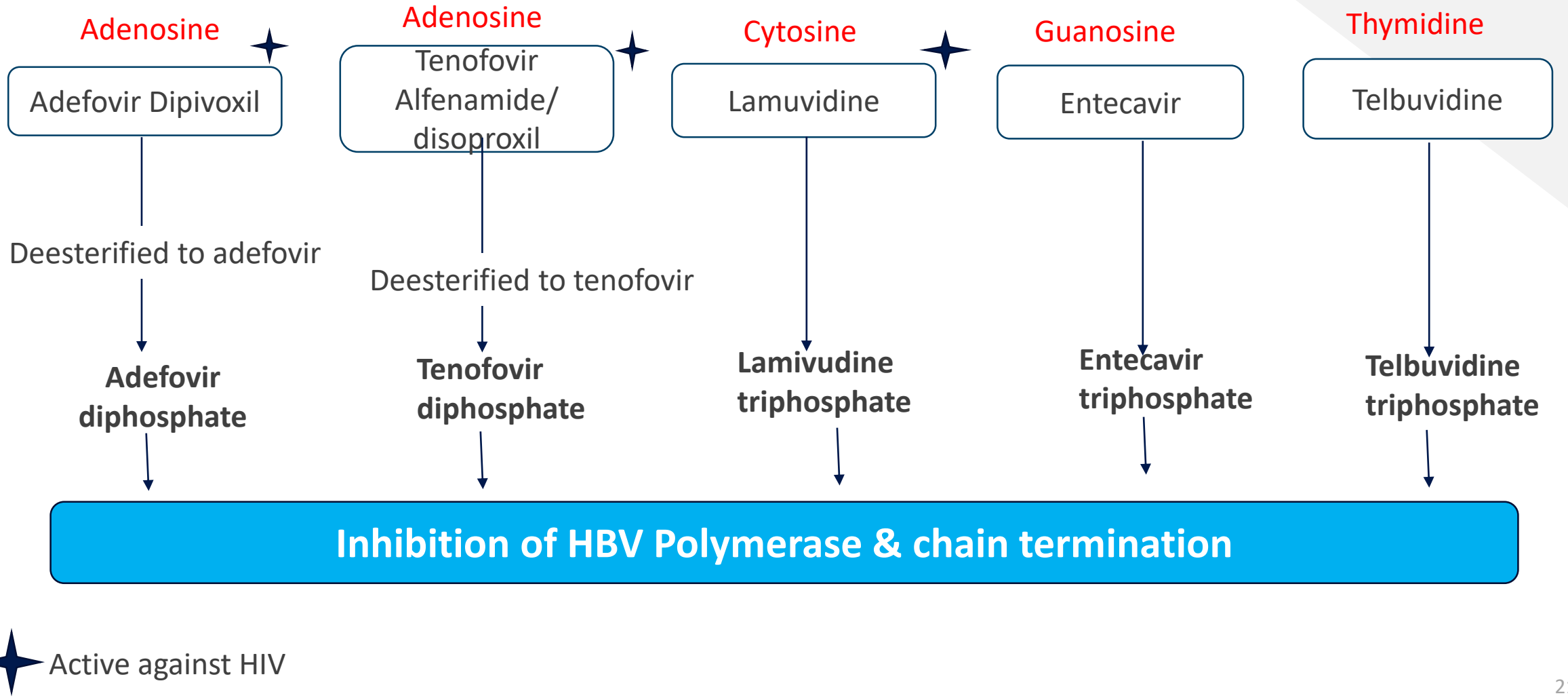
MECHANISM OF ACTION



Active against HIV

CORE-PHARMACOLOGY

DIRECTLY ACTING ANTIVIRALS

LIMITATIONS

1. **HBV Resistance**
   - ➢ High rate of viral replication
   - ➢ Lack of proof reading capability of HBV polymerase
- DAA vary in their genetic barrier to development of resistance (Tenofovir & entecavir least resistant)
- Resistance leads to therapeutic failure & rapid resurgence of viral replication

2. Exacerbation of hepatitis (flares) upon sudden discontinuation

RESEARCH

Ye, J. and Chen, J., 2021. Interferon and hepatitis B: Current and future perspectives. *Frontiers in Immunology*, *12*, p.733364. doi.org/10.3389/fimmu.2021.733364

BIOETHICS

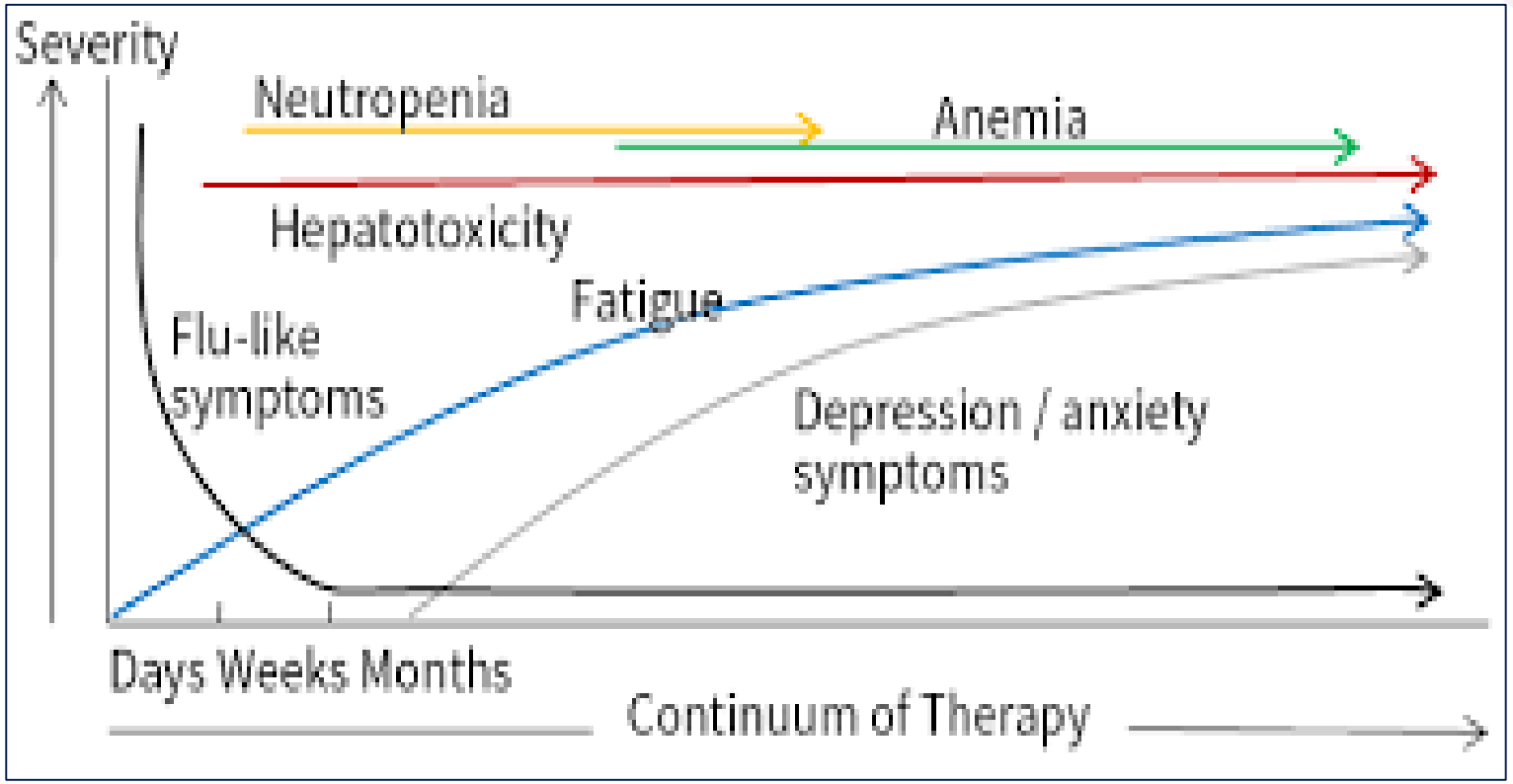
- Clinical trials involving testing newer drugs on humans require informed consent

ARTIFICIAL INTELLIGENCE

- FU, X., LUO, C., GAO, S., FU, X., LU, R. and RONG, H., 2021. **Establishment and Application of Artificial Neural Network Model in Predicting Clinical Efficacy of Interferon for Chronic Hepatitis B**. *China Pharmacy*, pp.1257-1261.

- Shang H, Hu Y, Guo H, Lai R, Fu Y, Xu S, Zeng Y, Xun Z, Liu C, Wu W, Guo J. **Using machine learning models to predict HBeAg seroconversion in CHB patients receiving pegylated interferon-α monotherapy**. *Journal of Clinical Laboratory Analysis*. 2022 Nov 1:e24667

END OF LECTURE ASSESSMENT



- Identify the drug most likely responsible for the adverse effects in Fig
- Give the mechanism of action
- Write important clinical indications