BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu, India

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Unit-III

Antiviral Agents, Anticancer Agents

Dr. P.S.Dhivya

Guest Lecturer

Department of Biomedical Science

DRUG DISCOVERY & ASSAY DEVELOPMENT

ANTIVIRAL AGENTS

ANTIVIRAL DRUG

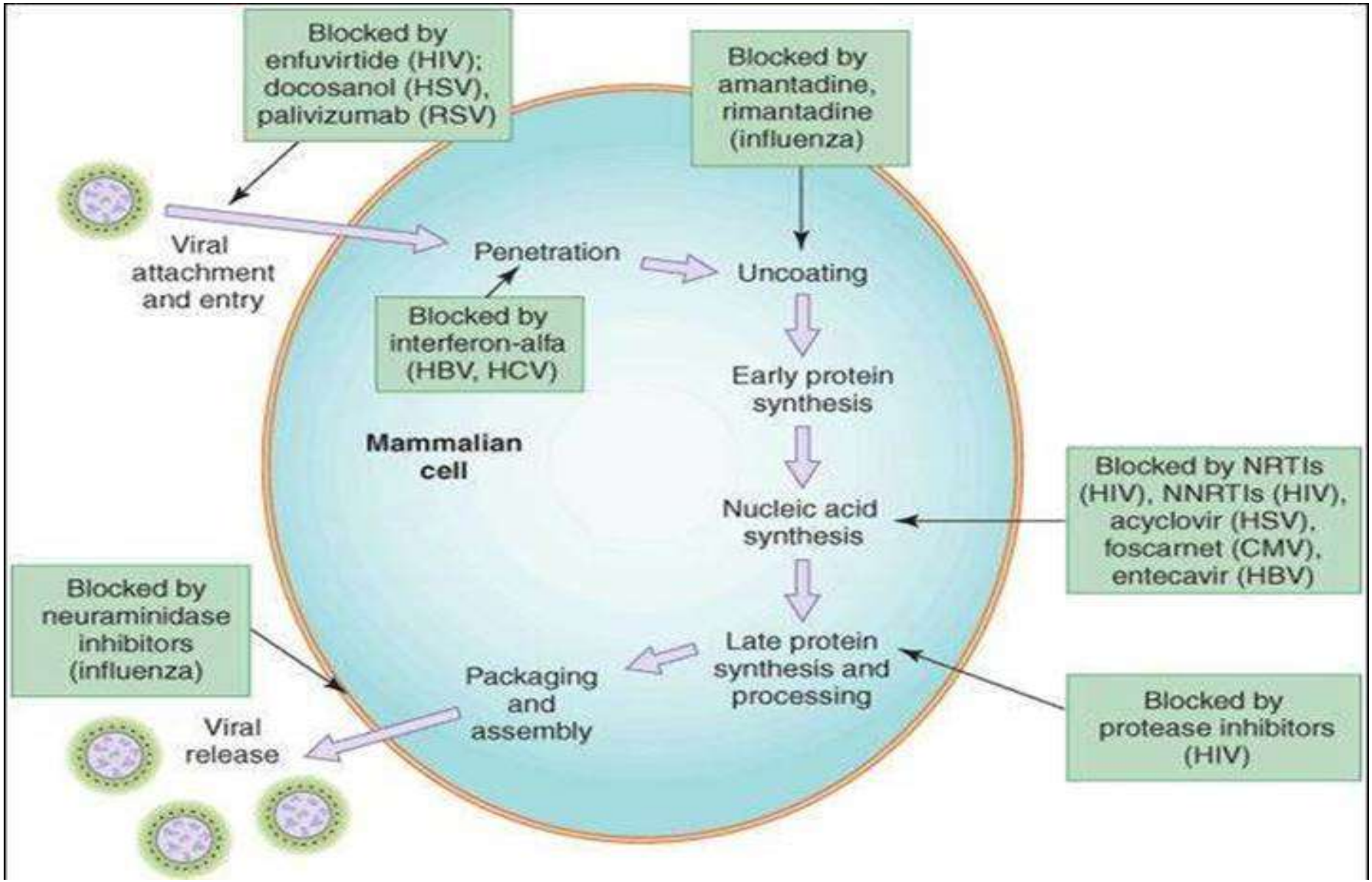
- Antiviral drugs are a class of medicines particularly used for the treatment of viral infection.
- Drugs that combat viral infections are called antiviral drugs.
- Viruses are among the major pathogenic agents that cause number of serious diseases in humans, animals and plants.
- Many antiviral drugs are Purine or Pyrimidine analogs.Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.

Developing strategies for the antiviral drugs are focused on two different approaches:

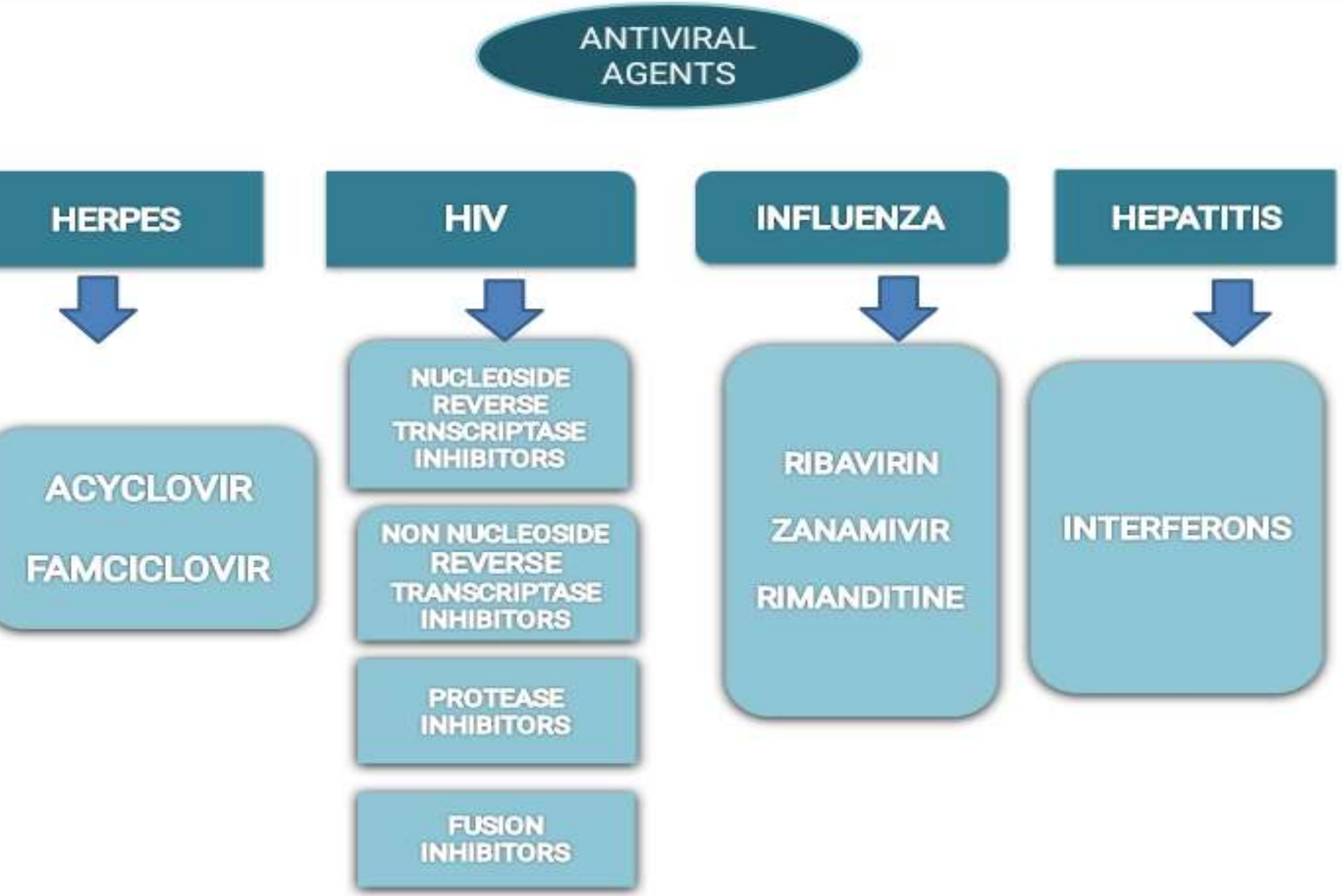
1. Targeting the viruses themselves or the host cell factors.

2. Antiviral drugs that directly target the viruses include the inhibitors of virus attachment, inhibitors of virus entry, uncoating inhibitors, polymerase inhibitors, protease inhibitors, inhibitors of nucleoside and nucleotide reverse transcriptase and the inhibitors of integrase.

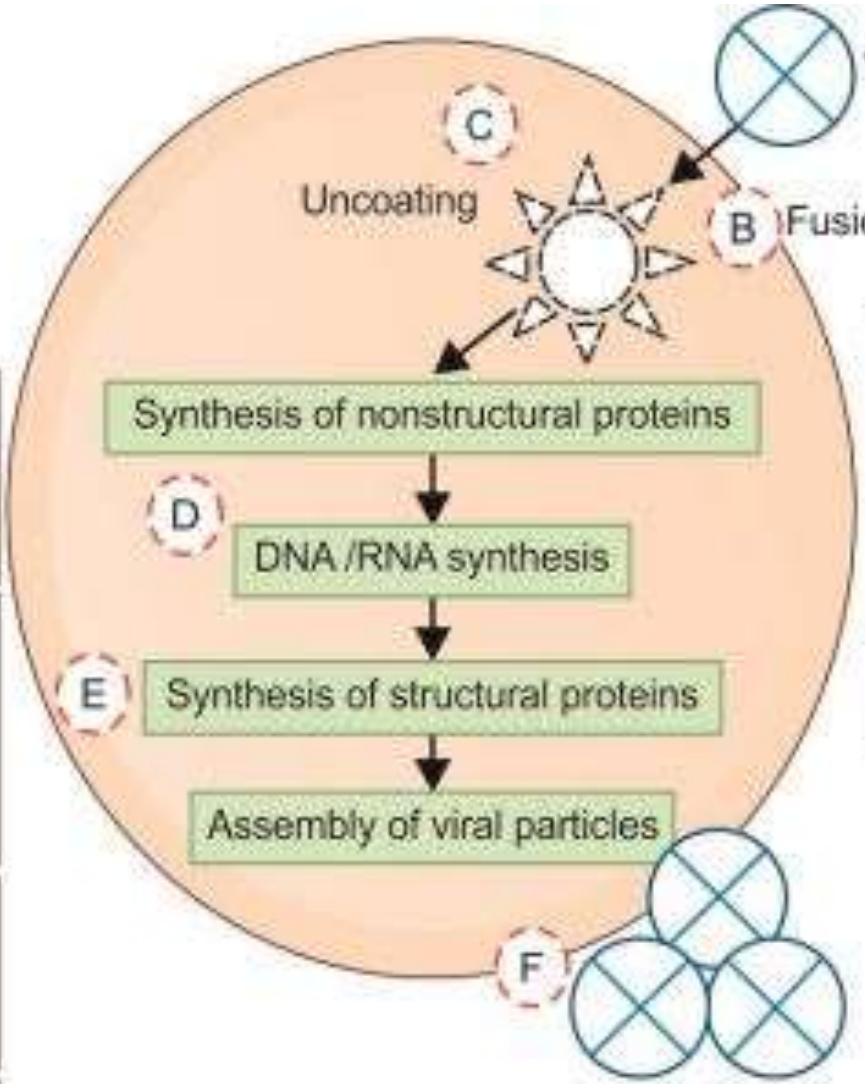
MECHANISM OF ANTIVIRAL AGENTS



CLASSIFICATION OF ANTIVIRAL AGENTS



Targets / Strategies	**Enzymes / Mechanisms**	**Antiviral Drugs**	**Viruses**
Viral enzymes	Polymerase	Acyclovir, Ganciclovir, Penciclovir, Lamivudine, Adefovir, Entecavir, *Valopicitabine*	Herpes viruses HBV *HCV*
	Protease	Amprenavir, Atazanavir, Ritonavir, Tipranavir *VX-950*	HIV *HCV*
	Neuraminidase	Oseltamivir, Zanamivir	Influenza virus
Cellular targets	Receptors or co-receptors	Maraviroc, *Vicriviroc, TNX-355, Pro-140*	HIV
	Capping enzyme	Ribavirin	HCV
	Immune response	Interferons	HBV, HCV
		Actilon	*HCV*
Other viral targets	*Attachment proteins*	*BMS-488043*	*HIV*
	Fusion proteins	Enfuvirtide	HIV
	Disassembly/Uncoating	Amantadine, Rimantadine *Pleconaril*	Influenza virus, *Picornaviruses*
	Virion maturation	*Bevirimat UK-201844*	HIV
Novel strategies	Antisense RNA *Ribozymes*	Fomivirsen	CMV retinitis



D Viral DNA polymerase
Acyclovir
Famciclovir
Foscarnet

D Antiretroviral drugs
NRTI(zidovudine lamivudine)
NRTI(Nevirapine Efavirenz)

E protease inhibitors
Saquinavir
Ritonavir

F Inhibit exit
Neuraminidase Inhibitors

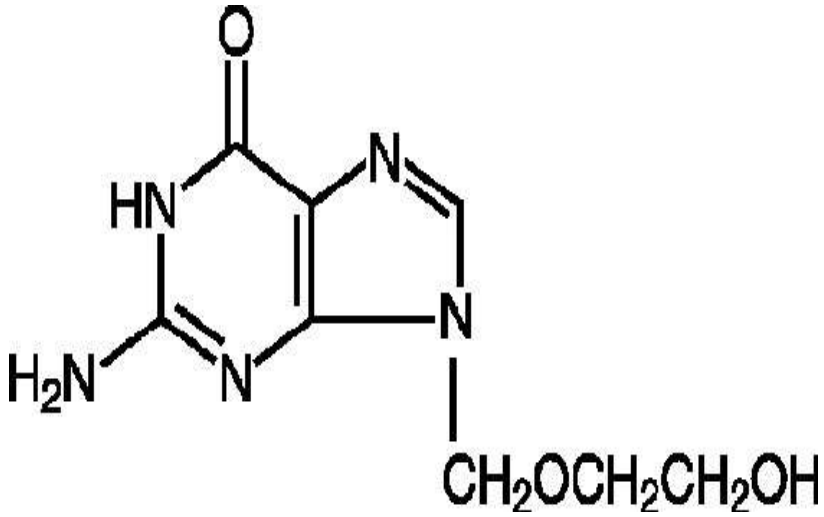
A Inhibit fusion
Immunoglobulin
Enfuviritide (HIV)
Docosanol (HSV)

B Inhibit penetration
IFN-alfa (HBV,HCV)

C Inhibit uncoating
Amantadine

DRUGS FOR HERPES-ACYCLOVIR

- ACYCLOVIR is a guanosine analogue.
- Inhibits DNA synthesis and viral replication .
- Prodrug.
- ACYCLOVIR is thus selectively activated in cells infected with herpes virus
- Uninfected cells do not phosphorylate acyclovir



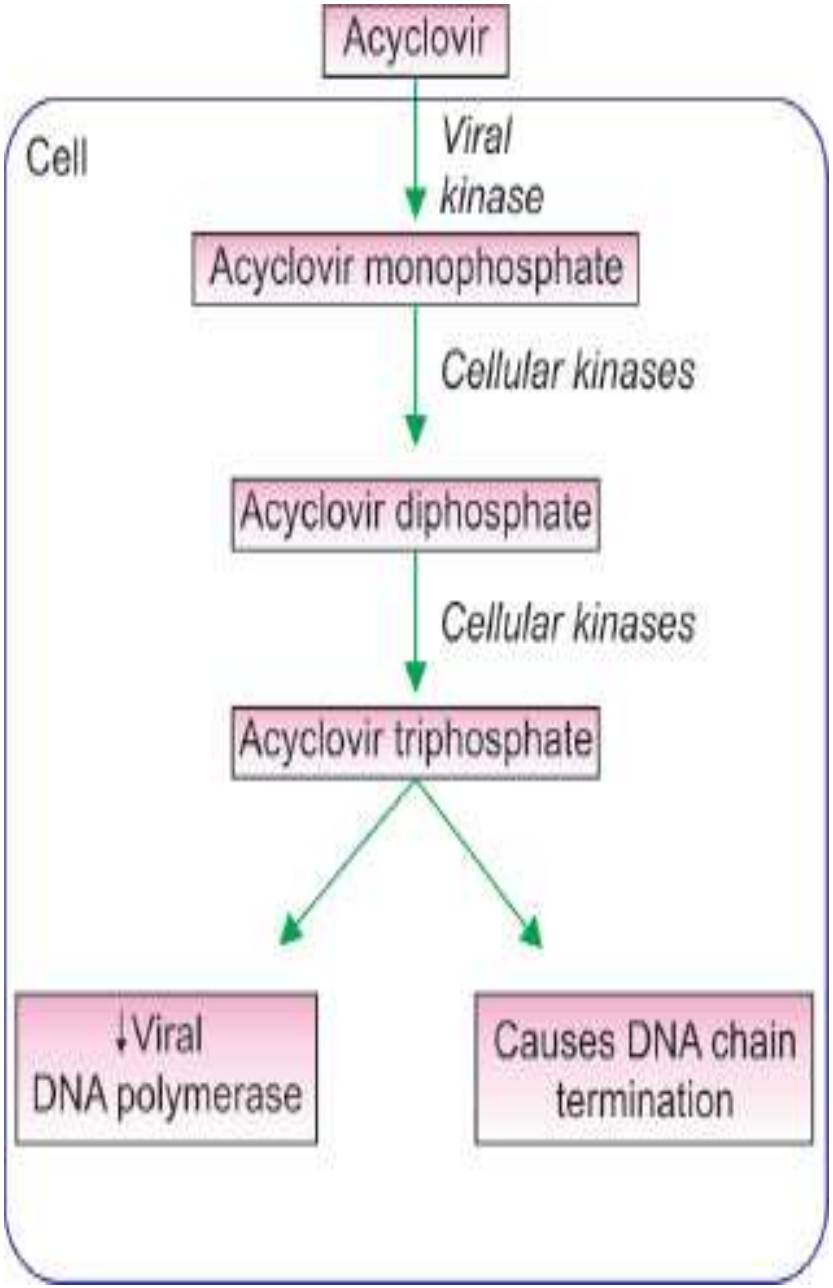
PHARMACOKINETICS

- ✓ **Oral bioavailability ~ 20-30%**
- ✓ **Distribution in all body tissues including CNS**
- ✓ **Renal excretion: > 80%**
- ✓ **Half life: 2-5 hours**
- ✓ **Administration: Topical, Oral , IV depending on severity and recurrences.**

MECHANISM OF ACTION

- **ACYCLOVIR is guanosine analogue,active against hepes simple virus,varialla zoster virus,and Epstein Barr virus.**

- Acyclovir is monophosphorylated in the cell by the herpes virus encoded enzyme thymidine kinase .
- Virus inflected cells are most susceptible.
- The monophosphate analogue is converted to the di and triphosphate forms by the host cell kinase.
- Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA ,causing premature DNA chain termination.



Therapeutic uses of Acyclovir

- **Genital Herpes (HSV–II)** Acyclovir 5% ointment. Late & severe cases, orally or Iv infusion
- **(HSV–I) Mucocutaneous** : Remains localized to lips and gums (Acyclovir skin cream)
- **H.Simplex encephalitis:** IV/8h for 10 days.
- **H. Simplex keratitis:** Acyclovir eye ointment.
- **Chickenpox :** Oral 400mg TDS for 7 days
- **Herpes zoster infections:** Acyclovir less active

Adverse Effects:

- Oral : Headache, nausea, vomiting, diarrhea, vertigo
- IV : Phlebitis, rash , hypotention Nephrotoxicity

DRUGS FOR INFLUENZA-RIBAVIRIN

Is a guanosine analogue.

MECHANISM OF ACTION

- inhibit viral RNA polymerases..
- It is a guanosine (ribonucleic) analog used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor
- Ribavirin is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form, it interferes with RNA metabolism required for viral replication.

PHARMACOKINETICS

- Absorption is increased if it is taken with a fatty meal
- drug distribution in primates have shown retention in all tissues, except brain
- The drug and its metabolites are eliminated in the urine Ribavirin.

USES

- Treat respiratory syncytial virus (RSV).
- Treat influenza A and B.
- HCV , HBV in combination with Interferon alpha .

ADVERSE EFFECTS

- Hemolytic anemia
- Teratogenic in pregnancy

DRUGS FOR HIV

1.NRTI (nucleoside/nucleotide Reverse transcriptase inhibitors)

Drugs: •Tenofovir •Didanosine

MECHANISM OF ACTION

NRTIs act by competitive inhibition of HIV-1 reverse transcriptase – Incorporation into growing viral DNA chain causes premature chain termination due to inhibition of binding with the incoming nucleotide.

ADVERSE EFFECTS

- **neurotoxic**
- **neuropathy Pancreatitis**

2. NNRTI (non-nucleoside Reverse transcriptase inhibitors)

Drugs: •Delavirdine •Etravirine

MECHANISM OF ACTION

Bind directly to HIV-1 reverse transcriptase, resulting in inhibition of RNA and DNA dependent polymerase activity. It do not require phosphorylation to be active

ADVERSE EFFECTS

- Skin rash
- GI intolernce

3. PI (Protease inhibitors)

Drugs: •Indinavir •Ritonavir

MECHANISM OF ACTION

PIs prevent the processing of viral proteins into functional conformations, resulting immature, noninfectious viral particles

ADVERSE EFFECTS

Redistribution of accumulation of body fat

4. FI (Fusion inhibitors)

Drugs: •Enfuvirtide

MECHANISM OF ACTION

Fusion inhibitor that blocks HIV entry into the cell ,binds to subunit of the viral envelope glycoprotein.

ADVERSE EFFECTS

local injection site reactions.

DRUG DISCOVERY AND DEVELOPMENT

- TOPIC: **ANTI CANCER AGENTS**

INTRODUCTION

ANTICANCER DRUGS

- Anticancer drug also called ANTINEOPLASTIC drug,

  any drug that is effective in the treatment of malignant, or cancerous, disease.

- There are several major classes of anticancer drugs: these include alkylating agents, antimetabolites, natural products, and hormones.

- Discovery of anticancer agents started after 1940's. Most of the agents were discovered in 1950-1970.

AIM OF THE CANCER THERPY

- Cure or prolong remission
- Palliation
- Adjuvant chemotherapy

CURED

- Present cause has been addressed
- Signs and symptoms have faded
- Healing has completed
- No more medicines are needed

REMISSION

- Present cause has not been addressed
- Some signs and symptoms diminished
- Healing might have progressed
- Medicines are often necessary

PALLIATION

- Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and other problems, physical, psychosocial and spiritual.

- Life prolonged by chemotherapy: Breast cancer, ovarian cancer, myeloma, prostatic carcinoma, neck and lung cancer.

ADJUVANT CHEMOTHERAPY

- Drugs used to clear residual malignant cells after surgery/radiotherapy.

- Adjuvant chemotherapy may achieve apparent cure, especially in early breast cancer, lung cancer and colonic cancer.

THERAPEUTIC EFFECT OF ANTICANCER AGENTS

- Cancer arise form a single malignant cell, the therapeutic goal of cancer chemotherapy may require "total tumour cell kill".

- Therapeutic effect achieved by killing actively "growing tumour cells".

- Anticancer agents should act only at "specific stages in the cell cycle".

Classification of anticancer agents

- Major class of drugs
- A. Cytotoxic drugs
- B. Targeted drugs
- C. Hormonal drugs

a.Cytotoxic drugs

- 1.Alkalyting agents
- 2.Platinum coordination: Cisplatin, Carboplatin, Oxaliplatin
- 3.Antimetabolites
- 4.Microtubule damaging agents:Vincristine, Vinblastine,Vinorelbine,Paclitaxel,Docetaxel
- 5.Topoisomerase-2 inhibitors: Etoposide
- 6.Topoisomerase-1 inhibitors: Topotecan, Irinotecan
- 7.Antibodies:Actinomycin D, Doxorubicin, Mitomycin C.
- 8.Miscellaneous: Hydroxyurea, Arsenic trioxide

b.Targeted drugs

- 1.Tyrosine proteinkinase inhibitors: Imatinib, Nilotinib
- 2.EGF receptor inhibitors : Gefitinib, Erlotinib
- 3.Angiogenesis inhibitors: Bevacizumab
- 4.Proteasome inhibitors: Bortezomab
- 5.Unarmed monoclonal antibody: Rituximab, Trastuzumab

c.Hormonal drugs

- 1.Glucocarticodes:Prednisolone
- 2.Estrogen: Fosfestrol
- 3.Aromatase inhibitors: Letrozole, Anastrozole
- 4.Antiandrogen: Flutamide
- 5.GnRH analogues: Nafarelin, Triotorelin
- 6.Progestins: Hydroxyprogesterone acetate

EAMPLES OF ANTICANCER DRUGS

DOCETAXEL:

- DOCETAXEL is a taxoid antineoplastic agent used in the treatment of various cancers, such as locally advanced or metastatic breast cancer, metastatic prostate cancer, gastric adenocarcinoma, and head and neck cancer.
- BRAND NAME: Taxotere
- GENERIC NAME: Docetaxel
- DRUG BANK ACCESSION NUMBER: DB01248
- TYPE: Small molecule
- WEIGHT: Average-807.8792
- CHEMICAL FORMULA: C43H53NO14

MECHANISM OF ACTION

- Docetaxel interferes with the normal function of microtubule growth.
- Whereas drugs like colchicine cause the depolymerization of microtubules in vivo, docetaxel arrests their function by having the opposite effect; it hyper-stabilizers their structures.
- This destroys the cells ability to use its cytoskeleton in a flexible manner. Specifically, docetaxel binds to the β-subunit of tubulin.
- Tubulin is the “building block” of microtubules, and the binding of docetaxel locks these building blocks in place.

- The resulting microtubule/ docetaxel complex does not have the ability to dissemble.
- This adversely affects cell function because the shortening and lengthening of microtubules is necessary for their function as a transportation highway for the cell.
- Chromosomes, for example, rely upon this property of microtubules during mitosis.

EPIRUBICIN:

- Epirubicin is an anthracycline topoisomerase II inhibitor used as an adjuvant to treating axillary node metastases in patients who have undergone surgical resection of primary breast cancer.
- BRAND NAME: Ellence, Pharmorubicir PFS
- GENERIC NAME: Epirubicin
- DRUG BANK ACCESSION NUMBER: DB00445
- TYPE: Small molecule
- WEIGHT: Average- 543.5193
- CHEMICAL FORMULA: C27H29NO11

MECHANISM OF ACTION

- Epirubicin has antimitotic and cytotoxic activity.
- It inhibits nucleic acid (DNA & RNA) and protein synthesis through a number of proposed mechanisms of action: Epirubicin forms complexes with DNA by intercalation between base pairs, and it inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the religation portion of the ligation-religation reaction that topoisomerase II catalyzes.
- It also interferes with DNA replication and transcription by inhibiting DNA helicase activity.

ANTIMICROBIAL AGENTS

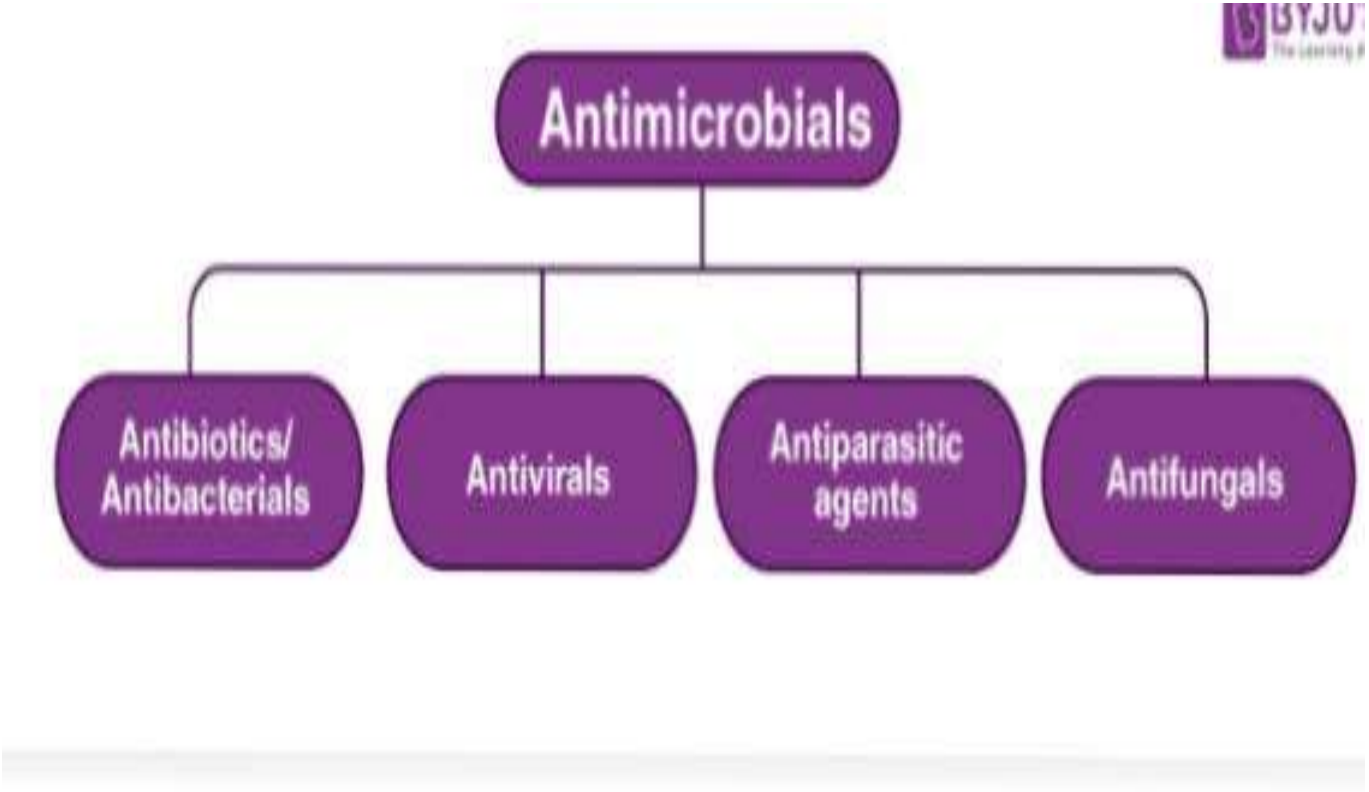
Definition

- An antimicrobial agent is defined as **a natural or synthetic substance that kills or inhibits the growth of microorganisms such as bacteria, fungi and algae.**

Selection of antimicrobial agents

- Selection of the most appropriate antimicrobial agent requires **knowing**
- 1) the organism's identity
- 2) the **organism's susceptibility** to antibiotic.
- 3) the **site of the infection**
- 4) patient factors
- 5) the safety of the antibiotic.
- 6) the cost of therapy.

Classification



1. ***Antibacterial drug:*** A drug that is used to inhibit the pathogenic activity of bacteria is called as antibacterial drugs. Example: Zithromax.
2. ***Antifungal drug:*** A drug that is used to prevent the fungal activity in the host is called an antifungal drug. Example: Miconazole
3. ***Antiviral agent:*** A drug which is used to stop the pathogenic action of a virus is called as antiviral agents. Example: Tamiflu.
4. ***Antiparasitic drug:*** A drug that is used to prevent the growth of pathogenic parasites. Example: Anthelmintics

General characteristics of antimicrobial drugs

- Side effects – undesirable effects of drugs on host cells
- Narrow-spectrum drugs – attack only a few different pathogens
- Broad-spectrum drugs – attack many different pathogens
- Cidal agent - kills microbes
- Static agent - inhibits growth of microbes

Advantages of combination of antimicrobial agents

1-Therapy of sever infection in which a cause is unknown.(community-acquired pneumonia).

2-treatment of polymicrobial infection.(hepatic , brain abscesses.

3-enhancement of antibacterial activity of drug (synergism)enterococcal endocarditis.

4-prevention of emergence of resistance microorganisms. (tuerculosis).

Disadvantages of combination of antimicrobial agents

1- increased risk of toxicity

2-eradication of normal host flora(super infection).

3-increase cost.

DRUGS FOR ANTIBACTERIAL

Aminoglycosides

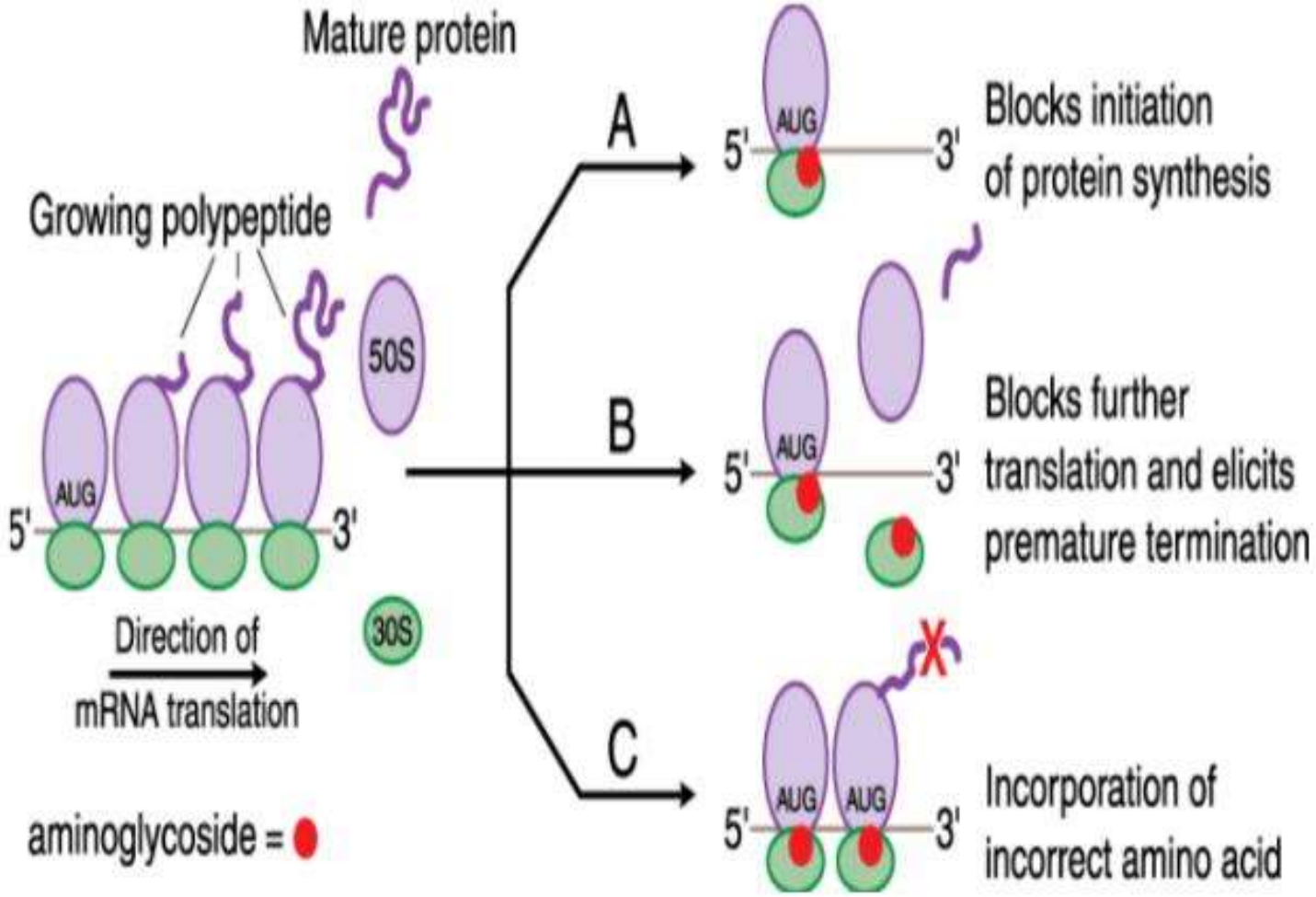
1. Aminoglycosides are group of natural and semi -synthetic antibiotics. They have polybasic amino groups linked glycosidically to two or more aminosugar like: sterptidine, 2-deoxy streptamine, glucosamine

2. Aminoglycosides which are derived from: Streptomyces genus are named with the suffix –**mycin.** While those which are derived from Micromonospora are named with the suffix –**micin.**

Mechanisms of action

Aminoglycosides bind to the 16S rRNA of the 30S subunit and inhibit protein synthesis.

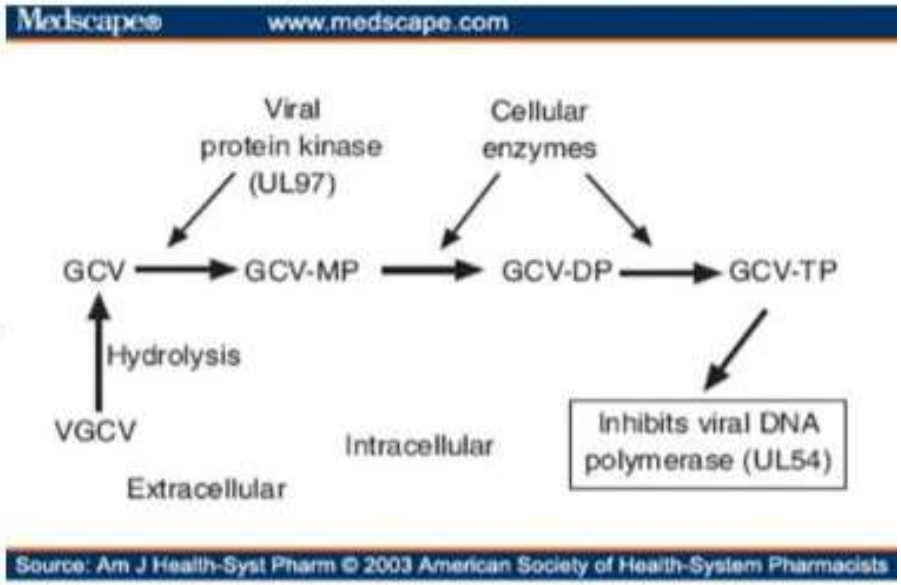
1. **Transport of aminoglycoside through cell wall and cytoplasmic membrane.**
   a) Diffuse across cell wall of gram negative bacteria by porin channels.
   b) Transport across cell membrane by carrier mediated process liked with electron transport chain
2. **Binding to ribosome resulting in inhibition of protein synthesis**


Mature protein
Growing polypeptide
50S
30S
AUG
5'
3'
Direction of
mRNA translation
aminoglycoside =
A
B
C
Blocks initiation
of protein synthesis
Blocks further
translation and elicits
premature termination
Incorporation of
incorrect amino acid

DRUG FOR ANTIVIRAL

Ganciclovir mechanism of action

- Competes with deoxyguanosine triphosphate similar to acyclovir
- However in CMV, viral-encoded phosphotransferase converts to ganciclovir triphosphate
- Unlike acyclovir, ganciclovir contains a 3'-hydroxyl group, allowing for DNA to continue



Adverse effects of ganciclovir

- reversible pancytopenia (most common)
- Fever
- Rash
- Phlebitis,
- Confusion
- Renal dysfunction
- Psychiatric disturbances
- Seizures

Drug for anti-parasitic

Anthelmintic Mechanism of action

- a. Drugs affecting energy production

i. Inhibitors of fumarate reductase and glucose uptake, binding of tubulin in mitochondria.

Ii. Inhibitors of (mitochdrial) phosphorylation

iii. Inhibitors of glycolysis

b. Drugs causing paralysis

i. Cholinergic agents

ii. GABA agonists

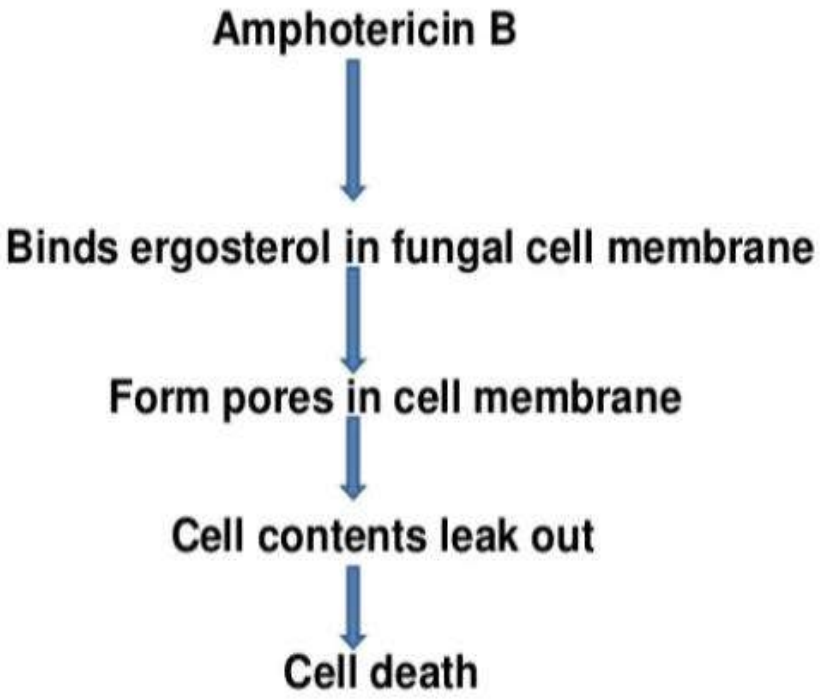
iii. Muscle hyperpolarizer

iv. Acetyl cholinesterase inhibitors

v. Acetylcholine mimic

Drug for antifungal

Amphotericin B



Separation Techniques

- Chromatography is an important biophysical technique that enables the separation, identification, and purification of the components of a mixture for qualitative and quantitative analysis. Proteins can be purified based on characteristics such as size and shape, total charge, hydrophobic groups present on the surface, and binding capacity with the stationary phase. Four separation techniques based on molecular characteristics and interaction type use mechanisms of ion exchange, surface adsorption, partition, and size exclusion. Other chromatography techniques are based on the stationary bed, including column, thin layer, and paper chromatography. Column chromatography is one of the most common methods of protein purification.

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- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.