7. IMMUNO-MODULATING DRUGS:

IMMUNOSTIMULANT DRUGS

CLINICAL PHARMACOLOGY OF IMMUNOMODULATING DRUGS

DR SHAMS SULEMAN

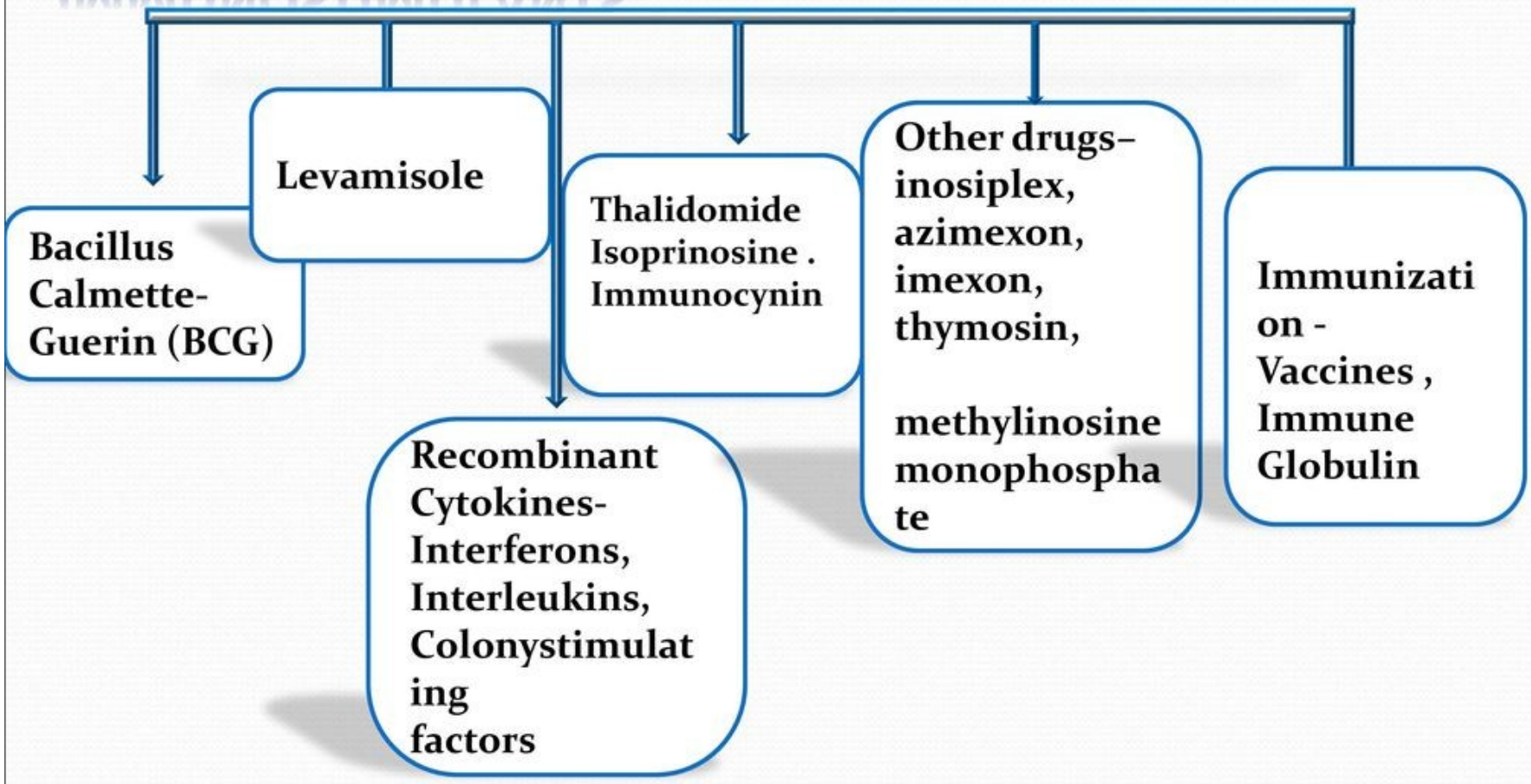
LEARNING OBJECTIVES

- Describe mechanism of action of immunostimulant drugs
- Describe clinical uses and adverse effects of immunostimulant drugs
- Describe the advantages and disadvantages of various combinations of immunomodulating drugs

IMMUNOSTIMULANTS

- Aldesleukin
- Interferon: α, β, γ
- BCG (Bacille Calmette Guerrian)
- Recombinant TNF α
- Thalidomide
- Levamisole
- Lipopolysaccharides; Gram negative endotoxins
- G-CSF / GM-CSF / Oprelvekin

IMMUNOSTIMULANTS

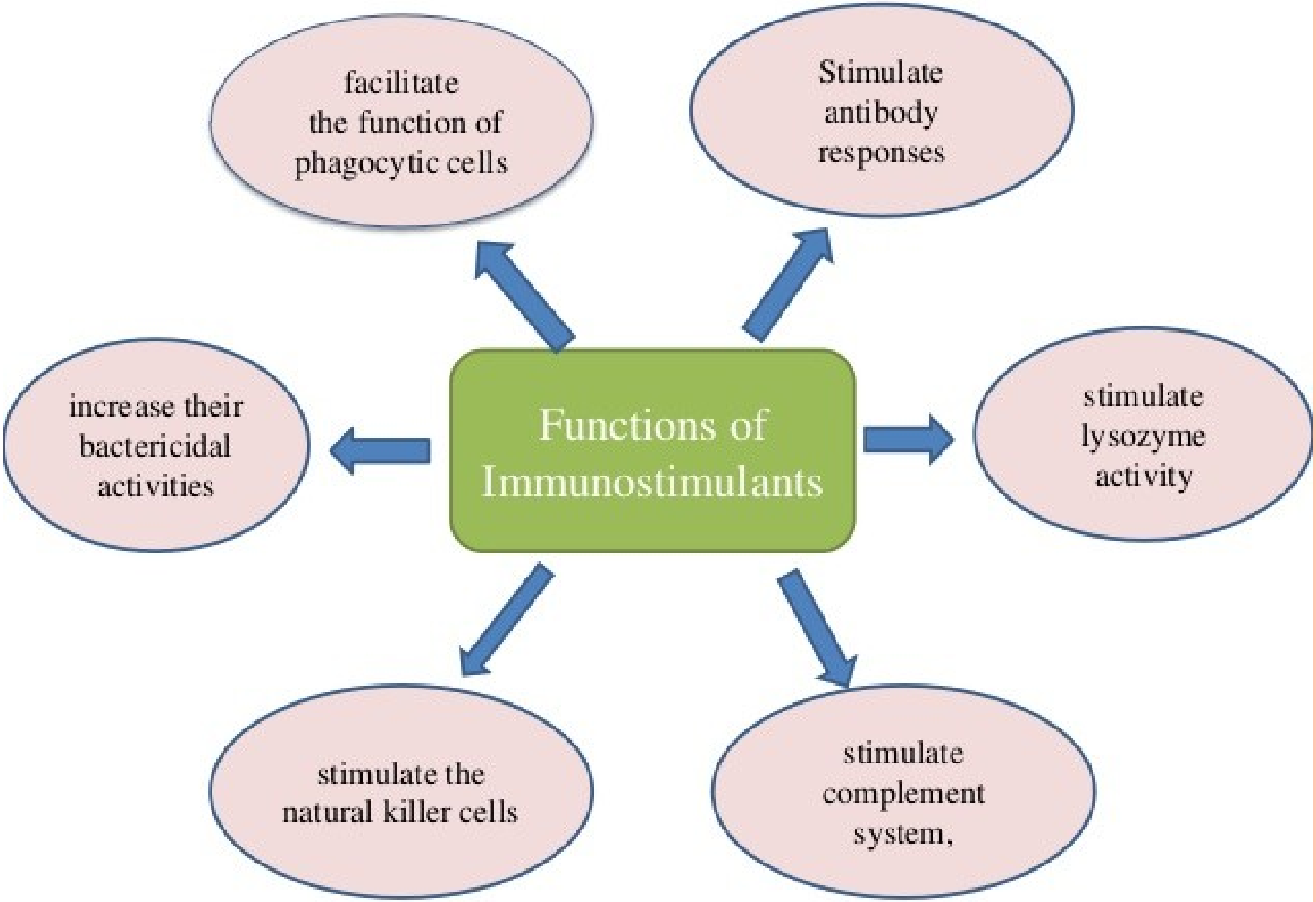


Cytokines

- INF
- IL
- TNF
- Hemopoietic growth factors (G-CSF, M-CSF, GM-CSF, etc)
- These are now available for use by rDNA technology
- Applications in the treatment of viral infections, autoimmune and neoplastic diseases

Immunostimulants

- Increase the immune responsiveness of patients who have either selective or generalized immunodeficiency.
- Used in immunodeficiency disorders, chronic infectious diseases, cancer and HIV.


facilitate
the function of
phagocytic cells
Stimulate
antibody
responses
increase their
bactericidal
activities
Functions of
Immunostimulants
stimulate
lysozyme
activity
stimulate the
natural killer cells
stimulate
complement
system,

Immunostimulants

USES:

- immunodeficiency disorders
- Chronic infections
- cancer


PROLEUKIN®
18 x 10⁶ IU
Aldesleukin
Powder for solution for infusion
Poudre pour solution perfusion
Polvo para solución perfusion
1 vial / 1 flacon de / 1 vial de 22 x 10⁶ IU (1.1 mg/ml)
NOVARTIS
PROLEUKIN
18 x 10⁶ IU
Aldesleukin

Aldesleukin

Mode of action

- The drug is a *recombinant version of interleukin-2.*
- It induces proliferation of B and T cells (including cytotoxic T cells) and activation of natural killer cells and lymphokine-activated killer cells.
- The mechanism of antitumor activity is unknown but is probably related to the activation of cytotoxic T cells.

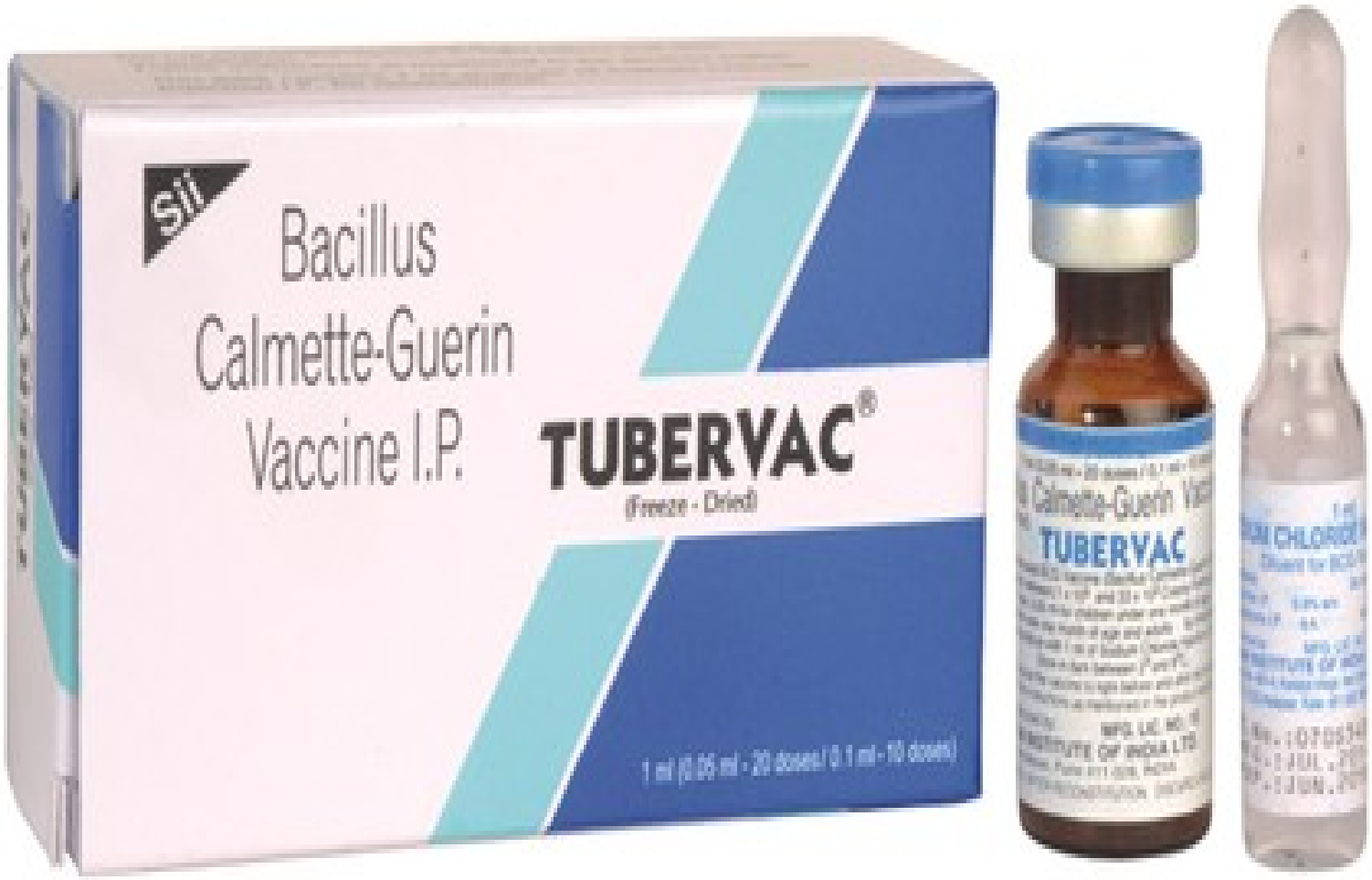
Toxicity

- Hypotension (70%),sinus tachycardia (70%), pulmonary congestion (50%) and edema (50%).
- Acute renal failure(60%)
- Mental status changes (70%)
- Nausea/vomiting and diarrhea (70%)
- Anemia, thrombocytopenia (70%).

Clinical uses

- Renal cell carcinoma, malignant melanoma

BCG


SII
Bacillus
Calmette-Guerin
Vaccine I.P.
TUBERVAC®
(Freeze - Dried)
1 ml (0.05 ml - 20 doses / 0.1 ml - 10 doses)
TUBERVAC

BCG vaccine

- Bacille Calmette Guerin (BCG).
- First used in 1921.
- Only vaccine available today for protection against tuberculosis.
- It is most effective in protecting children from the disease.
- Given 0.1 ml intradermally.
- Duration of Protection 15 to 20 years
- Efficacy 0 to 80%.

- Should be given to all healthy infants as soon as possible after birth unless the child presented with symptomatic HIV infection.

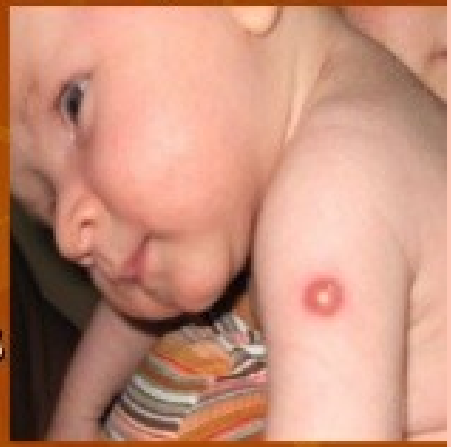
Bacillus Calmette-Guerin (BCG)

Live, attenuated culture of BCG strain of Mycobacterium Bovis

MOA

Induction of a granulomatous reaction at the site of administration. It causes activation of macrophages to make them more effective killer cells

Bacillus Calmette-Guerin Vaccine (BCG



SIDE EFFECTS

- ***Local***
  - Skin ulceration, regional lymphadenitis
  - Subcutaneous abscess
- ***Generalized***
  - Anaphylaxis, generalized BCG infection
  - (rare): osteitis
  - Potential factors affecting the rate of adverse reactions include the BCG dose, vaccine strain, and method of vaccine administration

Bacille Calmette-Guerin Vaccine

Recommendations for use

- At birth or at 6 weeks with other vaccines
- Catch-up vaccination with BCG: till 5 years of age

CLINICAL PHARMACOLOGY

About Bacille Calmette-Guerin (BCG) vaccine

BCG vaccine named after two French scientists Albert Calmette and Camille Guerin

- First tested on humans in 1921
- Effective in preventing severe forms of TB and leprosy among children
- Recent epidemiological studies correlate BCG with prevention of Covid-19
- Countries where BCG is universally administered have reported less mortality and morbidity due to Covid-19, studies claimed
- WHO maintains more evidence is needed and it does not recommend BCG for prevention of Covid-19

TYPES OF INTERFERON

TYPE I:

Interferon-alpha (leukocyte interferon, about 20 related proteins)
leukocytes, etc

Interferon-beta (fibroblast interferon)
fibroblasts, epithelial cells, etc

TYPE II:

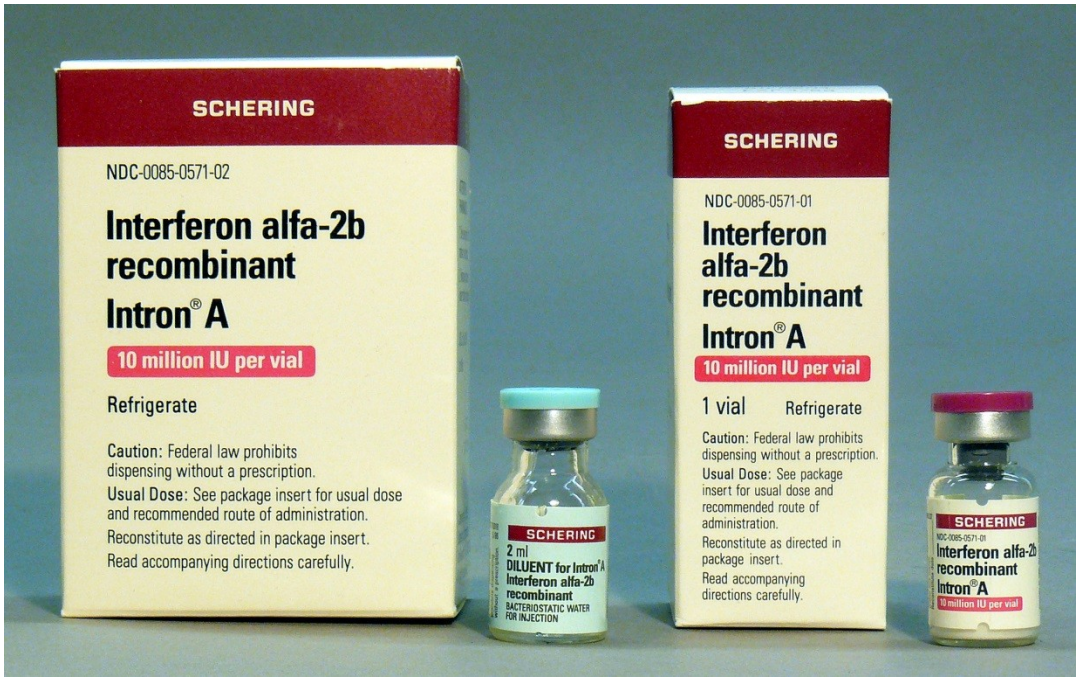
Interferon-gamma (immune interferon)
certain activated T-cells, NK cells

INDUCTION OF INTERFERON

A. IFN-α & β (Type-I- IFNs)	When prototypic cell of origin is exposed to **-Viruses** **-Double stranded RNA** **- Cytokines**
B. IFN-γ (Type-II- IFNs)	Following a number of immunological stimuli including :- **-T-cell specific antigen** **-Staphylococcal enterotoxin -A And** **-Mitogens (Phyto haemagglutinin ,Phorbol Ester etc)**

Morley,Michael. The pharmacology of lymphocytes. Barlin Heidelberg. Springer. 1988.print

INTERFERON ALPHA



- Inducible glycoprotein
- Recombinant DNA
- Glomerular filtration, tubular reabsorption
- All known steps are blocked

Alpha Interferon-2a (Roferon A)

- Protein chain that is 165 amino acids long
- Produced using recombinant DNA technology
- Non-glycosylated protein
- Short half life, short terminal elimination of half life, a large volume of distribution, and a larger reduction in renal clearance.
- These problems were resolved by pegylating alpha-2a resulting in peginterferon alpha-2a that is named Pegasys.

INTERFERON ALPHA: INDICATIONS

- HBV
- HCV
- Condylomata acuminata
- Hairy cell leukemia
- CML (Chronic myeloid leukemia)
- Multiple myeloma
- Non Hodgkin lymphoma (Low grade)
- Cutaneous T cell lymphoma
- Myeloproliferative thrombocytosis
- Kaposi sarcoma
- Renal cell carcinoma
- Malignant melanoma

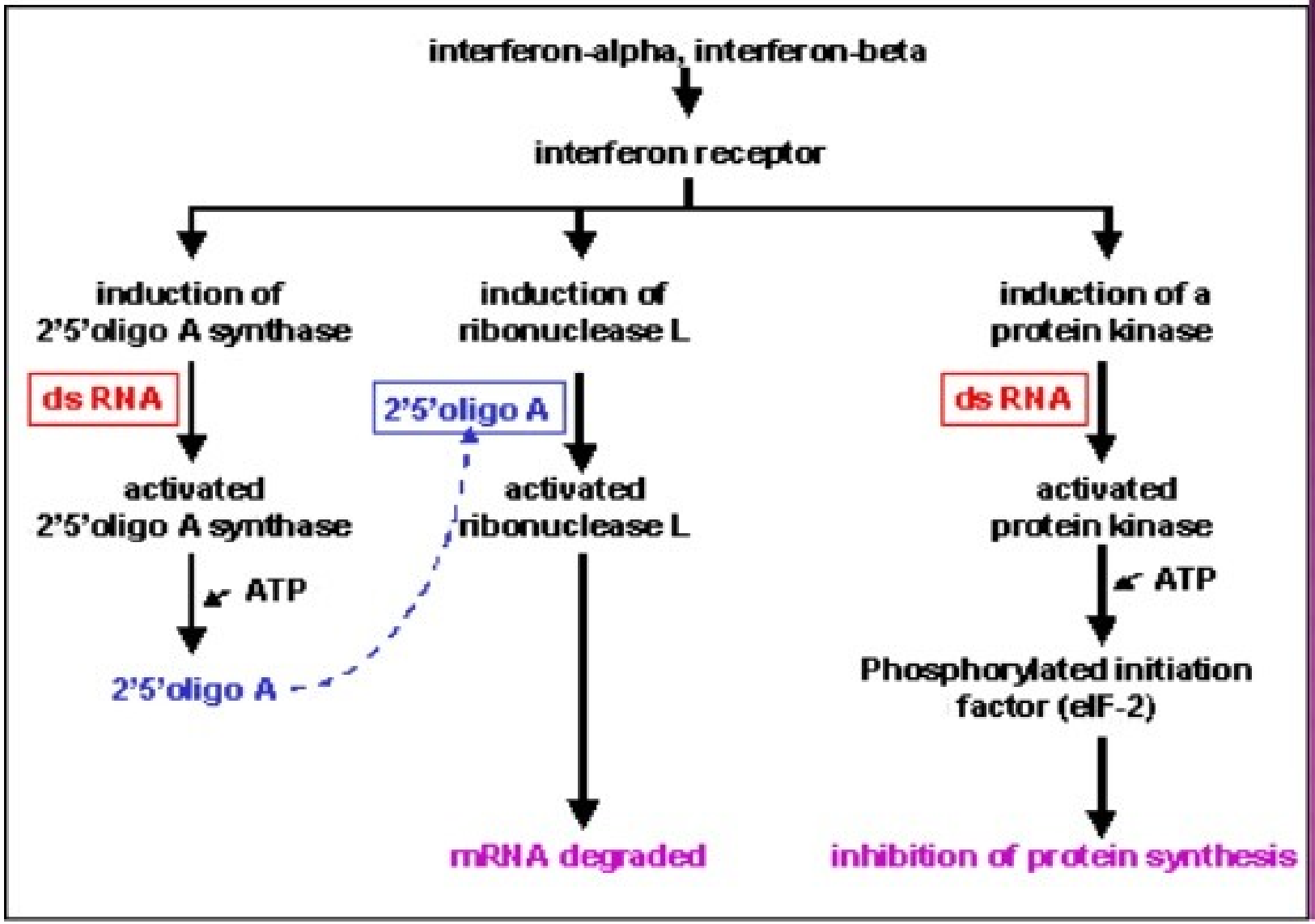
Mechanism of action :

Interferon alpha binds to type I interferon receptors (IFNAR1 and IFNAR2c) which, upon dimerization, activate two Jak (Janus kinase) tyrosine kinases (Jak1 and Tyk2). These transphosphorylate themselves and phosphorylate the receptors. The phosphorylated INFAR receptors then bind to Stat1 and Stat2 (signal transducers and activators of transcription)which dimerize and activate multiple (~100) immunomodulatory and antiviral proteins. Interferon alpha binds less stably to type I interferon receptors than interferon beta.

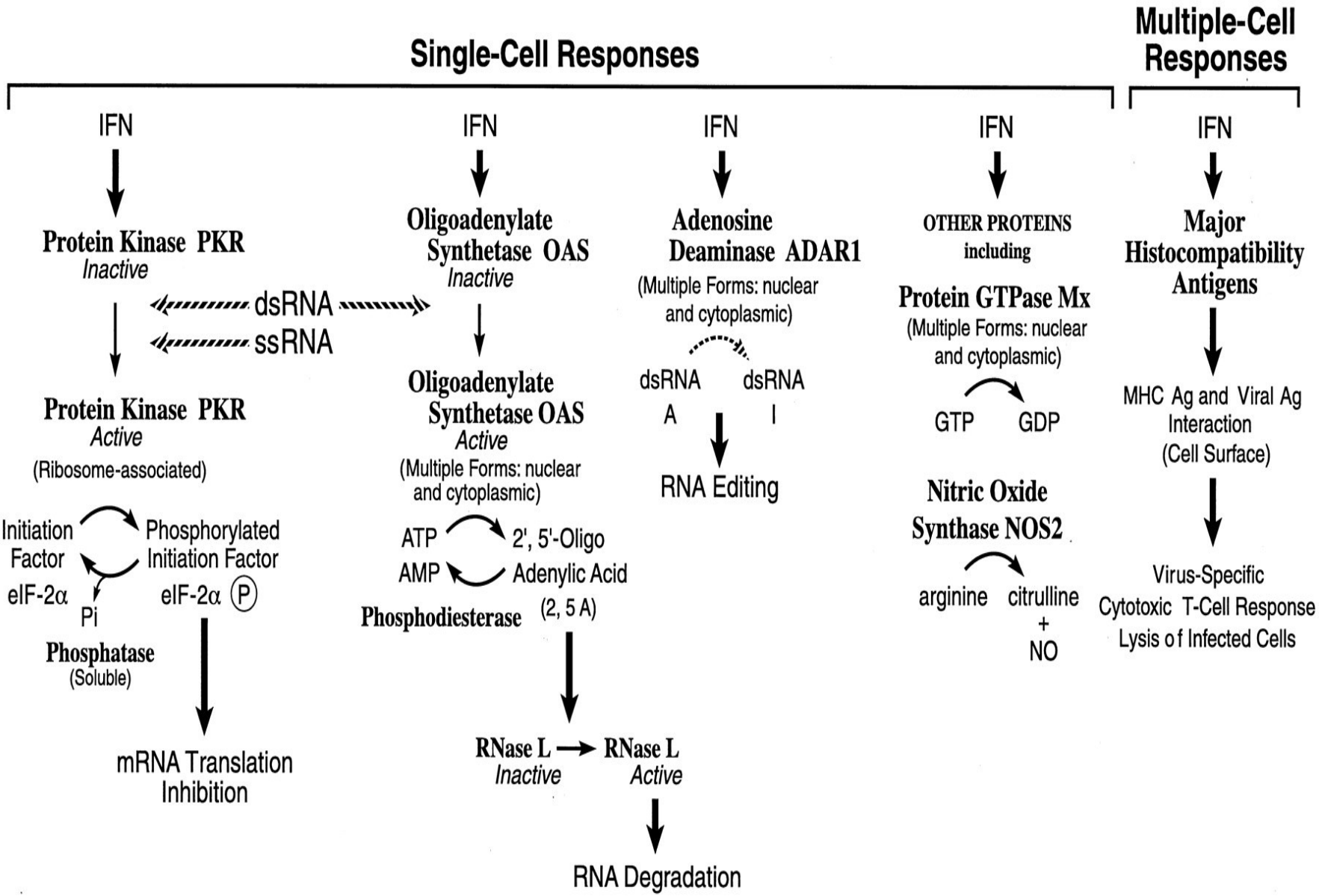
Absorption :

Absorption is high (greater than 80%) when administered intramuscularly or subcutaneously.

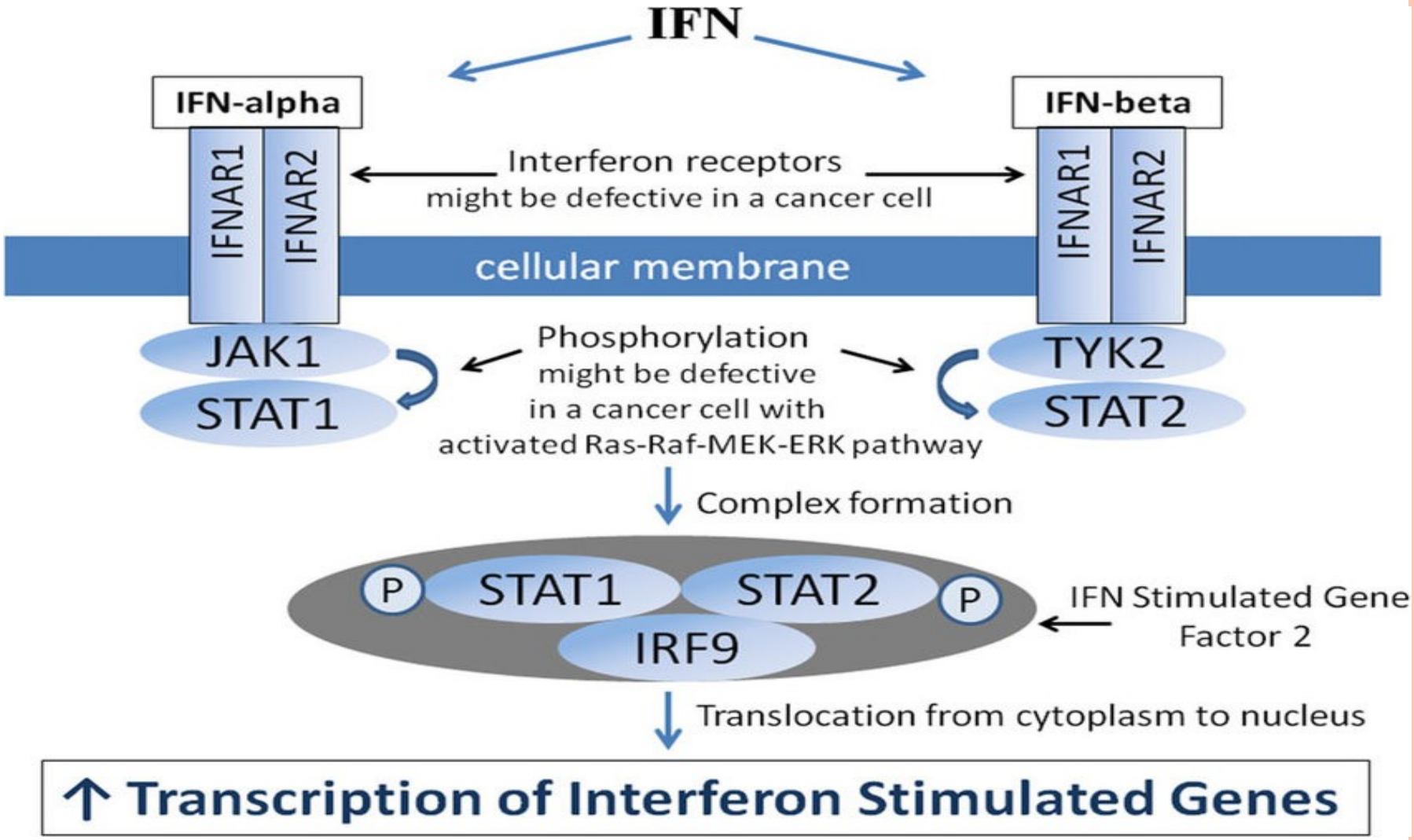
ANTIVIRAL MECHANISM OF INTERFERON



Antiviral Actions of Interferon



MOA IN MALIGNANCIES



INTERFERON ALPHA: TOXICITY

HEMATOLOGIC TOXICITIES

- Hematologic toxicities
  -anemia, neutropenia, and thrombocytopenia.
  Appear to be dose related, rarely reported in lower-dose regimens.
- Neutropenia requiring dosage reduction reported in 26% to 60% of patients receiving high-dose interferon-α.
- Neutropenic fevers or infections requiring antibiotic administration or hospitalization are quite rare.
- Thrombocytopenia -rarely severe enough to warrant dosage reductions.

INTERFERON ALPHA

CONTRAINDICATIONS

- Seizures
- Advanced hepatic and renal failure
- With immunosupressants
- Transplant (B.M, organ)
- Psoriasis

CAUTION

- Diabetes, driving, children
- Abortifacient

MONITER

- Hemoglobin, platelet count
- SGPT

INTERFERON ALFACON

- Monotherapy, 9-15 mcg 3 times a week SC

PEG INTERFERON

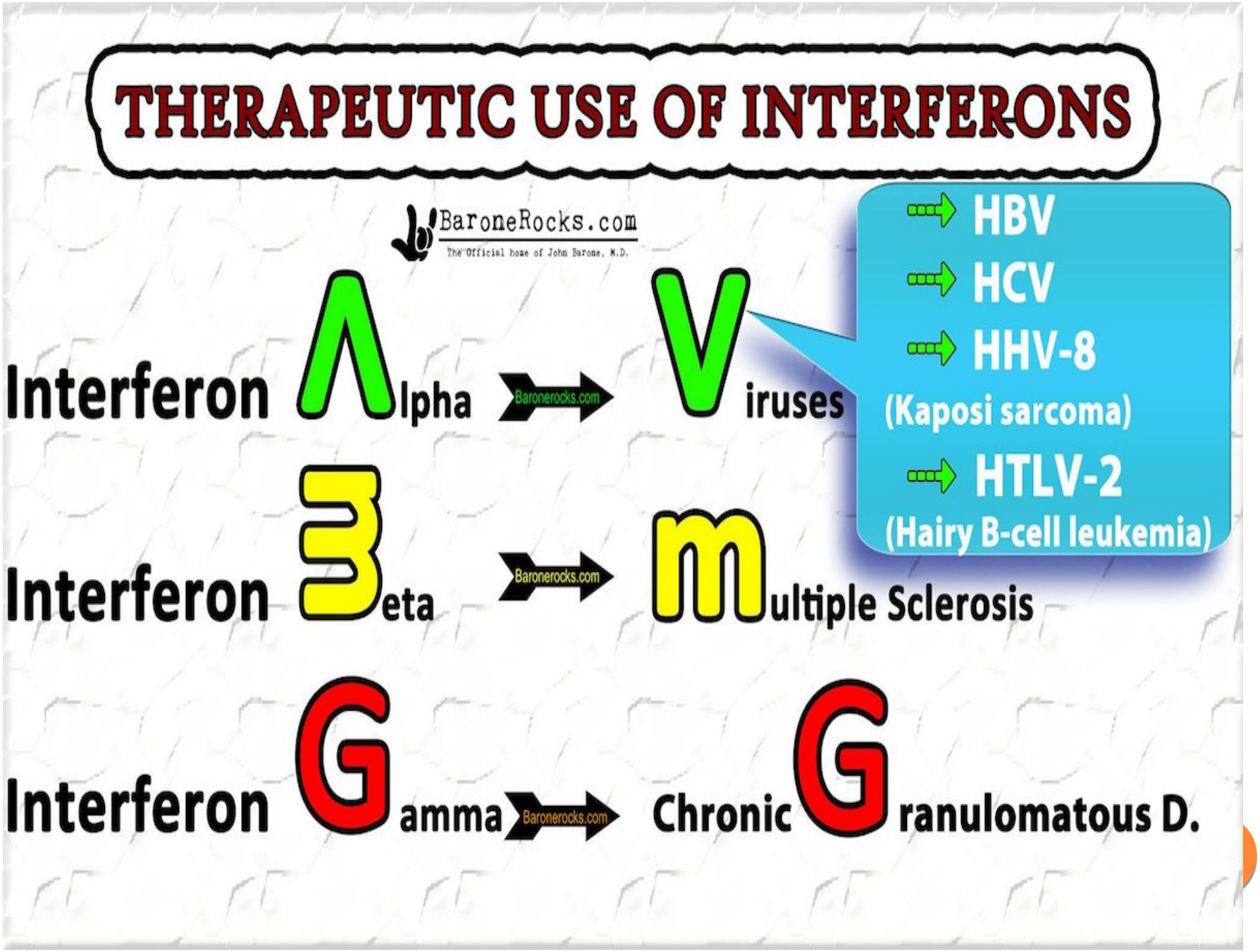
- Polyethylene glycol
  - Increased size, slow clearance
- Once a week
- Given with ribavirin

Interferon alpha

- Pegylated IFNs advantages:
  - Longer half life
  - Administered once a week rather than 3/week
  - Sustained conc rather than peaks and troughs after each injection
  - Twice as effective as standard IFN

PEG IFN alpha **2b**	PEG IFN alpha **2a**
12 kD, linear	40kD, branched
DOSE: 1.5 micro gm /kg (weight based)	180 ug
STORAGE: room temp	refrigerated

THERAPEUTIC USE OF INTERFERONS



CLINICAL PHARMACOLOGY

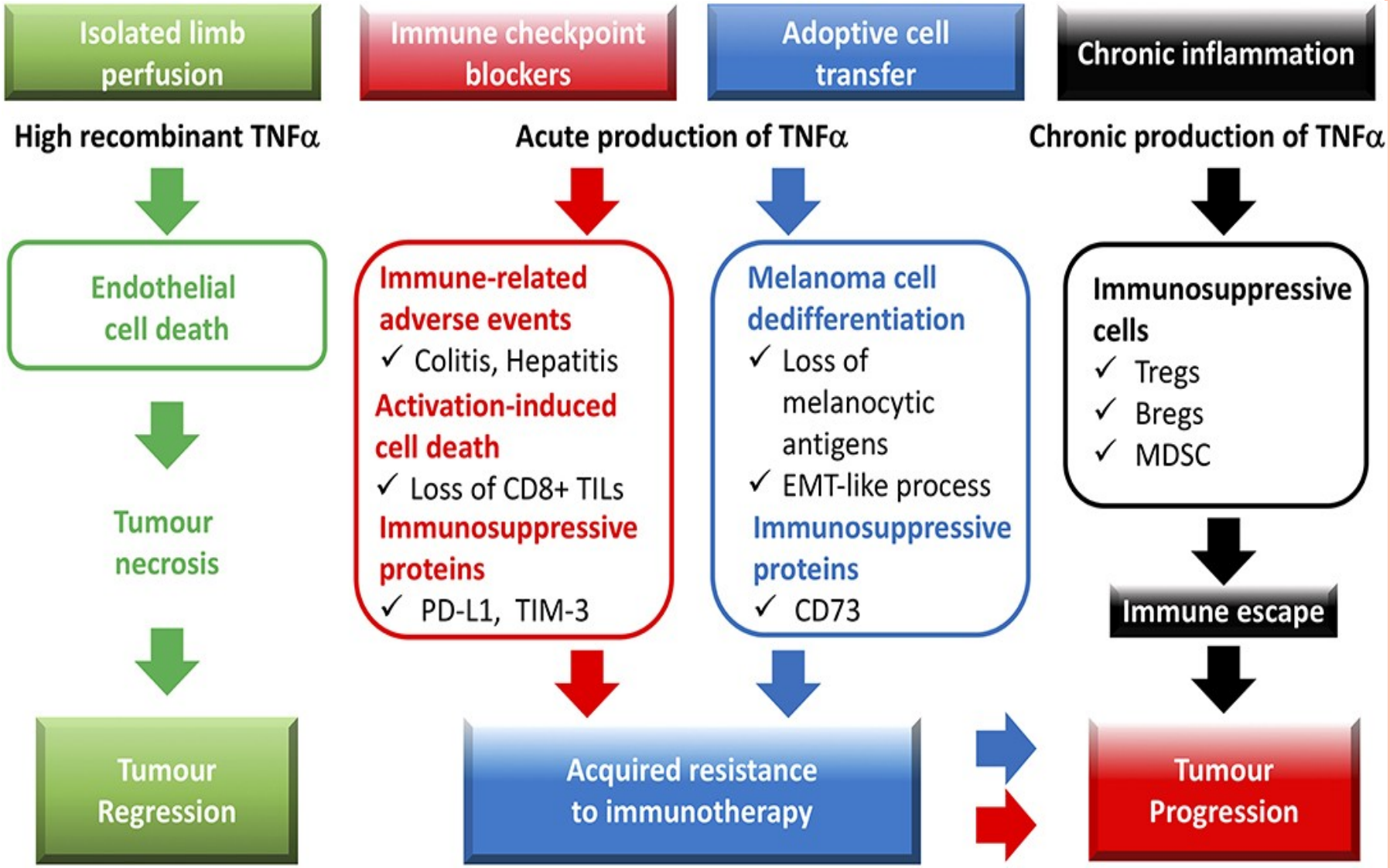
Drugs for Hepatitis Viruses

- Interferon-
- Interferon Alfacon
- PEGylated Interferon (2a, 2b)
- Lamivudine
- Emtricitabine
- Tenofovir
- Adefovir Dipivoxil

Drugs for Hepatitis Viruses

- Entacavir
- Ribavirin
- Ganicyclovir
- Telbivudine
- Clevudine
- Valtrocitabine
- Alamifovir

TNF ALPHA PARADOX




KETRESS
(Levamisole)
tablets 40 mg
ICI PAKISTAN
10 x 3 Tablets
Warning : To be sold on prescription of a registered medical practitioner only.
Each film coated tablet contains Levamisole 40 mg as Levamisole Hydrochloride Ph. Eur.

Levamisole, Tetramisole

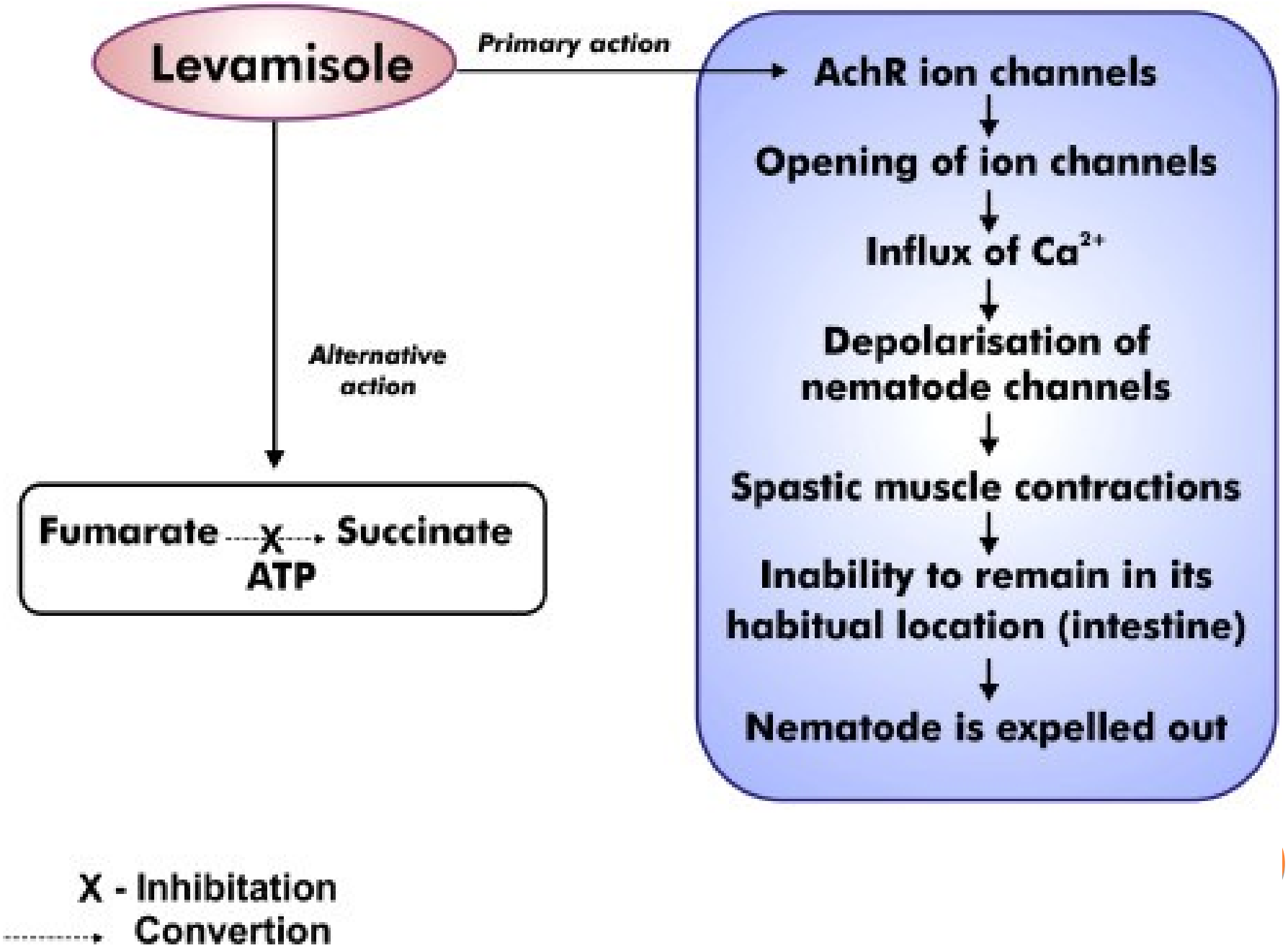
- Tetramisole (D) and levamisole (L) are optical isomers. Levamisole is more active and more preferred.
- They are active against large number of nematodes but their use is restricted to only **ascariasis** and **ancyclostomiasis** because of poor action against other worms.

MOA:

- They stimulate ganglia in worms and cause tonic paralysis → explusion of live worms.
- May also interfere with carbohydrate metabolism (inh. **Fumarate reductase**)

ADRS:

Nausea, abdominal pain, fatigue, drowsiness or insomnia is low.


Levamisole
Primary action
AchR ion channels
Opening of ion channels
Influx of Ca^{2+}
Depolarisation of nematode channels
Spastic muscle contractions
Inability to remain in its habitual location (intestine)
Nematode is expelled out
Alternative action
Fumarate
X
Succinate
ATP
X - Inhibitation
Convertion

Levamisole

- Originally Antihelminthic (drugs that expel parasitic worms)
- Restores depressed immune function of B cells, T cells, Monocytes, Macrophages

USES

- Adjuvant therapy with 5-FU in colon cancer
- Immunodeficiency associated with Hodgkins disease.

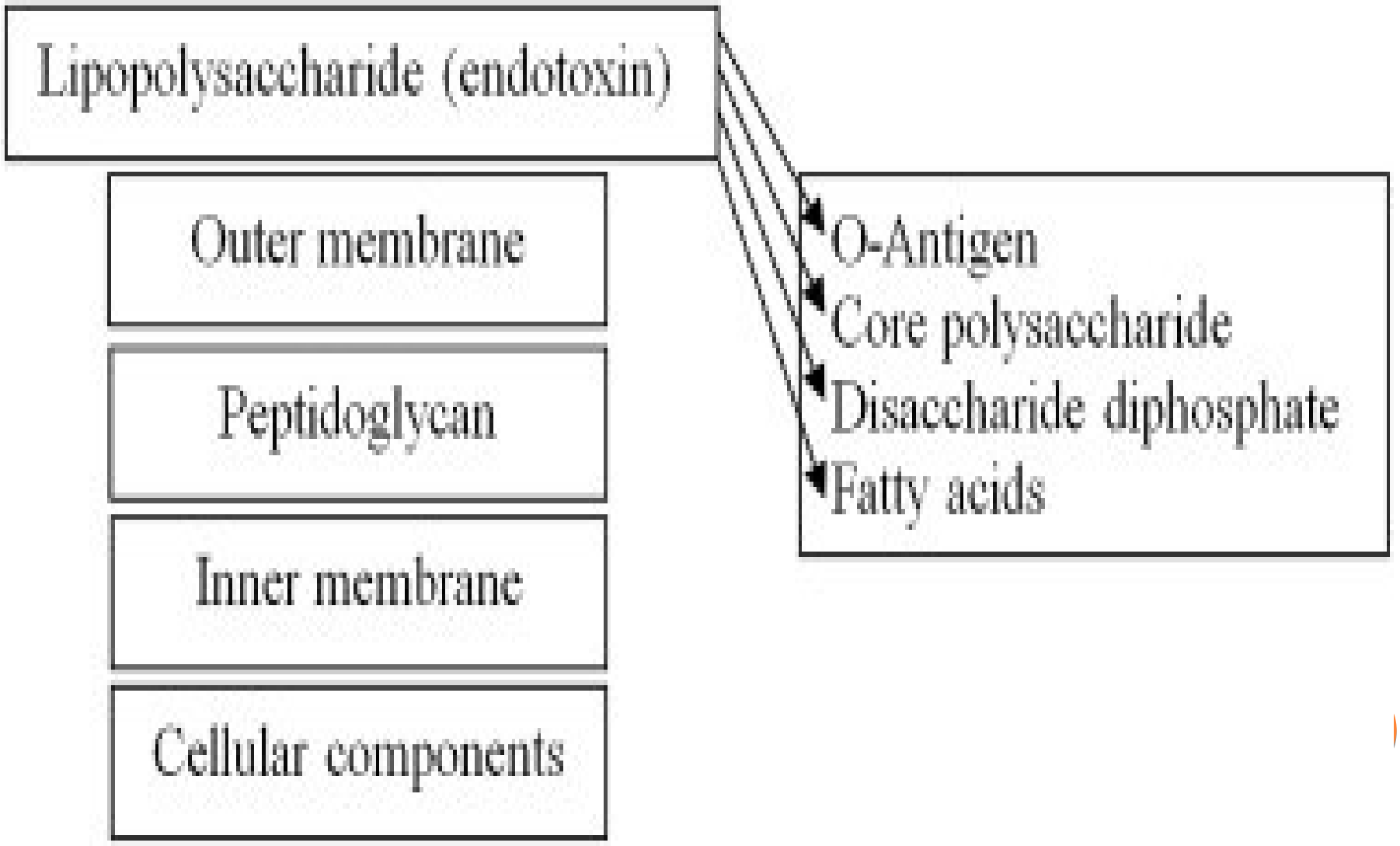
Toxicity

- Fatal Agranulocytosis

ACTIVE VACCINATION

- Active vaccination is the process of injecting individuals with microbial antigens, heat-killed microbes or attenuated living microbes to induce **antibody production and memory B-cells formation.**
- The individual acquires the ability to respond to the microbe he/she has been vaccinated against.

LIPOPOLYSACCHARIDES



TYPES OF VACCINES

Live vaccines	Live Attenuated vaccines	Killed Inactivated vaccines	Toxoids	Cellular fraction vaccines	Recombinant vaccines
•Small pox variola vaccine	•BCG •Typhoid oral •Plague •Oral polio •Yellow fever •Measles •Mumps •Rubella •Intranasal Influenza •Typhus	•Typhoid •Cholera •Pertussis •Plague •Rabies •Salk polio •Intra-muscular influenza •Japanise encephalitis	•Diphtheria •Tetanus	•Meningococcal polysaccharide vaccine •Pneumococcal polysaccharide vaccine •Hepatitis B polypeptide vaccine	•Hepatitis B vaccine

Thalidomide:

- Increases TNFα in patients who are HIV-seropositive.
- But Decreases circulating TNFα in patients with erythema nodosm leprosum
- suggested that the drug affects angiogenesis.
- Teratogenicity is an undesirable effect.

Isoprinosine:

- Isoprinosine is a complex of the pacetamidobenzoate salt of N,N-dimethylamino-2- propanol and inosine (3:1 molar ratio)

ISOPRINOSINE

Leads the production of cytokines such as IL-1, IL-2, and IFN- **γ**, increase proliferation of lymphocytes in response to mitogenic or antigenic stimuli

Therapeutic uses:

Herpes simplex infection, Measles viruses

Adverse reactions:

Rise in uric acid in serum and urine, Nausea

Isoprinosine(Inosiplex)

- Complex of the pacetamidobenzoate salt of N,N-dimethylamino-2- propanol: inosine in a 3:1 molar ratio

MOA

- Augment production of cytokines such as IL-1, IL-2 and IFN-γ ,increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes

Therapeutic uses

- Herpes simplex infections, subacute sclerosing panencephalitis,acute viral encephalitis caused by herpes simplex, Epstein-Barr and measles viruses

Adverse effects

- Minor CNS depressant, transient nausea and rise of uric acid in serum and urine

Immunocynin

- Stable form of haemocynin, a non-haeme, oxygen carrying,copper-containing protein found in arthropods and molluses

Therapeutic uses:

- Urinary bladder cancer.

Adverse effects:

- Rare-mild fever

Hematopoietic Drugs (cont'd)

- Erythropoietic drugs
  - epoetin alfa (Epogen, Procrit)
  - darbepoetin alfa (Aranesp)
- Colony-stimulating factors (CSFs)
  - filgrastim (Neupogen)
  - pegfilgrastim (Neulasta)
  - sargramostin (Leukine)
- Platelet-promoting drugs
  - oprelvekin (Neumega)

III. AGENTS USED TO TREAT NEUTROPENIA

- Myeloid growth factors or granulocyte colony–stimulating factors (G-CSF), such as
- 1- filgrastim
- 2- tbo-filgrastim
- 3- pegfilgrastim

Filgastrim

- A single, non-glycosylated, polypeptide chain that contains 175 amino acids and has a molecular mass of 18.8 KD.
- Half-life ~ 3.5 hrs (IV or SC)
- Clearance increases as blood neutrophil concentration increases. (negative feedback mechanism)

Pegfilgrastim is a polyethylene glycol-conjugated version of filgrastim designed for longer half-life, thereby necessitating fewer injections. ~33 hours

G-CSF

- The activity is restricted to neutrophils and their stimulation, proliferation and fucntion.
- R_x- Filgrastin, Pegfilgrastim
- Use : 1. treatment of severe neutropenia after chemotherapy
  2. Congential neutropenias

- Route – I.V/S.C

ADR –Bone pain
skin reaction
splenomegaly

SARGRAMOSTIM:
HUMAN RECOMBINANT GRANULOCYTE MACROPHAGE COLONY- STSSTIMULATING FACTOR (GM-CSF)

GMCSF

- Can stimulate prloiferation, differentiation and function of myeloid stem lineages.

- R_x- Sargomostin
- It stimulates myelopoiesis

- Use –

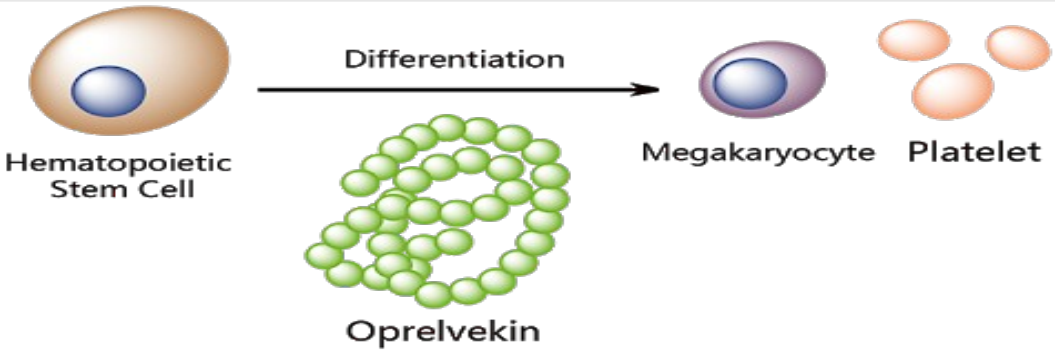
1. neutropenia induced in cancer chemotherapy
2. Myeloid reconstitution after BMT

- Route – i.v/s.c

- ADR – Bone pain
  - Dyspnea, Rash
  - SVT arrhthmias
  - Inc hepatic enzymes.

Related medications - Oprelvekin

- Recombinant IL-11
- Produced by E. coli.
- Increases platelet levels which were reduced due to chemotherapy.
- IL-11 is a growth factor that stimulates proliferation of hematopoietic stem cells and megakaryocyte progenitor cells resulting in increased platelet production.



Oprelvekin (Interleukin-11)

- Brand name: Neumega
  - Thrombopoietic growth factor
  - Recombinant DNA technology
- Uses
  - Used with myelosuppressive chemotherapy to minimize thrombocytopenia and to decrease the need for platelet transfusions
- Adverse effects
  - Fluid retention
  - Cardiac dysrhythmias
  - Effects on the eye
  - Sudden death

CLINICAL PHARMACOLOGY

ADVANTAGES OF IMMUNOMODULATORS OVER ANTIMICROBIALS

Sl.No.	Antimicrobials	Immunomodulators
1	Problem of rapid emergence of resistance	They circumvent the emergence of resistance since they do not act on microbes directly
2	In immunocompromised animals, it work poorly	It is the treatment option for immunocompromised animals
3	Specific therapy	Broad spectrum of activity against viral and fungal as well as bacterial diseases and may provide nonspecific emergency-treatment options in the event of the emergence of a novel pathogen or a bio warfare attack

(Gallois *et al.*, 2008)

PHYSICAL IMMUNOSUPPRESSANTS

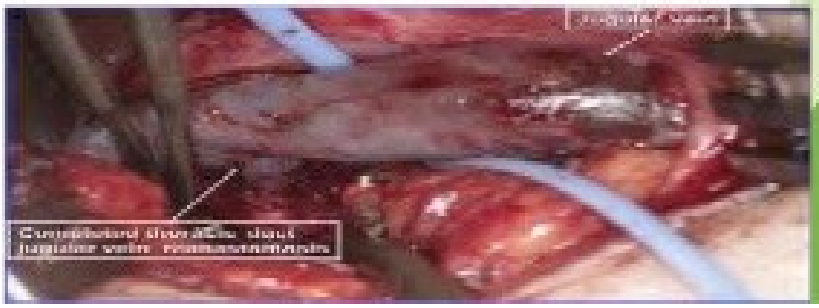
- Total Lymphoid Irradiation (TLI):
- Fractionated irradiation focused on Lymphoid tissues, with shielding of Bone marrow, Lungs ,Non lymphoid tissues
- Induces formation of large granular Lymphocytes lacking T,B & Macrophage markers which non specifically suppresses Ag -specific cytolytic arm of Allogenic immune reactions
- TLI can induce true Transplantation tolerance to Renal allografts in humans
- UV-B light is absorbed by skin Urocanic acid & undergoes isomerization to Cis form which induces suppression through effect on Dendritic APC
- **Adverse Effects:**
- Myelosuppression
- Skin changes
- Nausea and vomiting

PHYSICAL IMMUNOSUPPRESSANTS

- ***Plasmapheresis:***
- removing plasma hemocomponent that is circulating with pathogens and replacing it with a suitable solution
- Useful adjunct to chemotherapy for removing circulating immunoglobulins or immunoglobulin components in multiple myeloma and other dysproteinemias
- Rapidly removes pathogenic antibody
- Must be combined with B lymphotoxic drug to prevent rebound (e.g. cyclophosphamide, steroids)
- Combination with IVIg very powerful
- Risks include cardiovascular instability

PHYSICAL IMMUNOSUPPRESSANTS

- Thoracic duct drainage:
- Woodruff demonstrated that synergism of thoracic-duct drainage with lymphoid-depleting modality, antilymphocyte serum
- effective and safe in decreasing the immunologic response of the recipient of renal transplants from genetically related donors
- Lymphocytapheresis using TDD is very selective for removing lymphocytes (especially helper T-cells)

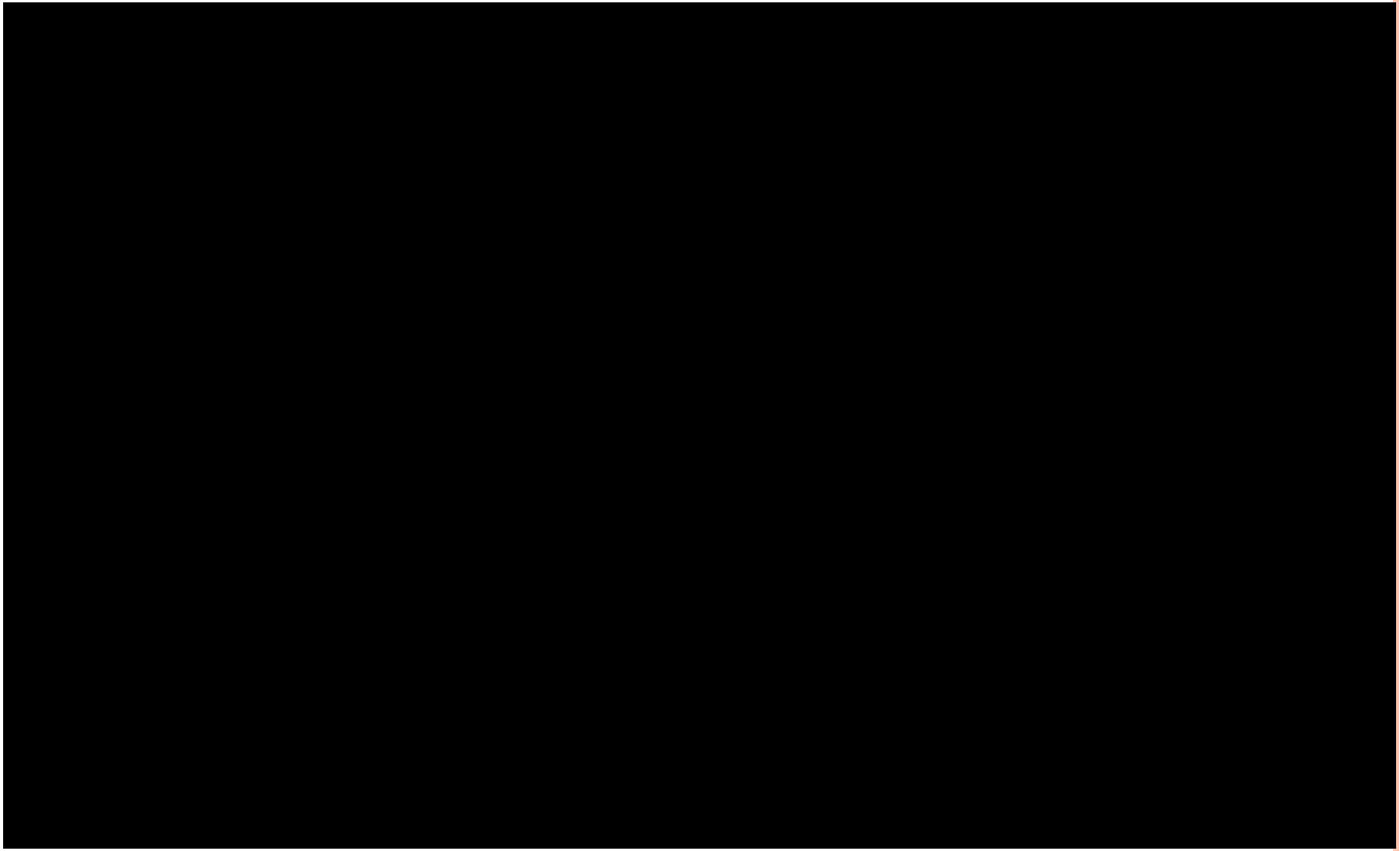


INTERFERON IN MALIGNANT MELANOMA

Dosing and Administration

- Recommended Dose
  - Induction
    - 20 million IU/m^2
  - Maintenance
    - 10 million IU/m^2
- Administration
  - Induction
    - Administer intravenously over 20 minutes on 5 consecutive days per week for 4 weeks
  - Maintenance
    - Administer subcutaneously 3 times per week for 48 weeks

INTERFERON IN CML



Sites of Action of Selected Immunosuppressive Agents on T-Cell Activation

DRUG	SITE OF ACTION
• Glucocorticoids	Glucocorticoid response elements in DNA (regulate gene transcription)
• Muromonab-CD3	T-cell receptor complex (blocks antigen recognition)
• Cyclosporine	Calcineurin (inhibits phosphatase activity)
• Tacrolimus	Calcineurin (inhibits phosphatase activity)
• Azathioprine	Deoxyribonucleic acid (false nucleotide incorporation)
• Mycophenolate Mofetil	Inosine monophosphate dehydrogenase (inhibits activity)
• Daclizumab, Basiliximab	IL-2 receptor (block IL-2-mediated T-cell activation)
• Sirolimus	Protein kinase involved in cell-cycle progression (mTOR) (inhibits activity)

CLINICAL PHARMACOLOGY

Hyper-acute Rejection

- mediated by preformed recipient antibodies against donor antigen.
- these antibodies are present in receiver at the time of organ implantation.
- hyper acute rejection occurs immediately after reperfusion of the transplanted organ.
- Can readily notice the changes within few minutes.

CLINICAL PHARMACOLOGY

Acute rejection

- acute cellular rejection
- acute humoral rejection

Acute cellular

- Mediated by the cytotoxic T cells, leads to interstitial and vascular damage.
- Seen in months after transplantation.
- Suppressing the T cells is effective at preventing the acute rejection.

Acute humoral rejection

- Recipients B cells become sensitized to donor antigens.
- Antibodies are produced within 7-10 days.
- Antibody responses directs to endothelial cells (acute vascular rejection).

Chronic Rejection

- believed to be both humoral and cellular in nature.
- does not occur until months or years after transplantation.
- chronic inflammation caused, by the response of activated T cells to donor antigen.
- Activated T cells release cytokines that recruit macrophages into the graft.

CYCLOSPORINE/ TACROLIMUS

Activated T cells produces IL_2 via Dephosphorilation of NAFT
(nuclear factor activated T cell - a cytoplasmic transcription factor)

↓

Calceneurin is needed for dephosphorilation
(Cytoplasmic Phosphatase)

↓

Translocates to nucleus

↓

Transcriptin of IL_2 gene.

- Cyclosporine bind s to cyclophilin - binding protein.
- Tacrolimus binds to FKBP – FK binding protein.

SIROLIMUS

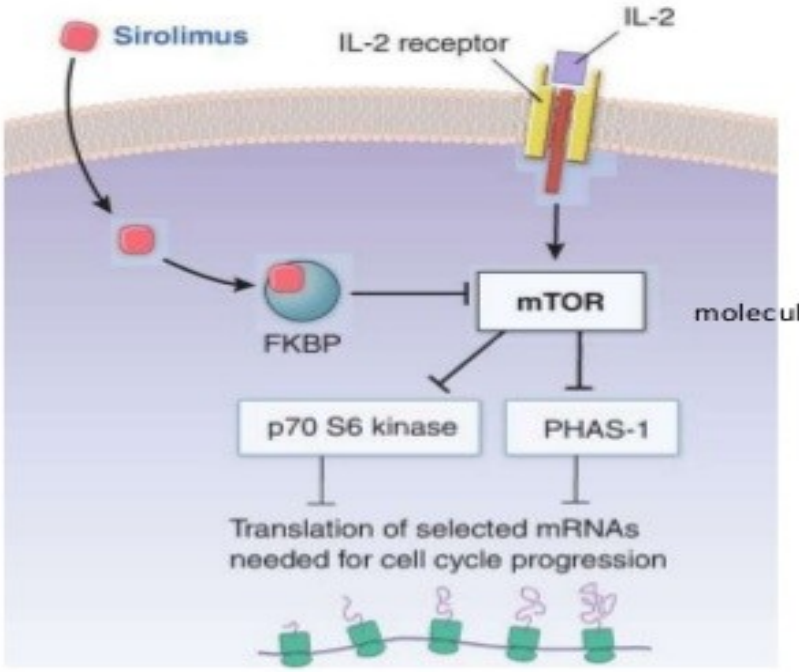
Sirolimus (rapamycin)

- Obtained from bacteria Streptomyces hygroscopicus.
- Binds to FKBP,
- FKBP- sirolimus complex does not inhibit calcineurin.
- Instead it blocks IL_2 receptor signalling required for T cell proliferation.
- FKBP- sirolimus complex binds to molecular target of rapamycine (mTOR)

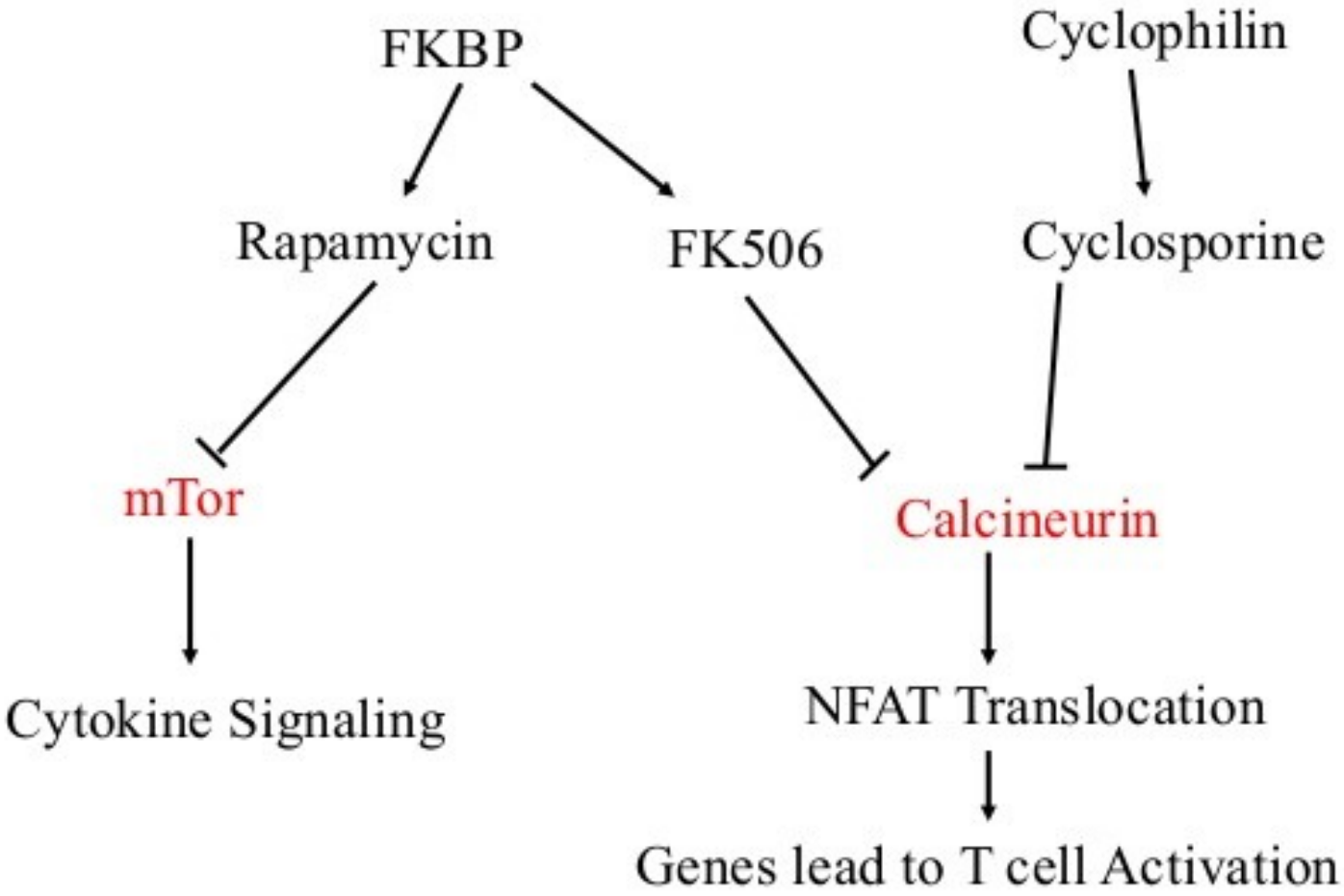
SIROLIMUS

- Which inhibits p70 - S6 kinase and PHAS-1 activity, which responsible for translation.

- Thus mTOR inhibition causes cell division arrests at G1 phase.



Targets of Immunosuppressants



DMARDs

- **1.Methotrexate (Mtx.)**

- **2. Agents used in mild disease or in combination with MTX.**
  - Hydroxychloroquine
  - Sulfasalazine
  - Minocycline

- **3.Traditional DMARDs -(limited used currently)**
  - Gold salts (Aurothiomalate sodium).....X
  - d-Penicillamine.....X
  - Azathioprine

- 4. **Biological agents**
  - Cyclosporine
  - Infliximab

  Leflunomide

- ***Methoterxate, Azathioprine, Cyclosporine are IMMUNOSUPPRESANT***
- ***Leflunomide IMMUNO MODULATOR***

Recent Advances

- Voclosporin: semisynthetic analog of cyclosporin.

  More potent & less nephrotoxic. (phase2b clinical trials)

- CC-122 (avadomide) - Derivative of thalodimide

  - Clinical potential for multiple myeloma and NHL

REFERENCES

- **Basic and Clinical Pharmacology: Katzung BG, Masters SB, Trevor AJ. 14th Edition.**
- **Katzung & Trevor's Pharmacology: Examination & Board Review. 12th Edition**
- **Lippincott's Illustrated Reviews: Pharmacology, Clark MA, Finkel R, Rey JA, Whalen K. 7th Edition**
- **Goodman & Gilman's The Pharmacological Basis of Therapeutics: Brunton LL. 12th Edition**

Email address for queries on the topic

drshams11@hotmail.com