IMMUNOSUPPRESSANT DRUGS

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INTRODUCTION OF IMMUNE SYSTEM

- Immunity : Ability of an organism to recognize and defensed itself against specific pathogens or antigens.
- Immune response: Third line of defense. Involves production of antibodies and generation of specialized lymphocytes against specific antigens.
- Antigen : Molecules from a pathogen or foreign organism that provoke a specific immune response.

THE IMMUNE SYSTEM IS THE THIRD LINE OF DEFENSE AGAINST INFECTION

Nonspecific defense mechanisms		**Specific defense mechanism (immune system)**
First line defense	Second line defense	Third line defense
✔Skin ✔Mucous membranes ✔Secretions of skin and mucous membranes	✔Phagocytic white blood cells ✔Antimicrobial proteins ✔Inflammatory response	✔Lymphocytes ✔Antibodies

IMMUNE SYSTEM

- Immune system include two main arms

1) Cell –mediated immunity.

2) Humoral (antibody –mediated immunity).

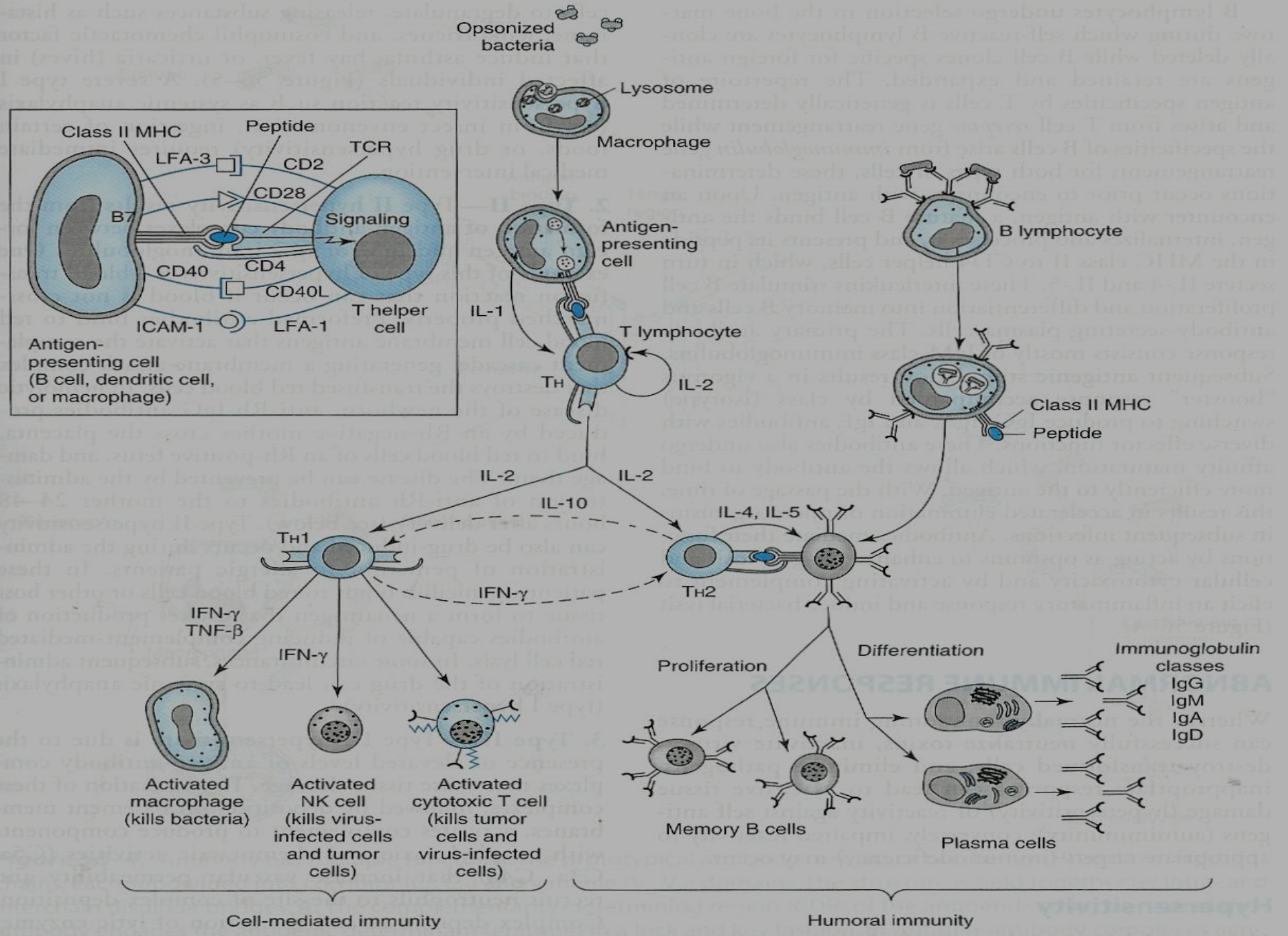
TYPES OF IMMUNITY

Innate or genetic immunity :

- Immunity an organism is born with
- Genetically determined
- May be due to lack of receptors or other molecules required for infection

Acquired immunity:

- Immunity that an organism develops during lifetime.
- Not genetically determined.
- May be acquired naturally or artificially.


Opsonized bacteria
Lysosome
Macrophage
Antigen-presenting cell
B lymphocyte
Class II MHC
Peptide
TCR
LFA-3
CD2
CD28
B7
Signaling
CD40
CD4
CD40L
ICAM-1
LFA-1
T helper cell
Antigen-presenting cell (B cell, dendritic cell, or macrophage)
IL-1
T lymphocyte
TH
IL-2
Class II MHC
Peptide
IL-2
IL-2
IL-10
IL-4, IL-5
TH1
TH2
IFN-γ
IFN-γ
TNF-β
IFN-γ
Proliferation
Differentiation
Immunoglobulin classes
IgG
IgM
IgA
IgD
Activated macrophage (kills bacteria)
Activated NK cell (kills virus-infected cells and tumor cells)
Activated cytotoxic T cell (kills tumor cells and virus-infected cells)
Memory B cells
Plasma cells
Cell-mediated immunity
Humoral immunity

CYTOKINES

- Cytokines are soluble , antigen-nonspecific signaling proteins that bind to cell surface receptors on a variety of cells.

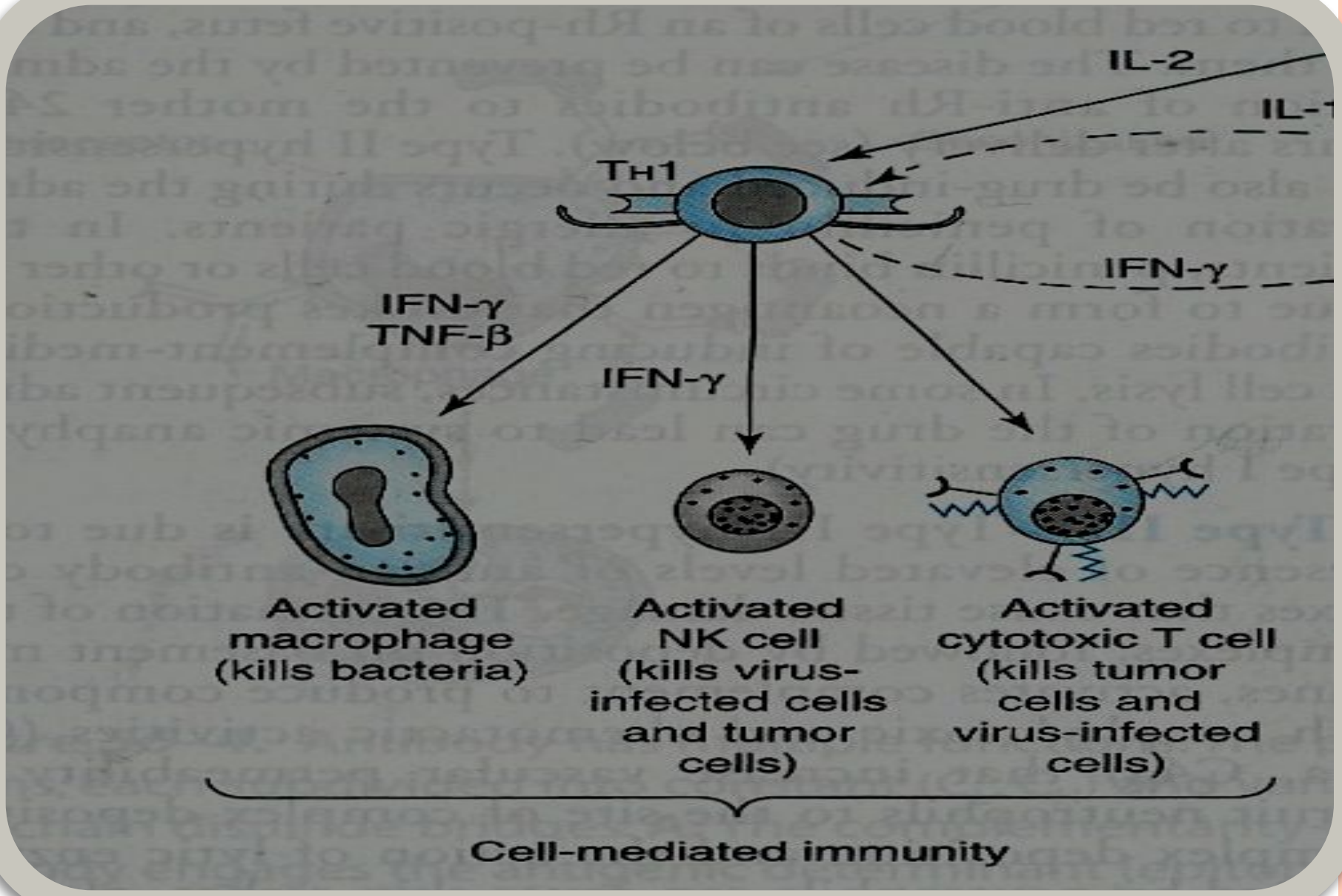
- Cytokines include
  - Interleukins,
  - Interferons (IFNs),
  - Tumor Necrosis Factors (TNFs),
  - Transforming Growth Factors (TGFs)
  - Colony-stimulating factors (CSFs).

- IL-2 stimulates the proliferation of antigen-primed (helper) T cells.

Cell-mediated Immunity

- TH1 produce more IL-2, TNF-β and IFN-γ.
- Activate
  - NK cells (kill tumor & virus-infected cells).
  - Cytotoxic T cells (kill tumor & virus-infected cells).
  - Macrophages (kill bacteria).

CELL-MEDIATED IMMUNITY

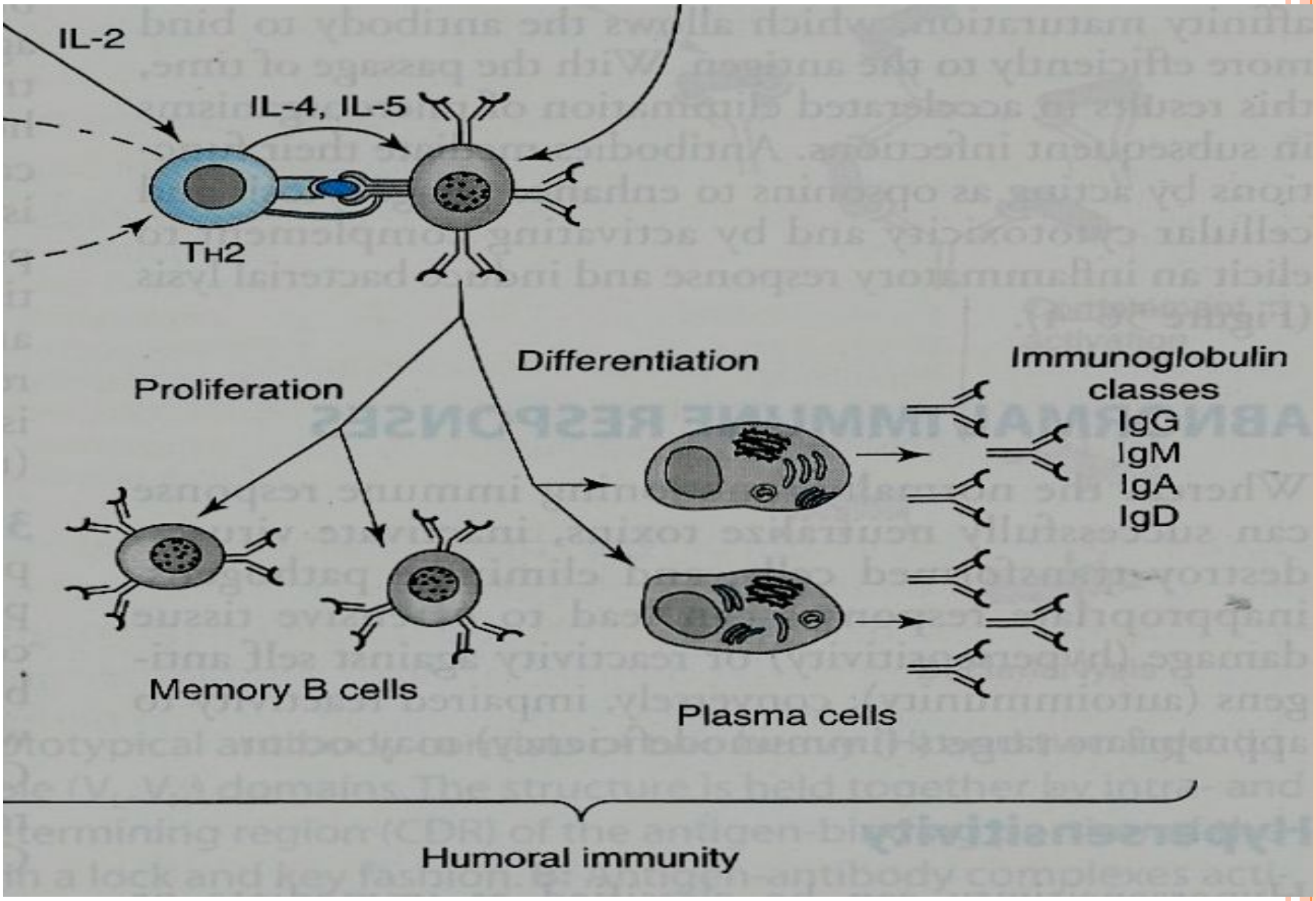


Humoral Immunity

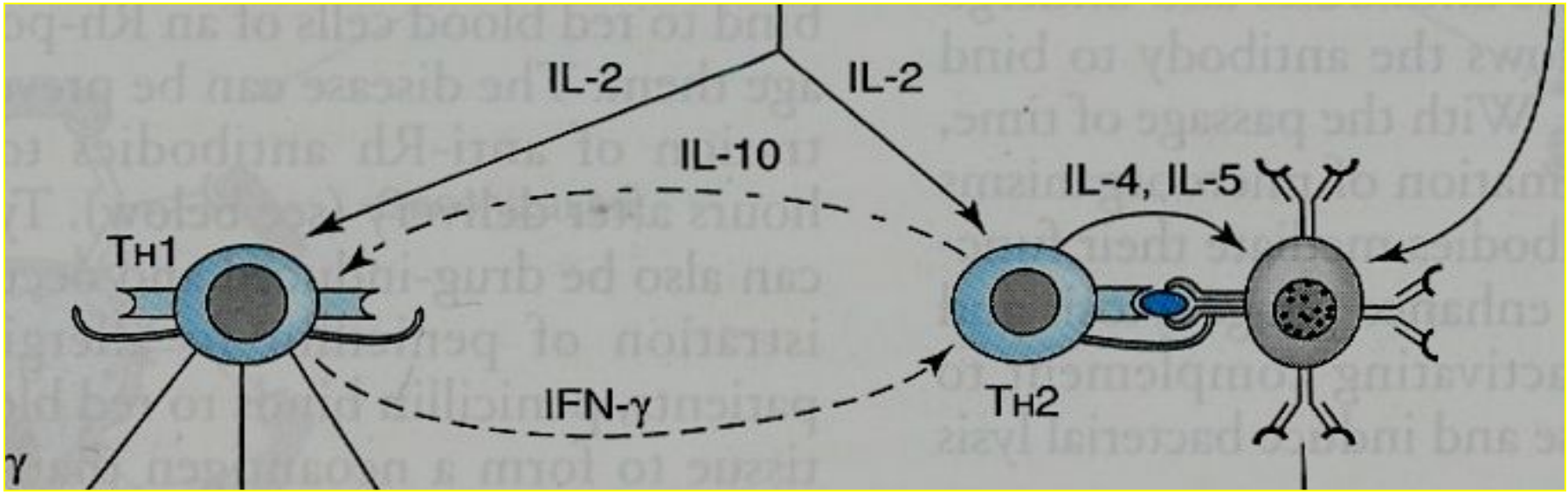
B-lymphocytes → TH2 produces (interleukins) IL-4 & IL-5 which in turn causes:

- B cells proliferation & differentiation into
  - Memory B cells
  - Antibody secreting plasma cells

HUMORAL IMMUNITY



Mutual regulation of T helper lymphocytes



- TH1 → interferon-γ:
  inhibits TH2 cell proliferation TH2 cells
- TH2 → IL-10:
  inhibits TH1 cytokine production

WHAT IS IMMUNOSUPRASSANT?

- Any of a variety of substance used to prevent production of antibodies.
- They are commonly used to prevent rejection by a recipients body of an organ transplanted from a donor.
- Immunosuppressive drug has one meaning: a drug that lowers the body's normal immune response.

IMMUNOSUPPRESSANT DRUGS

I. inhibitors of cytokine (IL-2) production or action:

1) Calcineurin inhibitors
   - Cyclosporine
   - Tacrolimus (FK506)

2) Sirolimus (rapamycin).

II. Inhibitors of cytokine gene expression

- Corticosteroids

III. Cytotoxic drugs

- Inhibitors of purine or pyrimidine synthesis (Antimetabolites):
  - **Azathioprine**
  - **Myclophenolate Mofetil**
  - **Leflunomide**
  - **Methotrexate**
- Alkylating agents

  Cyclophosphamide

IV. Immunosuppressive antibodies

that block T cell surface molecules involved in signaling immunoglobulins

- **antilymphocyte globulins (ALG).**
- **antithymocyte globulins (ATG).**
- **Rho (D) immunoglobulin.**
- **Basiliximab**
- **Daclizumab**
- **Muromonab-CD3**

VI. Interferon

VI. Thalidomide

I) Inhibitors of cytokines (IL-2) production or action

- **Inhibitors of cytokines (IL-2) production**

  Calcineurin inhibitors

  - Cyclosporine
  - Tacrolimus (FK506)

- **Inhibitors of cytokines (IL-2) action**

  Sirolimus (rapamycin).

CYCLOSPORINE

Chemistry

Cyclosporine is a fungal polypeptide composed of 11 amino acids.

Mechanism of action:

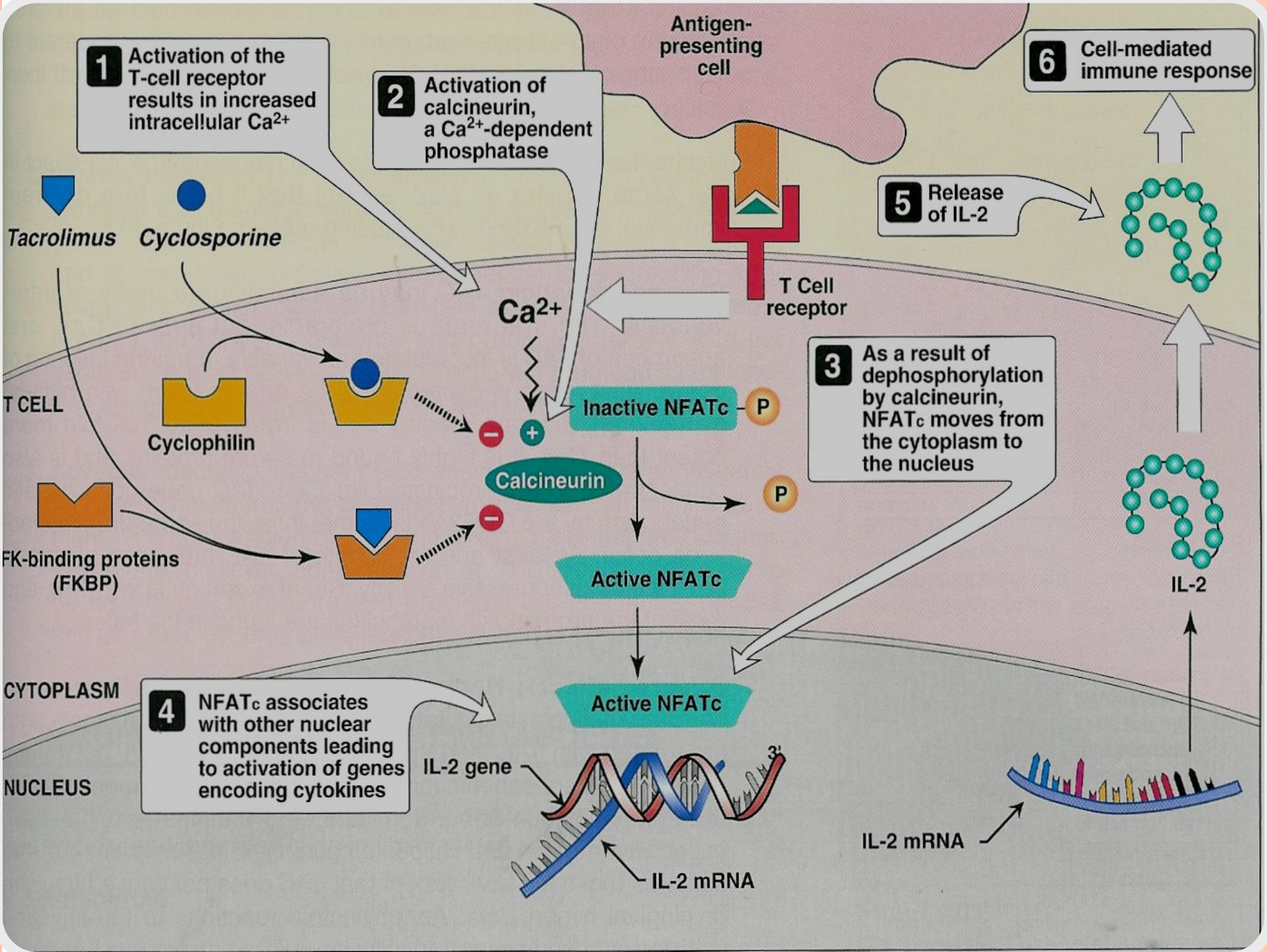
- Acts by blocking activation of T cells by inhibiting interleukin-2 production (IL-2).
- Decreases proliferation and differentiation of T cells.

- Cyclosporine binds to cyclophilin (immunophilin) intracellular protein receptors.

- Cyclosporine- immunophilin complex inhibits calcineurin, a phosphatase necessary for dephosphorylation of transcription factor (NFATc) required for interleukins synthesis (IL-2).

- NFATc (Nuclear Fcator of Activated Tcells).

- Suppresses cell-mediated immunity.


Antigen-presenting cell
1 Activation of the T-cell receptor results in increased intracellular Ca^{2+}
2 Activation of calcineurin, a Ca^{2+}-dependent phosphatase
6 Cell-mediated immune response
5 Release of IL-2
Tacrolimus
Cyclosporine
T Cell receptor
Ca^{2+}
T CELL
Cyclophilin
Inactive NFATc
P
3 As a result of dephosphorylation by calcineurin, NFATc moves from the cytoplasm to the nucleus
Calcineurin
P
FK-binding proteins (FKBP)
Active NFATc
IL-2
CYTOPLASM
4 NFATc associates with other nuclear components leading to activation of genes encoding cytokines
Active NFATc
NUCLEUS
IL-2 gene
3'
IL-2 mRNA
IL-2 mRNA

- **Pharmacokinetics:**
  - Can be given orally or i.v. infusion
  - orally (25 or 100 mg) soft gelatin capsules, microemulsion.
  - Orally, it is slowly and incompletely absorbed.
  - Peak levels is reached after 1– 4 hours, elimination half life 24 h.
  - Oral absorption is delayed by fatty meal (gelatin capsule formulation)
  - Microemulsion

(has higher bioavailability-is not affected by food).

- 50 – 60% of cyclosporine accumulates in blood (erythrocytes – lymphocytes).
- metabolized by CYT-P450 system (CYP3A4).
- excreted mainly through bile into faeces, about 6% is excreted in urine.

Therapeutic Uses:

- Organ transplantation (kidney, liver, heart) either alone or with other immunosuppressive agents (Corticosteroids).
- Autoimmune disorders (low dose 7.5 mg/kg/d). e.g. endogenous uveitis, rheumatoid arthritis, active Crohn's disease, psoriasis, psoriasis, nephrotic syndrome, severe corticosteroid-dependent asthma, early type I diabetes.
- Graft-versus-host disease after stem cell transplants

Adverse Effects (Dose-dependent)
Therapeutic monitoring is essential

- Nephrotoxicity
(increased by NSAIDs and aminoglycosides).
- Liver dysfunction.
- Hypertension, hyperkalemia.
(K-sparing diuretics should not be used).
- Hyperglycemia.
- Viral infections (Herpes - cytomegalovirus).
- Lymphoma (Predispose recipients to cancer).
- Hirsutism
- Neurotoxicity (tremor).
- Gum hyperplasia.
- Anaphylaxis after I.V.

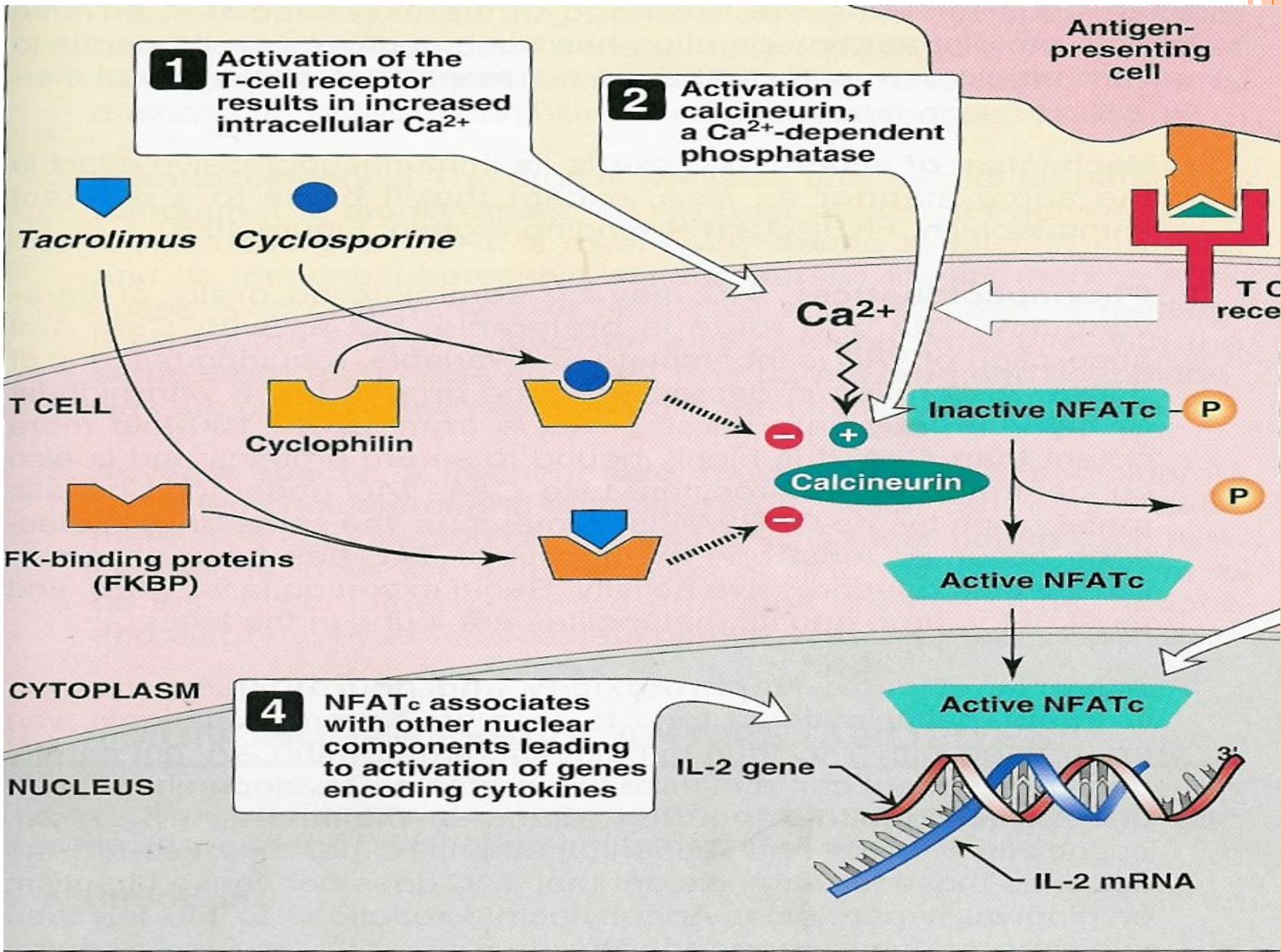
Drug Interactions

- **Clearance of cyclosporine is enhanced by co-administration of CYT p 450 inducers *(Phenobarbitone, Phenytoin & Rifampin)* → rejection of transplant.**

- **Clearance of cyclosporine is decreased when it is co-administered with *erythromycin or Ketoconazole, Grapefruit juice* → cyclosporine toxicity.**

TACROLIMUS (FK506)

- a fungal macrolide antibiotic.
- Chemically not related to cyclosporine
- both drugs have similar mechanism of action.
- The internal receptor for tacrolimus is immunophilin (FK-binding protein, FK-BP).
- Tacrolimus-FKBP complex inhibits calcineurin.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FK-binding proteins (FKBP)
Active NFATc
CYTOPLASM
Active NFATc
4 NFATc associates with other nuclear components leading to activation of genes encoding cytokines
NUCLEUS
IL-2 gene
3'
IL-2 mRNA

Kinetics

- Given orally or i.v or topically (ointment).
- Oral absorption is variable and incomplete, reduced by fat and carbohydrate meals.
- Half-life after I.V. form is 9-12 hours.
- Highly bound with serum proteins and concentrated in erythrocytes.
- metabolized by P450 in liver.
- Excreted mainly in bile and minimally in urine.

USES as cyclosporine

- Organ and stem cell transplantation
- Prevention of rejection of liver and kidney transplants (with glucocorticoids).
- Atopic dermatitis and psoriasis (topically).

Toxic effects

- **Nephrotoxicity (more than CsA)**
- **Neurotoxicity (more than CsA)**
- **Hyperglycemia (require insulin).**
- **GIT disturbances**
- **Hperkalemia**
- **Hypertension**
- **Anaphylaxis**

NO hirsutism or gum hyperplasia

- **Drug interactions as cyclosporine.**

What are the differences between CsA and TAC ?

TAC is more favorable than CsA due to:

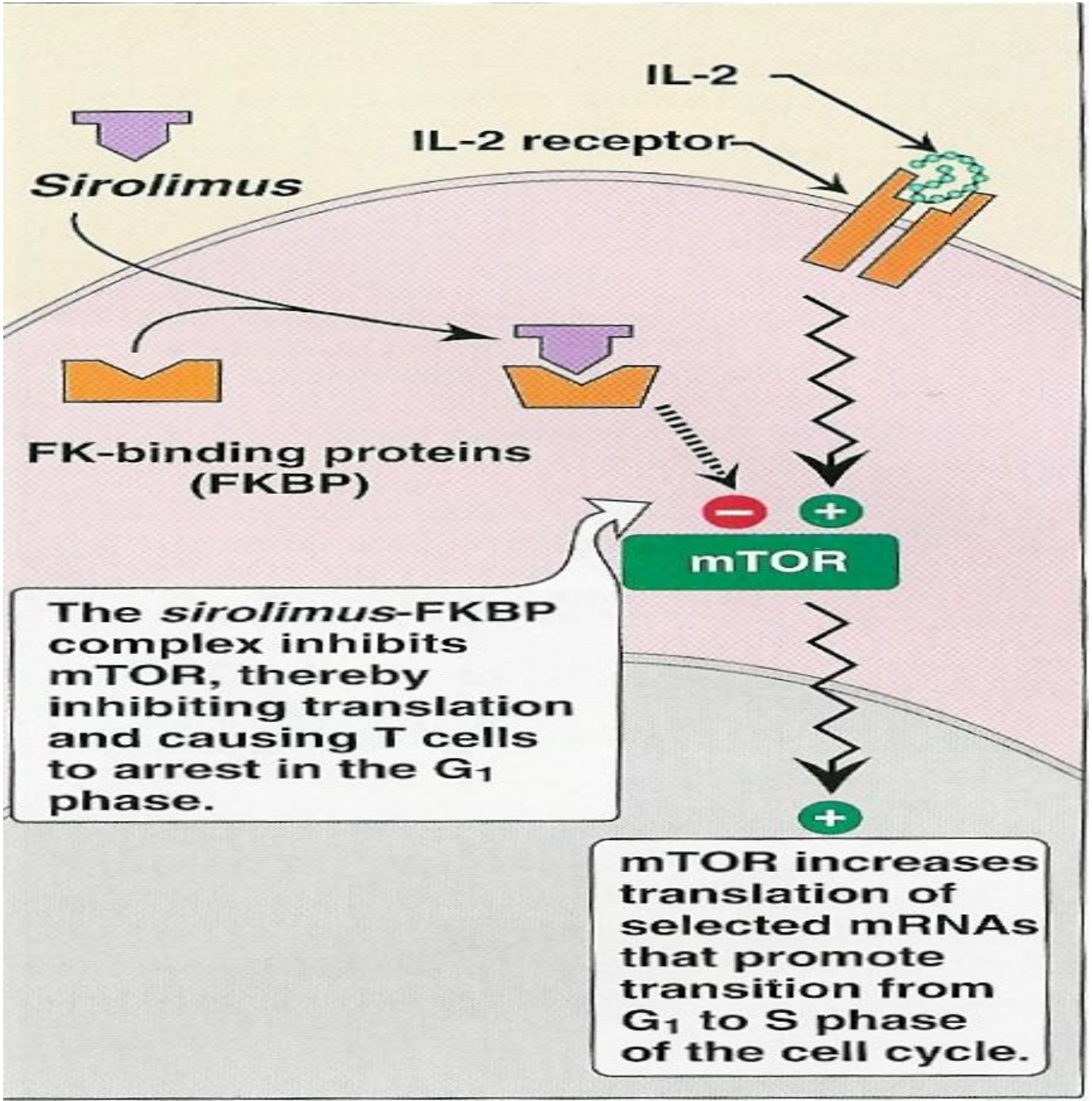
- **TAC is 10 – 100 times more potent than CsA in inhibiting immune responses.**
- **TAC has decreased episodes of rejection.**
- **TAC is combined with lower doses of glucocorticoids.**

But

- **TAC is more nephrotoxic and neurotoxic.**

Sirolimus (Rapamycin)

- SRL is macrolide antibiotic.
- SRL is derived from fungus origin.
- It binds to FKBP a binds to mTOR (mammalian Target Of Rapamycin).nd the formed complex
- mTOR is serine-threonine kinase essential for cell cycle progression, DNA repairs, protein translation.
- SRL blocks the progression of activated T cells from G1 to S phase of cell cycle (Antiproliferative action).
- It Does not block the IL-2 production but blocks T cell response to cytokines.
- Inhibits B cell proliferation & immunoglobulin production.


IL-2
IL-2 receptor
Sirolimus
FK-binding proteins
(FKBP)
mTOR
The sirolimus-FKBP complex inhibits mTOR, thereby inhibiting translation and causing T cells to arrest in the G1 phase.
mTOR increases translation of selected mRNAs that promote transition from G1 to S phase of the cell cycle.

Pharmakinetics

- Given orally and topically, reduced by fat meal.
- Extensively bound to plasma proteins
- metabolized by CYP3A4 in liver.
- Excreted in feces.

Pharmacodynamics

- Immunosuppressive effects
- Anti- proliferative action.
- Equipotent to CsA.

USES

- Solid organ allograft
- Renal transplantation alone or combined with (CSA, tacrolimus, steroids, mycophenolate).
- Heart allografts
- In halting graft vascular disease.
- Hematopoietic stem cell transplant recipients.
- Topically with cyclosporine in uveoretinitis.
- Synergistic action with CsA

Toxic effects

- Hyperlipidaemia (cholesterol, triglycerides).
- Thrombocytopenia
- Leukopenia
- Hepatotoxicity
- Hypertension
- GIT dysfunction

Inhibitors of cytokine gene expression

Corticosteroids

- Prednisone
- Prednisolone
- Methylprednisolone
- Dexamethasone

They have both anti-inflammatory action and immunosuppressant effects.

Mechanism of action

- bind to glucocorticoid receptors and the complex interacts with DNA to inhibit gene transcription of inflammatory genes.
- Decrease production of inflammatory mediators as prostaglandins, leukotrienes, histamine, PAF, bradykinin.
- Decrease production of cytokines IL-1, IL-2, interferon, TNF.
- Stabilize lysosomal membranes.
- Decrease generation of IgG, nitric oxide and histamine.
- Inhibit antigen processing by macrophages.
- Suppress T-cell helper function
- decrease T lymphocyte proliferation.

Kinetics

Can be given orally or parenterally.

Dynamics

1. Suppression of response to infection
2. anti-inflammatory and immunosuppresant.
3. Metabolic effects.

Indications

- are first line therapy for solid organ allografts & haematopoietic stem cell transplantation.
- Autoimmune diseases as refractory rheumatoid arthritis, systemic lupus erythematosus, asthma
- Acute or chronic rejection of solid organ allografts.

Adverse Effects

- Adrenal suppression
- Osteoporosis
- Hypercholesterolemia
- Hyperglycemia
- Hypertension
- Cataract
- Infection

III. Cytotoxic drugs

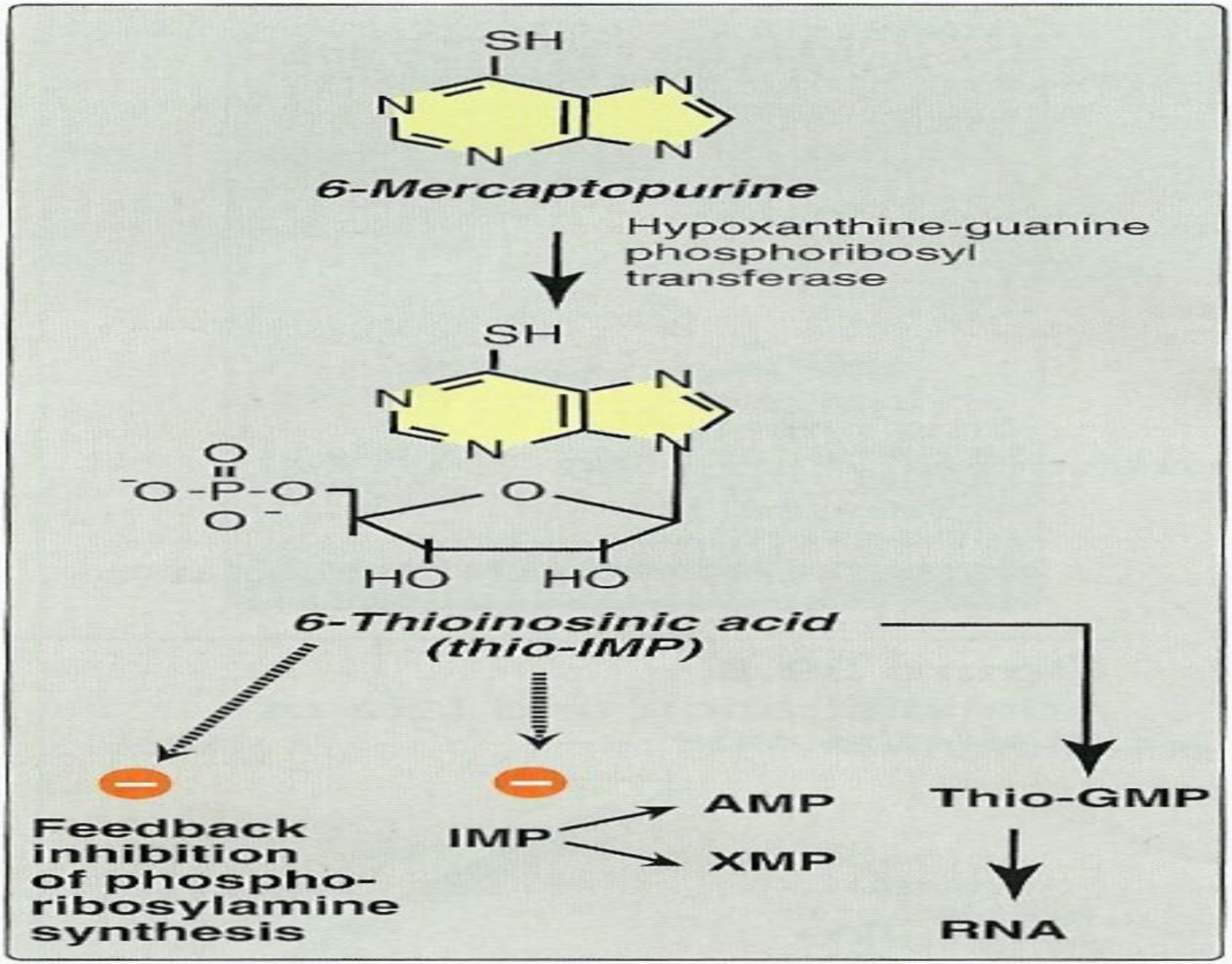
- **Inhibitors of purine or pyrimidine synthesis (Antimetabolites):**
  - Azathioprine
  - Myclophenolate Mofetil
  - Leflunomide
  - Methotrexate
- **Alkylating agents**

  Cyclophosphamide

AZATHIOPRINE

CHEMISTRY:

- Derivative of mercaptopurine.
- Prodrug.
- Cleaved to 6-mercaptopurine then to 6-mercaptopurine nucleotide, thioinosinic acid (nucleotide analog).
- Inhibits *de novo* synthesis of purines *required for lymphocytes proliferation*.
- Prevents clonal expansion of both B and T lymphocytes.


SH
N
N
N
N
6-Mercaptopurine
Hypoxanthine-guanine
phosphoribosyl
transferase
SH
N
N
N
N
O
O-P-O
O
O
HO
HO
6-Thioinosinic acid
(thio-IMP)
Feedback
inhibition
of phospho-
ribosylamine
synthesis
IMP
AMP
XMP
Thio-GMP
RNA

Pharmacokinetics

- orally or intravenously.
- Widely distributed but does not cross BBB.
- Metabolized in the liver to 6-mercaptopurine or to thiouric acid (inactive metabolite) by xanthine oxidase.
- excreted primarily in urine.

Drug Interactions:

- Co-administration of allopurinol with azathioprine may lead to toxicity due to inhibition of xanthine oxidase by allopurinol.

USES

- Acute glomerulonephritis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Crohn’ s disease.

Adverse Effects

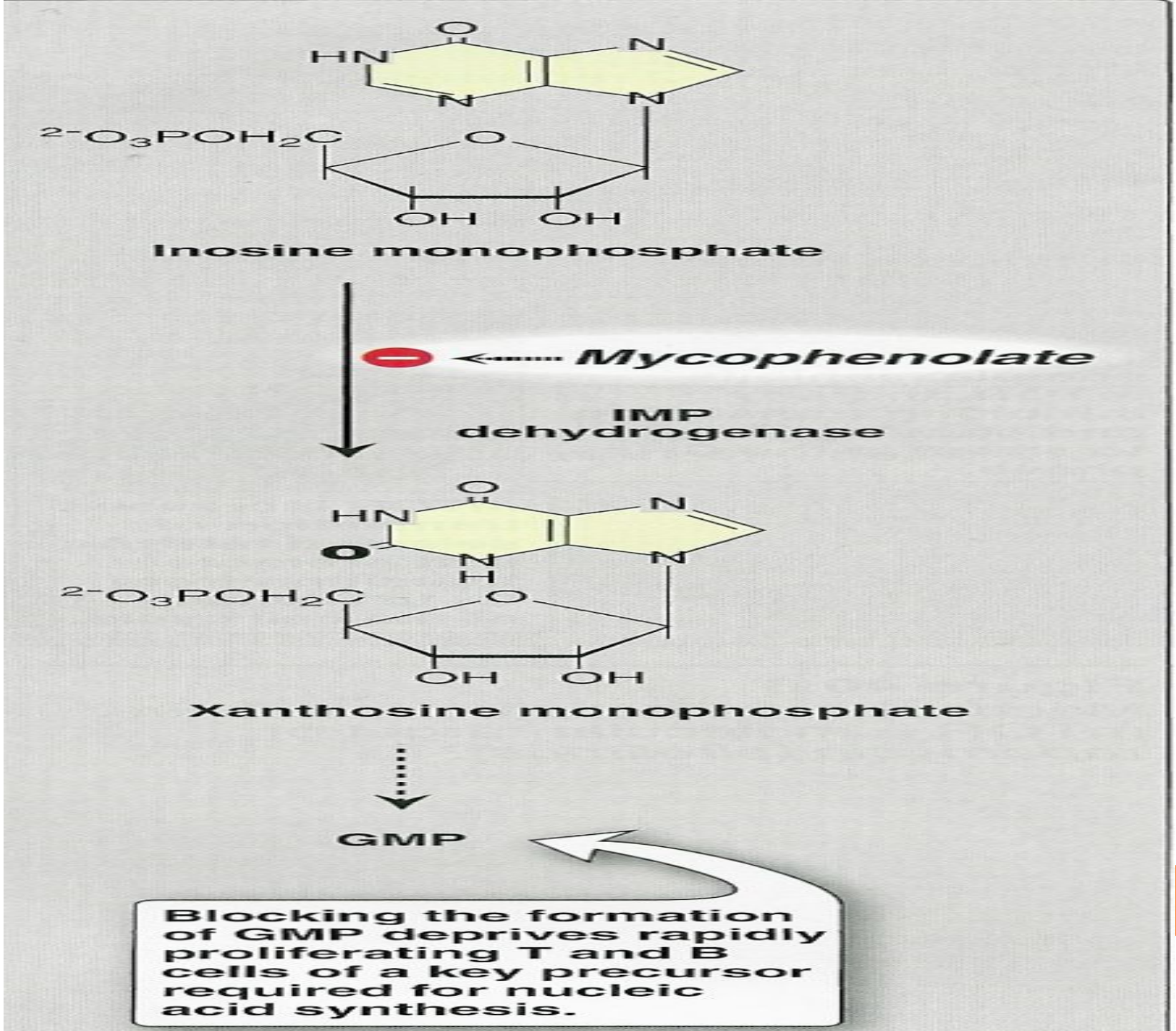
- Bone marrow depression: leukopenia, thrombocytopenia.
- Gastrointestinal toxicity.
- Hepatotoxicity.
- Increased risk of infections.

MYCOPHENOLATE MOFETIL

- Is a semisynthetic derivative of mycophenolic acid from fungus source.
- Prodrug; is hydrolyzed to mycophenolic acid.

Mechanism of action:

- Inhibits *de novo* synthesis of purines.
- mycophenolic acid is a potent inhibitor of inosine monophosphate dehydrogenase (IMP), crucial for purine synthesis →deprivation of proliferating T and B cells of nucleic acids.


Inosine monophosphate
Mycophenolate
IMP dehydrogenase
Xanthosine monophosphate
GMP
Blocking the formation of GMP deprives rapidly proliferating T and B cells of a key precursor required for nucleic acid synthesis.

Pharmacokinetics:

- Given orally, i.v. or i.m.
- rapidly and completely absorbed after oral administration.
- It undergoes first-pass metabolism to give the **active moiety, mycophenolic acid (MPA).**
- MPA is extensively bound to plasma protein.
- metabolized in the liver by glucuronidation.
- Excreted in urine as glucuronide conjugate
- Dose : 2-3 g /d

CLINICAL USE:

- Solid organ transplants for refractory rejection.
- Steroid-refractory hematopoietic stem cell transplant patients.
- Combined with prednisone as alternative to CSA or tacrolimus.
- Rheumatoid arthritis, & dermatologic disorders.

ADVERSE EFFECTS:

- GIT toxicity: Nausea, Vomiting, diarrhea, abdominal pain.
- Leukopenia, neutropenia.
- Lymphoma

Contraindicated during pregnancy

LEFLUNOMIDE

- A prodrug
- Active metabolite undergoes enterohepatic circulation.
- Has long duration of action.
- Can be given orally
- antimetabolite immunosuppressant.
- Pyrimidine synthesis inhibitor
- Approved only for rheumatoid arthritis

Adverse effects

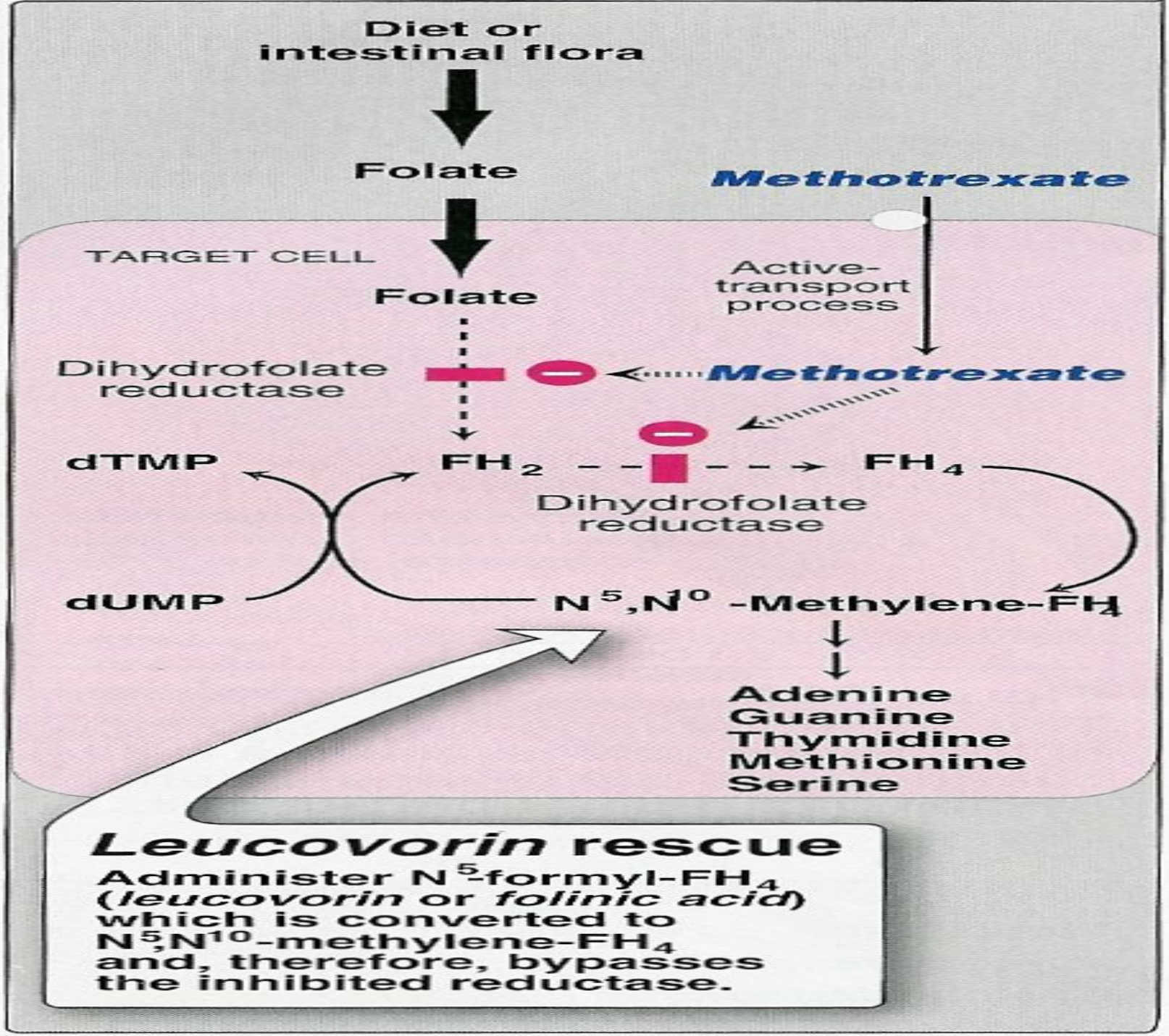
1. Elevation of liver enzymes
2. Renal impairment
3. Teratogenicity
4. Cardiovascular effects (tachycardia).

Methotrexate

- a folic acid antagonist
- Orally, parenterally (I.V., I.M).
- Excreted in urine.
- Inhibits dihydrofolate reductase required for folic acid activation (tetrahydrofolic)
- Inhibition of DNA, RNA &protein synthesis
- Interferes with T cell replication.
- Rheumatoid arthritis & psoriasis and Crohn disease
- Graft versus host disease

Adverse effects

- Nausea-vomiting-diarrhea
- Alopecia
- Bone marrow depression
- Pulmonary fibrosis
- Renal & hepatic disorders


Diet or intestinal flora
Folate
Methotrexate
TARGET CELL
Folate
Active-transport process
Dihydrofolate reductase
Methotrexate
dTMP
FH_2
FH_4
Dihydrofolate reductase
dUMP
N^5,N^{10}-Methylene-FH_4
Adenine
Guanine
Thymidine
Methionine
Serine
Leucovorin rescue
Administer N^5-formyl-FH_4 (leucovorin or folinic acid) which is converted to N^5,N^{10}-methylene-FH_4 and, therefore, bypasses the inhibited reductase.

Cyclophosphamide

- Alkylating agent to DNA.
- Prodrug, activated into phosphamide.
- Is given orally& intravenously
- Destroy proliferating lymphoid cells.
- Anticancer & immunosuppressant
- Effective in autoimmune diseases e.g rheumatoid arthritis & systemic lupus erythrematosus.
- Autoimmune hemolytic anemia

Side Effects

- Alopecia
- Hemorraghic cystitis.
- Bone marrow suppression
- GIT disorders (Nausea -vomiting-diarrhea)
- Sterility (testicular atrophy & amenorrhea)
- Cardiac toxicity

Antibodies

block T cell surface molecules involved in signaling immunoglobulins

- antilymphocyte globulins (ALG).
- antithymocyte globulins (ATG).
- Rho (D) immunoglobulin.
- Basiliximab
- Daclizumab
- Infliximab

Antibodies preparation

1. by immunization of either horses or rabbits with human lymphoid cells producing mixtures of polyclonal antibodies directed against a number of lymphocyte antigens (variable, less specific).

2. Hybridoma technology

- produce antigen-specific, monoclonal antibody (homogenous, specific).
- produced by fusing mouse antibody-producing cells with immortal, malignant plasma cells.
- Hybrid cells are selected, cloned and selectivity of the clone can be determined.
- Recombinant DNA technology can be used to replace part of the mouse gene sequence with human genetic material (less antigenicity-longer half life).
- Antibodies from mouse contain Muro in their names.
- Humanized antibodies contain ZU or XI in their names.

Antilymphocyte globulins (ALG) &Antithymocyte globulins (ATG)

- Polyclonal antibodies obtained from plasma or serum of horses hyper-immunized with human lymphocytes.
- Binds to the surface of circulating T lymphocytes, which are phagocytosed in the liver and spleen giving lymphopenia and impaired T-cell responses & cellular immunity.

Kinetics

- Given i.m. or slowly infused intravenously.
- Half life extends from 3-9 days.

Uses

- Combined with cyclosporine for bone marrow transplantation.
- To treat acute allograft rejection.
- Steroid-resistant rejection.

Adverse Effects:

- Antigenicity.
- Leukopenia, thrombocytopenia.
- Risk of viral infection.
- Anaphylactic and serum sickness reactions (Fever, Chills, Flu-like syndrome).

Muromonab-CD3

- Is a murine monoclonal antibody
- Prepared by hybridoma technology
- Directed against glycoprotein CD3 antigen of human T cells.
- Given I.V.
- Metabolized and excreted in the bile.

Mechanism of action

- The drug binds to CD3 proteins on T lymphocytes (antigen recognition site) leading to transient activation and cytokine release followed by disruption of T-lymphocyte function, their depletion and decreased immune response.
- Prednisolone, diphenhydramine are given to reduce cytokine release syndrome.

Uses

- Used for treatment of acute renal allograft rejection & steroid-resistant acute allograft
- To deplete T cells from bone marrow donor prior to transplantation.

Adverse effects

- Anaphylactic reactions.
- Fever
- CNS effects (seizures)
- Infection
- Cytokine release syndrome (Flu-like illness to shock like reaction).

Rh_o (D) immune globulin

- Rho (D) is a concentrated solution of human IgG containing higher titer of antibodies against Rh_o (D) antigen of red cells.
- Given to Rh-negative mother within 24-72 hours after delivery of Rh positive baby (2 ml, I.M.) to prevent hemolytic disease of the next Rh positive babies (*erythroblastosis fetalis*).

Adverse Effects

- Local pain
- Fever

Monoclonal antibodies

Basiliximab and Daclizumab

- Obtained by replacing murine amino acid sequences with human ones.
- Basiliximab is a chimeric human-mouse IgG (25% murine, 75% human protein).
- Daclizumab is a humanized IgG (90% human protein).
- Have less antigenicity & longer half lives than murine antibodies

Mechanism of action

- IL-2 receptor antagonists
- Are Anti-CD25
- Bind to CD25 (α-subunit chain of IL-2 receptor on activated lymphocytes)
- Block IL-2 stimulated T cells replication & T-cell response system
- Basiliximab is more potent than Daclizumab.

- Given I.V.
- Half life Basiliximab (7 days)
- Daclizumab (20 days)
- are well tolerated - only GIT disorders

USES

- Given with CsA and corticosteroids for Prophylaxis of acute rejection in renal transplantation.

Monoclonal antibodies

Infliximab

- a chimeric human-mouse IgG
- Directed against TNF-α
- Is approved for ulcerative colitis, Crohn's disease &rheumatoid arhritis

Omalizumab

- a humanized monoclonal IgE
- Directed against Fc receptor on mast &basophils
- Is approved for asthma in steroid-refractory patient

INTERFERONS

Three families:

- Type I IFNs (IFN-α, β):
- acid-stable proteins; act on same target cell receptor
- induced by viral infections
- leukocyte produces IFN-α
- Fibroblasts & endothelial cells produce IFN-β
- **Type II IFN (IFN-γ):**
- acid-labile; acts on separate target cell receptors
- Produced by Activated T lymphocytes.

Interferon Effects:

IFN- γ : Immune Enhancing

- increased antigen presentations with macrophage, natural killer cell, cytotoxic T lymphocyte activation

IFN- α, β :

- effective in inhibiting cellular proliferation

(more effective than IFN- γ in this regard)

VI. INTERFERONS

- Recombinant DNA cloning technology.
- Antiproliferative activity.
- Antiviral action
- Immunomodulatory effect.

USES:

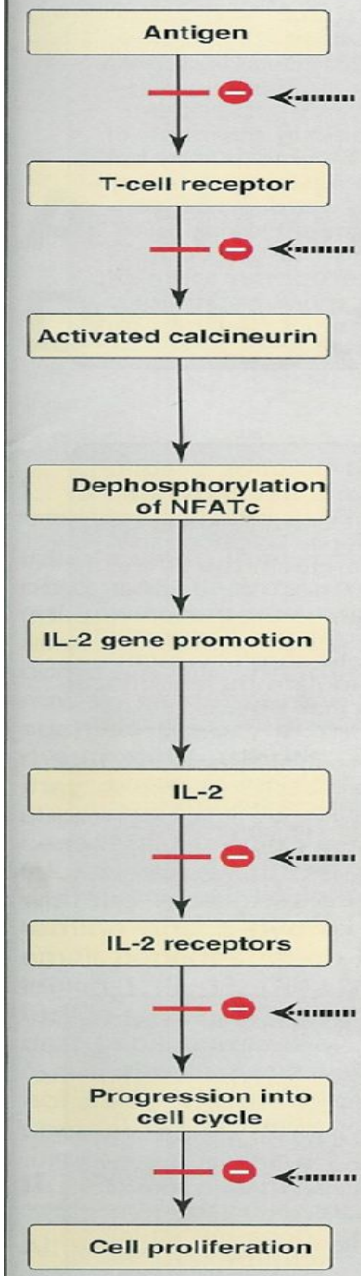
- Treatment of certain infections e.g. Hepatitis C (IFN- α).
- Autoimmune diseases e.g. Rheumatoid arthritis.
- Certain forms of cancer e.g. melanoma, renal cell carcinoma.
- Multiple sclerosis (IFN- β): reduced rate of exacerbation.
- Fever, chills, myelosuppression.

THAMLIDOMIDE

- A sedative drug.
- Teratogenic (Class-X).
- Can be given orally.
- Has immunomodulatory actions
- Inhibits TNF-α
- Reduces phagocytosis by neutrophils
- Increases IL-10 production

USES

- Myeloma
- Rheumatoid arthritis
- Graft versus host disease.
- Leprosy reactions
- treatment of skin manifestations of lupus erythematosus



DRUG	ACTION	ADVERSE EFFECTS
Antithymocyte globulins	Destruction of T lymphocytes	Profound immunosuppression
Muromonab-CD3	Destruction of T lymphocytes	Cytokine release syndrome
Cyclosporine	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, hepatotoxicity
Tacrolimus (FK506)	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, diabetes
Basiliximab	Blocks the IL-2 receptor	Gastrointestinal disorders
Daclizumab	Blocks the IL-2 receptor	Gastrointestinal disorders
Sirolimus	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea
Azathioprine	Inhibits purine synthesis	Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia
Mycophenolate mofetil	Inhibits purine synthesis	GI upset, nausea, diarrhea, leukopenia, tumors, increases susceptibility to infection

CLINICAL USES OF IMMUNOSUPPRESSIVE AGENTS

DISEASE	AGENT USED
Autoimmune Disease:	
Acute glomerulonephritis	Prednisone*, mercaptopurine. Cyclophosphamide.
Autoimmune haemolytic anaemia.	Prednisone*, cyclophosphamide, mercaptopurine, azathioprine, high dose δ-globulin.

Organ transplant:	
• Renal • Heart	**Cyclosporine, Azathioprine, Prednisone, ALG, Tacrolimus.**
• Liver	**Cyclosporine, Prednisone, Azathioprine, Tacrolimus.**
• Bone marrow	**Cyclosporine, Cyclophosphamide, Prednisone, Methotrexate, ALG, total body radiation.**

Thymocytes cells that develop in the thymus and serve as T cell precursors.