# 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<br>✔Mucous membranes<br>✔Secretions of skin and mucous membranes | ✔Phagocytic white blood cells<br>✔Antimicrobial proteins<br>✔Inflammatory response | ✔Lymphocytes<br>✔Antibodies |

# IMMUNE SYSTEM

- Immune system include two main arms

1) Cell –mediated immunity.

2) Humoral (antibody –mediated immunity).

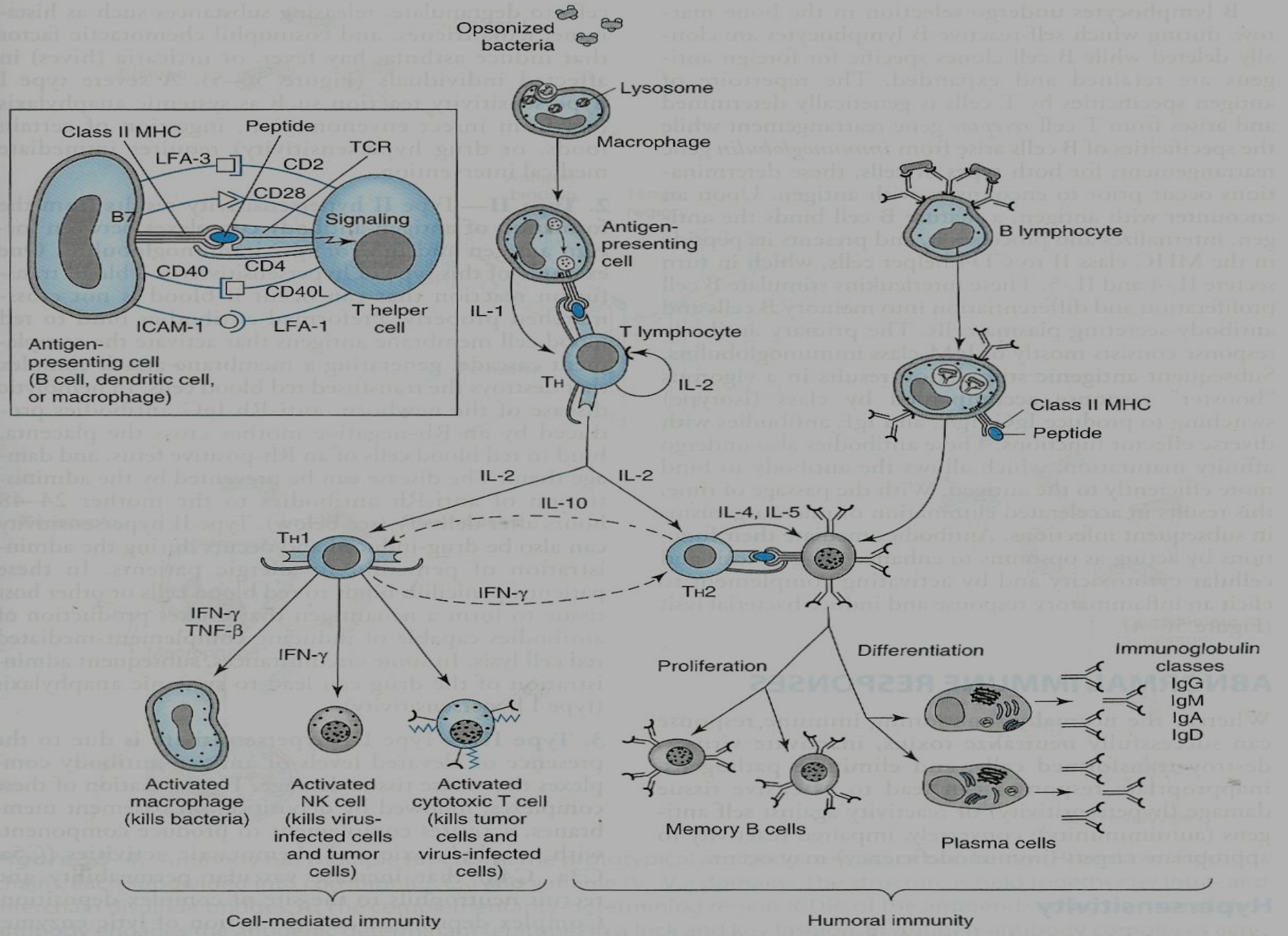
# TYPES OF IMMUNITY

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.

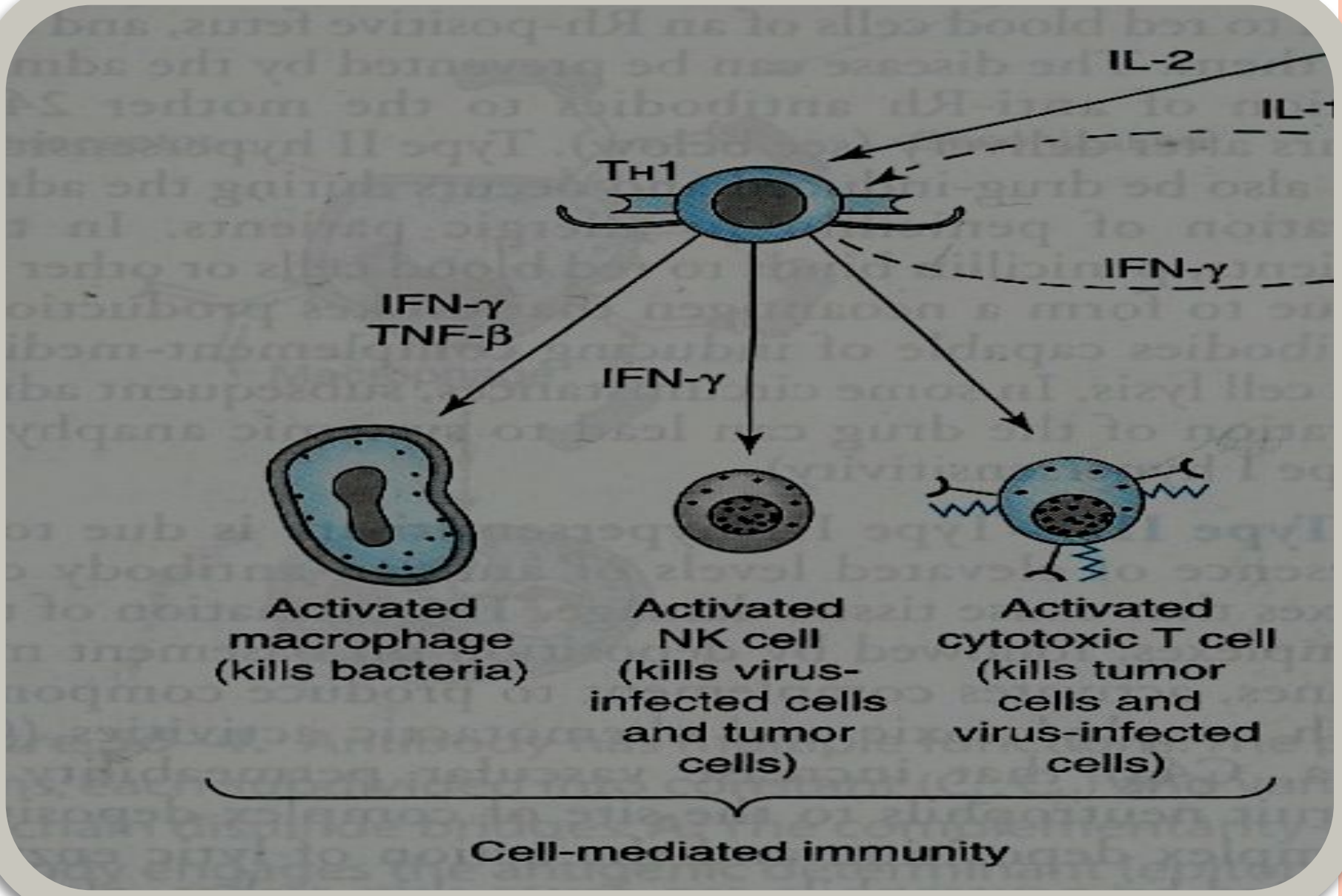
- Cytokines include
  - Interleukins,
  - Interferons (IFNs),
  - Tumor Necrosis Factors (TNFs),
  - Transforming Growth Factors (TGFs)
  - Colony-stimulating factors (CSFs).

- 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

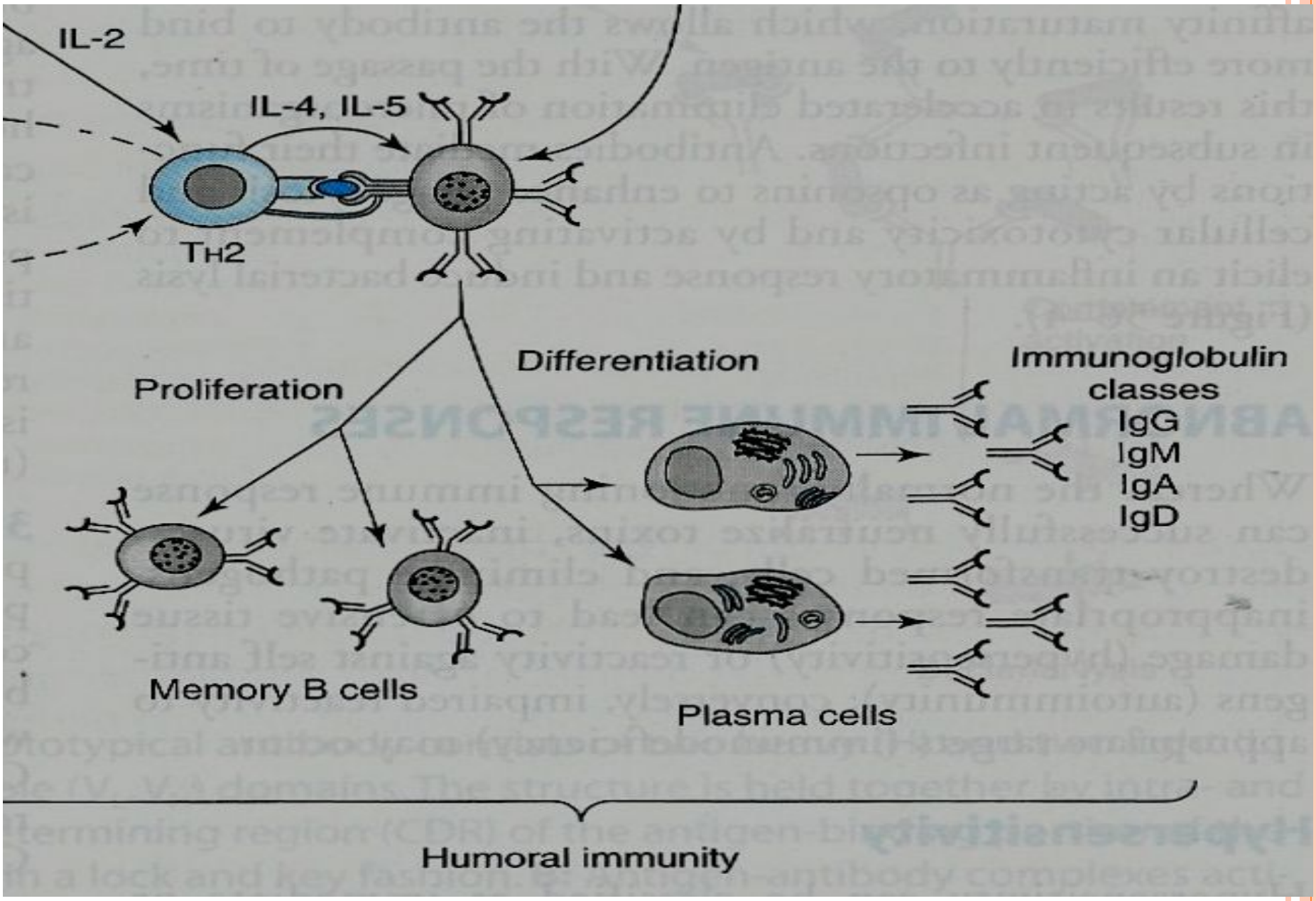


# Humoral Immunity

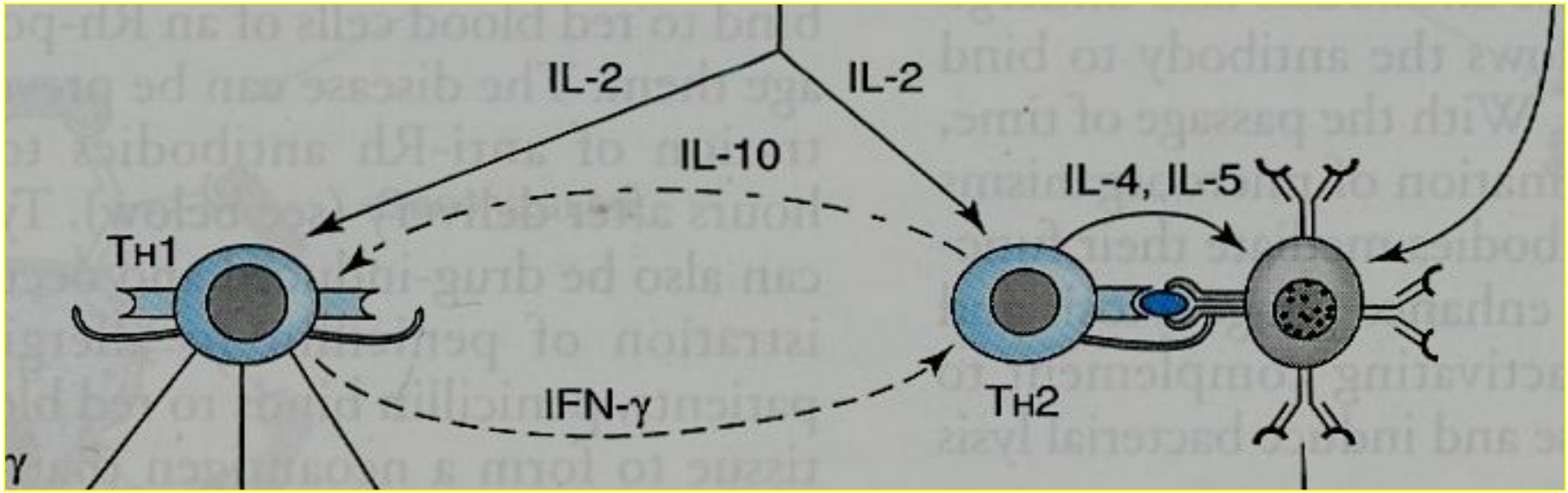
B-lymphocytes → TH2 produces (interleukins) IL-4 & IL-5 which in turn causes:

- 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:

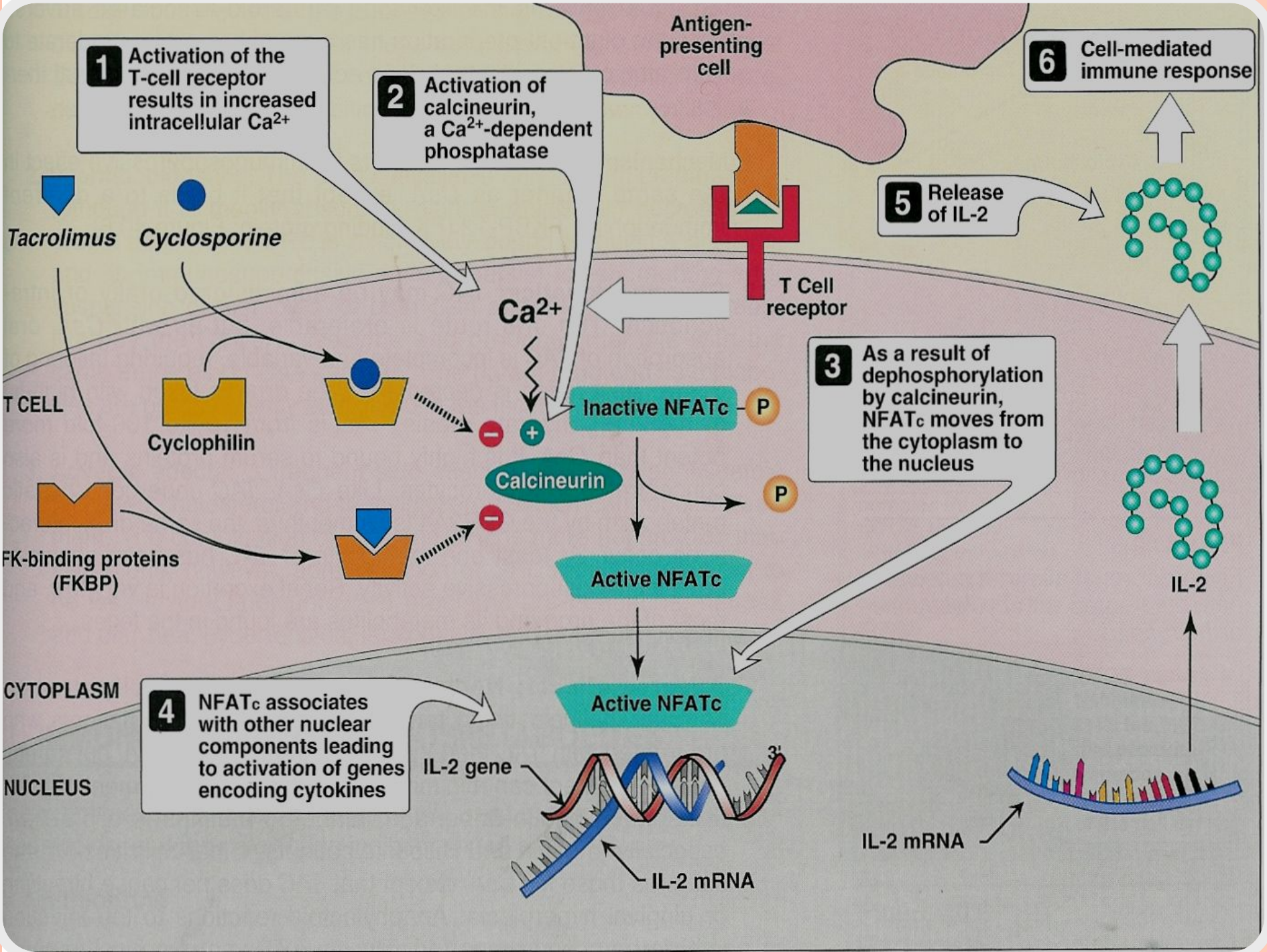
- Acts by blocking activation of T cells by inhibiting interleukin-2 production (IL-2).
- Decreases proliferation and differentiation of T cells.

- 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.

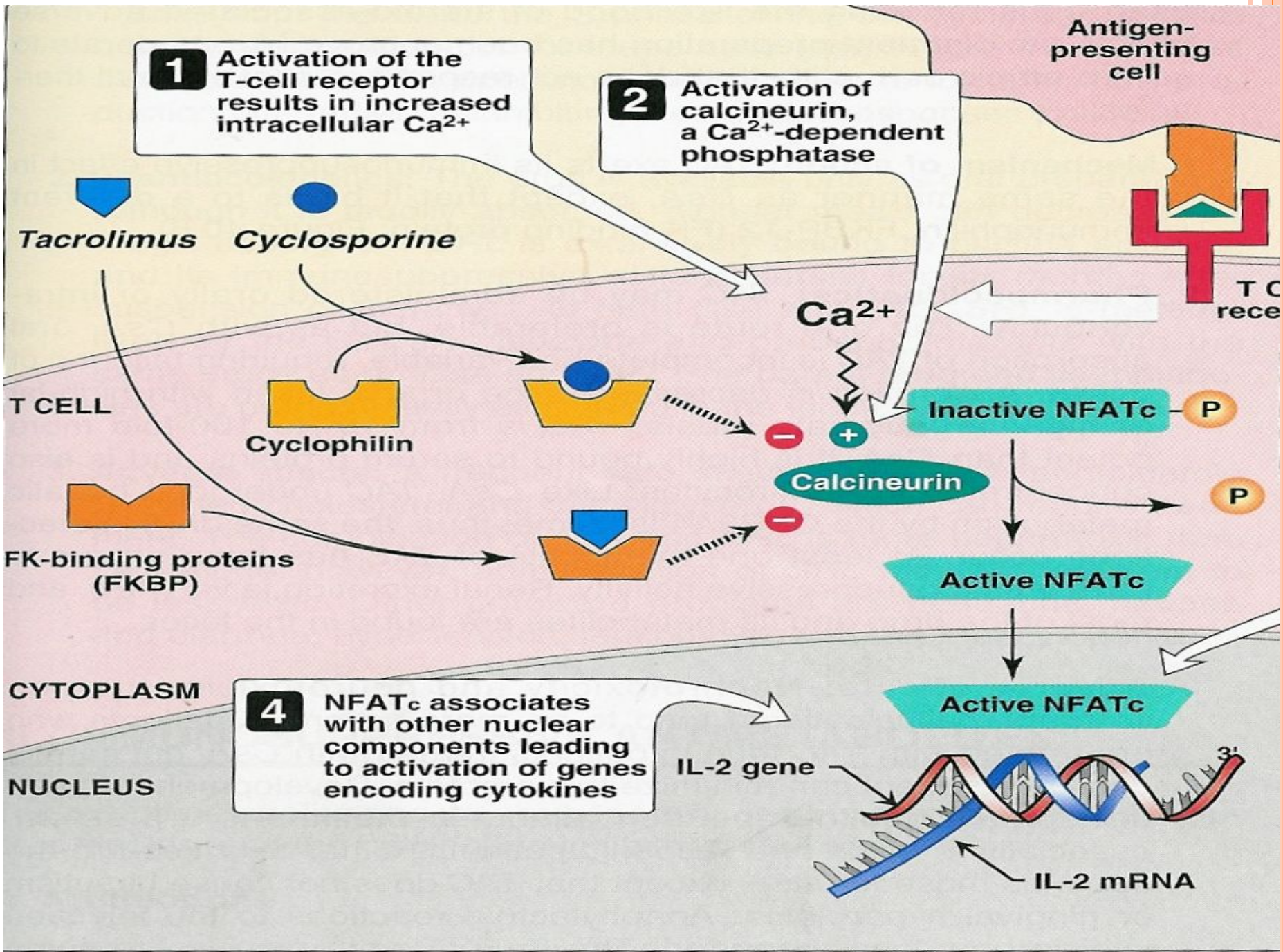
## Drug Interactions

- **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.


1 Activation of the T-cell receptor results in increased intracellular $Ca^{2+}$
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Antigen-presenting cell
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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:

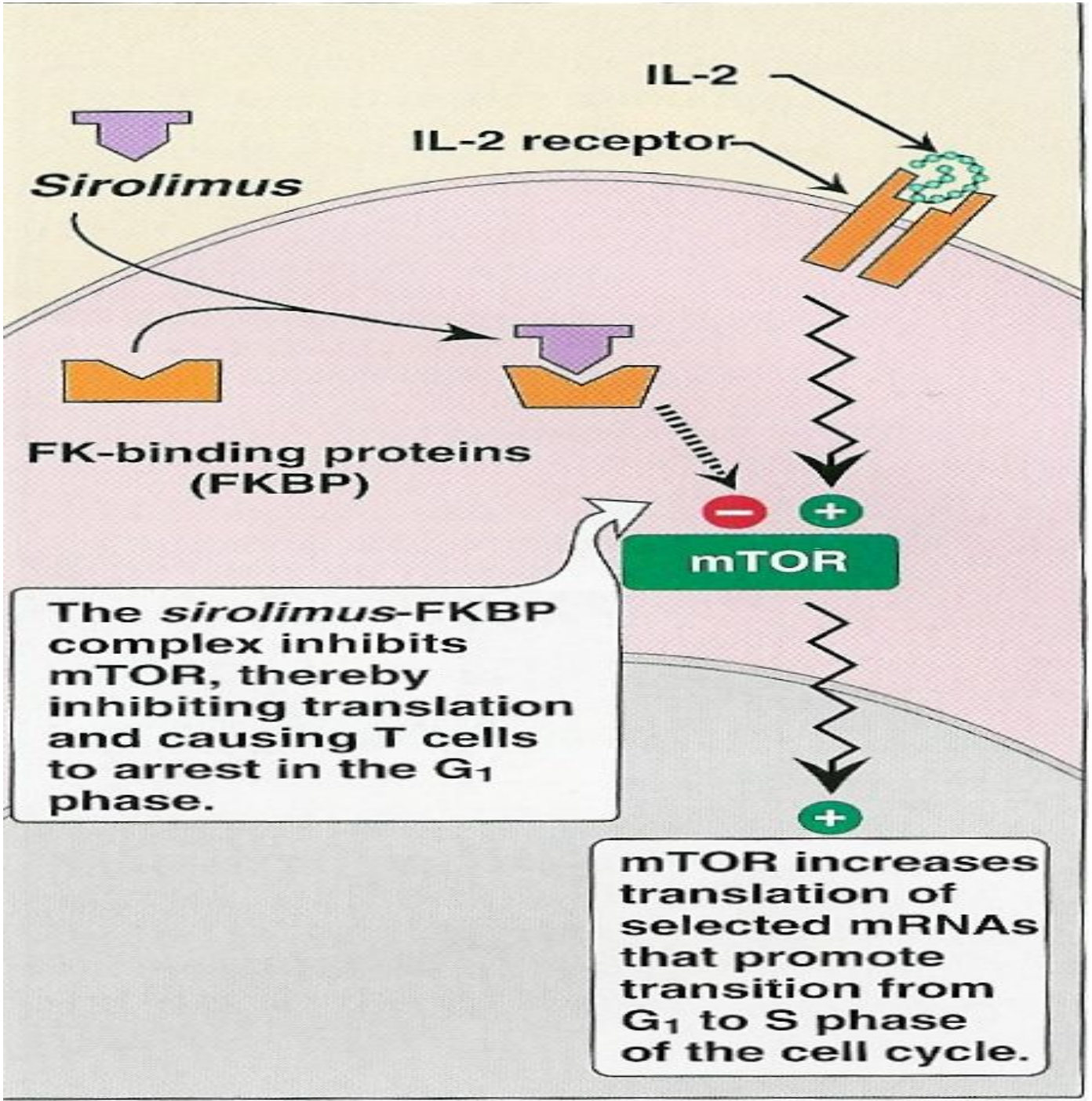
- **TAC is 10 – 100 times more potent than CsA in inhibiting immune responses.**
- **TAC has decreased episodes of rejection.**
- **TAC is combined with lower doses of glucocorticoids.**

## 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

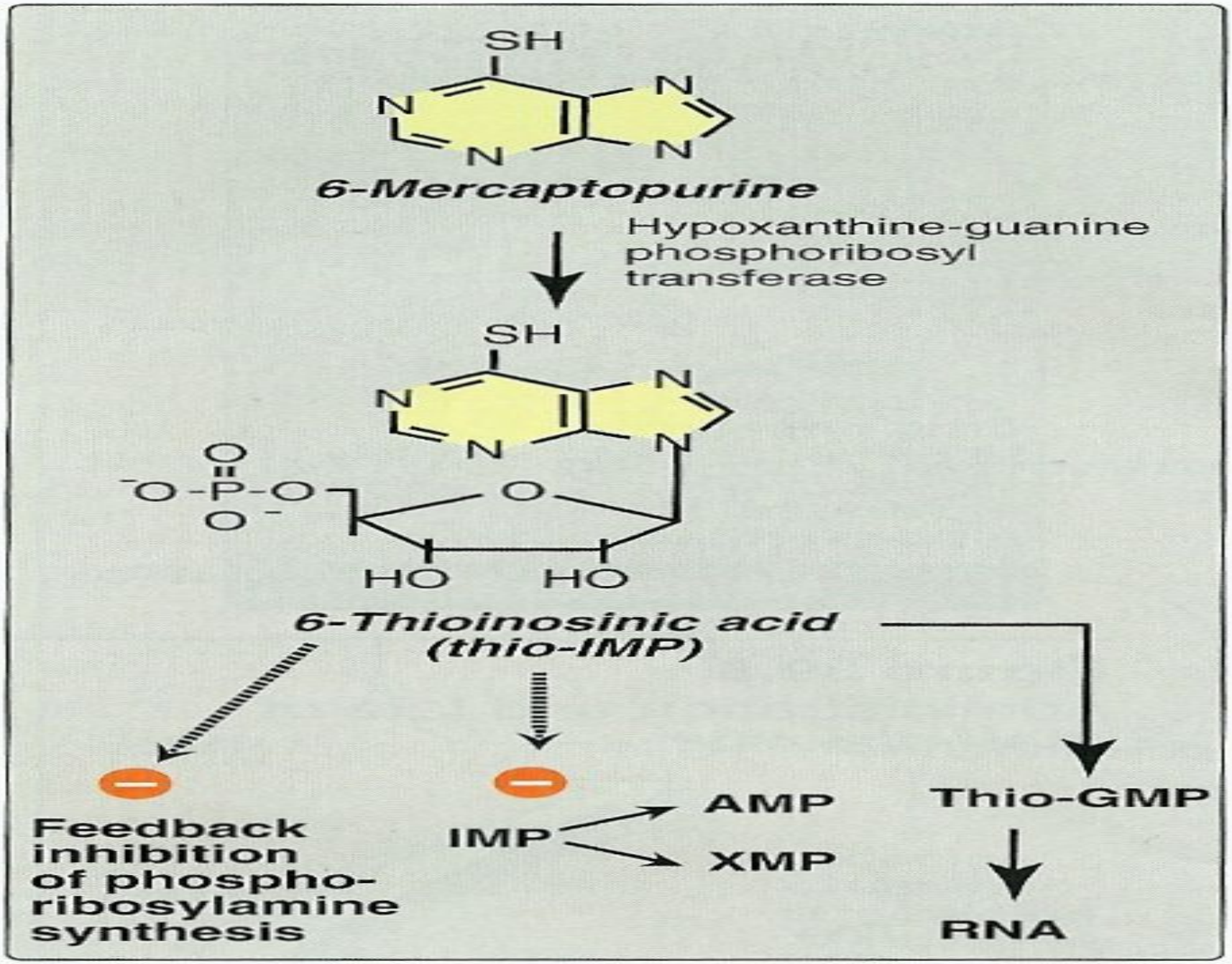
- **Inhibitors of purine or pyrimidine synthesis (Antimetabolites):**
  - Azathioprine
  - Myclophenolate Mofetil
  - Leflunomide
  - Methotrexate
- **Alkylating agents**

  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

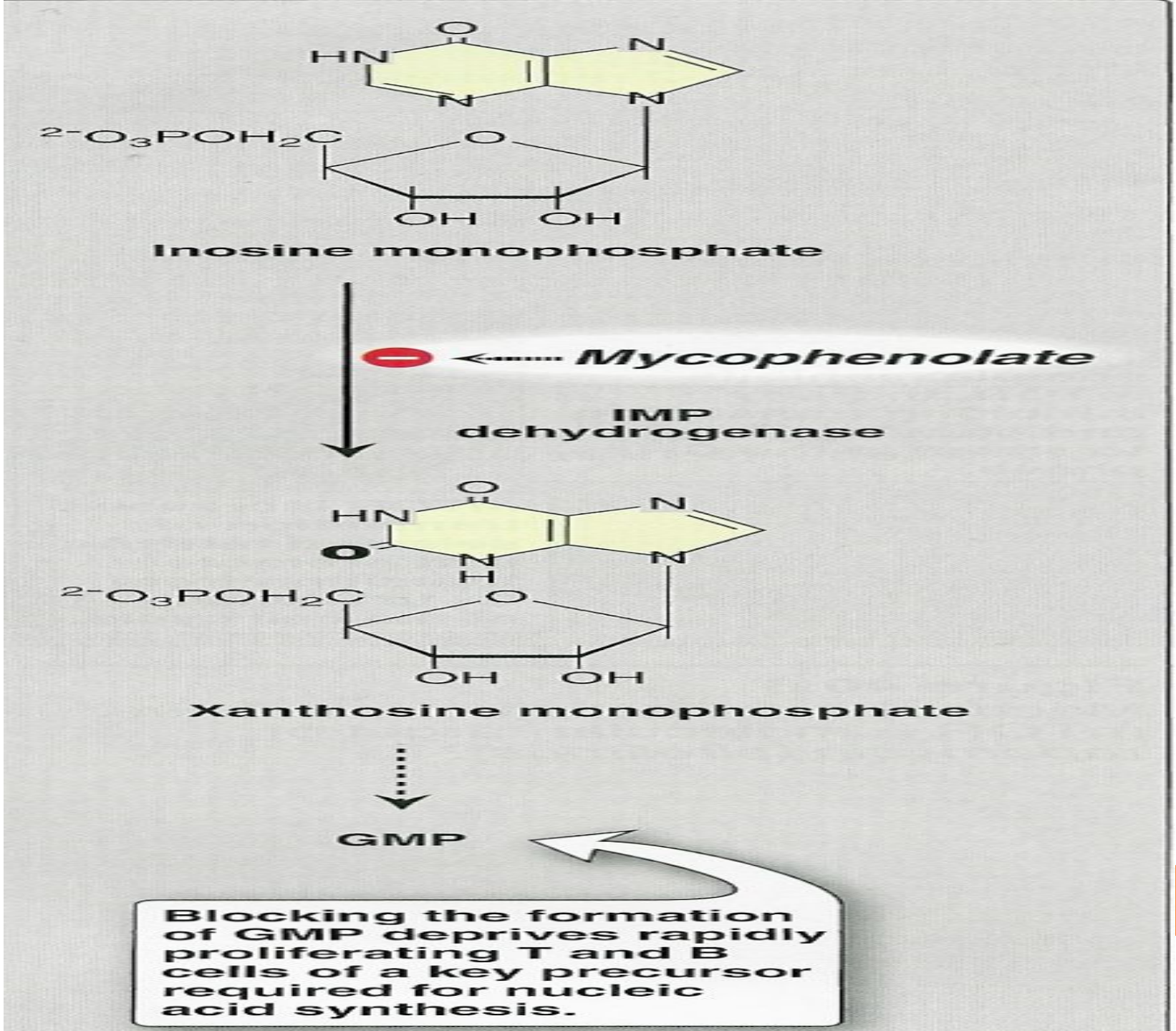
- Bone marrow depression: leukopenia, thrombocytopenia.
- Gastrointestinal toxicity.
- Hepatotoxicity.
- Increased risk of infections.

# 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

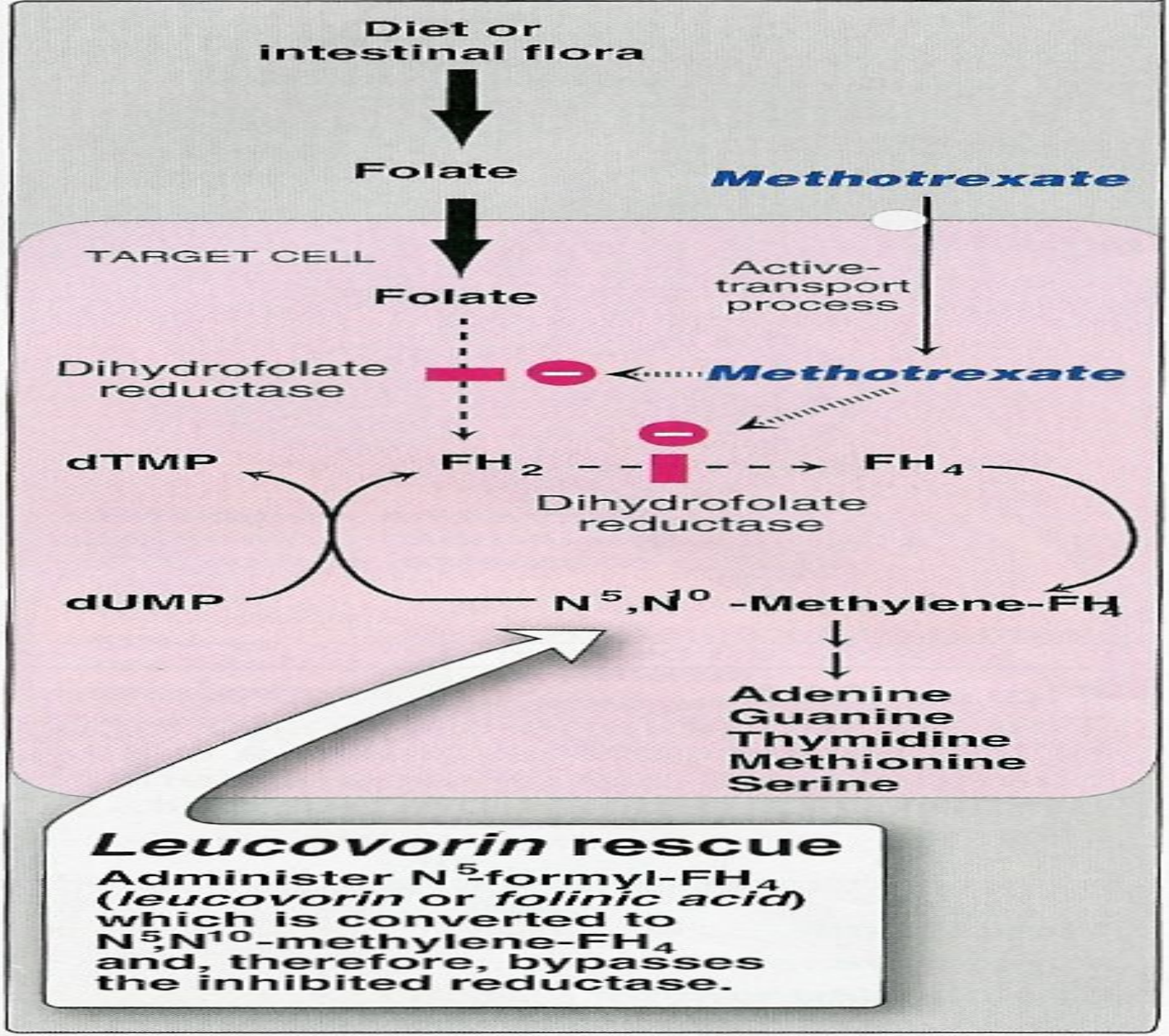
1. Elevation of liver enzymes
2. Renal impairment
3. Teratogenicity
4. Cardiovascular effects (tachycardia).

## 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:**

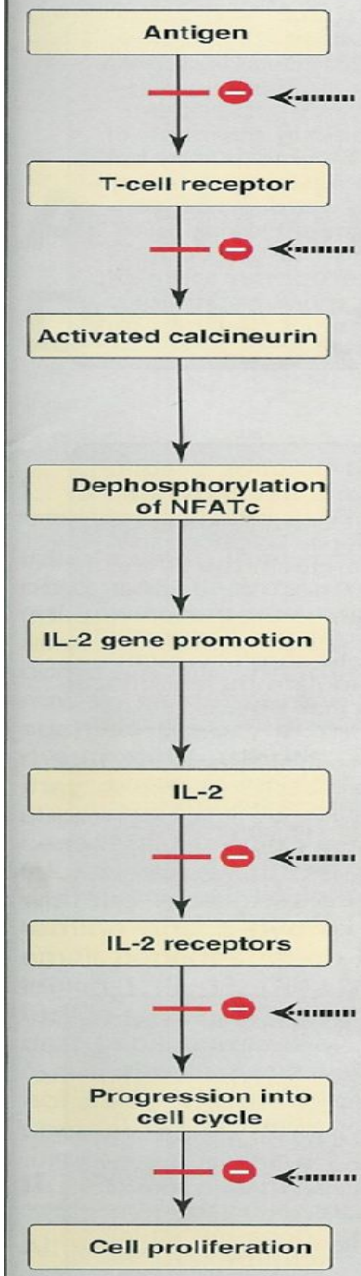
- Treatment of certain infections e.g. Hepatitis C (IFN- α ).
- Autoimmune diseases e.g. Rheumatoid arthritis.
- Certain forms of cancer e.g. melanoma, renal cell carcinoma.
- Multiple sclerosis (IFN- β): reduced rate of exacerbation.
- Fever, chills, myelosuppression.

# 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<br>• 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.