



# Immunomodulators

***Dr. Nashwa Abo-Rayah***

***Assistant prof. (clinical & experimental  
pharmacology)***

***Mu'tah University- Faculty of Medicine***



# Immunosuppressants

# **Classification of immunosuppressants**

- **Glucocorticoids**
- **Cytostatics**
- **Drugs acting on immunophilins**
- **Antibodies**
- **Others**

## [I] Glucocorticoids

- Corticosteroids are the most widely used "front-line" therapy for the treatment of clinical GVHD.
- The most commonly utilized corticosteroid is methylprednisolone and dexamethasone.

### **Immunosuppressive mechanism:**

- 1. Inhibition of T-cell function (cell-mediated immune response):** by inhibiting release of cytokines interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, and TNF-alpha, the most important of which is IL-2.
- 2. Inhibition of B-cell function (humoral immunity):** by inhibition of antibody production.
- 3. Inhibition of inflammatory events:** cell adhesion, migration, chemotaxis, inflammatory mediators, etc.

## [I] Glucocorticoids

### Clinical uses (as immunosuppressants):

1. Suppression of GVHD.
2. Treatment of autoimmune disease: such as rheumatoid arthritis, SLE, rheumatic fever, nephrotic syndrome, etc.

### Adverse effects:

In addition to their immunosuppressive effects, which set the stage for infectious complications, side effects include Cushingoid features, hyperglycemia, salt and water retention, skin and muscle atrophy, osteoporosis and cataract (posterior polar cataract).

## [III] Cytostatics

Cytostatics inhibit cell division. They inhibit the proliferation of both T cells and B cells.

In immunotherapy, they are used in smaller doses than in the treatment of malignant diseases.

### Examples of cytostatic drugs used as immunosuppressants:

- **Alkylating agents:** cyclophosphamide
- **Antimetabolites:**
  - Folic acid antagonists: methotrexate
  - Purine analogues: azathioprine

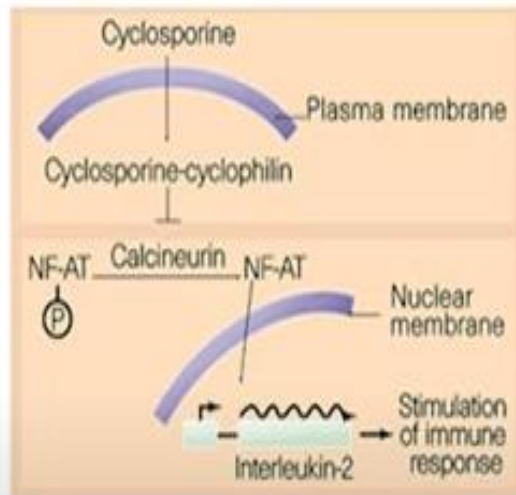
## [III] Drugs acting on immunophilins

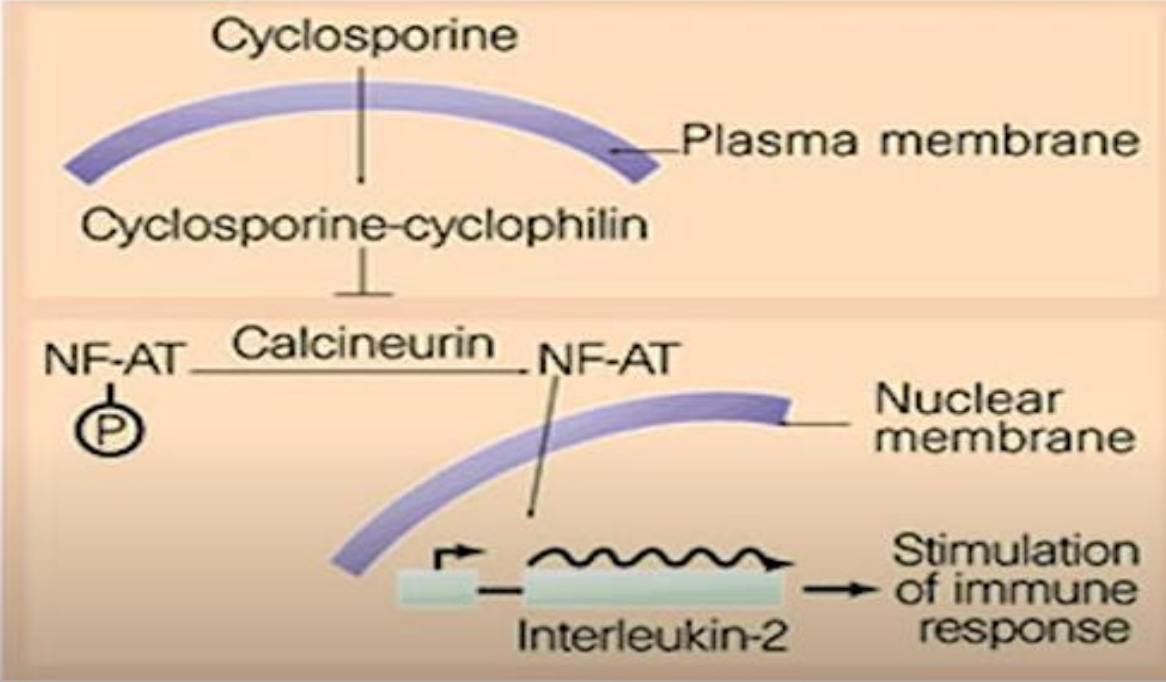
### 1. Ciclosporin (also spelled cyclosporine and cyclosporin)

- It is a natural peptide (11 amino acid) derived from a soil fungus.
- Discovered in 1970 from new strains of fungi isolated from soil samples taken from Norway.

#### Mechanism of action

Ciclosporin binds to cytoplasmic protein called **cyclophilin** (**immunophilin**) of T-lymphocytes ... The ciclosporin-cyclophilin complex then inhibits a transcriptional factor called **calcineurin** which is responsible for **transcription of IL-2**.







## [III] Drugs acting on immunophilins

### 1. Cyclosporin (also spelled cyclosporine and cyclosporin)

#### Clinical uses

Prevention of GVHD.

Treatment of autoimmune diseases.

#### Adverse effects

Nephrotoxicity: the most common.

Hypertension

Hyperkalemia

Hypertrichosis (hirsutism)

Hyperglycemia

Hyperlipidemia

Hyperuricemia

Gum hyperplasia

#### N.B.

In post renal transplant, the 2 most common causes of declining renal function are graft rejection and cyclosporine toxicity.

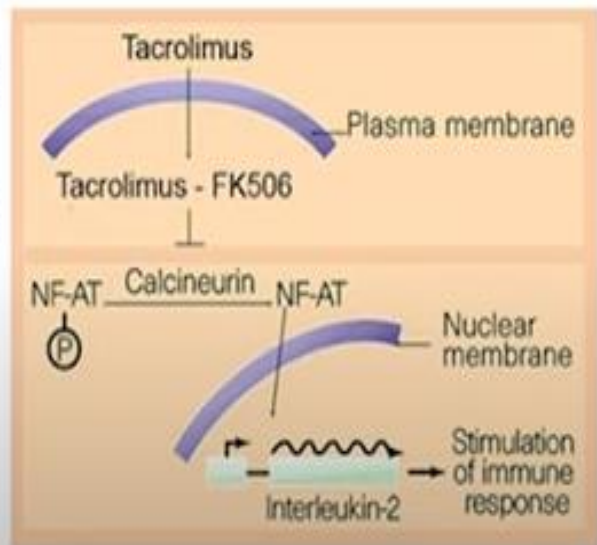
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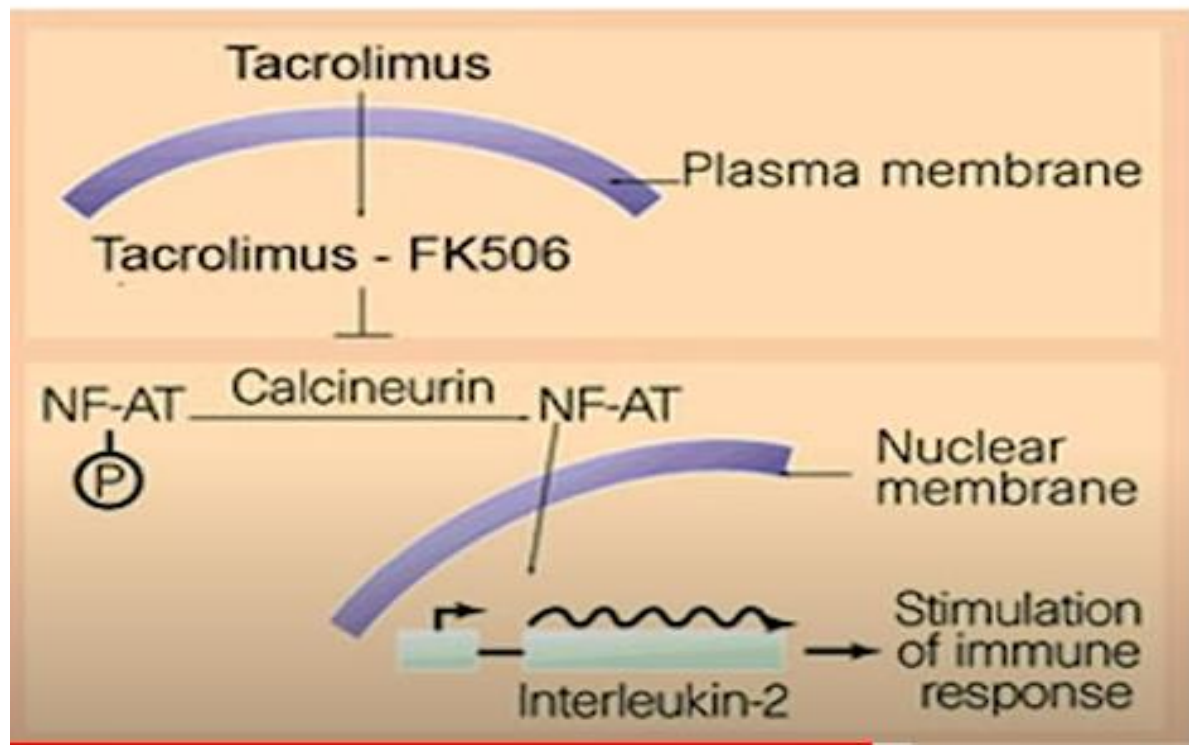
## [III] Drugs acting on immunophilins

### 2. Tacrolimus (also known as FK506)

The mechanism of action, uses, and adverse effects are very similar to ciclosporin except in:

- It is macrolide lactone derived from certain species of **bacteria**.
- It is 200 times **more potent** than ciclosporin.
- It binds to the cytoplasmic protein called **FK506** in the T-cells, then the complex inhibits **calcineurin** → inhibition of IL-2 synthesis.





## [IV] Antibodies

### T-cell receptor directed antibodies:

**Muromonab-CD3** is monoclonal antibody that prevents T-cell activation and proliferation by binding the T-cell receptor CD3 present on all differentiated T cells.

### B-cell receptor directed antibodies:

**Rituximab** is monoclonal antibody that prevents B-cell activation and proliferation by binding the B-cell receptor CD20.

### IL-2 receptor directed antibodies:

**Daclizumab** is monoclonal antibody that binds to CD25, the IL-2 receptor of T-cells.

### TNF binding antibodies:

**Infliximab** and **adalimumab** are monoclonal antibodies that bind to TNF-a preventing it from inducing the synthesis of IL-1 and IL-6 by immune cells.

## [V] Other Drugs

### **Mycophenolate mofetil**

- Mycophenolic acid acts as selective inhibitor of *Inosine-5'-monophosphate dehydrogenase (IMPDH)*, which is a key enzyme in the synthesis of guanosine nucleotide. In contrast to other human cell types, lymphocytes B and T are very dependent on this process.
- Mycophenolate mofetil is used in combination with ciclosporin or tacrolimus in transplant patients.



# **Immunostimulants**

## [B] Immunostimulating Agents

### Types of Immunostimulants

- Colony stimulating factors
- Interferons
- Interleukins
- Bacterial vaccines
- Viral vaccines

## [I] Colony stimulating factors

### Granulocyte/macrophage colony stimulating factor (GM-CSF)

- GM-CSF is a recombinant protein expressed in yeasts. Its principal action is to stimulate myelopoiesis in granulocyte-macrophage pathways as well as megakaryocytic and erythroid progenitor cells.
- It is given i.v. in cases of neutropenia and aplastic anemia, and to stimulate stem cells after bone marrow transplantation.

### Granulocyte colony stimulating factor (G-CSF; Filgrastim)

- G-CSF stimulates maturation of immature neutrophils.
- Uses: Neutropenia due to cancer chemotherapy.



## [II] Interleukins

### **Aldesleukin (Proleukin)**

is a synthetic form of interleukin-2 (IL-2). It is given s.c. to elicit immune response in cases of metastatic renal cell carcinoma and metastatic melanoma (i.e. a type of cancer immunotherapy).



### **Oprelvekin (Neumega)**

is a recombinant IL-11 approved for treatment of thrombocytopenia. Interleukin-11 (IL-11) is a protein produced by fibroblasts and stromal cells in the bone marrow. It acts on specific cell receptors to stimulate growth of primitive megakaryocytes to form mature platelets.



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THANK YOU