Immunomodulatory drugs

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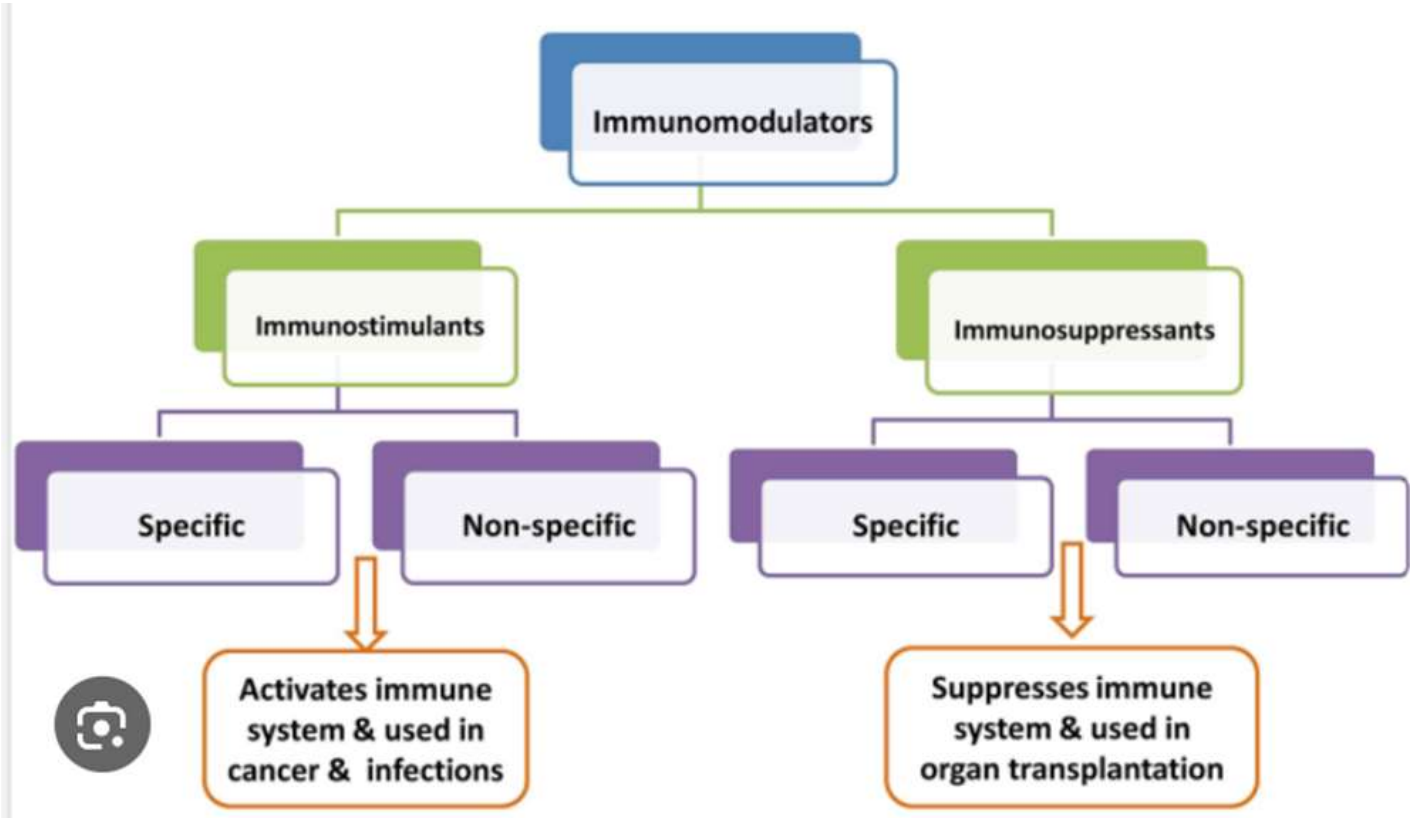
Immunomodulatory drugs

- Drugs that **change the immune system** so it works more effectively.
- They include treatments that **increase** or **decrease** the immune response


Immunomodulators
Immunostimulants
Immunosuppressants
Specific
Non-specific
Specific
Non-specific
Activates immune system & used in cancer & infections
Suppresses immune system & used in organ transplantation

Immunosuppressants

What are immunosupressants?

- Drugs used to dampen immune response in organ transplantation and autoimmune diseases.

Classification of immunosuppressants

- Glucocortecoids
- Cytostatics
- Drugs acting on immunophilins
- Antibodies
- Others

[I] Glucocorticoids

- Corticosteroids are the most widely used "front-line" therapy for the treatment of clinical GVHD (**Graft-versus-host disease**)

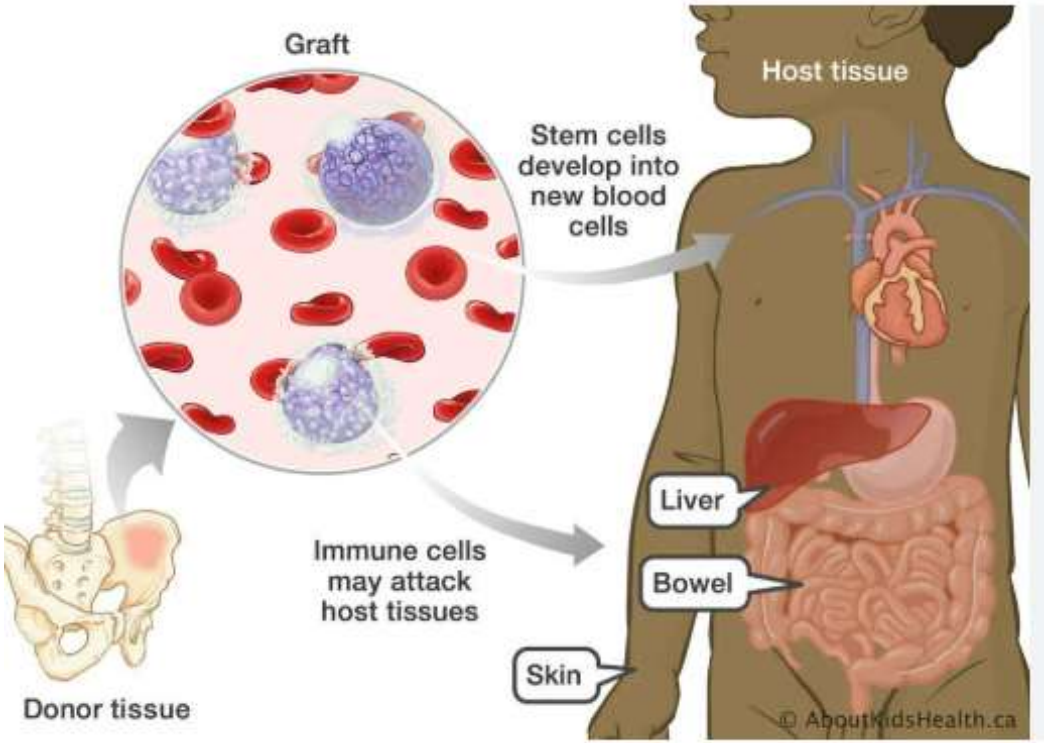
- The most commonly utilized corticosteroid is methylprednisolone and dexamethasone.

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.


Graft
Host tissue
Stem cells develop into new blood cells
Liver
Bowel
Skin
Immune cells may attack host tissues
Donor tissue
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GVHD

[I] Glucocorticoids

Clinical uses (as immunosupressants):

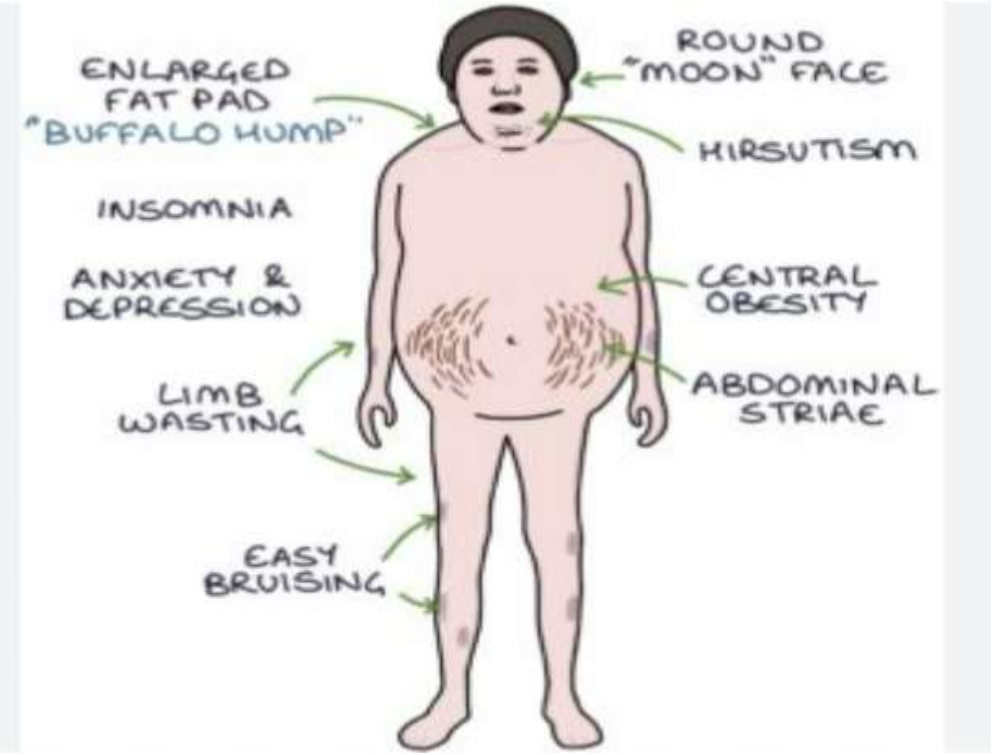
1. Suppression of GVHD.

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 retension**, **skin and muscle atrophy**, **osteoporosis** and **cataract** (posterior polar catacact).

Posterior polar cataract



Cushingoid features

[II] 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:**

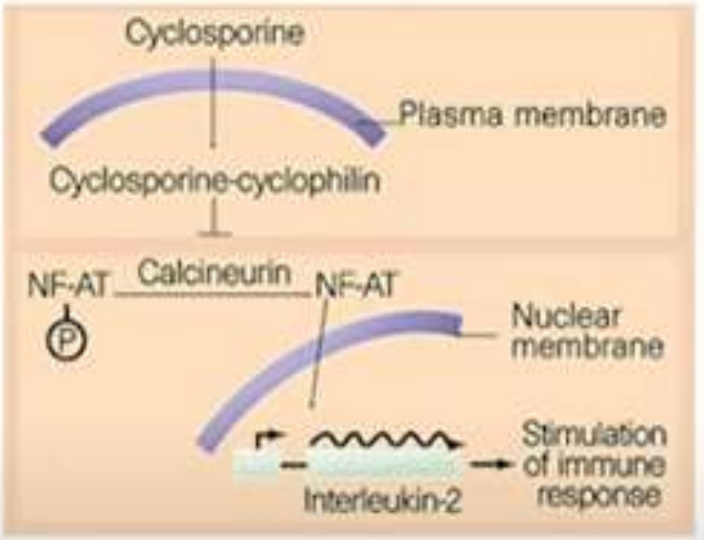
  Folic acid antagonists: methotrexate

  Purine analogues: azathioprine

[III] Drugs acting on immunophilins

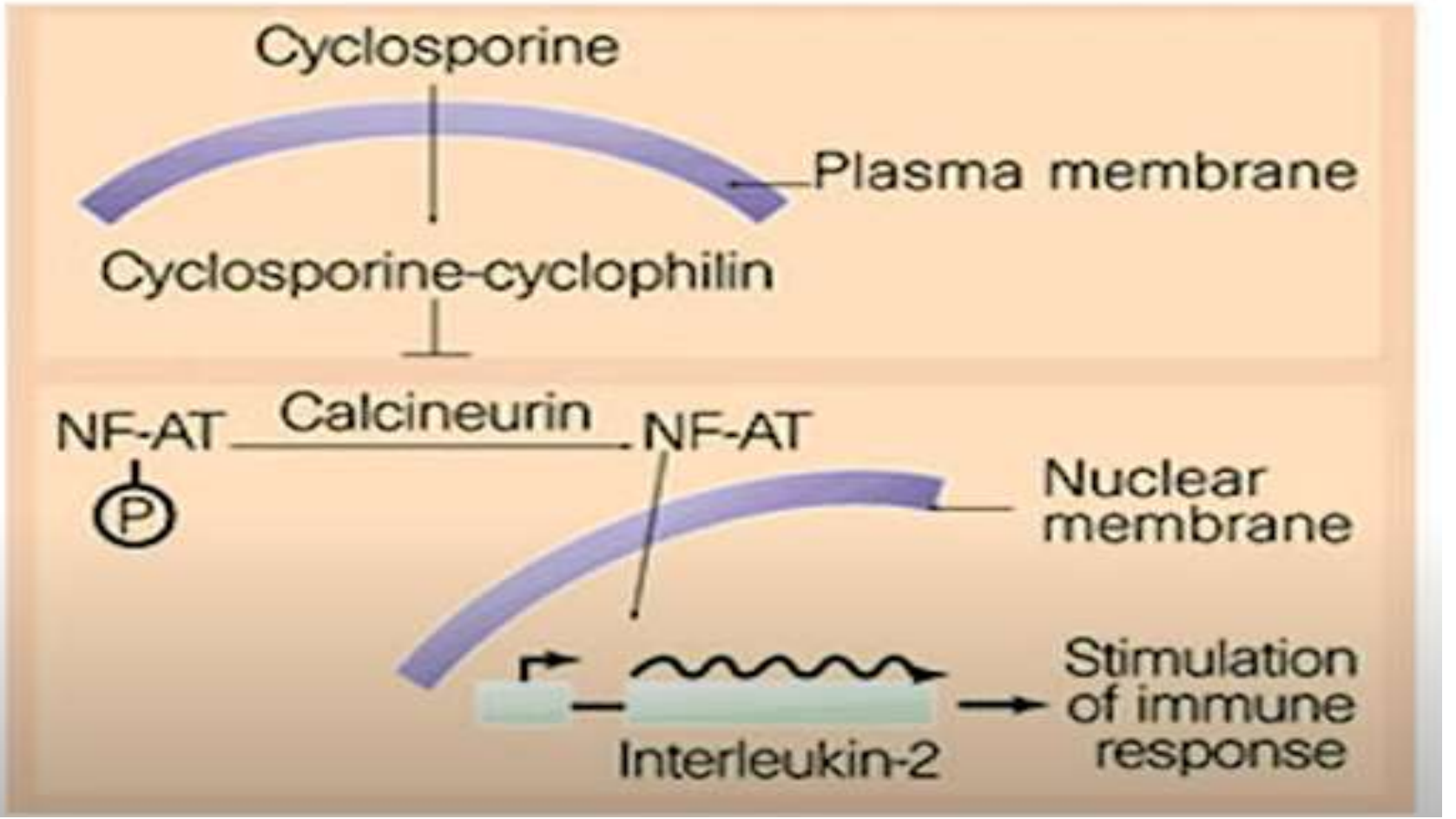
1. Ciclosporin (also spelled cyclosporine and cyclosporin)

- 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 clicosporin-cyclophillin complex then inhibits a transcriptional factor called **calcineurin** which is responsible for **transcription of IL-2**.


Cyclosporine
Plasma membrane
Cyclosporine-cyclophilin
NF-AT
Calcineurin
NF-AT
P
Nuclear membrane
Stimulation of immune response
Interleukin-2

[III] Drugs acting on immunophilins

1. Ciclosporin (also spelled cyclosporine and cyclosporin)

Clinical uses

Prevention of GVHD.

Treatment of autoimmune diseases.

Adverse efects

Nephrotoxicity: the most common.
Hypertension
Hyperkalemia
Hypertrichosis (hirsutism)
Hyperglycmeia
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.

Everything is increased

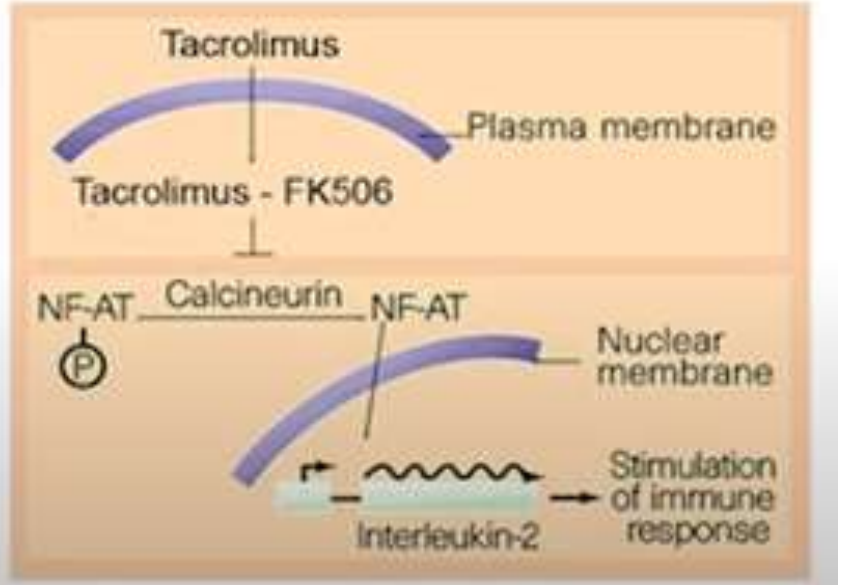
Gum hyperplasia

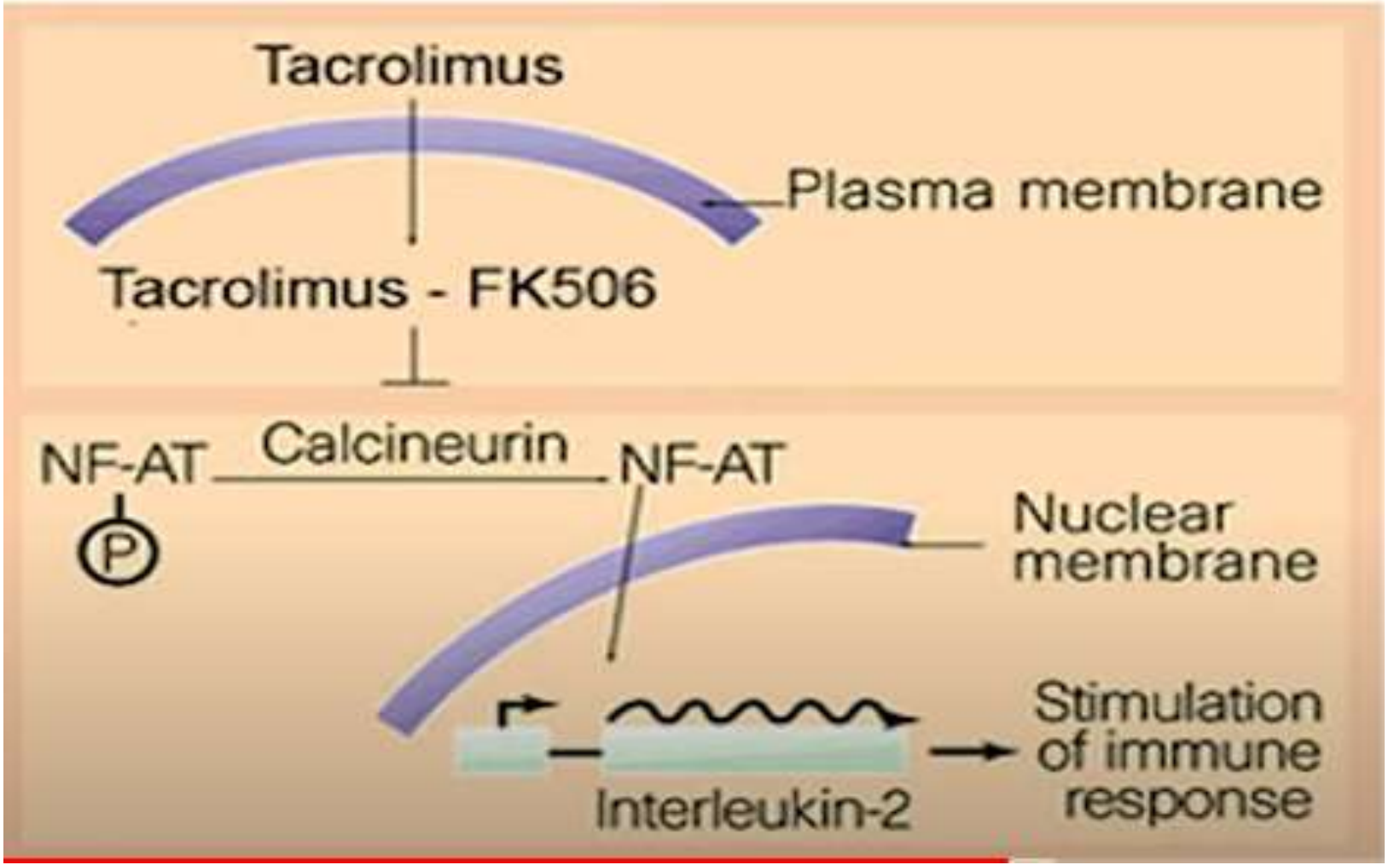
[III] Drugs acting on immunophilins

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 caled **FK506** in the T-cells, then the complex inhibits **calcineurin** → inhibition of IL-2 synthesis.




Tacrolimus
Plasma membrane
Tacrolimus - FK506
NF-AT
Calcineurin
NF-AT
P
Nuclear membrane
Stimulation of immune response
Interleukin-2

[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.

Immunostimulants

- Drugs which **stimulate** the immune system by increasing the activity of any of its components
- Used in immunocompromised patients, cancer and infections

- **Specific immunostimulants**: stimulate an immune response to a **specific antigen** (a toxin or other foreign substance: bacteria or virus which induces an immune response in the body) such as **vaccines.**
- **Nonspecific immunostimulants**: act irrespective of antigenic specificity and are used in **immunodeficiency** and **chronic infections**.

[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