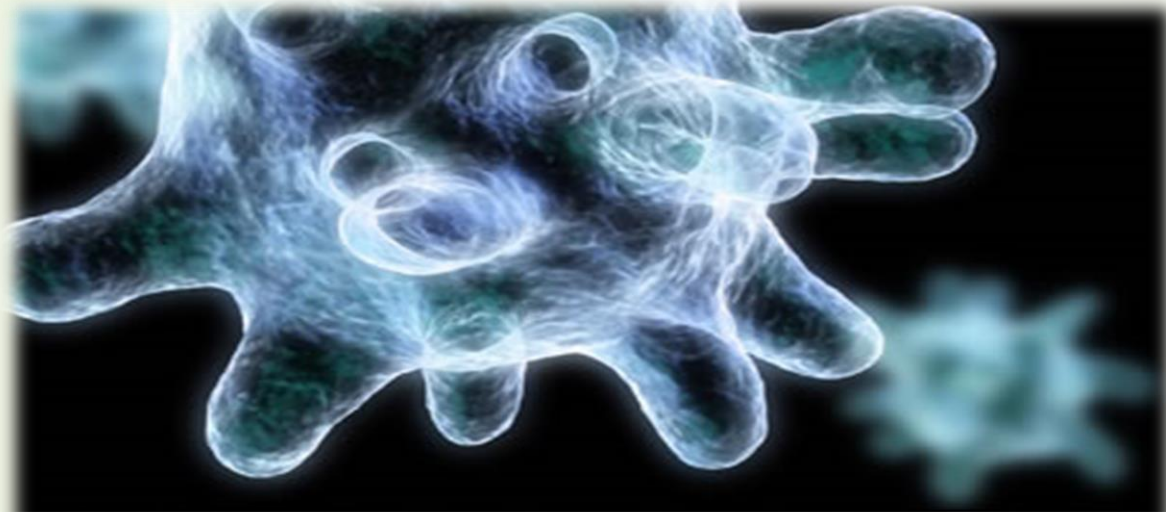


# IMMUNOMODULATORS



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**Session : (2019-2021)**




# Immunomodulators

- Immunomodulation is the process of modifying an immune response in a positive or negative manner by administration of a drug or compound.
- All drugs which modify immune response generally categorized as immunomodulators. These can either function as:
  1. Immunosuppressant.
  2. Immunostimulants.
- Some of these can have both the properties depending on which component of immune response they affect. There is also an upcoming generation of immunosuppressant called **tolerogens**.



# IMMUNOSUPPRESSANTS

- Immunosuppressive drugs are used to dampen the immune response in organ transplantation and autoimmune disease. However, such therapies require lifelong use and nonspecifically suppress the entire immune system, exposing patients to considerably higher risks of infection and cancer.
  - Drugs are now available that more selectively inhibit rejection of transplanted tissues while preventing the patient from becoming immunologically compromised.
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# CLASSIFICATION OF DRUGS:

## SELECTIVE INHIBITORS OF CYTOKINE PRODUCTION AND FUNCTION

*Belatacept* NULOJIX

*Cyclosporine* NEORAL, SANDIMMUNE

*Everolimus* AFINITOR, ZORTRESS

*Sirolimus* RAPAMUNE

*Tacrolimus* PROGRAF

## IMMUNOSUPPRESSIVE ANTIMETABOLITES

*Azathioprine* IMURAN

*Mycophenolate mofetil* CELLCEPT

*Mycophenolate sodium* MYFORTIC

## ANTIBODIES

*Antithymocyte globulins* ATGAM, THYMOGLOBULIN

*Basiliximab* SIMULECT

## ADRENOCORTICOIDS

*Methylprednisolone* MEDROL

*Prednisolone* ORAPRED, PRELONE

*Prednisone*

# 1) Selective inhibitors of cytokines production and function

- Cytokines are soluble, antigen-nonspecific signaling proteins that bind to cell surface receptors on a variety of cells.
- These cytokines collectively activate natural killer cells, macrophages, and cytotoxic T lymphocytes. Drugs that interfere with the production or activity of IL-2 significantly dampen the immune response and, thereby, decrease graft rejection

Cytokine	Actions
IL-1	<ul style="list-style-type: none"><li>• Enhances activity of NK cells</li><li>• Attracts neutrophils and macrophages</li></ul>
IL-2	<ul style="list-style-type: none"><li>• Induces proliferation of antigen-primed T cells</li><li>• Enhances activity of NK cells</li></ul>
IFN- $\gamma$	<ul style="list-style-type: none"><li>• Enhances activity of macrophages and NK cells</li><li>• Increases expression of MHC molecules</li><li>• Enhances production of IgG<sub>2a</sub></li></ul>
TNF- $\alpha$	<ul style="list-style-type: none"><li>• Cytotoxic effect on tumor cells</li><li>• Induces cytokine secretion in the inflammatory response</li></ul>



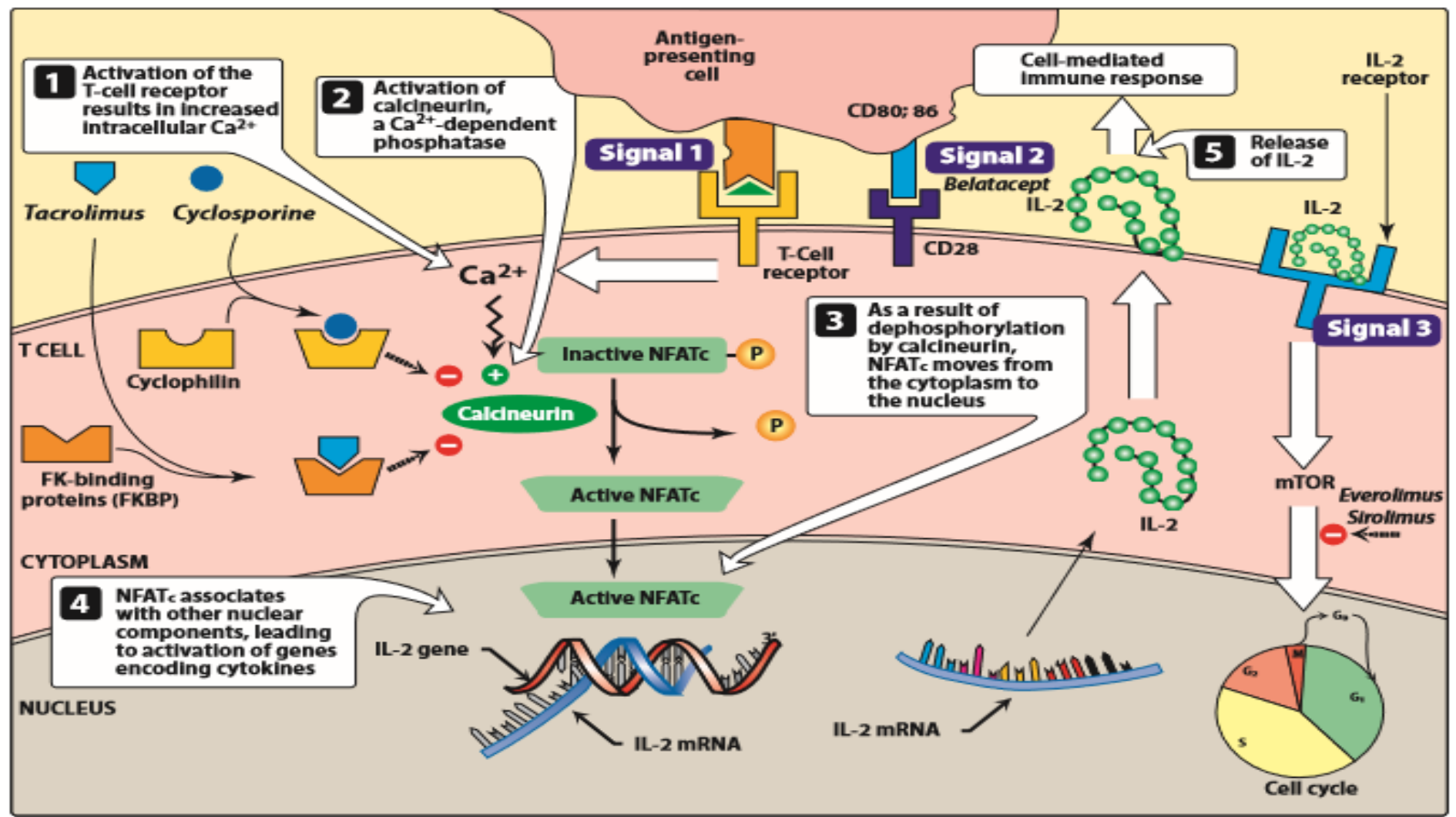


## **These are divided into further three main classes:**


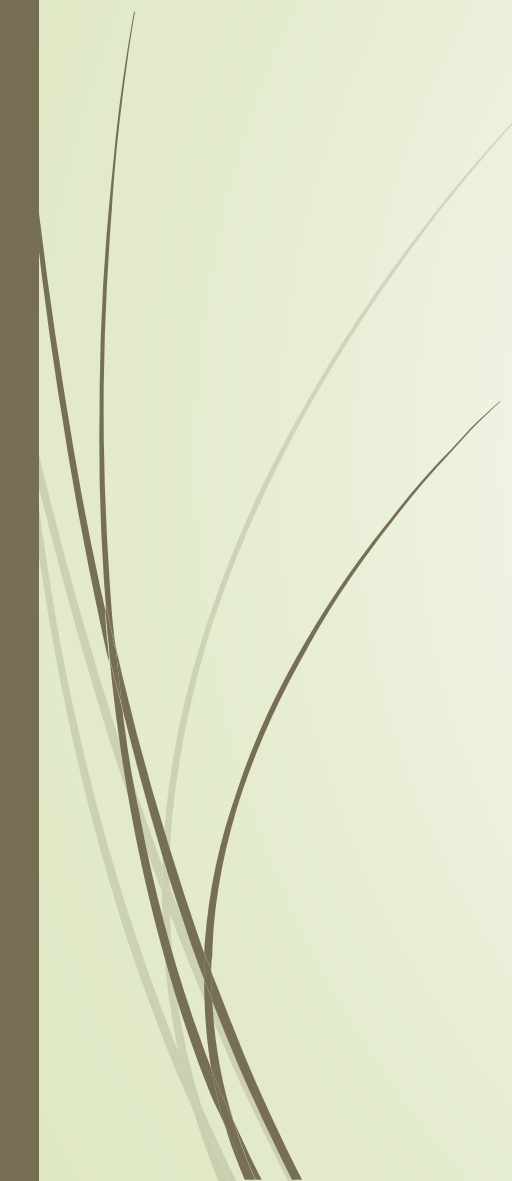
- a) calcineurin inhibitors (cyclosporine and tacrolimus)
- b) costimulation blockers (belatacept),
- c) mTOR inhibitors (sirolimus and everolimus).

## a) calcineurin inhibitors(cyclosporine)

- **MECHANISM OF ACTION:** After diffusing into the T cell, cyclosporine binds to a cyclophilin (more generally called an immunophilin) to form a complex that binds to calcineurin . Calcineurin is responsible for dephosphorylating NFATc (cytosolic Nuclear Factor of Activated T cells). Because the cyclosporine–calcineurin complex cannot perform this reaction, NFATc cannot enter the nucleus to promote reactions that are required for the synthesis of cytokines, including IL-2. The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the number of T lymphocytes.





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- **Therapeutic uses:** Cyclosporine is used to prevent rejection of kidney, liver, and cardiac allogeneic transplants .
  - **Adverse effects:** Many of the adverse effects caused by cyclosporine are dose dependent Nephrotoxicity is the most common and important adverse effect of cyclosporine. Reduction of the cyclosporine dosage can result in reversal of nephrotoxicity in most cases.



## **b) Costimulation blocker (belatacept)**

- **Mechanism of action:** Belatacept blocks CD28-mediated costimulation of T lymphocytes (signal 2) by binding to CD80 and CD86 on APCs. This prevents the downstream stimulatory signals promoting T-cell survival, proliferation, and IL-2 production.
- **Therapeutic uses:** Belatacept is used in kidney transplantation in combination with basiliximab and corticosteroids.



## **c) mTOR inhibitors (sirolimus)**

### **➤ MECHANISM OF ACTION:**

Sirolimus binds to the same cytoplasmic FK-binding protein as tacrolimus, but instead of forming a complex with calcineurin, sirolimus binds to mTOR (a serine/threonine kinase), interfering with signal 3. [Note: TOR proteins are essential for many cellular functions, such as cell cycle progression, DNA repair, and as regulators involved in protein translation.] .

**➤ Therapeutic uses:** Sirolimus is approved for use in renal transplantation, in combination with cyclosporine and corticosteroids,

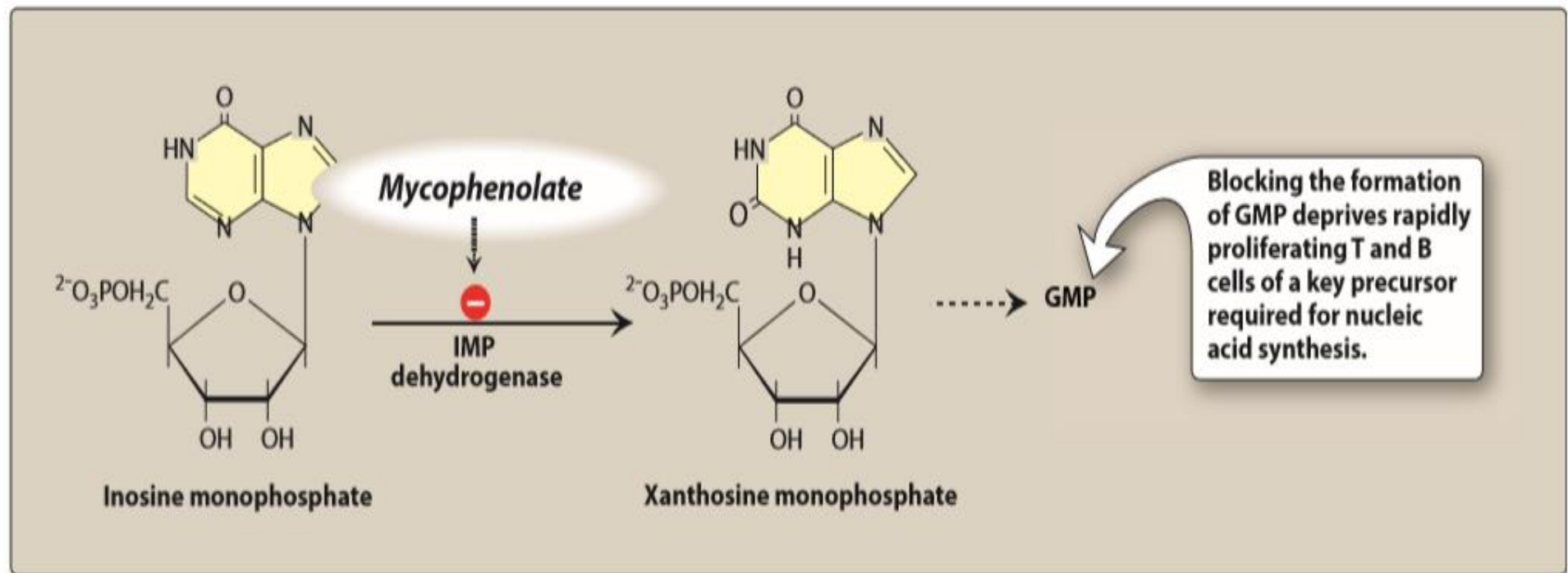
## **2)Antimetabolites**

### **➤ Azathioprine:**

It is a purine antimetabolite. Its selective uptake into immune cells and intracellular conversion to the active metabolite 6-mercaptopurine, which then undergoes further transformation to inhibit de novo purine synthesis and damage to DNA. It is approved for prevention of renal and other graft rejection.

### **➤ Mycophenolate mofetil (CELLCEPT):**

Mycophenolate mofetil is a pro drug that is rapidly hydrolyzed to the active drug, mycophenolic acid (MPA), a selective, noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an important enzyme in the de novo pathway of guanine nucleotide synthesis. B and T lymphocytes are highly dependent on this pathway for cell proliferation.



**Figure 47.6**

Mechanism of action of *mycophenolate*. GMP = guanosine monophosphate.



### **3)ANTIBODIES**

#### **➤ Muromonab CD3:**

Muromonab cd3 is a murine monoclonal antibody against the CD3 glycoprotein located near to the T cell receptor on helper T cells. It is used for treatment of acute rejection of renal allograft as well as cardiac and hepatic transplantation.

#### **➤ Antithymocyte globin (ATG):**

It is a polyclonal antibody purified from horse or rats immunized with human thymic lymphocytes. It binds to T-lymphocytes and depletes them. It is a potent immunosuppressant used for suppress acute allograft reject episodes.

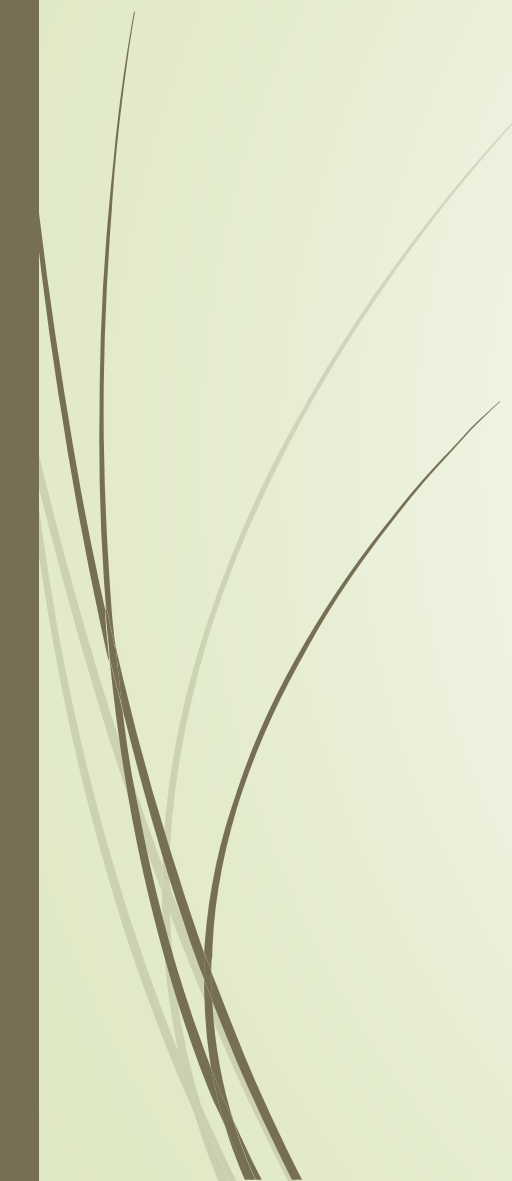
Other drugs of this category are:

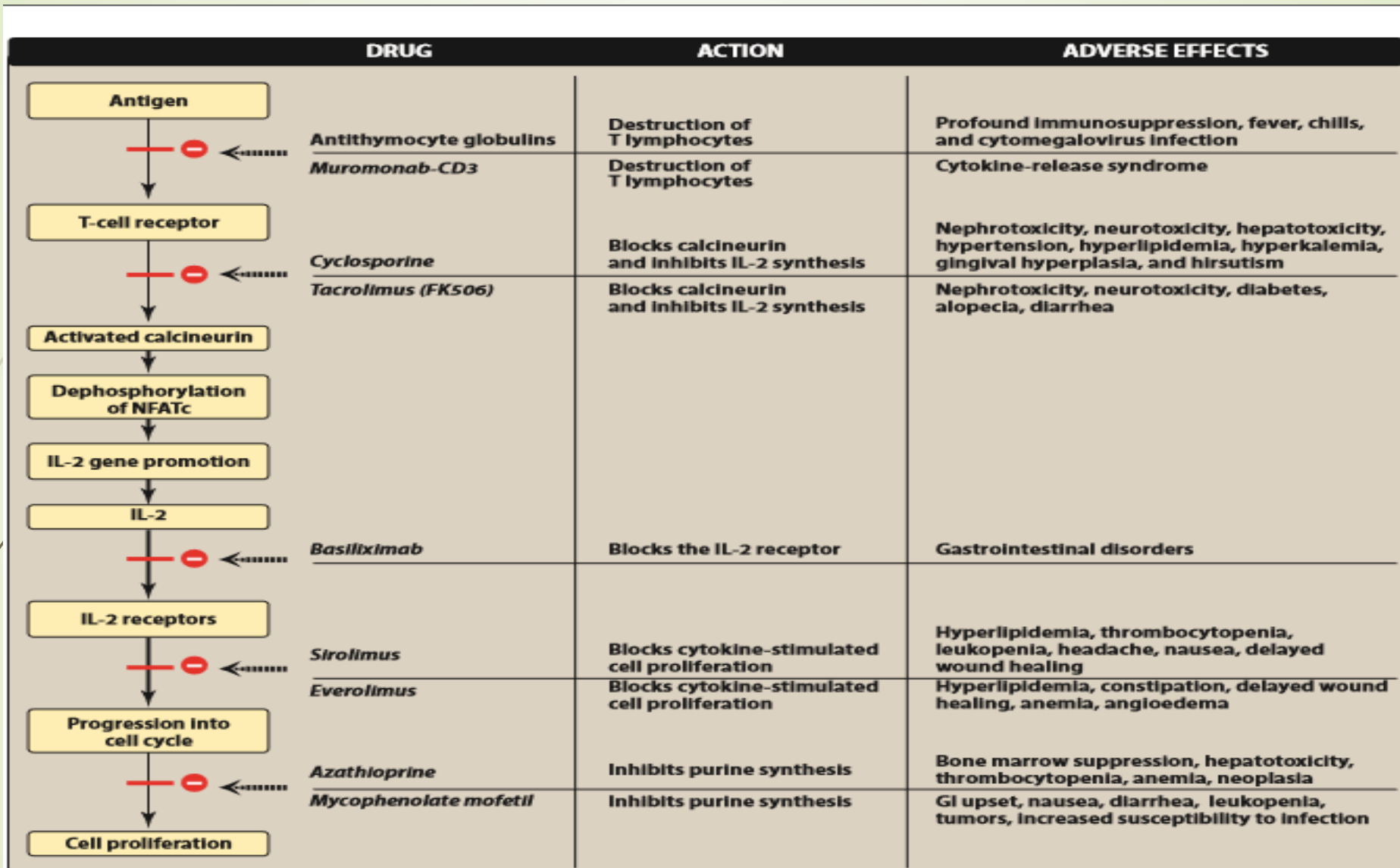
Rho (D) immune-globin,

Efalizumab



## **4)CORTICOSTEROIDS**

- Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids. Glucocorticoids inhibit the production by multiple cells of factors that are critical in generating the inflammatory response. As a result there is decreased release of vasoactive and chemo-attractive factors diminished secretion of lipolytic and proteolytic enzymes decreased extravasation of leukocytes to areas of injury and ultimately decreased fibrosis.
  - Key proinflammatory cytokines such as IL-1 and IL-6 are down regulated.
- 



**Figure 47.7**

Sites of action of immunosuppressants. IL-2 = interleukin-2; NFATc = cytosolic nuclear factor of activated T cells; GI = gastrointestinal.



# Immunostimulants

- Immunostimulants are substances that stimulate the immune system by inducing activation and increasing activity of any of its components. They are used in disorders includes immunodeficiency diseases, cancer, viral, fungal and certain autoimmune disorders.

Immunodeficiency disorders

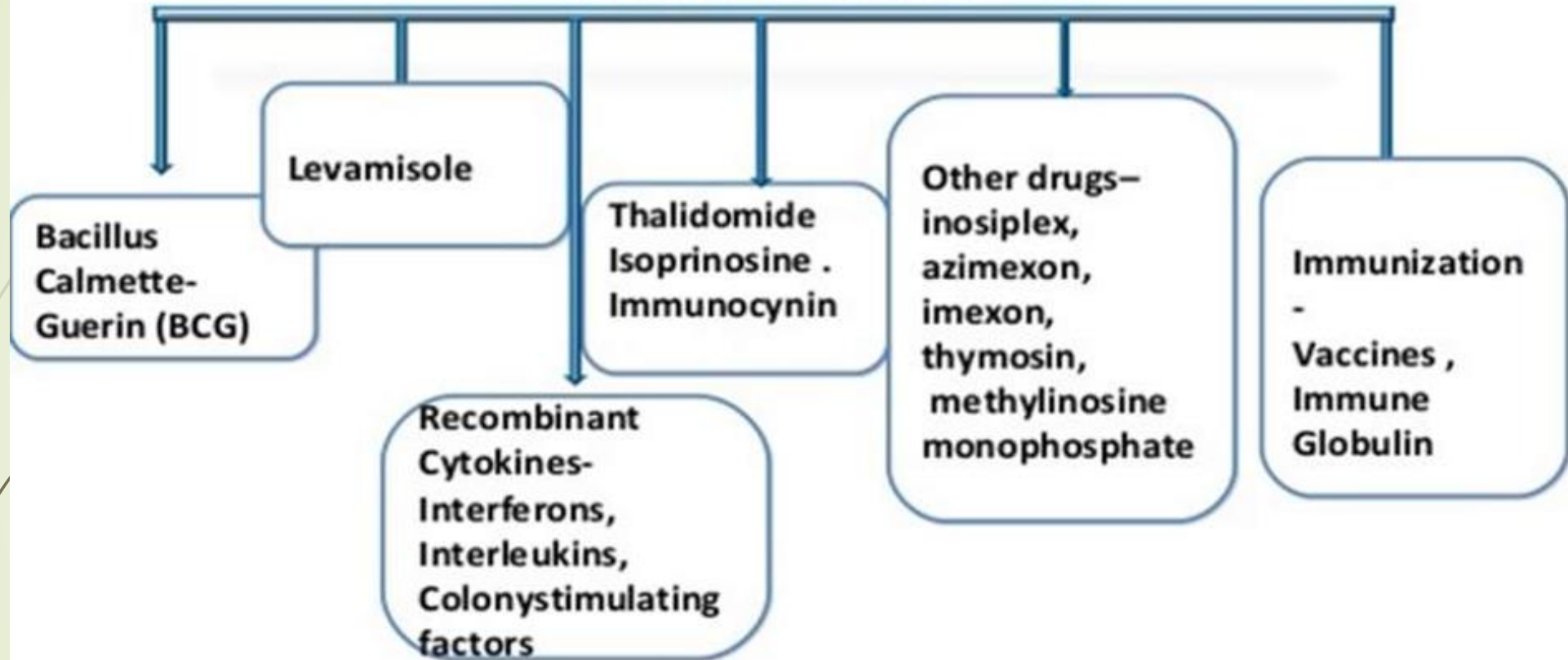
Chronic infections

Cancer

Autoimmunity

Organ transplantation

# IMMUNOSTIMULANTS







# LEVAMISOLE

- Levamisole was synthesized originally as an anthelmintic. It restores the depressed immune function of B lymphocytes, T lymphocytes, Monocytes and Macrophages. It targets at stimulation of phagocytosis and stimulation of regulatory T cells to restore homeostasis in a perturbed immune system.
- **Therapeutic uses:** Adjuvant therapy with 5- fluorouracil colon cancer, agranulocytosis. Used to treat immunodeficiency associated with Hodgkin disease.
- **Adverse Reactions:** Flu like symptoms, allergic manifestation, nausea and muscle pain.



# Bacillus Calmette Guerin (BCG)

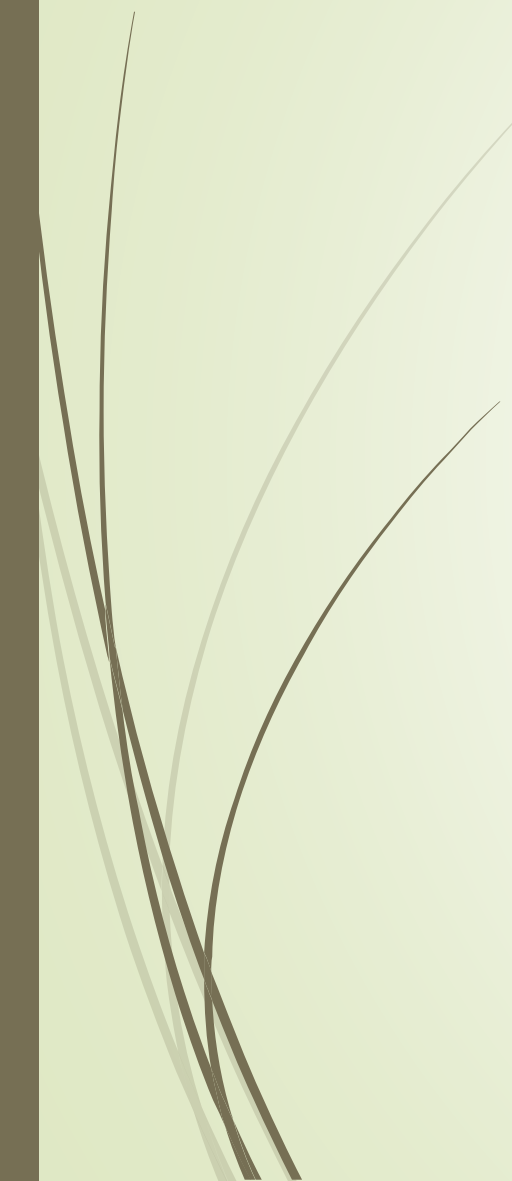
- Live, attenuated culture of BCG strain of Mycobacterium Bovis
- **Mechanism of action:** Induces granulomatous reaction at the site of administration. It causes activation of macrophages to make them more effective killer cells. Tried as an adjuvants
- **Therapeutic uses:** Treatment and prophylaxis of Bladder Carcinoma
- **Adverse Reactions:** Hypersensitivity shock chills



# RECOMBINANT CYTOKINES

- These are now use by rDNA technology Application in treatment of viral infection, autoimmune and neoplastic diseases

## INTERFERONS

- Antiviral
  - Anti neoplastic
  - Immunomodulatory activity
  - Bind to cell surface receptors and initiates intracellular events
  - Enzyme induction
  - Enhancement of immune activities
  - Increased phagocytosis
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## INTERFERON $\alpha$ -2B

- **Mechanism of action:** Interferon alfa-2b inhibits virus replication in virus-infected cells and suppresses cell proliferation; although the exact mechanism of action of ribavirin is not known, it has antiviral inhibitory activity against respiratory syncytial virus, influenza virus, and herpes simplex virus.
- **Therapeutic uses:** Hairy cell leukemia Malignant melanoma  
Hepatitis B
- **Adverse Reactions:** Flu like symptoms – Fever, chills, headache  
CVS Hypotension, Arrhythmia CNS- Depression, Confusion



## INTRERLEUKIN

- It is a protein that regulates the activities of white blood cells (leukocytes, often lymphocytes) that are responsible for immunity. IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self". IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by lymphocytes.
- **Therapeutic uses:** Metastatic renal cell carcinoma Melanoma  
Toxicity Hypotension





# THALIDOMIDE

- Birth defect.
- Contraindicated in women having child bearing potential.
- Enhanced T cell production of cytokines IL-2, IFN-  $\gamma$  .
- Increases TNF $\alpha$  in patients who are HIV seropositive.
- **Therapeutic uses:** Multiple Myeloma



# ISOPRINOSINE

- Leads the production of cytokines such as IL-1, IL- 2, and IFN- 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



# IMMUNIZATION

- **Active**

Stimulation with an antigen

- **Passive**

Preformed antibody



# Active immunization

- Vaccines
- Administration of antigen as a whole, killed organism, or a specific protein or peptide constituent of an organism.
- Booster doses.
- Anticancer vaccines.



# Immune globulins

- **Indications:** Individual is deficient in antibodies.immunodeficiency  
Individual is exposed to an agent, inadequate time for active immunization
- Rabies -Hepatitis





# REFERENCES

- Lippincott textbook of immunology .
  - Goodman and Gilman's "The Pharmacological basis of therapeutic" 10th edition .
  - Google
- 