

# Immuno pharmacology

Dr Malek Zihlif

# Where

- **Agents that modulate the immune system play an important role in:**
  - 1. Preventing the rejection of organ or tissue grafts**
  - 2. In the treatment of certain diseases that arise from dysregulation of the immune response.**
    - **Autoimmune diseases.**
    - **Immunodeficiency diseases.**

# Solid Organ and Bone Marrow transplantation

- Four types of rejection can occur in a solid organ transplant recipient: **hyper-acute, accelerated, acute, and chronic.**
- ◎ Transplant of organ introduces foreign tissue to the body
- ◎ The body's immune system sees this foreign tissue, thinks it's bad and start producing lymphokines including IL-2
- ◎ The lymphokines then activates the immune system even further, leading to a nasty cycle of foreign tissue destruction rejection

# Transplant Rejection agents complexity

- Many problems exist in currently approved regimens:
  - 1. Treatments are often very complex.**
  - 2. low patient compliance.**
  - 3. Therapeutic margins can be very narrow.**
  - 4. Pharmacokinetic interaction potential is high and causes problems.**

Unfortunately, these agents also have the potential to cause disease and to increase the risk of infection and malignancies.

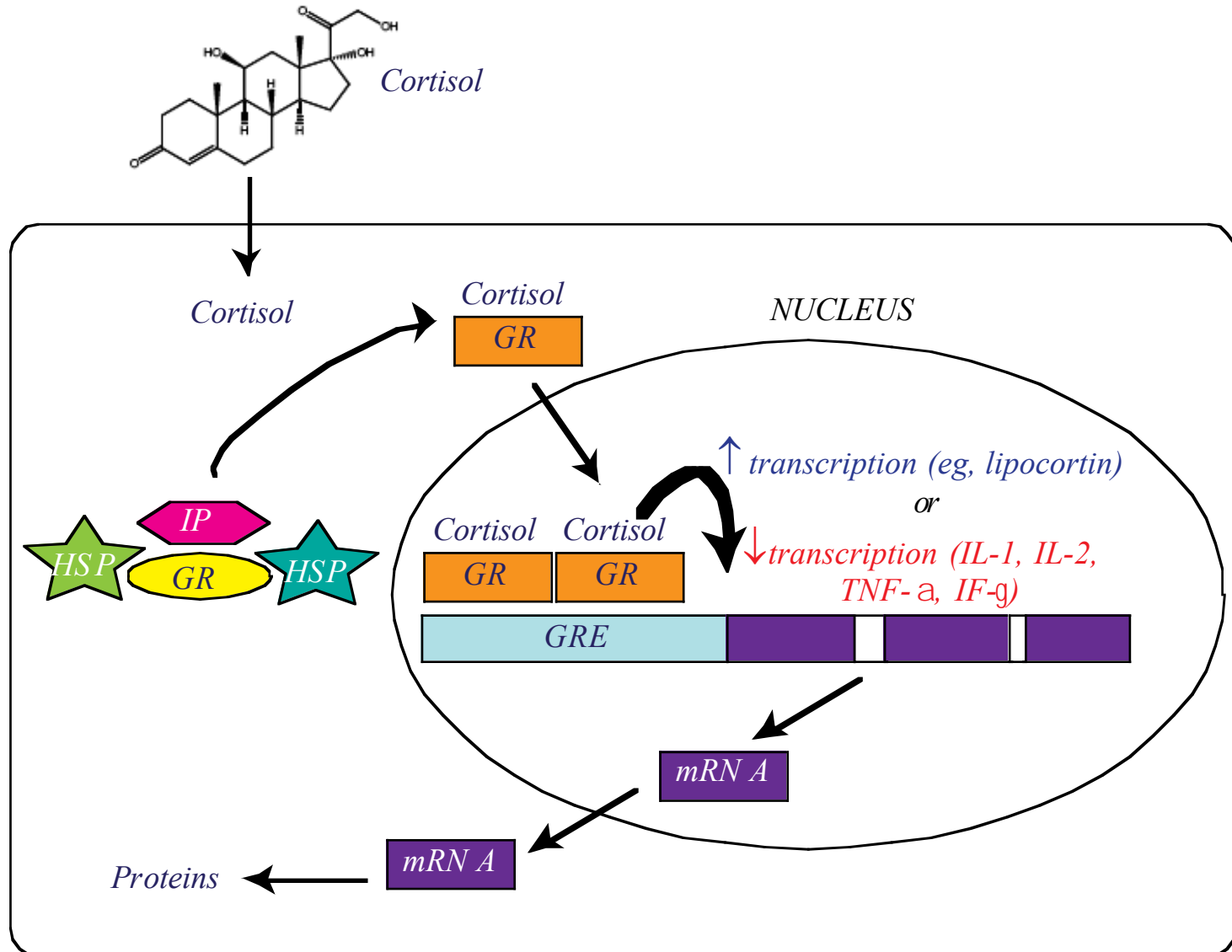
# Groups

- **Glucocorticoids**
- **Calcineurin inhibitors**
  - Cyclosporin A
  - Tacrolimus
- **IL-2 receptor 'mabs'**
  - Basiliximab
  - Daclizumab
- **Anti-metabolites**
  - Azathioprine
  - Mycophenolates
  - Leflunomide
- **m-TOR inhibitors**
  - Sirolimus

# Glucocorticoids

- Glucocorticoids suppress the cell-mediated immunity. inhibiting genes that code for the cytokines, the most important of which is IL-2.
- Smaller cytokine production reduces the T cell proliferation.
- Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and IL-2 receptors.
- Cellular immunity is more affected than humoral immunity.
- **Anti-inflammatory effects**

# Glucocorticoids Regulate Transcription



GR, glucocorticoid receptor; HSP, heat shock protein; IP, immunophilin; GRE, glucocorticoid receptor

# Clinically

- Glucocorticoids are first-line immunosuppressive therapy for both solid organ and hematopoietic stem cell transplant recipients and graft-versus-host disease (GVHD).
- idiopathic thrombocytopenic purpura and rheumatoid arthritis.
- Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products) that might cause undesirable immune responses.



# Side effect

- **Immunodeficiency**
- adrenal glands
- Hyperglycemia **Fat redistribution**
- growth failure, delayed puberty.
- excitatory effect on central nervous system (euphoria, psychosis)
- **Osteoporosis**
- **Cataracts**
- **Gastric ulcers** (prevent with omeprazole, misoprostol)

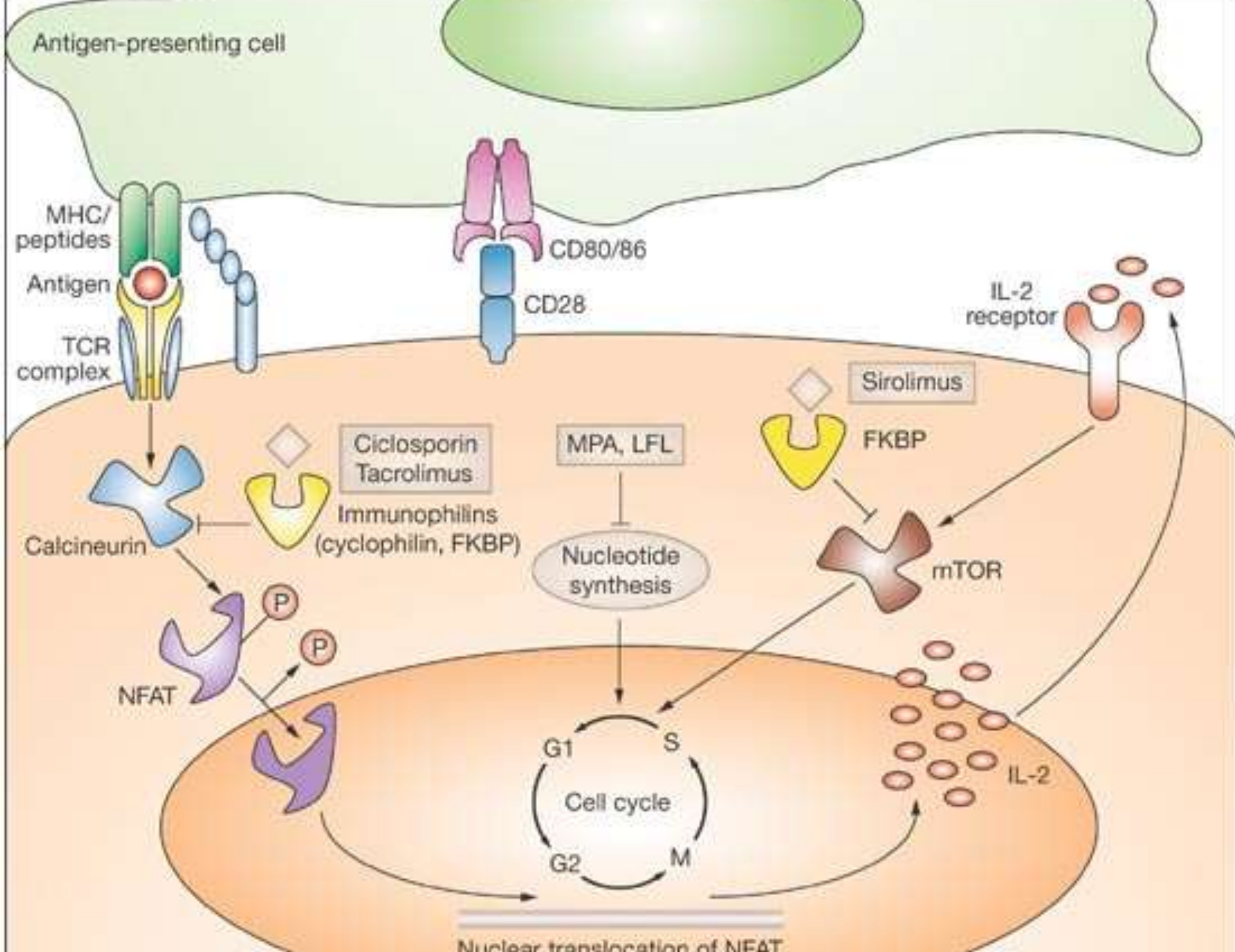


# Calcineurin Inhibitors

## Cyclosporine & Tacrolimus

1. human organ transplantation,
2. graft-versus-host disease after hematopoietic stem cell transplantation,
3. selected autoimmune disorders.

Both Inhibit the cytoplasmic phosphatase, calcineurin, which is necessary for the activation of a T-cell-specific transcription factor. This transcription factor, NF-AT, is involved in the synthesis of interleukins (eg, IL-2) by activated T cells.



# Complexity

- metabolized by the P450 3A enzyme system in the liver with resultant multiple drug interactions.
- Narrow therapeutic window
  - Levels too high: toxicities (i.e. nephrotoxicity, mental confusion, hyperglycemia and hypertension)
  - Levels too low: transplant rejection.
- Increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine,

# CYCLOSPORINE

## Monitoring Parameters:

- Cyclosporine trough levels.
- Serum electrolytes.
- Renal function.
- Hepatic function.
- Blood pressure.
- serum cholesterol.

# CYCLOSPORINE

- Cyclosporine ophthalmic solution is now available for severe dry eye syndrome, as well as ocular graft-versus-host disease.
- In combination with methotrexate, cyclosporine is a standard prophylactic regimen to prevent graft-versus-host disease after allogeneic stem cell transplantation.
- Cyclosporine has also proved useful in a variety of autoimmune disorders, including uveitis, rheumatoid arthritis, psoriasis, and asthma.

# Tacrolimus

- Because of the effectiveness of systemic tacrolimus in some dermatologic diseases, a topical preparation is now available. Tacrolimus ointment is currently used in the therapy of atopic dermatitis and psoriasis.

# Sirolimus (RAPAMUNE)

Inhibits immune cell growth through inhibiting the kinase activity of mammalian target of rapamycin (mTOR) and decreasing IL-2 activities.

Narrow therapeutic window

- Levels too high: toxicities (i.e. mental confusion, nephrotoxicity)
- Levels too low: transplant rejection

The target dose-range of these drugs will vary depending on clinical use.



# Anti-metabolites

- In immunotherapy, they are used in smaller doses than in the treatment of malignant diseases.
- They affect the proliferation of both T cells and B cells.

# Methotrexate

- is a folic acid analogue. It binds dihydrofolate reductase and prevents synthesis of tetrahydrofolate.
- It is used in the treatment of autoimmune diseases (for example rheumatoid arthritis or Behcet's Disease) and in transplantations.

# Azathioprine and mercaptopurine

- Azathioprine is the main immunosuppressive cytotoxic substance.
- It is extensively used to control transplant rejection reactions.

# MYCOPHENOLATE

- MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH).
- This leads to depletion of guanosine nucleotides
- Depletion of guanosine nucleotides has antiproliferative effects on lymphocytes (Both T and B-cells).

# MYCOPHENOLATE

- More effective than Azathioprine in preventing acute rejection
- It is used in combination with cyclosporine and prednisolone
- Mycophenolate mofetil is used in solid organ transplant patients for refractory rejection and,
- In combination with prednisone, as an alternative to cyclosporine or tacrolimus in patients who do not tolerate those drugs.
- In renal transplants, it's used with low-dose cyclosporine to reduced cyclosporine-induced nephrotoxicity.

The immune activation cascade can be described as a three-signal model.

Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC).

Signal 2 (costimulation) occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells.

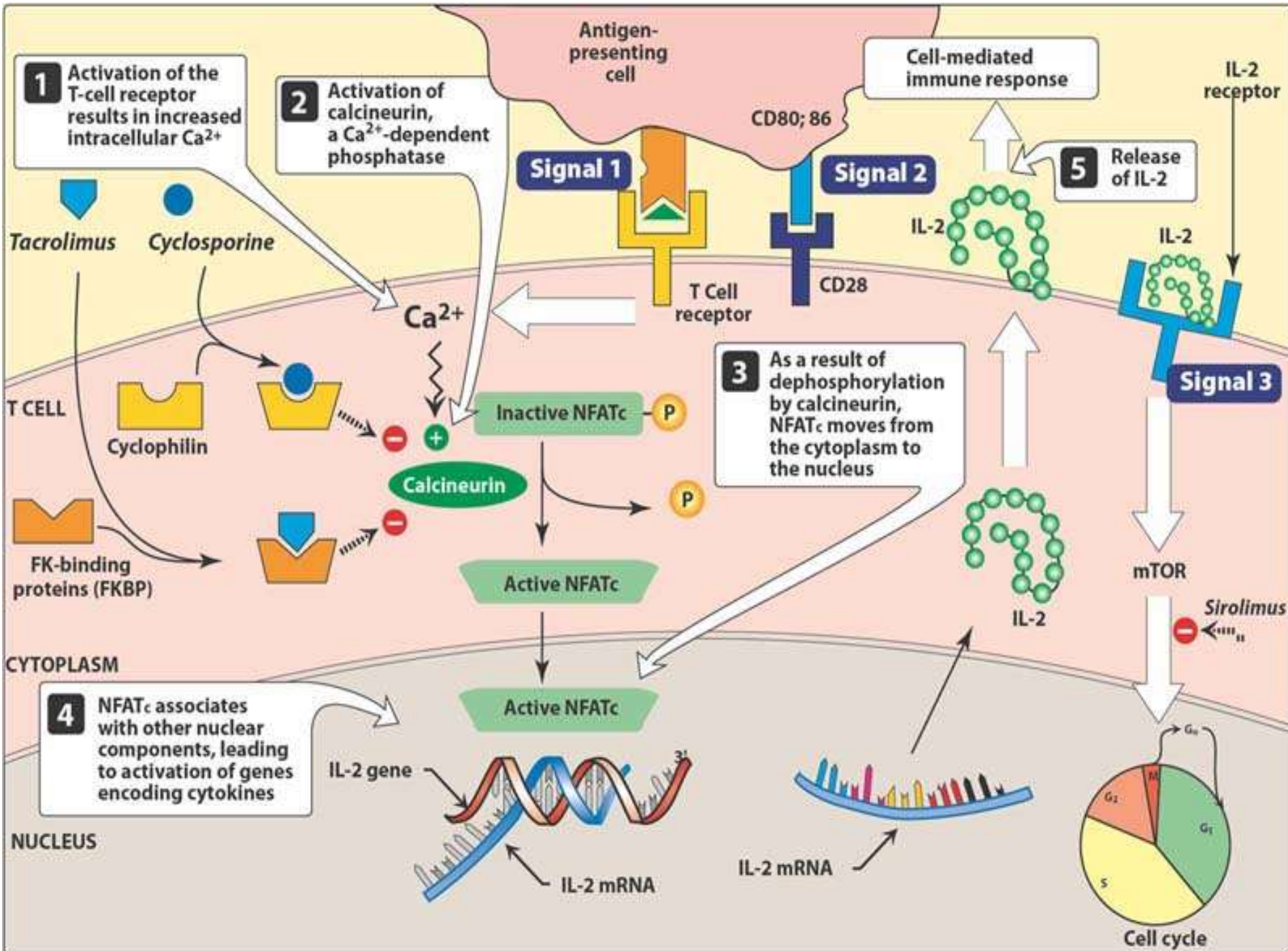
Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.



Production of cytokines such as interleukin (IL)-2, IL-15, CD154, and CD25.



IL-2 then binds to CD25 (IL-2 receptor) on the surface of other T cells to activate mammalian target of *rapamycin* (mTOR), providing Signal 3, the stimulus for T-cell proliferation.



# Immunosuppressive antibodies

- To suppress the activity of subpopulation of T-cells.
- To block co-stimulatory signals.
- Ab to the CD3 molecule of TCR (T cell receptor) complex results in a rapid depletion of mature T-cells from the circulation.
- It is used for treatment of acute rejection of renal allografts as well as for corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.
- It is also used to deplete T cells from donor bone marrow prior to transplantation.



# Anti CD3

Initial binding of *muromonab-CD3* to the antigen transiently activates the T cell and results in cytokine release (cytokine storm).

It is therefore customary to premedicate the patient with *methylprednisolone*, *diphenhydramine*, and *acetaminophen* to alleviate the cytokine release syndrome.

## IL-2-receptor antagonists

Ab specific for the high-affinity IL-2 receptor is expressed only on activated T-cell, blocks proliferation of T-cells activated in response to the alloantigens of the graft.

*Basiliximab* is said to be “chimerized” because it consists of 25 percent murine and 75 percent human protein.

*Daclizumab* is 90 percent human protein, and is designated “humanized.”

Both agents have been approved for prophylaxis of acute rejection in renal transplantation in combination with *cyclosporine/tacrolimus* and corticosteroids.

To treat donor’s bone marrow before it is transplanted.

# IL-2-receptor antagonists

- Both antibodies are given intravenously.
- The serum half-life of *daclizumab* is about 20 days, and the blockade of the receptor is **120 days**.
- The serum half-life of *basiliximab* is about 7 days. Usually, two doses of this drug are administered—the first at 2 hours prior to transplantation, and the second at 4 days after the surgery.
- well tolerated, Their major toxicity is gastrointestinal.

# Immunosuppression therapy in kidney transplantation

- **Methyl Prednisolone 500 mg IV just prior to transplantation and again at 24 hours.**

## **Tacrolimus led triple therapy.**

- Tacrolimus 0.1 mg/kg/day given as two doses at 10:00 and 22:00
- Prednisolone 20 mg once daily at 08:00
- Azathioprine 1-2 mg/kg (usually 75-100 mg) at 08:00 and  
Initially 1-2 mg/kg once daily. Maintenance 1 mg/kg once daily.

# Prednisolone

Normally reduced according to the following schedule:

- 20 mg daily 1 month started on day 2
- 15 mg daily 1 month
- 10 mg daily 1 month
- 5 mg daily thereafter

This schedule may be altered if rejection occurs.

- All patients to receive Ranitidine (150 mgs od) along with Prednisolone.
- Steroid withdrawal should be discussed with the patient and they should be informed of the risk of rejection.
- The steroids should be withdrawn according to the following schedule:

**Decrease by 1 mg per month till 0mg**

# Tacrolimus

- Whole blood trough levels to be checked on Mondays, Wednesdays and Fridays.
- The target level for the first six months is 10 ng/ml (range 8-12 ng/ml) and 5-10 ng/ml after six months.

# **Patients who have an increased risk of rejection**

- **Tacrolimus led triple therapy, but with MMF substituted for Azathioprine.**
- Tacrolimus as per standard regime
- Prednisolone as per standard regime
- Mycophenolate Mofetil 2 grams/day given as two doses at 0800 and 2000 (note: not at the same time as Tacrolimus)

# Basiliximab

- **Given to patients with expected delayed graft function** to allow reduced Tacrolimus dose (0.05mg/kg/day given as two doses), and sometimes to patients believed to be at increased risk of rejection.

## **Dose**

- 20mg given 2 hours prior to transplantation
- 20mg given on day 4 post transplant

The first dose must not be administered until it is absolutely certain that the patient will receive the graft.

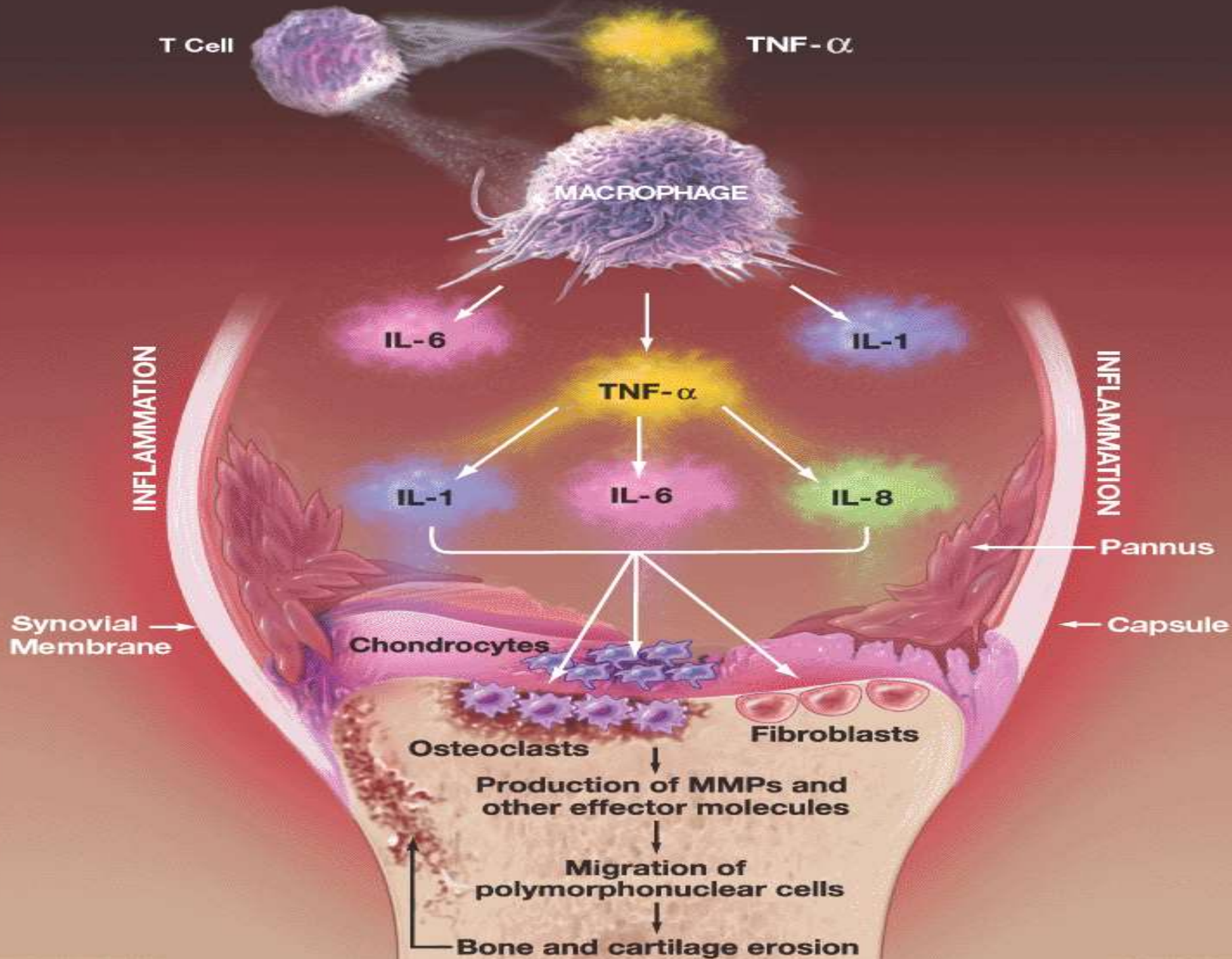


# Autoimmune Disease

- An immune reaction against self
- Mechanism unknown, arises out of a failure in immune regulation
- Examples:
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Multiple sclerosis (MS)
  - Insulin-dependent diabetes mellitus
  - Many more

# Infliximab and Adalimumab

- Anti TNF- $\alpha$
- Approved by the FDA in 1998
- Designated for use in patients who did not respond to methotrexate.
- Proven to slow the clinical progression of rheumatoid arthritis



# Side Effects of TNF Inhibition

- **Infection**
  - Tuberculosis
  - Serious resulting in death
- **Neurologic**
  - Multiple Sclerosis, seizures, inflammation of the ocular nerve
- **Worsening of Congestive Heart Failure**
  
- Remember  
STOP if develop a fever, have an infection,

# Rituximab

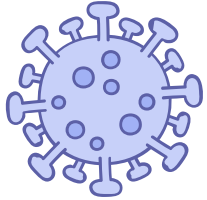
- Anti-B cell (CD20) antibody
- First approved in 1997 for use in B-cell lymphoma
- Given in combination with Methotrexate
- Directed for patients who do not respond to Anti-TNF treatments
- Indicates the rheumatoid arthritis has a B cell component to its pathology

# **Anti-IgE Antibodies**

**Drugs that reduce the amount of IgE to mast cells**

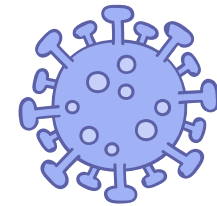
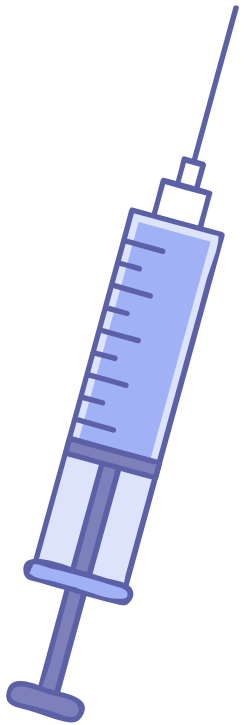
**inhibits synthesis of IgE by B-lymphocytes**

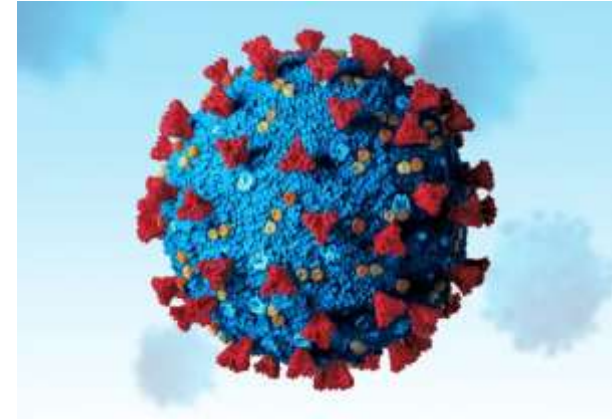
- **Omalizunab (anti-IgE Mab)**



# The role of interleukin 6 inhibitors in severe COVID-19 therapy

Dr. Malik Zihlif

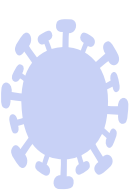




- Rapid replication of the virus increases the viral load and enhances viral cytopathic effects
- This results in the rapid progression of the immunoinflammatory process leading to CSS (cytokine storm syndrome)
- **IL-6** seems to play a crucial role among all cytokines involved in the pathogenesis of CSS

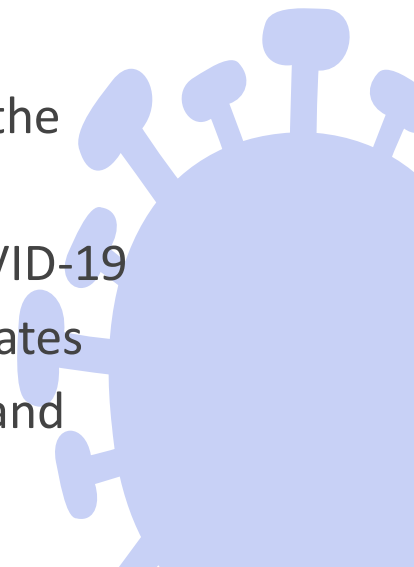
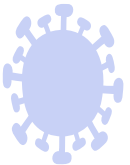






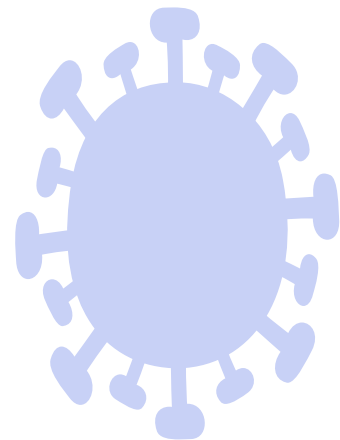
# IL-6 role in COVID-19

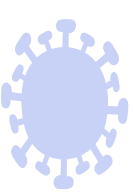
- Interleukin-6 (IL-6) is a member of the **pro-inflammatory cytokine** family, induces the expression of a variety of proteins responsible for acute inflammation
- IL-6 plays a crucial role in the immunopathogenesis of COVID-19 and is supported by data from numerous studies reporting increased serum concentrations of this cytokine, mainly in the severe cases.
- A meta-analysis of COVID-19 cases (n = 1302) indicates that the level of IL-6 was **3-fold higher** in patients with severe vs mild/moderate COVID-19 ( $p < 0.001$ ), and that high baseline IL-6 concentration correlates with the development of bilateral lung damage ( $p = 0.001$ ) and pyrexia ( $p = 0.001$ ).



# IL-6 inhibitors

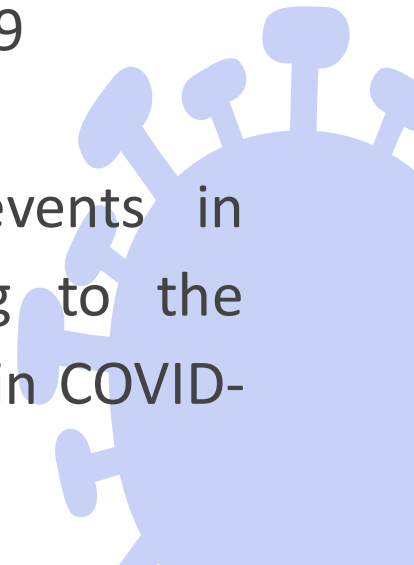
- Two of the larger trials showed a clinical benefit in 15–20% of patients if IL-6 blockade was administered early after hospitalization and used in combination with dexamethasone (compared with dexamethasone alone).
- The efficacy of IL-6 targeting depends on:
  - The underlying health status of the patient
  - The severity of the disease
  - The timing of the intervention.



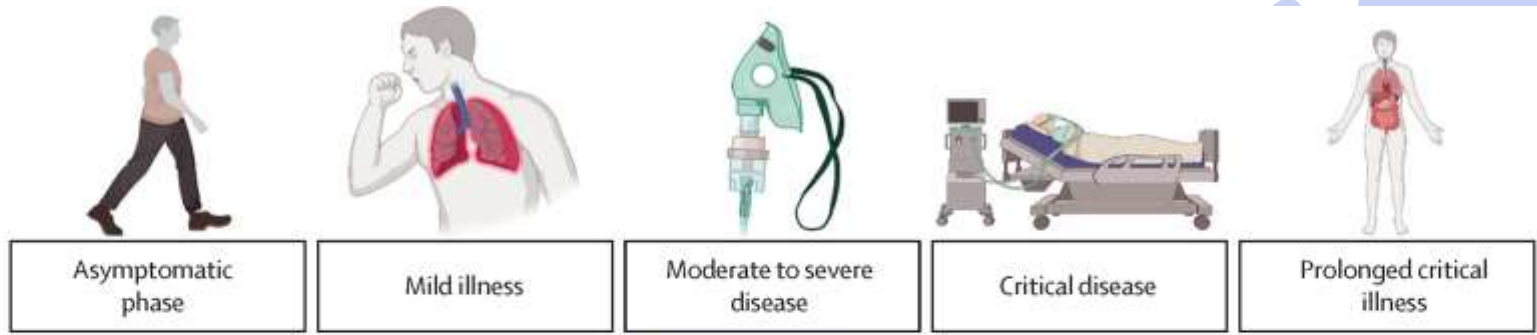


# IL-6 inhibitors

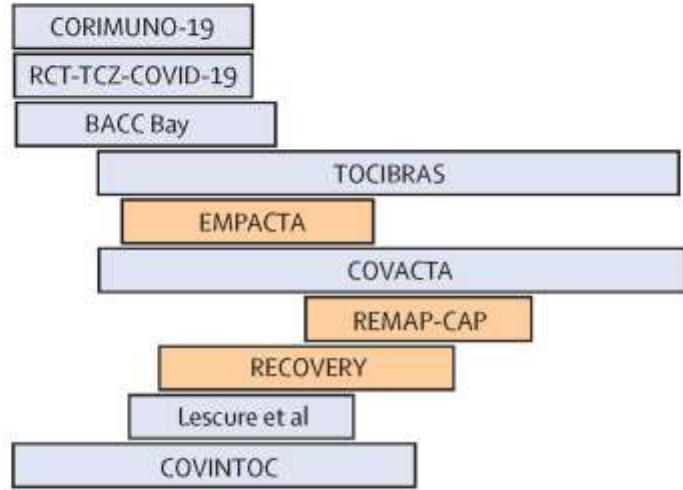
- Despite multiple trials, it is still difficult to judge who will benefit from IL-6 blockade in COVID-19.
- As IL-6 promotes immune processes associated with resistance to infection, there are real concerns that IL-6 neutralization could interfere with anti-viral responses or increase susceptibility to secondary respiratory infections in hospitalized patients with COVID-19
- Encouragingly, the incidence of adverse events in relevant trials appear minimal likely owing to the targeted (1–2 doses) use of these antagonists in COVID-19



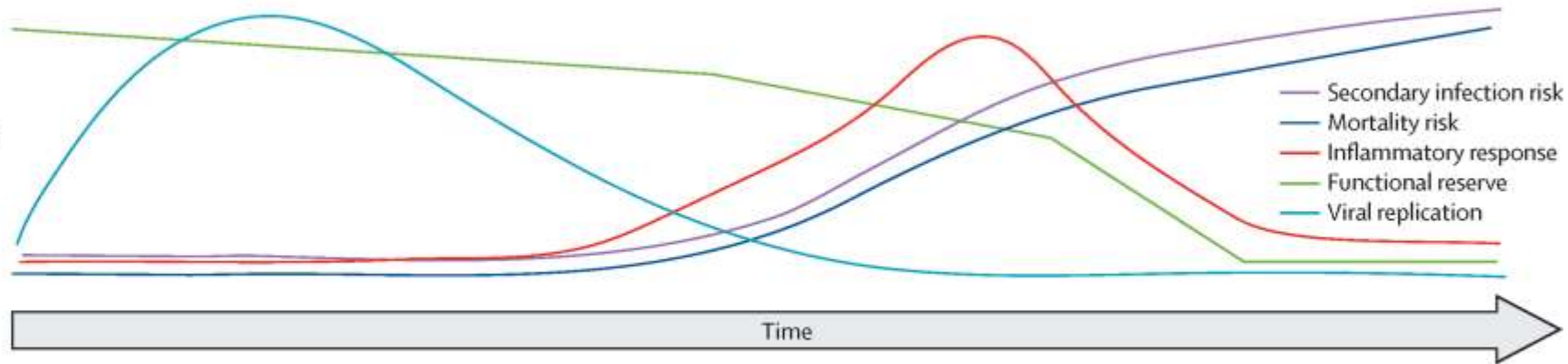
Clinical stage



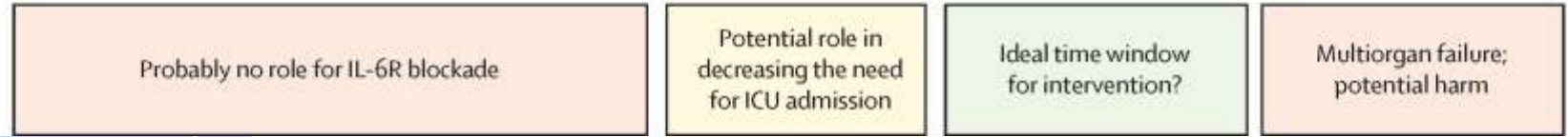
Evidence from RCTs

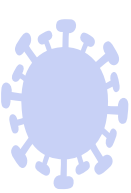


Main physiological features



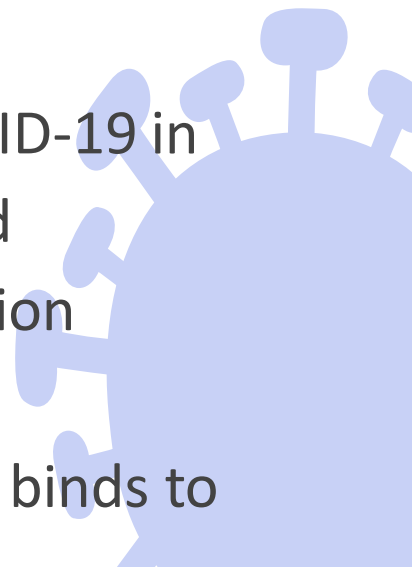
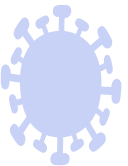
Potential role of IL-6R blockade

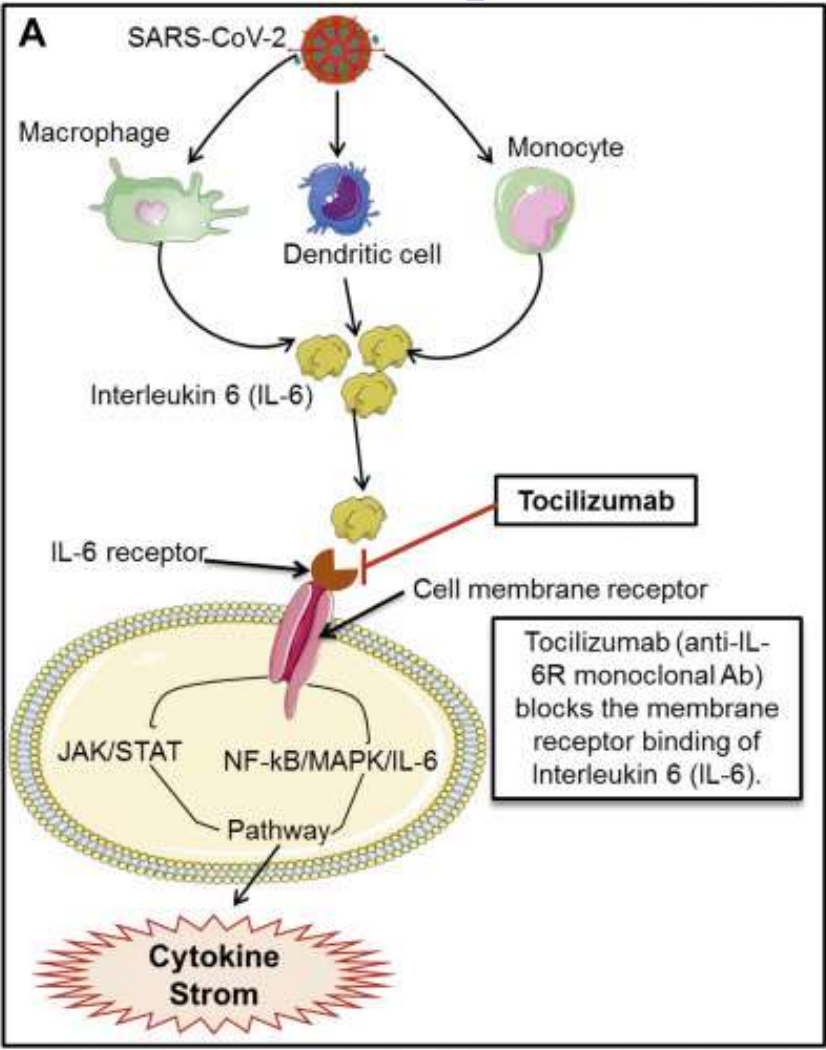




# IL-6 Inhibitors

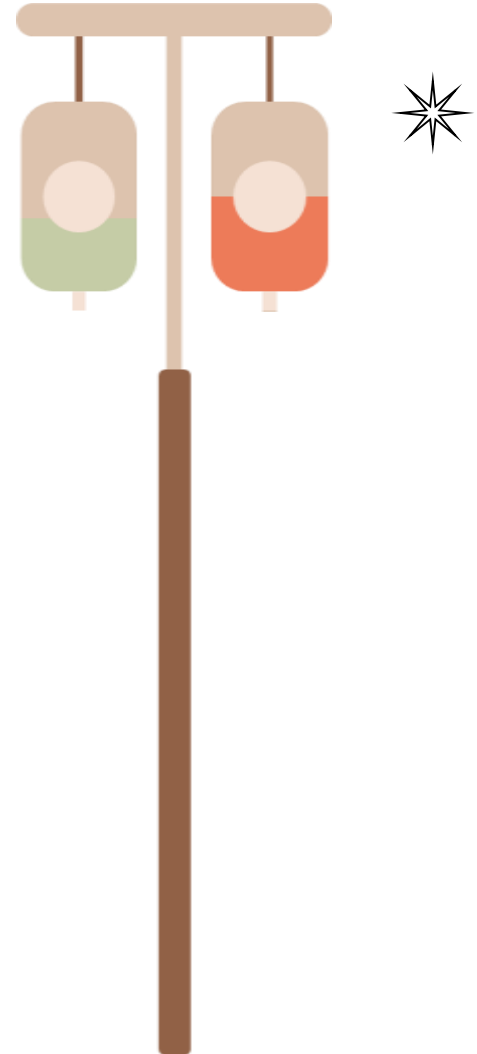
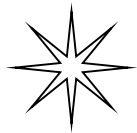
- **Tocilizumab:** A recombinant humanized monoclonal antibody IL-6 receptor inhibitor used to treat inflammatory and autoimmune conditions
- It is an interleukin-6 (IL-6) receptor antagonist (both forms) used to treat Cytokine Release Syndrome (CRS), Giant Cell Arteritis (GCA), and Rheumatoid Arthritis (RA)
- tocilizumab was approved by the European Commission in December 2021 to treat COVID-19 in adults receiving systemic corticosteroids and supplemental oxygen or mechanical ventilation
- **Sarilumab:**
  - is a human recombinant IgG1 antibody that binds to both forms of interleukin 6 receptors (IL-6R)

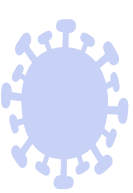






# IL-17 & IL-17 inhibitors

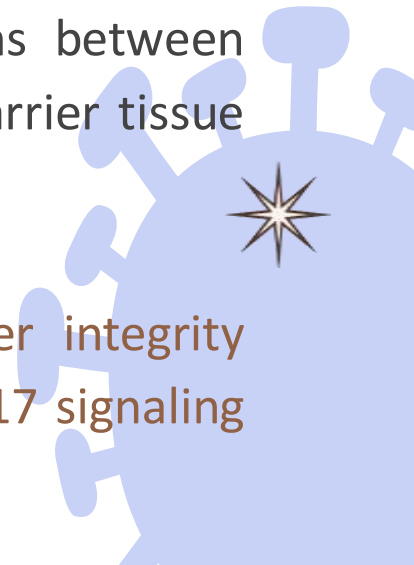




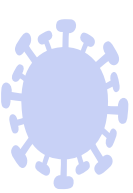
# IL-17 physiological role



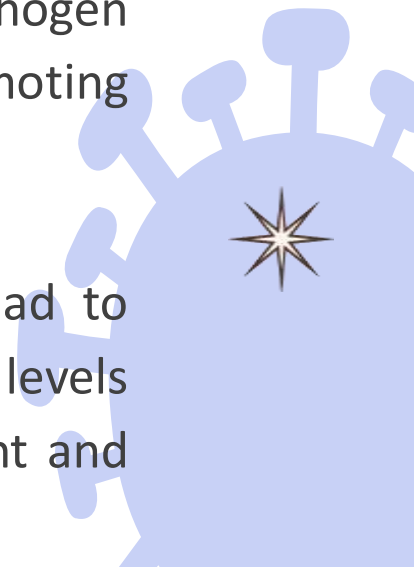
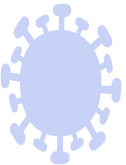
- IL-17, a **proinflammatory cytokine**, plays a pivotal role in inflammatory processes
- It's closely associated with **host defence responses**, and responses to various infections including fungal infections (candida), and bacterial infections
- IL-17 plays an important role in **barrier maintenance**. It protects the mucosal barrier by maintaining tight junctions between epithelial cells. It is also a powerful promoter of barrier tissue healing
- IL-17 is essential in maintaining intestinal barrier integrity which is disrupted by excessive blockade of the IL-17 signaling pathway

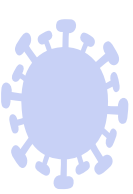






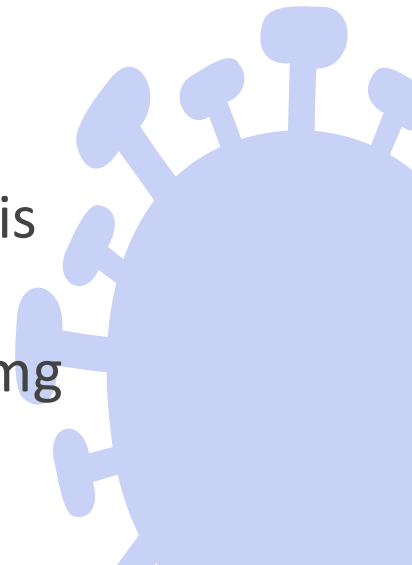
- Although IL-17 expression induces physiological reactions for host immune defense mechanism and tissue healing, chronic IL-17 activation promotes autoimmunity and cancer by orchestrating harmful responses
- The production and levels of IL-17 maintained in the body are **relatively low** and **stable** under **normal** physiological conditions.
- In contrast, Th17 cell activation is enhanced during pathogen invasion, and IL-17 secretion is **increased**, promoting inflammation.
- As a result, the disruption of IL-17 production can lead to autoimmune diseases and tissue destruction. **Excessive** levels of IL-17 in the body are associated with the development and exacerbation of several autoimmune diseases.

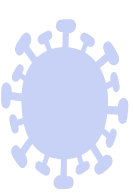




# IL-17 inhibitors- **Secukinumab**

- **Secukinumab** is a recombinant human IgG1/kappa mAb
- targets IL-17A and prevents it from binding to and interacting with its receptor (IL-17R).
- The binding prevents the downstream production of proinflammatory cytokines and chemokines that contribute to the onset of various diseases
- Secukinumab was approved by the FDA for the treatment of moderate-to-severe plaque psoriasis
- The dose is two subcutaneous injections of 150 mg (300 mg), weekly for the first 4 weeks, and then every 4 weeks.



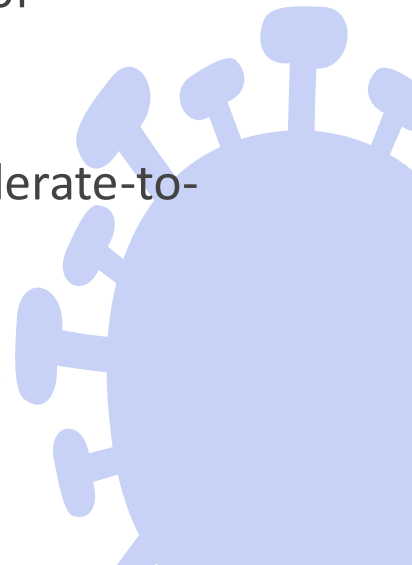


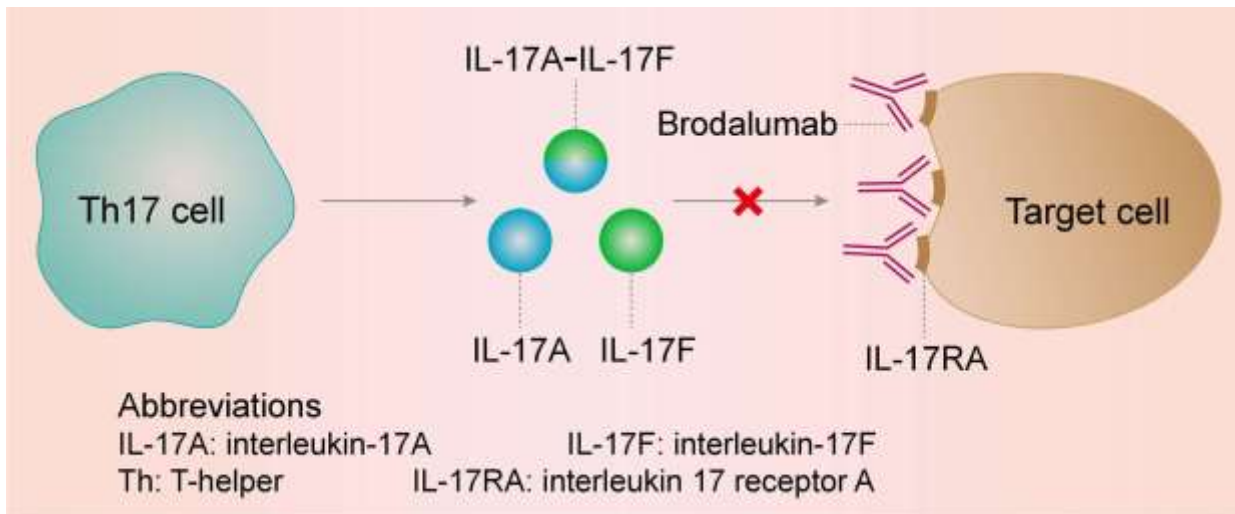
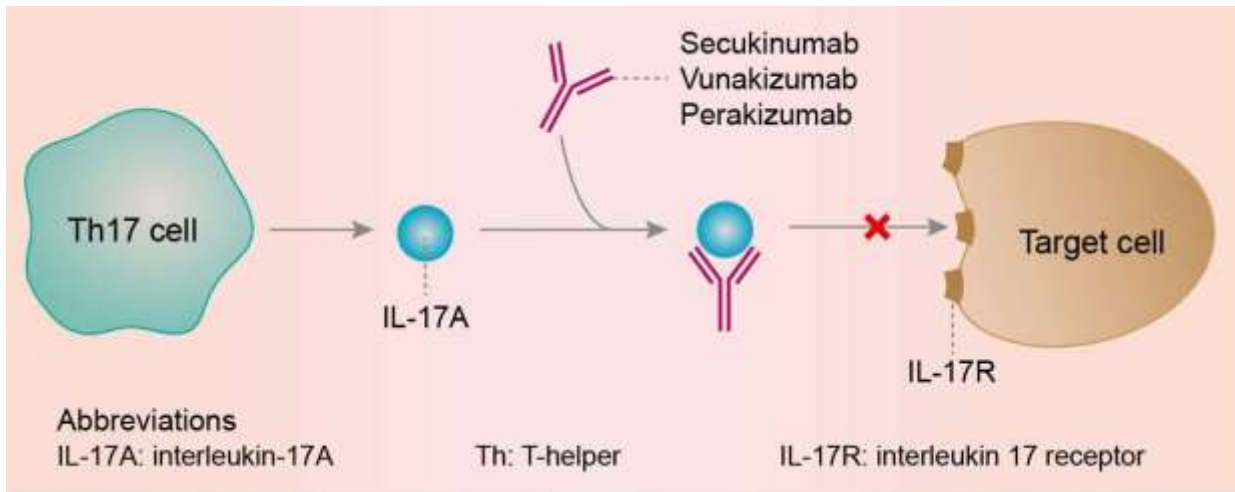
# IL-17 inhibitors



- **Brodalumab:**

- a human IgG2 mAb
- **inhibits ALL IL-17 cytokines** (unlike secukinumab, which directly inhibits IL-17A production only) by preventing interactions with their receptors
- Inhibiting IL-17RA prevents IL-17- mediated release of proinflammatory chemokines and protein kinases
- Brodalumab was approved for the treatment of moderate-to-severe plaque psoriasis
- **Side effects:** The most common adverse effects were nasopharyngitis (12.1%) and oral candidiasis in 4.9%







# Immunostimulants

- Increase the immune responsiveness of patients who have either selective or generalized immunodeficiency.
- Use for immunodeficiency disorders, chronic infectious diseases, cancer and HIV.

# Cytokines

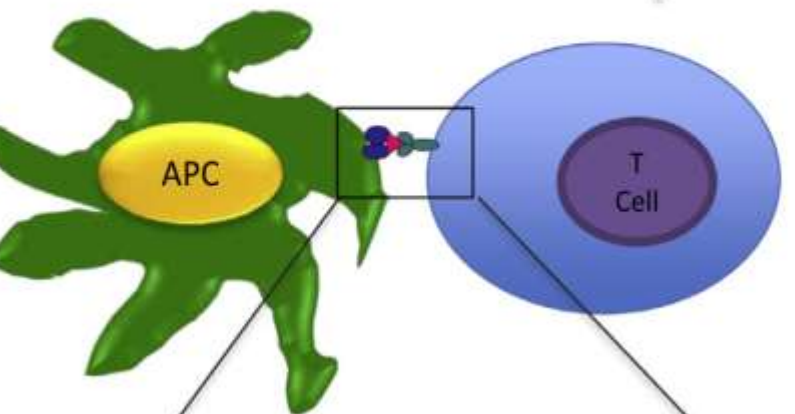
- **Interferon (INF):** INF- $\alpha$ , $\beta$ , $\gamma$ 
  - Antiviral, anticancer, immunomodulating effects.
  - Antiviral effects : INF- $\alpha$ , $\beta$  > INF- $\gamma$
  - immunomodulating effects: INF- $\gamma$
  - Adverse Effects: flu-like symptoms, fatigue, malaise
- **Interleukin-2 (IL-2)**
  - T cell proliferation, T<sub>H</sub>, NK, LAK cell activation
  - Treatment of malignant melanoma, renal cell carcinoma, Hodgkin disease
  - Adverse Effects: fever, anorexia, etc .

# Cancer Immunotherapy

- Immune checkpoints refer to inhibitory pathways of the immune system that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage.
- Tumors misuse immune-checkpoint to evade the immune system clearance, in particular to avoid tumor-antigen specific T-cell responses



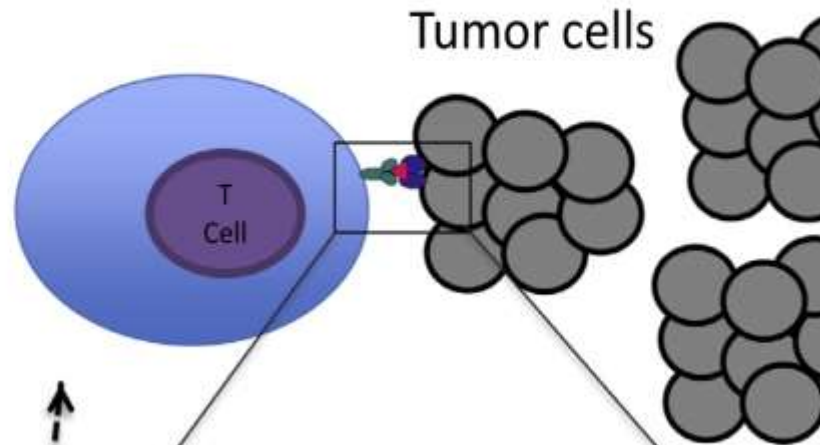
# Early immune response: T cell activation



Lymph node

Blood vessel

# Effector Phase



Tumor cells

Peripheral tissues

