

# Immuno pharmacology

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# 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.

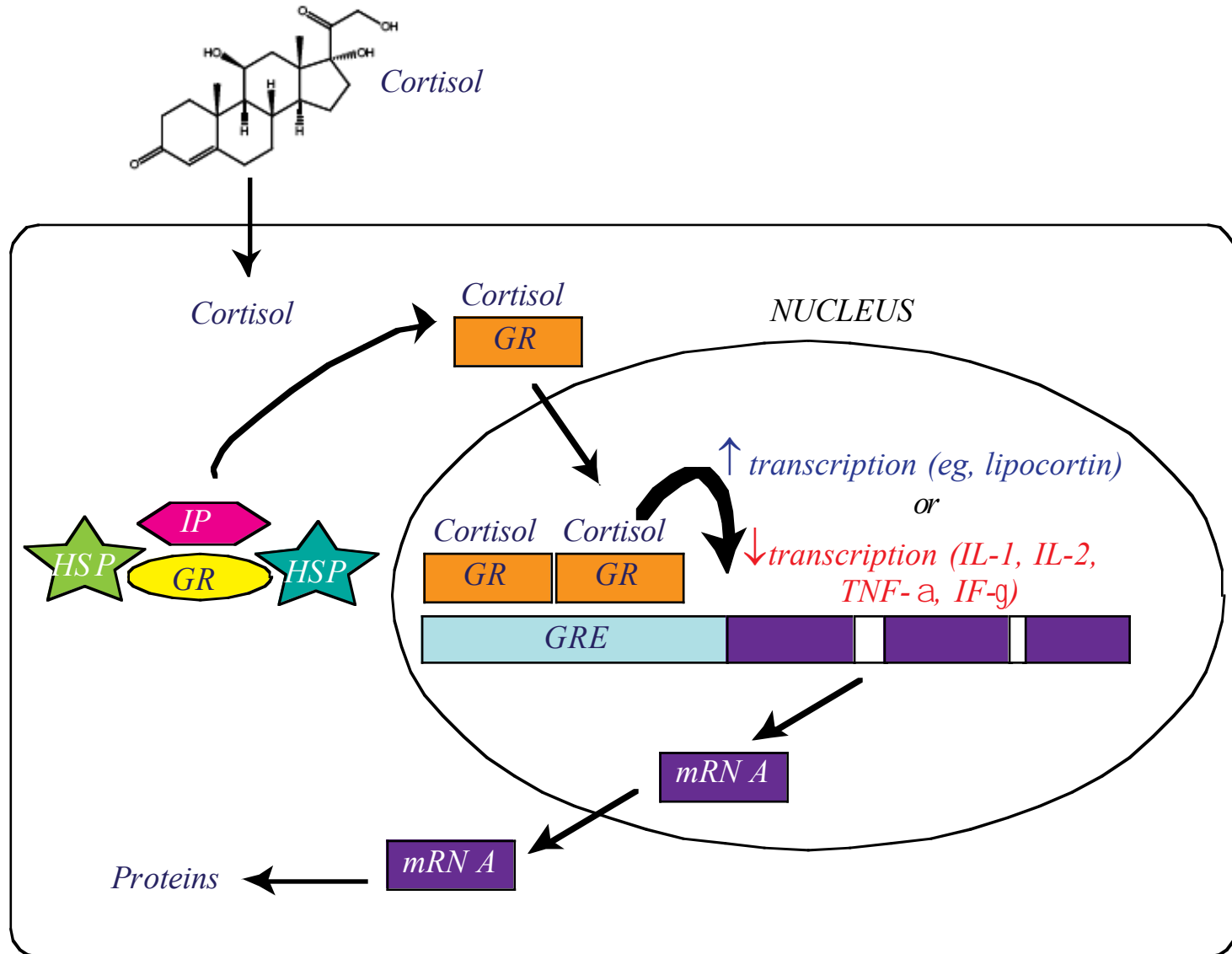
# Groups

- **Glucocorticoids**
- **Calcineurin inhibitors**
  - **Ciclosporin 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)

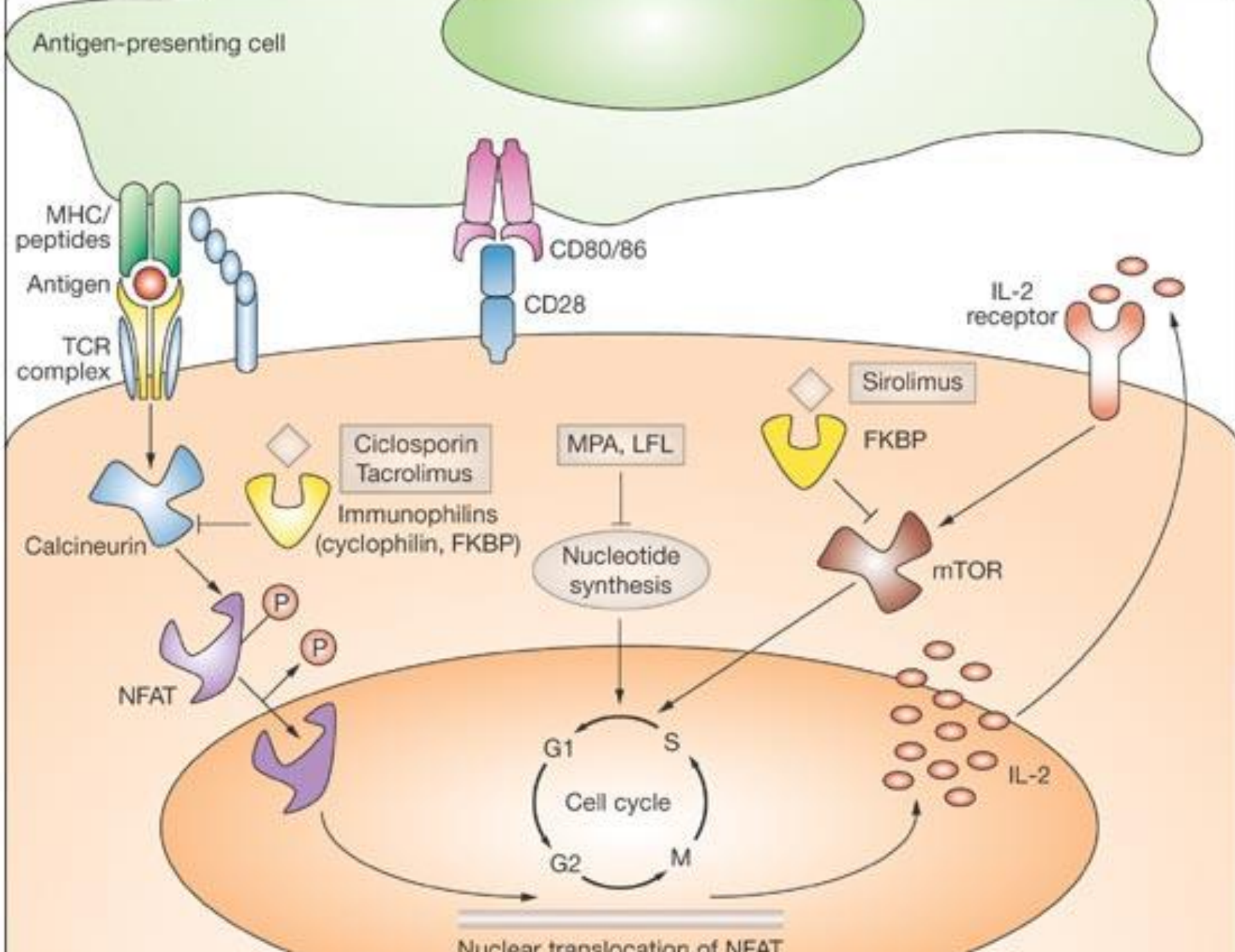


# Calcineurin Inhibitors

## 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 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.

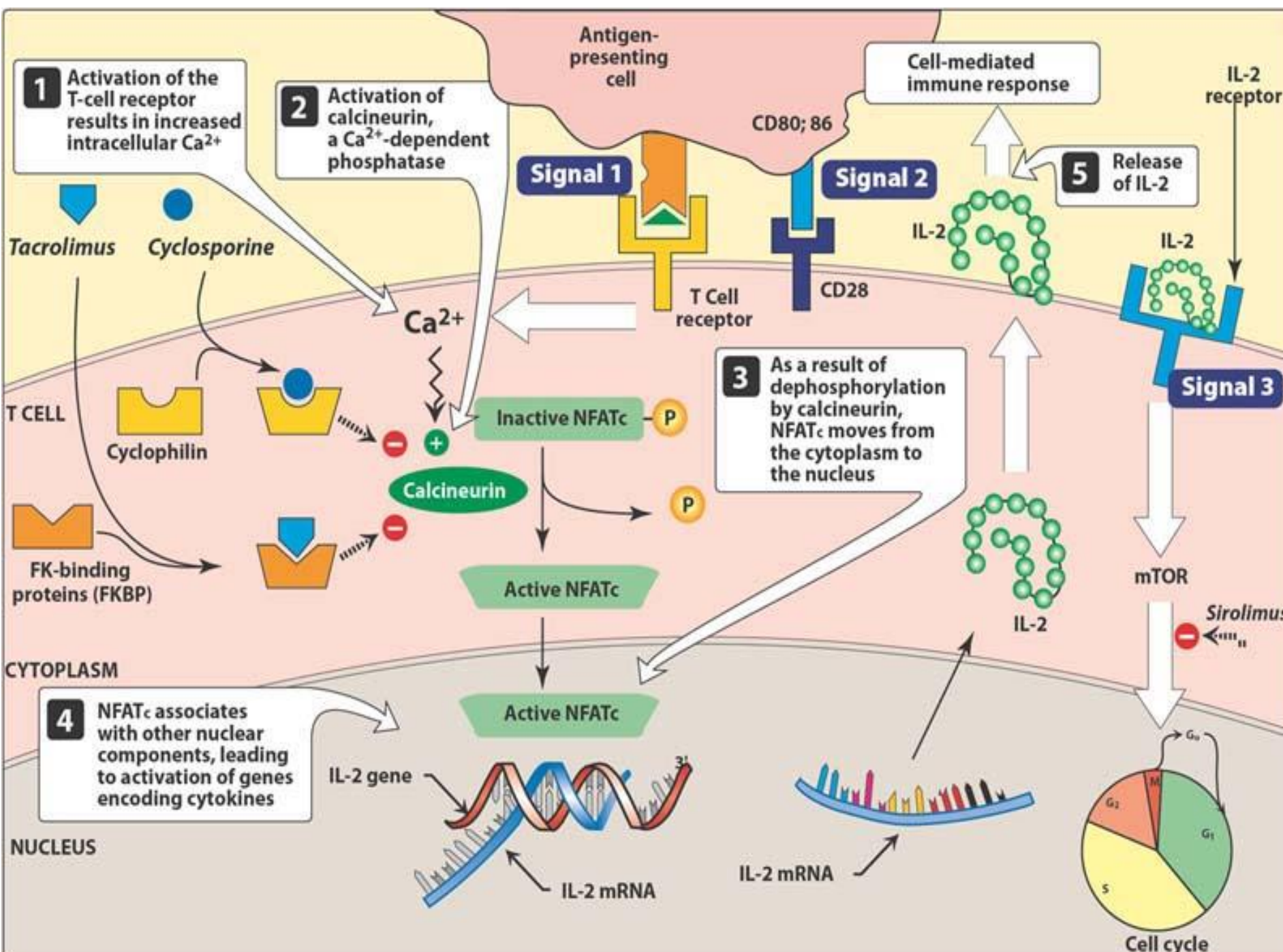
Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.



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

T Cell

TNF- $\alpha$

MACROPHAGE

IL-6

IL-1

TNF- $\alpha$

IL-1

IL-6

IL-8

INFLAMMATION

INFLAMMATION

Synovial Membrane

Pannus

Capsule

Chondrocytes

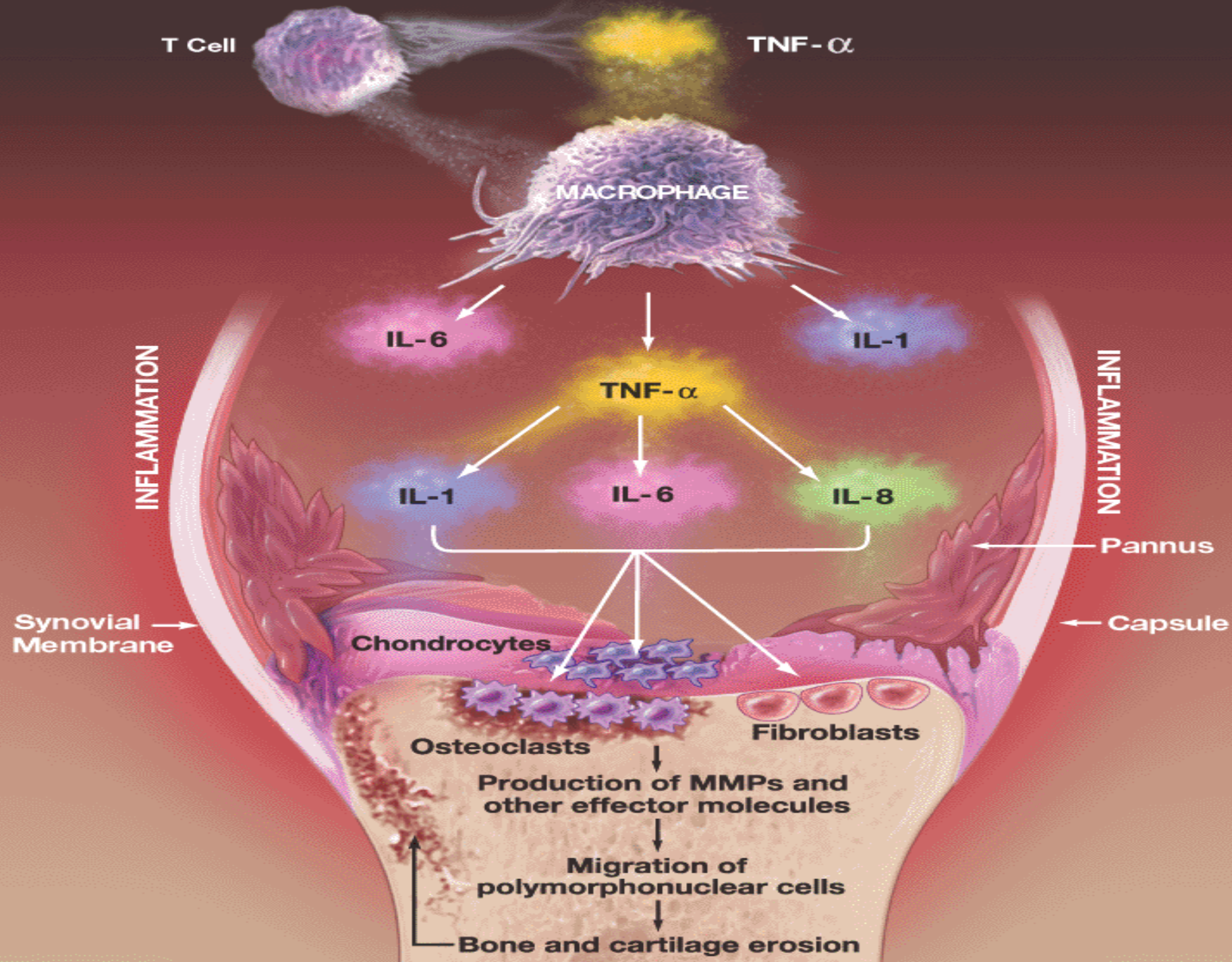
Osteoclasts

Fibroblasts

Production of MMPs and  
other effector molecules

Migration of  
polymorphonuclear cells

Bone and cartilage erosion



# 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 Omalizunab**

Biologic antibody therapy (Omalizumab; Xolair) binds IgE in the circulation and prevents it from activating mast cells and basophils.

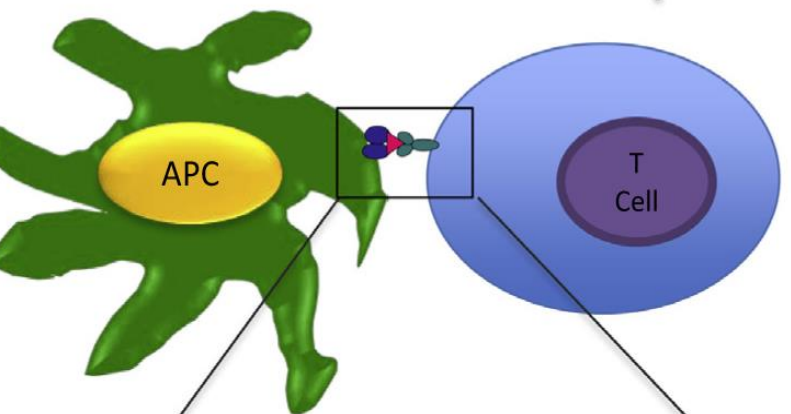
Anti IgE therapy is recommended as an add-on to optimized standard therapy in asthmatics 12 years and older who need continuous or frequent treatment with oral corticosteroids.

Elevated serum IgE

# Cancer Immunotherapy

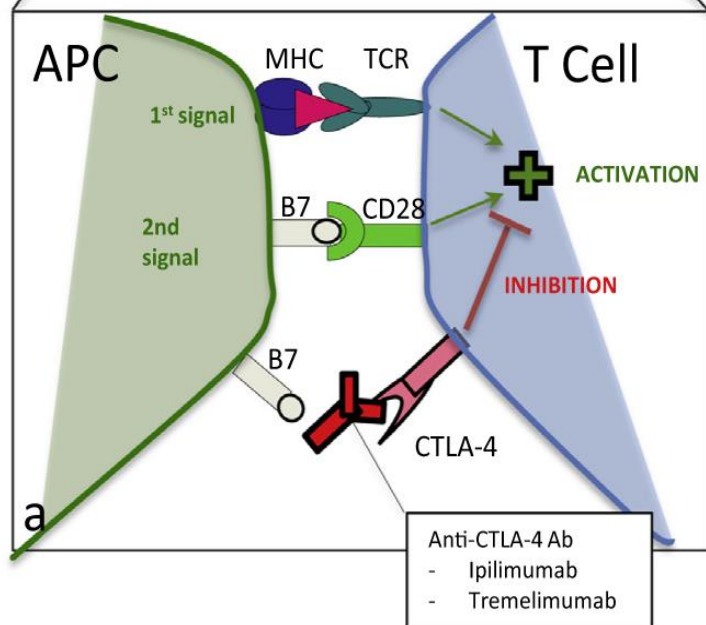
- Immune checkpoints refer to inhibitory pathways of the immune system that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage.
- Tumors misuse immune-checkpoint to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

## Early immune response: T cell activation



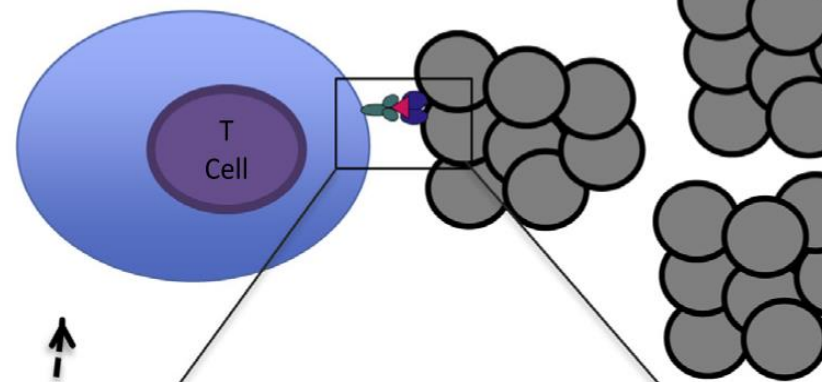
Lymph node

Blood vessel

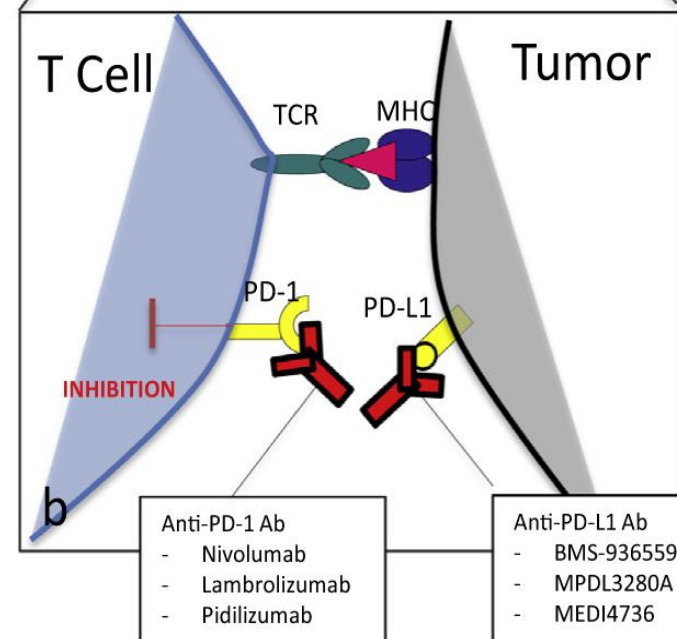


## Effector Phase

Tumor cells



Peripheral tissues





# 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 .