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.

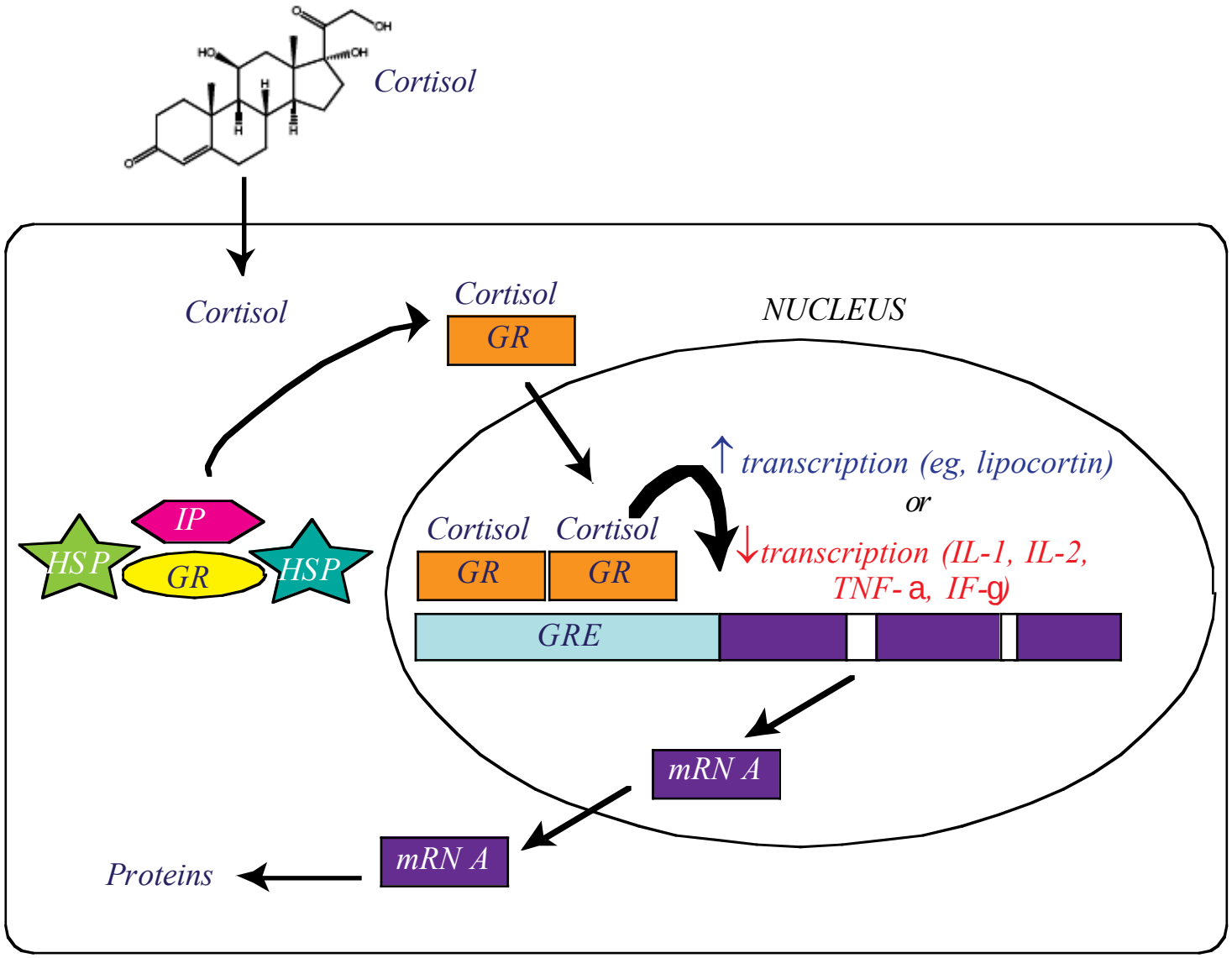
Groups

- **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)

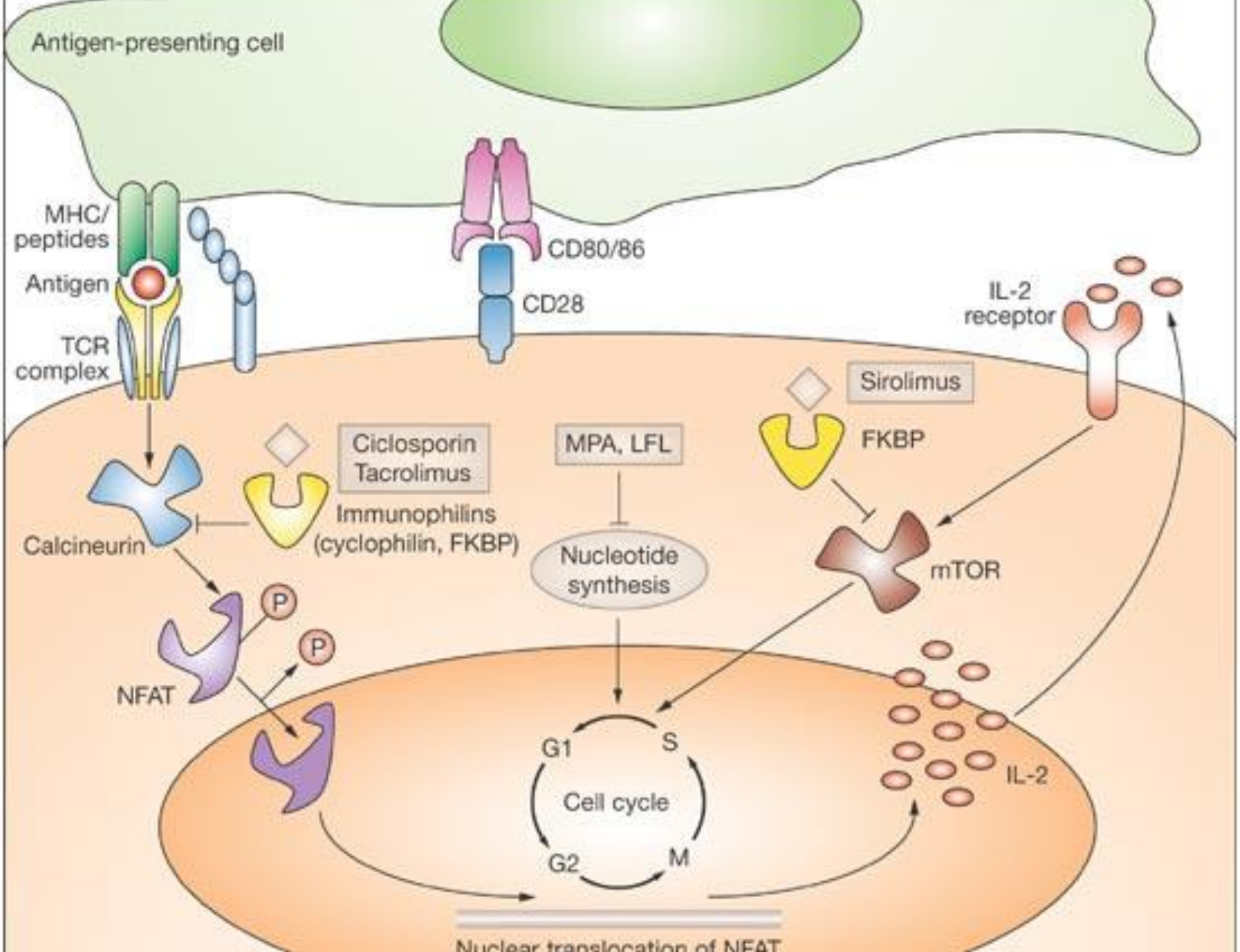
Calcineurin Inhibitors
Cyclosporine & Tacrolimus

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.


Antigen-presenting cell
MHC/
peptides
Antigen
TCR
complex
CD80/86
CD28
IL-2
receptor
Sirolimus
FKBP
Ciclosporin
Tacrolimus
Immunophilins
(cyclophilin, FKBP)
MPA, LFL
Calcineurin
Nucleotide
synthesis
mTOR
P
P
NFAT
G1
S
Cell cycle
G2
M
IL-2
Nuclear translocation of NFAT

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 dehydrogenese (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 prednisolne
- 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.

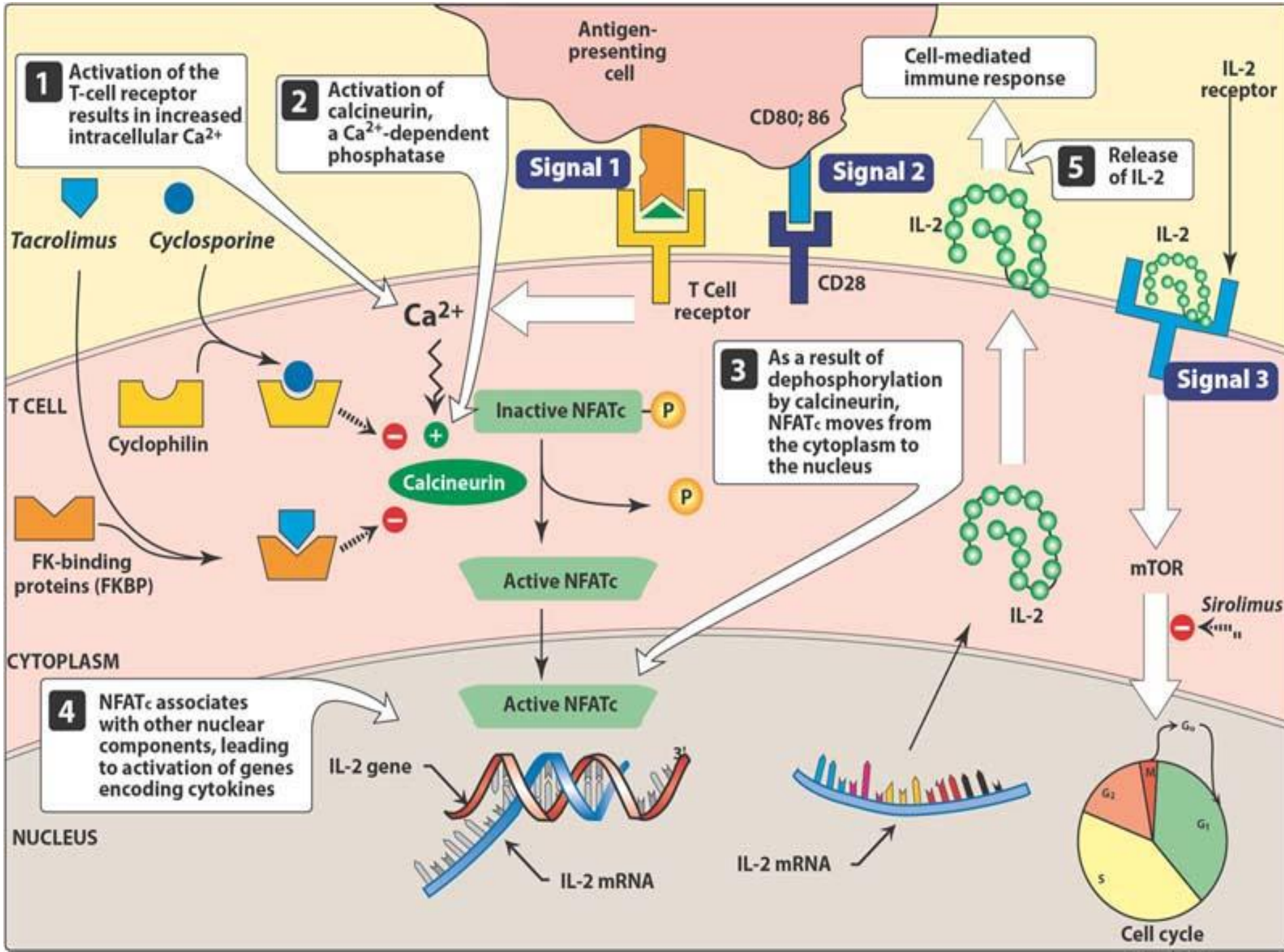
Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.

↓

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.


1 Activation of the T-cell receptor results in increased intracellular Ca^{2+}
2 Activation of calcineurin, a Ca^{2+}-dependent phosphatase
Antigen-presenting cell
CD80; 86
Signal 1
Signal 2
T Cell receptor
CD28
Cell-mediated immune response
5 Release of IL-2
IL-2 receptor
IL-2
IL-2
Signal 3
Tacrolimus
Cyclosporine
Ca^{2+}
T CELL
Cyclophilin
Inactive NFATc
P
Calcineurin
P
3 As a result of dephosphorylation by calcineurin, $NFAT_c$ moves from the cytoplasm to the nucleus
FK-binding proteins (FKBP)
Active NFATc
IL-2
mTOR
Sirolimus
CYTOPLASM
4 $NFAT_c$ associates with other nuclear components, leading to activation of genes encoding cytokines
Active NFATc
IL-2 gene
3'
NUCLEUS
IL-2 mRNA
IL-2 mRNA
Cell cycle

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/t*acrolimus 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 kidnay 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

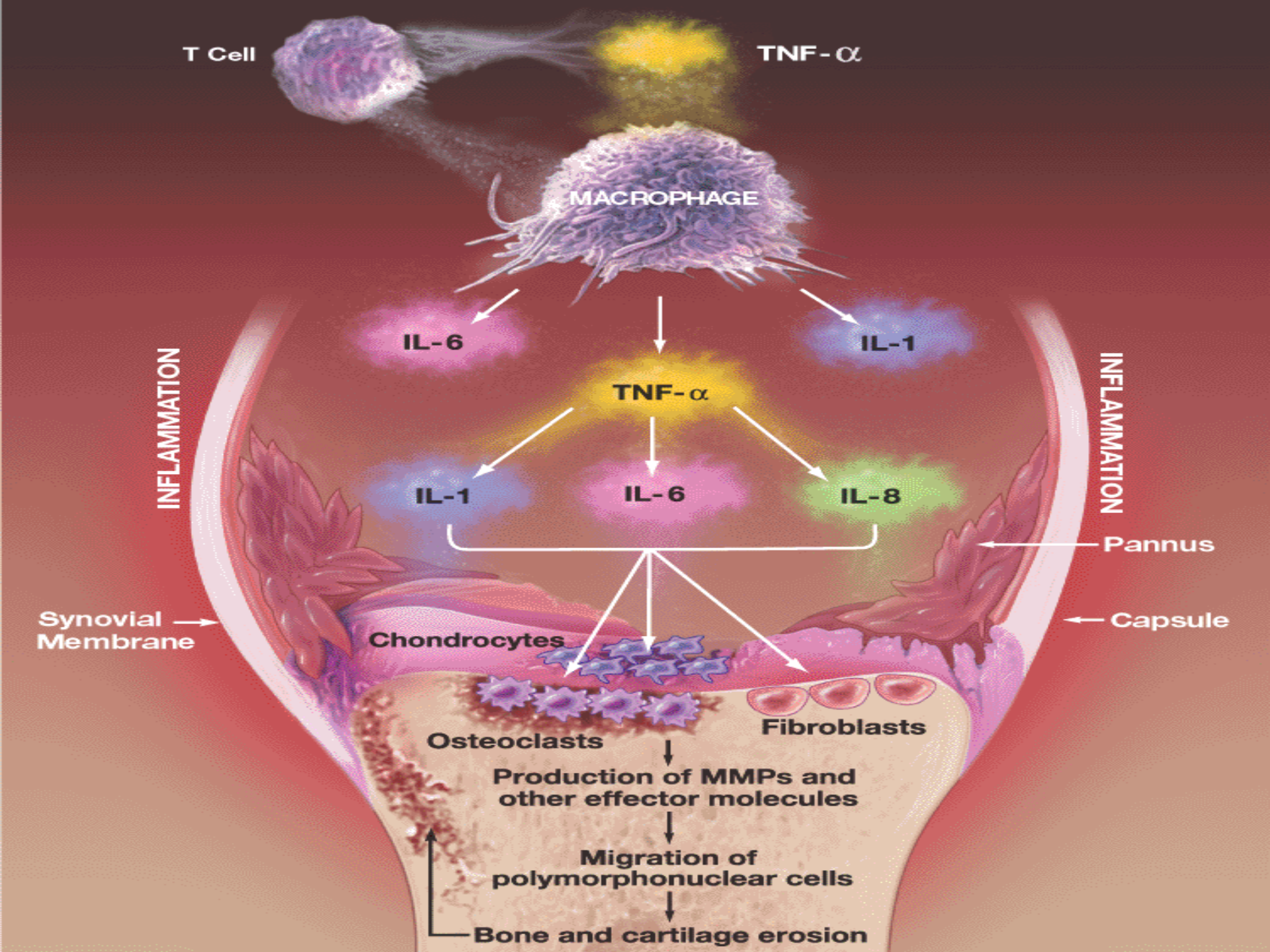
- An immune reaction against self
- Mechanism unknown, arises out of a failure in immune regulation
- Examples:
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Multiple sclerosis (MS)
  - Insulin-dependent diabetes mellitus
  - Many more

Infliximab and Adalimumab

- Anti TNF-α
- 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-α
MACROPHAGE
IL-6
IL-1
TNF-α
IL-1
IL-6
IL-8
INFLAMMATION
INFLAMMATION
Pannus
Synovial Membrane
Capsule
Chondrocytes
Fibroblasts
Osteoclasts
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

Drugs that reduce the amount of IgE to mast cells

inhibits synthesis of IgE by B-lymphocytes

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

Immunostimulants

- Increase the immune responsiveness of patients who have either selective or generalized immunodeficiency.

- Use for immunodeficiency disorders, chronic infectious diseases, cancer and HIV.

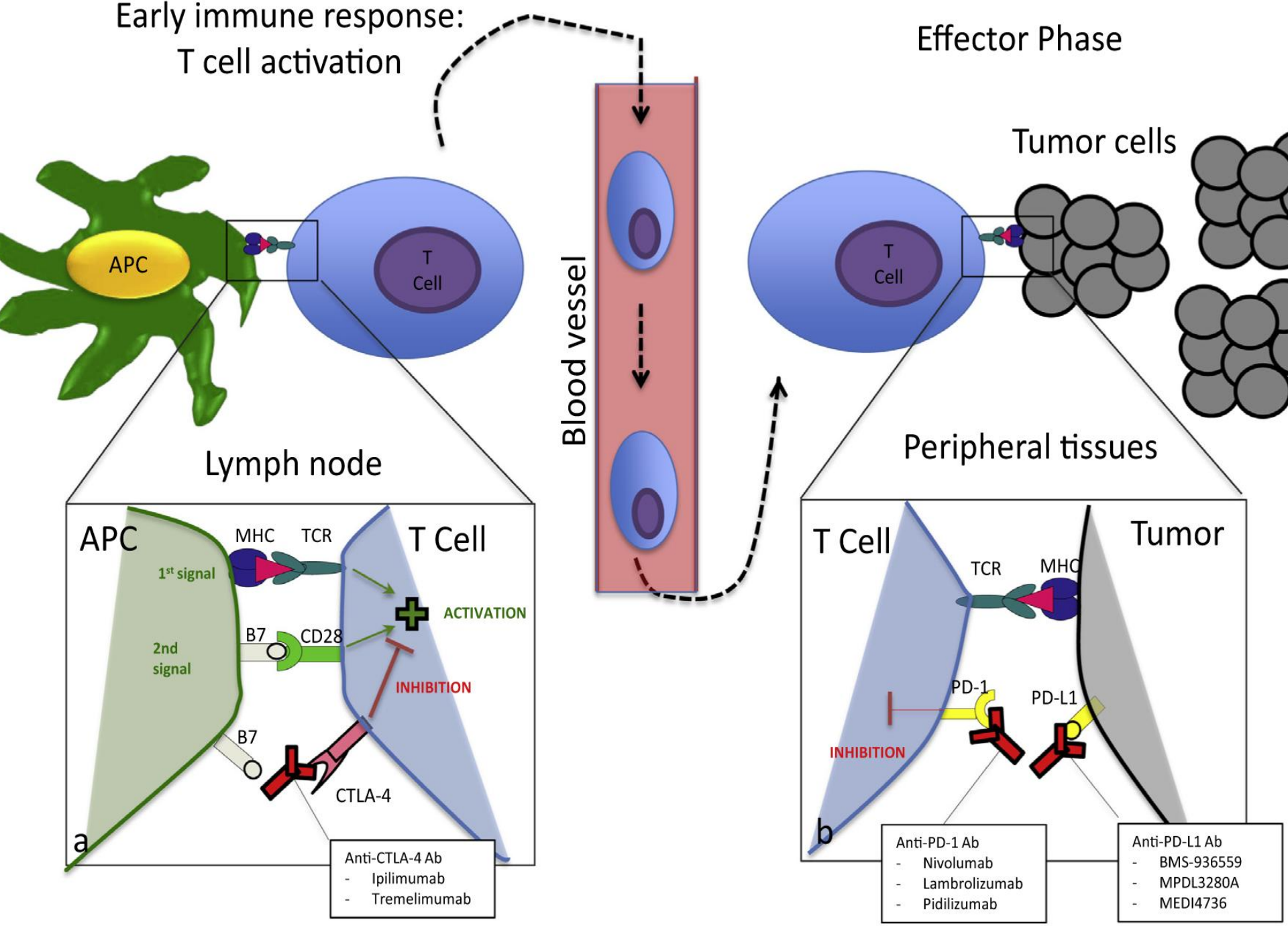
Cytokines

- Interferon (INF): INF-α,β,γ
  - Antiviral, anticancer, immunomodulating effects.
  - Antiviral effects : INF-α,β＞ INF-γ
  - immunomodulating effects: INF-γ
  - Adverse Effects: flu-like symptoms, fatigue, malaise
- Interleukin-2 (IL-2)
  - T cell proliferation, T_H, 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
Effector Phase
APC
T Cell
Blood vessel
Tumor cells
T Cell
Lymph node
Peripheral tissues
APC
MHC
TCR
T Cell
1st signal
2nd signal
B7
CD28
ACTIVATION
INHIBITION
B7
CTLA-4
a
Anti-CTLA-4 Ab
- Ipilimumab
- Tremelimumab
T Cell
Tumor
TCR
MHC
PD-1
PD-L1
INHIBITION
b
Anti-PD-1 Ab
- Nivolumab
- Lambrolizumab
- Pidilizumab
Anti-PD-L1 Ab
- BMS-936559
- MPDL3280A
- MEDI4736