IMMUNOLOGY

Modified no.

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Immuno pharmacology

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- we use the immune system to attack cancer cells,so to imagine how the the immune therapy work we will take some examples (transplantation like:kidney ,lung and the most important bone marrow transplant), and these are foreign bodies and of course there will be some rejection and it can be (acute,chronic) ,acute it can be around one week to one month

Where

When we use immuno pharmacology?

- **Agents that modulate the immune system play an important role in:**

1. **Preventing the rejection of organ or tissue grafts**
   (as the rejection made by T cells toward transplanted organ, we need to inhibit it)

2. **In the treatment of certain diseases that arise from dysregulation of the immune response.**
   - **Autoimmune diseases.**
   - **Immunodeficiency diseases.**

In covid 19 , exaggeration in the immune response causes manifestations and may cause death

Solid Organ and Bone Marrow transplantation

- Four types of rejection can occur in a solid organ transplant recipient: **hyper-acute, accelerated, acute,** and **chronic.**

  During the surgery — Within days — Within 3 months — Within years

⊙ 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

IL-2 cause migration of the immune cells

⊙ The lymphokines then activates the immune system even further, leading to a nasty cycle of foreign tissue destruction rejection

■ **NOTE:** the main target is IL-2 "cellular immunity "

■ **NOTE:** IL-2 has an outocrine effect

Narrow spectrum agents ➡️ special way to deal with them

Transplant Rejection agents complexity

- Many problems exist in currently approved regimens:

1. **Treatments are often very complex.** Many drugs
2. **low patient compliance.** Patients neglect taking medication
3. **Therapeutic margins can be very narrow.** Accurate doses to avoid toxicity
4. **Pharmacokinetic interaction potential is high and causes problems.** May contraindicate with other drugs

Remember : P450 metabolism

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

Note : even identical twins have different MHC

=when we transplant any organ (heart, kidney, lung...etc) we need to do all possible ways to inhibit immune rejection, this mean that we need to control all ways that activate the immune system, so we do combination of drugs with different mechanisms of action and different toxicity BUT as we say these drugs are used for years maybe 4 or 5 with average of 3 years, and have narrow therapeutic window so the patient must take them in time to avoid over toxicity (on the kidney) or under activity (means there is rejection).

- **NOTE**: "all drugs are toxic material and toxicity determiners by the dose"
- In transplantation we should be serious so use combined therapy .

We should avoid all ways of rejection by combination of drugs that have different mechanisms & different toxicity

Groups

- Glucocorticoids
- Calcineurin inhibitors
  - Ciclosporin A
  - Tacrolimus
- IL-2 receptor 'mabs'
  - Basiliximab
  - Daclizumab

Monoclonal antibodies

Selective drugs , bind in specific location in the body

- Anti-metabolites
  - Azathioprine
  - Mycophenolates
  - Leflunomide
- m-TOR inhibitors
  - Sirolimus

TOR : a protein has a role in cell cycle ▶ so we need to inhibit it to stop the T cells proliferation (immune system cells)

NOTE: to attack IL-2 we give corticoids or anti metabolites ,IL-2 antagonist,m-ToR inhibitors

Used for asthma patients
(magical drugs)

Glucocorticoids

- Glucocorticoids suppress the cell-mediated immunity. inhibiting genes that code for the cytokines, the most important of which is IL-2. + IL -1

- 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.
  remember that IL-1 is important in activation and migration of T-cells

- Cellular immunity is more affected than humoral immunity.
  because smaller doses will affect cellular immunity.

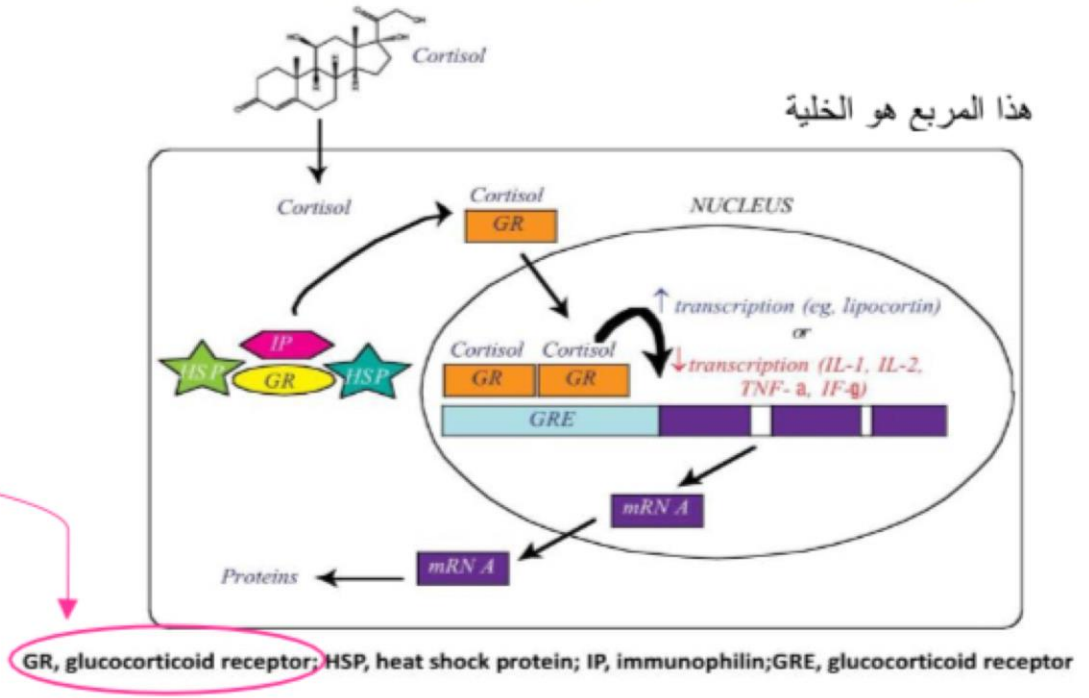
- **Anti-inflammatory effects** + Immunosuppressive effect

Glucocorticoids are also anti-inflammatory drugs (they are the strongest anti-inflammatory drugs), so we will use it in lots of cases (its magical drug).

- **NOTE:** سؤال لطيف من الدكتور
- If we give Glucocorticoids how many gene will be affected.? Around 1500 genes . For example there will be increases in expression of lipocortin (very important memories this one) , (IL-2,IL-1,INF-gamma) will be decreased and that make sense to decrease the immunity. All of these changes depend on the dose

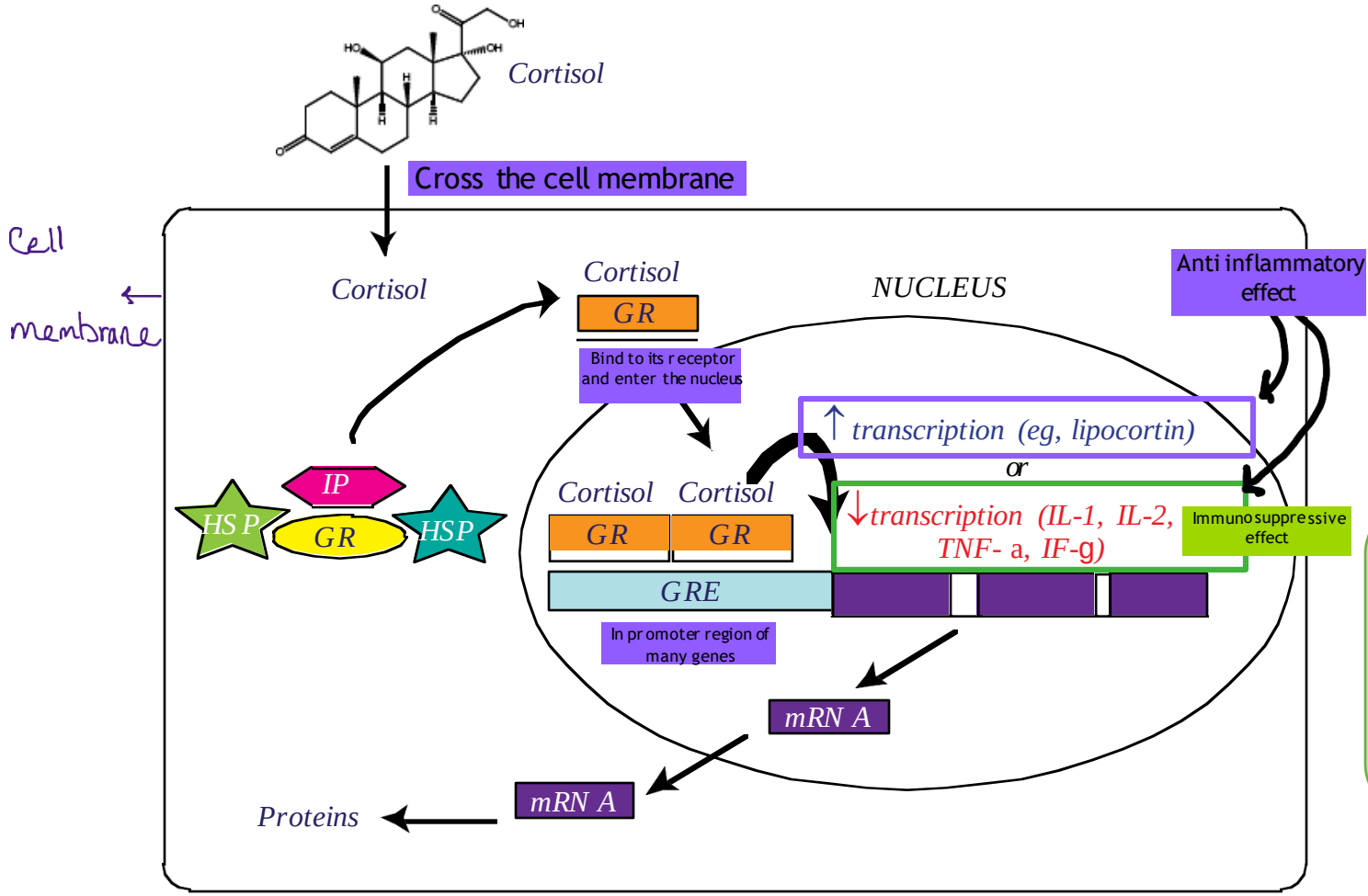
look at the picture... Cortisol (which is found in our bodies) cross the cell membrane, then it binds to its receptor inside the cell,, then this complex (GR) enter the nucleus, then it bind to glucocorticosteroid receptor element (GRE) which found in the promoter region of many many genes (nearly quarter of the genes),,it induce some of them and inhibit the other; inhibit transcription of (IL-1, IL-2,TNF- a, IFN- g) which are responsible of T cell activation so it inhibit cellular immunity which is responsible of rejection, & increase transcription of (lipocortin) which has anti-inflammatory effect (by this glucocorticoids has anti-inflammatory effect).

Glucocorticoids Regulate Transcription



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

Glucocorticoids Regulate Transcription



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

NOTE: Be aware. That the type of receptor here is intracellular receptor.

Solid organs : liver ,kidney , heart , and lung

hematopoietic stem cell transplantation: bone marrow transplantation

Clinically

- Glucocorticoids are first-line immunosuppressive therapy for both solid organ and hematopoietic stem cell transplant recipients and graft-versus-host disease (GVHD).

Without reason

idiopathic thrombocytopenic purpura and rheumatoid arthritis.

Red spots on the skin because internal bleeding

immune disorder in which the blood doesn't clot normally ،cause excessive bruising and bleeding due to low level of platelets

autoimmune disorder that primarily affects joints.

- Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for otheragents (eg, blood products) that might cause undesirable immune responses

Like anaphylaxis

When I give the patient a dye for the purpose of an examination in the hospital and I want to avoid the allergy that can happen

- **The complementing this slide:** We give the **Glucocorticoids(IV)** before the transplantation and after the transplant by this way we inhabit The acute rejection . If I want to transplant a bone marrow, we should treat the donor to decrease the number of T cells. To overcome the effect of trans graft host disease.

- **The complementing this slide:** Keep in your minds. That there is no drugs better than it glucose steroids. against allergic rhinitis
  Also, we should know. That we have two type of asthma. atopic asthma and non-atopic asthma and in both type we will give a glucosesteroids but the difference between two types is the atopic asthma there is high number of IgE and a non-atopic a low numbers ofIgE.

Change 25% of expressed genes in the body

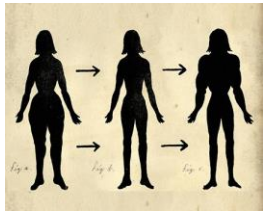
High doses (IV or IM) 500 mg before transplantation
Then 20 mg daily doses for 6 months
{Tipparing}

Side effect

Fat redistribution

Moon face : flushed and round face

BFR syndrome

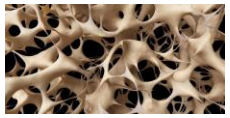


- **Immunodeficiency**
- adrenal glands
- Hyperglycemia Fat redistribution

gloconeogenisis

- growth failure, delayed puberty.
- excitatory effect on central nervous system (euphoria, psychosis) depression

It's Lipophilic so can cross BBB and cause CNS diseases

- Osteoporosis 

Bones become brittle and fragile from loss of tissue

- Cataracts 

Lead to increase in the ocular pressure

- Gastric ulcers (prevent with omeprazole, misoprostol)
- Hypertension

Calcineurin Inhibitors Cyclosporine & Tacrolimus

1. human organ transplantation,

2. graft-versus-host disease after hematopoietic stem cell transplantation,

- **NOTE: T cells from the donor's organ would attack the host, so we give the donor these drugs before taking the graft from them.**

3. selected autoimmune disorders.

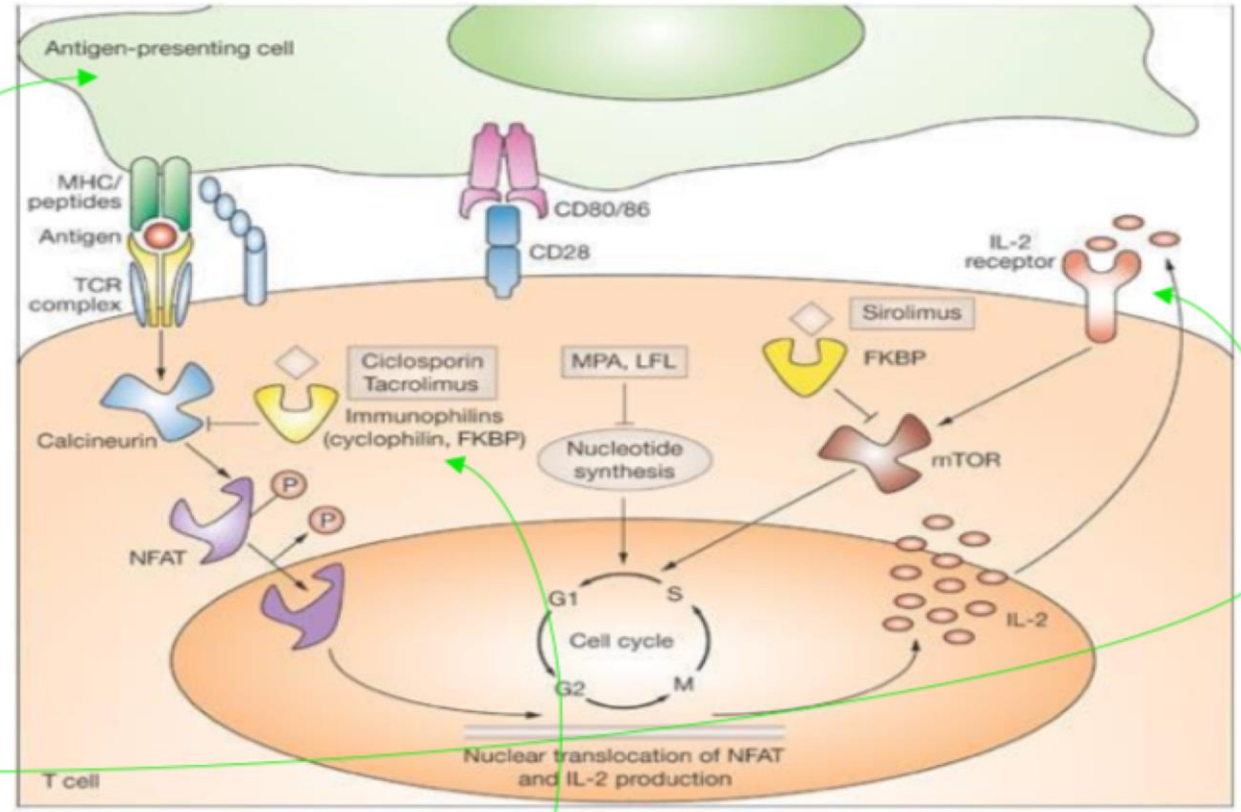
Both Inhibit the cytoplasmic phosphatase, calcineurin, which is necessary for the activation of a T-cell-specific transcription factor. This transcription factor, NF-AT, is involved in the synthesis of interleukins (eg, IL-2) by activated T cells.

- **NOTE: these drugs are given alongside glucocorticosteroids to suppress T cell proliferation because they proliferate very fast.**
- **Only one of these drugs are given (either cyclosporine, tacrolimus or sirolimus which we will discuss soon).**

- **NOTE: Calcineurin inhibitors suppress the immunity by stopping T cell proliferation**

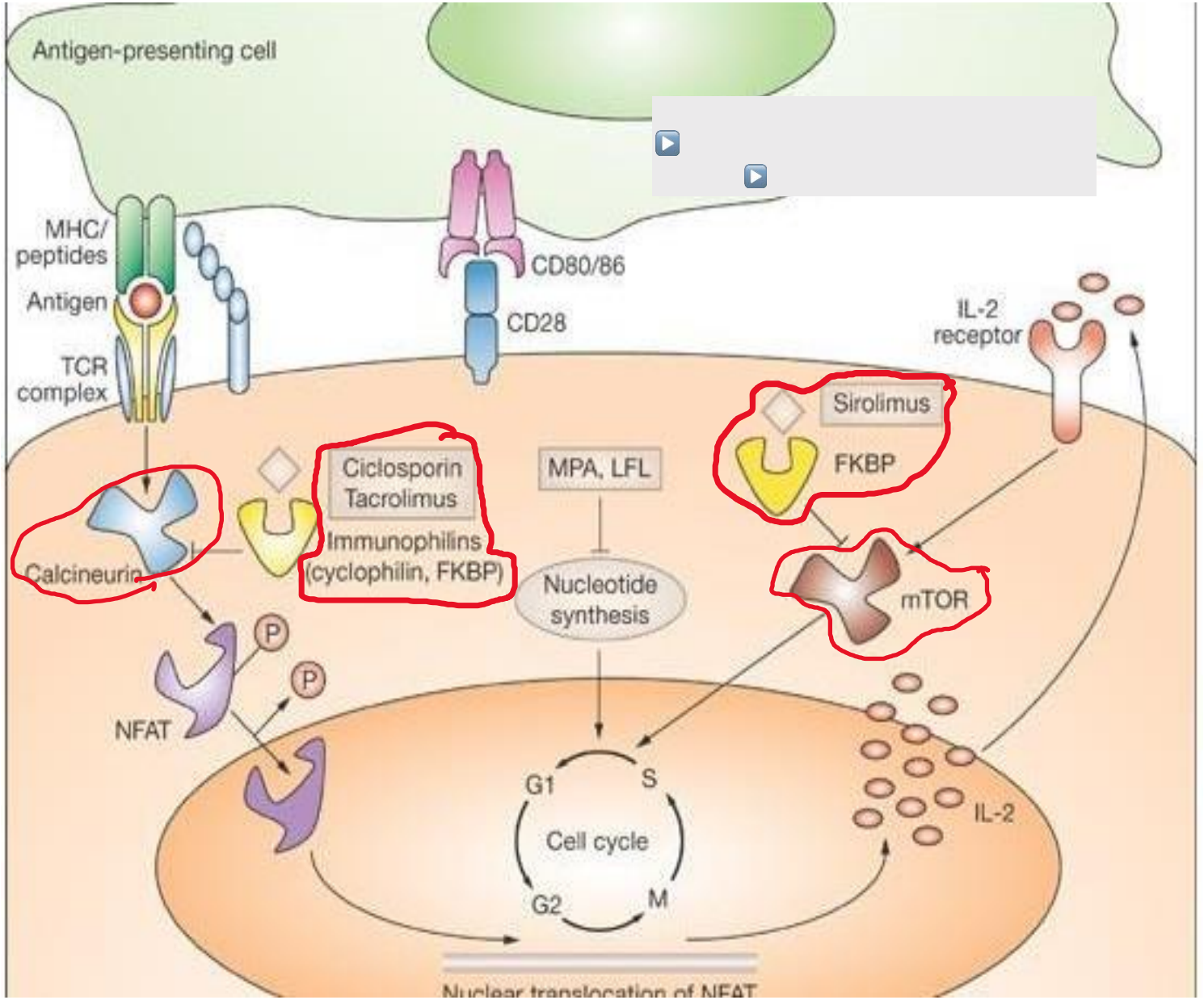
So these drugs will affect indirectly the gene expression so its effect is less than glucocorticoid (because it has direct effect).

Look at the figure -as we see APC will activate T- cell by MHC binding to TCR which activates calcineurin, calcineurin as a phosphatase it dephosphorylates NFAT which in turn inter the nucleus and increase the expression of IL-2, IL-2 exit the cell and bind to its receptor on the cell surface (autocrine) which increase the activation and migration of T-cells.



our drugs in the cell bind to immnuophilins which has 2 types (cyclophilin which bind cyclosporine, FKBP which bind tacrolimus), now immunophilin when activated it inhibits calcineurin which in turn inhibit IL-2 and T-cell activation.

- The complementing this slide:
- Remember that when an APC activates a T cell, the T cell releases IL-2 making an autocrine signal to make itself proliferate.
- Calcineurin is secreted when an APC activates a T cell leading to its proliferation by IL-2.
- We have two drugs called Cyclosporine and Tacrolimus, they attach to molecules called immunophilins inhibiting Calcineurin, therefore no T cell activation.
- We use them as immunosuppressants.
- Sirolimus is another T cell inhibitor and immunosuppressant, it activates an intracellular receptor that inhibits mTor (part of IL-2 cascade that promotes T cell activation), it is called FKBP.



Complexity

- metabolized by the P450 3A enzyme system in the liver with resultant multiple drug interactions.

- **NOTE: the extreme variation of P450 3A enzyme among the population make finding the optimal therapeutic dose very complex.**
- **To overcome this problem we test the pharmacokinetics of the drug in the patient before properly administering the drug to the patient.**

- Narrow therapeutic window
- . Levels too high: toxicities (i.e. nephrotoxicity, mental confusion, hyperglycemia and hypertension)
- . Levels too low: transplant rejection.

- We used to think that immunosuppressants increase the risk of lymphoma but that turned out to be false very recently.

CYCLOSPORINE

Measure conc in patient's blood

Monitoring Parameters:

- Cyclosporine trough levels. — To prevent drug - drug interaction
- Serum electrolytes.
- Renal function. — Kidney toxicity
- Hepatic function. — Liver toxicity
- Blood pressure.
- serum cholesterol.

NOTE: We should monitor the cyclosporine concentrations and side effects (and other immunosuppressants) to make sure the patient doesn't develop very bad side effects.

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.

- **NOTE: it has similar effects to cyclosporine.**
- **It has more efficacy than cyclosporine and its less toxic.**
- **But it has a special side effect : diabetes millitus.**

Sirolimus (RAPAMUNE)

- Closely related with Cyclosporine & Tacrolimus.

- 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.

Sirolimus (RAPAMUNE)

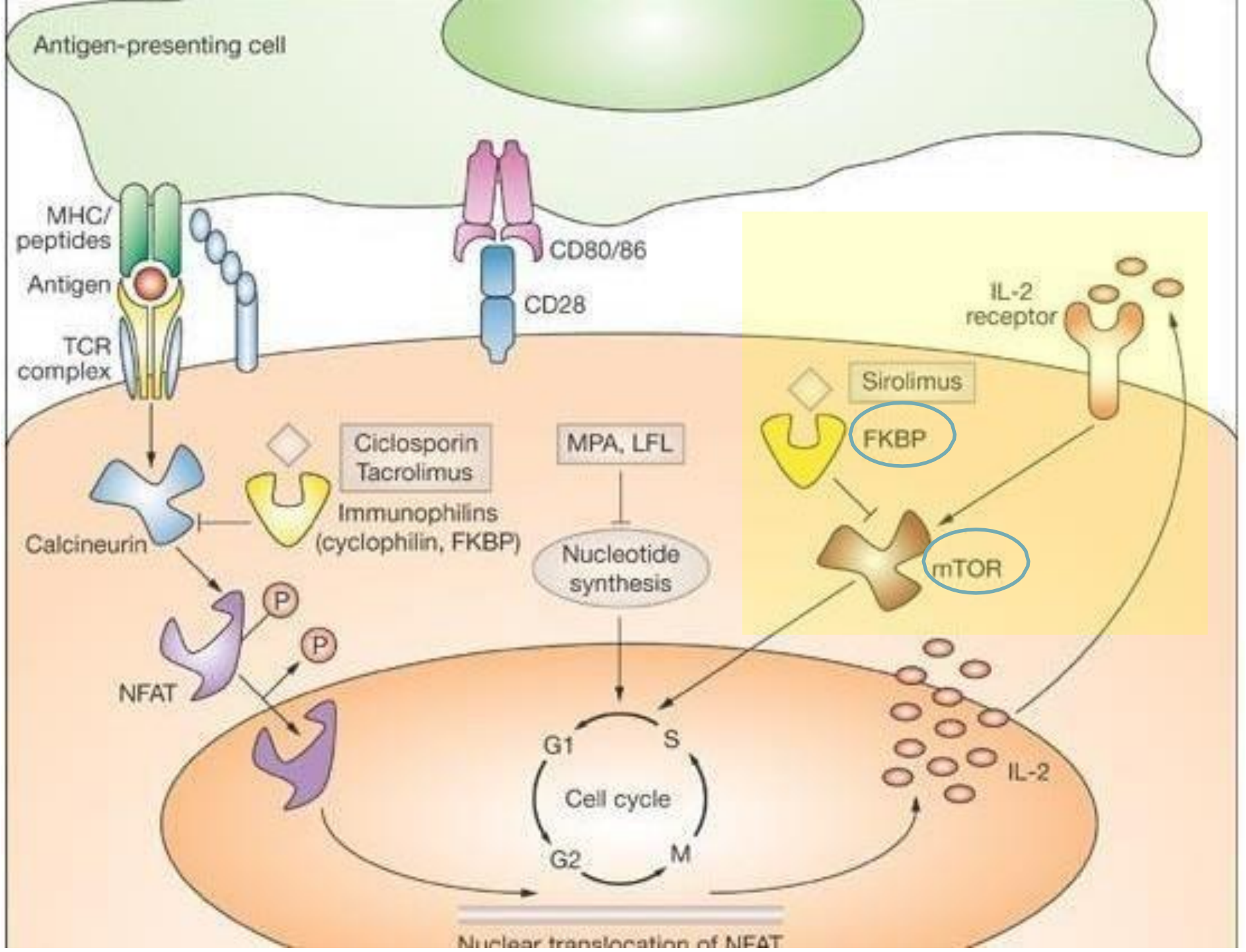
Mechanism of action:

- Sirolimus bind with FKBP, then FKBP will inhibit mTOR, the function of mTOR in normal statue as the following: It will be affected by IL-2, then it will enable the cell to enter the cell cycle and induce more proliferation of T-cells. So, Sirolimus will inhibit its action.

- Sirolimus and Calcineurin inhibitors are interchangeable which mean that we can't use them together, e.g. We either chose (Cyclosporin or Tacrolimus or Sirolimus).
  We can’t use cyclosporin with tacrolimus, or using sirolimus with tacrolimus, or using sirolimus with cyclosporin. We use only one of these 3 drugs to be self-acting alone.

- Although they have different mechanisms. however, there is a problem in its toxicity and there are some similarities in their mechanisms.

Sirolimus bind with FKBP, then FKBP will inhibit the mTOR, the function of mTOR in normal statue which will be affected by IL-2 and enable the cell to enter the cell cycle and produce more proliferation of T-cells.
So, Sirolimus will inhibit its action.



Quick Review

- Glucocorticoid (Glucocorticosteroid) has multiple side effects. However, we must use such drug. It is known also as the magical drug because there is no drug rather than Glucocorticosteroid can suppress pre- and post-organ transplantation rejection.

- Calcineurin inhibitors will inhibit eventually the production of IL-2 and autocrine activation for T-cell.

- These drugs are complex drugs, because we have a narrow therapeutic index. if you increase the drug concentration within the blood of your patient you will produce nephrotoxicity.

- Metabolized by the P450 3A (CYP 3A4, CYP 3A5), : CYP 3A4 and CYP 3A5 are polymorphic (has SNP single nucleotide polymorphism) which means that everyone has different activity of them.

Quick Review

- Any drug inhibits CYP 3A4 or CYP 3A5 will increase the concentration of Cyclosporine & Tacrolimus in the blood (drug-drug interaction).

- Cyclosporine & Tacrolimus are calcineurin inhibitors. However, one of them produce more toxicity than the other (Cyclosporine more toxic than Tacrolimus).

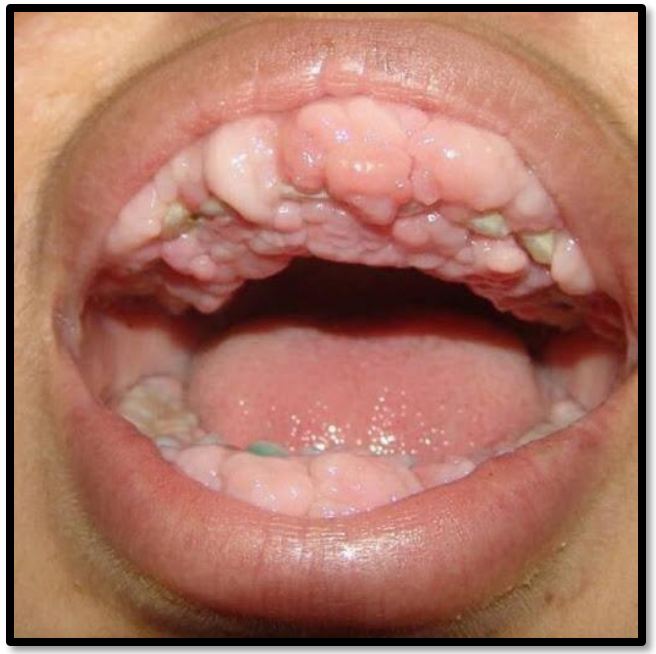
- Tacrolimus can cause diabetes mellitus and hyperglycemia, cyclosporin won't cause diabetes mellitus.

- Cyclosporine can cause Gingival Hyperplasia, we call it as trademark adverse effect, because there are only 3 or 4 drugs that can cause Gingival hyperplasia. The 2nd drug from these drugs is Calcium-channel blockers.

Quick Review

- Google: Gingival hyperplasia is an overgrowth of gum tissue around the teeth.

Just for clarification - Gingival hyperplasia



Anti-metabolites

- **Anti-metabolites decreases DNA metabolites leads to decrease T, B, bome marrow cells replications.As a result, decreases rejection possibility.**
- **Anit-metabolites are NON selective.**
- **Ex:DHFR, Azathioprine and mercaptopurine.**

- 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 better than anti-metabolites, it is selective.**

- 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).

- **MPA used in chronic rejection.**

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.

isn't used in early stage of treatment.

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.

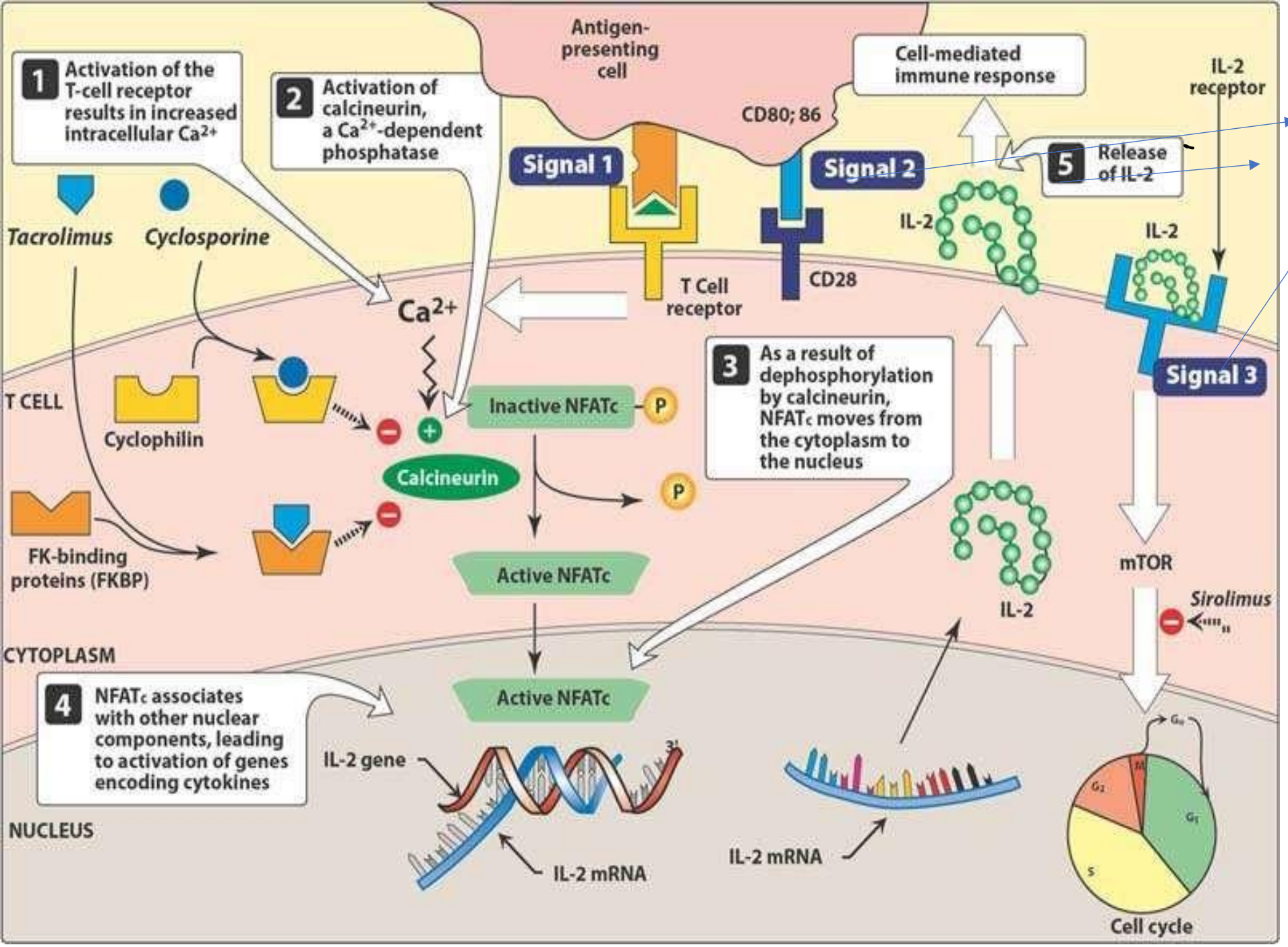
Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.

↓

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.



- Monoclonal antibodies target signal sites

Immunosuppressive antibodies (Monoclonal antibodies)

- To suppress the activity of subpopulation of T-cells.
- To block co-stimulatory signals.

Monoclonal antibodies are administered IV or IM, because those are protein in structure so won't be active if are administered orally .

- 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

- Drugs names that are mentioned in this slide aren't for memorization

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

- mAbs have prolonged half life"weeks to months" and they block either receptors or ligands

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

- To control initial reactions.

IL-2-receptor antagonists

- **Drugs names are important here** 😃

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.

- **Explanation: Abs** made up of domains from different species, those which made mainly from human proteins are called **Humanized .**
- **More humanized ab,more expensive,less rejection**

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.

- **Due to its prolonged half life, it stays long time leads to prevent acute rejection.**

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.

- **It doesn't have HIGHLY toxicity, because it deals with cell-mediated immunity**

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(the dose must be individualized and needs monitoring)/day given as (two doses at 10:00 and 22:00)-> To maintain steady state.
- Prednisolone 20 mg once daily at 08:00pm because cortisol is released normally in the morning.
- 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.

- **The very TIME is very important , it is associated with pharmacokinetics.**
- **Mycophenolate is used as reservoir.**

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

NOTE:

- تفاصيل الأمراض غير مطالبين فيها المهم الpharma

Rheumatoid arthritis

NOTE:

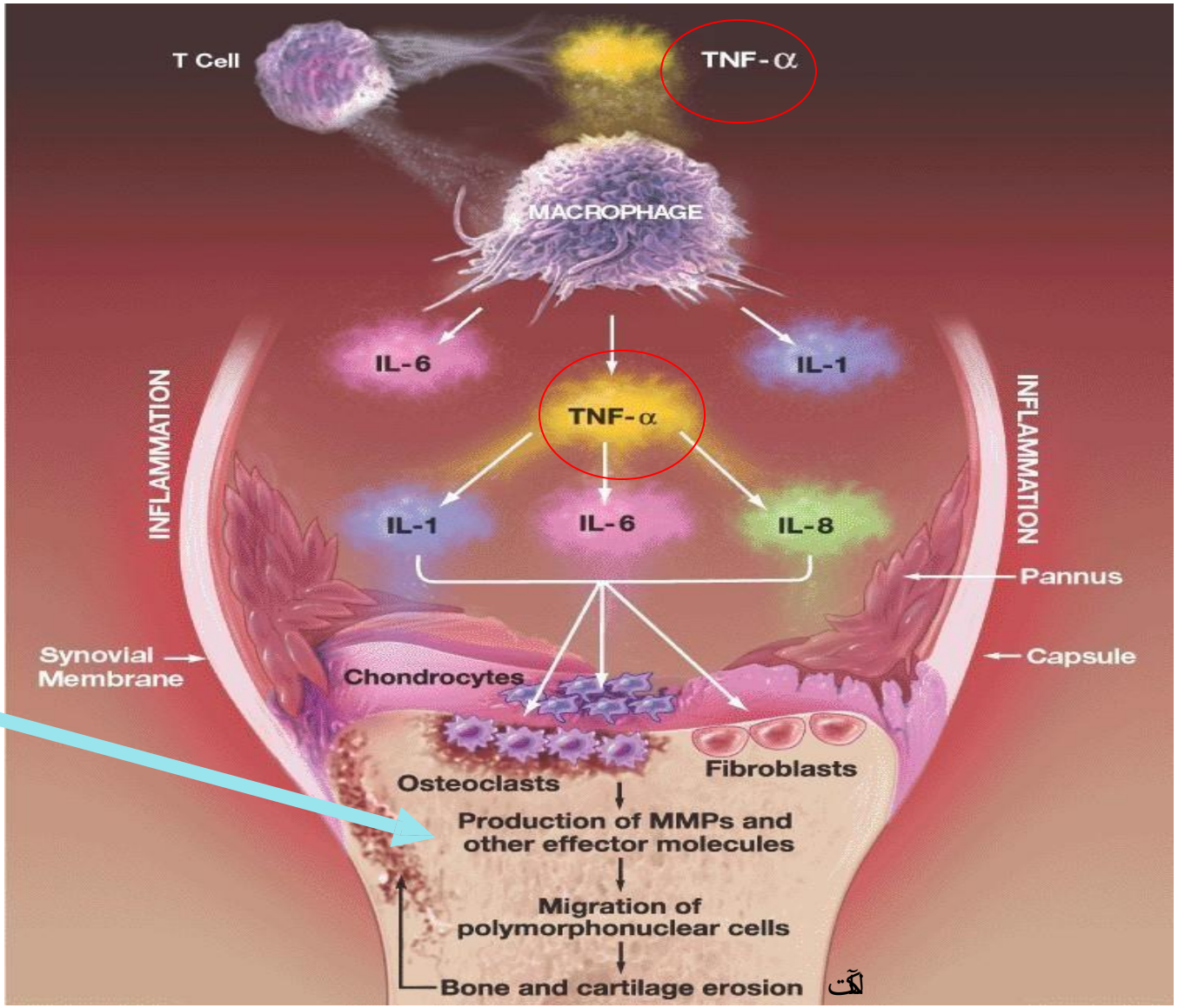
Macrophages will Secrete IL-1,IL-6 and TNF-α. Macrophage will go to the synovial fluid and can attack the chondrocytes and it will induce some problems on fibroblast and osteoclasts through TNF-α, which can stimulate IL- 1, IL-6 and IL-8. Then it will lead to all of the following

And this can cause deformities.

We can give Anti-IL-1, Anti-IL-6, Anti-IL- 8,…

But the question arise why we don't give the Anti TNF-α. And here is the Infliximab and Adalimumab.

NOTE: Pay attention we inhibits the TNF alpha which is secreted from T cells



Infliximab and Adalimumab

- Anti TNF-α
- Approved by the FDA in 1998

NOTE: Adal = عادل
تسهيل للحفظ

- Designated for use in patients who did not respond to methotrexate.

NOTE: Methotrexate هو الأساس

- Proven to slow the clinical progression of rheumatoid Arthritis.

NOTE: Rheumatoid arthritis cann't be treated because it is degenerated , we just slow the progression same as diabetes mellitus

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**

NOTE: The latent TB will reactive النايم بصحا
Which is serious infection

- Remember

STOP if develop a fever بسرعة,because the patient might have an infection, eg. TB

Rituximab

NOTE: ريتا

- Anti-B cell (CD20) antibody

NOTE: Blocks CD20 receptor on B cells

- 15-20% of rheumatoid arthritis cases there will be involvement of B-cells.
- First approved in 1997 for use in B-cell lymphoma

NOTE: Used to treat Leukemia as cancer drug

- 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.

NOTE: Why it is given to rheumatoid arthritis patients?
There are many types of rheumatoid arthritis some types have B cell involvement so we inhibit B cells.

Anti-IgE Antibodies Omalizumab

NOTE: أمل أعطت أمل لمرضى الربو Asthma

- Asthma has something to do with allergy, and this allergy related to IgE. (Meaning: If the patient had an elevated concentration of IgE, we would give him Omalizumab.

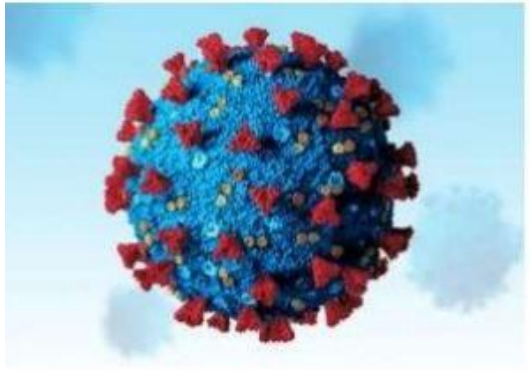
NOTE: It cures شفاء تام asthma in 30% of atopic asthma patients , however, it is very expensive

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

- It binds to a protein not receptor

- 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.



- Rapid replication of the virus increases the viral load and enhances viral cytopathic effects
- NOTE:CSS is responsible reason for most of Corona virus mortalitiez, CSS is highly dependent on IL eht fo notiacilper dipar :erafl lariV 6 suriv
- 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

NOTE: read only trials aren't required

- 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.

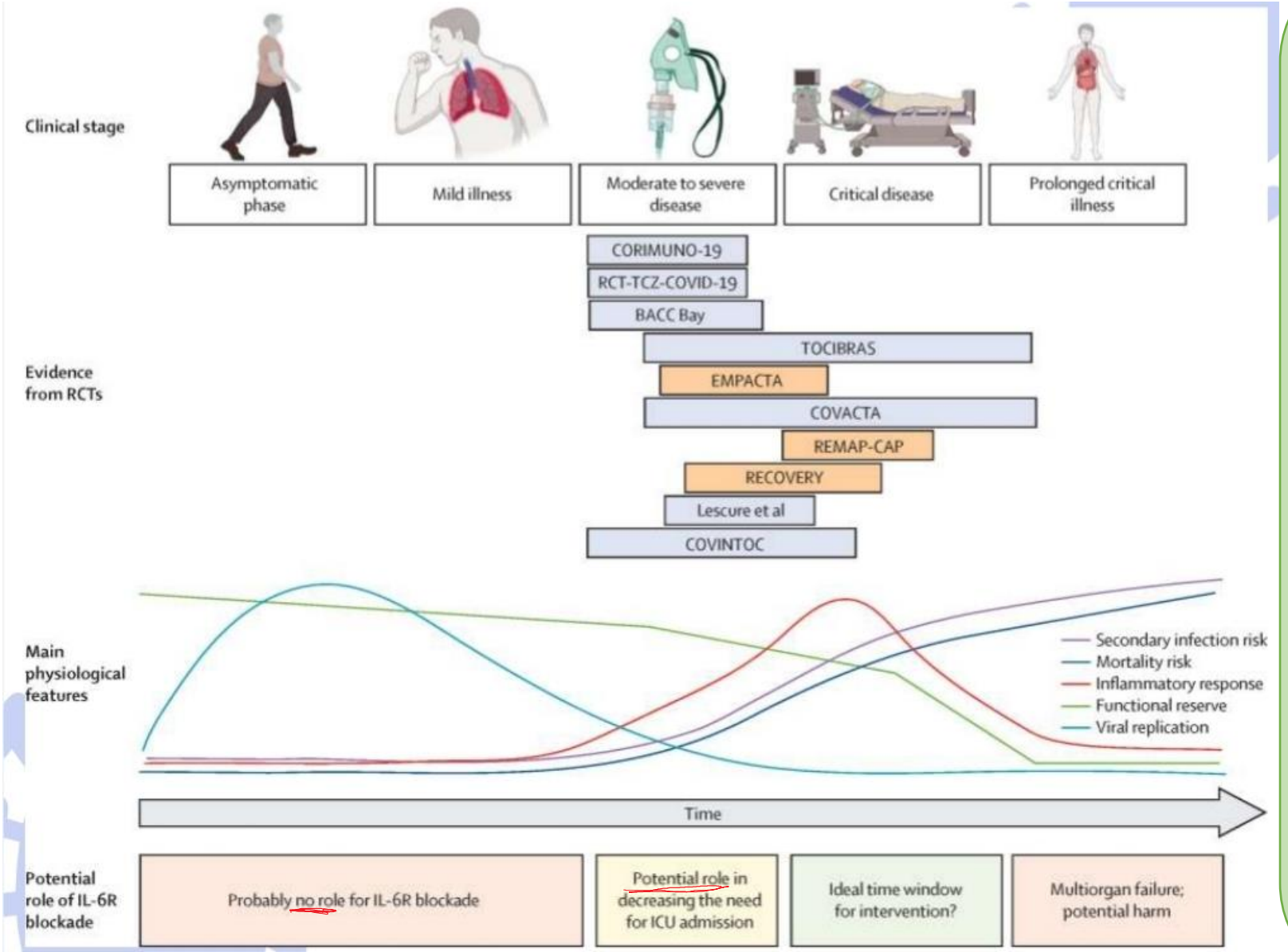
IL-6 Inhibitors

NOTE: read only trials aren't required

- 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 withresistance to infection, there are real concerns that IL-6neutralization 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 inrelevant trials appear minimal likely owing to thetargeted (1–2 doses) use of these antagonists in COVID- 19



NOTE:

In immunotherapy it is important when to treat. You should know the course of the disease.
Pay attention, when to use tocilizumab (anti IL)6

Note it doesn't have a role in treating mild /moderate case, because we are not inhibiting the virus replication"viral flare" when it is mild and moderate the immune system can treat corona virus without interventions,

we use tocilizumap in moderate to severe case and critical diseases

We don't give it in prolonged critical illness because it develops multiple organ failure and potential harm ،hence there is an increase the susceptibility to secondary infection and mortality risk because you are giving anti immuno and anti inflammatory drugs بتنزل المناعة

Prolonged critical illness:
المريض صابه
CSS
و تأثر فيها ولكن تخطاها

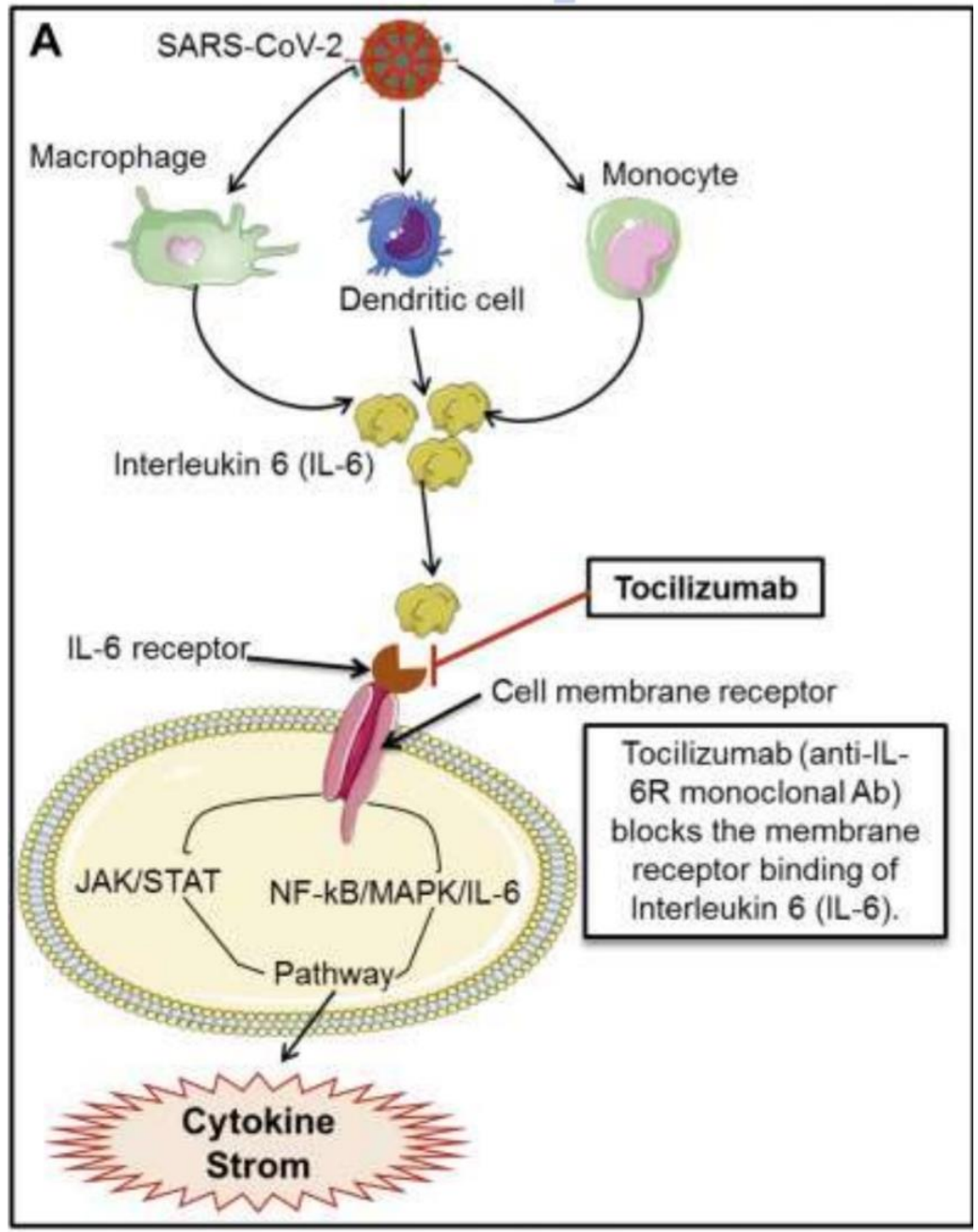
Same thing we do when we use Glucocorticoid or anti IL6

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 bothformsofinterleukin6receptors(IL6R)


A
SARS-CoV-2
Macrophage
Monocyte
Dendritic cell
Interleukin 6 (IL-6)
Tocilizumab
IL-6 receptor
Cell membrane receptor
JAK/STAT
NF-kB/MAPK/IL-6
Pathway
Tocilizumab (anti-IL-6R monoclonal Ab) blocks the membrane receptor binding of Interleukin 6 (IL-6).
Cytokine Strom

IL-17 physiological role

NOTE:
Th17 : T helper cells 17 which produces IL-17

ركزوا علىfungal infection

- IL-17, a **proinflammatoy** cytokine, plays a pivotal role ininflammatory 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

NOTE: Prevent the Peneration of microbes

IL-17 is essential in maintaining intestinal barrier integrity which is disrupted by excessive blockade of the IL-17 signalingpathway

NOTE:
If there is a lot of releasing IL17 will cause chronic IL-17

- Although IL-17 expression induces physiological reactions for host immune defense mechanism and tissue healing, chronic IL17 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

- **NOTE:** سكاكين
- **Psoriasis :** الصدفيةwhich is an auto immune disease
- **Doses aren't required**

Secukinumab is a recombinant human IgG1/kappa mAb

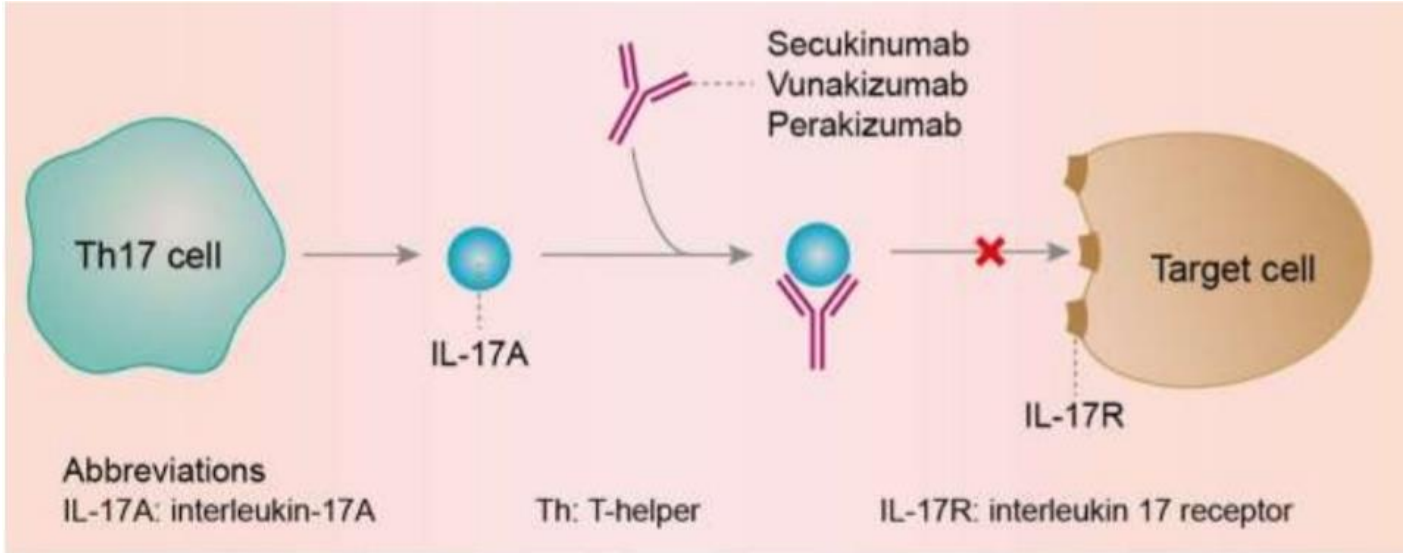
- targets IL-17A and prevents it from binding to and interacting with its receptor (IL-17R).

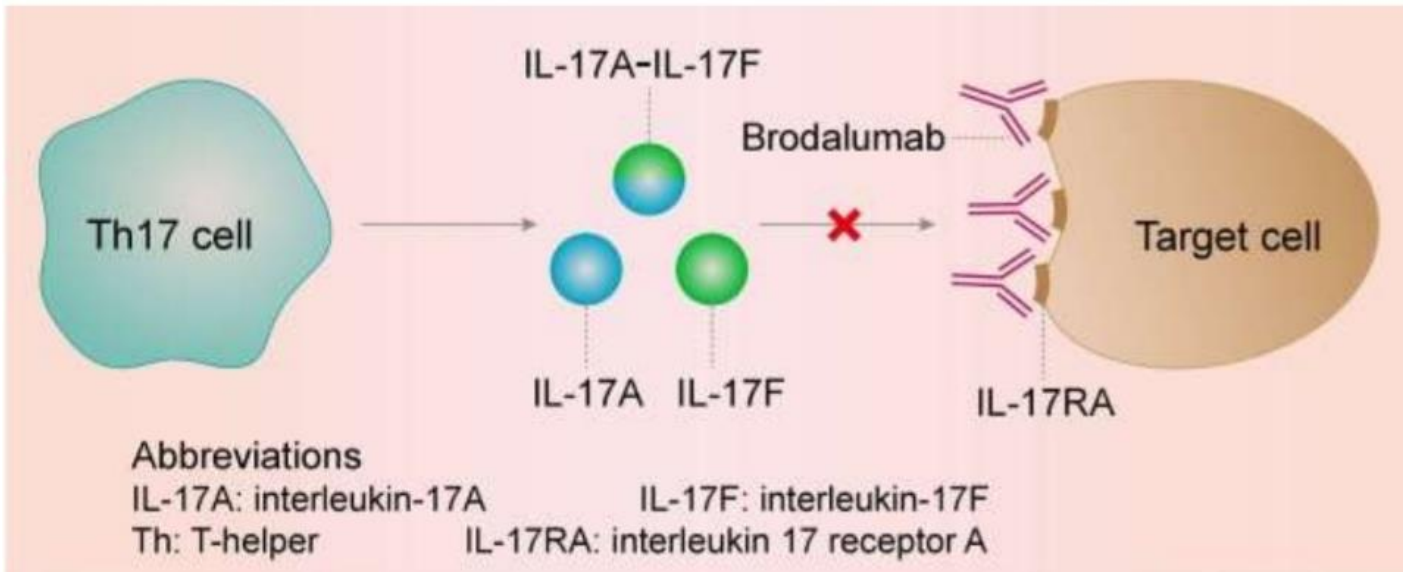
- The binding prevents the downstream production of proinflammatory cytokines and chemokines that contribute to the onset of various diseases Secukinumab was approved by the FDA for the treatment of moderate-to-severe plaque psoriasis

- 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%


Secukinumab
Vunakizumab
Perakizumab
Th17 cell
IL-17A
Target cell
IL-17R
Abbreviations
IL-17A: interleukin-17A
Th: T-helper
IL-17R: interleukin 17 receptor


IL-17A-IL-17F
Brodalumab
Th17 cell
Target cell
IL-17A
IL-17F
IL-17RA
Abbreviations
IL-17A: interleukin-17A
IL-17F: interleukin-17F
Th: T-helper
IL-17RA: interleukin 17 receptor A

Immunostimulants (زيادة المناعة)

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

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

Cytokines Therapy

NOTE:
All the previous slides are discussing immune suppression
Now we will talk about immuno inhacement by giving IL 2 and INF

- 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

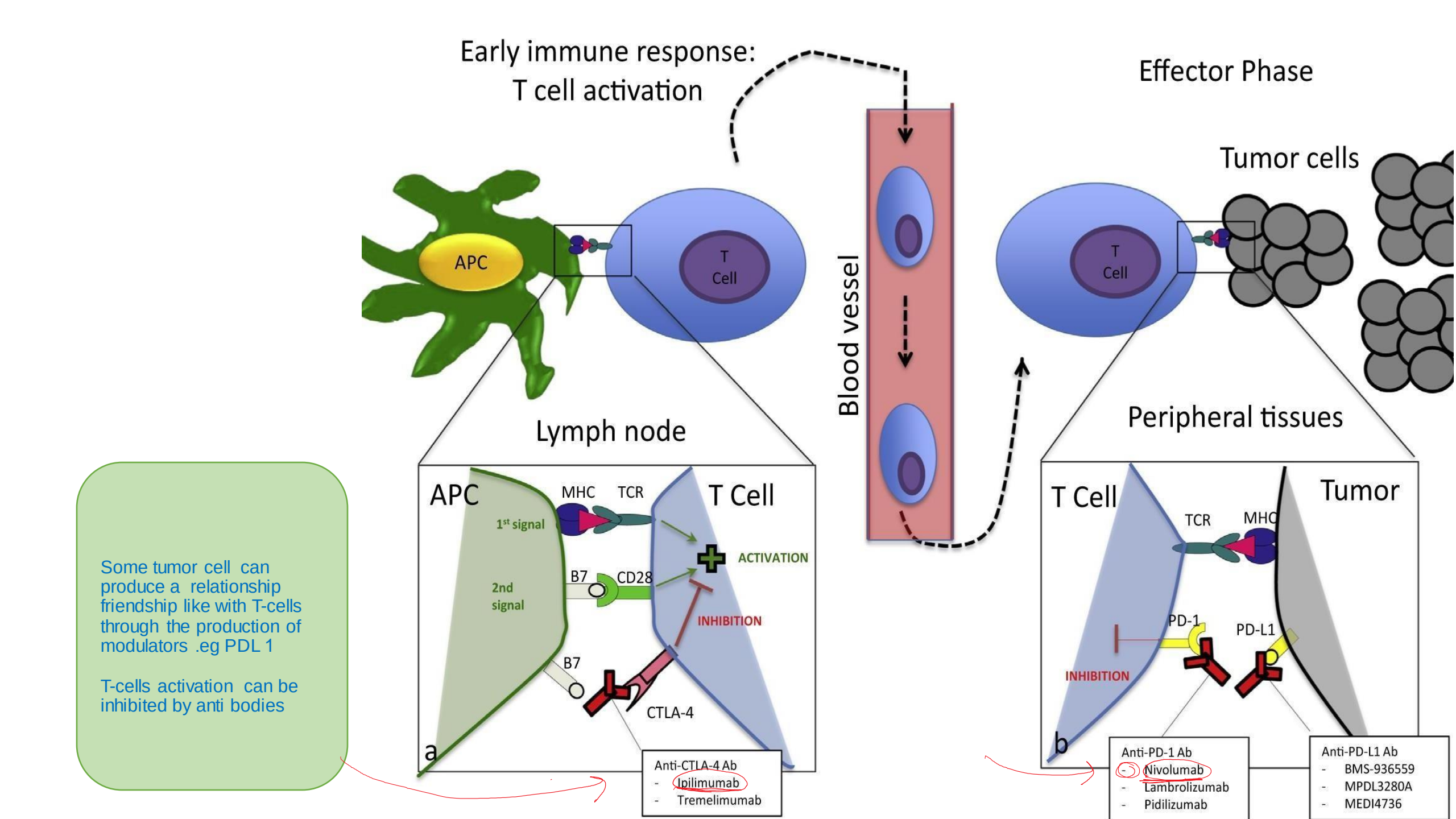
NOTE:How to treat Hepatitis C , B?By giving INF- alpha

- 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



Some tumor cell can produce a relationship friendship like with T-cells through the production of modulators .eg PDL 1

T-cells activation can be inhibited by anti bodies

V2:

slide 52,59 we fix them

Slide 56 we complete the last sentence and fix the first one

When we say fix we mean like الكلام معكوس كان وزبطناه