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.**
  - depend on compatibility between donor and recipent
  - we aim to inhibit acute and chronic rejection

  - 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**
  - reduce IL-2
  - **Ciclosporin A**
  - **Tacrolimus**
- **IL-2 receptor 'mabs'**
  - IL-2 Ab
  - **Basiliximab**
  - **Daclizumab**
- **Anti-metabolites**
  - **Azathioprine**
  - **Mycophenolates**
  - **Leflunomide**
- **m-TOR inhibitors**
  - regulate cell cycle.
  - **Sirolimus**

* intracellular receptors: "for hormones"
- PK receptor
- GPCR
- Gated channels receptor

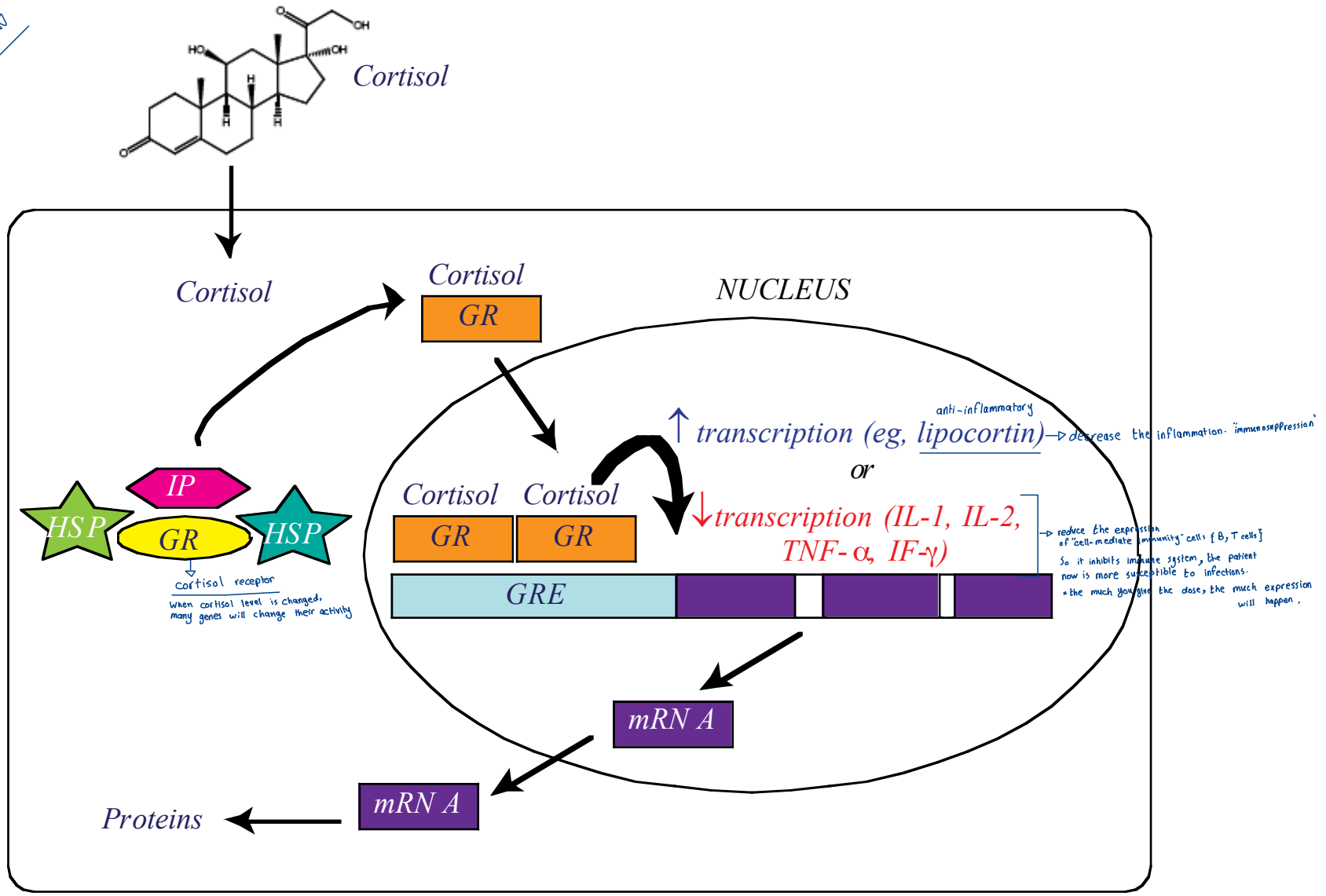
Glucocorticoids

- cortisol is the best drug for allergy
* ماعني أي دواء للحبة غير الـ cortisol

- 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

endocrine
not imp now



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.

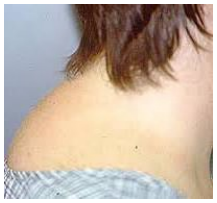
- Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma or as premedication for other agents (eg, blood products) that might cause undesirable immune responses.

Side effect

depends on time and dose.
duration.
time of administration " infx or inflammation."

- **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)

tapering عشان صيك بتوقف ال cortisol تدريجيا وهاي اسمها
الدكتور حكى فحط الرقم
suppression
"after 21 days"
negative feedback
Hypertension.



so it is adminstrated for short period.

من طريقة حكي الدكتور بس انه في مليار ال side effect

IL 2

increase the expression of IL-2

Calcineurin Inhibitors Cyclosporine & Tacrolimus

هم نوف متى بستخدمه.

the best immunosupprressants

1. human organ transplantation,

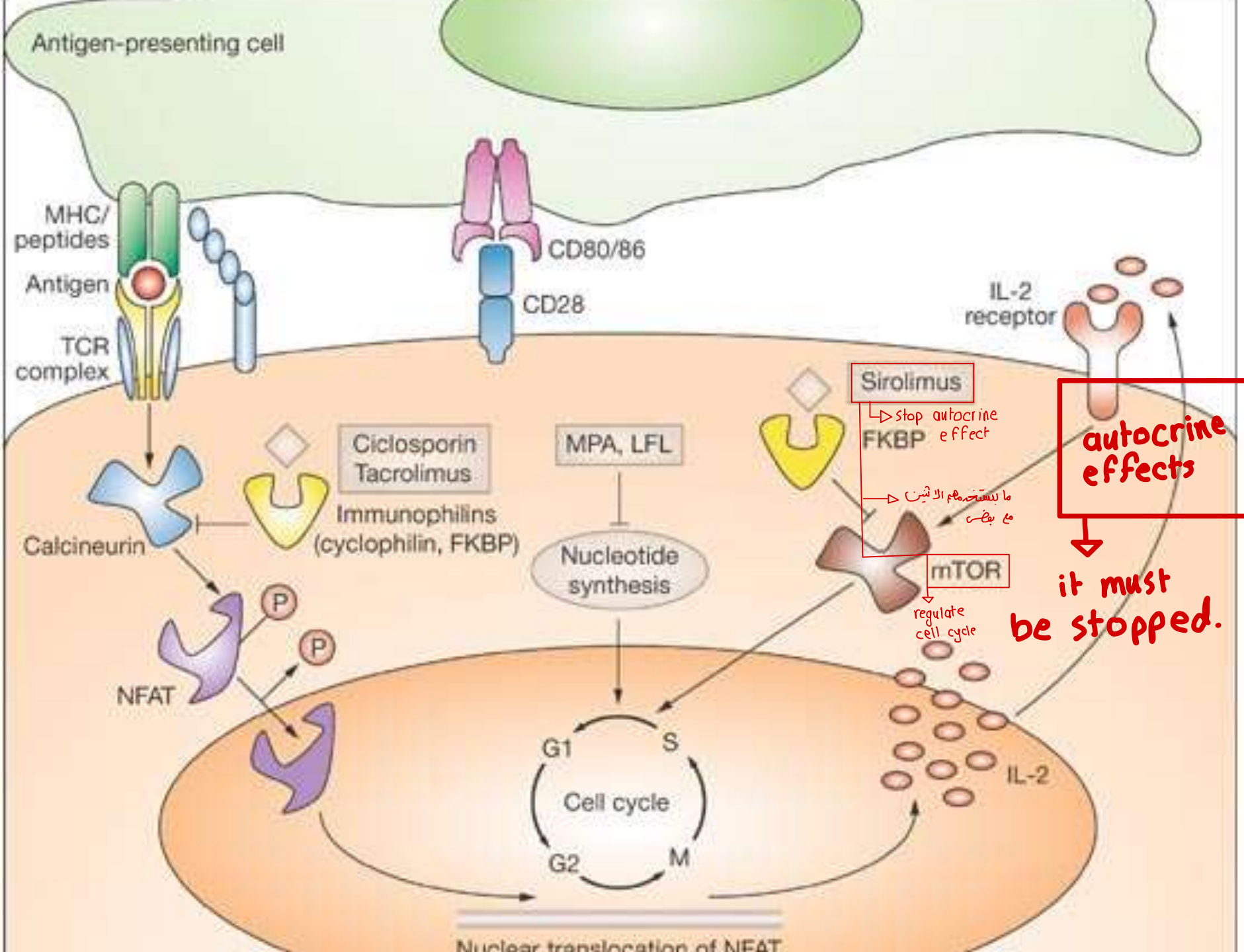
2. graft-versus-host disease after hematopoietic stem cell transplantation, GVHD it can use as prophylaxis or treatment. "for donor and recipient" إذا: الـ cortisol ما عمل اشي. خصوصا عشان زراعة الـ HSC.

* لازم نفصل cell-mediated immunity خصوصا الـ T cells.

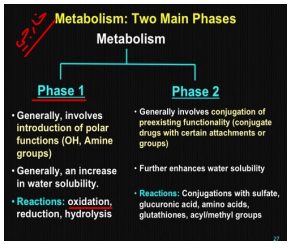
3. selected autoimmune disorders.

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.

هاي الـ mechanism مهمة للفهم "موجودة بالصورة فقط".


Antigen-presenting cell
MHC/
peptides
Antigen
TCR
complex
CD80/86
CD28
IL-2
receptor
Sirolimus
stop autocrine
effect
FKBP
ما بيستخدمهم الاثنين
مع بعض
autocrine
effects
it must
be stopped.
Ciclosporin
Tacrolimus
Immunophilins
(cyclophilin, FKBP)
MPA, LFL
Calcineurin
Nucleotide
synthesis
mTOR
regulate
cell cycle
P
P
NFAT
G1
S
Cell cycle
G2
M
IL-2
Nuclear translocation of NFAT

SNP : A single nucleotide polymorphism (abbreviated SNP, pronounced snip) is a genomic variant at a single base position in the DNA. Scientists study if and how SNPs in a genome influence health, disease, drug response and other traits.



Complexity

Cyt P450: play a Key role in phase I metabolism.

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

- Narrow therapeutic window → to keep the dose within therapeutic range → monitoring and titration
  - Levels too high: toxicities (i.e. nephrotoxicity, mental confusion, hyperglycemia and hypertension)
    - ↳ cause DM, if Tacrolimus dose more than 30% / Cyclosporine dose more than 17% → imp
  - Levels too low: transplant rejection, organ failurer, death.
    - ↳ means low level of immunosuppression

most severe → leads to reject transplantation → ليش بنعطيهم ؟ حتى عنا غيرهم

Tacrolimus is more effective, but more probability to cause DM.

- ~~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

1) dihydroreductase inhibitors → inhibits purine synthsis
2) mercaptopurine and azothioprine → false metabolites act as stop codons and leads to stop cell cycle "S phase", and P53 "tumor suppressor gene" cause apoptosis

→ decrease DNA metabolites → decrease {T, B cells
bone marrow cells } replication → decrese rejection possibility.
not selective

- 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

→ better than anti metabolites, it is selective

MPA

- 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).

– 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. isn't used early
- 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.

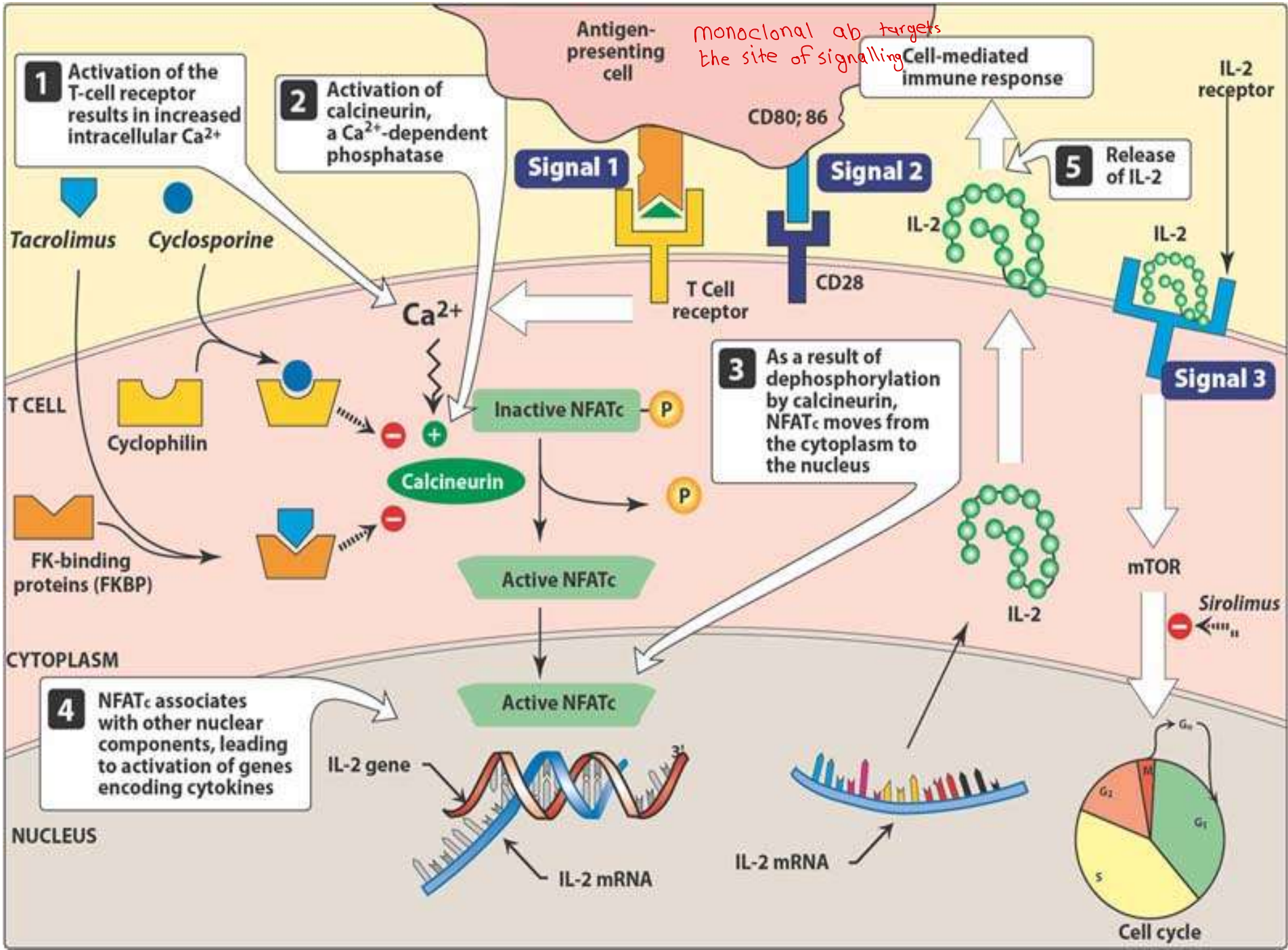
Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.

↓

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.


Antigen-presenting cell
monoclonal ab targets the site of signalling
Cell-mediated immune response
IL-2 receptor
1 Activation of the T-cell receptor results in increased intracellular Ca^{2+}
2 Activation of calcineurin, a Ca^{2+}-dependent phosphatase
CD80; 86
Signal 1
Signal 2
5 Release of IL-2
Tacrolimus
Cyclosporine
IL-2
IL-2
T Cell receptor
CD28
Ca^{2+}
3 As a result of dephosphorylation by calcineurin, $NFAT_c$ moves from the cytoplasm to the nucleus
Signal 3
T CELL
Cyclophilin
Inactive NFATc
P
Calcineurin
P
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'
IL-2 mRNA
IL-2 mRNA
NUCLEUS
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.

* اسماء ال drugs بهاي السلايد مش مطلوبة.

Anti CD3

"first monoclonal antibody"

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

- monoclonal antibodies have prolonged half life "weeks to months"
- monoclonal antibodies block either the receptor or ligand.

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

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."

- more humanized ab, more expensive, less rejection.

Both agents have been approved for prophylaxis of acute rejection in renal transplantation in combination with *cyclosporine/t*acrolimus and corticosteroids. → because it stays long time so 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.

However, it doesn't have high toxicity, because it deals with cellular 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/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.

الدكتور ماجد

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

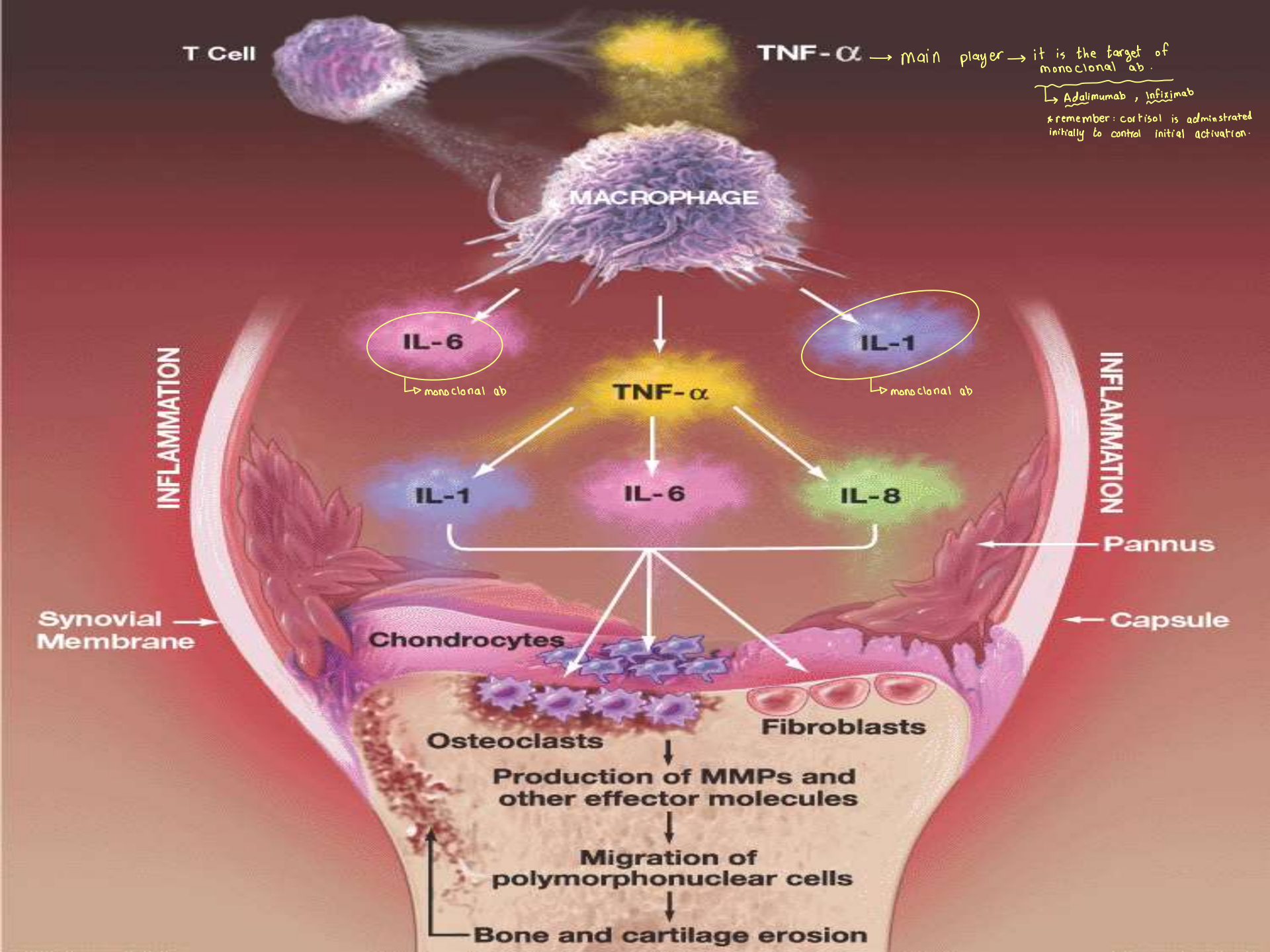
- An immune reaction against self
- Mechanism unknown, arises out of a failure in immune regulation
- Examples:
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Multiple sclerosis (MS)
  - Insulin-dependent diabetes mellitus
  - Many more

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 → main player → it is the target of monoclonal ab.
↳ Adalimumab , Infliximab
*remember: cortisol is administrated initially to control initial activation.
MACROPHAGE
IL-6
monoclonal ab
IL-1
monoclonal ab
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 → leads to death
  * عشان هيك ما بنطيهم لوقت طويل
- Remember

STOP if develop a fever, have an infection,

↳ يعني اذا صارلي fever معناه انه في infx وهذا الـ infx عم يكبر tb ← stop!!!

Rituximab

- Anti-B cell (CD20) antibody
- First approved in 1997 for use in B-cell lymphoma
- Given in combination with Methotrexate منهم
- Directed for patients who do not respond to Anti-TNF treatments
- Indicates the rheumatoid arthritis has a B cell component to its pathology → important → يعني ال B cells بتحبب بتشتغل لتزيد المرض فبنعطلها inhibition عشان يقل المرض

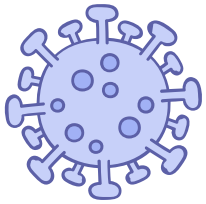
Anti-IgE Antibodies

Drugs that reduce the amount of IgE to mast cells

use in Atopic asthma
↳ Ig dependent

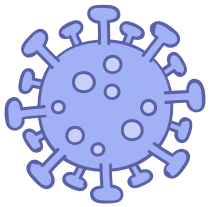
inhibits synthesis of IgE by B-lymphocytes

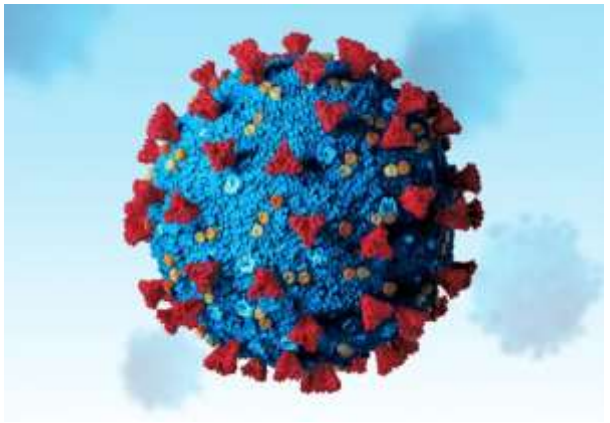
- **Omalizunab (anti-IgE Mab)**



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

Dr. Malik Zihlif





- Rapid replication of the virus increases the viral load and enJhances viral cytopathic effects
- This results in the rapid progression of the immunoinflammatory process leading to CSS (cytokine storm syndrome) and severe pneumonia.
  - it must be stopped by cortisol
  - anti-IL6 في حالة ما استجاب الى بنطيه
  - Personalized لازم نعمل
  - High IL6 level → anti IL6 بنطي
  - Low → No
- **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

ال trials مش مطلوبات

- 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).

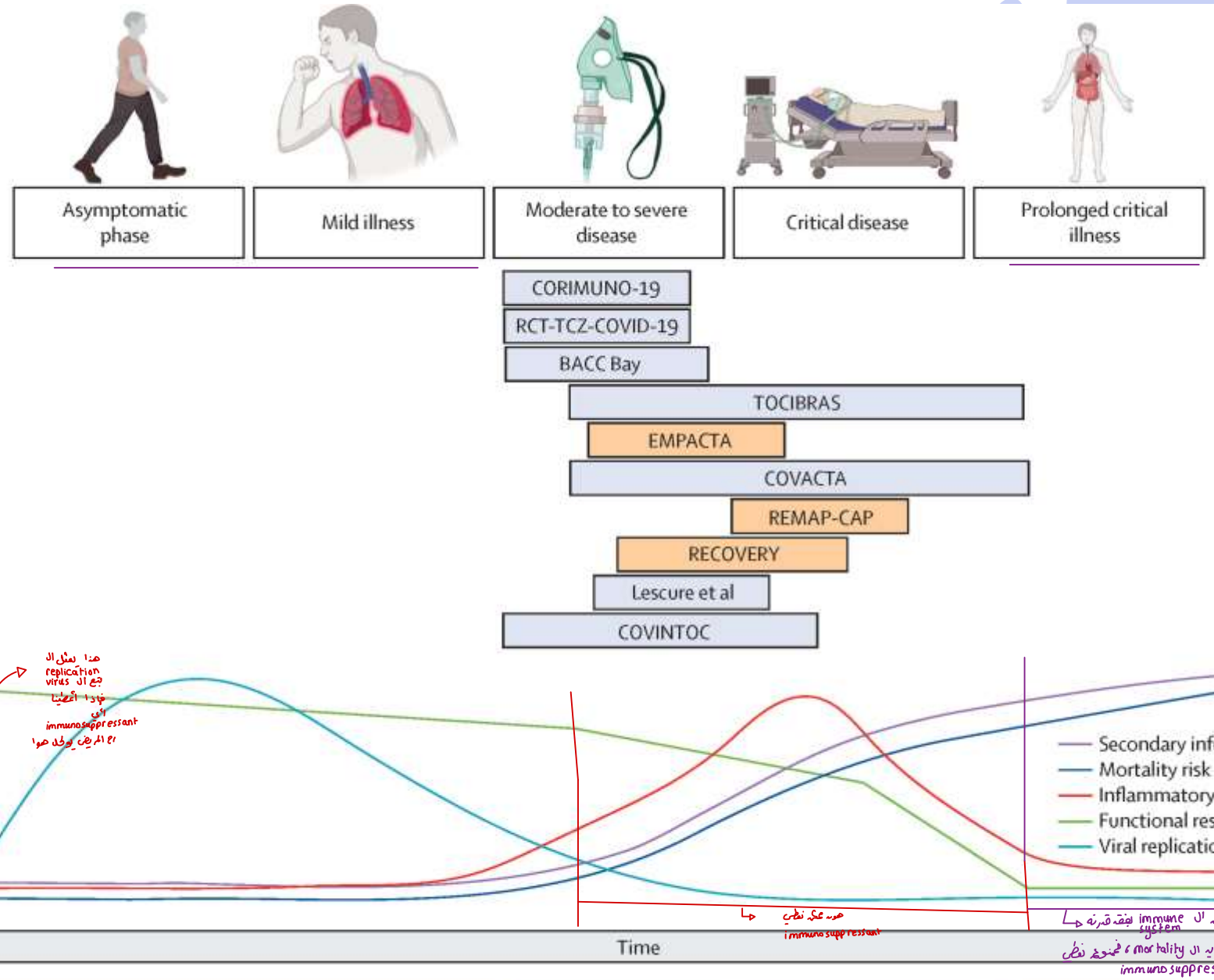
- The efficacy of IL-6 targeting depends on:
  - The underlying health status of the patient
  - The severity of the disease
  - The timing of the intervention.

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

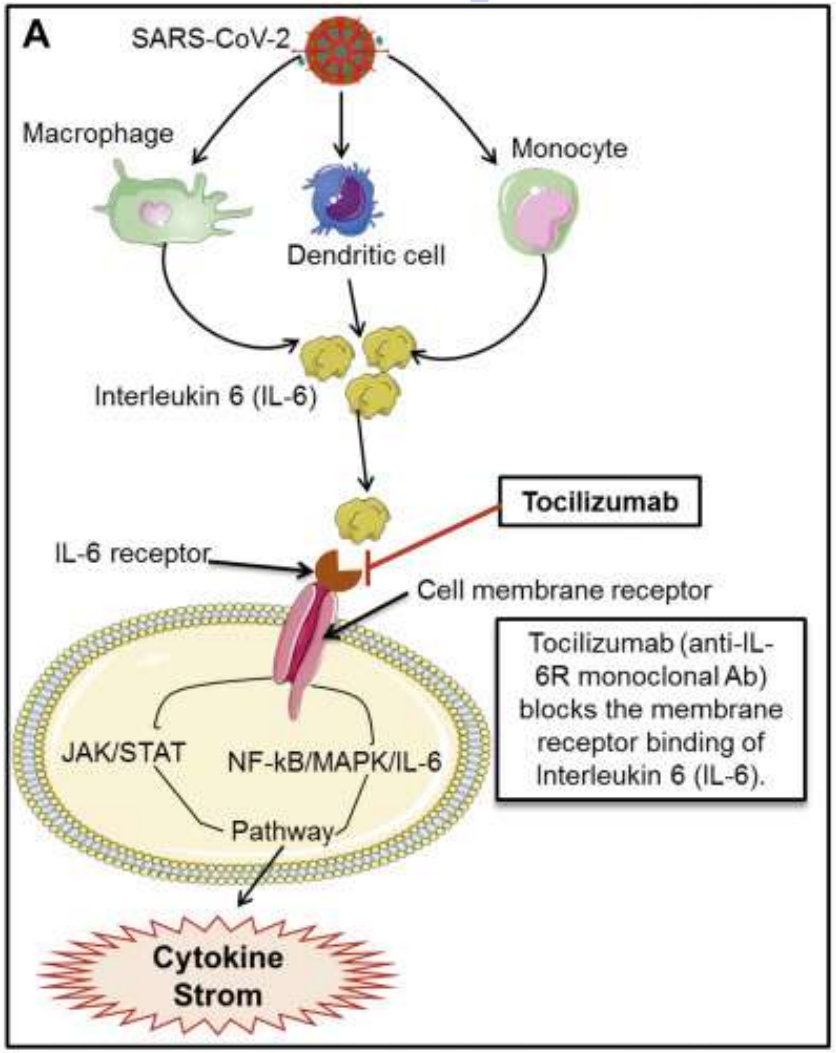
- Encouragingly, the incidence of adverse events in relevant trials appear minimal likely owing to the targeted (1–2 doses) use of these antagonists in COVID-19


Clinical stage
Asymptomatic phase
Mild illness
Moderate to severe disease
Critical disease
Prolonged critical illness
Evidence from RCTs
CORIMUNO-19
RCT-TCZ-COVID-19
BACC Bay
TOCIBRAS
EMPACTA
COVACTA
REMAP-CAP
RECOVERY
Lescure et al
COVINTOC
Main physiological features
Secondary infection risk
Mortality risk
Inflammatory response
Functional reserve
Viral replication
Time
Potential role of IL-6R blockade
Probably no role for IL-6R blockade
Potential role in decreasing the need for ICU admission
Ideal time window for intervention?
Multiorgan failure; potential harm

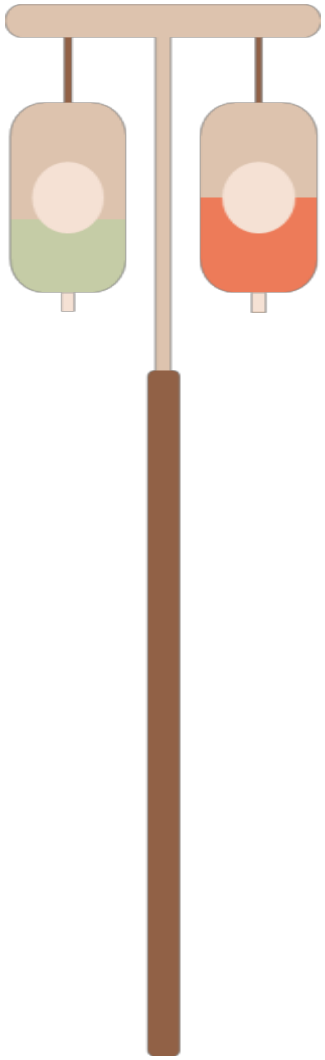
IL-6 Inhibitors

- **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


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

IL-17 & IL-17 inhibitors



IL-17 physiological role

- IL-17, **a proinflammatoy 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.

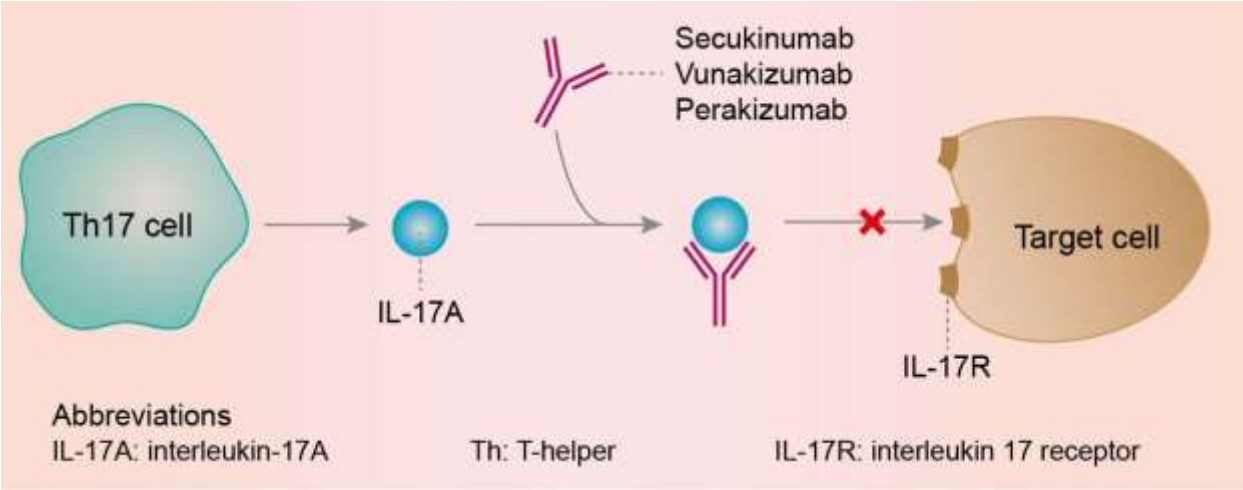
- As a result, the disruption of IL-17 production can lead to autoimmune diseases and tissue destruction. **Excessive** levels of IL-17 in the body are associated with the development and exacerbation of several autoimmune diseases.

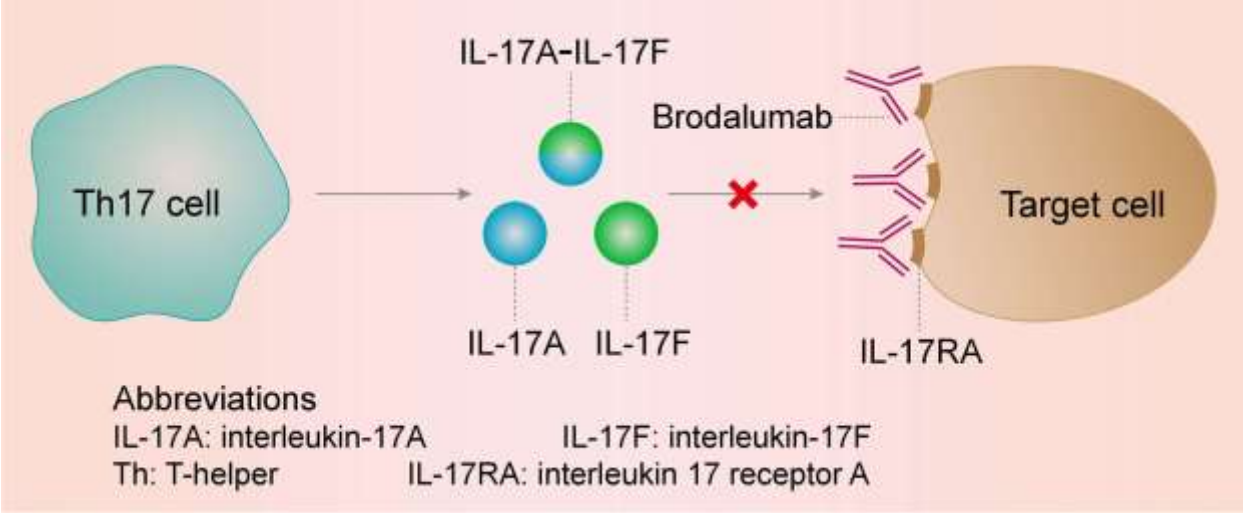
IL-17 inhibitors- **Secukinumab**

- **Secukinumab** is a recombinant human IgG1/kappa mAb
  - target the ligand "not the receptor"
- 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 (الصدفية)
- 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

المشكلة هون انه الcancer بصير بدون ما ال immune sys يعرف ، فلازم نزيد قدرته 😊

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

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

BCG vaccine in bladder cancer.

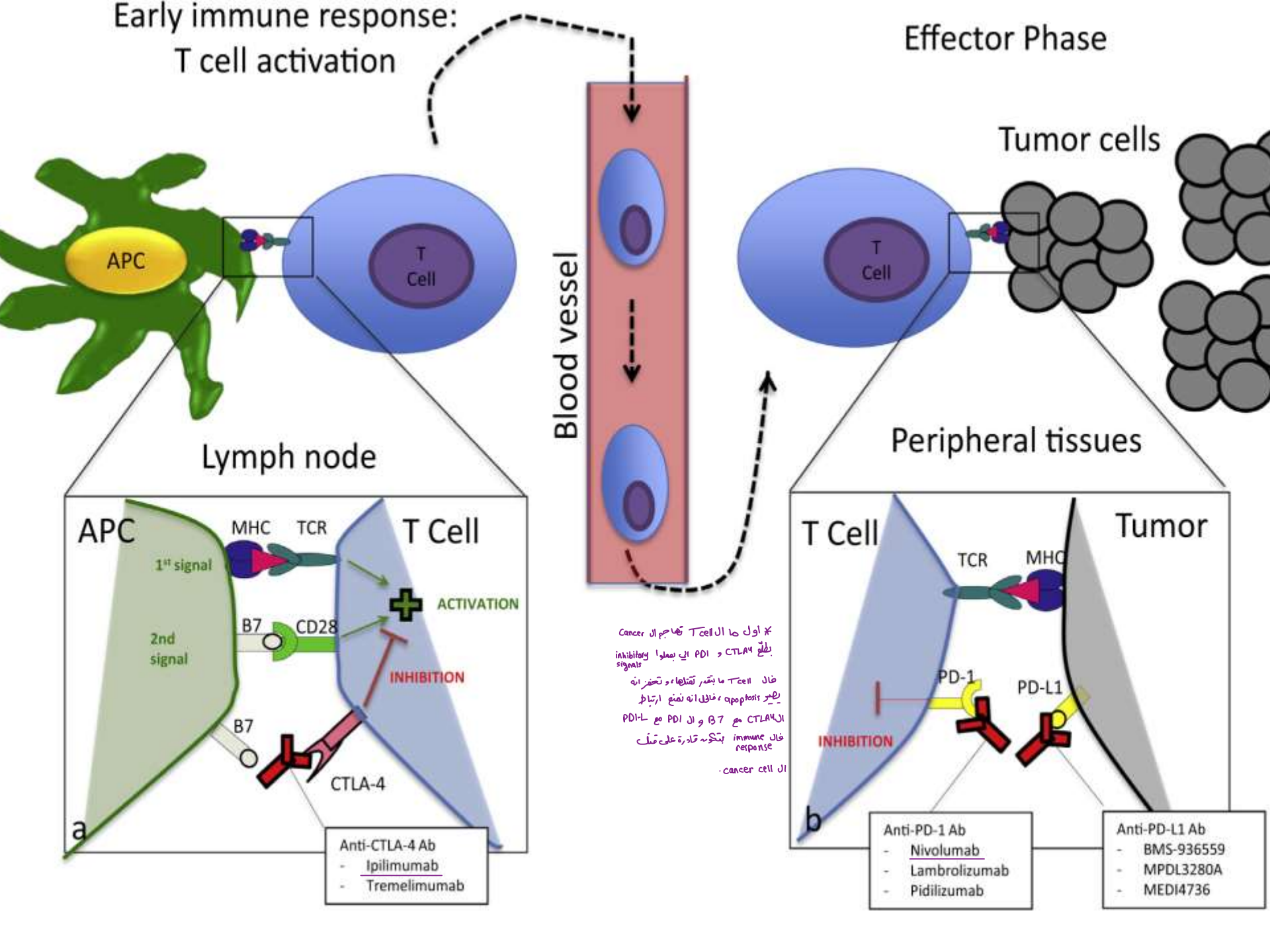
Cytokines

- 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



* أول ما الـ T cell تهاجم الـ cancer بتطلع CTLA4 و PD1 اللي بعملوا inhibitory signals فالـ T cell ما بتقدر تقتلها، و تحفز انه يصير apoptosis، فالحل انه نمنع ارتباط الـ CTLA4 مع B7 و الـ PD1 مع PD1-L فالـ immune response بتكون قادرة على قتل الـ cancer cell.