

Immunosuppressant drugs

- بِسْمِ اللَّهِ نَبْدَأُ..

- the main principle for create this type of drugs was alternative T lymphocyte to enhance the Lymphocyte function وتحديداً الـ body immunity rather than antibody

Pharmacology 3 Dr.

Rawan Abudalo

Department of Clinical Pharmacy and Pharmacy Practice

Faculty of Pharmaceutical Sciences

Hashemite University

IMMUNE SYSTEM

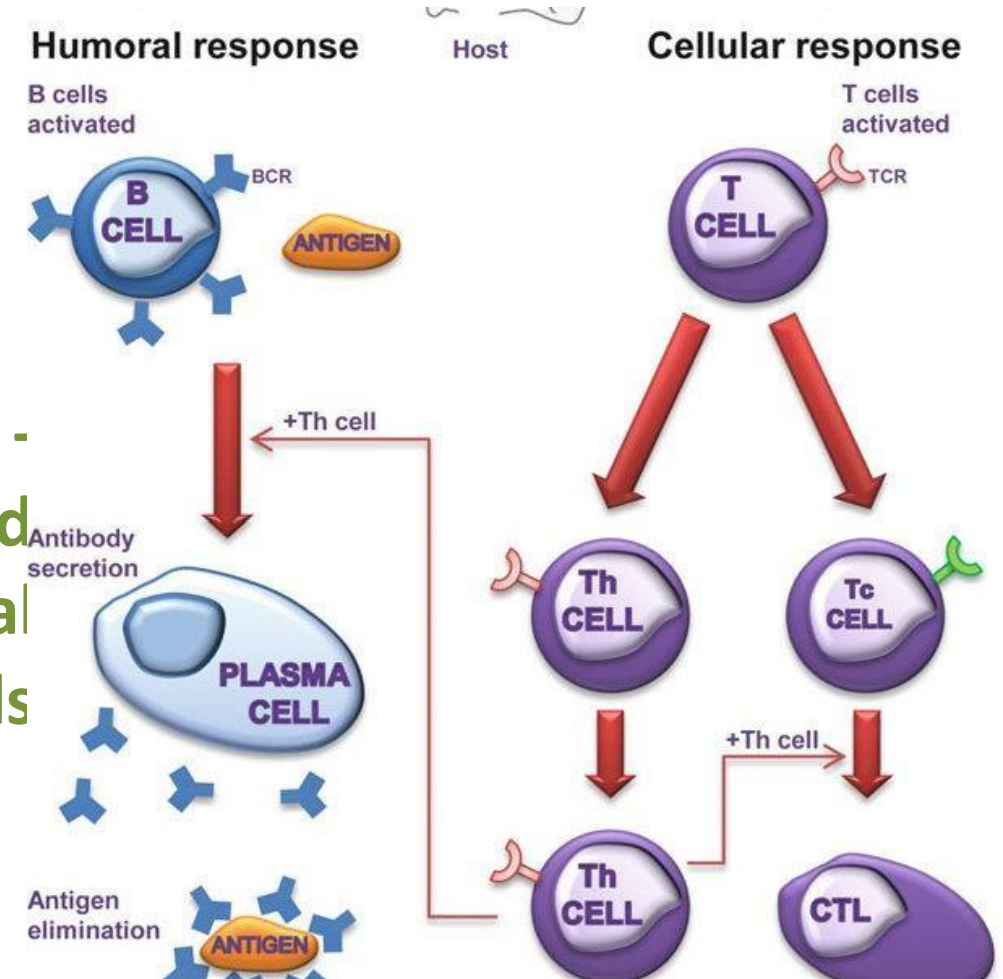
Immune system include two main arms

1) Cell –mediated immunity.

Cell mediated immunity unnder control بينما ال -
by T cells Or T lymphocyte and it activated
microphages and and another cells like normal
kill cells . ✓

.2Humoral (antibody –mediated
immunity).

Humoral unnder control by تُعتبر ال -
lymphocyte



Cell-mediated Immunity

- بتلعب دور مُهم جداً بال Organs rejection (الرفض
المناعي لنقل الأعضاء).

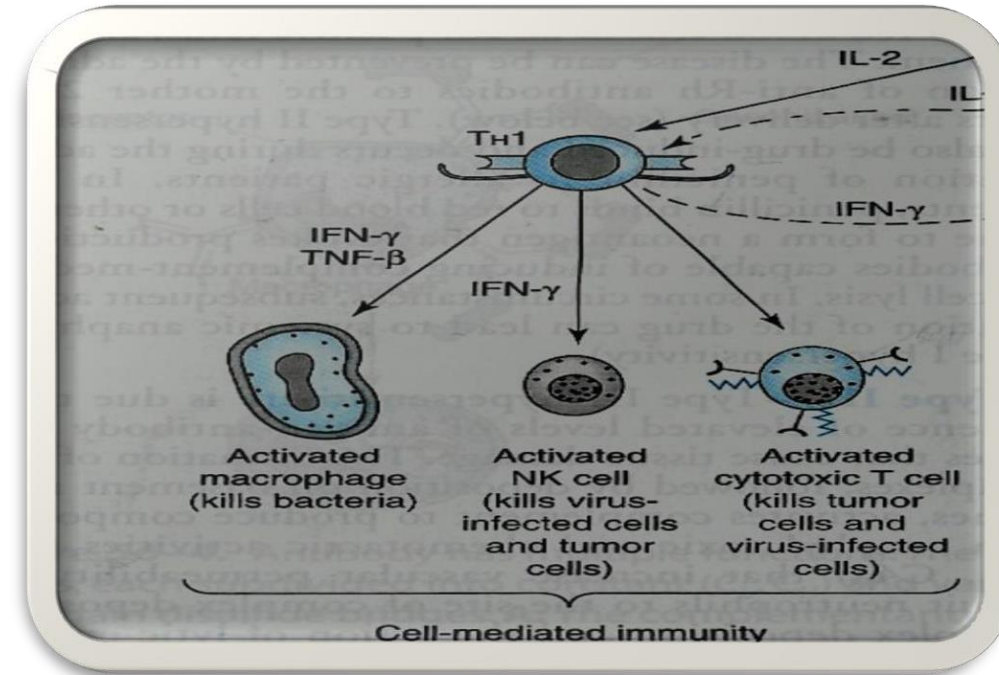
TH1 produce more IL-2, TNF- β and IFN- γ .

Activate:

NK cells (kill tumor & virus- infected cells).

Cytotoxic T cells (kill tumor & virus- infected cells).

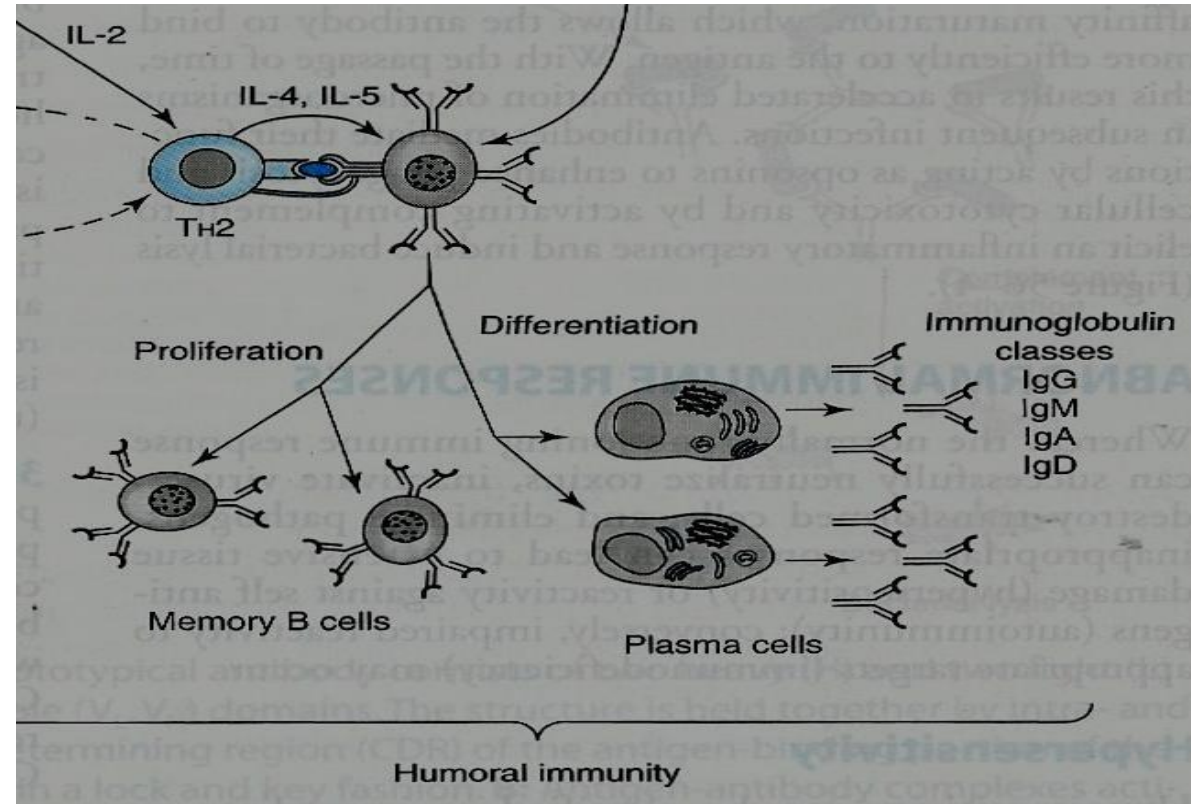
Macrophages (kill bacteria).



Humoral Immunity

B-lymphocytes :
TH2 produces (interleukins) which in turn causes:

- B cells proliferation & differentiation into
- Antibody secreting plasma cells



Immune system activation

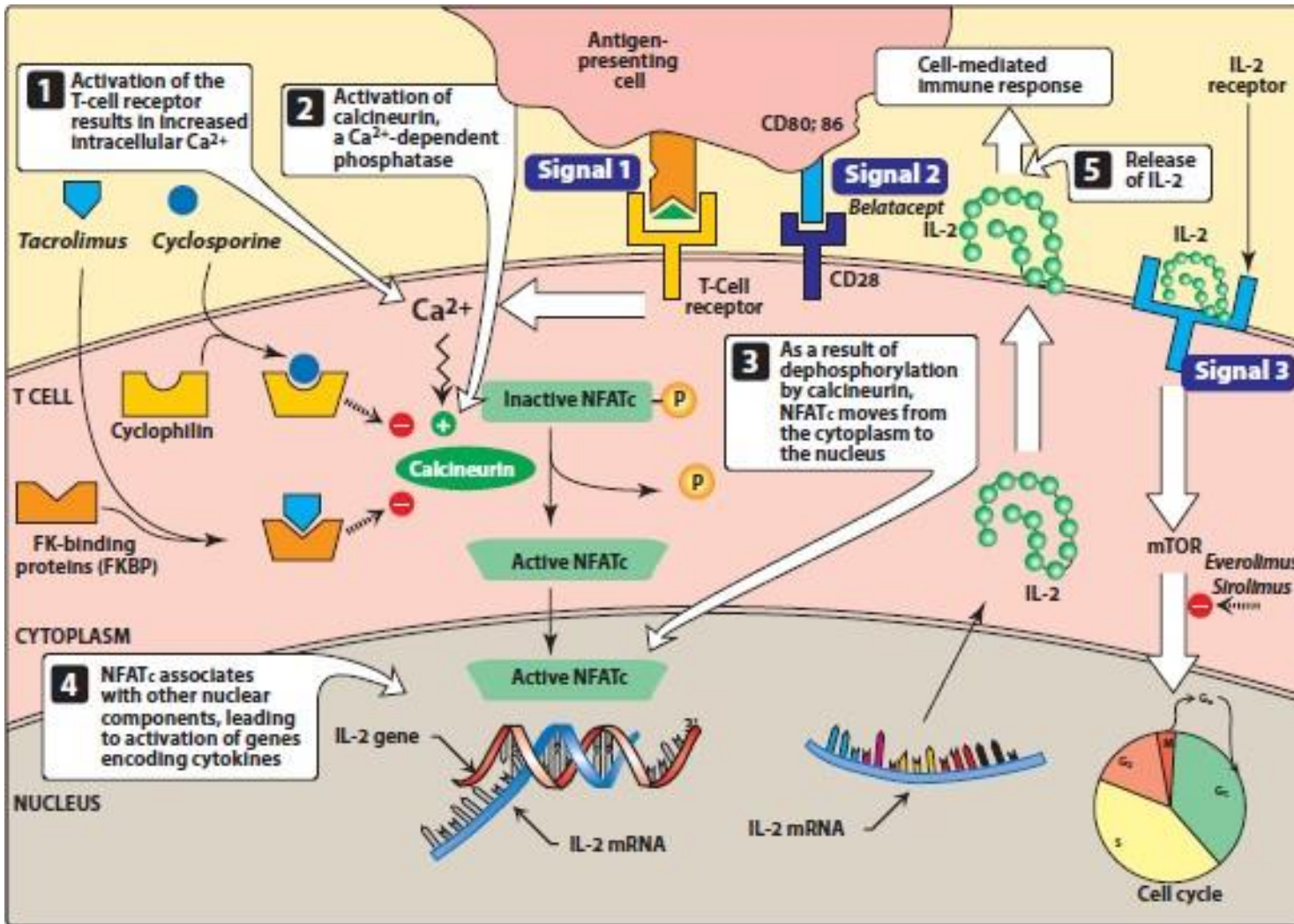
- The immune activation cascade can be described as a three-signal model:
- Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC).
- Signal 2, also referred to as co-stimulation, occurs when CD80 and CD86 on the surface of 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**.

- These pathways trigger the production of cytokines such as interleukin (IL)-2.
- IL-2 then binds to CD25 (also known as the IL-2 receptor) on the surface of other T cells to activate mammalian target of *rapamycin* (mTOR), providing signal 3
- Signal 3, the stimulus for T-cell proliferation.

Immune activation cascade

اللي أنتو شايفينه بالصورة
 هو عبارة عن ال steps
 which the immune
 system used to make
 immunity، فكل اللي رح
 نحكي عنه بهاد الجزء هو
 كيف أدوية ال
 immunosuppressant
 بتشتغل عن طريق تثبيط
 هاي الخطوات as a
 target site.



Mechanism of action of immunosuppressive agents. IL-2 = interleukin-2;
 mTOR = mammalian target of rapamycin;
 NFATc = cytosolic nuclear factor of activated T cells; mRNA = messenger
 RNA.

- Immunosuppressive drugs can be categorized by their mechanism of action:

- 1) interference with cytokine production or action.

- في أدوية رح تلعب على ال Cytokine 2 ✓.

- 1) disruption of cell metabolism, preventing lymphocyte proliferation.

- أو أدوية بتعمل preventing lymphocyte proliferation (يعني بتقلل عُمرها) ✓.

- 1) mono- and polyclonal antibodies that block T-cell surface molecules.

- هاي النقطة ما رح نحكي عنها (حاجة حلوة في المادة العفشة دي 😊)، بس إجمالاً هاي الأدوية

- بتلعب على ال block of receptors of T-cell عن طريق ال inhibition of signal 2 which

- 1 ✓ restimulate signal.

IMMUNOSUPPRESSANT DRUGS

I. inhibitors of cytokine (IL-2) production or action:

1) Calcineurin inhibitors

- Cyclosporine

- Tacrolimus (FK506)

2) Sirolimus (rapamycin).

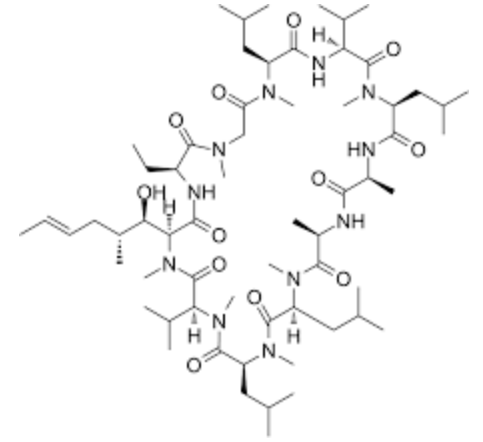
II. Inhibitors of cytokine gene expression

● Corticosteroids

- تُعتبر الـ Corticosteroids is the most famous familiar as immunosuppressive drugs.

CYCLOSPORINE

- قبل ما نبدأ نحكي عن الأدوية، لازم تعرفوا إنه رح تشوفوا أغلب الـ immunosuppressive drugs was taken as a combination to try used a lowest dose to prevent adverse side effects. ✓



Chemistry

- Cyclosporine is a a cyclic polypeptide

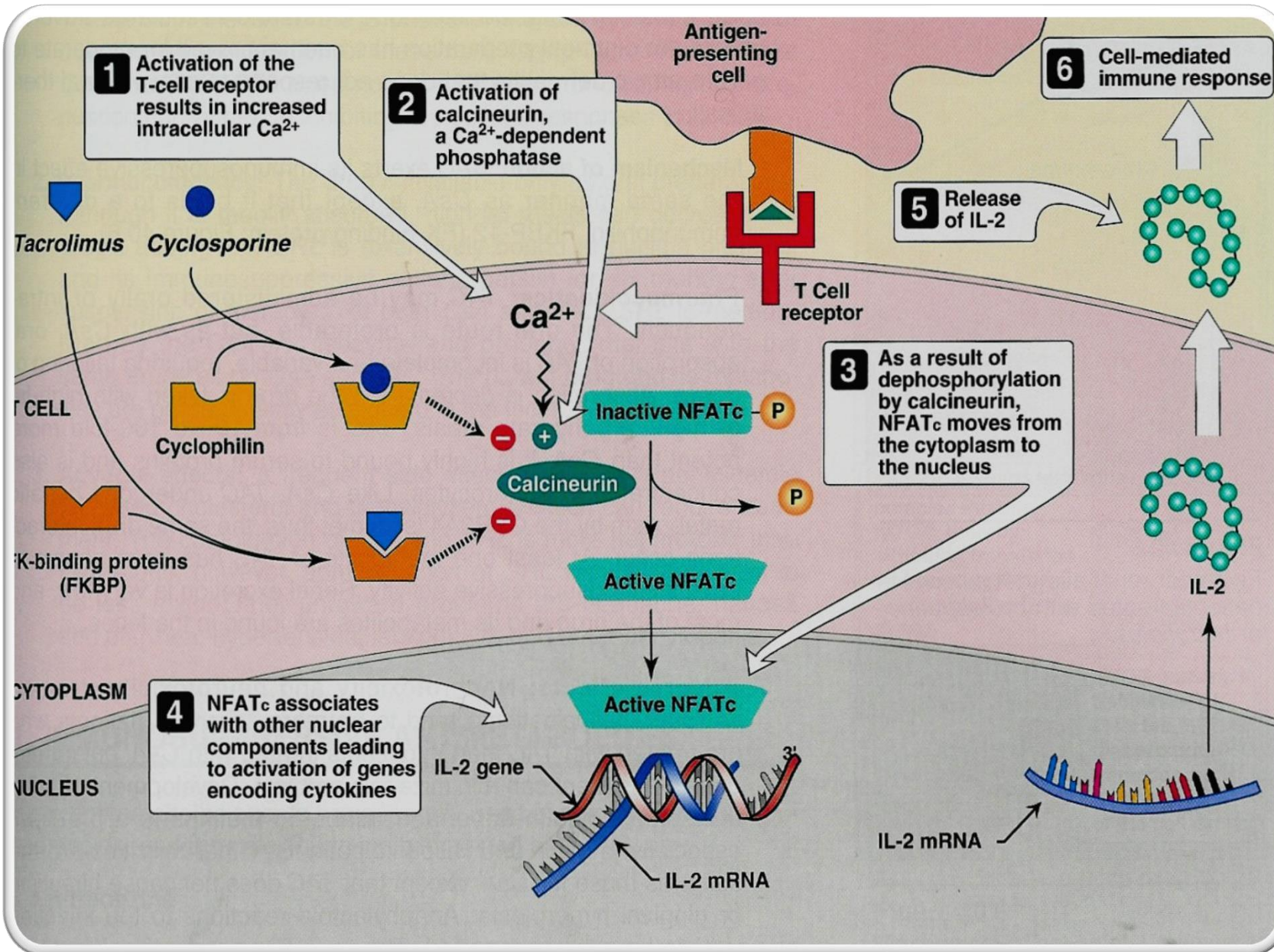
Mechanism of action:

- Acts by blocking activation of T cells by inhibiting interleukin-2 production (IL-2).

- بعمل شُغله هاد من خلال الـ action on Calcineurin. ✓

- Decreases proliferation and differentiation of T cells.

- Cyclosporine binds to **cyclophilin (immunophilin)** intracellular protein receptors.
- Cyclosporine- immunophilin complex inhibits calcineurin, a phosphatase necessary for dephosphorylation of transcription factor **(NFATc)** required for interleukins synthesis (IL-2).
- **NFATc (cytosolic nuclear factor of activated T cells).**
- Suppresses cell-mediated immunity.



ال - Cyclosporine inhibits
 - inteoking formation be cause
 Cyclosporine will bind
 binding ، و هاد ال Cyclophilin
 inhibits Calcineurin
 inhibition of Calcineurin wil
 ..inhibition of NFACT
 - طبعاً صغاري هاد ال NFATc لو صوله
 dephosphoralation رح يعمل
 2.production of IL-

Pharmacokinetics:

- Can be given orally or i.v. infusion
- metabolized by CYT-P450 system (CYP3A4).

مُشكّلتِي أنا بال metabolism إنها بتسمح لـ Cyclosporine إنه تزيد ال-
Bioavailability (يعني بالنهاية الدواء بطلع برا الخلية ربصرله bad of
(absorption).

- excreted mainly through bile into faeces, about 6% is excreted in urine

Therapeutic Uses:

- Organ transplantation (kidney, liver, heart) with other immunosuppressive agents (Corticosteroids).
- هو دوا فعّال جداً في Organ transplantation (وزي ما حكينا أوّل شي إنّّه لازم يكون عندي combination؛ فهون بصرله combination with Corticosteroids).
- Treatment of psoriasis, rheumatoid arthritis and a variety of other autoimmune diseases

Adverse Effects (Dose-dependent) Therapeutic monitoring is essential

- أهم حاجة كذاكي تكون عامل dose calculation for limit a toxicity of these drugs



● Nephrotoxicity

(increased by NSAIDs and aminoglycosides).

- تخيل يا رعاك الله لو في لحظة تهور ما حسبت جرعة الـ Cyclosporine وأعطيته لشخص بوخد NSAIDs and aminoglycosides!، ساعتها بنوقفلك مُحامي يدافع عنك تخافش



● Liver dysfunction.

● Hypertension, hyperkalemia.

- كثير مُهم تنتبه على مُستوى البوتاسيوم مع هاد النوع من الأدوية، وخاصةً لو تأخذ مع أدوية بترفع بوتاسيوم الدم.

● Hirsutism

● Neurotoxicity (tremor).

Drug Interactions

- Clearance of cyclosporine is enhanced by co- administration of CYT p 450 inducers (*Phenobarbitone, Phenytoin & Rifampin*) → ???????

- يعني ما بلحق يحكي ال Cyclosporine يا هادي إلا وهو طالع من الجسم بسبب الأدوية الثلاث هدول الي يعتبرهم increased in hepatic metabolism 😊.

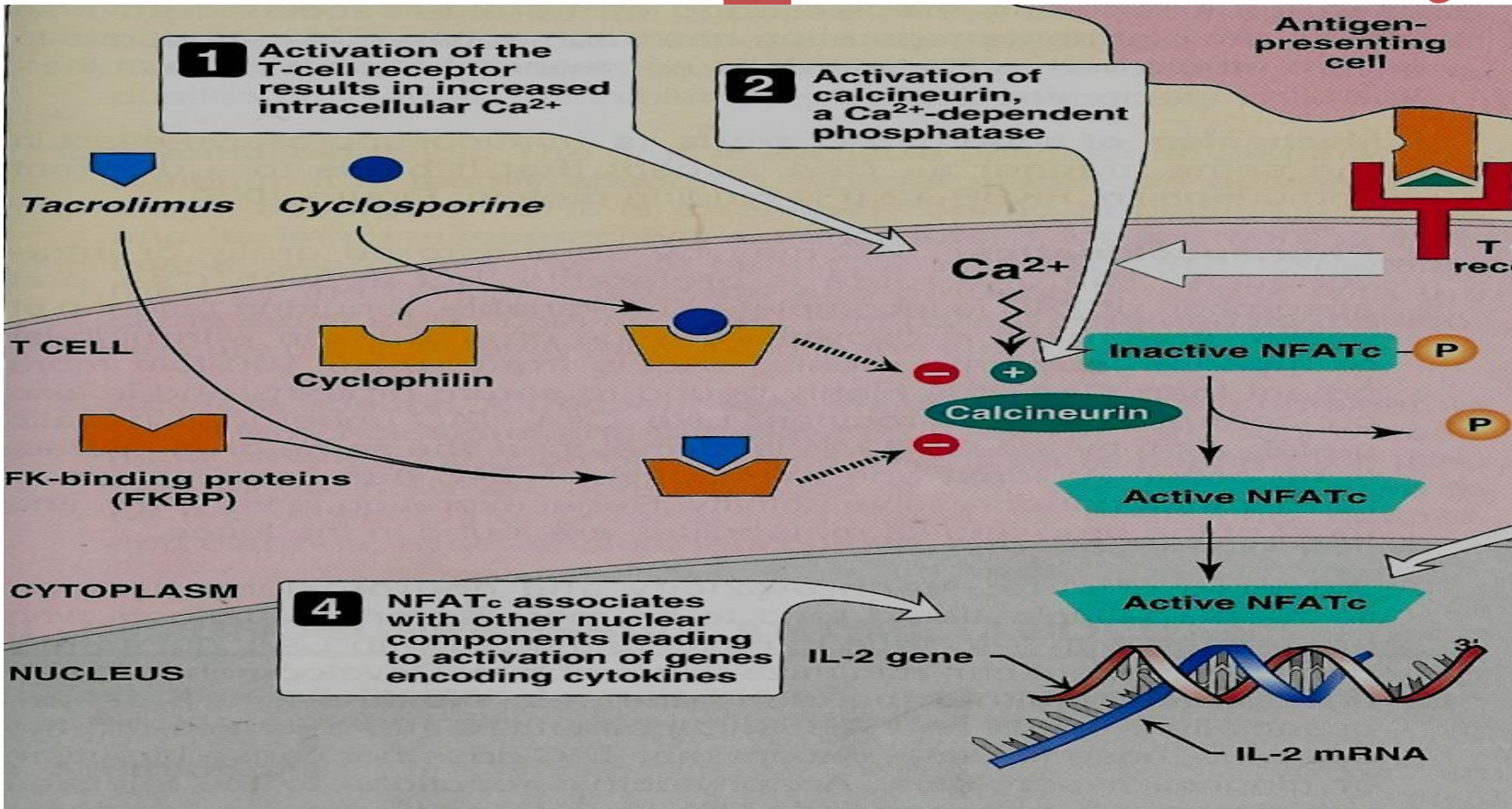
- Clearance of cyclosporine is decreased when it is co-administered with *erythromycin or Ketoconazole, Grapefruit juice* → ?????????

- هون في أدوية بتعمل العكس، بتعمل inhibition of cyclosporine metabolism (ووقتها هيفرقع المريض منّا والله 😞).

TACROLIMUS

- Chemically not related to cyclosporine
- both drugs have similar mechanism of action .

- نفس ال MOA لـ CYCLOSPORINE ✓ .



- لكنه يرتبط بـ Receptors ثانيين، زي الـ ..FKBP

وهاد الـ Binding again will causing inhibition of Calcineurin and in similar to cyclosporine, the binding of tarclimus will prevent formation of IL-

✓ 2

Kinetics

- Given orally or i.v or topically (ointment).

- يستخدم موضعي كونه بعالج ال a topic dermatitis (الأكزيما).

- Oral absorption is variable and incomplete metabolized by P450 in liver.
- Excreted mainly in bile and minimally in urine.

USES as cyclosporine

- Prevention of rejection of liver and kidney transplants (with glucocorticoids).
- Atopic dermatitis and psoriasis (topically).

Toxic effects

- تقريباً عنده .toxic effects similar to cyclosporine

- Nephrotoxicity (more than CsA)
- Neurotoxicity (more than CsA)
- Hyperglycemia (require insulin).
- Hyperkalemia
- Hypertension

NO hirsutism or gum hyperplasia

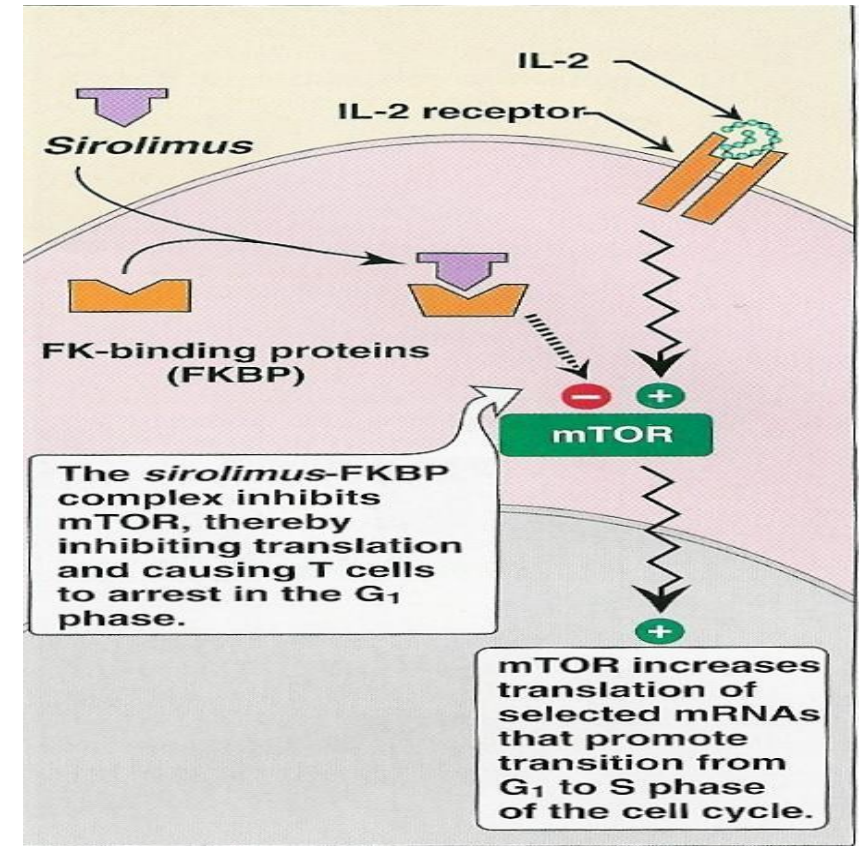
- هاد الشي مش موجود بال Tacrolimus، على خلاف ال Cyclosporine.

- Drug interactions as cyclosporine.

Sirolimus (Rapamycin)

- Is derived from fungus origin.
- It binds to FKBP resulting in an active complex that inhibits the kinase activity of mammalian target of rapamycin(mTOR)
- inhibition of T lymphocyte proliferation by بعمل -
✓ inhibition of MTOR or rapamycin
- mTOR is serine-threonine kinase essential for cell cycle progression, DNA repairs, protein translation.
- SRL blocks the progression of activated T cells from G1 to S phase of cell cycle (Antiproliferative action).
- It Does not block the IL-2 production but blocks T cell response to cytokines.

- على خلاف الـ Cyclosporine and Trichomonas، الـ Sirolimus ما إله تأثير على الـ IL-2.



- إحنا حكيينا لو ارتبط الـ IL-2 بمستقبلاته؛ فهاد رح يعمل Stimulation of T lymphocyte proliferation وهاي الـ metabolism can be inhibited by Sirolimus.

Pharmakinetics

- Given orally and topically, reduced by fat meal.
 - decrease in absorption of Sirolimus **الـ fat meal يعمل بتعمل**
- Extensively bound to plasma proteins
- metabolized by CYP3A4 in liver.
- **Excreted in feces.**

Pharmacodynamics

- Immunosuppressive effects
- Anti- proliferative action.

Toxic effects

Hyperlipidaemia (cholesterol, triglycerides).

- بزيد مُستويات الكوليسترول والـ **triglycerides**.

Thrombocytopenia

-Affect on amounts of platet in blood and causing
Thrombocytopenia .

Leukopenia

-Decrease the white blood cells .

GIT dysfunction

- ومُمكن يسبّب **vomiting and diarrhea**.

Inhibitors of cytokine gene expression

Corticosteroids


- **Prednisone**

- هاد prodrug.

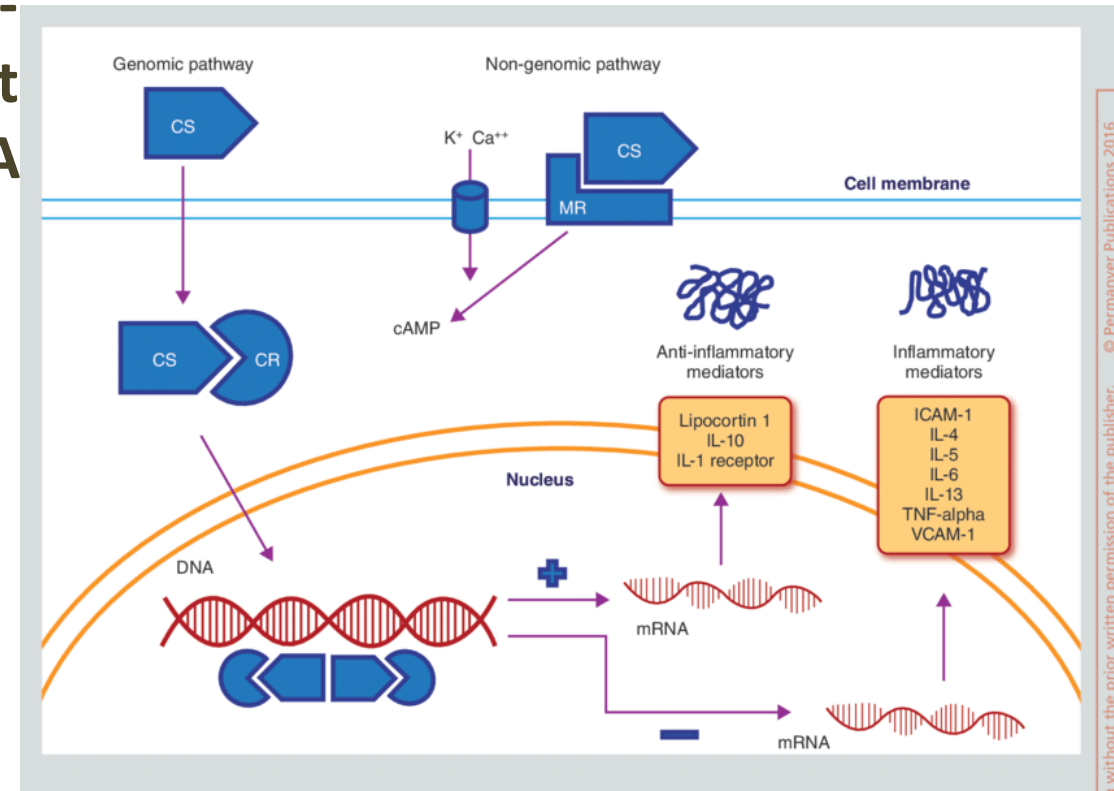
- **Prednisolone**
- **Methylprednisolone**
- **Dexamethasone**

They have both anti-inflammatory action and immunosuppressant effects.

Mechanism of action

MOA of Corticosteroids as a J1-immunosuppressive drugs is complex because it  has a MultiMOA

- bind to glucocorticoid receptors and the complex interacts with DNA to inhibit gene transcription of inflammatory genes.
- Decrease production of inflammatory mediators as prostaglandins, leukotrienes, histamine,
- Decrease production of cytokines IL-1, IL-2, interferon, TNF.
- Stabilize lysosomal membranes.
- Inhibit antigen processing by macrophages.
- Suppress T-cell helper function
- decrease T lymphocyte proliferation.



Kinetics

Can be given orally or parenterally.

- في منها topically عادي، بس كـ Anti-inflammatory effect only.

Dynamics

1. Suppression of response to infection
2. anti-inflammatory and immunosuppresant.
3. Metabolic effects.

- بتأثر على الـ Ca and glucose، وكمين بتزيد الـ gastric acid production. 

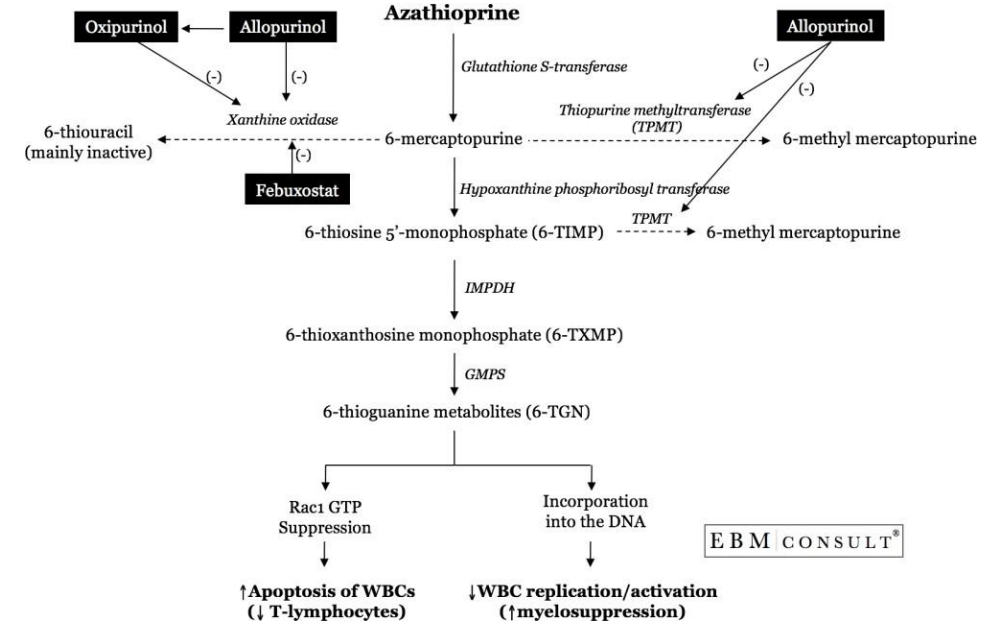
Indications

- are first line therapy for organ allografts & haematopoietic stem cell transplantation.
- Allografts = from person to another person .
- Autoimmune diseases as refractory rheumatoid arthritis, systemic lupus erythematosus, asthma.

AZATHIOPRINE

CHEMISTRY:

- Derivative of mercaptopurine.
- Prodrug.
- Cleaved to 6-mercaptopurine then to 6-mercaptopurine nucleotide, thioinosinic acid (nucleotide analog).
- Inhibits de novo synthesis of purines required for lymphocytes proliferation.



-هاي الصورة حكت الدكتور مش مهمة (لأنها بدعاش تفاصيل).

احتفلوا هون عالصيق عشان بتكونوا خلصتوا دراسة المادة



Pharmacokinetics

- orally or intravenously.
- Widely distributed but does not cross BBB.

Drug Interactions:

- Co-administration of allopurinol with azathioprine may lead to toxicity due to inhibition of xanthine oxidase by allopurinol.

- بما إنه بتحوّل لـ 6-mercaptopurine؛ فأنا بعرف إنه ال side effects

.  enirupotpacrem-6 and drug Interactions are similar to

USES

Systemic lupus erythematosus

Rheumatoid arthritis

Crohn's disease.

S/E: myelosuppression

Mycophenolate mofetil

- Is a semisynthetic derivative of mycophenolic acid from fungus source.
- **Prodrug**; is hydrolyzed to **mycophenolic acid**.

Mechanism of action:

- **Inhibits *de novo*** synthesis of purines.
- mycophenolic acid is a potent inhibitor of inosine monophosphate dehydrogenase (IMP), crucial for purine synthesis
→ deprivation of proliferating T and B cells of nucleic acids.

