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.**

All types of rejection should be prevented

- 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

Immunosuppressive drugs work impressively well, to the point we routinely prescribe prophylactic medications, such as antimicrobials, for opportunistic infections.

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** alter gene expression to reduce T cell proliferation.
- **Calcineurin inhibitors** Main stream immunosuppressants
  - Ciclosporin A
  - Tacrolimus
- **IL-2 receptor 'mabs'**
  - Basiliximab
  - Daclizumab

IL-2 plays a major role in rejection + migration and proliferation of immune cells

- **Anti-metabolites** also used in cancer therapy
  - Azathioprine

    6-mercaptopurine (its active metabolite), is used in Acute lymphocyte leukemia (ALL) for induction + maintenance. In immunosuppression a lower dose is sufficient.
  - 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.

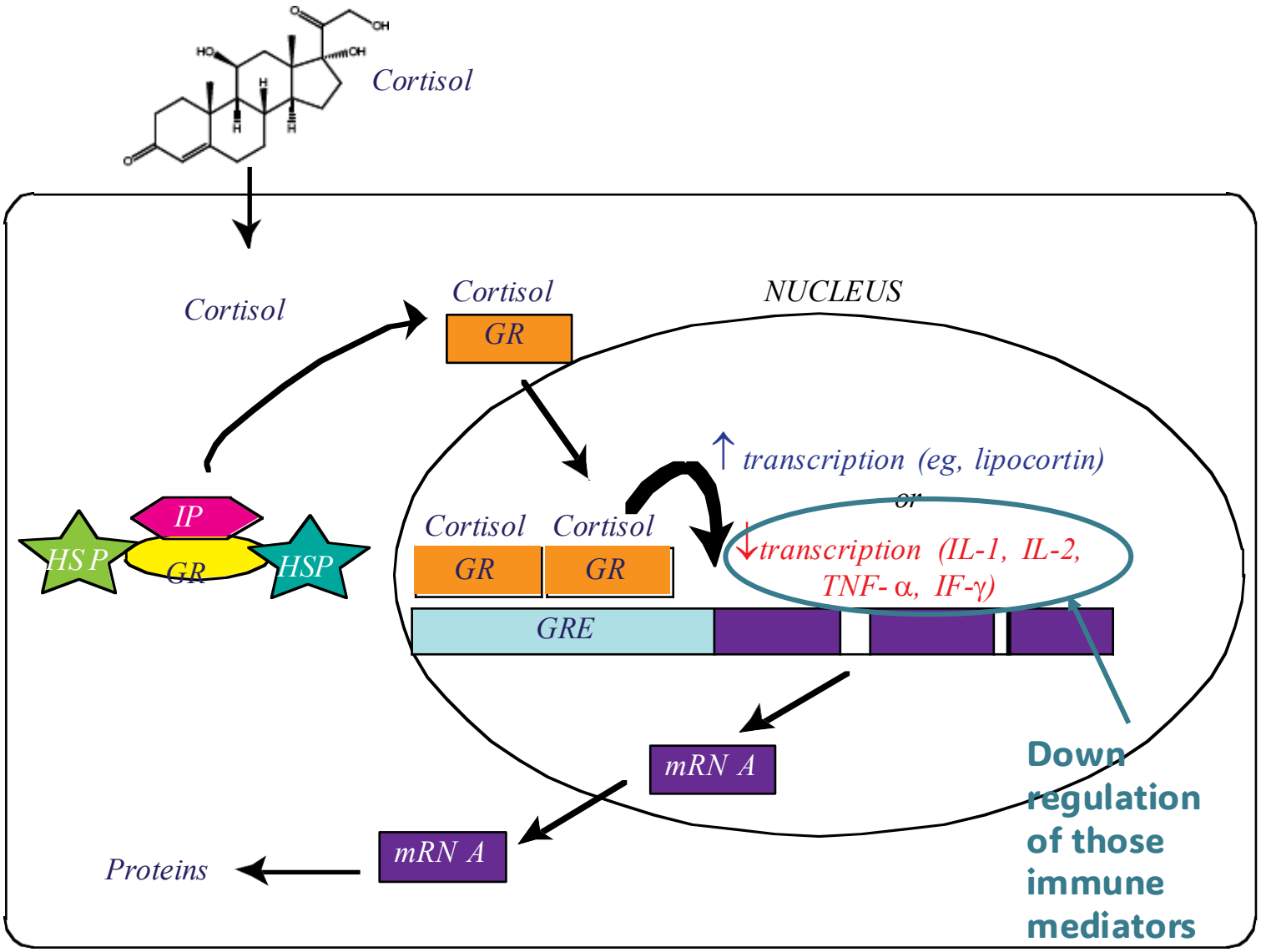
- Smaller cytokine production reduces the T cell proliferation.

- 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 important**

Glucocorticoids Regulate Transcription



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

Glucocorticosteroids Mechanism of Action

Glucocorticoids are magic drugs, that can the alter gene expression of up to 1500 genes!

As shown in the previous diagram glucocorticoids bind to intracellular receptors that translocate into the nucleus and regulate gene expression.

They down regulate immune mediators, namely IL-2 which is responsible for autocrine/paracrine stimulation of T cells proliferation.

Glucocorticoids also upregulate lipocortin a protein that inhibits phospholipase A2 and reduces production of inflammatory modulators thus responsible for inducing anti-inflammation.

Glucocorticoids have a variety of usage: their main use is immunosuppression but they are also useful in treating asthma/allergic rhinitis.

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. **Via their anti-inflammatory action**

Side effect

- **Immunodeficiency**
- adrenal glands **when used for longer than 21 days**
- Hyperglycemia Fat redistribution
- growth failure, delayed puberty.
- excitatory effect on central nervous system (euphoria, psychosis) **+ depression**

- Osteoporosis
- Cataracts **glaucoma (increase in eye pressure)**
- Gastric ulcers (prevent with omeprazole, misoprostol)
- **Hypertension**

Very important

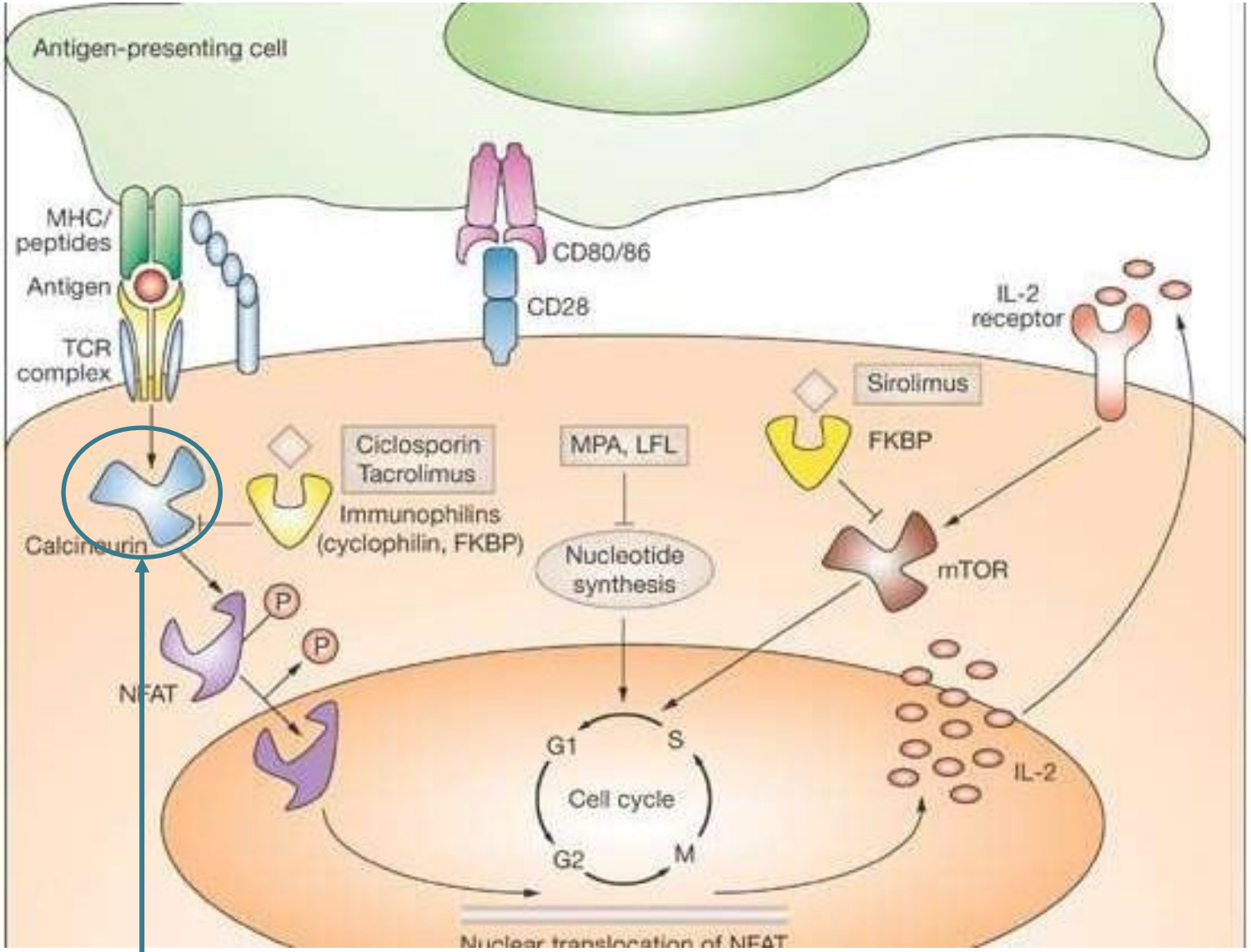
Calcineurin Inhibitors
Cyclosporine & Tacrolimus

1. human organ transplantation,

2. graft-versus-host disease after hematopoietic stem cells transplantation, **basically the blood and immune cells are donor derived whilst the organs and tissues are the recipient's. The graft is the immune cells themselves!**
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.

Their sole use is immune suppression



Calcineurin activates NFAT that translocate to the nucleus, as a transcription factor, and induces IL-2 production.

Complexity

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

Detrimental in Kidney transplantation since too high-> toxicity but too low-> rejection

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

Very effective drugs that can't be avoided. Constant drug level monitoring is essential. A specific concentration is calculated based on body weight, liver enzymes (polymorphism causes variation in their activity). Contraindicated if drug level monitoring is unavailable. Other drugs metabolized by CYP3A4 such as rifampicin can also alter calcineurin inhibitor levels.

- 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. **Proof of renal activity**
- Renal function.
- Hepatic function. **Ex. ALT,AST enzymes**
- Blood pressure. **Anti-hypertensive drugs may be prescribed**
- serum cholesterol. **Increases slightly, we prescribe statins**
- **Blood Glucose.**

You may be asked which drug "causes diabetes", important to note that tacrolimus raises blood sugar even more so than cyclosporine. Though generally Tacrolimus is less toxic than cyclosporines in all other parameters (hyperlipidemia, liver toxicity, hypertension), blood sugar levels is the exception. So, we almost always prefer Tacrolimus, except in patients with diabetes mellitus or high risk of diabetes, we prefer cyclosporines instead.

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.

Good substitute for cyclosporine (2nd option)

Sirolimus (RAPAMUNE)

Inhibits immune cell growth through inhibiting the kinase activity of mammalian target of rapamycin (mTOR) and decreasing IL-2 activities.

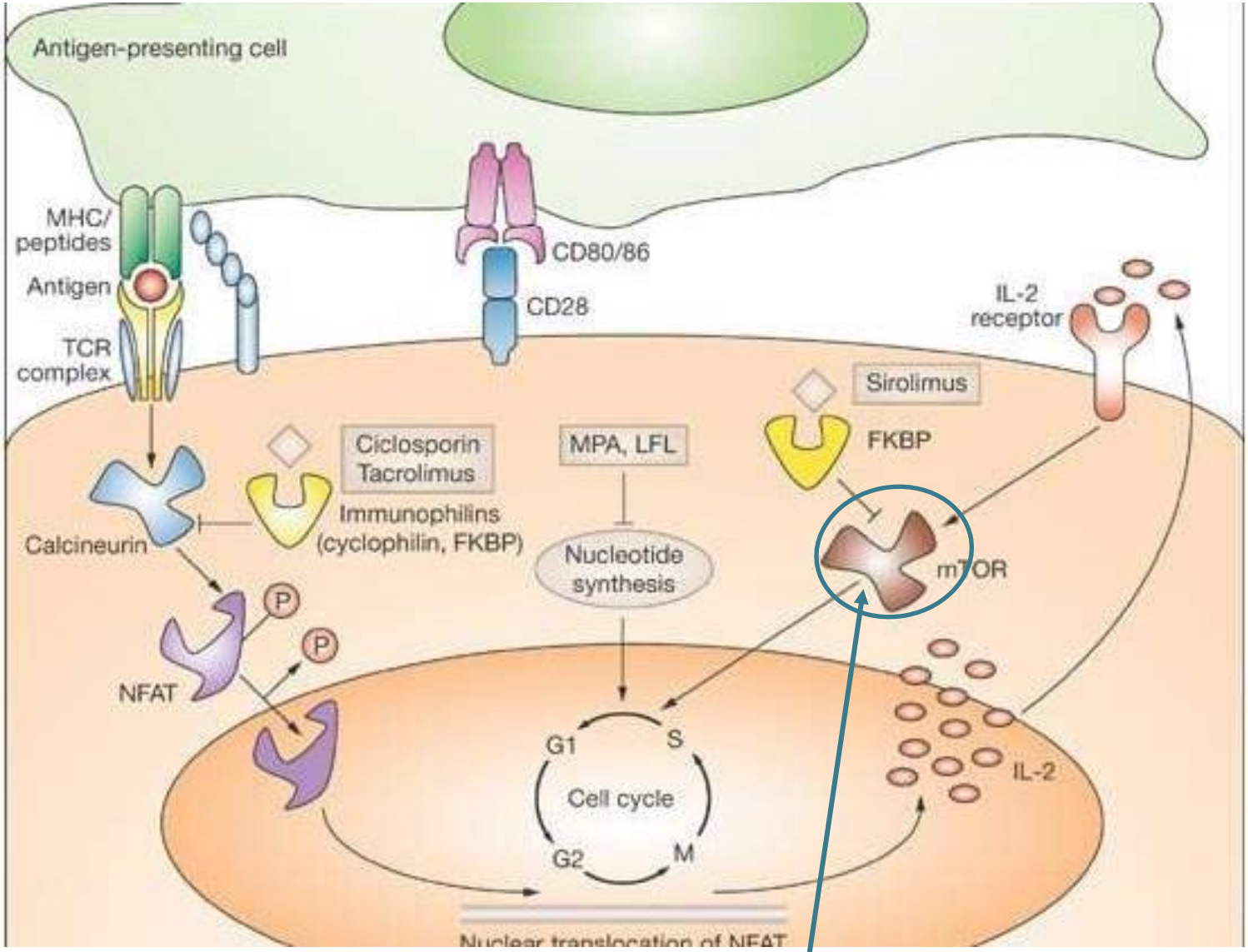
Narrow therapeutic window

- Levels too high: toxicities (i.e. mental confusion, nephrotoxicity)
- Levels too low: transplant rejection

Still requires level monitoring

If a patient has pre-existing renal disease we may switch to this drug instead

The target dose-range of these drugs will vary depending on clinical use.



Important regulator of cell growth + metabolism "cell driver." Causes T-cell proliferation and differentiation. Again, we are inhibiting the cellular immunity

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. **Non-selective**

Boosters for other immunosuppressants. Prescribed in a lower dose compared to their anti-cancer use.

As mentioned in the HLS course, anti-metabolites, are drugs that mimic natural nucleotides, blocking DNA synthesis. This leads to cell cycle arrest.

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

Most important anti-metabolite in transplantation!

- 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.

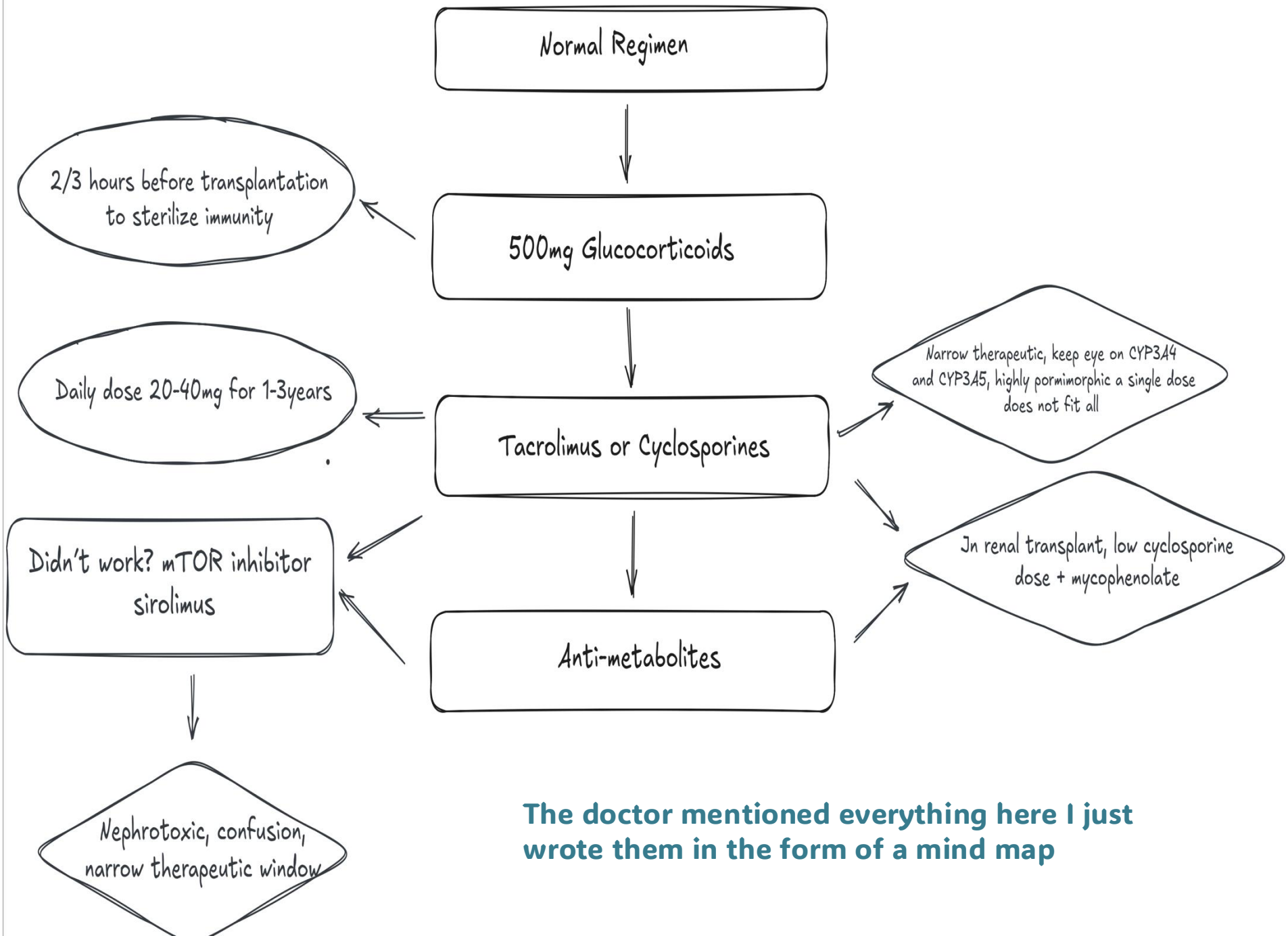
Both Signals 1 and 2 activate several intracellular signal transduction pathways one of which is the calcium-calcineurin pathway.

↓

Production of cytokines such as interleukin (IL)-2, IL-15, CD154, and CD25.

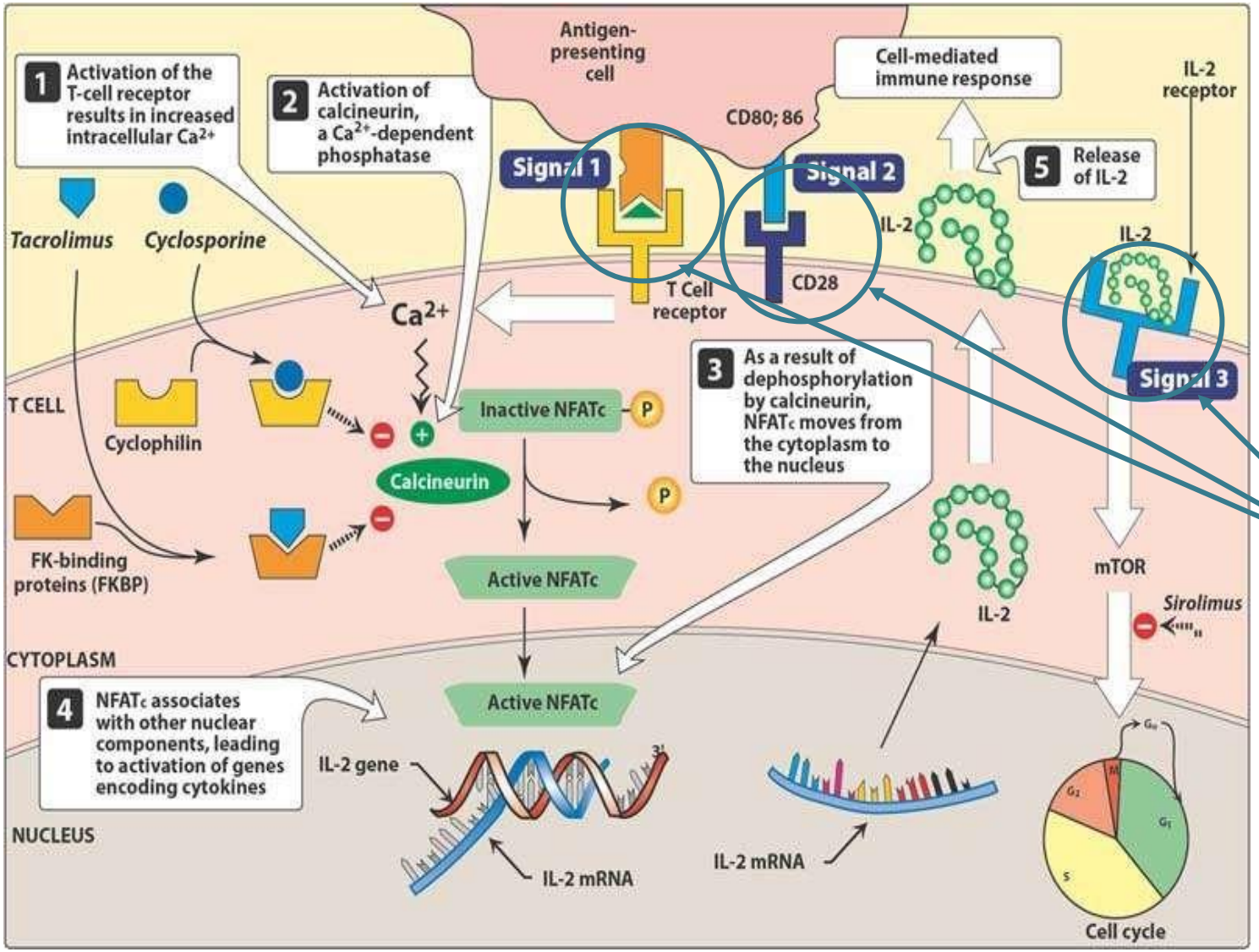
↓

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.



The doctor mentioned everything here I just wrote them in the form of a mind map

If normal regimen did not work, we utilize monoclonal antibodies. They're highly specific and effective, they also spare the kidneys (not nephrotoxic)



Targets

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.

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. **Basically antibodies against receptors**

Basiliximab is said to be "chimerized" because it consists of 25 percent murine **from rats** and 75 percent human protein.

Daclizumab is 90 percent human protein, and is designated "humanized." **newer, more expensive**

- **In targeted antibody therapy, there's a possibility that your immune system will develop antibodies against the injected antibodies, causing the deactivation of therapy. The more the humanized the less the risk of this occurring. If you were asked which drug is at more risk of deactivation? The answer will be basiliximab (it's also more inducing of allergy)**

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.

- **As mentioned previously the immune cells in bone marrow/immune stem cells transplantations, are donor derived. They could attack the recipient's organs and tissues, thus we could give the donor IL-2 antagonists before transplantation.**

IL-2-receptor antagonists

-Both antibodies are given intravenously.

The time span between the first and second injection is 2 weeks, then 3 months, 6 months, 12 months

-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.

We worry about opportunistic infections

Question:How can the half life be 20 days and the drug's activity 120days?!
Answer:The drug gets phagocytosed, deposited inside cells and its release sustained for longer periods. The actual half life in the circulation is only 20 days but the cells cause sustained release that work up to 120 days.

Anti CD3

Antigenic + toxic so we don't use it clinically and it's not required

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.

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.

Doctor did not explain from slide 31-35

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

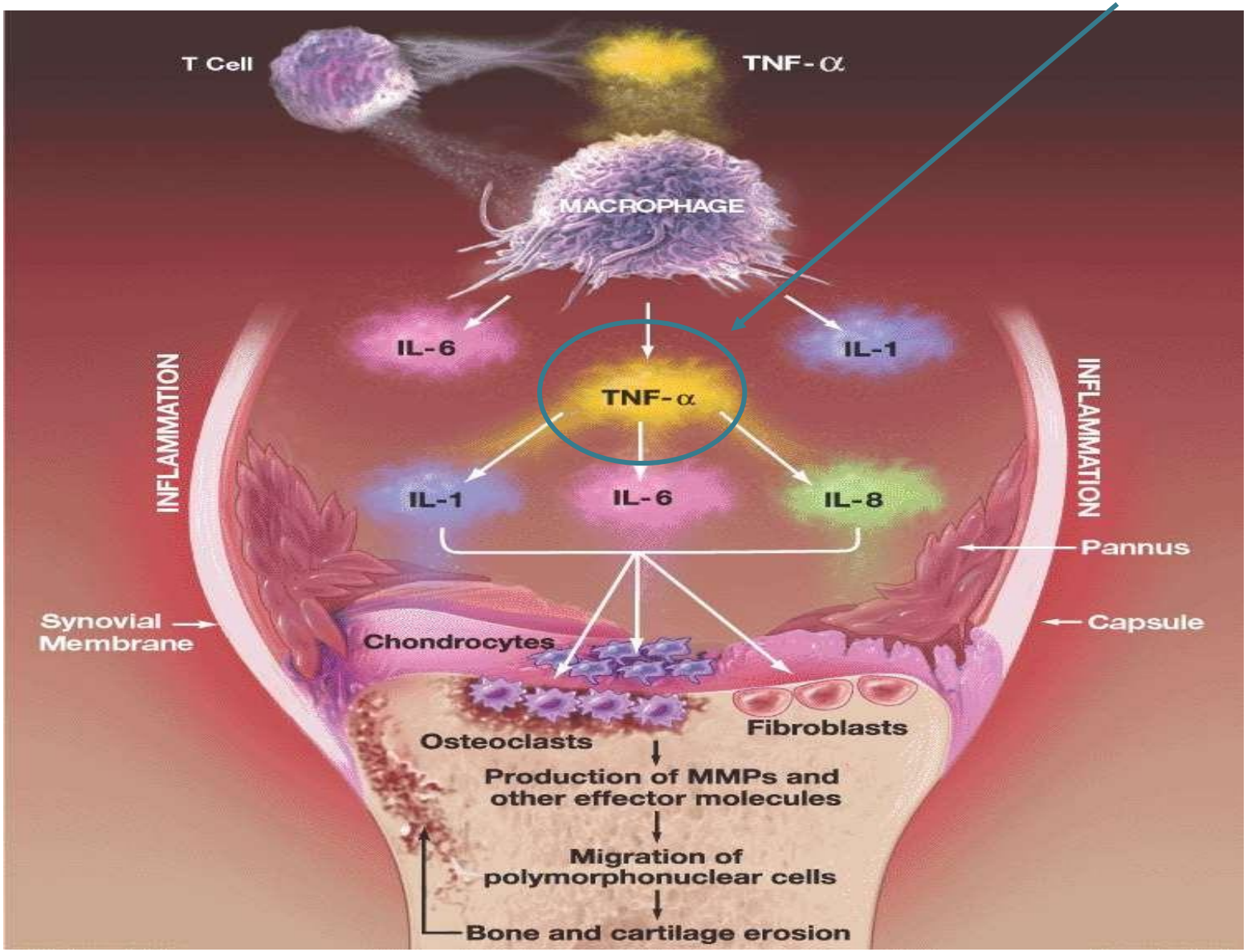
The first dose must not be administered until it is absolutely certain that the patient will receive the graft.

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

Rheumatoid Arthritis Mechanism

Main mediator of the disease



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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

1st line therapy is methotrexate, not applicable? we use these drugs (anti-TNF)

Side Effects of TNF Inhibition

- **Infection**
  - Tuberculosis **(latent, more severe)**
  - Serious resulting in death
- Neurologic
  - Multiple Sclerosis, seizures, inflammation of the ocular nerve
- Worsening of Congestive Heart Failure **? Unknown why**

- Remember

STOP if develop a fever, have an infection,

Rituximab

- Anti-B cell (CD20) antibody
  Basically inhibition of B-cell immunity
- 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

May consider anti- IL-1 if methotrexate, anti-TNF and anti-B cell, do not work.

Anti-IgE Antibodies

Drugs that reduce the amount of IgE to mast cells

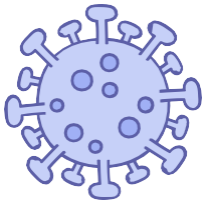
IgE in atopic asthma is elevated, these drugs could be applicable in those cases too.

inhibits synthesis of IgE by B-lymphocytes

-Omalizunab (anti-IgE Mab)

آمل gives you hope

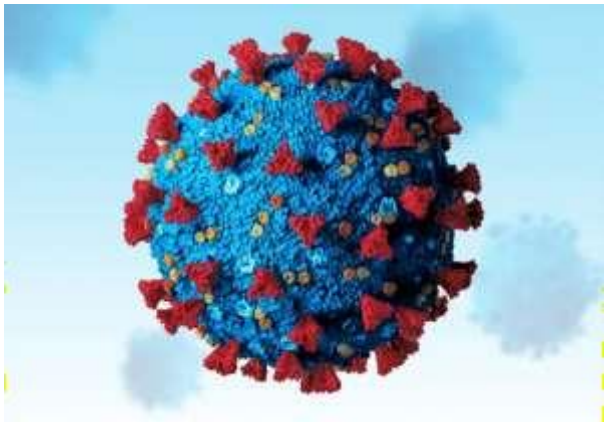
6 injections during the year



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

Dr. Malik Zihlif

Doctor did not explain from slide 42-55



- 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)
- **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

- 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).

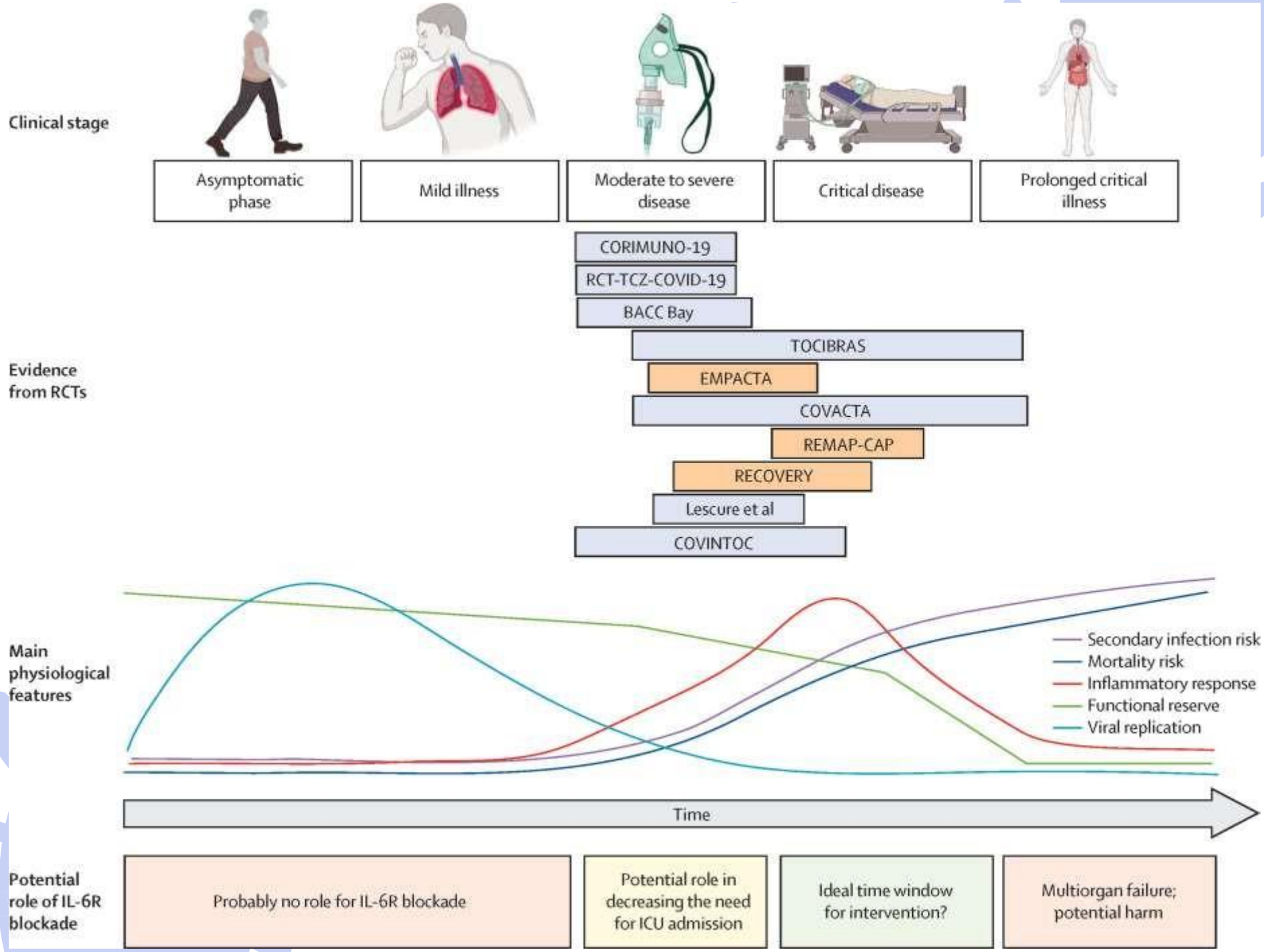
- The efficacy of IL-6 targeting depends on:
  - The underlying health status of the patient
  - The severity of the disease
  - The timing of the intervention.

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

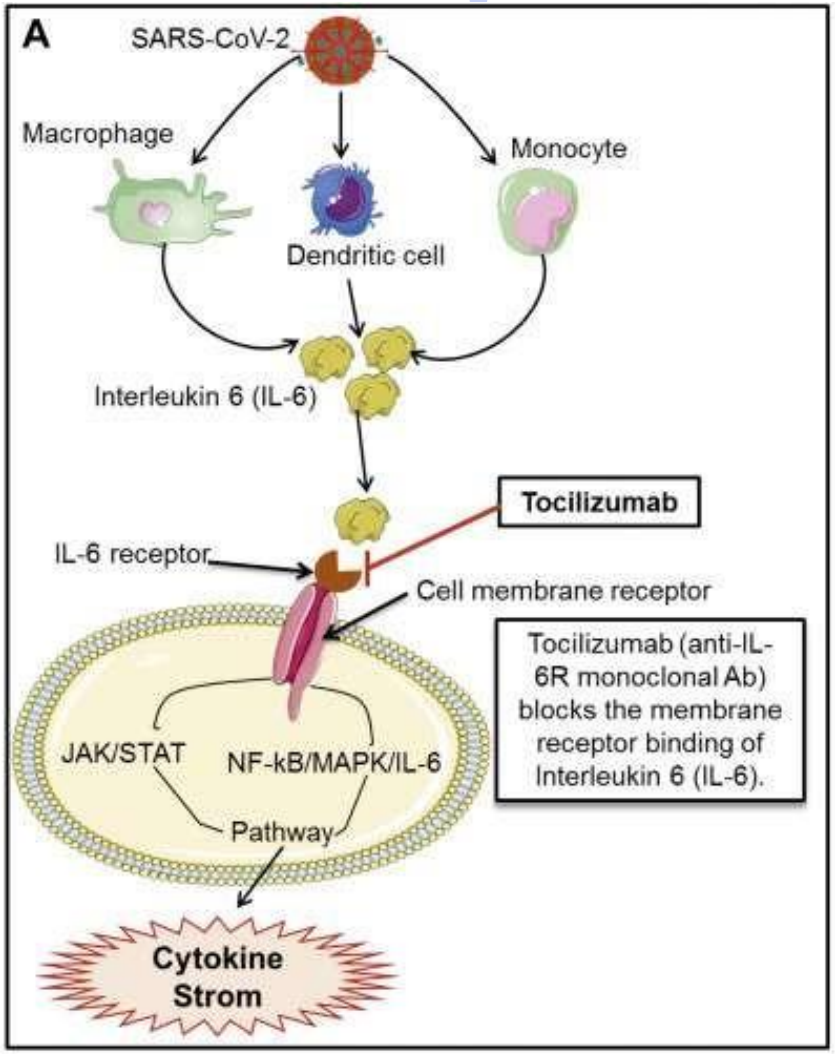
- Encouragingly, the incidence of adverse events in relevant trials appear minimal likely owing to the targeted (1–2 doses) use of these antagonists in COVID-19


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

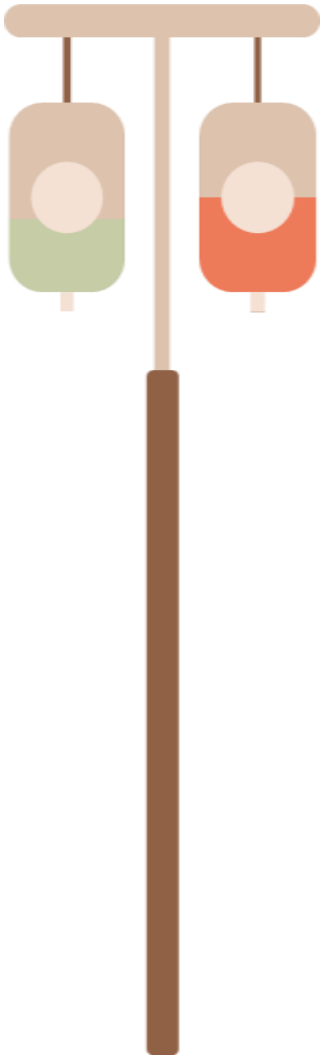
IL-6 Inhibitors

- **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.

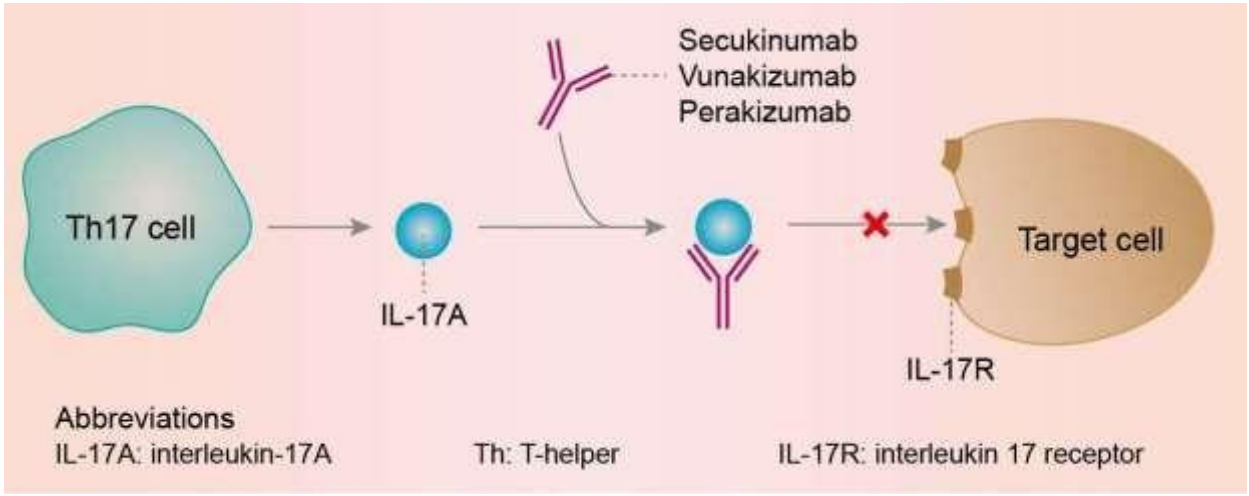
- As a result, the disruption of IL-17 production can lead to autoimmune diseases and tissue destruction. **Excessive** levels of IL-17 in the body are associated with the development and exacerbation of several autoimmune diseases.

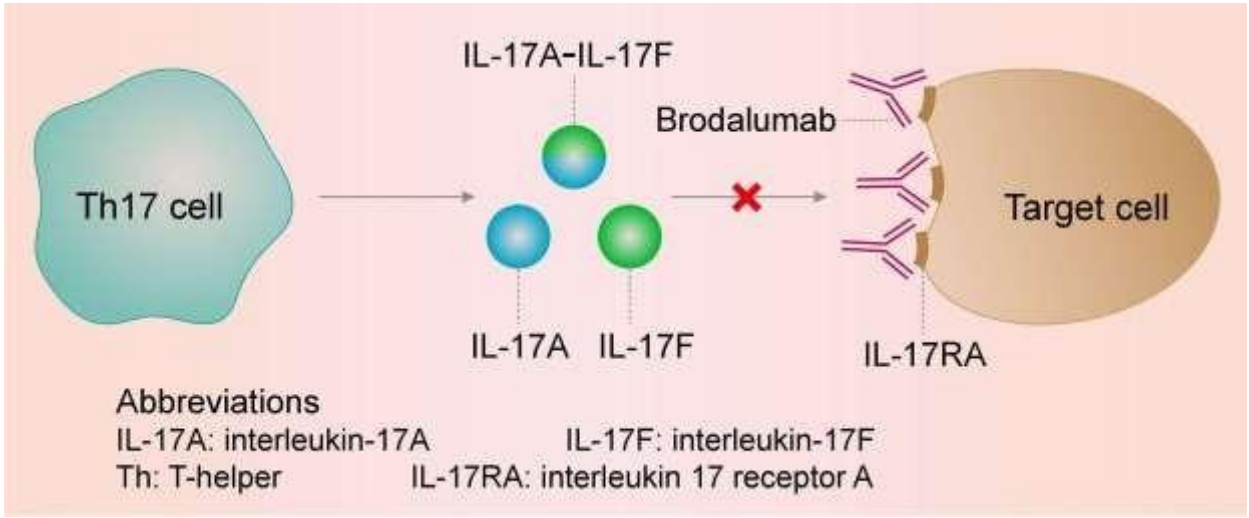
IL-17 inhibitors- **Secukinumab**

- **Secukinumab** is a recombinant human IgG1/kappa mAb
- 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

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

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

Cytokines

The opposite to what we used in immunosuppression

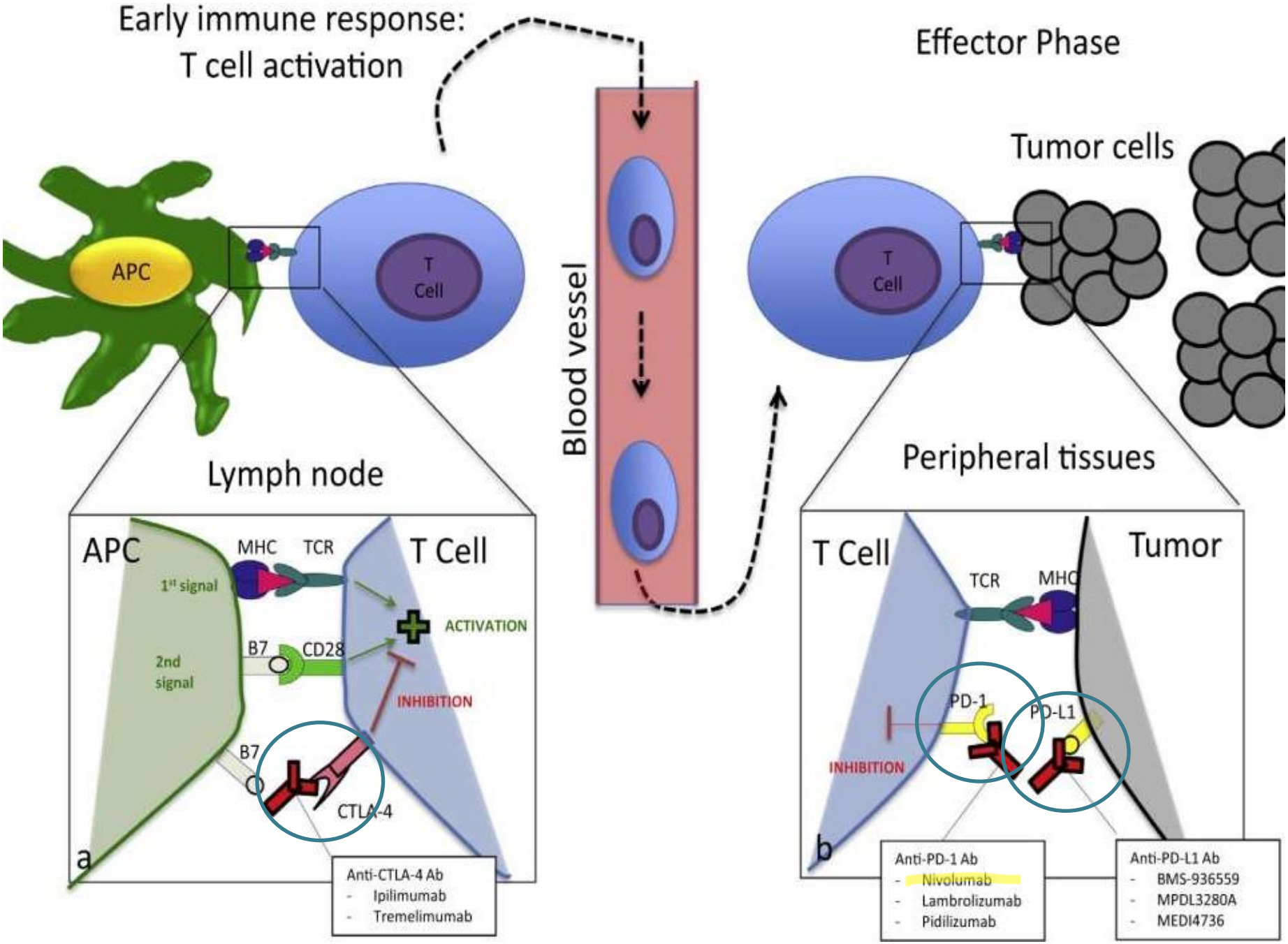
- Interferon (INF): INF-α,β,γ **used in hepatitis C ribavirin + INF-a, weak dose of 24 injections in 6months, in order to stimulate antiviral activity**
  - Antiviral, anticancer, immunomodulating effects.
  - Antiviral effects : INF-α,β > INF-γ
  - immunomodulating effects: INF-γ
  - Adverse Effects: 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 . **Extensive with minimal activity**

Remember that cancer is immune evasive, they escape T cells, so IL-2 who's responsible for T cell proliferation has limited activity, on the other INFs activity is more adequate due its stimulation of antigen presentation, thus partially overcoming the immunoevasion of the tumor.

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
Tumor cells
APC
T Cell
Blood vessel
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

Immune Checkpoint Inhibitors

The doctor said you should know Nivolumab. An anti-PD-1 Ab, adminstarted by injection and costs 5-6k Jod. It cures melanoma and some liquid tumors. Melanomas are immunologically vulnerable. (The doctor called them "weak" but they're biologically aggressive just immunologically susceptible.)

Unfortunately Nivolumab is less effective in other aggressive, bulky tumors. Especially cancers that form a lump with a hypoxic center. In these cases, they may extend the patient's lifespan والأعمار بيد الله

Surprisingly Nivolumab is active in colorectal cancers! Specifically those with genetic/satellite instability (chromosomal). Since they produce antigens that are responsive to treatment. Some colorectal cancers get cured with Nivolumab.

Ipilimumab an anti-CTLA-4 had a nice theoretical basis but a difficult clinical application, due to its immune toxicity. It can be used in tumors that lack clear immune infiltrates.

The doctor did not touch on the following topics:

1) **Immunosuppression therapy in kidney transplantation slide 31–35**
2) **The role of IL-6 inhibitors in severe COVID-19 Therapy 42-55**

I hope I made that clear, I am not sure if they are required, depends on the doctor's response.. (I just did not want to delay sending the file)