PHARMACOLOGY

Lecture 6: DMARDS

(Disease-Modifying Antirheumatic Drugs)

OBJECTIVES:

- Emphasize the rational for early treatment of RA
- Classify drugs used for treatment of RA
- Compare and contrast the advantages and disadvantages of NAISDs, Steroids and DMARDS in treatment of RA
- Explore the pharmacokinetic aspects and pharmacodynamic effects of selected DMARDs

Epidemiology of Rheumatoid Arthritis

- Affects 1-2% of the adult population.
- Is more common among **women** than in men(2-3 times).
- Usually appears between ages **25** and **40** years.
- The incidence also increases with **age**, peaking between the 4th and 6th decades.
- Causes **pain, disability** and **loss of function**.

* For more information on RA, we advise you to study lecture1 in immunology, and lecture4 in pathology "Arthritis"

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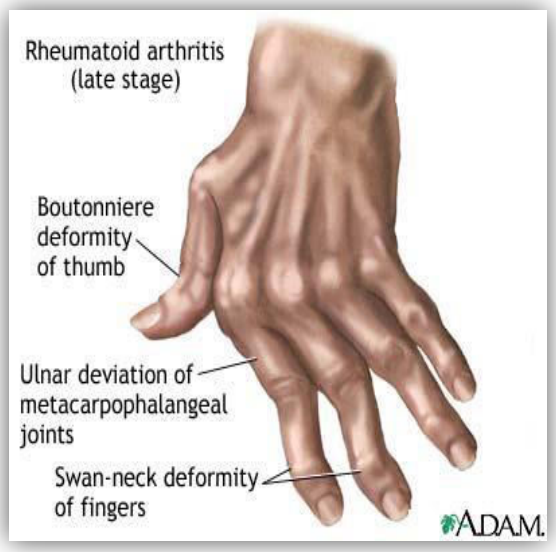
- Important.
- Extra notes.

Rheumatoid Arthritis:

Rheumatoid Arthritis (RA) is a **chronic autoimmune** disorder in which the normal immune response is directed against an individual's own tissue leading to:-

- **Decline in functional status.**
- **Work disability.**
- **Systemic Complications.**
- **Co-morbidity** (is the presence of one or more additional disorders).
- **Increased mortality.**



Pathogenesis:

The mechanism of action is **not clearly known**.
It is characterized by:

- Synovial inflammation and hyperplasia (or swelling).
- Autoantibody production, aka the rheumatoid factor (RF).
- **Cytokine-mediated inflammation**, which -including IL1 and TNF- drive the generation of reactive oxygen and nitrogen species .
- Cartilage and bone destruction (erosion and deformity), due to elaboration of **proteolytic enzymes** (metalloproteinases, e.g. collagenase) both by synovial lining cells and chondrocytes themselves.
- Systemic effects include Anemia, weight loss, osteoporosis, Renal, cardiovascular, and neurological complications, Which may cause mortality.

Rational for early treatment:

- Joint damage is an **early** phenomenon of rheumatoid arthritis.
- Episodes of pain and stiffness will occur before any X-ray changes.
- Joint erosions(تآكل) occur in up to 93% of patients within **less than 2 years** of disease activity.
- Disability occurs early – 50% of patients with RA will be work-disabled at **10 years.**
- Severe disease is associated with increased mortality
- **Early and aggressive treatment may have long-term benefits.**

You Tube Rheumatoid Arthritis

Drugs for Rheumatoid Arthritis

Drug	NSAIDs	Glucocorticoids	DMARDs*
Onset of Action	**Rapid**	**Intermediate**	**Slow**, Their effects take from 6 weeks up to 6 months to be evident
Effect on Disease	Does **not slow** the progression of the disease.	Temporary control of severe **exacerbations**. long-term use in patients with severe disease not controlled by other agents.	act on the immune system to **slow** (arrest) the progression of RA
		(**immunosuppressant**)	
symptomatic effects	Provides partial relief of pain and stiffness.	Anti-inflammatory	Have no analgesic effects
Formation of new deformity	Can not stop formation of new deformity.	Can not stop formation of new deformity	**Can not repair the existing damage, but prevent further deformity**
Clinical use	Used in **acute cases** to relief inflammation & pain.	Administered in low to moderate doses to achieve rapid disease-control before the onset of fully effective DMARD therapy	Used **in chronic cases** when the disease is progressing & causing deformities
Chronic use	Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.	Corticosteroids are too toxic for routine chronic use	

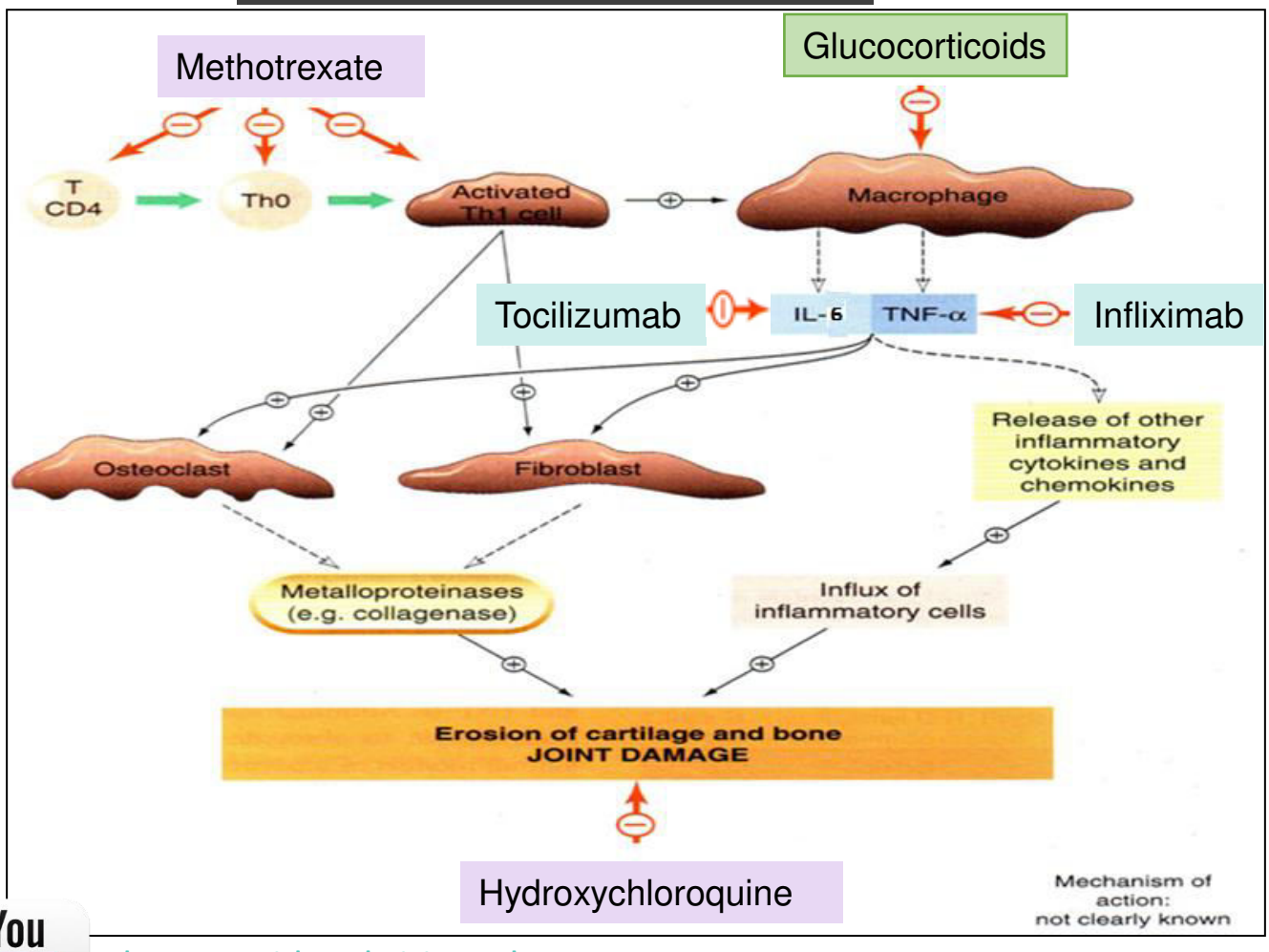
***DMARDs: Disease-modifying anti rheumatic drugs.**

Note that NSAIDs and Glucocorticoids only relief the symptoms of RA. DMARDs, on the other hand, arrest the progression of the disease.

Drugs for Rheumatoid Arthritis

- **Drugs for Rheumatoid Arthritis**
  - **Glucocorticoids**
  - **DMARDs***
    - **Classical**
      - **Methotrexate** for T cells
      - **Hydroxy-chloroquine** for lysosomal enzyme
    - **Biologic**
      - **Infliximab** for TNF-α
      - **Tocilizumab** for IL-6
  - **NSAIDs**

Target of each drug:



Rheumatoid Arthritis and DMARDs

1. Classical DMARDs: Methotrexate

1) Methotrexate

Overview

"Gold standard" for DMARD therapy & is **the first-line** DMARD for treating RA , used in 50–70% of patients

Mechanism of action

❖ **Used in high doses as cancer chemotherapy:**

Inhibits dihydrofolate reductase, Which is essential for thymidine & purine synthesis.
by inhibiting these, it destroys the DNA of malignant cells and prevents cell proliferation.

❖ **Used in much lower doses for RA:**

stimulates **adenosine** release from cells, producing an anti-inflammatory effect :

- Inhibition of polymorphonuclear chemotaxis .
- Inhibition of T-Cells, thus inhibiting cell-mediated immune reactions.
- Acts as immunosuppressant.

Pharmacokinetics

- **Administration : Orally (70% absorbed)**
- **Half life: 6–9 hours**
- Metabolized to a less active hydroxylated product (hydroxymetabolite)
- Excreted principally in the **urine**, but up to 30% may be excreted in bile.
- Given 7.5 – 30 mg weekly.

ADRS

- Bone marrow suppression
- Dyspepsia, Mucosal ulcers
- Hepatotoxicity
- Pneumonitis "inflammation of the walls of the alveoli in the lungs"
- Teratogenicity "congenital malformation"
- Leukopenia, anemia, stomatitis "inflammation of the mucous membrane of the mouth", GI ulcerations, and alopecia "loss of hair" are probably the result of **inhibiting cellular proliferation**
- **Monitoring :**

Full blood count, ALT "to test for hepatic injury" , Creatinine "for kidney function"

- **Management of ADRs:**

Folic acid : reduces GI & bone marrow effects (because methotrexate is an anti folate drug, patients should take folic acid to reverse some of the adverse effects)

METHOTREXATE medical animation

1. Classical DMARDs: Hydroxychloroquine

2) Hydroxychloroquine (anti-malaria)

Mechanism

- Stabilization of **lysosomal enzyme** activity, thus stopping erosion of bone and cartilage.
- Trapping free radicals
- Suppression of T lymphocyte cells response to mitogens
- Inhibition of leukocyte chemotaxis

Pharmacokinetics

- Rapidly absorbed and 50% protein-bound
- **Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes. It has long elimination half-life, reaching up to 45 days** **(which is why it accumulates in the eye causing retinal damage)**
- Highly concentrated within cells → increases intra-cellular pH

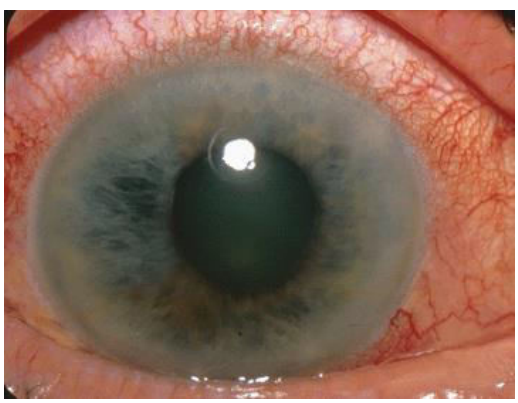
Clinical uses

- Has not been shown to delay radiographic (X-ray) progression of disease
- Generally used for treatment of early, mild disease. Because it has slow response (6 months) and only mild anti-rheumatic effect.
- It could also be used as adjunctive therapy in combination with other DMARDs, such as in increasing methotrexate efficacy

ADRS

- Least toxic, no blood tests is required
- Nausea & vomiting
- **It forms Corneal deposits, leading to Irreversible retinal damage**
- **Monitoring :**
- Ophthalmologic evaluation every 6 months.

To evaluate eye health after hydroxychloroquine



Summery of Classical DMARDs

Classical		
Blocking	**T-Cells**	**Lysosomal enzymes**
Drug	**Methotrexate**	**Hydroxychloroquine**
What is it?	• "Gold standard" for DMARD therapy. • First-line DMARD for treating RA • In 50–70% of patients.	----------
Mechanism	High doses for chemotherapy: Inhibits dihydrofolate reductase. Reduces thymidine & purine synthesis. Low doses for RA: stimulate adenosine release from cells. → Inhibition of PMN **chemotaxis** & **T-Cells.**	• Stabilize lysosomal enzyme activity • Trapping free radicals • Suppression of T lymphocyte cells response to mitogens • Inhibition of leukocyte chemotaxis
pharmacokinetics	• Approximately 70% absorbed after oral administration. • Metabolized to a less active hydroxylated product • Excreted in urine, but 30% may be excreted in bile. • Given 7.5 – 30 mg weekly. • T1\2 = 6-9h.	• Rapidly absorbed. • 50% protein-bound. • Extensively tissue-bound particularly in melanin-containing tissues such as the eyes • Highly concentrated within cells (increases intra-cellular pH) • T1\2 = 45 days.
ADRS	Bone marrow suppression, Dyspepsia, Mucosal ulcers, Hepatotoxicity, Pneumonitis, Teratogenicity, Leukopenia, anemia, stomatitis, GI ulcerations, and alopecia are probably the result of inhibiting cellular proliferation	• Least toxic, no blood tests is required • Nausea & vomiting • Corneal deposits • Irreversible retinal damage
Monitoring	**FBC, ALT, Creatinine**	**Ophthalmologic evaluation every 6 months**
Clinical uses	Act on the immune system to slow the progression of RA. Can be combined with other DMARDs. **Folic acid is taken with methotrexate to reduce GI & bone marrow ADR effects.**	• Has **not** been shown to delay radiographic progression of disease. • Used in increasing methotrexate efficacy. • 6 month response, mild anti-rheumatic effect. • Generally used for treatment of early, mild disease or as adjunctive therapy in combination with other DMARDs.

2. Biologic DMARDs

Biologic DMARDs are **genetically engineered** drugs that are used to modify imbalances of the immune system in autoimmune diseases. They are expensive, since they are made in the laboratories by genetic modification.

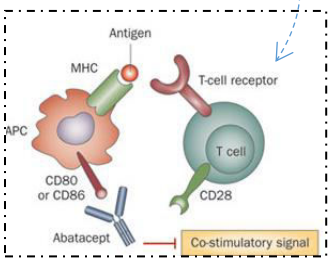
Classification

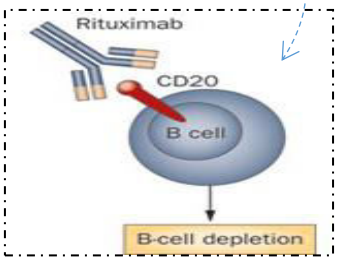
1. Agents that block, or modify the activity of selected cells in the immune system

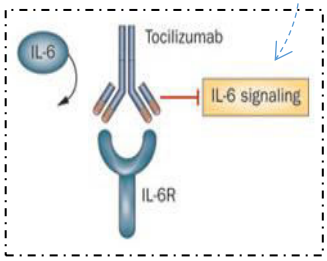
- **T-cell** modulating drug → **Abatacept**
- **B-cell** cytotoxic agent → **Rituximab**

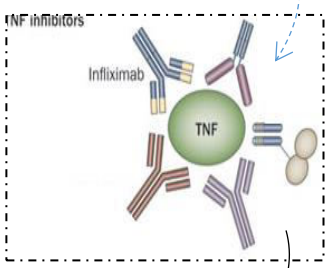
2. Agents blocking cytokines, which send signals between those immune cells

- **Anti-IL-6** receptor antibody → **Tocilizumab**
- **TNF- blocking** agents → **Infliximab**





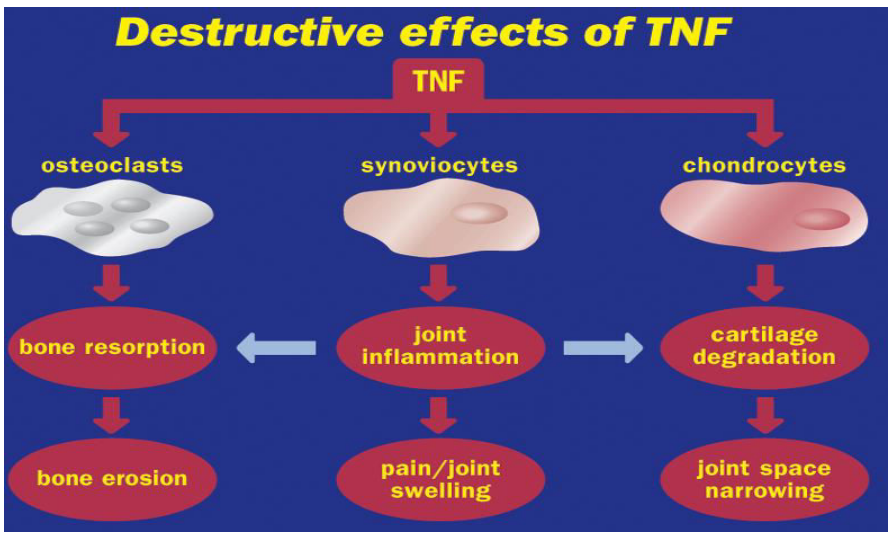




The suffix (**–mab**) → given by injection

Role of TNF on joint destruction

- Affects the **osteoclasts** which leads to bone resorption leading to bone erosion.
- Affects the **synoviocytes** leading to inflammation & activation of other cells.
- Affects the **chondrocytes** leading to cartilage degradation & narrowing of joint space.
- Induce production of other cytokines, as IL-1, IL-6.



2. Biologic DMARDs : Infliximab

1) Infliximab

Overview

Infliximab is a chimeric IgG1 monoclonal **antibody** (**mixture of genetically different tissue:** 25% mouse, 75% human), **that's why it could be rejected by the body** after intermittent administration, by electing human anti-chimeric **antibodies** in up to 62% of patients.
But if infliximab is used in **Concurrent therapy** with methotrexate, this will reduce the incidence of human anti-chimeric antibodies.
In addition to methotrexate, it could also be combined with hydroxychloroquine and other non biological DMARDs.

Mechanism of action

It complexes with soluble **TNF-α** (and possibly membrane- bound TNF-α) to prevent its interaction with the cell surface receptors.
This results in down-regulation of macrophage and T-cell function.

Pharmacokinetics

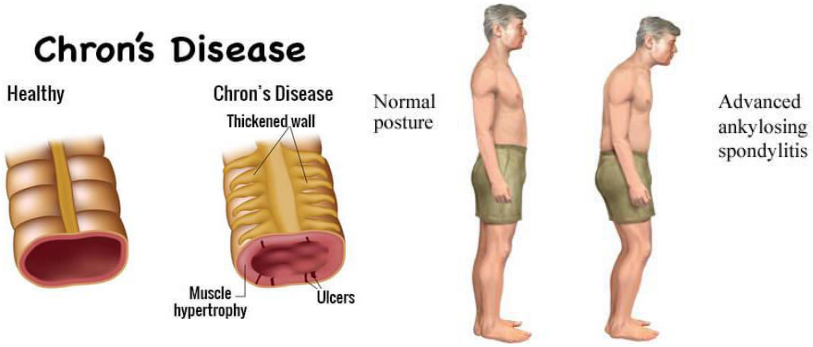
- It is given as intravenous infusion (I.V) with "**induction**" at 0,2,6 weeks and "**maintenance**" every 8 weeks.
- Terminal half-life is 9–12 days .

ADRS

- Upper respiratory tract infections, and activation of latent tuberculosis.
  Since it acts as an immunosuppressant.
- Infusion reaction (allergy reaction at site of infusion).
- Headache and Cough.
- Increase the risk of skin cancers (including melanoma).

Clinical uses:

- RA
- Ankylosing spondylitis
- Crohn's disease
- ulcerative colitis



Infliximab (Remicade)

2. Biologic DMARDs : Tocilizumab

2) Tocilizumab

Mechanism of action

It is a Monoclonal **antibody** that inhibits action of **IL-6**, by blocking IL-6 receptor.

IL-6 is a pro-inflammatory cytokine implicated in the pathogenesis of RA, With detrimental effects on both joint inflammation and cartilage damage.

Tocilizumab binds to membrane IL-6 receptors, blocking the activity of IL-6 in mediating signals that affect cytokine production and osteoclast activation, thus stopping joint inflammation and cartilage damage.

Pharmacokinetics

Administration : I.V every month. **Half life: Dose-dependent**

Drug interaction : IL-6 inhibits CYP450

CYPs are the major enzymes involved in drug metabolism, essential for the metabolism of some drugs such as cyclosporine and warfarin.

Tocilizumab restores the activity of the enzyme.

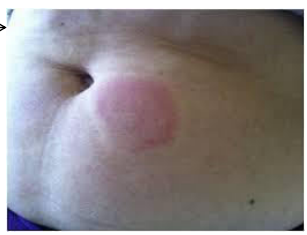
Clinical uses:

Monotherapy in adult with rheumatoid arthritis, and in children over 2 years with systemic juvenile arthritis "a childhood disease that affects the joints"

In combination with methotrexate or other non biologic anti-rheumatic drugs in patients with active rheumatoid arthritis not responding to TNF blockers or other biologic drugs.

ADRS

- Infusion reaction (allergy reaction at site of infusion) →



- Serious infection (bacterial, tuberculosis ,fungal)
- Increase in cholesterol level.
- Increase in liver enzymes.
- Decrease in WBCs.
- Neutropenia and thrombocytopenia **(reversible upon stopping the drug)**
- **Evaluation : Blood test used monthly** for increase in cholesterol, liver enzymes and decrease in WBCs.

Summery of Biologic DMARDs

Biologic		
Blocking cytokines	**TNF-α blocking agents**	**Anti-IL-6 receptor antibody**
Drug	**Infliximab**	**Tocilizumab**
Notes	Infliximab **is a chimeric** IgG_1 monoclonal antibody (25% mouse, 75% human) Elicits up to 62% incidence of human anti-chimeric antibodies.	**IL-6** is a proinflammatory cytokine implicated in the pathogenesis of RA
Mechanism of action	Infliximab→ Binds to human TNF-α → inhibition of its action with the cell surface receptors → results in down-regulation of macrophages & T-cell function	Tocilizumab → Binds to membrane IL-6 receptors → blocks the activity of IL-6 in mediating signals of cytokine production and osteoclast activation
T 1/2	Terminal half life = 9-12 days	Half-life is dose dependent
Administration	**IV infusion** • induction at 0,2 and 6 weeks. • Every 8 weeks regimen (Maintenance)	**monthly IV infusion**
ADRS	1. Headache 2. Cough 3. Infusion site reactions 4. Upper respiratory tract infections. 5. Activation of latent tuberculosis. 6. Increase the risk of skin cancer including melanoma. (Last 3 ADRs are the most dangerous)	1. Infusion reaction 2. Serious infections **3. Increase** in cholesterol level & liver enzymes **4. Decrease** in WBCs 5. Neutropenia & thrombocytopenia (reversible After stopping the drug)
Monitoring	----------	**Blood test will be monthly** used due to **increased** cholesterol, liver enzymes & **decrease** WBCs
Clinical uses	Approved for use in **RA, Ankylosing spondylitis, Crohn's, ulcerative colitis**. Combined with other non biological DMARDs	1. As monotherapy: • In **adult** with RA. • In **children** over 2 years with systemic juvenile arthritis. 2. Combined with other non biological DMARDs In patients with active rheumatoid arthritis.
Drug interactions	therapy with methotrexate decreases the prevalence of human anti-chimeric antibodies	Tocilizumab restore the activity of CYP450 enzyme (inhibited by IL-6) (Which is essential for the metabolism of cyclosporine & warfarin)

QUIZ

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

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