Mechanism Involved in Rheumatoid Arthritis and Treatment Strategy

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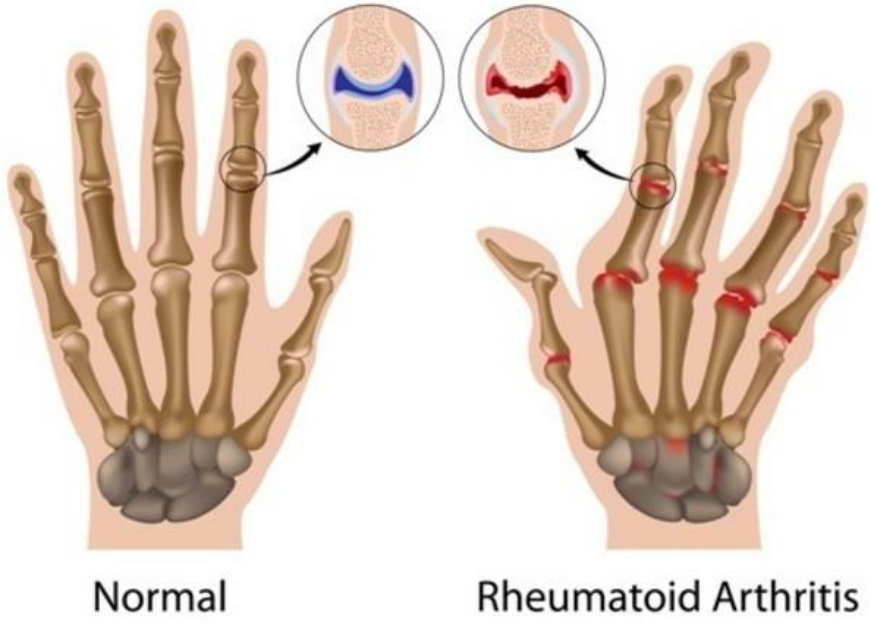
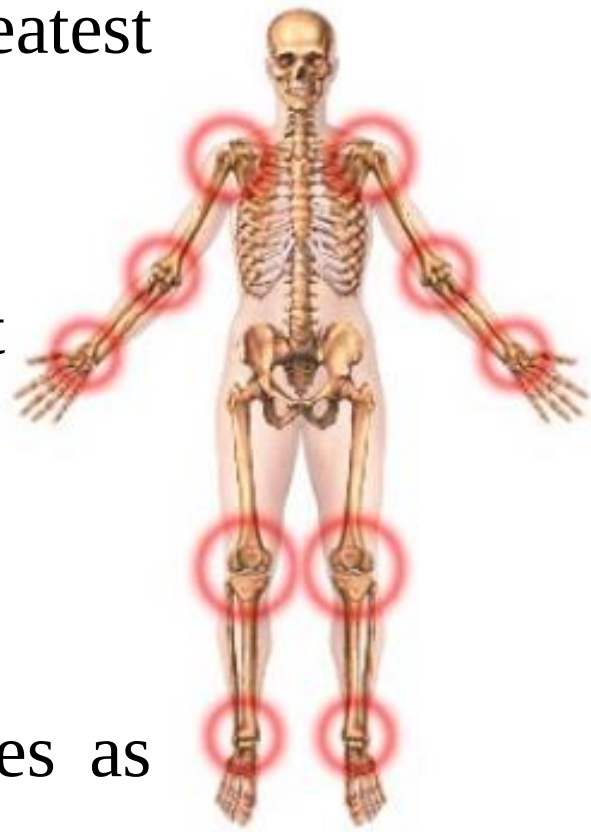
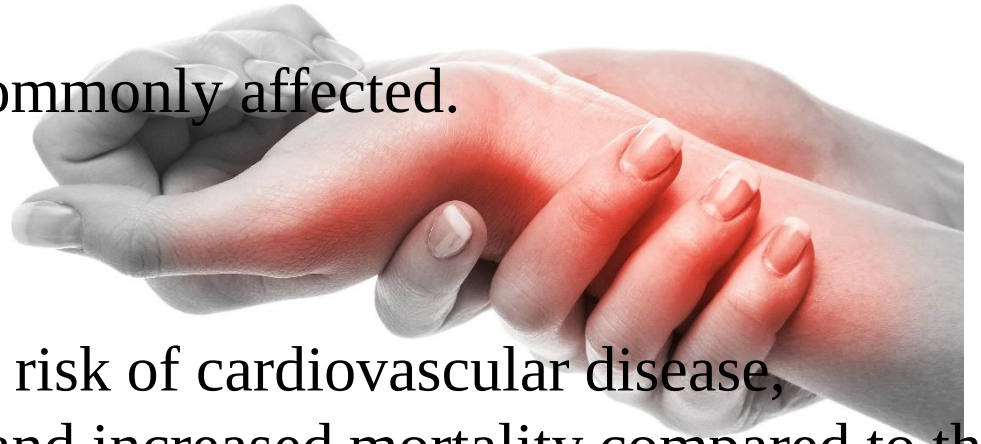


Rheumatoid Arthritis (RA)

- An inflammatory disease that exerts its greatest impact on those joints of the body
- affects the small joints of the hands and the feet
- affects approximately 1% of the population
- with women being affected two to three times as often as men



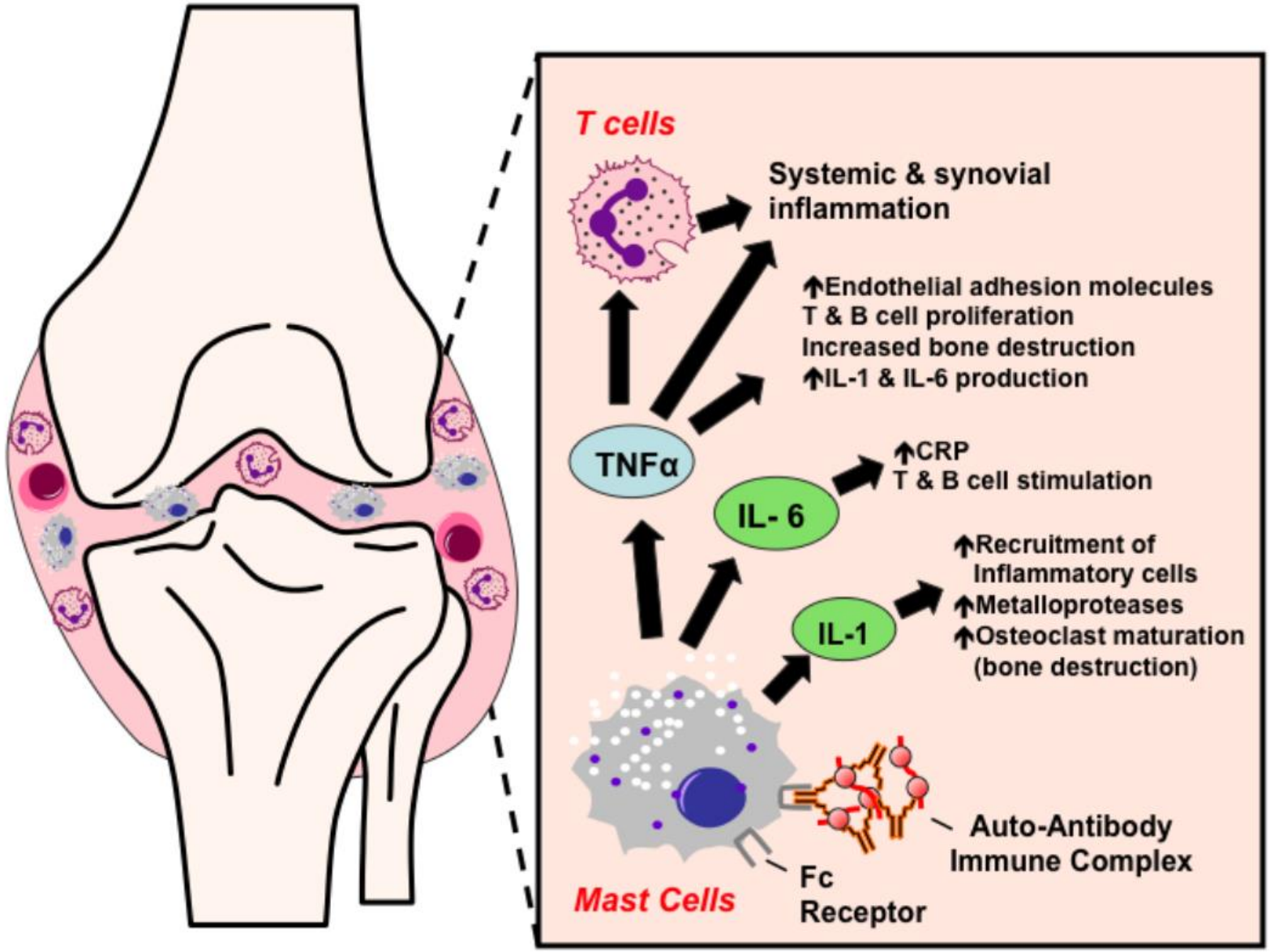
- Approximately 50% of the risk for RA is attributable to genetic factors
- Other tissues and organs are also commonly affected.



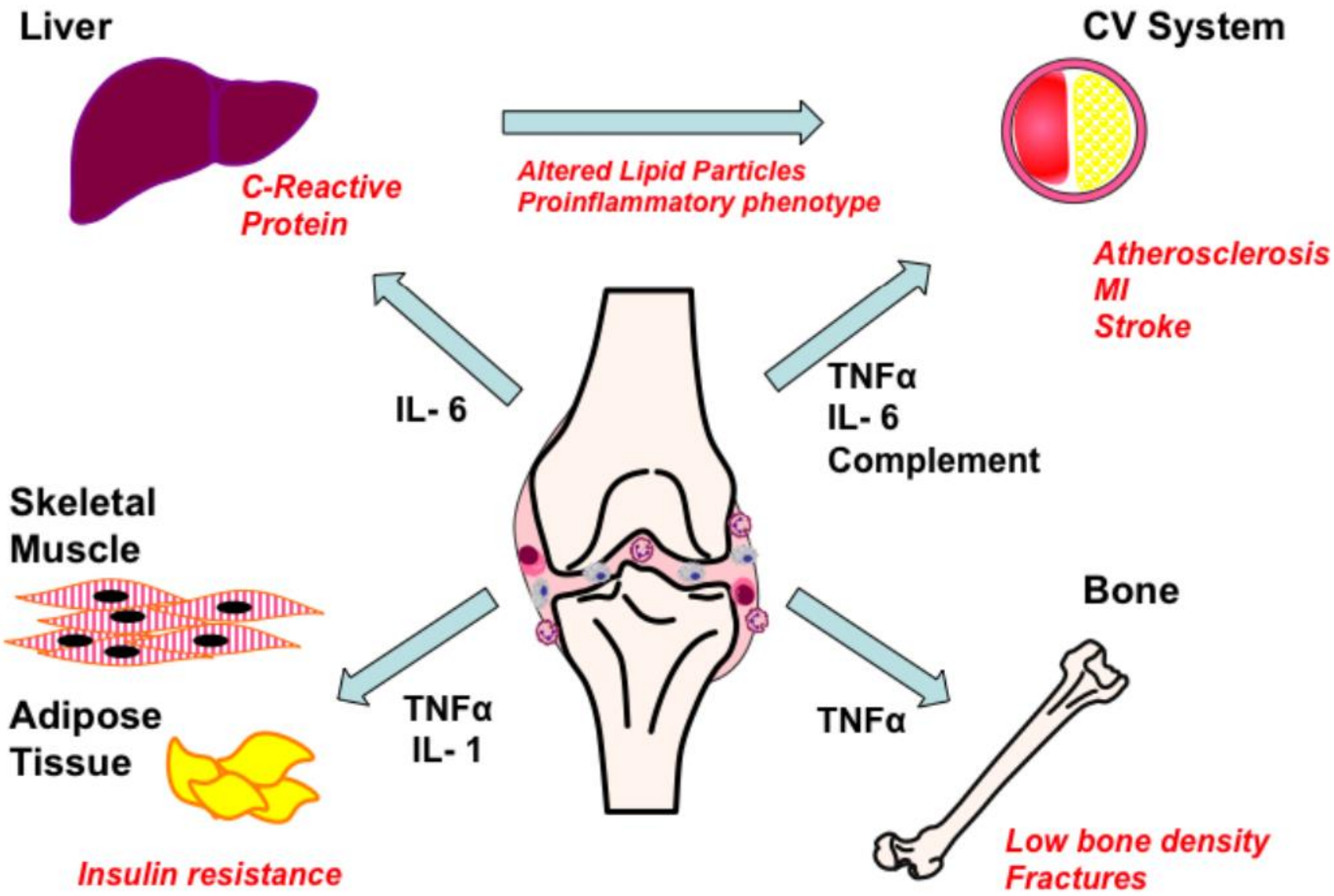
- Patients with RA have an increased risk of cardiovascular disease, osteoporosis, metabolic syndrome and increased mortality compared to the general population (standardized mortality rate ~1.5)
- Abnormalities in components of the immune system
- Release of large concentrations of proteins that drive inflammatory processes (such as (TNF-α))

Patients must have four of the seven criteria:

- Morning stiffness lasting at least 1 hour
- swelling in three or more joints
- swelling in hand joints
- symmetric joint swelling
- erosions or decalcification on x-ray of hand
- rheumatoid nodules
- abnormal serum rheumatoid factor



In rheumatoid arthritis autoimmune reactions stimulate macrophages and T cells to produce multiple inflammatory cytokines in the joints. This results in swelling and pain, progressive damage to cartilage and bone, and over time systemic effects that contribute to increased cardiovascular morbidity and mortality. The interactions between cytokines and multiple cell types underlying the pathogenesis of RA is more complex than illustrated.



Long-term systemic complications of rheumatoid arthritis. Inflammatory mediators produce effects in multiple organ systems that result in increased rates of metabolic syndrome, osteoporosis, cardiovascular disease & increased mortality that are not explained by traditional risk factors. Implicated cytokines include TNF-α, IL-1, IL-6 & complement immune complexes. (Adapted from McInnes & Schett, 2011).

Rheumatic therapy

NSAIDs, Glucocorticoid

Reduce inflammation and the pain

DMARD

modify the disease process and slowing down the damaging component of the disease process

Disease-Modifying Antirheumatic Drugs (DMARDs)

Conventional DMARDs

- Methotrexate
- Azathioporine
- Sulphasalazine
- Hydroxychloroquine
- leflunomide
- gold injections

Biological DMARDs

Anti-TNF: etanercept and infliximab

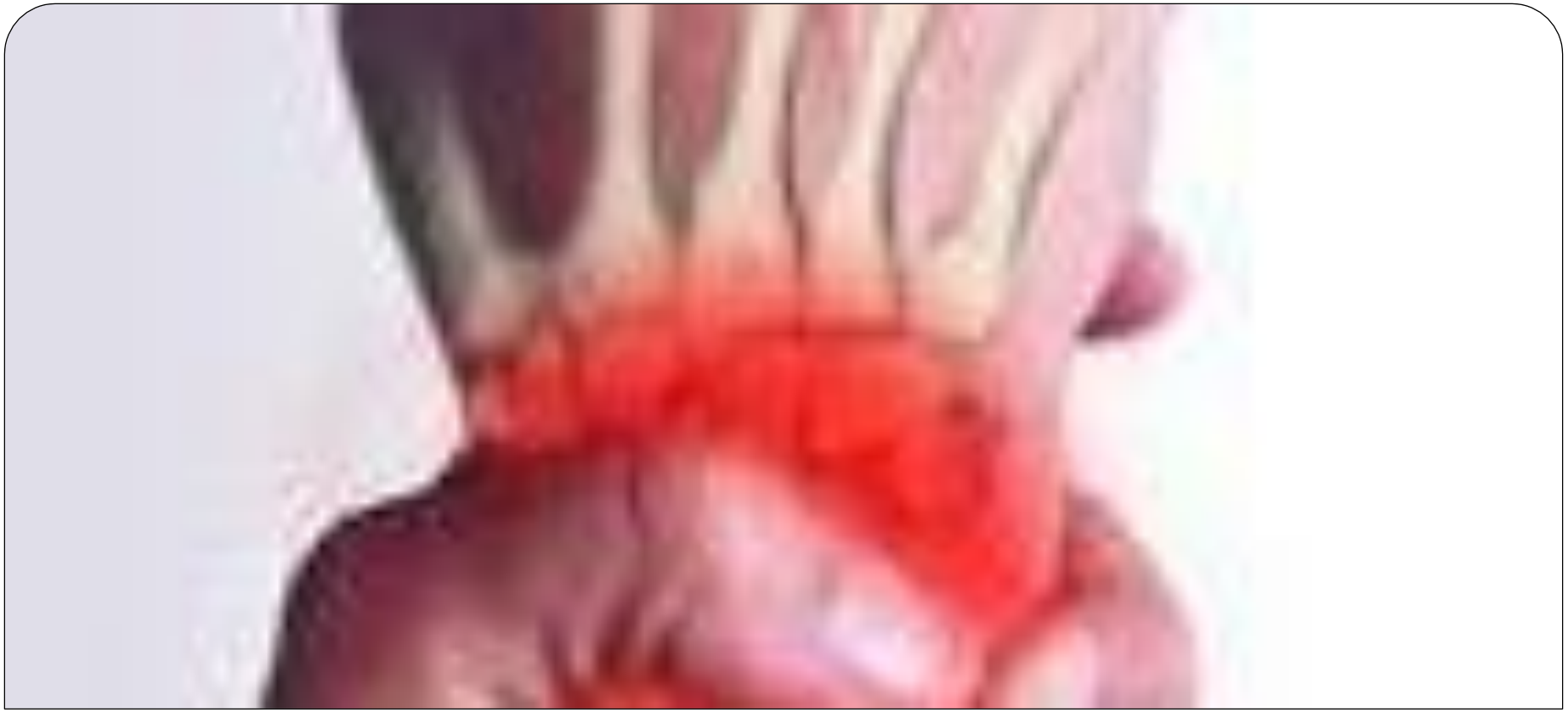
B-lymphocyte depletory : rituximab

Preventing T-lymp activation: abatacept

IL-1 receptor antagonist: Anakinra

anti- IL6 : Tocilizumab

JAK inhibitors: tofacitinib,..



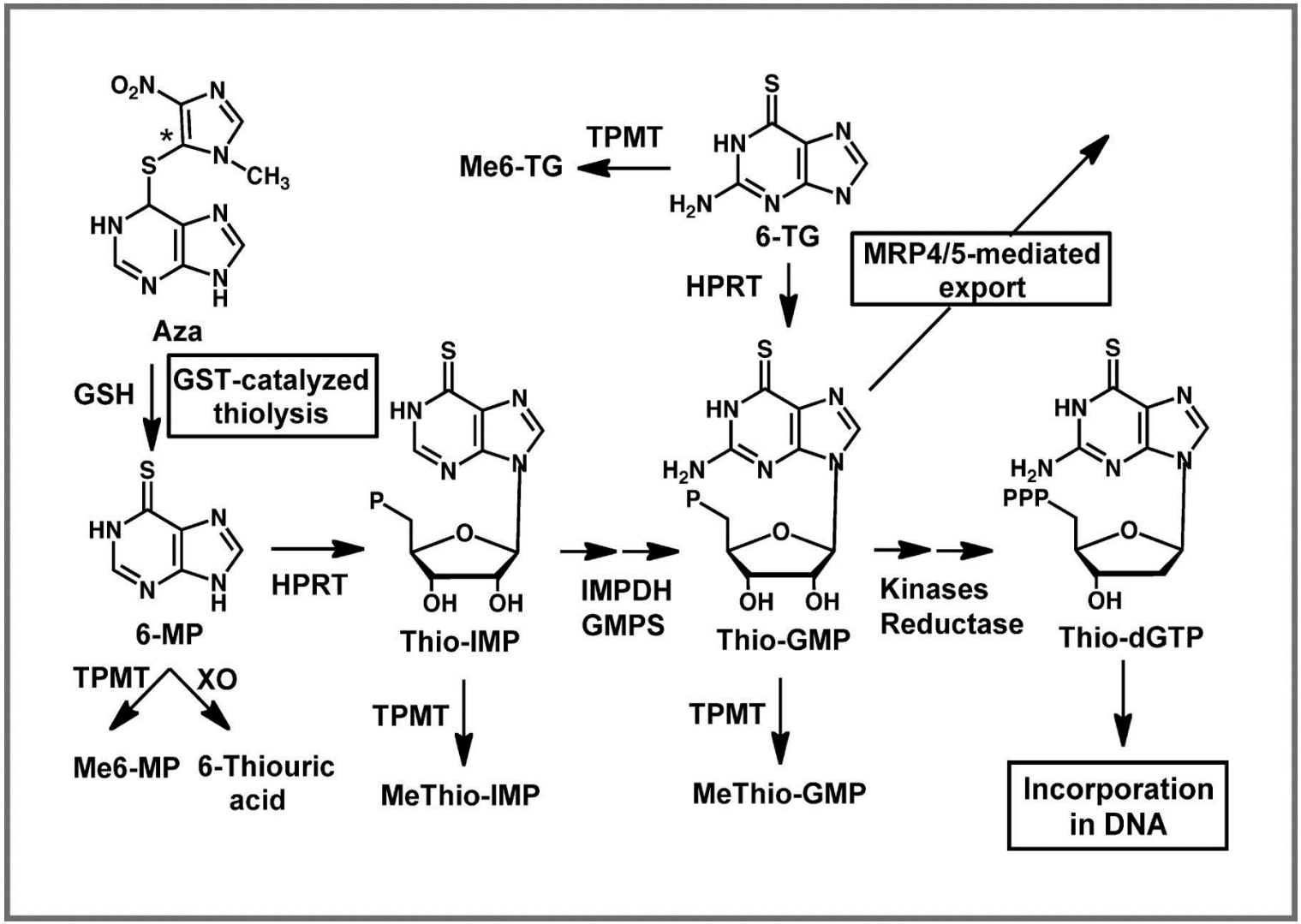
DMARDs

AZATHIOPRINE

Belongs to the chemical class of purine analogues

Prodrug of 6-MP

Acts through its major metabolite, 6-methylthioionosine monophosphate (6MTITP)



AZATHIOPRINE

- inhibiting an enzyme that is required for the synthesis of DNA. Thus it most strongly affects proliferating cells, such as the T cells and B cells of the immune system

- indications:
- Severe Rheumatoid Arthritis and prevention of transplant rejection
- systemic lupus erythematosus, Behcet's syndrome

AZATHIOPRINE

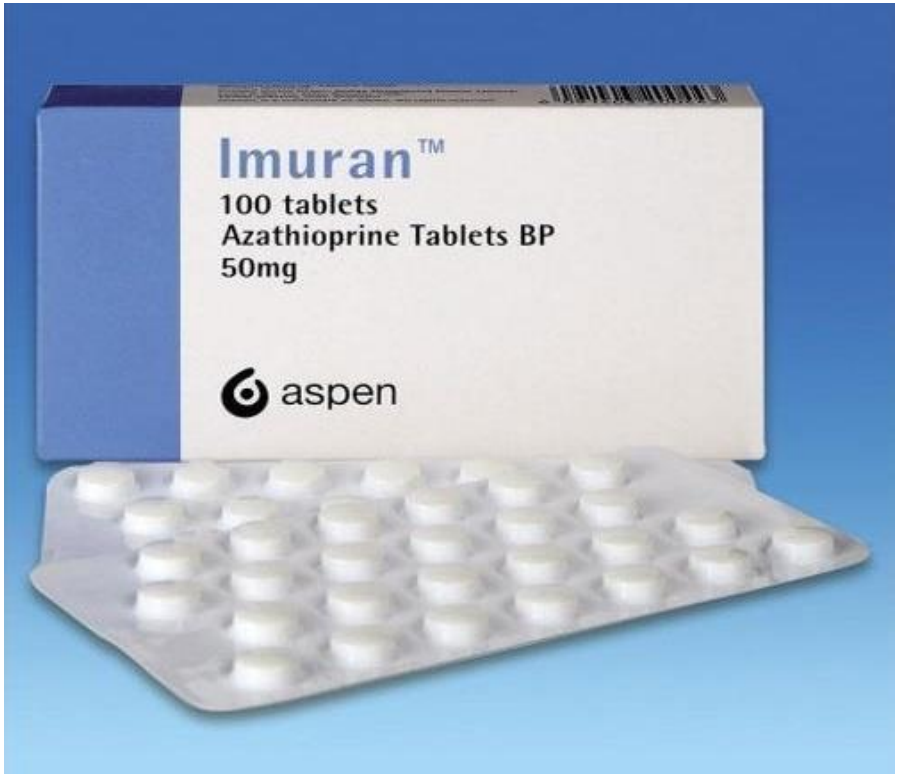
- **Adverse effect:**
  - Bone Marrow suppression (often first 7-10 day)
  - GI disturbances
  - increased in risk for infections and malignancy

- **Interaction:**
  - The inhibition of xanthine oxidase in patients receiving allopurinol is the basis for the azathioprine dosage reduction required in these patients (up to 75%)

AZATHIOPRINE

- Pregnancy: B

- Tablet: 25, 50 mg
- Injection powder: 50 mg



Chloroquine, Hydroxychloroquine

- Used for the treatment of **malaria**, RA & SLE
- Mechanism: unclear
  - They suppress the responsiveness of T lymphocytes,
  - decrease leukocyte chemotaxis,
  - stabilize lysosomal membranes,
  - inhibit DNA & RNA synthesis
  - trap free radicals
- Effects are seen after 12-24 weeks
- Other indications: juvenile chronic arthritis, Sjogren's syndrome

Sjogren’s syndrome

Hydroxychloroquine

- Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes
  - **Ocular toxicity**

    Ophthalmologic monitoring every 6–12 months
- Other toxicities include:

  Dyspepsia, nausea, vomiting, abdominal pain, rashes, and nightmares
- These drugs appear to be relatively safe in pregnancy

SULFASALAZINE

- Consists of **sulfapyridine & 5-amino-salicylic** acid connected by diazo bond
- Metabolized by bacteria in the colon

- Nearly all of the sulfapyridine is absorbed, while 5-ASA is largely excreted in the feces, consistent with the utility of 5-ASA in inflammatory bowel disease (IBD).

- Sulfasalazine or its metabolites inhibit the release of inflammatory cytokines

- **Sulfasalazine** is an **effective** treatment for **rheumatoid arthritis** (RA), producing improvements in disease parameters similar to those seen with penicillamine, hydroxychloroquine or oral or parenteral gold in comparative clinical trials.

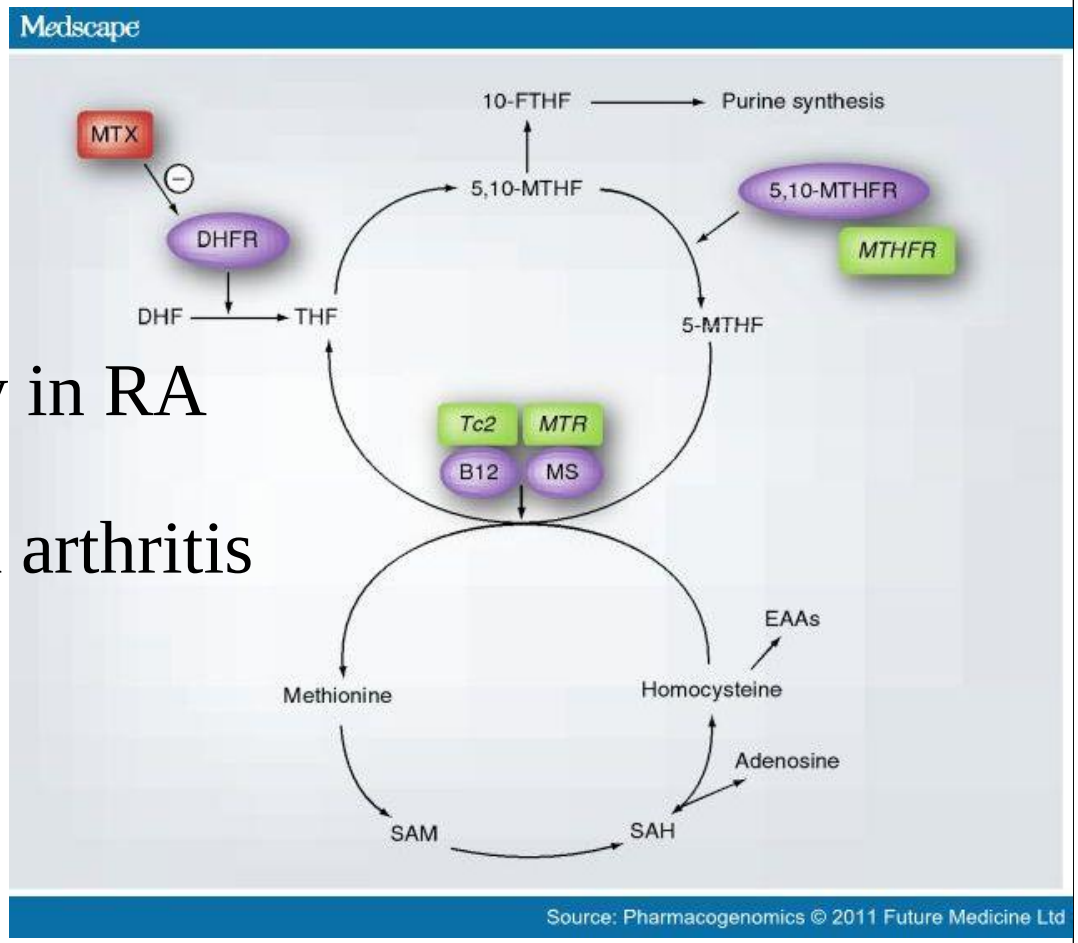
- A meta-analysis of studies investigating DMARD therapy, which included almost 5000 evaluable patients, concluded that sulfasalazine was close to methotrexate in terms of efficacy but was slightly less well tolerated.

- Most adverse events associated with sulfasalazine are minor and tend to occur within 3 months of starting therapy.

- **Side effects:**
  - Nausea, vomiting, headache, and rash.
  - Hemolytic anemia and methemoglobinemia
  - Neutropenia occurs in 1–5% of patients
  - Pulmonary toxicity
  - Reversible infertility occurs in men,
- Pregnancy: B

METHOTREXATE

- A potent **immunosuppressive** drug: inhibiting the metabolism of folic acid
- In high dose: cancer treatment
- Rapid onset, acceptable efficacy in RA
- **First choice** to treat rheumatoid arthritis



METHOTREXATE

- Early mortality is largely due to cardiovascular disease (CVD), which is the commonest cause of death in patients with RA
- Cardiovascular deaths were reduced by 70% among individuals treated with methotrexate.
- Max Dose: 25mg/wk
- once a week or divided in 3 dose, every 12 h

METHOTREXATE

- Side effects: Nausea, mucosal ulcers, dose-related **hepatotoxicity**, “Cytopenias, and an acute pneumonia-like syndrome

- The incidence of gastrointestinal and liver function test abnormalities can be reduced by:
  - **Daily Folic acid & weekly leucovorin**

- Contraindicated in pregnancy
  - Women: a cycle
  - Men: 3 months

METHOTREXATE

- **Interaction:**
  - With NSAIDs: increase MTX serum level
  - With trimethoprim: increase bone marrow toxicity
  - With leflunomide: liver toxicity

LEFLUNOMIDE

- TRIFLUNOMIDE (active metabolite) inhibits **dihydroorotate dehydrogenase** → an enzyme that catalyzes the fourth step in the *de novo* biosynthesis of pyrimidine → inhibits autoimmune T cell proliferation & production of autoantibodies by B cells

- Often combined with Mtx

- Oral, Strong protein binding, Enterohepatic circulation, Bile excretion

LEFLUNOMIDE

- Side Effects: GI (diarrhea,..), elevation of liver enzymes

- Drug Interaction:
  - Cholestyramine
  - Mtx (liver toxicity, bone marrow toxicity)

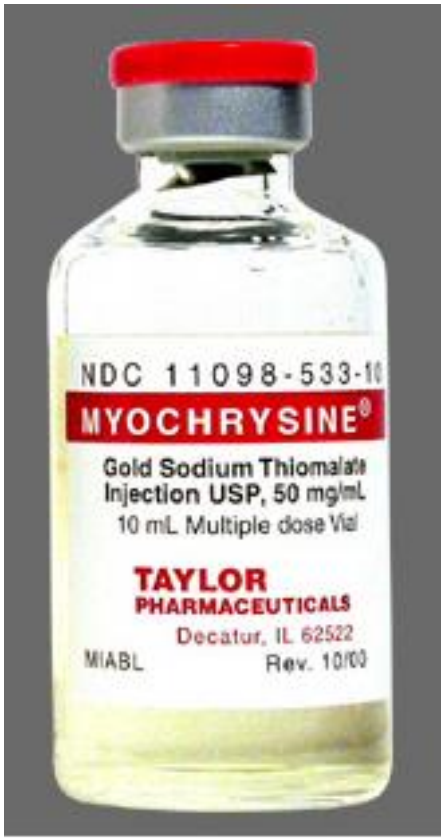
- Contraindicated in pregnancy
  - Teratogen??
  - Very long half-life of the active metabolite
  - Pregnancy after 2 years
  - Using Cholestyramine (8 g) every 8 h for 11 days

Gold injection

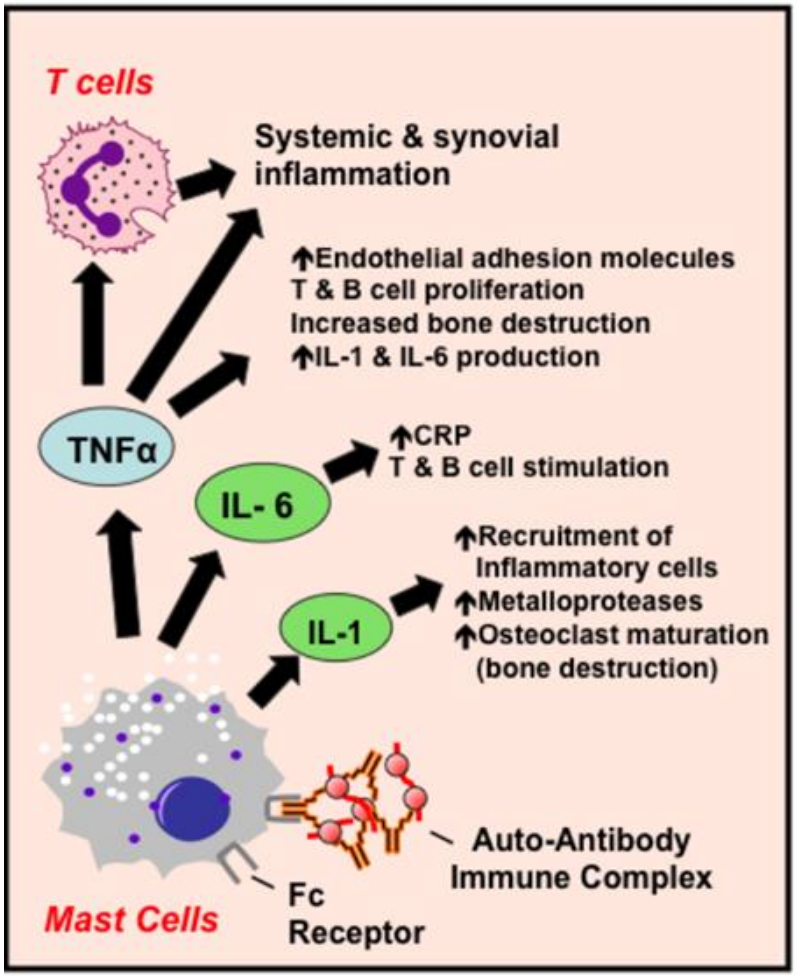
- **gold sodium thiomalate** is a gold compound that is used for its immunosuppressive anti-rheumatic effects.
- It is primarily given once or twice weekly by intramuscular injection for moderate-severe rheumatoid arthritis
- Its precise mechanism of action is unknown but act as immunomodulator
- Its anti-inflammatory effects remain even after cession for years!
-

- Its most common side effects are:
  - digestive (mostly dyspepsia, mouth swelling, nausea, vomiting and taste disturbance)
  - vasomotor (mostly flushing, fainting, dizziness, sweating, weakness, palpitations, shortness of breath and blurred vision)
  - dermatologic

- Pregnancy: C
  - secreted in breast milk



Biological DMARDs



Anti-TNF: etanercept and infliximab

B-lymphocyte depletory : rituximab

Preventing T-lymp activation: abatacept

IL-1 receptor antagonist: Anakinra

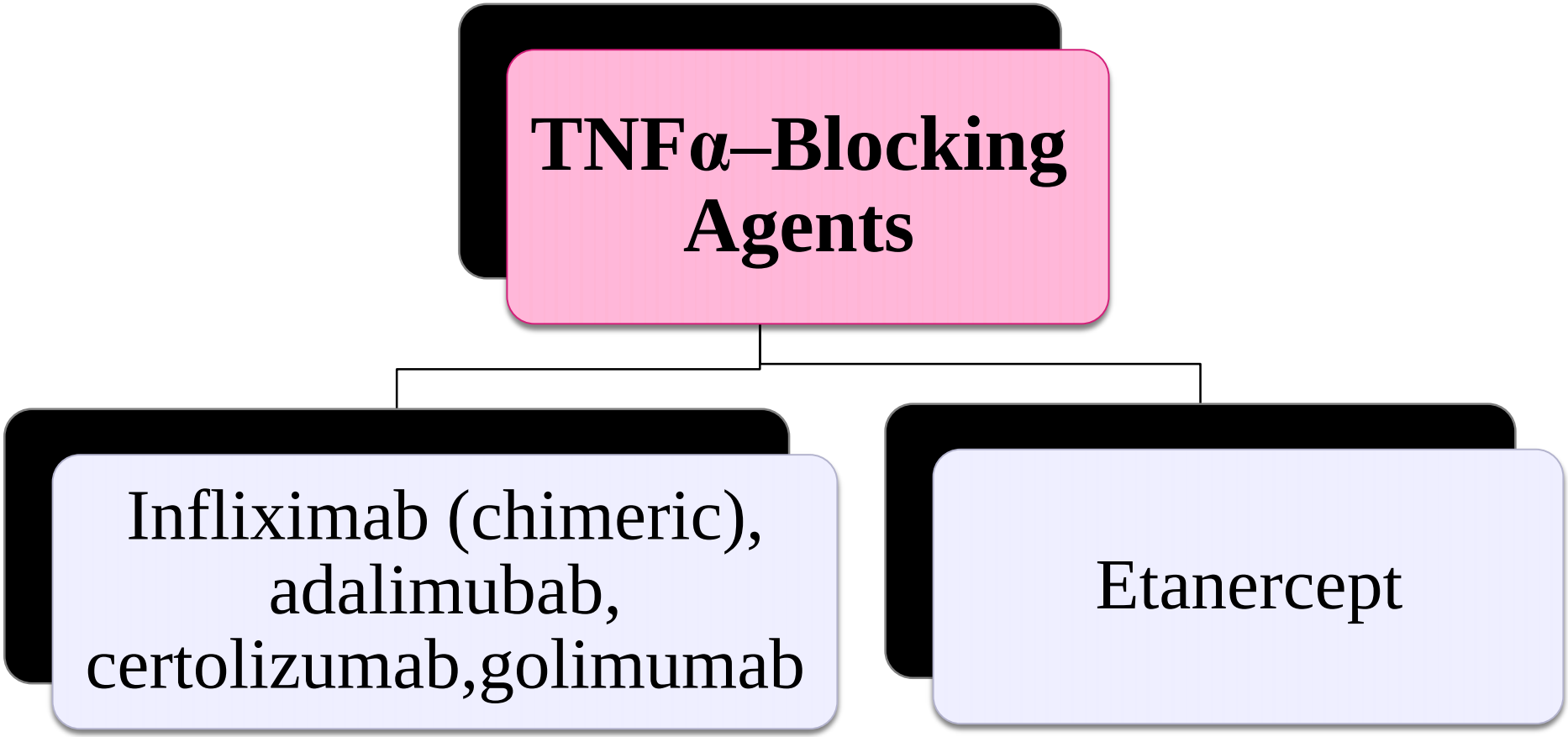
anti- IL6 : Tocilizumab

JAK inhibitors: tofacitinib,..

TNFα–Blocking Agents

- TNF- α appears to be particularly important in the inflammatory process.
- TNF- affects cellular function via activation of specific membrane-bound TNF receptors ($TNFR_1$, $TNFR_2$).

- **TNFα–Blocking Agents:**
  - **Receptor**: etanercept
  - **Anti-TNF-a**: infliximab, adalimubab, certolizumab, golimumab


TNFα–Blocking Agents
Infliximab (chimeric), adalimubab, certolizumab,golimumab
Etanercept

Adalimumab

- Adalimumab is a fully human IgG_1 anti-TNF monoclonal antibody.
- This compound complexes with soluble TNF- and prevents its interaction with cell surface receptors.
- This results in down-regulation of macrophage and T cell function.
- Indication:
  - treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and Crohn's disease

Adalimumab

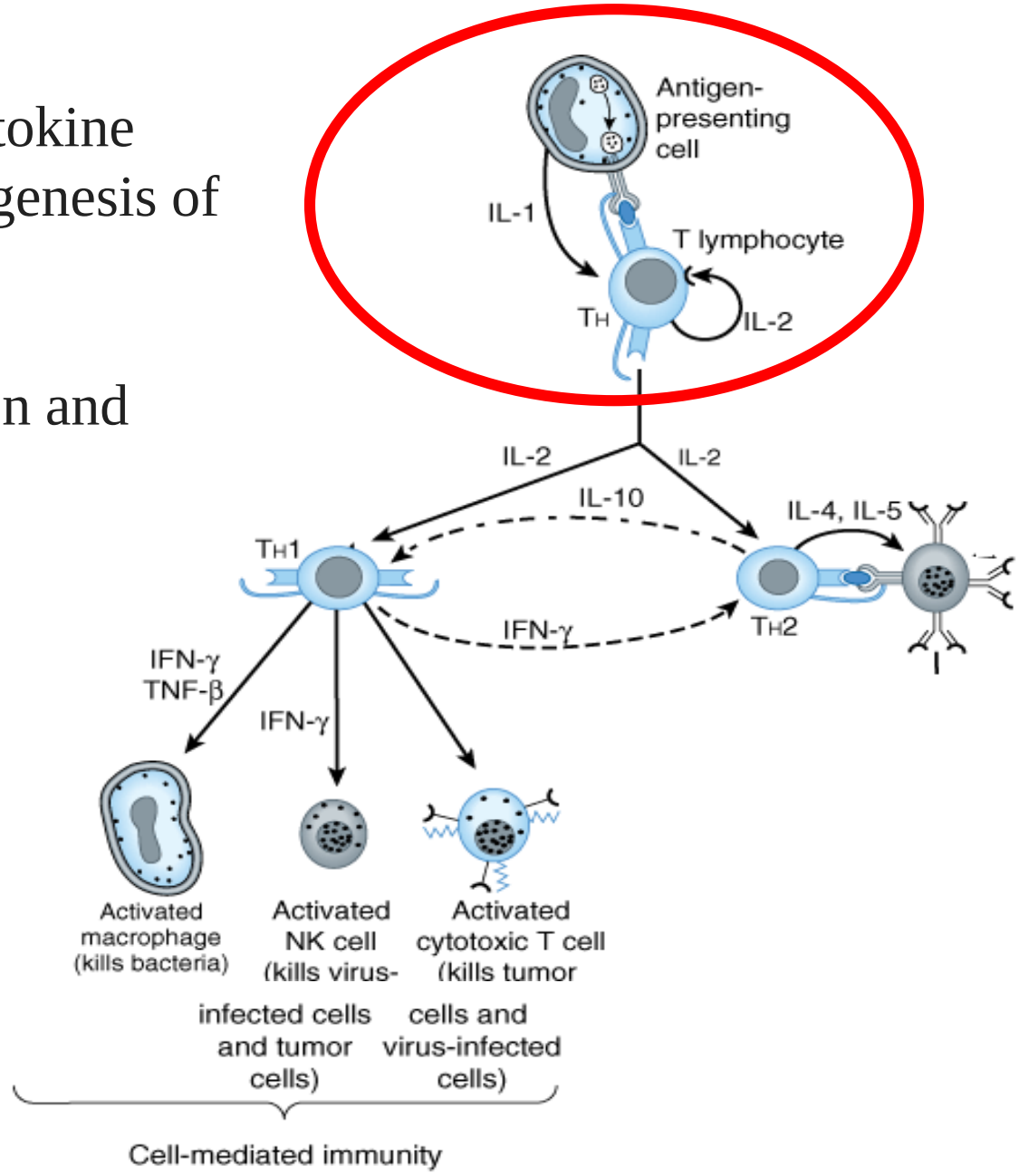
- Given subcutaneously
- half-life of 10–20 days.
- By merhotraxate:
  - Its clearance is decreased by more than 40%
  - reduction of the formation of human antimonoclonal antibody
- The usual dose in rheumatoid arthritis is 40 mg every other week

- **TNF-α blocking agents adverse effects:**
  - Increased the risk of bacterial infections and macrophage-dependent infection (including tuberculosis and other opportunistic infections)
  - Patients should be screened for latent or active tuberculosis before starting adalimumab or other TNF-–blocking agents

- **INFLIXIMAB:**
  - Chimeric Monoclonal Ab that binds with high affinity to human TNF-a
  - Higher antigenicity!
  - Given IV infusion
- **ETANERCEPT:**
  - A recombinant fusion protein that consists of 2 soluble TNF receptor moieties
  - **It binds 2 TNF-alpha molecule**s
  - Dose: 25mg SC twice weekly\
  - SE: increased the risk of bacterial infections , injection site reactions – pain, erythema, swelling, itching (20-40%)
- **Certolizumab**
  - it is a PEGylated Fab' fragment of a humanized TNF inhibitor monoclonal antibody
  - Higher half-life (once month)
  - Low antigenicity and lower antibody formation

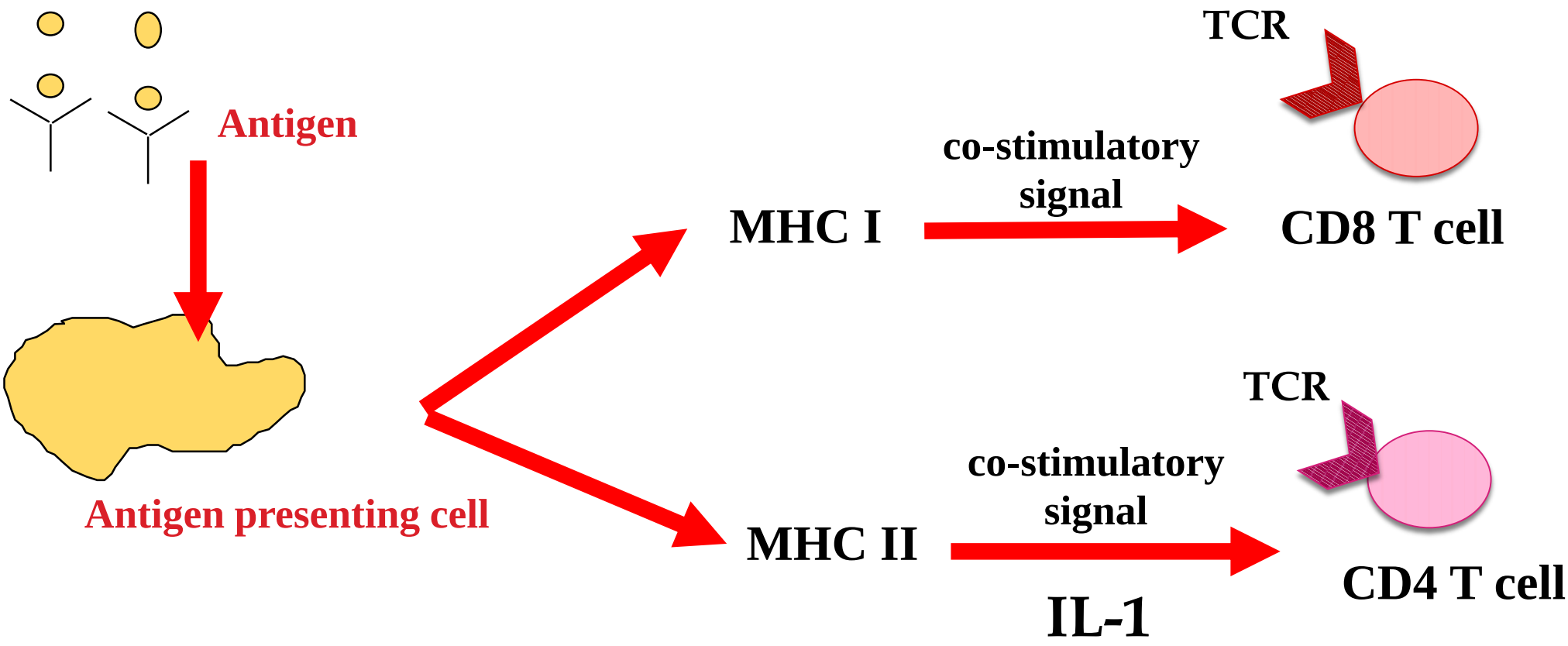
Interleukin-1is a primary cytokine that is involved in the pathogenesis of rheumatoid arthritis;

it contributes to inflammation and joint destruction.



Anakinra

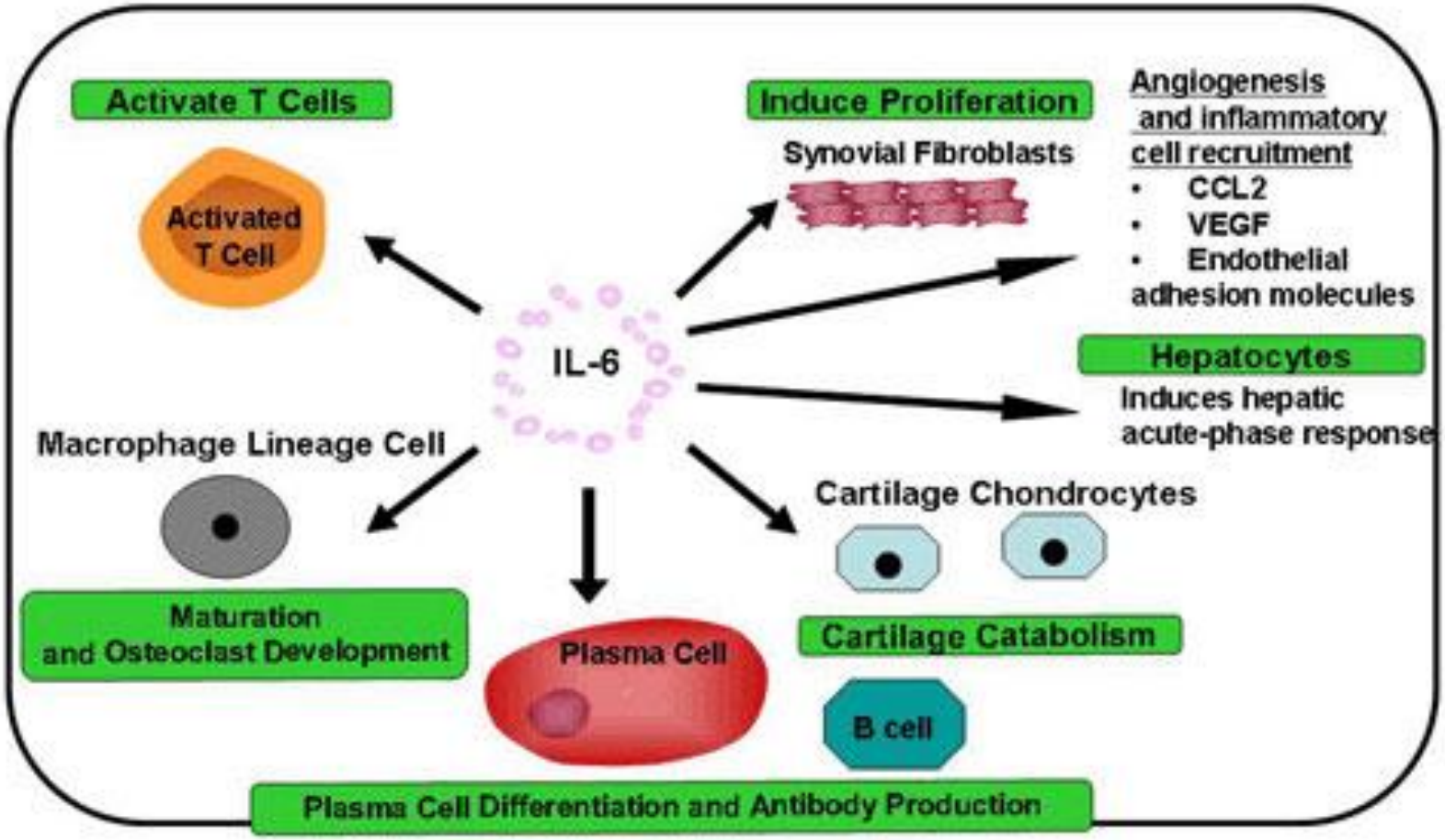
Anakinra (Kineret) is an IL-1 receptor antagonist that blocks the biologic activity of IL-1



Anakinra

- It is used as a second line treatment to manage symptoms of rheumatoid arthritis after treatment with a or some DMARD has failed
- Lower efficacy than TNFα–Blocking Agents
- Adverse effect: injection site reactions, headaches, and have increased levels of cholesterol in their blood
- Don’t increased risk of heart disease , therefore can be used in these patients
- Pregnancy: B

Proinflammatory Cytokines in RA: IL-6



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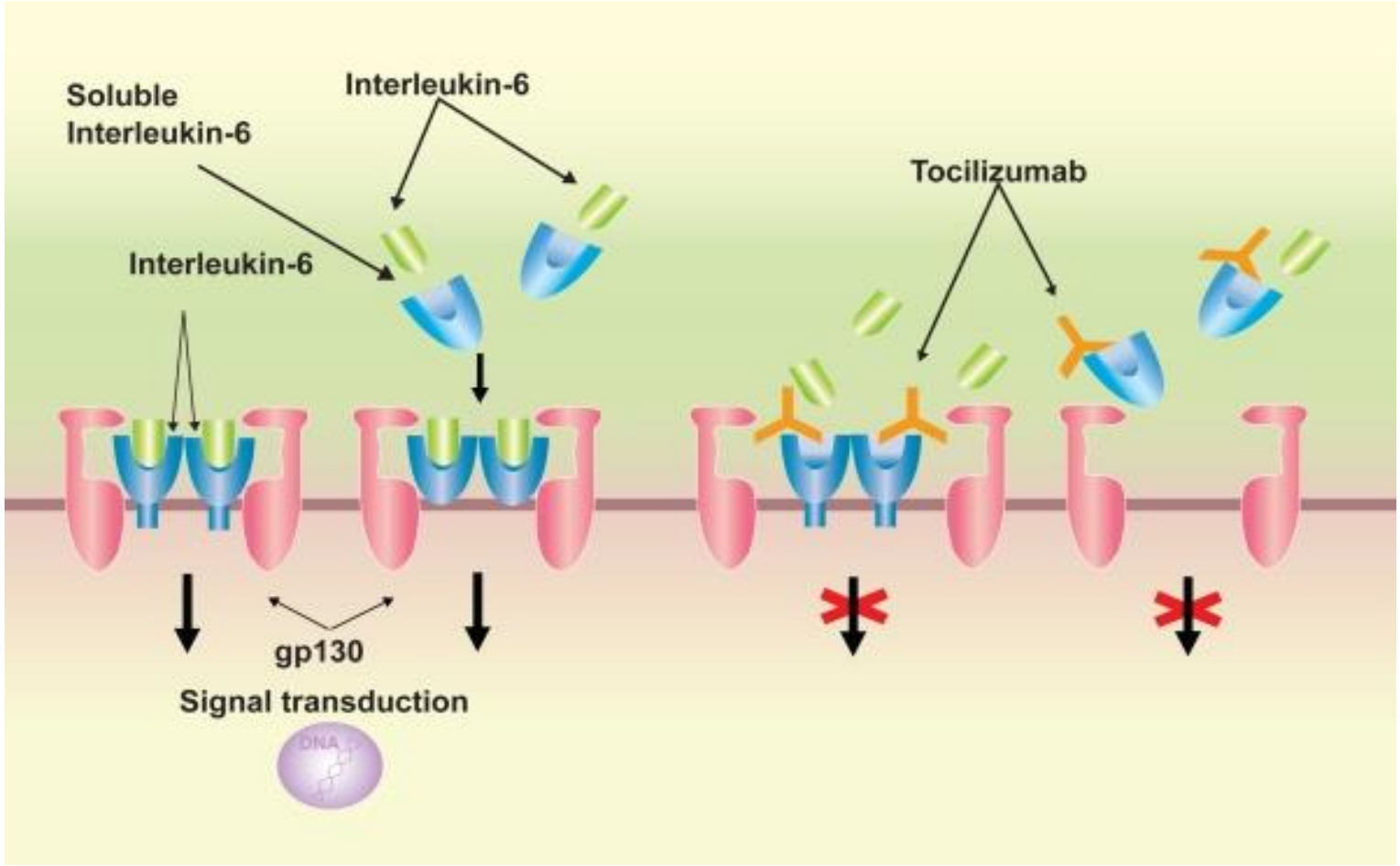
2. Doan T, et al. *J Clin Pharmacol*. 2005;45:751-762.
3. Gabay C. *Arthritis Res Ther*. 2006;8(suppl2):S3.

Medscape

Tocilizumab

A humanized monoclonal antibody against the interleukin-6 receptor (IL-6R).



Tocilizumab

- Tocilizumab is used for the treatment of moderate to severe rheumatoid arthritis, applied in combination with methotrexate, if other drugs like DMARDs and TNF alpha blockers have proven to be ineffective or were not tolerated.

- It can be used as a monotherapy for patients who do not tolerate methotrexate

- Adverse effects: increased risk of infection (upper respiratory tract infections, Nasopharyngitis..), headache, and high blood pressure (at least 5%). Elevation of enzyme alanine transaminase, Elevated total cholesterol levels were common.

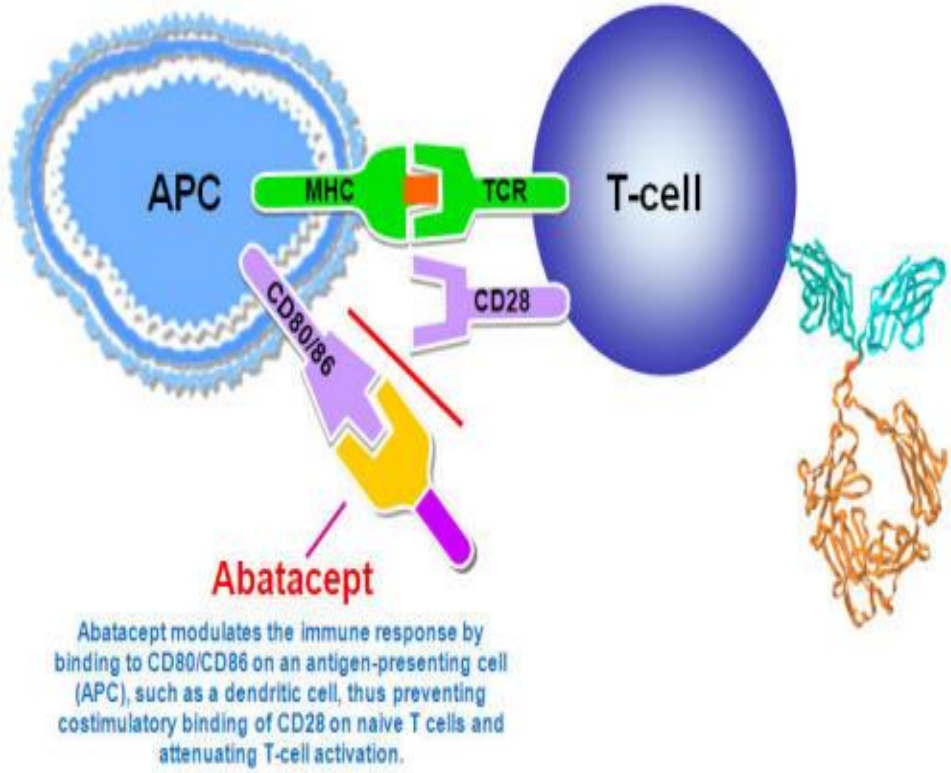
- Pregnancy: C

Abatacept

In order for a T cell to be activated and produce an immune response,

An APC must present two signals to the Tcell.

One of those signals is the major histocompatibility complex (MHC), combined with the antigen, and the other signal is the CD80 or CD86 molecule



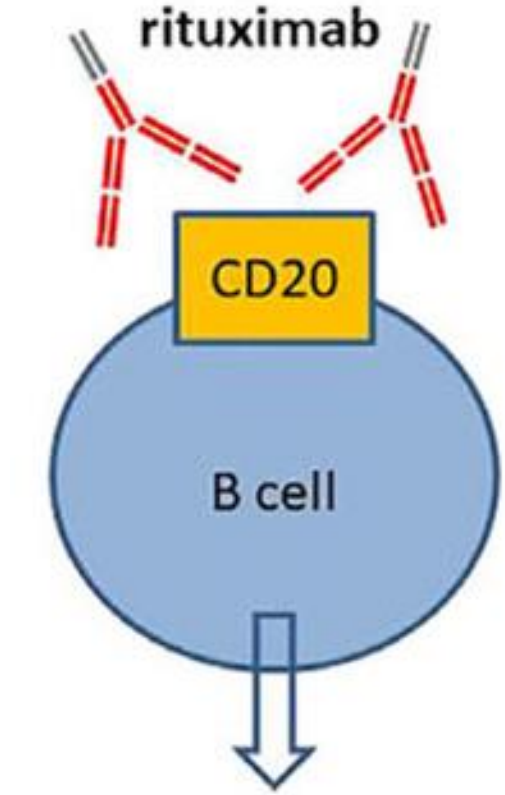
Abatacept binds to the CD80 and CD86 molecule, and prevents the second signal. Without the second signal, the T cell can't be activated

Abatacept

- Abatacept is used to treat adults with moderate to severe RA as a second line agent, and as a first line agent for people whose RA is severe and rapidly progressing (<6months)
- as monotherapy or in combination with other DMARDs in patients with moderate to severe rheumatoid arthritis
- increased risk of infection
- hypersensitivity reactions

Rituximab

- A chimeric monoclonal antibody that targets **CD20 on B lymphocytes,** When it binds to this protein it triggers cell death



Elimination of B-cells by antibody and complement mediated cytotoxicity and by apoptosis

Rituximab

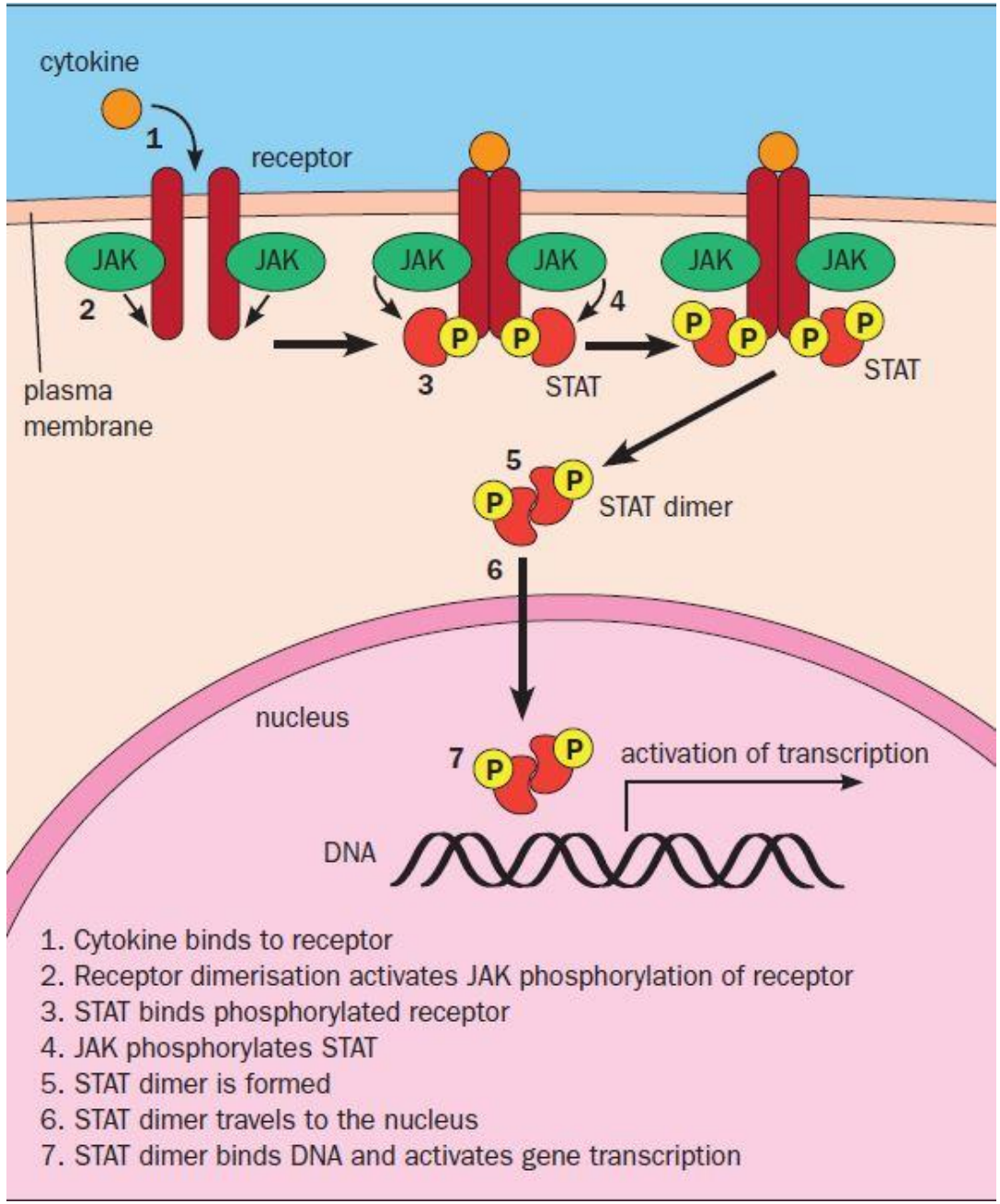
- **Indication:**
  - treatment of moderately to severely active rheumatoid arthritis in combination with methotrexate in patients with an inadequate response to one or more TNF- antagonists

- Develop **rashes** with the first 1000 mg treatment
  - **Pretreatment with glucocorticoids** (100 mg prednisolone) given intravenously 30 minutes prior to infusion

Jak/Stat pathway

Janus kinase enzymes (JAK1, JAK2, JAK3, and TYK2)

These enzymes normally promote inflammation and autoimmunity



JAK inhibitors

- Xeljanz (tofacitinib)
- Olumiant (baricitinib)
- Jakafi (ruxolitinib)
- Rinvoq (upadacitinib)

- All of the approved JAK inhibitors target all of the JAK enzymes.
- They are a small molecule-targeted treatment and are the first oral option to compare favourably to existing biologic DMARDs
- moderately-to-severely active rheumatoid arthritis who did not previously have an adequate response to methotrexate or tumor necrosis factor (TNF) inhibitor therapies

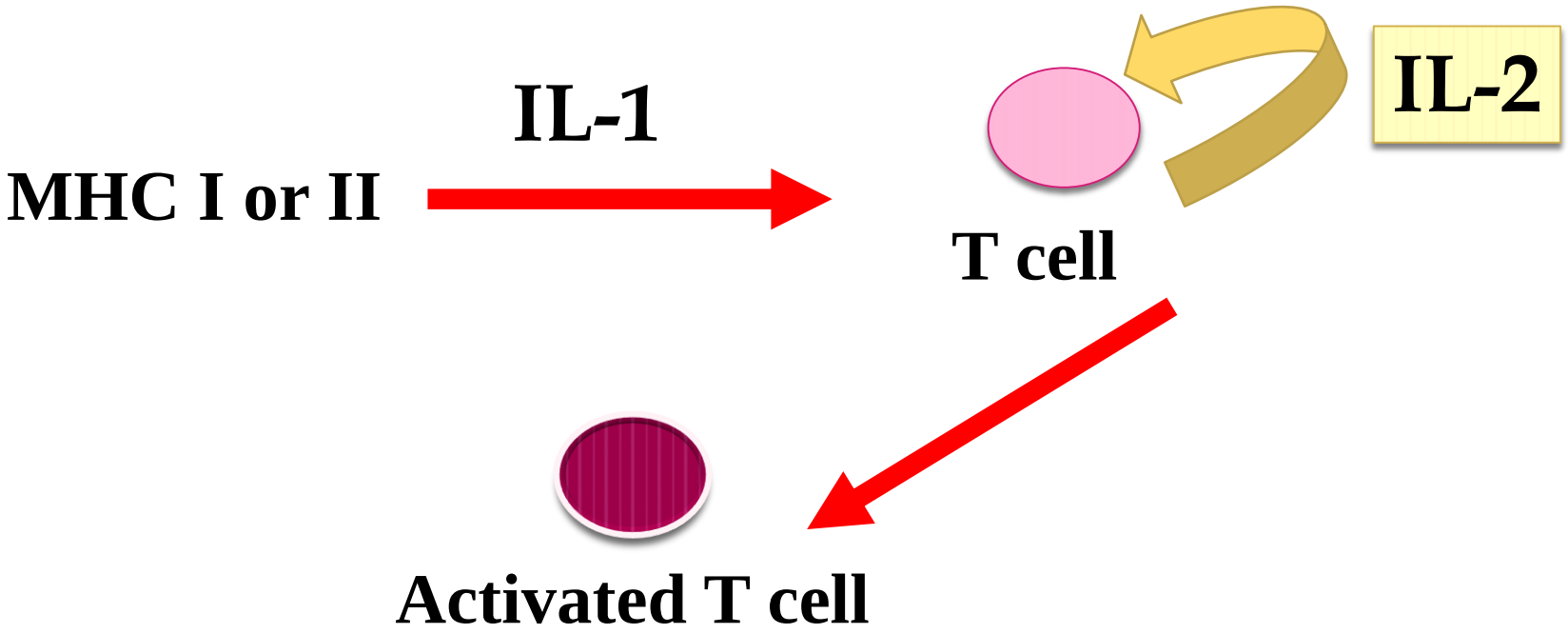
Side Effects

- Increase risk of infections. In clinical trials, a handful of people who took tofacitinib came down with tuberculosis (But the drugs have a short "half-life," which means that if you stop taking them, your body will soon get back its full ability to fight infection)
- Anemia
- Increased cholesterol level (taking a statindrug, such as atorvastatin
- a greater chance of getting blood clots when you use these drugs.

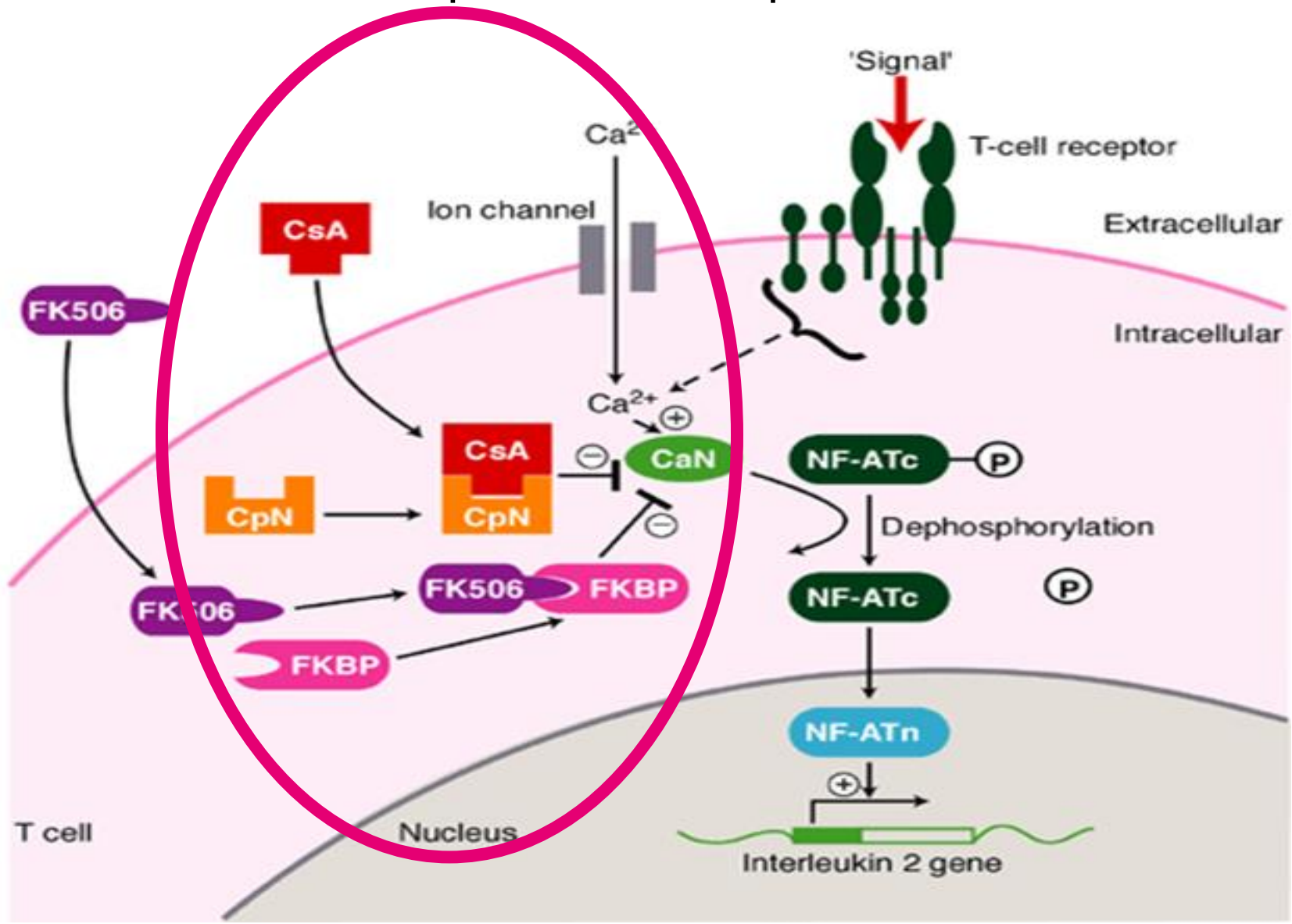
Other Drugs

CYCLOSPORINE

- Inhibits interleukin-2 translation and secondarily inhibits T-cell responsiveness

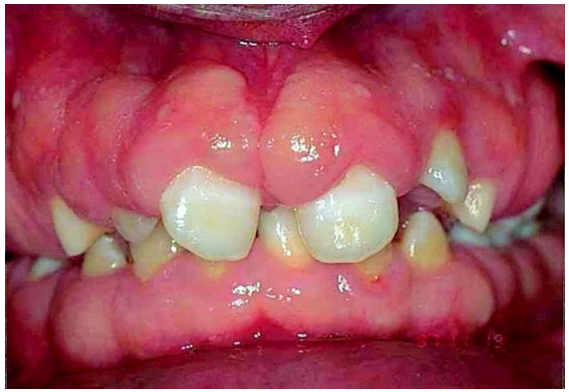


Calcineurin (a phosphatase) which is necessary for the activation of a T-cell-specific transcription factor



CYCLOSPORINE

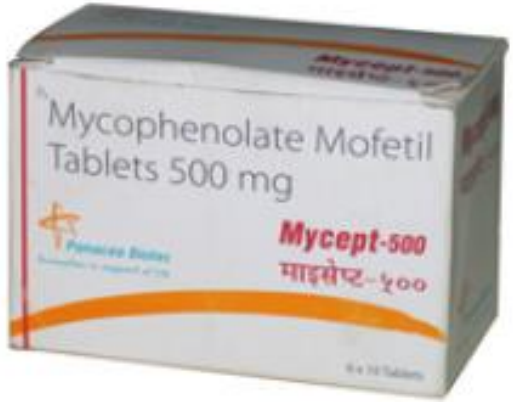
- Metabolized in the liver



- Dosage: 3-5mg/kg/d

- Toxicities: **nephrotoxicity**, HTN, hyperkalemia, hepatotoxicity, **gingival hyperplasia**, & hirsutism

Mycophenolate Mofetil



- Active metabolite: mycophenolic acid

- The active product inhibits **cytosine monophosphate dehydrogenase** in purine biosynthesiswhich is necessary for the growth of T cells and B cells

- Toxicities include gastrointestinal disturbances (N and V, diarrhea, abdominal pain), headache, hypertension, and reversible **myelosuppression**