Immunosuppressive and immunomodulatory agents

Immunosupressive agents

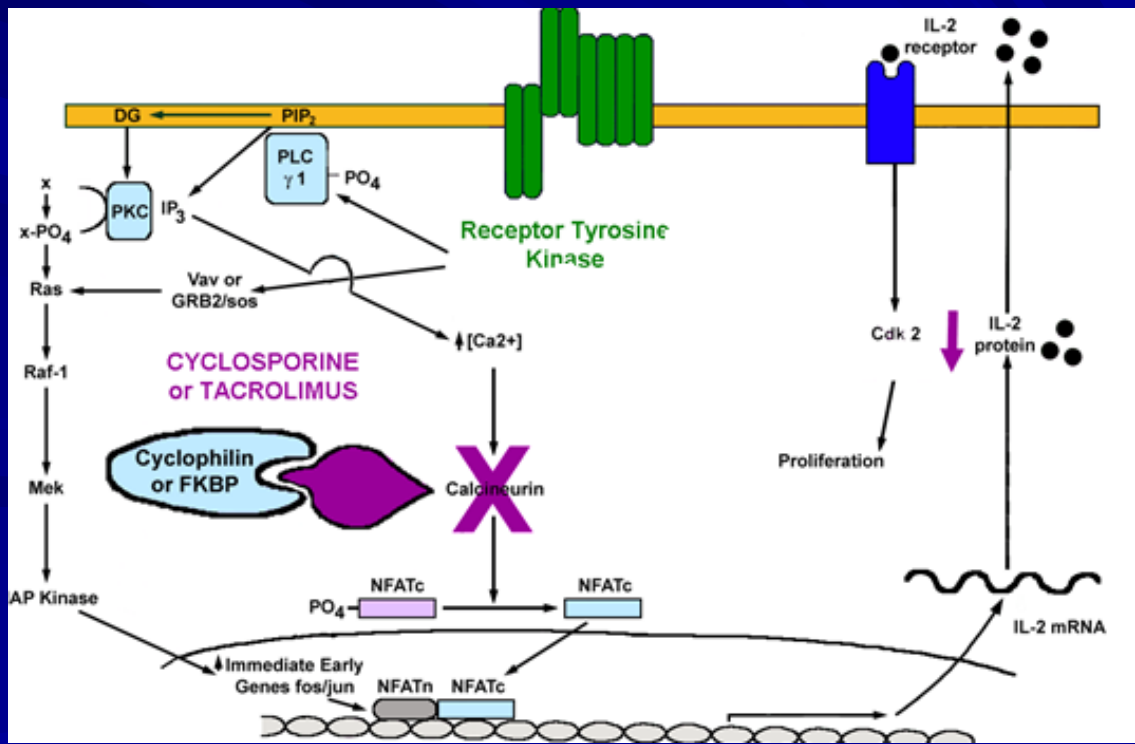
- Calcineurin inhibitors (immunophilin ligands) – cyclosporin, tacrolimus
- Proliferation signal inhibitors – sirolimus, everolimus
- Glucocorticosteroids
- Cytotoxic agents – antimetabolites (azathioprine, mycophenolate), alkylating agents (cyclophosphamide)
- Monoclonal antibodies

Immunosupressive agents - general indications:
Autoimmune diseases
Grafts rejection

Calcineurin inhibitors – cyclosporine, tacrolimus

- Cyclosporine act at an early stage in the antigen receptor-induced differentiation of T cells and blocks their activation.
- Cyclosporine binds to cyclophilin, a member of a class of intracellular proteins called immunophilins.
- Cyclosporine and cyclophilin form a complex that inhibits 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.

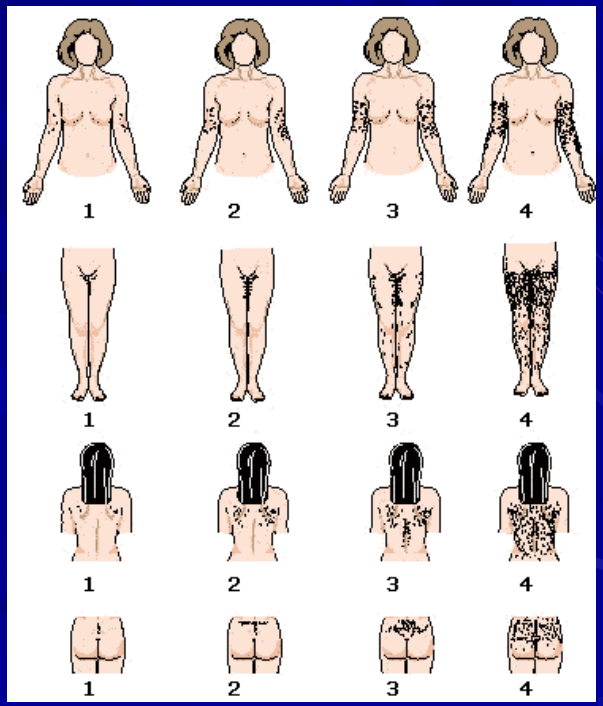
Tacrolimus (FK 506) binds to cytoplasmic peptidyl-prolyl isomerases that are abundant in all tissues. While cyclosporine binds to cyclophilin, tacrolimus binds to the immunophilin FK-binding protein (FKBP).
100 time more potent than cyclosporine



Calcineurin inhibitors –pharmacological effects

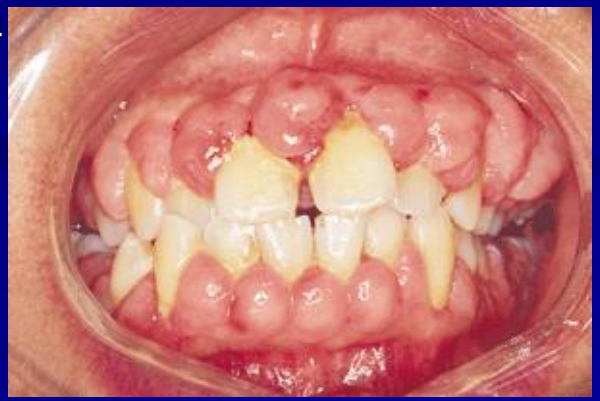
- Blocks IL-2 synthesis
- Supresses macrophages activation
- Inhibits release of IL-1, prevents formation of IL-1 receptors on CD_{4+} T cells
- Blocks the expression of IL-2 receptors on naïve T cells

Conclusion – main effect: T cells are not stimulated to proliferate in response to antigen



Adverse effects

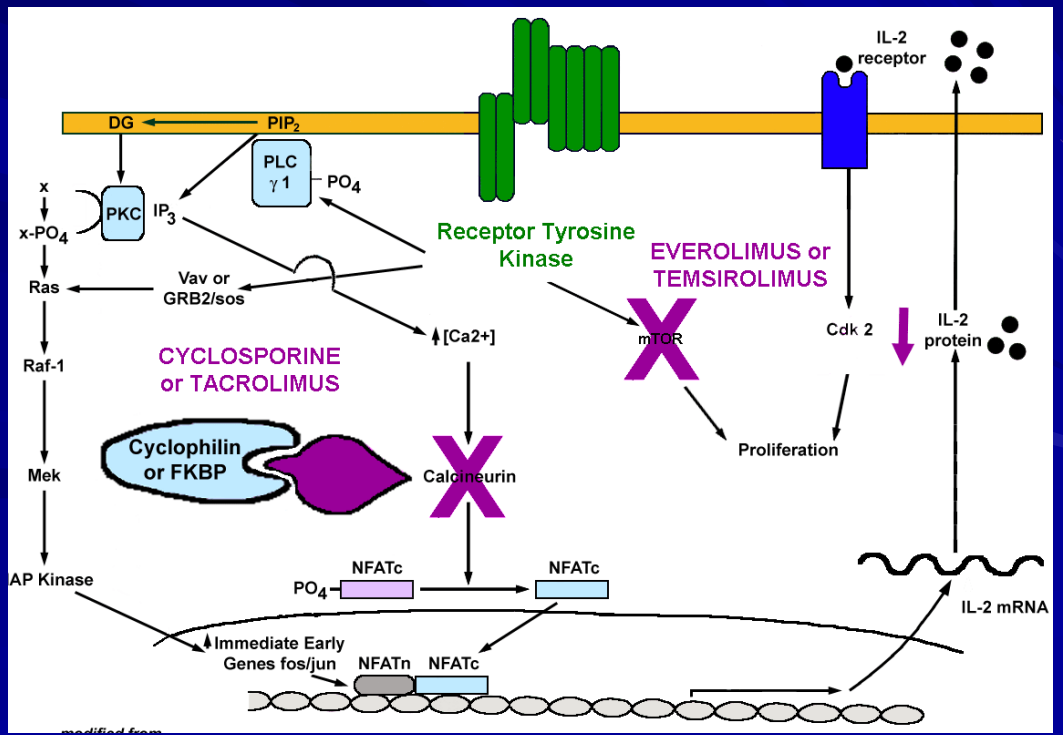
- Nephrotoxicity
- Hypertension
- CNS toxicity (seizures, depression)
- Hirsutism
- Hepatotoxicity
- Increased risk of neoplasms development
- Gingival hyperplasia



Proliferation signal inhibitors – sirolimus (rapamycin), everolimus

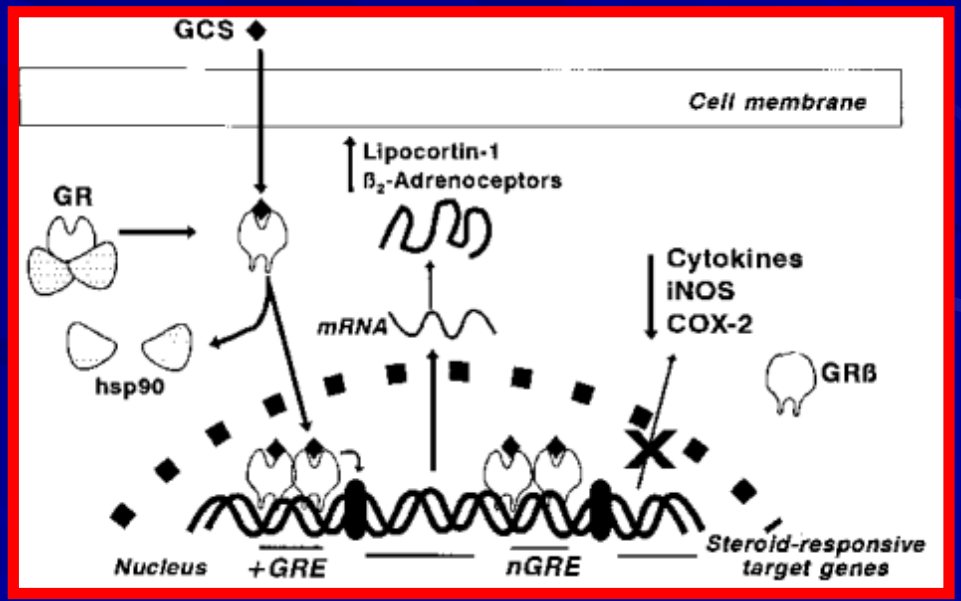
- **PSIs bind the circulating immunophilin FK506-binding protein 12, resulting in an active complex that blocks the molecular target of rapamycin (mTOR).**
- **The mTOR is a key component of a complex intracellular signaling pathway involved in cellular processes such as cell growth and proliferation, angiogenesis, and metabolism.**
- **Thus, blockade of mTOR ultimately can lead to inhibition of interleukin-driven T-cell proliferation.**
- **Both everolimus and sirolimus also may inhibit B-cell proliferation and immunoglobulin production.**

Adverse effects:
myelosuppression (especially thrombocytopenia)
hepatotoxicity
diarrhea
hypertriglyceridemia
pneumonitis



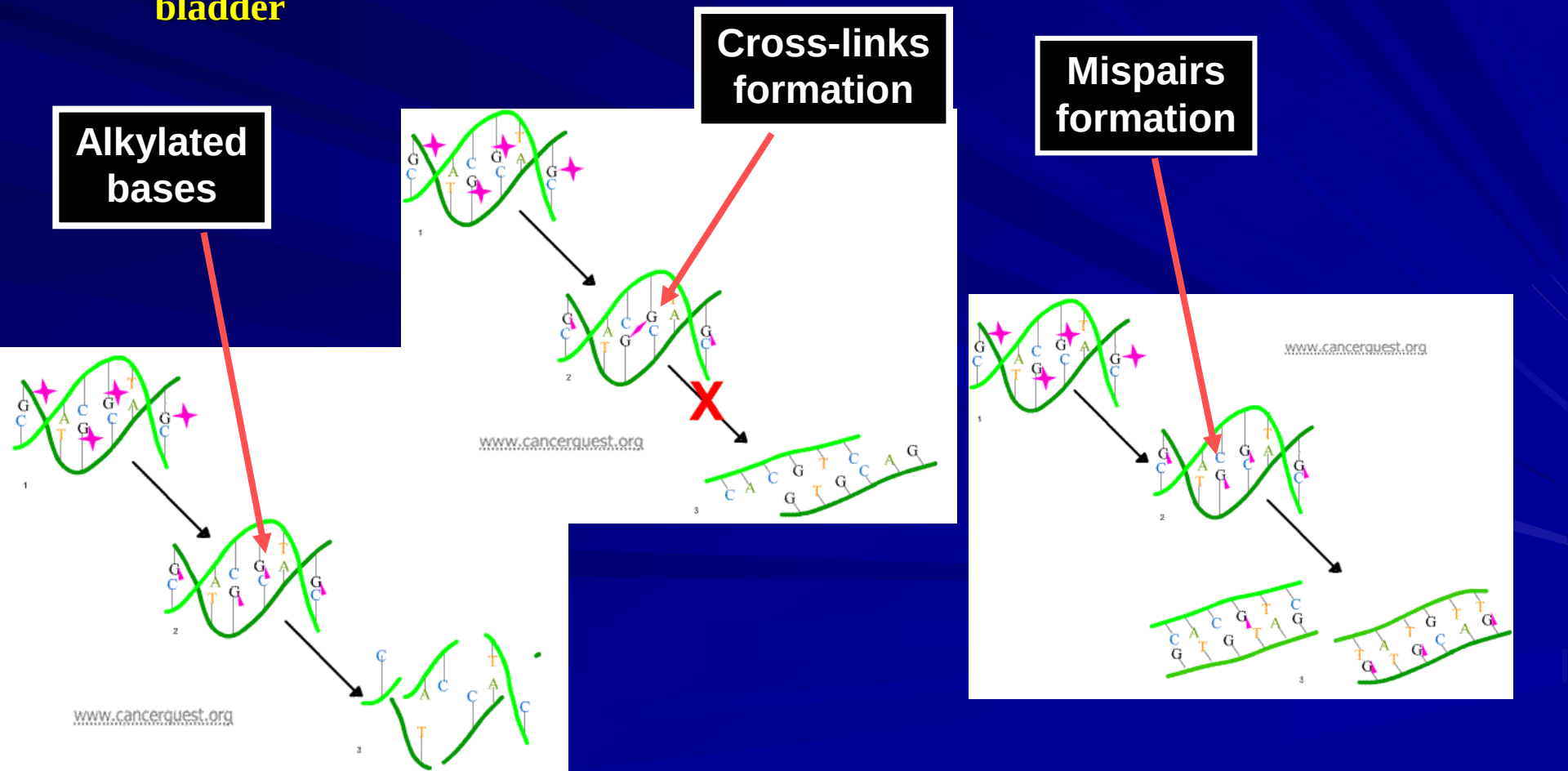
Glucocorticosteroids

- **Bind to the cytoplasmatic receptor. This complex interacts with DNA.Transcription of specific genes are inhibited or promoted**
- **Glucocorticoids are thought to interfere with the cell cycle of activated lymphoid cells. Affect cytokins and inflamatory proteins synthesis. Cellular immunity is more affected than humoral one**
- **Glucocorticoids are quite cytotoxic to certain subsets of T cells, but their immunologic effects are probably due to their ability to modify cellular functions rather than to direct cytotoxicity.**



Cytotoxic drugs: Cyclophosphamide

- Alkylating agent
- Alkyle groups (CH_3, C_2H_5) from cyclophosphamide are bound by DNA, RNA and proteins
- Ultimate effect: killing intensively multiplying cells including T-cells
- Adverse reaction:bone marrow depression, haemhorrhagic inflamation of the bladder

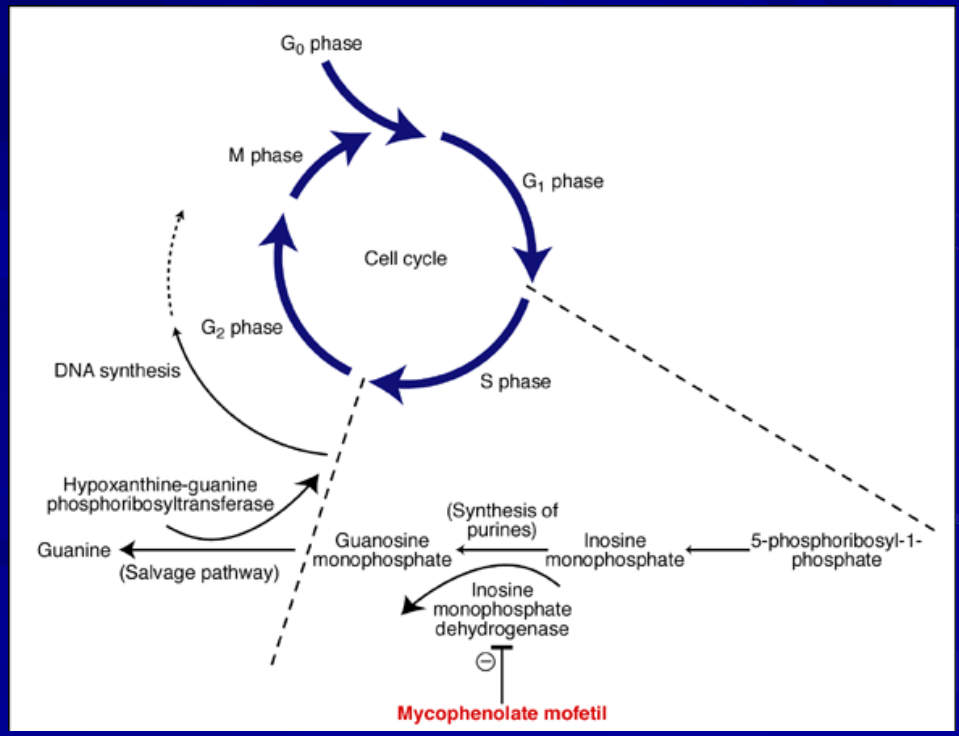


Antimetabolite- Mycophenolate mofetil (MMF)

- inhibits T- and B-lymphocyte responses, including mitogen and mixed lymphocyte responses, probably by inhibition of de novo synthesis of purines.
- Toxicities include: gastrointestinal disturbances (nausea and vomiting, diarrhea, abdominal pain) headache, hypertension, and reversible myelosuppression (primarily neutropenia).

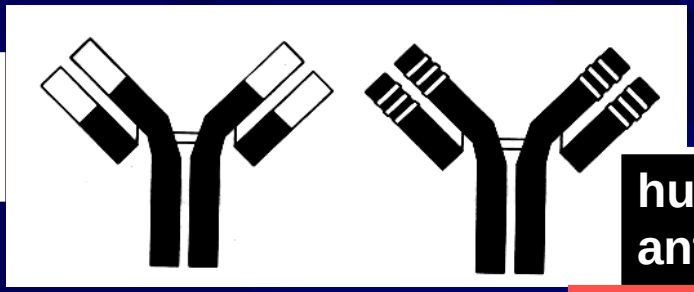
Antimetabolite-Azathioprine

- produces immunosuppression by interfering with purine nucleic acid metabolism at steps that are required for the lymphoid cell proliferation that follows antigenic stimulation.
- the purine analogs are thus cytotoxic agents that destroy stimulated lymphoid cells.
- cellular immunity as well as primary and secondary serum antibody responses can be blocked by these cytotoxic agents

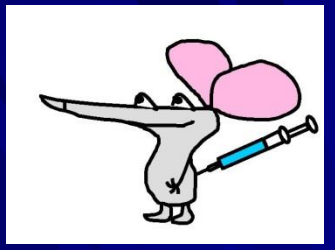


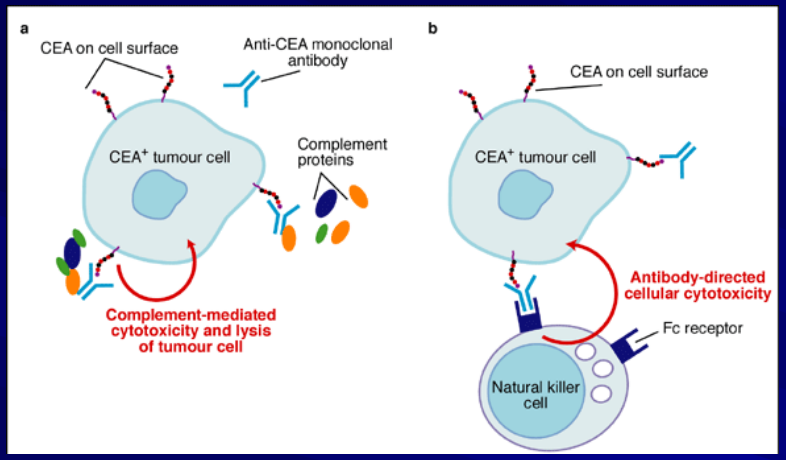
Monoclonal antibodies

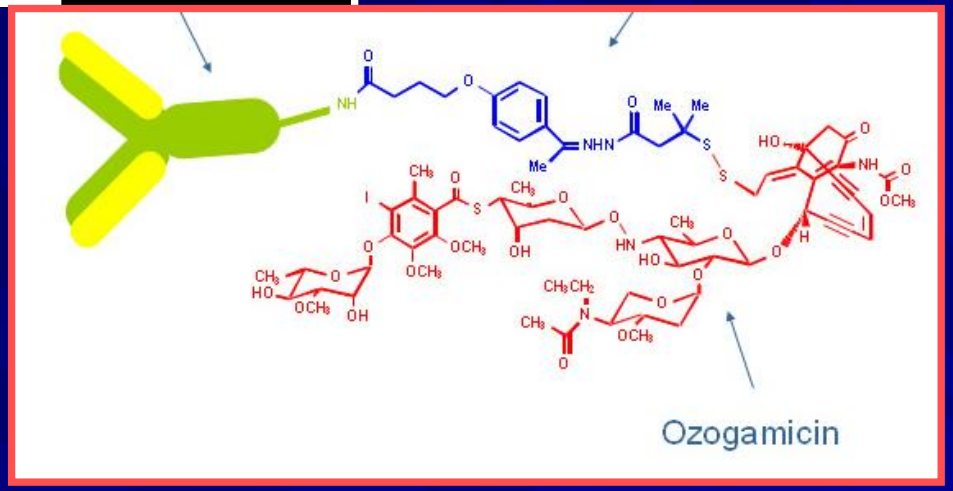
chimeric antibody



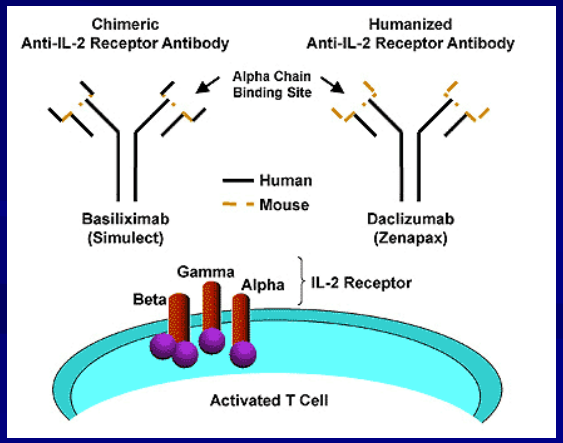
humanized antibody







1. Induce cytotoxic effect



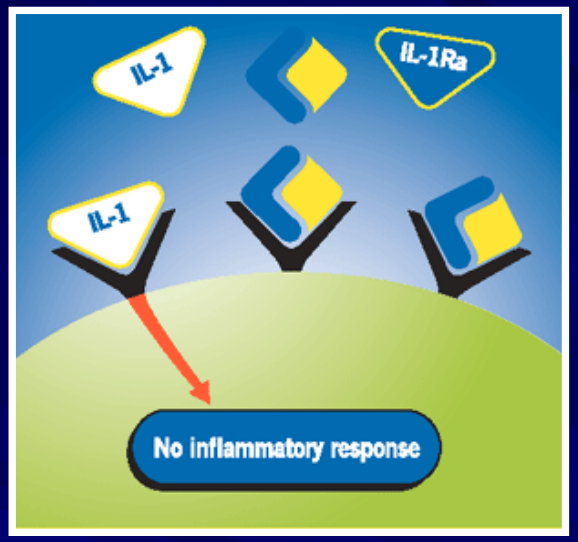
2. Inhibit binding receptors with their ligands

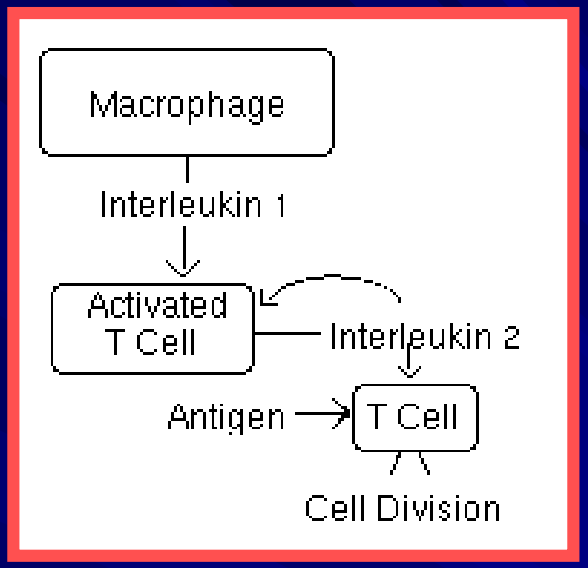
3.Transport radionuclides or toxins just to the target cells

Ultimate effect: apoptosis

Monoclonal antibodies adverse effects

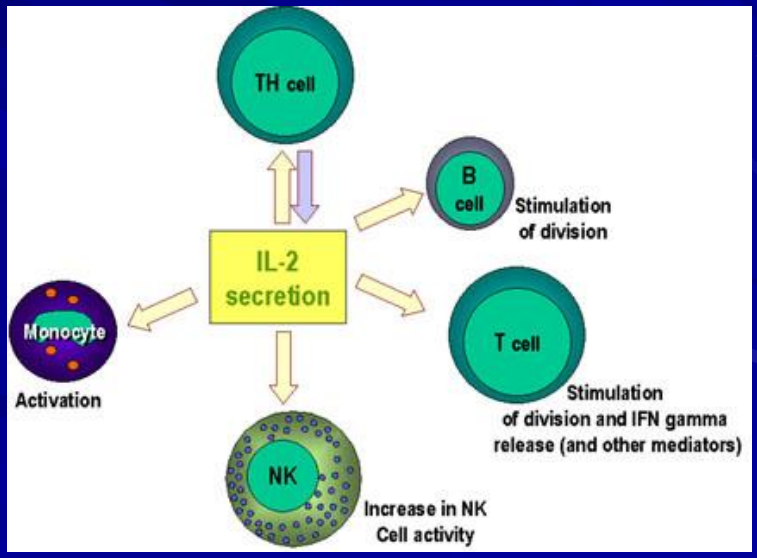
- infusion-related cytokine release syndrome
- 30 min post infusion – fever, chills, headache, fatigue, myalgia, arthralgia, skin reaction, repiratory disturbances, aseptic meningitis, pulmonary edema, hypotonia, arrhytmias, cardiac arrest
- baclizumab and daclizumab – rare
- systemic allergic reaction
- susceptability to infection and neoplasms development
- pancytopenia – mainly alemtuzumab





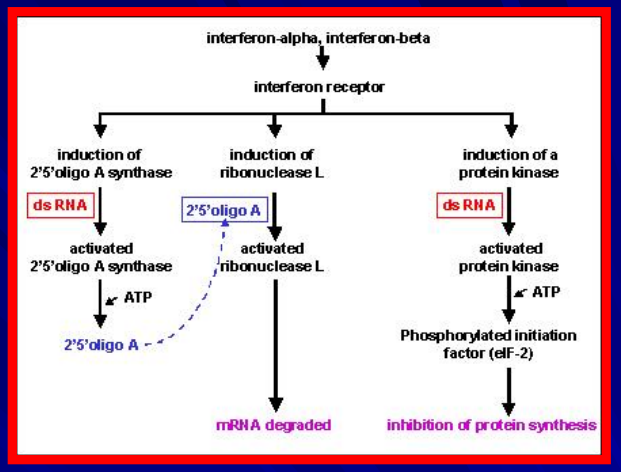
Interleukin-1 receptor antagonist - anakinra
Therapy of rheumatoid arthritis

Aldesleukin = IL-2
Effects: activation of NK-cells, stimulation T-cells proliferation
Therapeutic use: cancers-metastases, HIV
Adverse effects: leak syndrome (edema, reduced organ perfussion, hypotension), arrhythmias, MI, respiratory insufficiency, mental disturbances, increased infection



- INF alfa and beta
- Phosphorylate STAT (signal transducers and activators of transcription)
- STAT form than complex with nonphosphorylated protein, enter nucleus, binds to DNA and promotes transcription
- Only nonphosphorylated STAT can bind to DNA
- Indications: hairy cell leukemia, chronic melanogenous leukemia, genital warts, sarcoma Kaposi, hepatitis C, melanoma (INF-α), multiple sclerosis (INF-β)

Adverse effects: flu-like symptoms, Leukopenia, depression, hepatotoxicity



INF-gamma

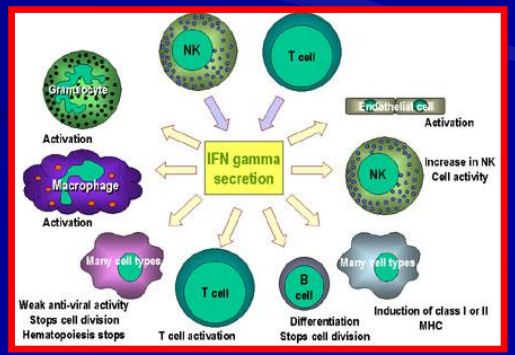
Antiviral activity

Stimulation of CD_{4+} TH_1 T-cells and macrophages

Supression of antibody production

Upregulation of MHC class II molecule expression on tumor cells

Therapeutic use: serious infections associated with granulomatous disease, malignant osteopetrosis, rheumatoid arthritis

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