Immunopharmacology

Munir Gharaibeh, MD, PhD, MHPE.

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Immunopharmacology

- **Immunosuppressive Agents.**
- **Immunomodulation Therapy.**
- **Immunologic Reactions to Dugs.**

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.

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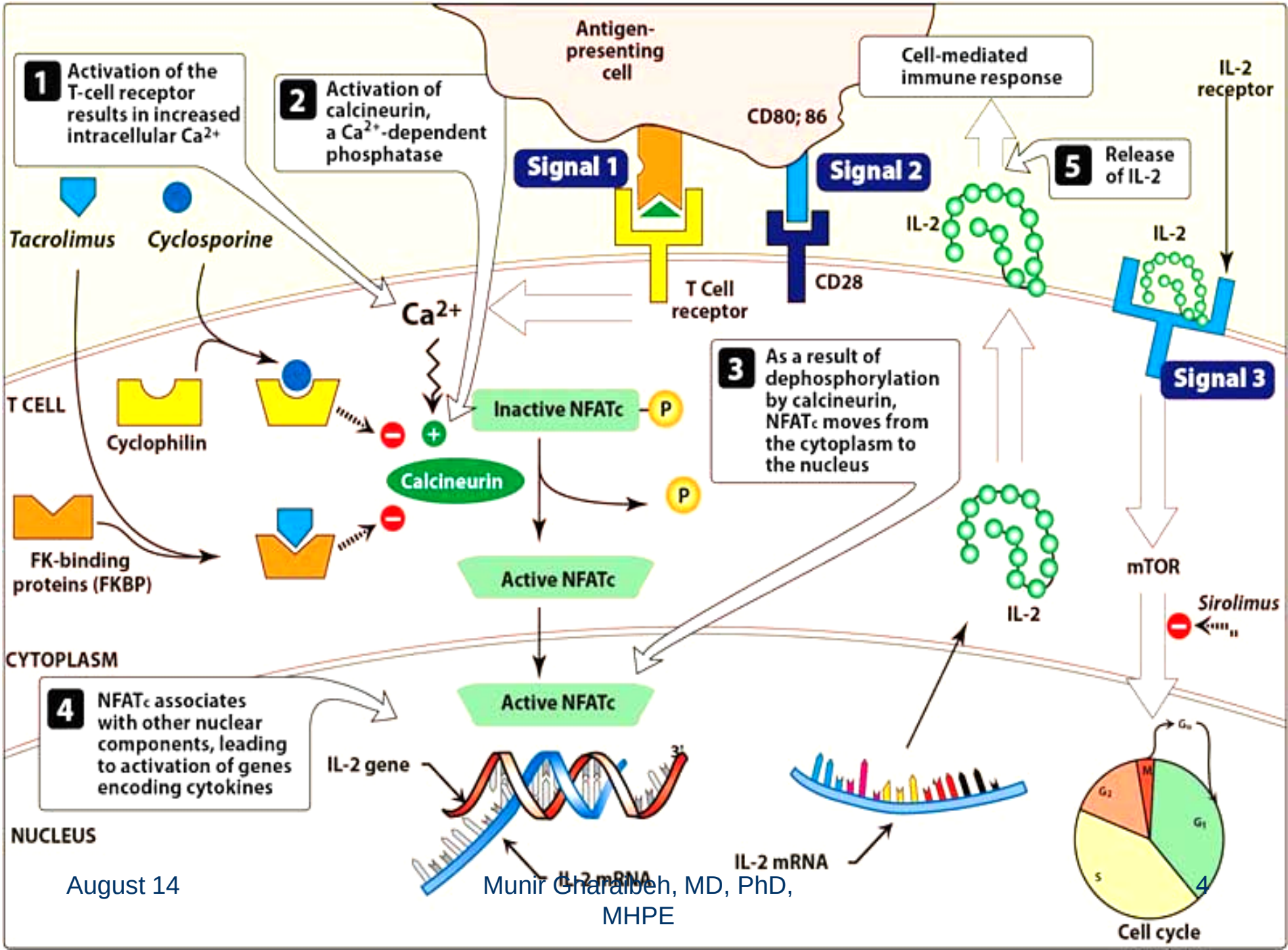
IL-2 then binds to CD25 (IL-2 receptor) on the surface of other T cells to activate mammalian target of *rapamycin* (mTOR), providing Signal 3, the stimulus for T-cell proliferation.


Antigen-presenting cell
1 Activation of the T-cell receptor results in increased intracellular Ca2+
2 Activation of calcineurin, a Ca2+-dependent phosphatase
Tacrolimus
Cyclosporine
Signal 1
Signal 2
CD80; 86
T Cell receptor
CD28
Cell-mediated immune response
5 Release of IL-2
IL-2 receptor
IL-2
IL-2
Signal 3
Ca2+
T CELL
Cyclophilin
Inactive NFATc
P
3 As a result of dephosphorylation by calcineurin, NFATc moves from the cytoplasm to the nucleus
Calcineurin
P
FK-binding proteins (FKBP)
Active NFATc
IL-2
mTOR
Sirolimus
CYTOPLASM
4 NFATc associates with other nuclear components, leading to activation of genes encoding cytokines
Active NFATc
IL-2 gene
IL-2 mRNA
IL-2 mRNA
NUCLEUS
Cell cycle

Immunosuppressive Agents

- **Clinical Uses:**
  - **Organ transplantation.**
  - **Autoimmune Disorders.**
  - **Isoimmune Disease, e.g. hemolytic disease of newborn.**
  - **Prevention of cell proliferation, e.g. coronary stents, neovascular macular degeneration.**

Immunosuppressive Agents

- **Glucocorticoids.**
- **Calcineurin Inhibitors.**
- **Proliferation Signal Inhibitors.**
- **Mycophenolate Mofetil.**
- **Thalidomide.**
- **Cytotoxic Agents.**
- **Immunosuppresive Antibodies.**
- **Monoclonal antibodies.**

Glucocorticoids

- **First hormonal agents recognized as having lympholytic properties.**
- **Cytotoxic to certain subsets of T cells.**
- **Decrease antibody responses.**
- **Increase catabolic rate of IgG.**
- **Have additional antinflammatory and antiallergic activities.**
- **Used in a variety of conditions.**
- **Have their own toxicities.**

Actions of Glucocorticoids

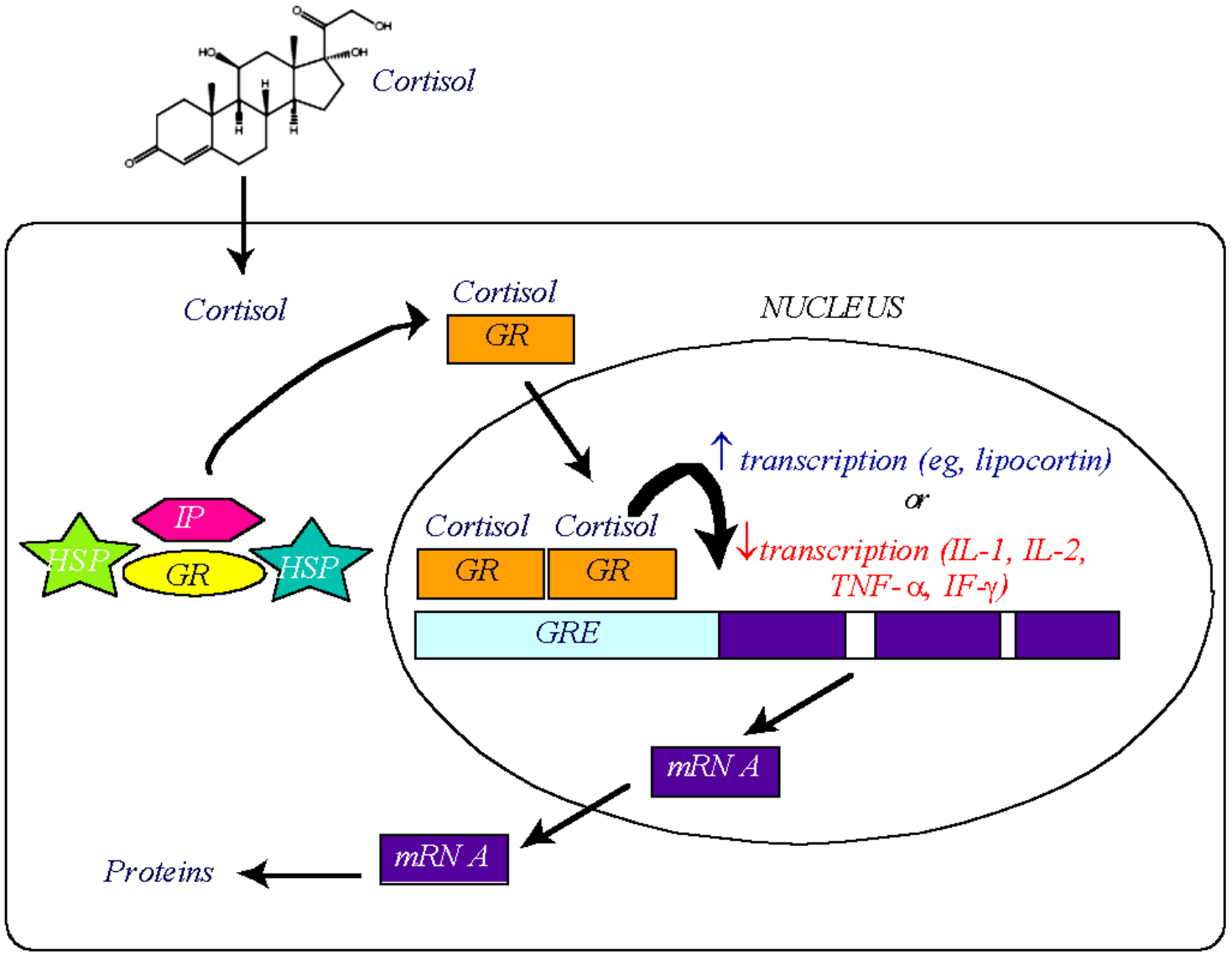
- **Glucocorticoids suppress the cell-mediated immunity. inhibiting genes that code for the cytokines, the most important of which is IL-2.**

- **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.**

Glucocorticoids Regulate Transcription



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

Clinical Uses of Glucocorticoids

- **First-line immunosuppressive therapy for:**
  - **Solid organ**
  - **Hematopoietic stem cell transplant recipients**
  - **Graft-versus-host disease (GVHD).**

- **Idiopathic thrombocytopenic purpura and rheumatoid arthritis.**

- **Bronchial asthma.**
- **Premedication for agents (e.g. blood products, and drugs) known to cause undesirable immune responses.**

Side Effects to Glucocorticoids

- Immunodeficiency
- adrenal glands
- Hyperglycemia and abnormal Fat redistribution
- Growth failure, delayed puberty.
- Excitatory effects on central nervous system (euphoria, psychosis)
- Osteoporosis
- Cataract
- Gastric irritation and ulceration.

Calcineurin Inhibitors

- **Cyclosporine:**
  - **Peptide antibiotic.**
  - **Works on an early stage of the antigen receptor-induced differentiation of T cells and blocks their activation.**
  - **Binds to an intracellular protein to form a complex which inhibits a cytoplasmic phosphatase, calcineurin, which is important for the activation of a T-cell specific transcription factor (NF-AT) which is involved in interleukin synthesis by activated Tcells.**

Cyclosporine

- **Given, orally, IV, by inhalation, or as ophthalmic solution.**
- **Metabolized by P450 3A enzyme system with resultant multiple drug interactions and variability in bioavailability, and consequently, there is a need for routine drug monitoring.**

Cyclosporine

- **Nephrotoxicity.**
- **Hypertension.**
- **Hyperglycemia.**
- **Liver dysfunction.**
- **Hyperkalemia.**
- **Altered mental status, seizures.**
- **Hairsutism.**
- **Lymphoma and other cancers (Kaposi's sarcoma, skin cancer) due to induction of TGF-β.**

Cyclosporin Monitoring Parameters

- Cyclosporine trough levels.
- Serum electrolytes.
- Renal function.
- Hepatic function.
- Blood pressure.
- Serum cholesterol.

Calcineurin Inhibitors

- **Tacrolimus:**
  - **Macrolide antibiotic.**
  - **Binds to the immunophylline FK-binding protein (FKBP) which inhibits calcineurin.**
  - **10-100 times more potent than cyclosporin.**
  - **Given orally, IV and topically.**
  - **Similar metabolism problems and toxicity to cyclosporin.**

Clinical Uses of Cyclosporine & Tacrolimus

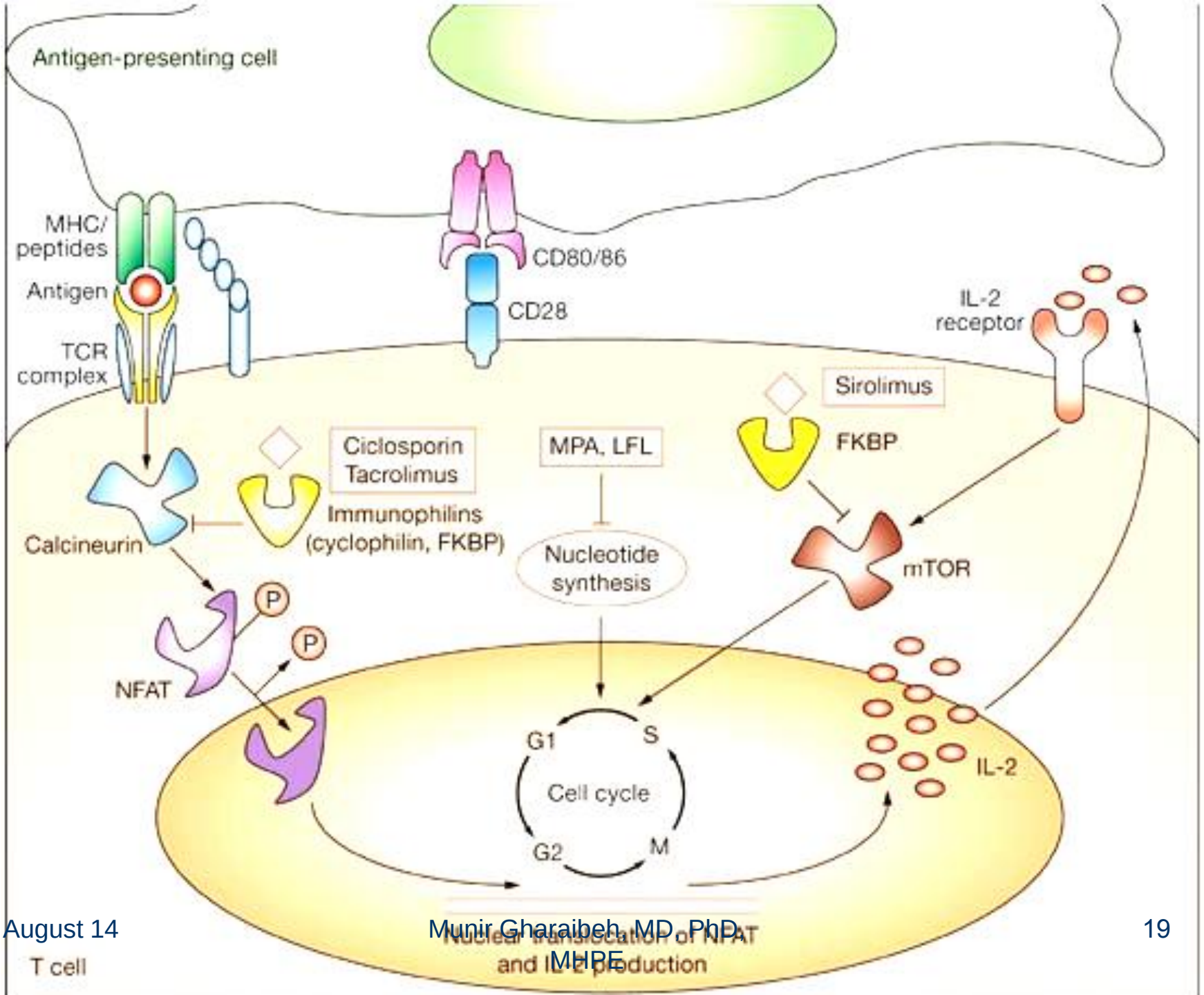
1. **Human organ transplantation,**

2. **Graft-versus-host disease after hematopoietic stem cell transplantation,**

3. **Selected autoimmune disorders, including uveitis, rheumatoid arthritis, psoriasis, and asthma.**

Proliferation Signal Inhibitors(PSIs)

- **Sirolimus(Rapamycin).**
- **Everolimus.**
  - **Bind the circulating immunophylline FK506-binding protein12.**
  - **The complex inhibits interleukin-driven T-cell and B-cell proliferation as well as immunoglobulin production.**
  - **Available for oral and topical administration.**
  - **Sirolimus-eluting coronary stents.**
  - **Renal toxicity is less common than with calcineurin inhibitors.**


Antigen-presenting cell
MHC/
peptides
Antigen
TCR
complex
CD80/86
CD28
IL-2
receptor
Sirolimus
FKBP
Ciclosporin
Tacrolimus
Immunophilins
(cyclophilin, FKBP)
MPA, LFL
Calcineurin
Nucleotide
synthesis
mTOR
P
P
NFAT
G1
S
Cell cycle
G2
M
IL-2
T cell

Mycophenolate Mofetil

- **Derived from a mold *Penicillium glaucus.***
- **Hydrolyzed to mycophenolic acid, the active immunosuppressive moiety.**
- **Given orally or IV.**
- **Plasma levels are monitored.**
- **Can cause N,V, D, abdominal pain, headache, hypertension, and reversible myelosuppression, primarily neutropenia.**

MYCOPHENOLATE

- 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.

Thalidomide

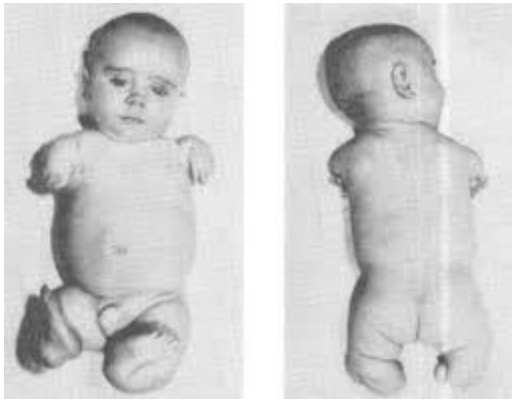
- **Historical sedative drug withdrawn in 1960s because of its teratogenicity (Phocomelia).**
- **Inhibits angiogenesis.**
- **Antiinflammatory.**
- **Inhibits tumor necrosis factor-alpha(TNF-α)**
- **Reduces phagocytosis by neutrophils.**
- **Increases production of IL-10**
- **Alters adhesion molecule expression.**
- **Enhances cell-mediated immunity via interaction with T cells.**

Thalidomide

- **Use continued only for leprosy.**
- **Very successful in multiple myeloma.**
- **Clinical trials in other diseases: myelodysplastic syndrome, AML, graft-versus- host disease, and solid tumors.**

Thalidomide

- **Toxicity:**
  - **Teratogenicity.**
  - **Peripheral neuropathy.**
  - **Constipation.**
  - **Rash.**
  - **Fatigue.**
  - **Hypothyroidism.**
  - **DVT.**
- **Lenalidomide**
- **CC-4047(Actimid).**
  - **Are much less toxic derivatives.**



Cytotoxic Agents

- **Azathioprine.**
- **Cyclophosphamide.**
- **Leflunomide.**
- **Hydroxychloroquine**
- **Others:**
  - **Vincristine.**
  - **Vinblastine**
  - **Methotrxate.**
  - **Cytarabine.**
  - **Pentostatin.**

Azathioprine

- **Prodrug of mercaptopurine.**
- **Metabolized by Xanthine oxidase (so dose is reduced when given with allopurinol) .**
- **Antimetabolite: interferes with purine nucleic acid metabolism, and consequently will destroy and inhibit lymphoid cell proliferation stimulated by antigens.**
- **Blocks cellular immunity as well as primary and secondary serum antibody responses.**

Azathioprine

- **Used in renal allograft, acute glomerulonephritis, SLE, RA, Crohn's Disease, MS, and ITP.**
- **Toxicity:**
  - **Bone marrow suppression.**
  - **Skin rashes, fever.**
  - **N, V, D.**
  - **Hepatic dysfunction and jaundice.**

Cyclophosphamide.

- **Alkylating agent.**
- **Destroys proliferating lymphoid cells.**
- **Alkylates some resting cells.**
- **Large doses can induce an apparent specific tolerance to a new antigen if the drug is administered simultaneously with, or shortly after, the antigen.**
- **Toxicity: Pancytopenia, hemorrhagic cystitis, N, V, cardiac toxicity, electrolyte disturbances.**

Immunosuppresive Antibodies

- **Hybridoma Technology, 1975.**
- **Molecular Biology >>>> Monoclonal Antibodies.**
- **Humanized Antibodies: “-umab” or “-umab”.**
  - **Replacing most of the regions, but keeping only the variable, antigen-specific regions intact.**
- **Chimeric Antibodies: “-imab” or “-ximab”.**
  - **Less complete replacement of the murine components.**

Hybridoma Technology

- **A technology of forming hybrid cell lines (called hybridomas) by fusing a specific antibody-producing B cell with a myeloma (B cell cancer) cell that is selected for its ability to grow in tissue culture and for an absence of antibody chain synthesis.**
- **The antibodies produced by the hybridoma are all of a single specificity and are therefore monoclonal antibodies .**

Immunosuppresive Antibodies

- **Antilymphocyte & Antithymocyte Antibodies.**
- **Muromonab.**
- **Immune Globulin Intravenous.**
- **Rh_o(D) Immune Globulin Micro-Dose.**
- **Hyperimmune Immunoglobulins.**

Antilymphocyte & Antithymocyte Antibodies

- **Used for over 100 years.**
- **Antiserum obtained by immunization of large animals with human lymphoid cells.**
- **ALG: acts on the small, long-lived peripheral lymphocytes that circulate between the blood and lymph. With continued use, T cells are also depleted.**
- **Consequently, delayed hypersensitivity and cellular immunity is impaired while humoral antibody formation remains relatively intact.**

Antilymphocyte & Antithymocyte Antibodies

- **Toxicity:**
  - **Local pain and erythema.**
  - **Anaphylaxis and serum sickness reactions**
  - **May precipitate in the glomeruli.**
  - **Histiocytic lymphomas at site of injection.**

Muromonab.

- **Murine monoclonal antibody directed against the CD3 molecule on the surface of human thymocytes and mature T cells.**
- **Blocks killing by cytotoxic human T cells.**
- **Used in renal allograft rejection.**

Muromonab

Initial binding of *muromonab* 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.

Intravenous Immune Globulins

- **Polyclonal human immunoglobulin(IgG).**
- **Prepared from pools of thousands of healthy donors.**
- **No specific antigenic target.**
- **Proved effective in immunoglobulin deficiencies, autoimmune disorders, HIV, bone marrow transplants, Kawasaki's Disease, SLE, ITP**

Rh_o(D) Immune Globulin Micro-Dose.

- One of the earliest major advances in immunopharmacology.
- Concentrated (15%) solution of human IgG containing a higher titer of antibodies against the Rh_o(D) antigen of the red cell.
- Given, to the mother, within 24-72 hours after the birth of an Rh-positive infant.
- Infant's red cells are cleared from circulation before the mother can generate a B-cell response against the Rh_o(D) antigen.
- This will protect against future hemolysis.

Hyperimmune Immunoglobulins

- **Made from pools of selected human or animal donors with high titers of antibodies against particular agents such as venoms, viruses or toxins, e.g. Rattlesnake or coral venoms, RSV, CMV, Varicella zoster, Herpes virus 3, HBV, rabies, Tetanus, and digoxin.**
- **Passive transfer of high titer antibodies will reduce risk or severity.**

Generation of Monoclonal Antibodies

- **Mice are immunized with the selected antigen.**
- **Spleen or lymph node is harvested.**
- **B cells are separated and fused to a suitable B cell myeloma that has been selected for its inability to grow in medium supplemented with hypoxanthine, aminopterin, and thymidine (HAT).**
- **The hybridomas expand in culture.**
- **Those of interest, based upon a specific screening technique, are then selected and cloned by limiting dilution.**

Antitumor MABs

- **Alemtuzumab.**
- **Bevacizumab.**
- **Ranibizumab.**
- **Cetuximab.**
- **Gemtuzomab.**
- **Panitumumab.**
- **Rituximab.**
- **Trastuzumab.**

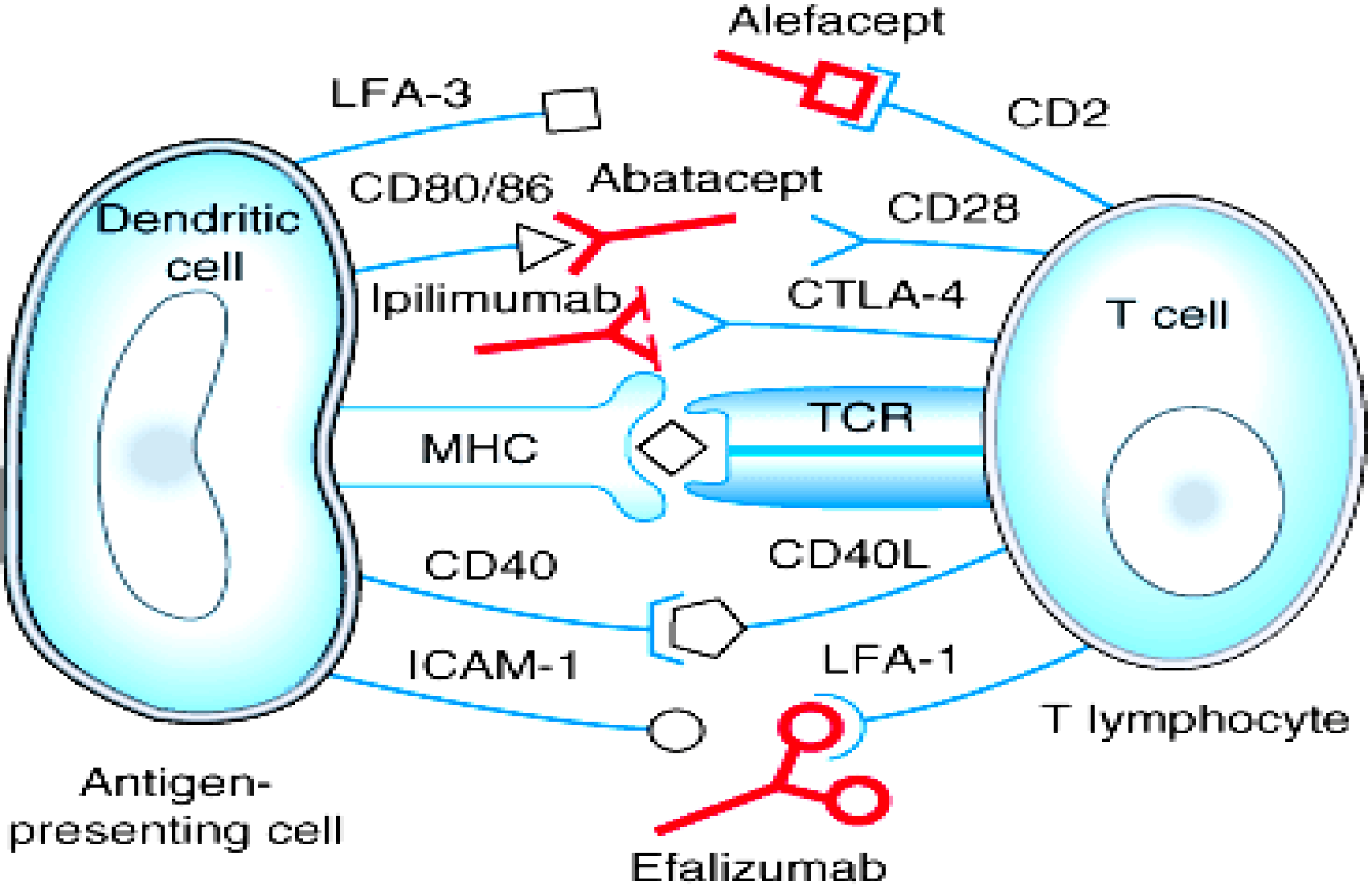
MABs to Deliver Isotopes to Tumors

- **Arcitumomab.**
- **Capromab.**
- **Ibritumomab.**
- **Nofetumomab.**
- **Satomomab.**
- **Tositumomab**

MABs used as Immunosuppressants and Antiinflammatory Agents

- **Anti-TNF-Alpha MABs:**
  - **Adalimumab.**
  - **Etanercept**
  - **Infliximab**
- **Abatacept**
- **Alefacept**
- **Basiliximab**
- **Daclizumab**
- **Efalizumab**
- **Omalizumab**
- **Abiximab**
- **Eculizumab**
- **Palivizumab**

Actions of some monoclonal antibodies



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: http://www.accessmedicine.com

Cytokines

- **Are a large and heterogeneous group of proteins with diverse functions.**
- **Mediate their effects through receptors, like hormones.**
- **May have antiproliferative, antimicrobial, and antitumor effects.**
- **Produced using gene cloning techniques.**
- **Have very short half lives, and given sc.**
- **All induce fever, flu-like symptoms, anorexia, fatigue, and malaise.**

Cytokines

- **Interferones: INF- α, β, and γ.**
- **Interleukins: 1-35.**
- **Tumor Necrosis factor: α, and β.**
- **Granulocyte colony-stimulating factor.**
- **Granulocyte-macrophage colony-stimulating factor.**
- **Macrophage colony-stimulating factor.**
- **Erythropoietin.**
- **Thrombopoietin**

Cytokines

- **Interferon (INF): INF-α,β,γ**
  - 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 .

Cytokine Inhibitors

- **Anakinra:**
  - **Is a recombinant form of the naturally occurring IL-1 receptor antagonist.**
  - **Approved for adult rheumatoid arthritis**

IMMUNOLOGIC REACTIONS TO DRUGS

- **Type I: IgE-mediated acute allergic reactions to stings, pollens, and drugs, including anaphylaxis, urticaria, and angioedema. IgE is fixed to tissue, mast cells and blood basophils, and after interaction with antigen the cells release potent mediators.**

- **Type II: Drugs often modify host proteins, thereby eliciting antibody responses to the modified protein. These allergic responses involve IgG or IgM in which the antibody becomes fixed to a host cell, which is then subject to complement-dependent lysis or to antibody-dependent cellular cytotoxicity.**

IMMUNOLOGIC REACTIONS TO DRUGS

- **Type III: Drugs may cause serum sickness, which involves immune complexes containing IgG and is a multisystem complement-dependent vasculitis that may also result in urticaria.**

- **Type IV: Cell-mediated allergy is the mechanism involved in allergic contact dermatitis from topically applied drugs or induration of the skin at the site of an antigen injected intradermally.**