IMMUNOSUPPRESSANT DRUGS

These are drugs which inhibit cellular /humoral or both immune response and have theirmajor use in organ transplantation and autoimmune diseases. The drugs are:

1. Calcineurin inhibitors (Specific T-cell inhibitors) Cyclosporine (Ciclosporin), Tacrolimus
2. Antiproliferative drugs (Cytotoxic drugs) Azathioprine, Cyclophosphamide, Methotrexate,Chlorambucil, Mycophenolate mofetil (MMF)
3. Glucocorticoids: Prednisolone and others
4. Antibodies: Muromonab CD3, Antithymocyte globulin (ATG), Rho (D) immuneglobulin

Calcineurin inhibitors (Specific T-cell inhibitors)

A. Cyclosporine

Cyclosporine [sye-kloe-SPOR-een] (*CsA*) is a lipophillic cyclic polypeptide composed of 11 amino acids (several are methylated on the peptidyl nitrogen). The drug is extracted from a soil fungus. *CsA* is used to prevent rejection of kidney, liver, and cardiac allogeneic transplants.

Mechanism of action: *Cyclosporine* preferentially suppresses cell-mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, *CsA* binds to a cyclophilin (more generally called an immunophilin) to form acomplex that binds to calcineurin. The latter is responsible for dephosphorylating NFATc (**c**ytosolic **N**uclear **F**actor of **A**ctivated **T** cells). The *CsA*-calcineurin complex cannot performthis reaction; thus, NFATc cannot enter the nucleus to promote the reactions that are required for the synthesis of a number of cytokines, including IL-2.

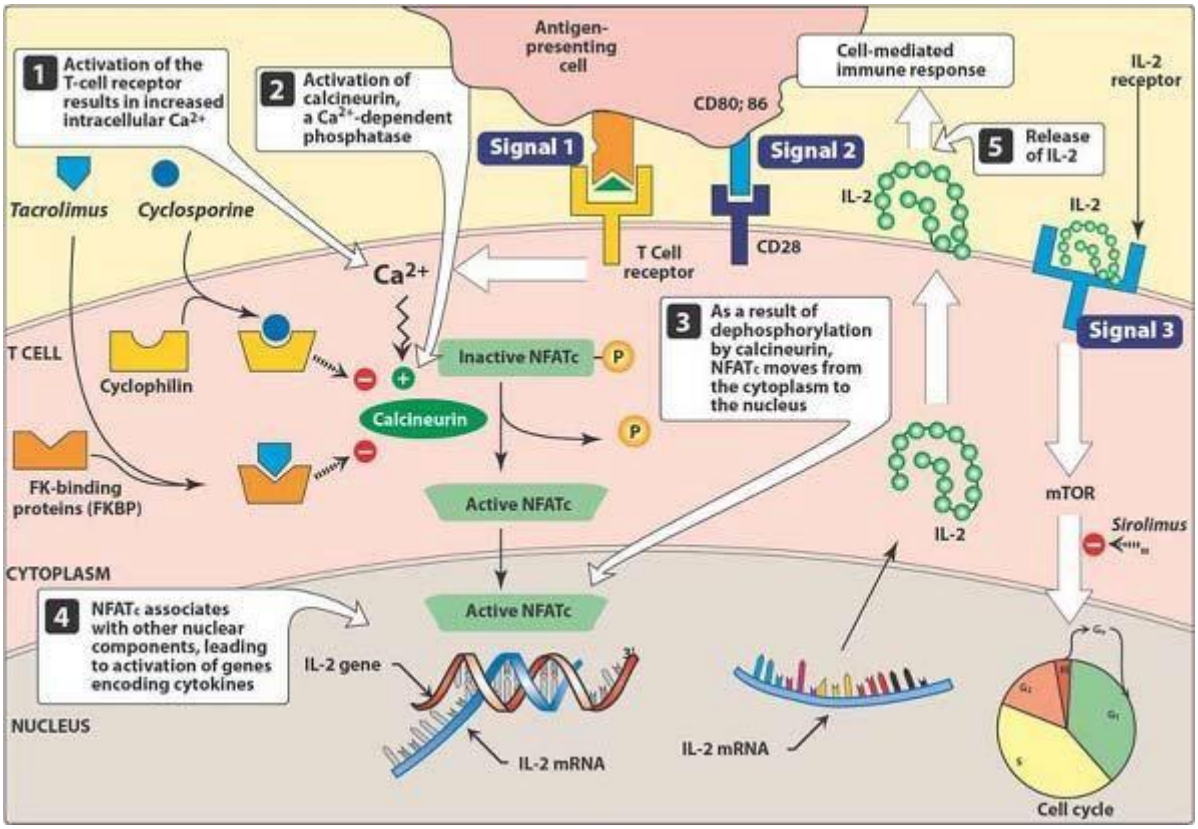
Pharmacokinetics: *Cyclosporine* may be given either orally or by intravenous infusion. Oral absorption is variable. Interpatient variability may be due to metabolism by a cytochrome P450 (CYP3A4) in the gastrointestinal tract, where the drug is metabolized. About 50 percentof the drug is associated with the blood fraction

Adverse effects: Many of the adverse effects caused by *CsA* are dose dependent; therefore, itis important to monitor blood levels of the drug. Nephrotoxicity is the

most common and important adverse effect of *CsA*. It is therefore critical to monitor kidney function.

B. Tacrolimus

Tacrolimus (*TAC*, originally called *FK506*) is a macrolide that is isolated from a soil fungus. *TAC* is approved for the prevention of rejection of liver and kidney transplants and is given with a corticosteroids and/or an antimetabolite. This drug has found favor over *CsA*, not only because of its potency and decreased episodes of rejection but also because lower doses of corticosteroids can be used, thus reducing the likelihood of steroid-associated adverse effects.An ointment preparation has been approved for moderate to severe atopic dermatitis that does not respond to conventional therapies.



Immunosuppressive Antimetabolites

Immunosuppressive antimetabolite agents are generally used in

combination withcorticosteroids, and the calcineurin inhibitors, *CsA* and *TAC*.

A. Azathioprine

Azathioprine [ay-za-THYE-oh-preen] was the first agent to achieve widespread use in organ transplantation. It is a prodrug that is converted first to *6-mercaptopurine* (*6-MP*) and then to the corresponding nucleotide, thioinosinic acid. The immunosuppressive effects of *azathioprine* are due to this nucleotide analog. Because of their rapid proliferation in the immune response and their dependence on the de novo synthesis of purines required for celldivision, lymphocytes are predominantly affected by the cytotoxic effects of *azathioprine*. [Its major nonimmune toxicity is bone marrow suppression. Concomitant use withangiotensin-converting enzyme inhibitors or *cotrimoxazole* in renal transplant patients canlead to an exaggerated leukopenic response.

Immunosuppressant antibodies:

Muromonab CD3 It is a murine monoclonal antibody against the CD3 glycoprotein located near to the T cell receptor on helper T cells. Binding of muromonab CD3 to the CD3 antigen obstructs the binding of MHC II-antigen complex to the T cell receptor: antigen recognitionis interfered, so that participation of T cells in the immune response is prevented and T cells rapidly disappear from circulation leading to an immune blocked state.

Mechanism of action: *Binding to the CD3 protein results in a disruption of T-lymphocyte function, because access of antigen to the recognition site is blocked. Circulating T cells are depleted; thus, their participation in the immune response is decreased. Because muromonab-CD3 recognizes only one antigenic site, the immunosuppression is less broad than that seen with the polyclonal antibodies. T cells usually return to normal within 48 hours of discontinuation of therapy.*

Muromonab CD3 has been used as induction therapy together with corticosteroids andazathioprine with delayed use of cyclosporine in 'sequential regimen' for organ transplantation. Thls serves to postpone potential nephro- and hepatotoxicity of cyclosporine.