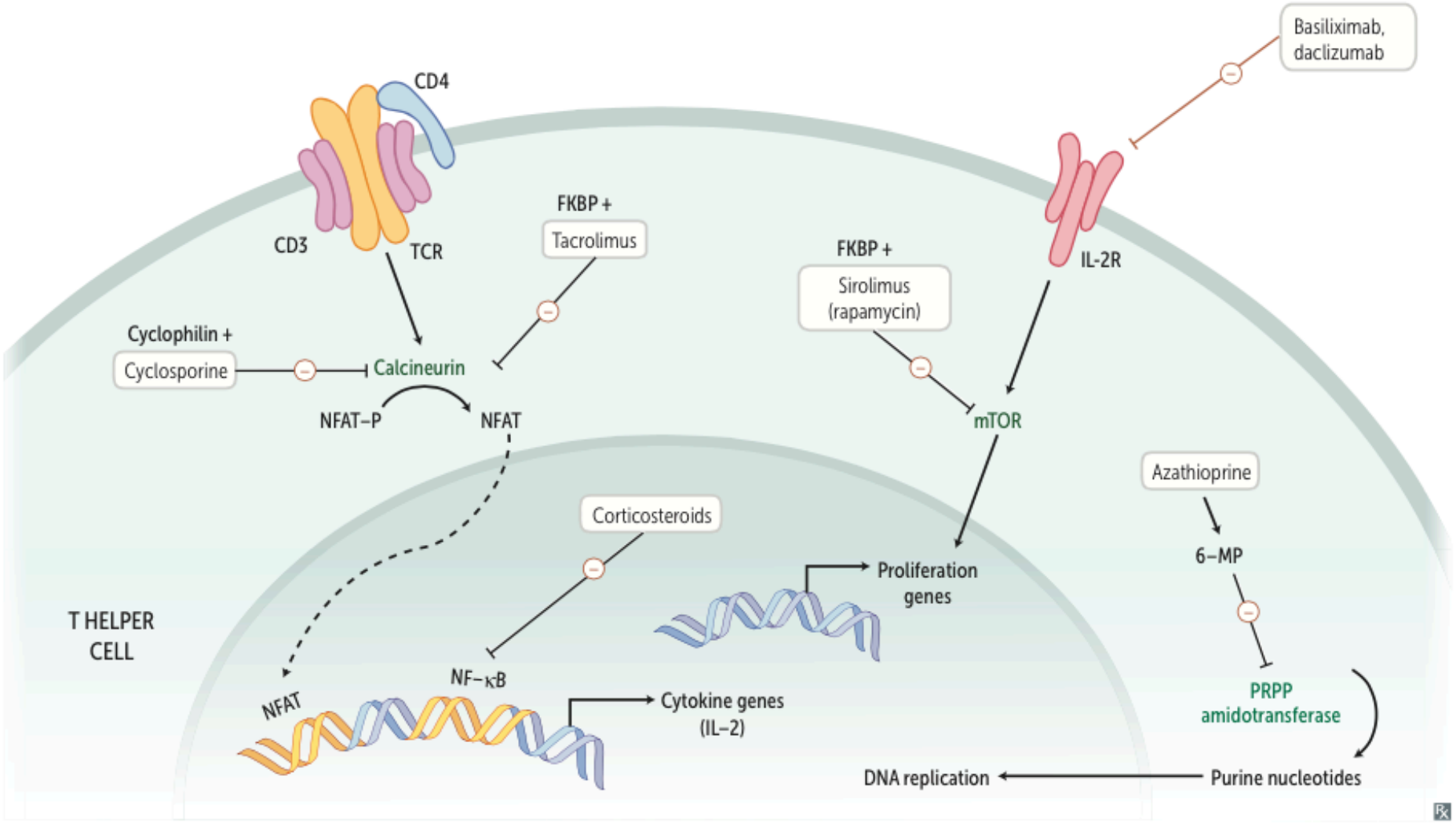
## Immunosuppression targets




**IMMUNOSUPPRESSANTS:** mainly used in *organ transplantation* & *autoimmune diseases*; associated with **high risk of infection + cancer**

- **Induction Therapy:** prophylaxis of rejection in transplantation (lymphocyte-depleting against-ATG & IL-2 blockers-Basiliximab)
- **Maintenance Therapy:** Calcineurin inhibitors, antimetabolites, steroids

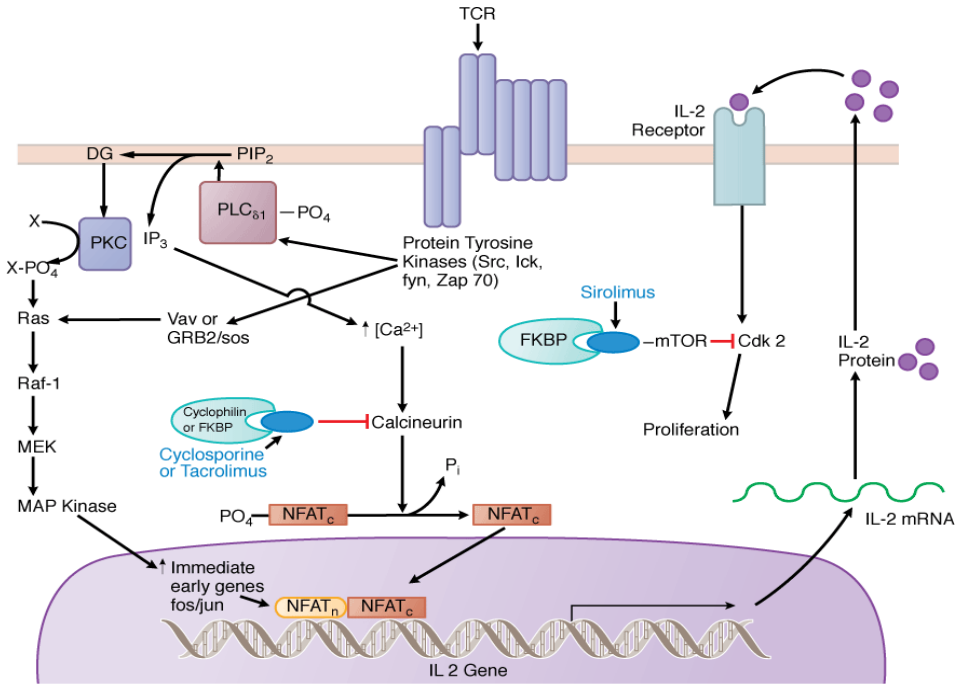
**Green** = Kaplan, Deja. First Aid, or Tulane

**Immunosuppressants** Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity. Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.

| DRUG | MECHANISM | USE | TOXICITY | NOTES |
|---|---|---|---|---|
| **Cyclosporine** | Calcineurin inhibitor; binds cyclophilin. Blocks T-cell activation by **preventing IL-2 transcription**. | Transplant rejection prophylaxis, psoriasis, rheumatoid arthritis. | **Nephrotoxicity**, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism. | Both calcineurin inhibitors are highly nephrotoxic. |
| **Tacrolimus (FK506)** | Calcineurin inhibitor; binds FK506 binding protein (FKBP). Blocks T-cell activation by **preventing IL-2 transcription**. | Transplant rejection prophylaxis. | Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism. | |
| **Sirolimus (Rapamycin)** | mTOR inhibitor; binds FKBP. Blocks T-cell activation and B-cell differentiation by **preventing response to IL-2**. | Kidney transplant rejection prophylaxis. | Anemia, thrombocytopenia, leukopenia, insulin resistance, hyperlipidemia; **not nephrotoxic**. | Kidney "sir-vives." Synergistic with cyclosporine. Also used in drug-eluting stents. |
| **Daclizumab, basiliximab** | Monoclonal antibodies; block IL-2R. | Kidney transplant rejection prophylaxis. | Edema, hypertension, tremor. | |
| **Azathioprine** | Antimetabolite precursor of 6-mercaptopurine. Inhibits lymphocyte proliferation by blocking nucleotide synthesis. | Transplant rejection prophylaxis, rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions. | Leukopenia, anemia, thrombocytopenia. | 6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol. Pronounce "azathio-purine." |
| **Glucocorticoids** | Inhibit NF-κB. Suppress both B- and T-cell function by ↓ transcription of many cytokines. | Transplant rejection prophylaxis (immuno-suppression), many autoimmune disorders, inflammation. | Hyperglycemia, osteoporosis, central obesity, muscle breakdown, psychosis, acne, hypertension, cataracts, avascular necrosis. | Can cause iatrogenic Cushing syndrome. |

# IMMUNOSUPPRESSANTS & IMMUNOMODULATORS

| CALCINEURIN INHIBITORS (CNI) | | | |
|---|---|---|---|
| **DRUG** | **MECHANISM** | **INDICATION** | **ADVERSE EFFECTS** |
| **CYCLOSPORINE**<br>*Erratic bioavailability* | Binds **CYCLOPHILIN (CpN)** oF T cells & inhibits Calcineurin's phosphatase activity → prevents dephosphorylation & translocation of NFAT → **inhibits IL-2 synthesis** (T cell activation) | **IMMUNOSUPPRESSION in ORGAN TRANSPLANTATION**<br>**(Kidney, Liver, & Cardiac transplantation)**<br>Rheumatoid arthritis, Psoriasis<br>Dry eye syndrome<br>***Generally administered with corticosteroids*** | **NEPHROTOXICITY**<br>HTN, HLD, **GUM HYPERPLASIA**<br><br>**GRAPEFRUIT JUICE ↑ blood levels** |
| **TACROLIMUS**<br>*Oral or IV* | Binds **FKBP-12** & inhibits Calcineurin's phosphatase activity → **inhibits IL-2 synthesis** (T cell activation) | **PROPHYLAXIS for GRAFT VS. HOST DISEASE**<br>**In combo w/ Methotrexate or Mycophenolate*<br>**SOLID ORGAN TRANSPLANTATION**<br>Atopic dermatitis, Psoriasis | Nephrotoxicity, Neurotoxicity, &<br>**DIABETES MELLITUS** |
| **mTOR INHIBITORS** | | | |
| **SIROLIMUS (RAPAMYCIN)** | Binds **FKBP-12** & forms complex **blocking mTOR** →<br>inhibition of IL-2 driven cell proliferation<br>**Doesn't inhibit Calcineurin or block IL-2, but ↓response to IL-2*<br>Prevents transition from G1 → S phase | **Prevent re-stenosis post-coronary angioplasty**<br>**PROPHYLAXIS of RENAL TRANSPLANT REJECTION**<br>**(Not recommended in Liver or Lung transplant pts)** | **LOW NEPHROTOXICITY** ☺<br>**HLD, Myelosuppression**, hepatoxicity, delayed wound healing |




Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:*

**Green** = Kaplan, Deja. First Aid, or Tulane

## CYTOTOXIC ANTI-METABOLITES

| DRUG | MECHANISM | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **AZATHIOPRINE** | **PRODRUG**<br>Cleaved to 6-mercaptupurine & **inhibits DNA synthesis**<br>***Affects both cell & humoral immunity*** | **RENAL TRANSPLANT REJECTION**<br>Rh arthritis, Crohn's, Multiple Sclerosis | **BONE MARROW SUPPRESSION:**<br>**Leukopenia, anemia, thrombocytopenia**<br>***Life-threatening in pts deficient in thiopurine S-methyltransferase***<br><br>*When used w/ Allopurinol, dose should be reduced by 1/3 or 1/4 |
| **CYCLOPHOSPHAMIDE** | ALKYLATING AGENT<br>**Destroys *proliferating* lymphoid cells & alkylates DNA** | Large dose: Transplant rejection reactions<br>Small doses: SLE, Autoimmune hemolytic anemia | **Hemorrhagic Cystitis**<br>SECONDARY MALIGNANCIES<br>(Carcinoma of the bladder) |
| **MYOCPHENOLATE MOFETIL (MMF)** | PRODRUG → Mycophenolate sodium<br>Inhibits inosine monophosphate dehydrogenase (IMPDH)<br>**Blocking GTP synthesis** in B & T lymphocytes | PROPHYLAXIS of REJECTION of KIDNEY, LIVER, & HEART TRANSPLANTATION<br><br>**Alternative to Cyclosporine or Tacromilus (combined w/ Prednisone)**<br><br>Steroid sparing agent in Lupus Nephritis, Psoriasis | **BLACK BOX WARNING: INCREASED RISK OF INFECTION & LYMPHOME** |
| **LEFLUNOMIDE** | PRODRUG<br>**Inhibits pyrimidine synthesis** | RHEUMATOID ARTHRITIS<br>Considered for organ transplant rejection | LIVER DAMAGE + RENAL IMPAIRMENT<br>*(so I guess don't use it in these transplants?)* |

## ANTIBODIES

| DRUG | MECHANISM | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **ANTI-LYMPHOCYTE (ALG) & ANTI-THYMOCYTE GLOBULIN (ATG)** | Deplete lymphocytes by direct cytotoxicity<br>Block lymphocyte function | **Prevent/Treat ACUTE REJECTION in ORGAN & BONE MARROW TRANSPLANT**<br>Stem cell transplants – Prevent GVHD | Fever, chills, anaphylaxis |
| **Rh(D) Ig** | Interacts directly with Rh(D) antigens & do not allow them to interact with maternal immune system | Prevent Hemolytic Disease of the Newborn<br>*Given at 28w, within 72 hours of birth*<br>***Contraindicated in Rh+ women, newborns*** | |

## MONOCLONAL ANTIBODIES

| DRUG | MECHANISM | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **MUROMONAB CD3 (OKT3)** WITHDRAWN FROM US$ | Binds **CD3-R** on mature T cells | **Treat ACUTE rejection in Kidney, Liver, & Heart transplants** | **Severe cytokine release syndrome** **Reduce symptoms w/ steroids/antihistamine* CNS disturbances |
| **BASILIXIMAB DACLIZUMAB** | Ab against **CD-25** on T cells (IL-2R α chain) **Blocks activation of T cells** by IL-2 | **Prophylaxis of ACUTE organ rejection following RENAL transplant** | Well-tolerated w/ ↓risk of opportunistic infections & lymphomas ☺ |
| **ALEMTUZUMAB** | Targets CD52 | **CLL** | |
| ALAFECEPT | Fusion protein – Prevents interaction of T cell CD2 from binding LFA-3 on APC | Psoriasis | |
| EFALIZUMAB | Blocks interaction of LFA-1 to ICAM-2 | Psoriasis | |
| **NATALIZUMAB** | Block cell adhesion of α4-integrin | **Multiple Sclerosis & Crohn's** | |

| | | | |
|---|---|---|---|
| **Autoimmune disease therapy** | | | |
| **Adalimumab, infliximab** | Soluble TNF-α | IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis | Etanercept is a decoy TNF-α receptor and not a monoclonal antibody |
| **Eculizumab** | Complement protein C5 | Paroxysmal nocturnal hemoglobinuria | |
| **Natalizumab** | α4-integrin | Multiple sclerosis, Crohn disease | α4-integrin: WBC adhesion Risk of PML in patients with JC virus |
| **Other** | | | |
| **Abciximab** | Platelet glycoproteins IIb/IIIa | Antiplatelet agent for prevention of ischemic complications in patients undergoing percutaneous coronary intervention | IIb times IIIa equals "absiximab" |
| **Denosumab** | RANKL | Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin) | Denosumab affects osteoclasts |
| **Digoxin immune Fab** | Digoxin | Antidote for digoxin toxicity | |
| **Omalizumab** | IgE | Allergic asthma; prevents IgE binding to FcεRI | |
| **Palivizumab** | RSV F protein | RSV prophylaxis for high-risk infants | PaliVIzumab—VIrus |
| **Ranibizumab, bevacizumab** | VEGF | Neovascular age-related macular degeneration | |

eja. First Aid, or Tulane

**IMMUNOMODULATING AGENTS:** *Modulate immune system, rather than suppress it*

- Used in immunodeficiency disorders, chronic infectious diseases, & cancer

| DRUG | MECHANISM | INDICATION | ADVERSE EFFECTS |
|---|---|---|---|
| **ALDESLEUKIN** | Recombinant IL-2 promotes production of CTL & activates NK cells | Metastatic Renal Cell Carcinoma<br>Malignant Melanoma | |
| **INTERFERON-α-2α** | | **Hepatitis B & C**<br>CML, Malignant Melanoma | |
| **INTERFERON-β-1A&B** | | Multiple Sclerosis | |
| **BCG** | | Tx & Prophylaxis of CIS in bladder | |
| **THALIDOMIDE (IMiD)** | **Inhibits angiogenesis** & has **anti-inflammatory + immunomodulatory effects** | **Erythema Nodosum Leprosum**<br>Multiple Myeloma | |

**Recombinant cytokines and clinical uses**

| AGENT | CLINICAL USES |
|---|---|
| Aldesleukin (IL-2) | Renal cell carcinoma, metastatic melanoma |
| Epoetin alfa (erythropoietin) | Anemias (especially in renal failure) |
| Filgrastim (G-CSF) | Recovery of bone marrow |
| Sargramostim (GM-CSF) | Recovery of bone marrow |
| IFN-α | Chronic hepatitis B and C, Kaposi sarcoma, malignant melanoma |
| IFN-β | Multiple sclerosis |
| IFN-γ | Chronic granulomatous disease |
| Romiplostim, eltrombopag | Thrombocytopenia |
| Oprelvekin (IL-11) | Thrombocytopenia |

| GLUCOCORTICOIDS | | | |
|---|---|---|---|
| **DRUG** | **MECHANISM** | **INDICATION** | **ADVERSE EFFECTS** |
| **PREDNISONE**<br>**METHYLPREDNISONE** | Suppress cell-mediated immunity by inhibit genes of IL-1-6, IL-8 & TNF-1 → ↓T activation<br>Suppress humoral immunity by ↓IL-2 expression in B cells | Transplantation rejection<br>Autoimmune diseases | |