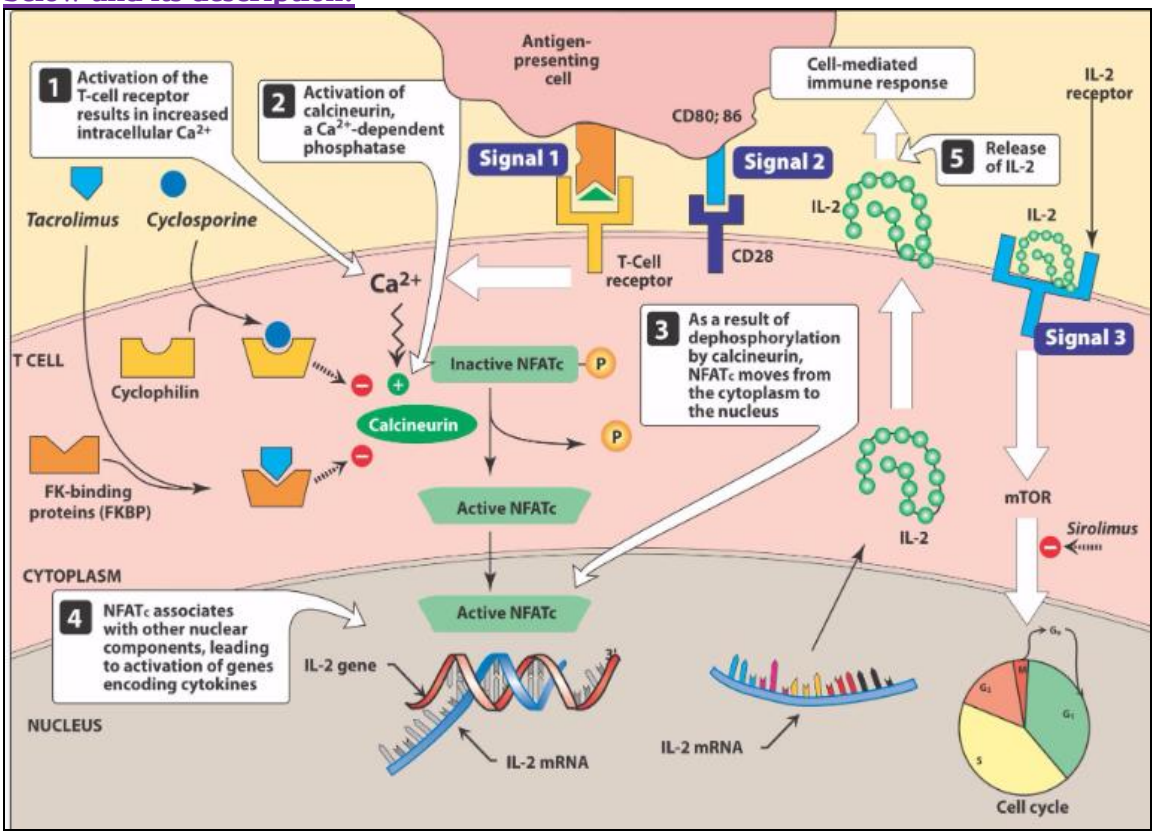
Unit IX – Problem 6 – Pharmacology: Immunosuppressants In Transplantation

- **Immune system (self vs. non-self):**
  - When a baby is being developed, the immune system learns to identify self and non-self antigens. The immune system reacts against foreign antigens (and this is the concept which is applied with rejection to transplanted organs).
- **What is the goal behind immunotherapy?**
  - To prevent rejection (main goal) or to minimize and control rejection –if it occurs- as soon as possible so transplantation succeeds.
- Remember that in organ rejection, cytotoxic T-cells (CD8+) of the recipient attack foreign MHC class-I antigens present in the transplanted organ from the donor. Therefore, rejection is prevented by inhibiting proliferation of T-cells mainly
- **Classes of immunosuppressive drugs:**
  - **Those which interfere with cytokine production/action. Therefore, inhibiting the immune reaction. This class includes the following:**

Calcineurine inhibitors	• **Cyclosporine:** ✓ Lipid-soluble drug ✓ Polypeptide ✓ Variable absorption ✓ Mechanism of action: blocking IL-2 production & secretion ✓ ADR: nephrotoxicity (most serious), hirsutism, hyperplasia of gums • **Tacrolimus:** ✓ It is a macrolide which is well-absorbed ✓ Mechanism of action: blocking IL-2 production & secretion ✓ ADR: diabetes (more likely). Hirsutism & hyperplasia of gums are unusual (in contrast to cyclosporine)
Co-stimulation blockers	**Belatacept**
MTOR (Mammalian Target OF Rapamycin) inhibitors	• **Sirolimus:** ✓ It is a macrolide with poor oral bioavailability ✓ Mechanism of action: inhibiting the activity of mTOR ✓ ADR: dyslipidemia, anemia, leucopenia & thrombocytopenia • **Everolimus**

  - **Those which disrupt cell metabolism:**
    - ✓ Azathioprine:
      - ❖ It is a mercaptopurine analogue.
      - ❖ *Mechanism of action*: inhibiting purine synthesis through hepatic metabolites.
      - ❖ *ADR*: represented by marrow suppression → leaukopenia (common), thrombocytopenia and anemia (uncommon).
    - ✓ Mycophenolate mofetil:
      - ❖ It is metabolized to mycophenolic acid.
      - ❖ *Mechanism of action*: inhibiting purine synthesis via inosine monophosphate dehydrogenase.
      - ❖ *ADR*: diarrhea and vomiting (GI) + leucopenia and red cell aplasia (blood).
    - ✓ Mycophenolate sodium (enteric-coated).
    - ✓ Methotrexate.
  - **Antibodies which block T-cell surface molecules (will be discussed in details later):**
    - ✓ Anti-thymocyte globulins.
    - ✓ Muromonab-CD3 (OKT3).
    - ✓ Basiliximab.
  - **Corticosteroids (will be discussed in details later):**
    - ✓ Prednisolone and methylprednisolone.

- **There are three signals which can be targeted by immunosuppressive drugs thus suppressing immune reaction. To understand these signals, look to the diagram below and its description:**



- Antigen presenting cell presents the antigen to T-lymphocyte (signal 1).
- Along with (signal 2), this will lead to activation of calcium-dependent calcineurin.
- IL-2 will be produced and released to bind to its receptor which is present on the surface of T-lymphocyte (signal 3).
- This will result in proliferation of T-cells and initiating the immune response.

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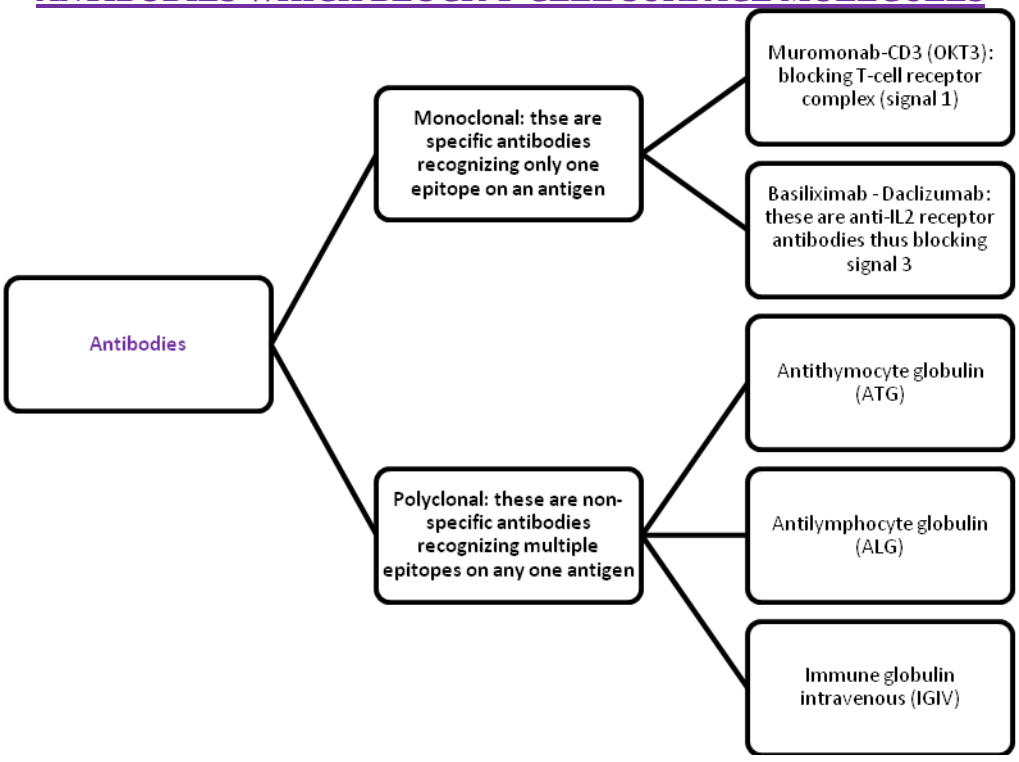
ANTIBODIES WHICH BLOCK T-CELL SURFACE MOLECULES



GLUCOCORTICOIDS

- **Mechanism of action**: binding to receptors inside cells + heat shock proteins → and regulating gene transcription.
- **Used in**: allergic and immunologic conditions. They are used in transplantation to prevent rejection or treat it (if it is already started).
- **Effects**: anti-inflammatory and immunosuppressive effects (mainly by suppressing T-cell function with minimal effect on humoral immunity).
- **Adverse effects:**
  - Growth retardation in children.
  - Osteopenia (reduced bone mass of lesser severity than osteoporosis) and avascular necrosis of bone.
  - Increased risk of infection: due to suppressed immunity.
  - Poor wound healing.
  - Cataracts.
  - Hyperglycemia.
  - Hypertension.
- **Notice that combined glucocorticoid/ calcineurine inhibitor regimens allow reduced doses or rapid withdrawal of steroids.**
- **There is increased bioavailability of corticosteroids with hypoalbuminemia and liver disease.**

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- **General principles:**
  - **Special regimens:**
    - ✓ Glucocorticoid-free regimens (when the patient is diabetic or a children).
    - ✓ Rapid steroid withdrawal (within one week after transplantation).
    - ✓ Dose reduction of calcineurin inhibitors or switching to sirolimus-based therapy at 3-4 months (why?)
      - ❖ Because recent data suggest that calcineurin inhibitors may shorten the graft half-life ($t_{1/2}$) by their nephrotoxic effects.
  - **Immunotherapy is composed of:**
    - ✓ Induction immunotherapy: through antibodies (monoclonal or polyclonal).
    - ✓ Maintenance immunotherapy:
      - ❖ Multiple drugs are given simultaneously → typically involving the following:
        - ➢ Calcineurin inhibitor (cyclosporine or tacrolimus).
        - ➢ Glucocorticoids.
        - ➢ Mycophenolate.

        Note: each of these drugs is directed at a different site in T-cell activation.
    - ✓ Treatment of established rejection through (notice that the treatment requires drugs directed against activated T-cells):
      - ❖ Glucocorticoids in high doses (pulse therapy).
      - ❖ Triple therapy: glucocortocoid + calcineurin inhibitor + anti-proliferative drug.
      - ❖ Antibodies: either monoclonal (such as muromonab-CD3) or polyclonal (such as antithymocyte globulin).
  - **There are four types of rejection:**

Type	Time	Mechanism	Treatment
Hyperacute	Minutes to hours	Preformed antidonor antibodies	No treatment
Accelerated	1-7 days	Reactivation of sensitized T-cells	No treatment
Acute	Weeks to months	Primary activation of T-cells	Combination of drugs (good response)
Chronic	Months to years	Both immunological & non-immunological factors	Combination of drugs (variable response)