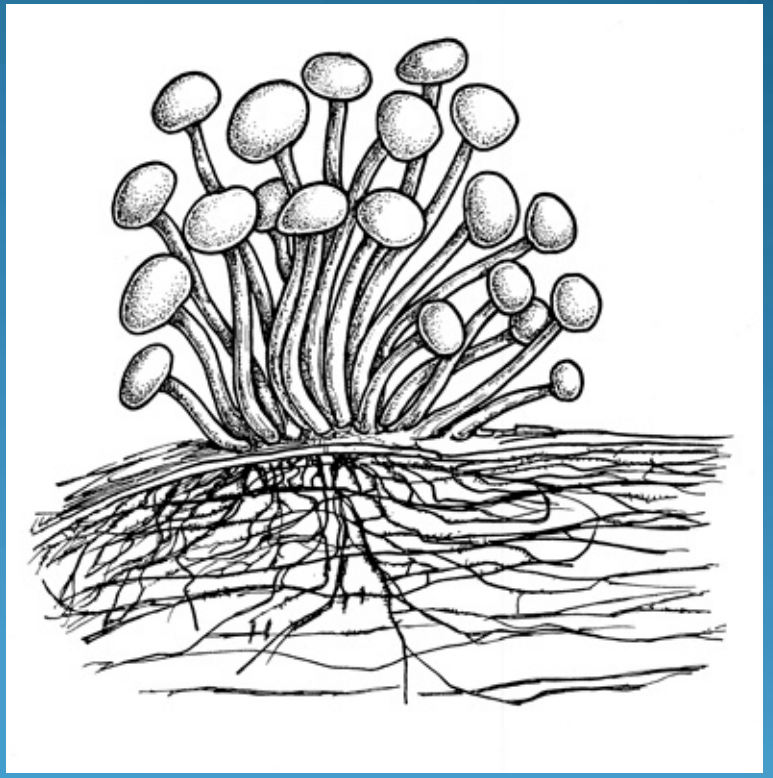
Cyclosporine

Cyclosporine (CsA)

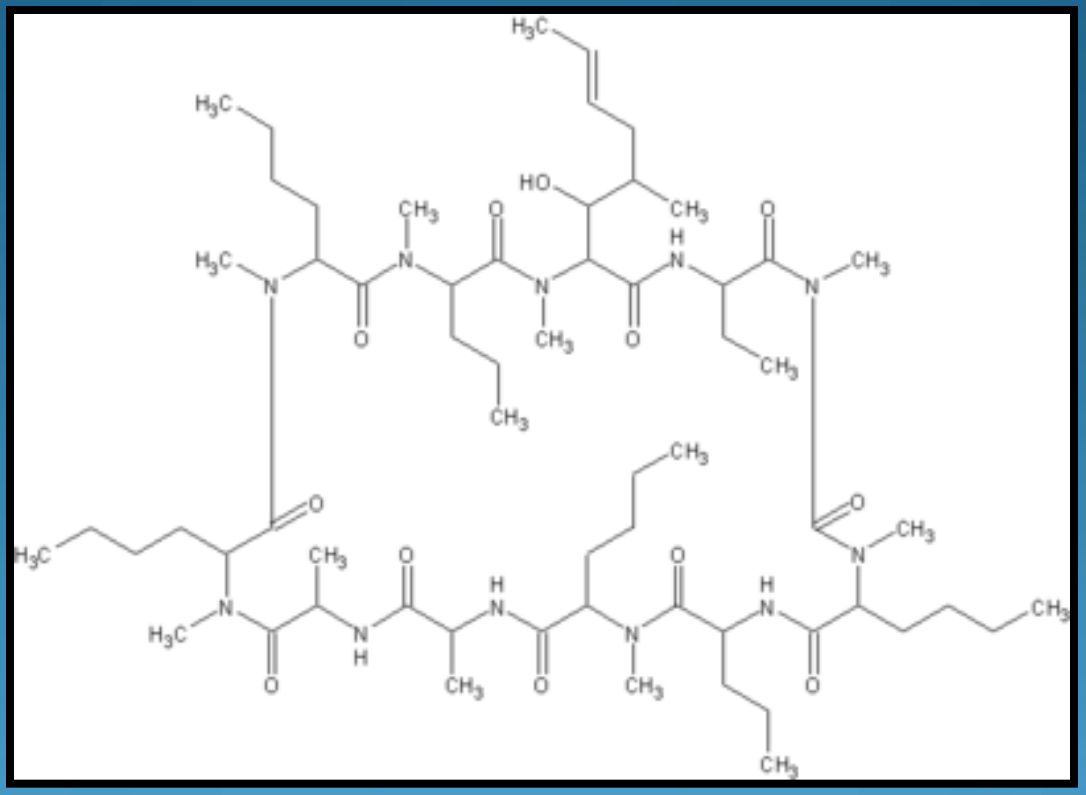
- Incidentally isolated from the soil fungus *Tolypocladium inflatum gams* during a search for antifungals.
- Weak antibiotic activity, but a potent immunosuppressive



Cyclosporine

- **1979**-Efficacy in Psoriasis was discovered in RA studies
- **1983**-FDA approved for organ rejection
- **1995**- Neoral (more bioavailable form) was approved for organ rejection
- **1997**- Neoral received Psoriasis/RA indication

Chemical Structure



Cyclosporine

a neutral cyclic peptide of 11 amino acids

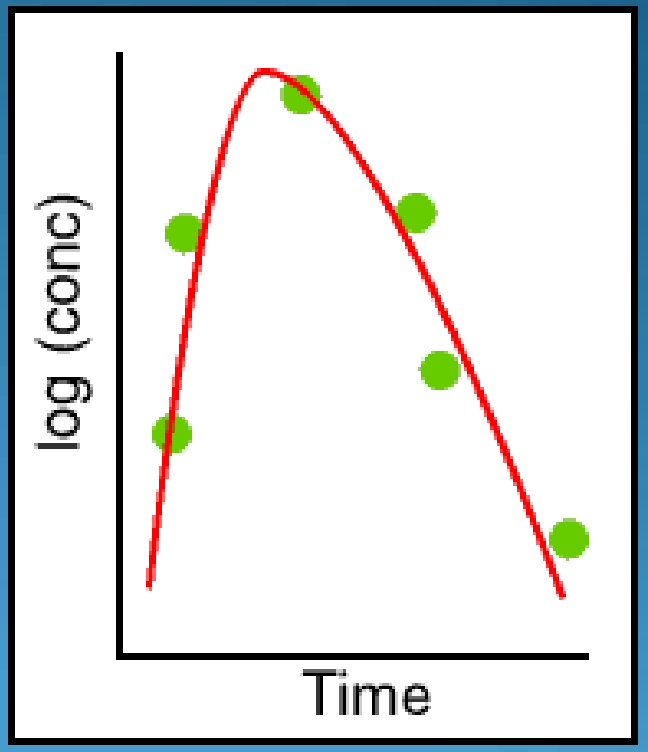
How supplied

- Sandimmune (no generic available)
  - Tablets-25, 50, 100 mg
  - Special formulations-IV/PO solution
  - Standard dose: 2.5-5 mg/kg/d

- Neoral (generic available)
  - Tablets-25, 100 mg
  - PO solution-100mg/ml
  - Standard dose: 2.5-4* mg/kg/d

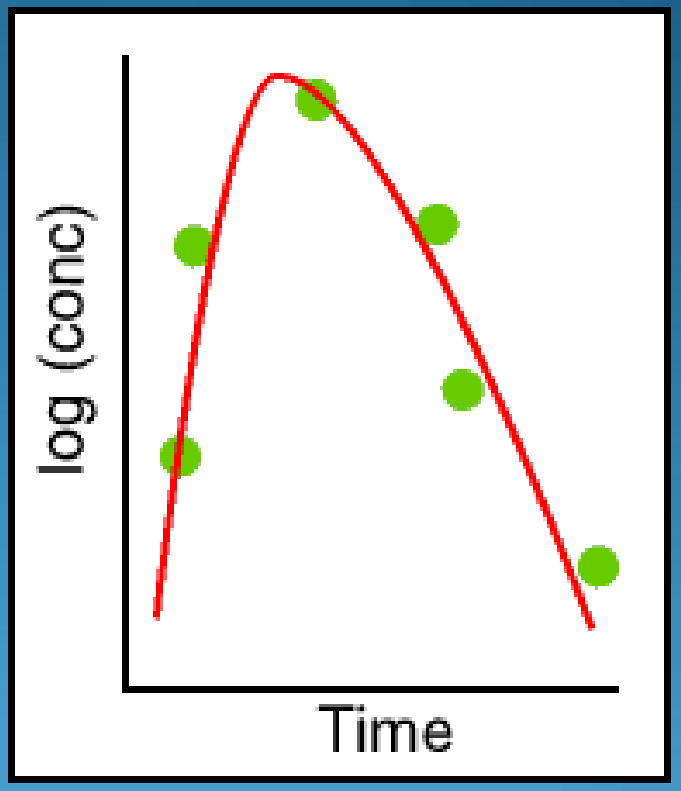
Pharmacokinetics

- Bioavailability
  - Sandimmune-30% and erratic
  - Neoral-Increased and with less variability than Sandimmune
- Absorption
  - 2-4 hours (both forms)
  - Accumulates in adipose tissue
- Protein Binding
  - 90% (both forms)



Pharmacokinetics

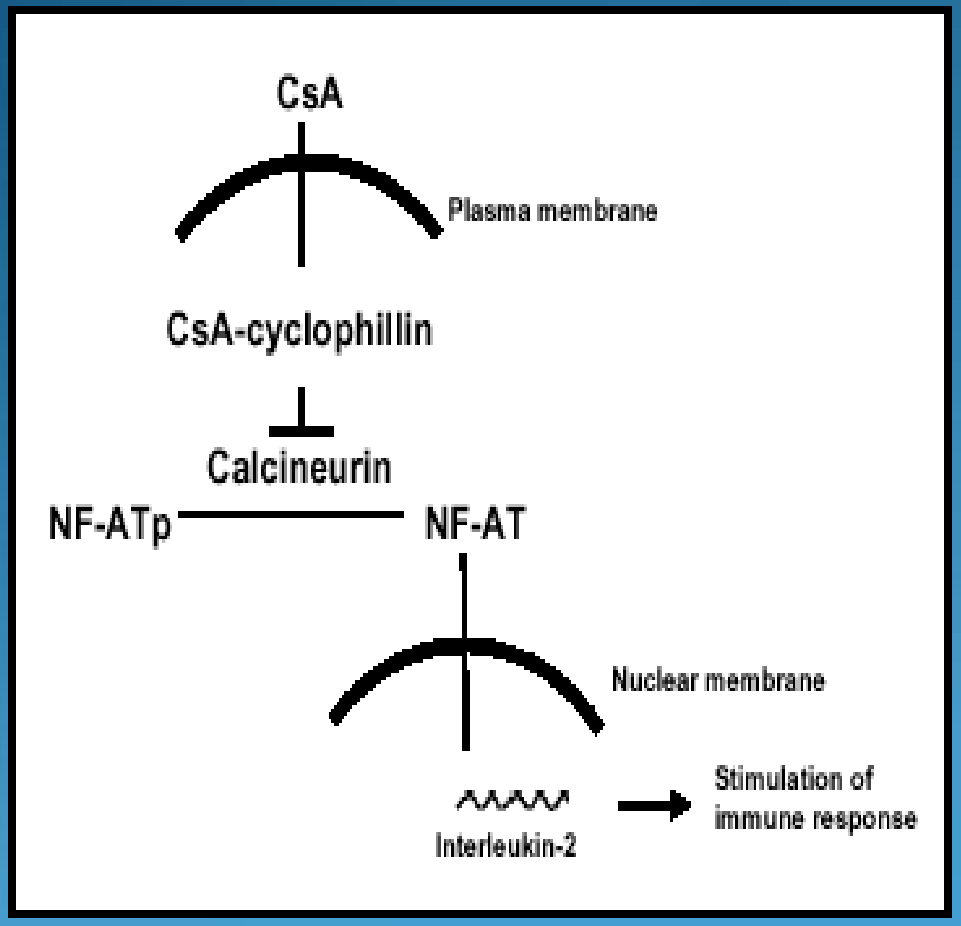
- $T_{1/2}$ of 5-18 hours
- Metabolism
  - Cytochrome P450 3A4 system in liver
- Excretion
  - Hepatobiliary, (Renal 6%)



Mechanism of Action

- Exerts its immunosuppressant effect by preventing:
  - proliferation of helper T cells
  - Maturation of killer T cells
  - Recruitment of macrophages
- Inhibits cells signalers such as IL-1, *IL-2, and gamma-INF

Mechanism of Action



- CsA binds to cyclophillin. This complex then binds to and (-)'s calcineurin, a Ca-dependent phosphatase.
- NFAT cannot be dephosphorylated and IL-2 expression is diminished

Mechanism of Action

- Inhibits INF-gamma and in turn down regulates ICAM-1 expression which is responsible for cellular trafficking
- Decrease chemotactic ability of neutrophils
- ? Antiproliferative effect of keratinocytes (in vitro vs. in vivo)

Clinical Use

- FDA indications in Dermatology
  - Psoriasis
  - Severe Psoriasis
  - Recalcitrant, treatment-resistant Psoriasis
  - Disabling Psoriasis

- Contraindications
  - Absolute-renal insufficiency, uncontrolled HTN, Clinically cured or persistent malignancy (except NMSC)
  - Relative-Age<18 or >64 years, controlled HTN, Administration of Live, attenuated vaccine, on meds that interfere wit CsA, active infection or evidence of immunodeficiency, concomitant phototx, MTX, or other immunosuppressive, pregnancy or lactation (Class C), unreliable patients.

Specific Patients for CsA Therapy

- Patients with severe Psoriasis who have failed to respond to at least one systemic therapy
- Patients who can't tolerate or have CI to other systemic therapies
  - Women of child bearing potential
  - PUVA logistically difficult
  - MTX inappropriate
- Patients with severe, acute flare-ups

Off Label Uses

- Atopic Dermatitis
  - Starting doses 5 mg/kg/d, maintenance doses 2 mg/kg/d.

- Pyoderma Gangrenosum
  - Doses of 5-7 mg/kg/d were used at the outset with tapering doses below 5 mg/kg/d.
  - On average, took 2-3 months for ulcer to heal.

Adverse Effects

- **Renal**
  - Renal dysfunction
- **Cardiovascular**
  - Hypertension
- **Neurological**
  - Tremor, Headache, Paresthesia, Hyperesthesia
- **Mucocutaneous**
  - Hypertrichosis, Gingival hyperplasia

Adverse Effects

- **Gastrointestinal**
  - Nausea, Abdominal discomfort, Diarrhea
- **Musculoskeletal**
  - Myalgia, Lethargy, Arthralgia
- **Laboratory Abnormalities**
  - Hyperkalemia
  - Hyperuricemia
  - Hypomagnesemia
  - Hyperlipidemia

Nephrotoxicity

- If serum Cr increases by 25-30% from baseline, a decrease in dose must be made.

- No reported cases in world literature of renal failure or clinically significant kidney damage from CsA therapy in Psoriasis.

Hypertension

- Incidence: 27% of psoriatic patients on CsA therapy
- Mild, reversible
- Mechanism:
  - Direct vasoconstrictive effect on vascular smooth muscle in kidney
  - Secondary to primary renal dysfunction

Malignancy Risk

- When maximum dose of 5 mg/kg/d is used by psoriatic patients, not on other immunosuppressant, who are generally healthy, and on therapy that is not used longer than 2 years continuously, an increased risk of malignancy is not evident.

Drug Interactions

- Drugs that (-) CYP 3A4
  - Macrolides, Fluoroquinolones, cephalosporin, doxycycline, azoles, protease inhibitors, CCB's, H2 antihistamines, corticosteroids, diuretics, coumadin, allopurinol, amphotericin B, OCP's, Reglan, Grapefruit
- Drugs that (+) CYP 3A4
  - Rifampin, nafcillin, anticonvulsants, octreotide, ticlopidine

Drug Interactions

- Drugs that potentiates Nephrotoxicity
  - Aminoglycosides, Bactrim, Vancomycin, Amphotericin B, NSAIDS, Immunosuppressant
- Other
  - Digoxin, Lovastatin, Prednisolone, ACE Inhibitors, Potassium supplements and Potassium sparing diuretics.

Baseline Assessment

- Thorough H&P to rule out existence of active infection or tumor
- Baseline Blood Pressure (at least 2)
- Labs
  - Baseline SCr (At least 2)
  - Other methods of Renal evaluation (BUN/UA)
  - CBC/ LFT's
  - Fasting Lipid Profile
  - Chemistry (K, Mag, Uric Acid)

Monitoring

- Follow up q 2 weeks for 1-2 months and then q monthly
- Exam-BP check at each visit
- Repeat labs
  - BUN/Cr, UA
  - CBC/ LFT's/ Chemistry
  - Lipids (every other visit)
- On select Patients, may consider CsA level, CrCl (if >6 mos. of tx), or kidney Bx

Dosing

- Maximum Dermatologic Dose=5mg/kg/d (*4mg/kg/d)
- Two schools of thought
  - High dose initially and taper down
  - Low dose initially and taper up
- Reevaluate at 1 month for efficacy and increase dose by 0.5-1.0 mg/kg/d q 2 weeks to max dose if needed.
- End point-3 months of max dose and no response, then CsA should be discontinued

Dosing

- Obese Patients-calculate dosage using Ideal body weight (**Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet. Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.**)

- When converting from Sandimmune to Neoral use a 1:1 strategy and follow labs closely.

Duration of Therapy

- According to FDA guidelines, CsA can be used for up to 1 year continuously; up to 2 years based on world wide consensus.

- Optimal duration: 3-4 mos. of therapy. Use CsA as an acute agent and then transition to another agent.

Sequential Therapy

- Clearing phase-Transition phase-Maintenance phase
- Safest combination: CsA to Acitretin
  - Exclusively mutual side effect profile
  - Past experience
- Optimal because you utilize the quick fix property of CsA and the long term safety efficacy of Acitretin

Cyclosporine Cost

- **UVA**
  - 25 mg, $47.90 ($1.60/tab)
  - 100 mg. $137.35 ($4.58/tab)
- **Walmart**
  - 25 mg, $49.32 ($1.64/tab
  - 100 mg, $171.46 ($5.72/tab)
- **CVS**
  - 25 mg, $51.99($1.73/tab)
  - 100 mg, $198.99($6.63/tab)