3. **IMMUNOMODULATING DRUGS =**

IMMUNOPHILIN LIGANDS
&
ENZYME INHIBITORS

DR SHAMS SULEMAN

LEARNING OBJECTIVES

- Describe mechanism of action of Immunophilin ligands.
- Describe clinical uses and adverse effects of Immunophilin ligands
- Describe mechanism of action of enzyme inhibitors
- Describe clinical uses and adverse effects of enzyme inhibitors

IMMUNOPHILIN LIGANDS (ANTIBIOTICS)

- Cyclosporine A (CsA)
- Tacrolimus (TAC)
- Pimecrolimus
- Mammalian target of rapamycin (MTOR) inhibitors
  - Sirolimus (SIR)
  - *(Rapalogs) of SIR*
    - Evorilimus
    - Temsirolimus
- Fingolimod

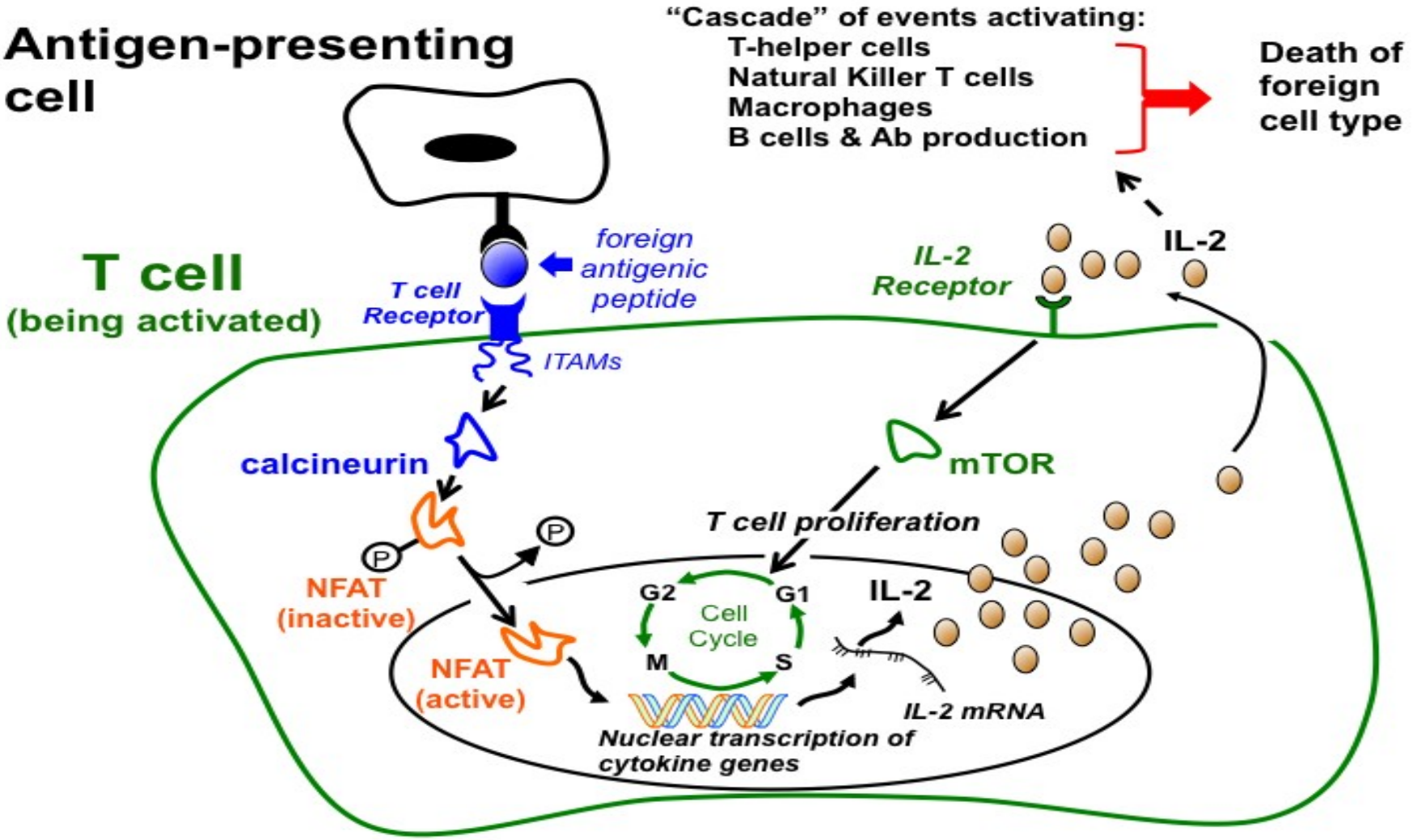
IMMUNOSUPPRESSANTS

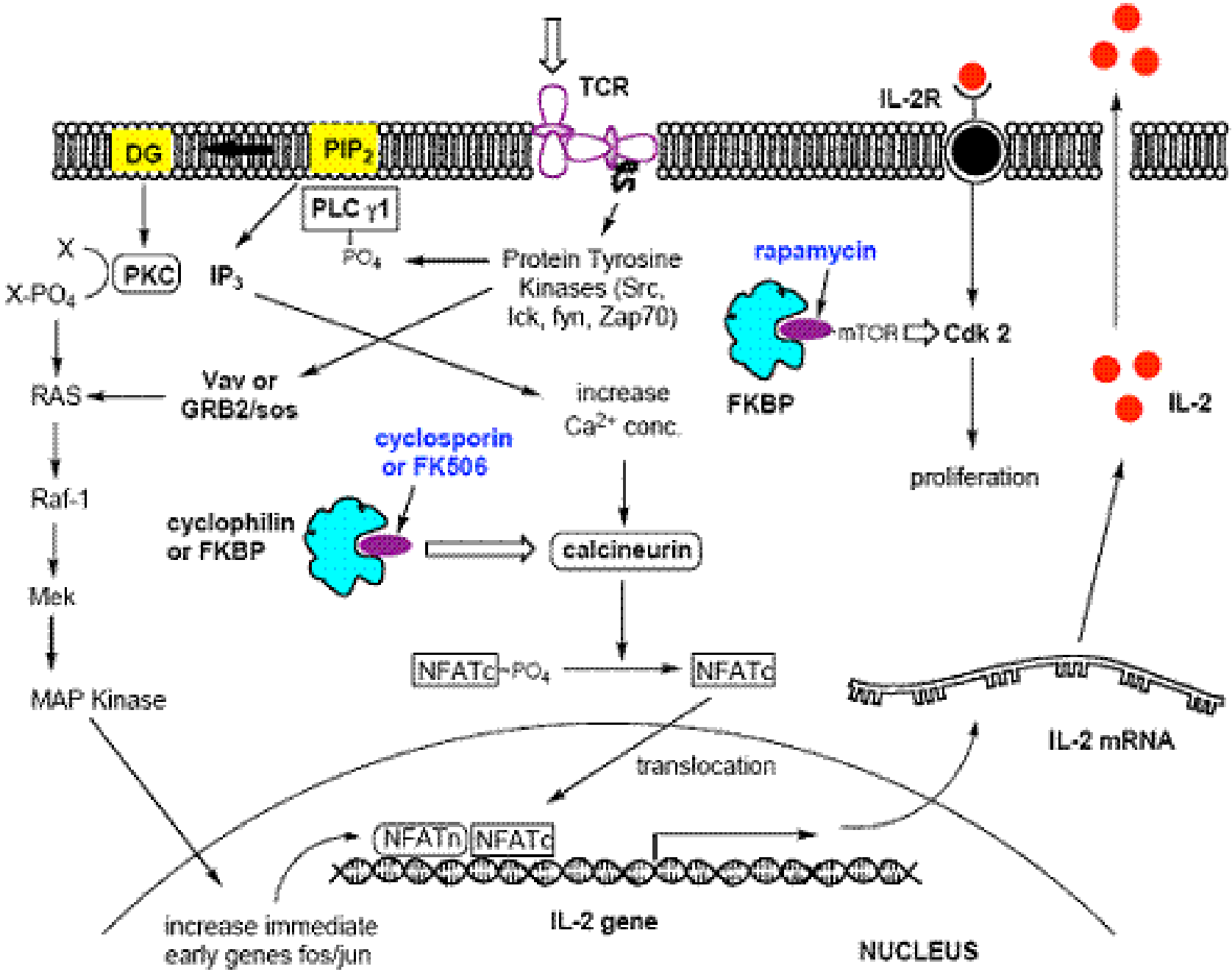
- **B:-Immunophilin ligands ; Antibiotics**
  - Cyclosporine A (CsA)
  - Tacrolimus (TAC)
  - Pimecrolimus
  - Mammalian target of rapamycin (MTOR) inhibitors
    - Sirolimus (SIR)
    - Evorilimus
    - Temsirolimus
  - Fingolimod

ENZYME INHIBITORS

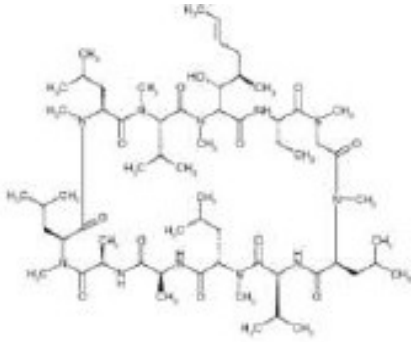
- Mycophenolate Mofetil (MMF)
- Mycophenolate sodium(MMS)
- Mizoribine
- Leflunamide / FK778
- Pentostatin (ADA inhibitor)

IMMUNOPHILIN LIGANDS (ANTIBIOTICS): OVERVIEW




TCR
IL-2R
DG
PIP2
PLC γ1
PO4
Protein Tyrosine Kinases (Src, lck, fyn, Zap70)
X
X-PO4
PKC
IP3
rapamycin
mTOR
Cdk 2
FKBP
RAS
Vav or GRB2/sos
increase Ca2+ conc.
IL-2
cyclosporin or FK506
proliferation
Raf-1
cyclophilin or FKBP
calcineurin
Mek
NFATc-PO4
NFATc
MAP Kinase
translocation
IL-2 mRNA
NFATn
NFATc
IL-2 gene
increase immediate early genes fos/jun
NUCLEUS

Cyclosporine



- Neoral : oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment

- Description
  - 11-amino-acid cyclic peptide from *Tolypocladium inflatum*
- Mechanism
  - Binds to cyclophilin; complex inhibits calcineurin phosphatase and T-cell activation

CYCLOSPORINE

- Lipophilic peptide antibiotic
- MOA = Cyclophilin --- calcineurin

  Decreased dephosphorylation of NFATc.

  Decreased IL 2 production (also IL 3 /INFα)

  Doesn't affect IL 2 already produced .
- Pharmacokinetics

  Oral /IV /eye drops /inhalation

  Cyt p450 3A4 , t ½ =27 hours

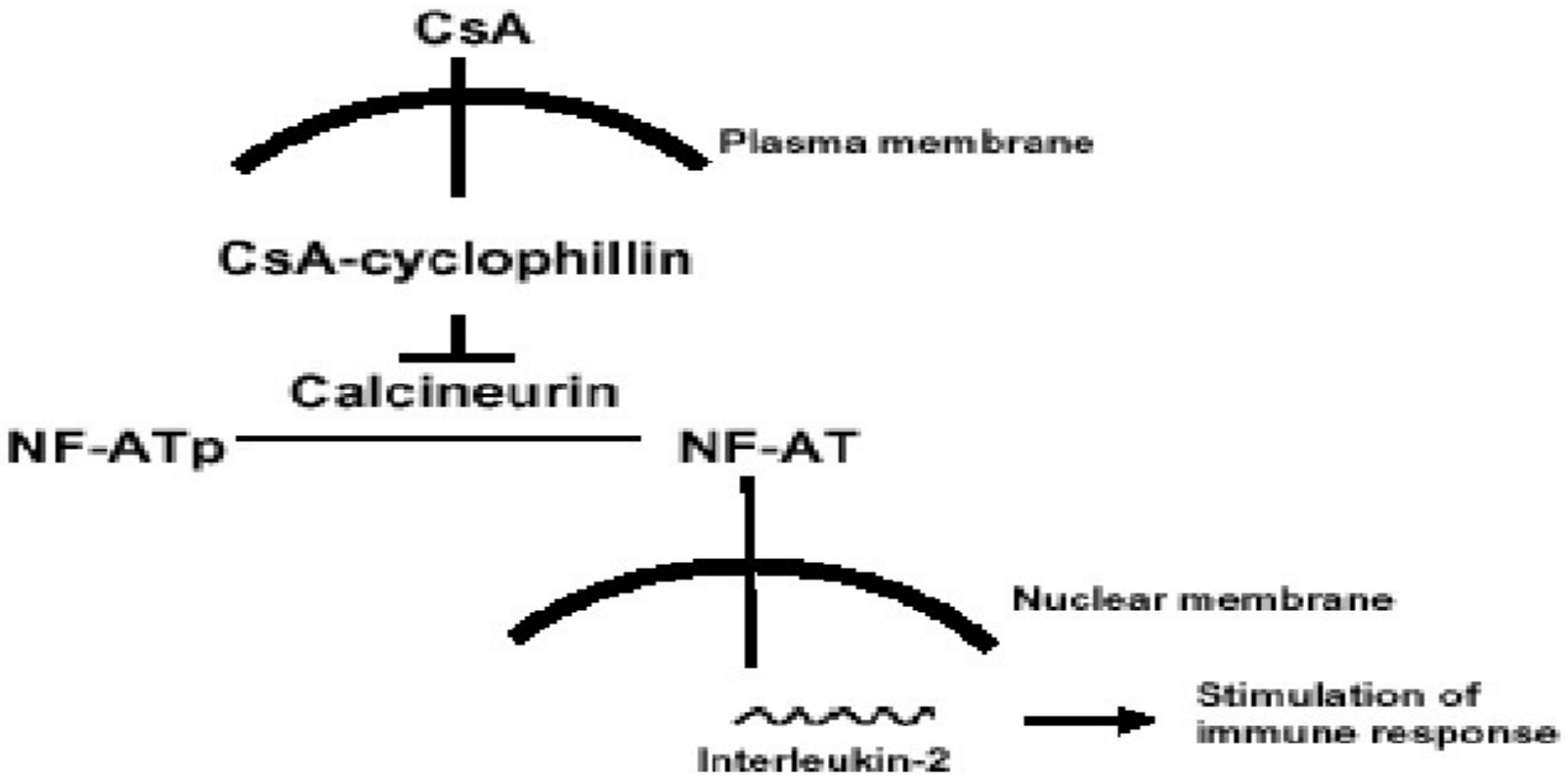
ADVERSE EFFECTS:

- Sustained rise in BP
- Precipitation of diabetes
- Anorexia (lack of appetite for food)
- Lethargy (lack of energy)
- Opportunistic infections
- Hirsutism (abnormal growth of hairs)

PHARMACOKINETICS:

- Oral bioavailability is low.
- Metabolized in liver by CYP3A4.
- Excreted in bile
- Plasma $t_{1/2}$ is 4-6hr and 12-18hr.
- **Dose:** 10-15mg/kg/day

CYCLOSPORIN: MOA



CYCLOSPORINE

PHARMACOKINETICS

- Oral, IV == common use
- Cyclosporine ophthalmic solution =

  for severe xeropthalmia and ocular graft-versus-host disease

- Inhaled cyclosporine ==

  being investigated for use in lung transplantation

CYCLOSPORINE

THERAPEUTIC USES

- Solid organ transplant rejection.

(liver, lung, pancreas, eye, kidney, heart)

Some times sole immunosuppressant for cadaveric transplantation of the kidney, pancreas, and liver.

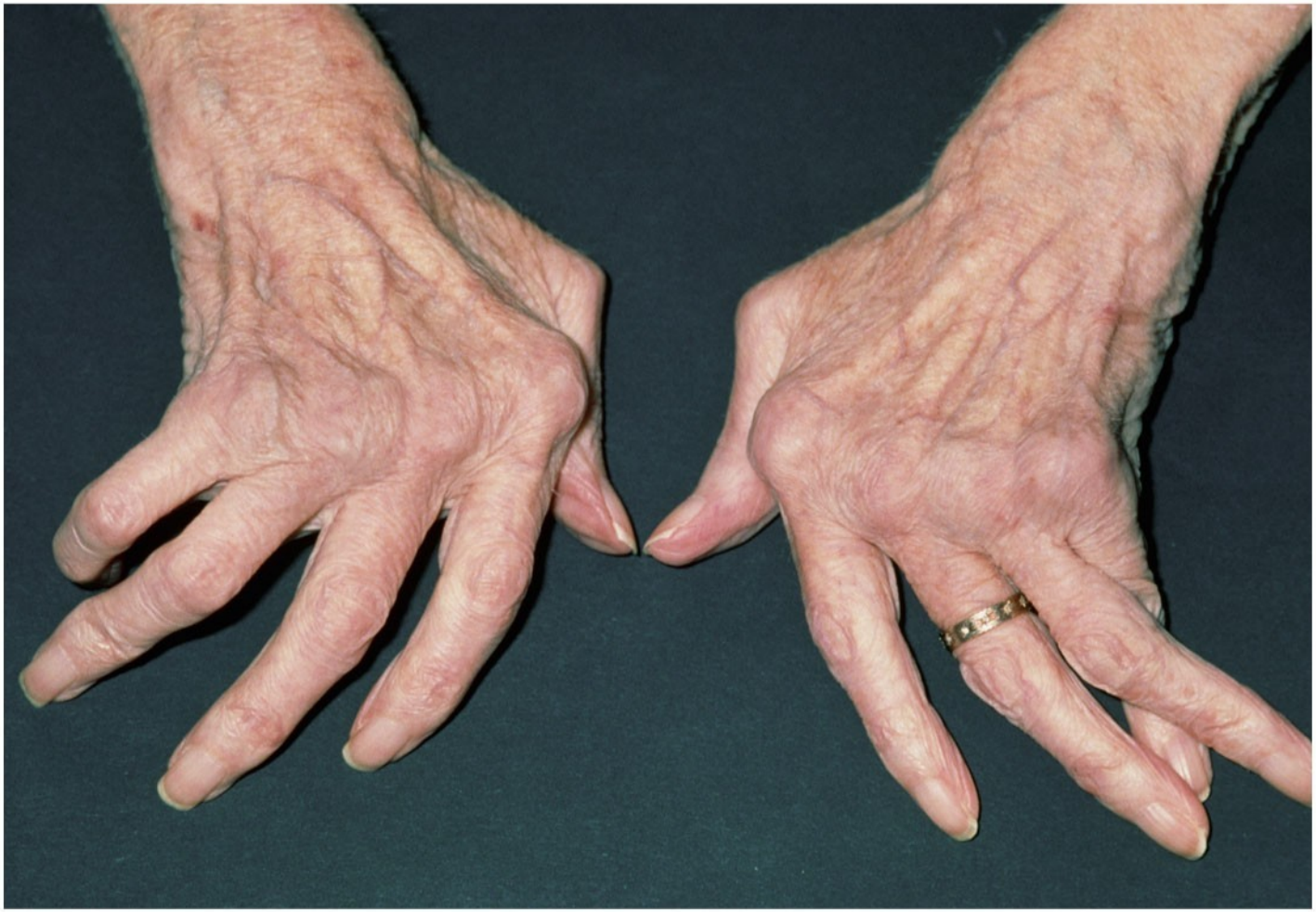
- Hematopoietic stem cell transplant rejection.

In combination with methotrexate, a standard prophylactic regimen to prevent graft-versus-host disease after allogeneic stem cell transplantation.

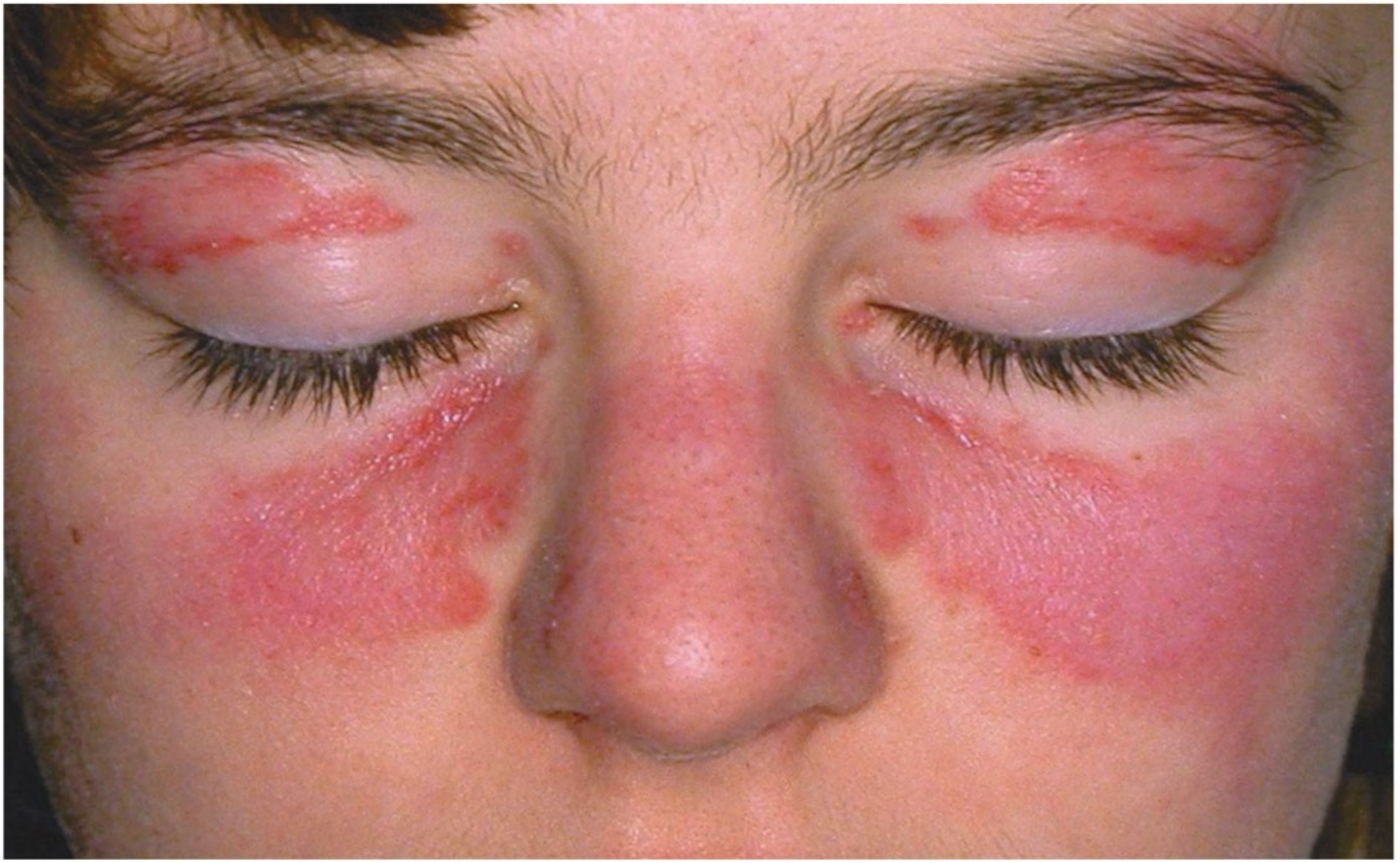
THERAPEUTIC USES

- Rheumatoid arthritis
- Psoriasis
- SLE
- Sjogren's syndrome, Xerostomia
- Bronchial asthma
- Uveitis

The crippling distortion of joints characteristic of rheumatoid arthritis



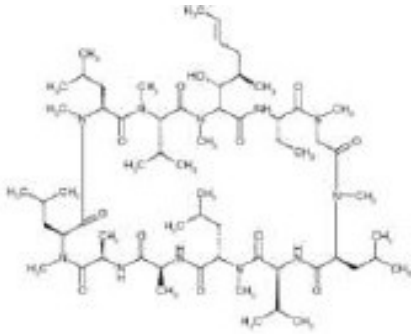
BUTTERFLY rash of systemic lupus



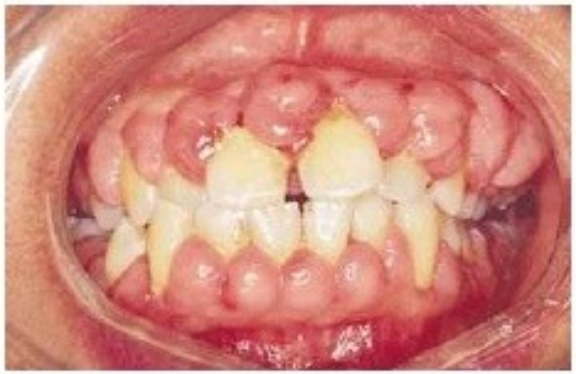
CYCLOSPORINE

- Inflammatory bowel disease
- Behcet' s syndrome
- Nephrotic syndrome
- Insulin dependant diabetes mellitus

Cyclosporine



- Side effect
  - Nephrotoxicity, hemolytic–uremic syndrome, hypertension, neurotoxicity, gum hyperplasia, skin changes, hirsutism, post-transplantation diabetes mellitus, hyperlipidemia; trough monitoring or checking levels two hours after administration required



CYCLOSPORINE

Adverse Effects

- Nephrotoxicity
- Neurotoxicity
- Hepatotoxicity
- Hirsutism
- Hypersensitivity
- Hypertension
- Hyperkalemia
- Hyperglycemia
- Hyperlipidemia
- Hyperplasia of gum

CYCLOSPORINE

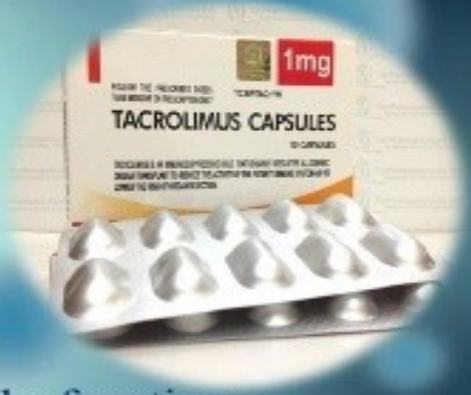
TOXICITY

- Very negligible bone marrow toxicity.
- Rarely = increased incidence of lymphoma and Kaposi's sarcoma, skin cancer
- Cyclosporine induces TGF-β, which promotes tumour invasion and metastasis

TACROLIMUS
(STREPTOMYCES TSUKUBIENSIS)

TACROLIMUS (FK506)

- Binds to FK-binding protein → inhibits T-cell activation
- 10-100 times more potent than cyclosporine
- Liver & kidney transplant
- Oral or IV : $t_{1/2}$ = 9-12 hrs
- Toxicity:
  - nephrotoxicity, neurotoxicity, hyperglycemia, GI dysfunction



Calcineurin inhibitors (Specific T-cell inhibitors)

2. TACROLIMUS :

- It's a new molecule chemically differ from Cyclosporine but having the same mechanism of action and is 100 times more potent.
- **Pharmacokinetics :-**

  → Administered orally as well as i.v. infusion.

  → Oral absorption is variable and decreases with food.

  → Metabolized by CPY3A4.

  → Excreted in bile.

Dose :- 0.05-0.1mg/kg BD oral

TACROLIMUS

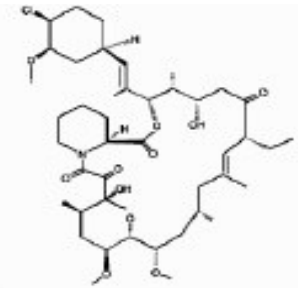
USES

- same as Cyclosporine
- Currently = Atopic dermatitis, psoriasis

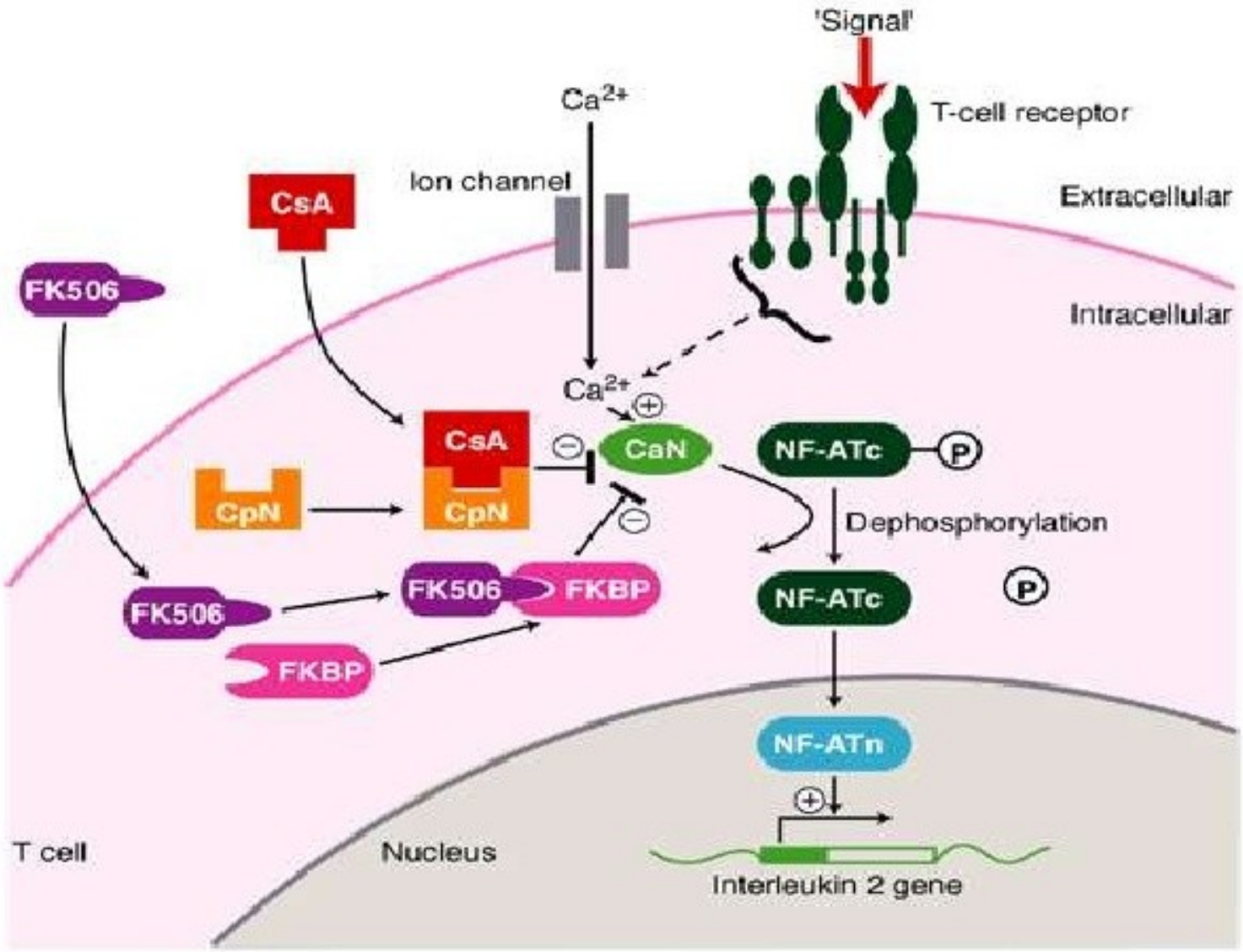
ADVERSE EFFECTS

- Same as CsA
- However, no hirsutism or gum hyperplasia like CsA
- Additional to CsA it can cause:-
  - Opthalmitis
  - Hallucinations
  - post transplant diabetes.

Pimecrolimus

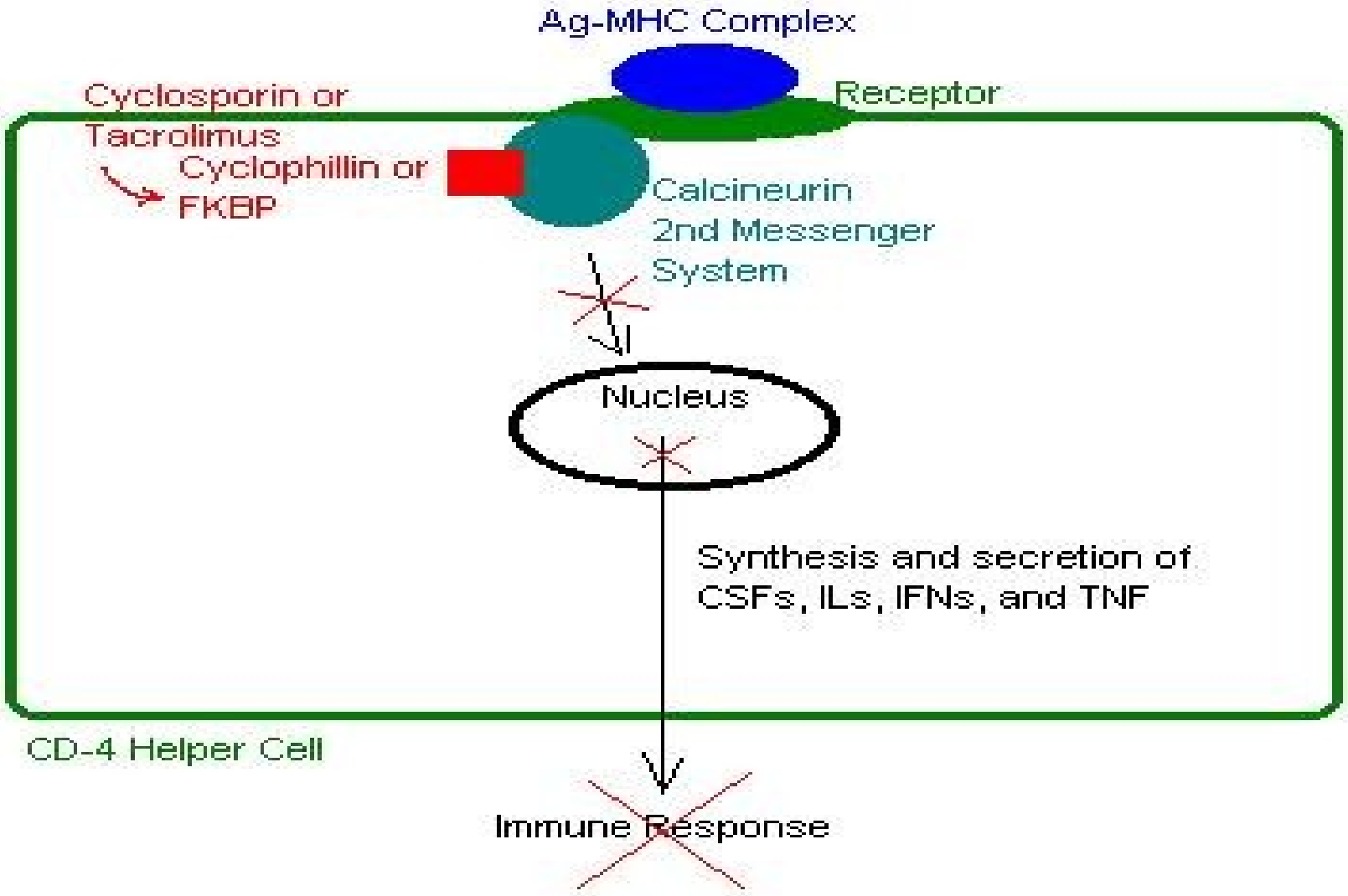


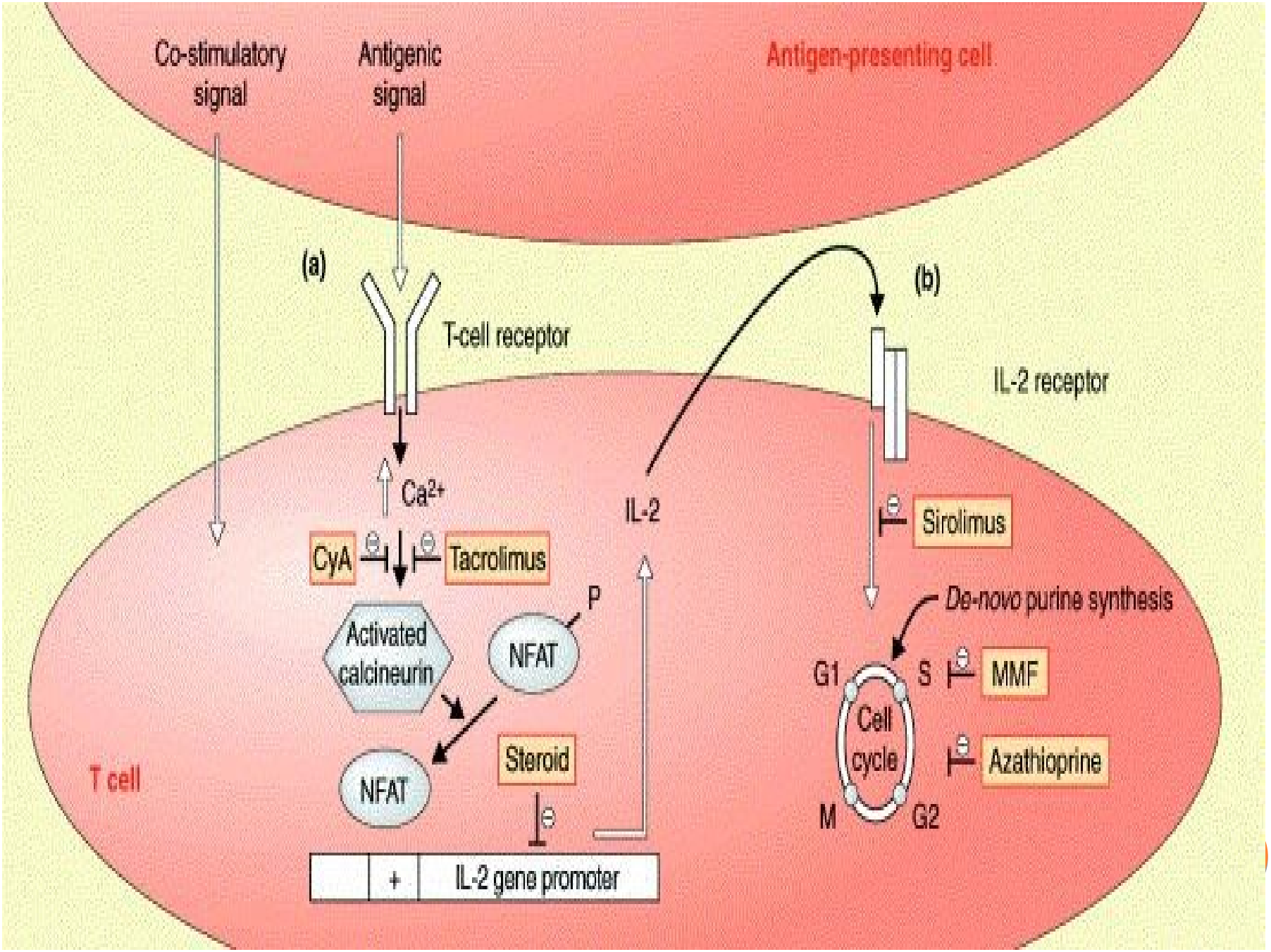
- Elidel – cream 1%
- Description
  - ascomycin macrolactam derivative
- Mechanism
  - Binds to macrophilin-12 and inhibits calcineurin
  - Inhibits T-cell activation by inhibiting the synthesis and release of cytokines from T-cells
  - Prevents the release of inflammatory cytokines and mediators from mast cells
  - Similar mode of action to tacrolimus but is more selective
    - no effect on dendritic (Langerhans) cells
    - lower permeation through the skin than topical steroids or topical tacrolimus



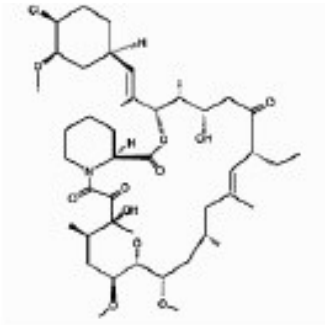
Mechanism of action of cyclosporine or tacrolimus (FK506)

Mechanism of Action of Cyclosporin and Tacrolimus -- Complex of the former with cyclophillin or the later with FKBP will bind to and inhibit the actions of calcineurin




Co-stimulatory signal
Antigenic signal
Antigen-presenting cell
(a)
T-cell receptor
(b)
IL-2 receptor
Ca^{2+}
IL-2
CyA
Tacrolimus
Sirolimus
P
Activated calcineurin
NFAT
De-novo purine synthesis
G1
S
MMF
Cell cycle
Azathioprine
M
G2
T cell
NFAT
Steroid
+
IL-2 gene promoter

Pimecrolimus



- Prescribed for
  - *second-line therapy* for the short- term and non-continuous chronic treatment of mild to moderate atopic dermatitis
  - not indicated for use in children less than 2 years of age
- Side effect
  - impetigo, skin infection , superinfection (infected atopic dermatitis)
  - Anaphylactic reactions, ocular irritation
  - Lymphomas, basal cell carcinoma, malignant melanoma, squamous cell carcinoma

SIROLIMUS

PHARMACOKINETICS

- Oral and topical only
- Metabolism == Cyp. P450 3A4 /P glycoprotein
- Requires loading dose
- Synergistic with cyclosporine

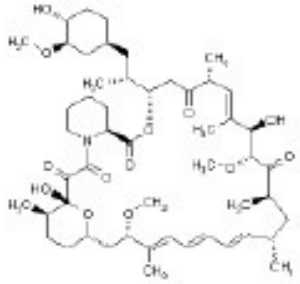
PHARMACOKINETICS

- Half-life is about 60 hours,
- That of Everolimus is about 43 hours
- Elimination is similar to that of cyclosporine

being substrates for both cytochrome P450 3A and p-glycoprotein

- Use with cyclosporine can increase the plasma levels of both sirolimus and everolimus
- Drug levels need to be monitored

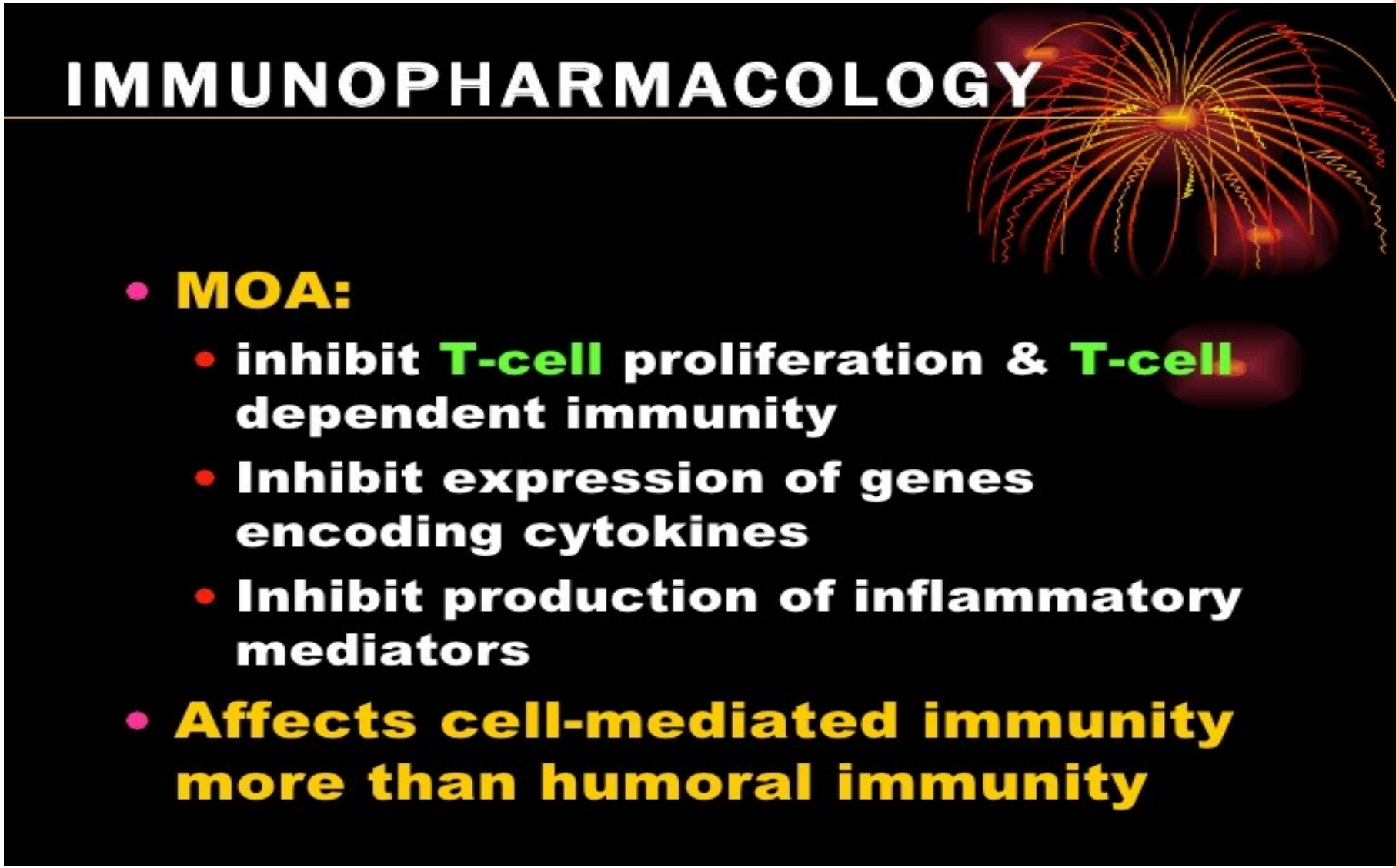
Sirolimus

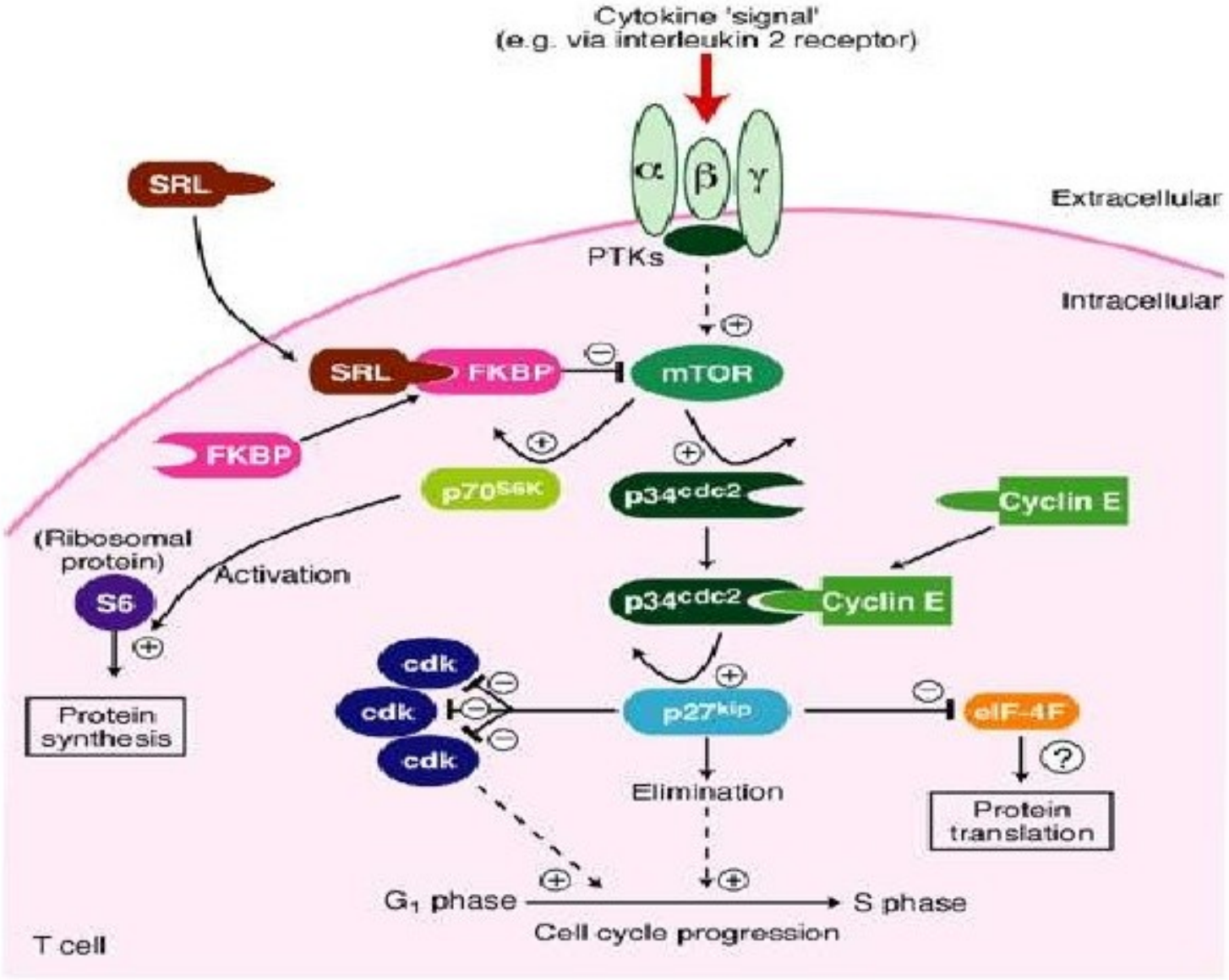


- Rapamycin
- Description
  - Triene macrolide antibiotic from *Streptomyces hygroscopicus* from Easter Island (Rapa Nui)

- Mechanism
  - Binds to FKBP12; complex inhibits target of rapamycin and interleukin- 2–driven T-cell proliferation
  - arresting the cell cycle in the G1 phase

SIROLIMUS

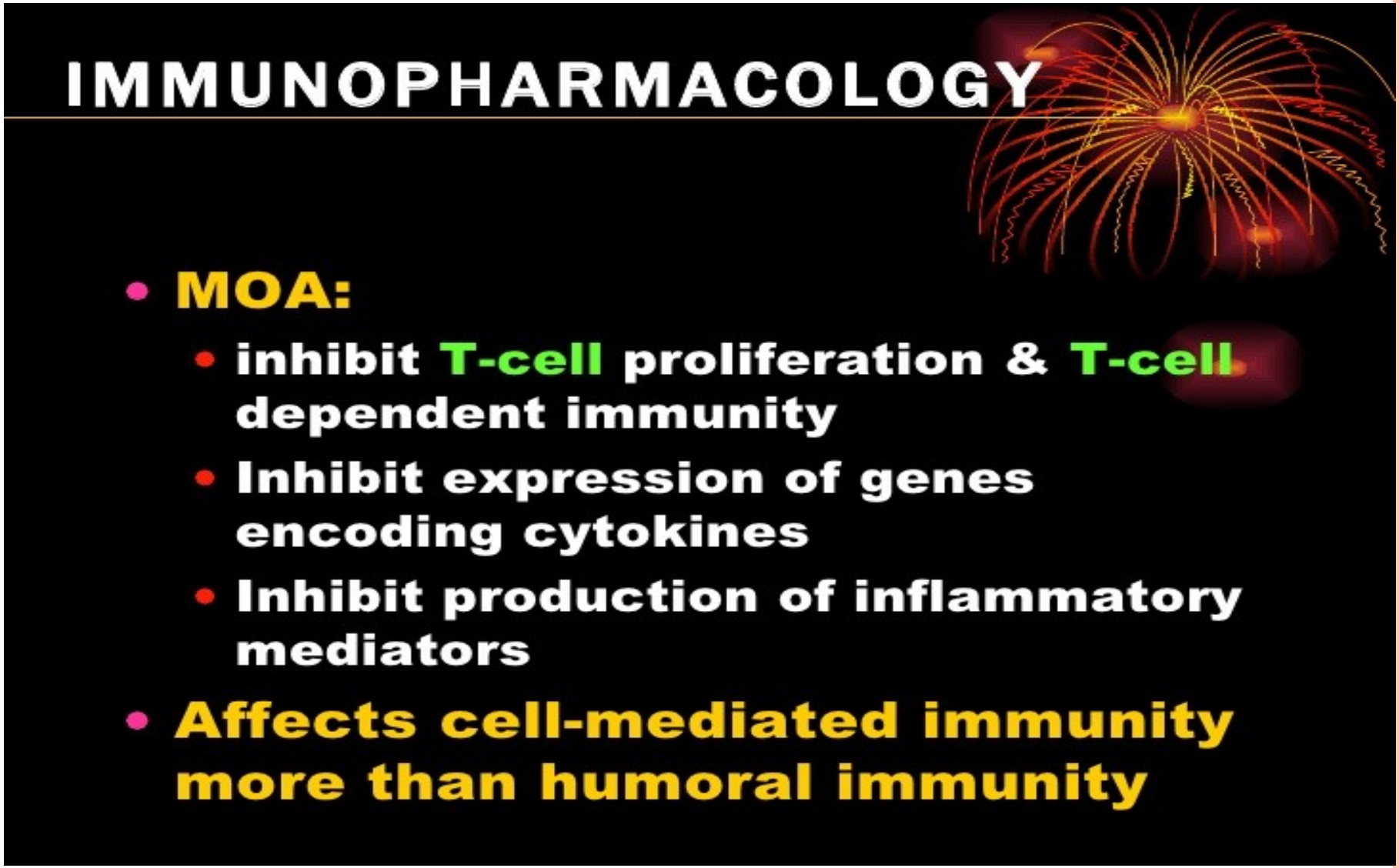

IMMUNOPHARMACOLOGY
• MOA:
• inhibit T-cell proliferation & T-cell dependent immunity
• Inhibit expression of genes encoding cytokines
• Inhibit production of inflammatory mediators
• Affects cell-mediated immunity more than humoral immunity



Mechanism of action of sirolimus (rapamycin)

Expert Reviews in Molecular Medicine © 2000 Cambridge University Press

SIROLIMUS


IMMUNOPHARMACOLOGY
• MOA:
• inhibit T-cell proliferation & T-cell dependent immunity
• Inhibit expression of genes encoding cytokines
• Inhibit production of inflammatory mediators
• Affects cell-mediated immunity more than humoral immunity

SIROLIMUS

USES

- To prevent rejection of Solid organ allografts.

  Used alone and in combination with corticosteroids, cyclosporine, tacrolimus, and mycophenolate mofetil

- Steroid resistant hemopoeitic stem cell transplantation

  For steroid-refractory acute and chronic graft-versus-host disease.

- Eluted coronary stents = to prevent restenosis

USES

- Renal transplant = to prevent graft intimal changes

  Because nephrotoxicity is of major concern with calcineurin inhibitors, Sirolimus is frequently employed as first line immunosuppressant therapy due to its safe renal profile

- Cardiac transplant = (Everolimus)
- Cyclosporine withdrawal protocols
- Targeted therapy for various cancers = Both Temsirolimus and Everolimus
- Topical Sirolimus
  - Dermatologic disorders
  - Chorio -retinitis, in combination with cyclosporine,

SIROLIMUS

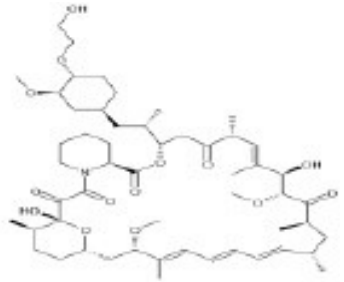
Adverse Effects

- Hyperlipidemia (cholesterol, triglycerides).
- Thrombocytopenia
- Leukopenia
- Hepatotoxicity
- Hypertension
- GIT dysfunction

ADVERSE EFFECTS

- Pneumonitis
- Headache
- Increased incidence of haemolytic-uremic syndrome

Everolimus



- Certican : Derivative of Rapamycin
- Mechanism
  - Works similarly to Rapamycin as an mTOR (mammalian target of rapamycin) inhibitor
  - lead to a hyper-activation of the kinase AKT via inhibition on the mTORC1 negative feedback loop while not inhibiting the mTORC2 positive feedback to AKT.
  - This AKT elevation can lead to longer survival in some cell types
- Prescribed for
  - Heart transplant reduce chronic allograft vasculopathy
    Howard J. Eisen: N Engl J Med 2003;349:847-58
  - Advance renal cancer
  - Vascular stent

FINGOLIMOD

- Immunosuppressant
- Sphingosine l-phosphate receptor modulator
- Mainly used to treat relapsing multiple sclerosis

Fingolimod

- FTY720
- Description
  - Sphingosine-like derivative of myriocin from ascomycete fungus
- Mechanism
  - Works as an antagonist for sphingosine-1-phosphate receptors on lymphocytes, enhancing homing to lymphoid tissues and preventing egress, causing lymphopenia

Fingolimod

- Prescribed for
  - Renal transplant
  - Multiple sclerosis : reduced the number of lesions detected on MRI and clinical disease activity

    (Ludwig Kappos N Engl J Med 2006;355:1124-40)
- Side effect
  - Reversible first-dose bradycardia, potentiated by general anesthetics and beta-blockers; nausea, vomiting, diarrhea, increased liver-enzyme
  - infections, skin cancer and, recently, a case of haemorrhaging focal encephalitis

ENZYME INHIBITORS

MYCOPHENOLATE MOFETIL (MMF)

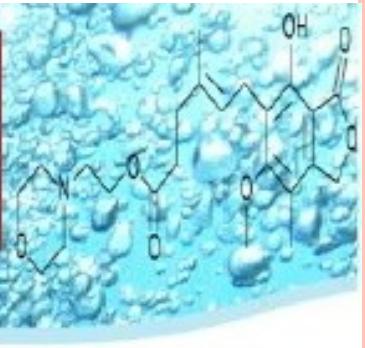
PHARMACOKINETICS

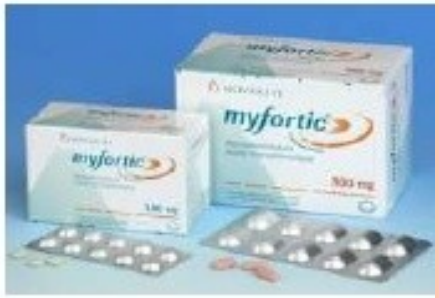
- Semisynthetic derivative of mycophenolic acid, isolated from the mold *penicillium glaucus*
- Hydrolysed to mycophenolic acid (MPA) the active immunosuppressive
- Available in both oral and intravenous forms.

- Oral form is rapidly metabolized to Mycophenolic acid.

- Although the cytochrome p450 3A4 system is not involved, some drug interactions still occur.

Mycophenolate mofetil

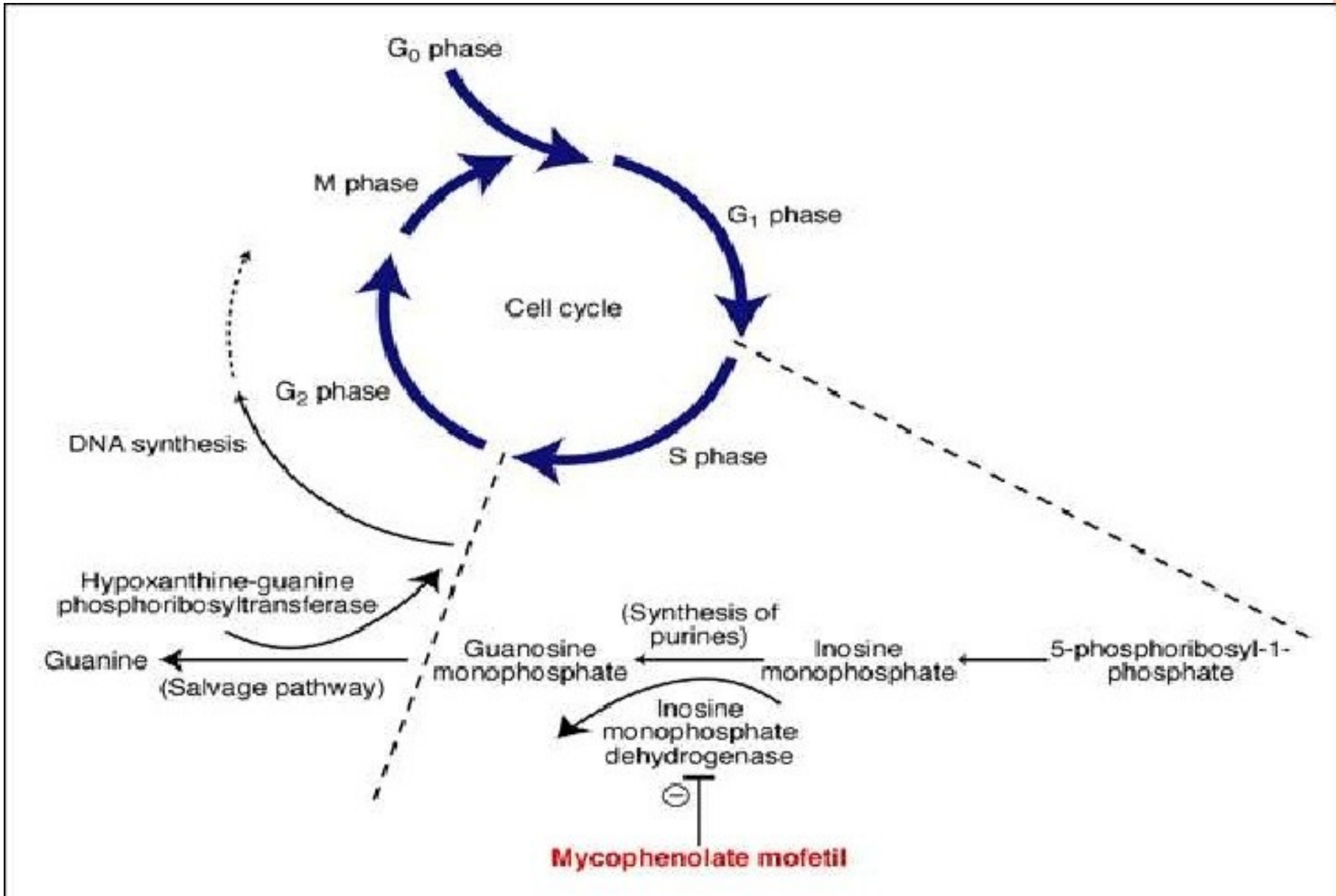




- Cellcept oral and injection
- Myfortic : mycophenolate sodium
- Description
  - Mycophenolic acid from penicillium molds
- Mechanism
  - Inhibits synthesis of inosine monophosphate dehydrogenase (IMPDH); blocks purine synthesis, preventing proliferation of T and B cells

MMF VERSUS MMS(MYCOPHENOLATE SODIUM)

- Enteric Coated **mycophenolate sodium**
- Was developed to reduce the upper-gastrointestinal (GI) effects of **MMF**
- Unlike oral **MMF** which releases MPA **in the** stomach, MMS releases MPA **in the** small intestine.
- The absolute bioavailability of EC **mycophenolate sodium** is 72%.



Mechanism of action of mycophenolate mofetil

MYCOPHENOLATE MOFETIL

. PHARMACOLOGICAL ACTIONS

- Inhibits T- and B -lymphocyte responses, including mitogen and mixed lymphocyte responses, by inhibition of synthesis of purines.

USES

- Solid organ transplant rejection refractory to conventional treatment
- Combination with prednisone, as an alternative to cyclosporine or tacrolimus in patients who do not tolerate those drugs.
- Prophylaxis and treatment of both acute and chronic graft-versus-host disease in hematopoietic stem cell transplant patients.
- Anti proliferative properties == cardiac transplant recipients.

  first-line drug for chronic allograft vasculopathy

USES

- Lupus nephritis
- Rheumatoid arthritis
- Inflammatory bowel disease

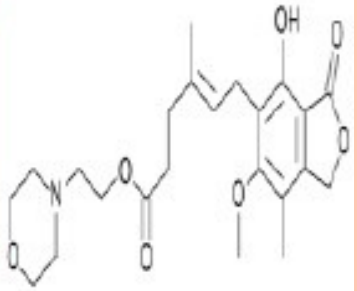
TOXICITY

- Dermatologic disorders
- Gastrointestinal disturbances (nausea, vomiting, diarrhoea, abdominal pain)
- Headache
- Hypertension
- Reversible myelosuppression (neutropenia).

TOXICITIES

- Gastrointestinal disturbances (nausea,vomiting,diarrhea, abdominal pain)
- Headache,
- Hypertension, and
- Reversible myelosuppression (neutropenia).

Mycophenolate mofetil



- Prescribed for
  - Renal, liver and cardiac transplant
  - Lupus nephritis
- Side effect
  - GI symptoms (mainly diarrhea), neutropenia, mild anemia; blood-level monitoring not required but may improve efficacy; absorption reduced by cyclosporine
  - lymphomas and other malignancies, particularly of the skin
  - Infection, CMV
  - Progressive Multifocal Leukoencephalopathy (PML)

MIZORIBINE (MZB)

- Approved in Japan in 1984
- Isolated from mold *Eupenicillum Brefeldianum*
- Imidazole nucleoside
- Metabolites = MZ-5-P
- Selective inhibition of inosine monophosphate (IMP) synthetase and guanosine monophosphate synthetase
- Complete inhibition of guanine nucleotide synthesis without incorporation into nucleotides
- Mizoribine is superior to azathioprine
- May not cause damages to normal cells and normal nucleic acid.

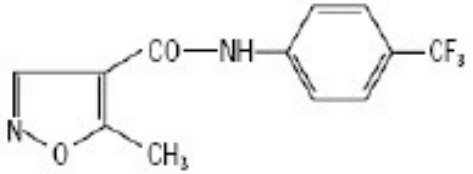
USES (MZB)

- Lupus Nephritis
- Renal transplantation
- Steroid -resistant nephrotic syndrome
- IgA nephropathy
- Rheumatoid arthritis

LEFLUNOMIDE

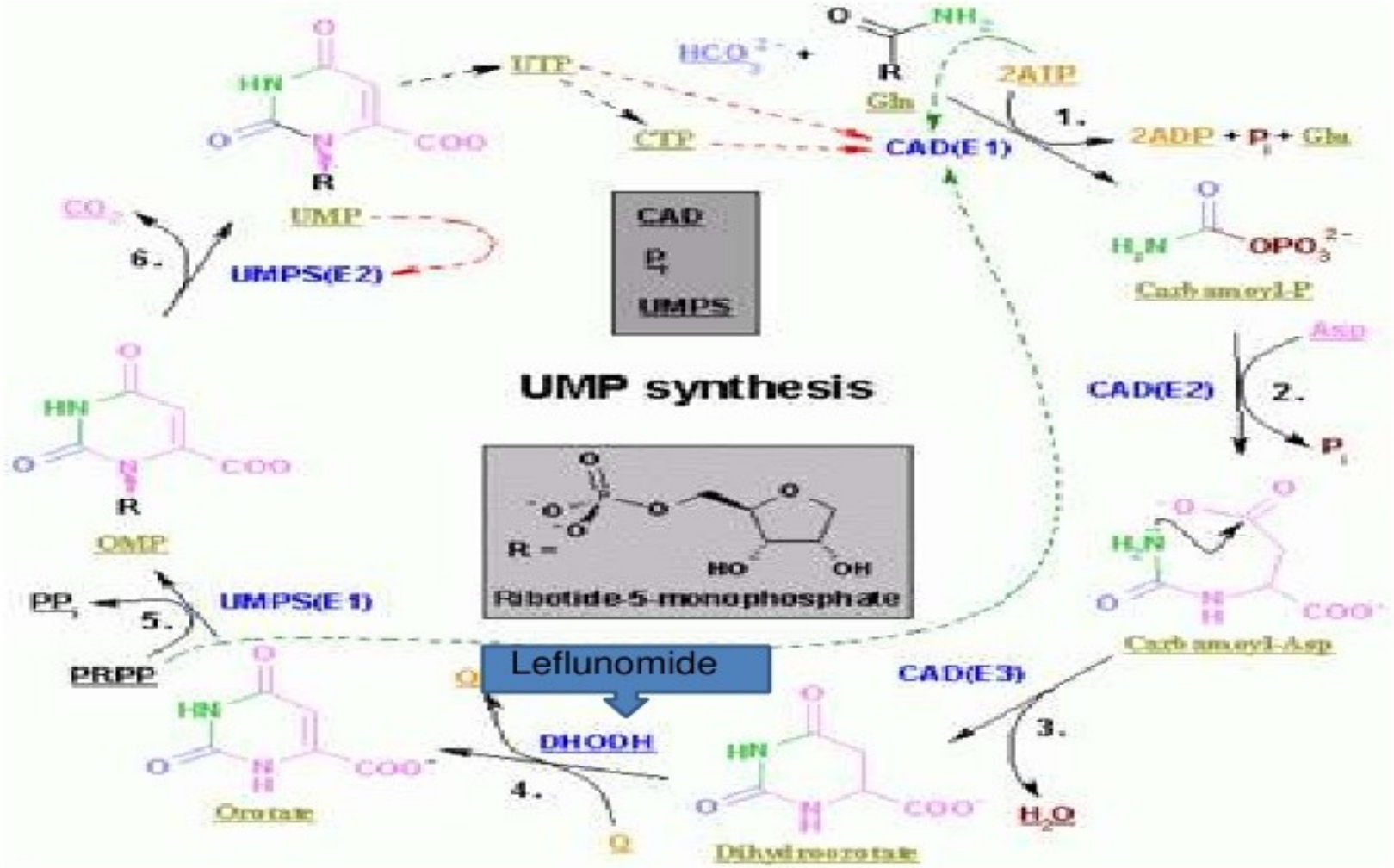
- A prodrug of an inhibitor of pyrimidine synthesis (rather than purine synthesis).
- Orally active, and long half-life of several weeks.
- Should be started with a loading dose, but it can be taken once daily after reaching steady state.

Leflunomide

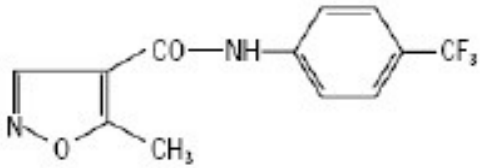


- Arava oral administration as tablets containing 10, 20, or 100 mg
- Description
  - pyrimidine synthesis inhibitor
- Mechanism
  - Dihydroorotate dehydrogenase inhibitor
  - antiproliferative activity
  - Several in vivo and in vitro experimental models have demonstrated an anti-inflammatory effect

LEFLUNOMIDE



Leflunomide



- Prescribed for
  - RA: reduction in signs and symptoms, and inhibition of structural damage and improvement in physical function

    (loading dose of 100 mg per day for three days only was used followed by 20 mg per day)

    Aspirin, NSAIDS and/or low dose corticosteroids may be continued during treatment with ARAVA

  Psoriatic arthritis, AS
- Side effect
  - diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash
  - high BP, chest pain and abnormal heartbeats
  - increase the risk to patients of infections

LEFLUNOMIDE

ANTI VIRAL

- Cytomegalovirus (CMV) =
  :alternative to Ganciclovir
  :inhibits viral capsid assembly

FK778

- malononitrilamides
- Description
  - active derivative of leflunomide
- Mechanism
  - Inhibits pyrimidine synthesis, blocking proliferation of T and B cells
- Side effect
  - Anemia; other effects not known; in phase 2 trials kidney transplant

PENTOSTATIN

- (-)Adenosine deamine
- Streptomyces antibioticus
- Accumulation of adenosine
- Incorporate in DNA

* Route IV, t ½ - 5.7 hrs
* Excreted in kidney
* A/E: BM suppression ,Renal,CNS
* Uses: Hairy cell leukemia,CLL,CML

Pentostatin

Inhibits adenosine deaminase

↓

Accumulation of adenosine & deoxyadenosine

↓

Inhibits ribonucleotide reductase

↓

Blocks DNA synthesis

S adenosyl homocysteine accumulation

↓

Toxic to lymphocytes

Used in
Hairy cell leukemia

PENTOSTATIN

- Adenosine deaminase inhibitor
- Ideally = Antineoplastic agent for lymphoid malignancies
- Also = Steroid -resistant graft-versus-host disease after allogeneic stem cell transplantation
- Preparative regimens prior to allogeneic stem cell transplantation to prevent allograft rejection.

Agent: Pentostatin (Nipent®)

- Indications: GvHD
- Route: IV
- Common Side Effects
  - Central nervous system: Fever, chills, headache
  - Dermatologic: rashes
  - Gastrointestinal: Nausea/vomiting/diarrhea
  - Hepatotoxicity
  - Renal toxicity
  - Myelosuppression
  - Respiratory: pulmonary edema

- Special Considerations:
  - Combined use with Fludarabine may lead to severe, even fatal, pulmonary toxicity

CLINICAL PHARMACOLOGY

Table 3. Safety categories during pregnancy and lactation of immunomodulator drugs most commonly used in ophthalmology (2)

Active principle	FDA category (use in gestation)	Lactation
Adalimumab	B	Avoid
Azatioprin	D	Avoid
Cyclophosphamide	D	Avoid
Cyclosporine A	C	Avoid
Chlorambucil	D	Avoid
Daclizumab	C	Avoid
Etanercept	B	Avoid
Infliximab	B	Avoid
Methotrexate	D	Avoid
Mycophenolate mofetil	C	Avoid
Tacrolimus	C	Avoid

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