

Immunobiology of Immunosuppressant Agents (2016)

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P. A. GORER 1907 - 1961



SIR PETER MEDAWAR 1915

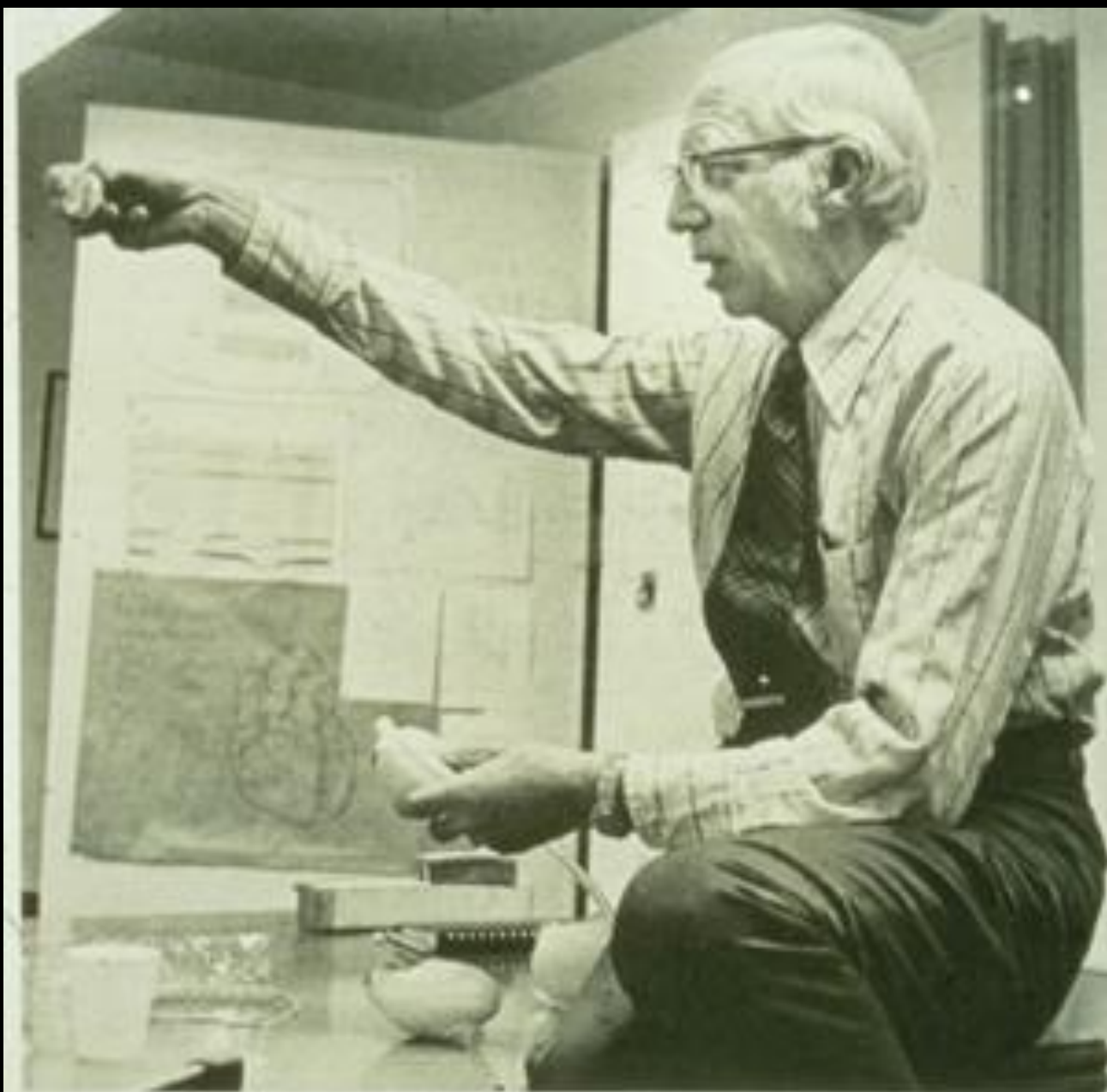


Photo by Ray Stevens, New York

WILLEM KOLFF



Fig. 1.7 Dr J.E. Murray, Dr J.P. Merrill and Dr J.H. Harrison, who successfully carried out renal transplantation between this set of identical twins on 23 December 1954.

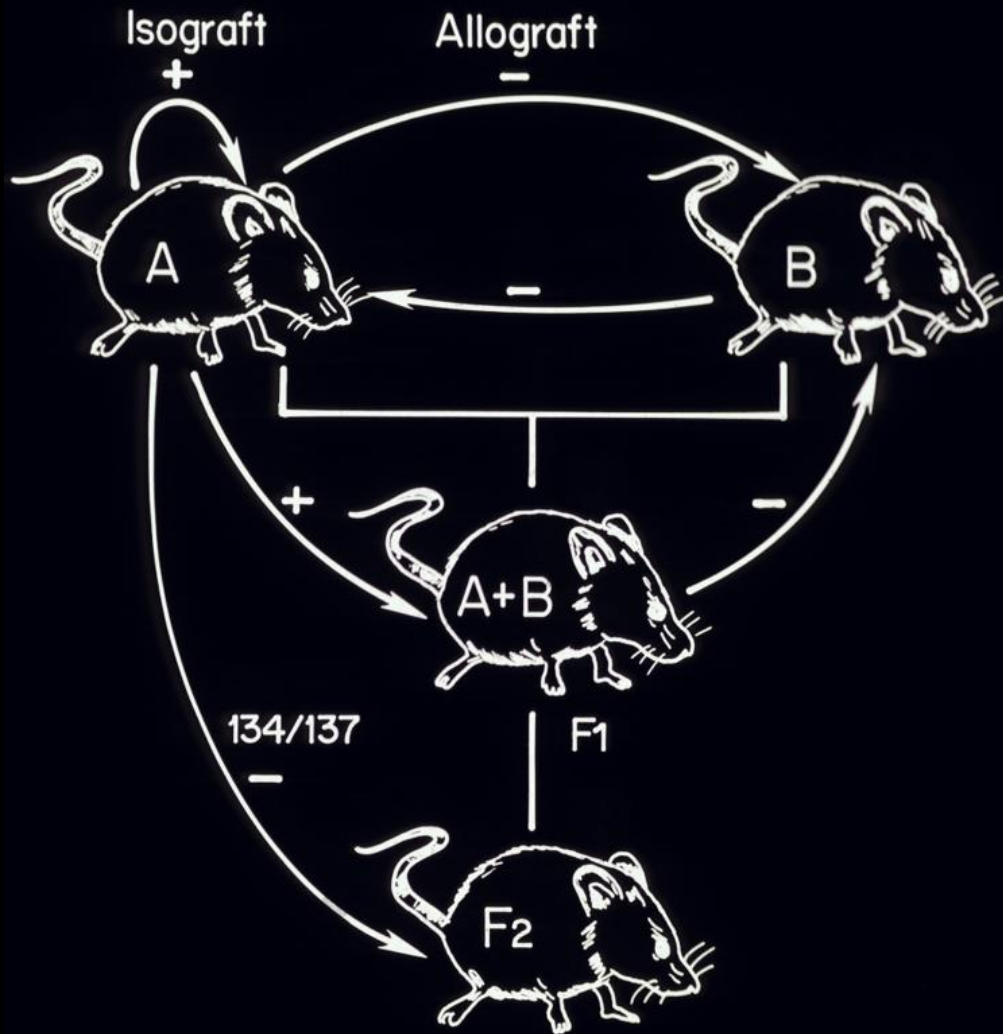
RENAL TRANSPLANT IN THE 20TH CENTURY

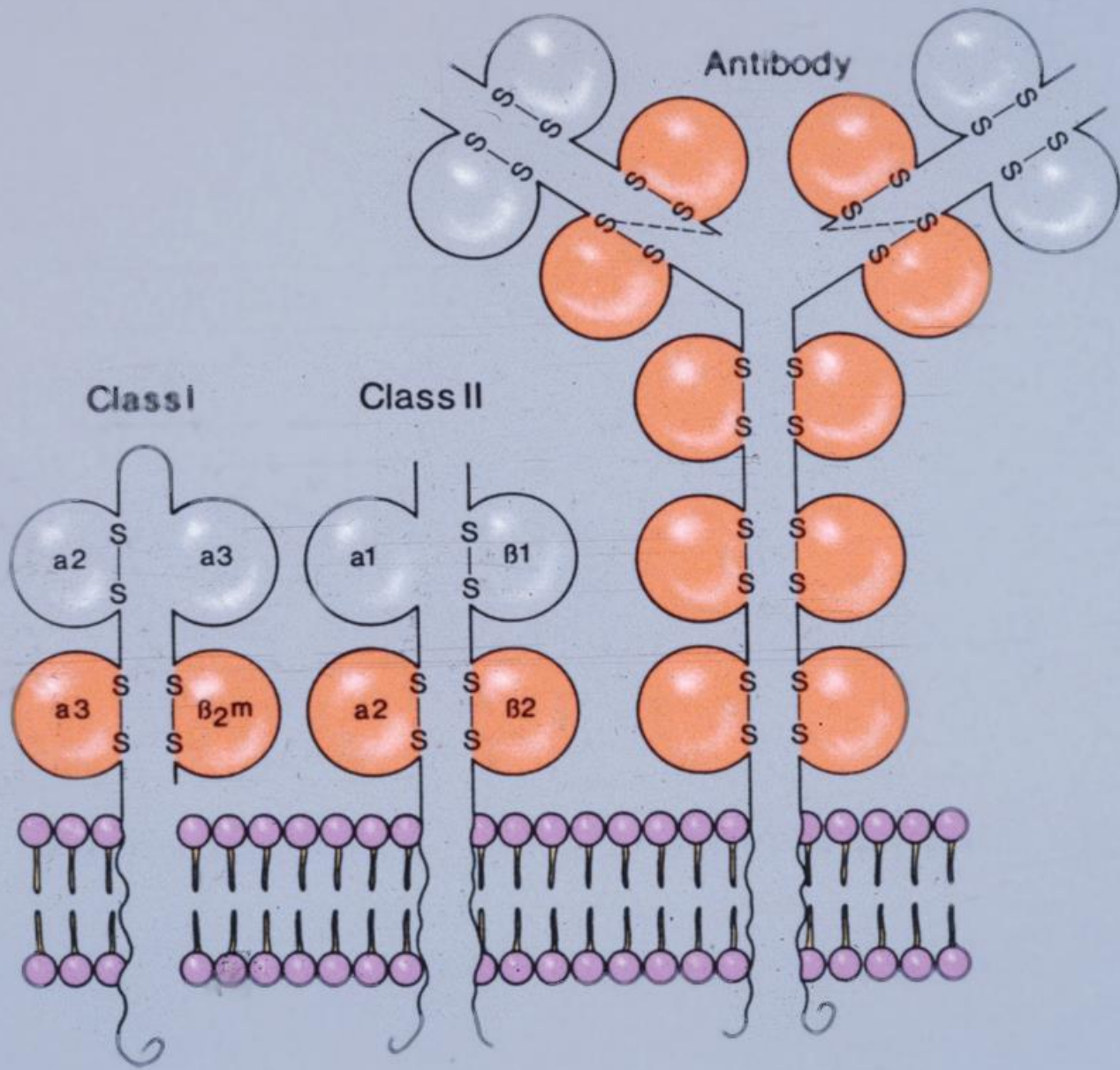
A HISTORY OF IMMUNOSUPPRESSIVE DRUGS

- | | | |
|--------------|----------------|---|
| ERA 1 | 1953-63 | THE EXPERIMENTAL PERIOD |
| ERA 2 | 1963-83 | THE AZATHIOPRINE ERA-INCREASING PATIENT POPULATION FOR TRANSPLANT, WITH INCREASING PT SURVIVAL AT EXPENSE OF GRAFT SURVIVAL |
| ERA 3 | 1983-93 | THE CYCLOSPORINE A ERA-MARKED IMPROVEMENT IN EARLY GRAFT SURVIVAL, ALL ORGANS ARE NOT CLINICALLY TRANSPLANTABLE, CHRONIC REJECTION REMAINS A PROBLEM |
| ERA 4 | 1993-? | THE DESIGNER DRUG ERA-KNOWLEDGE OF TRANSPLANT IMMUNOLOGY ALLOWS GRAFTING OF NEW AGENTS |

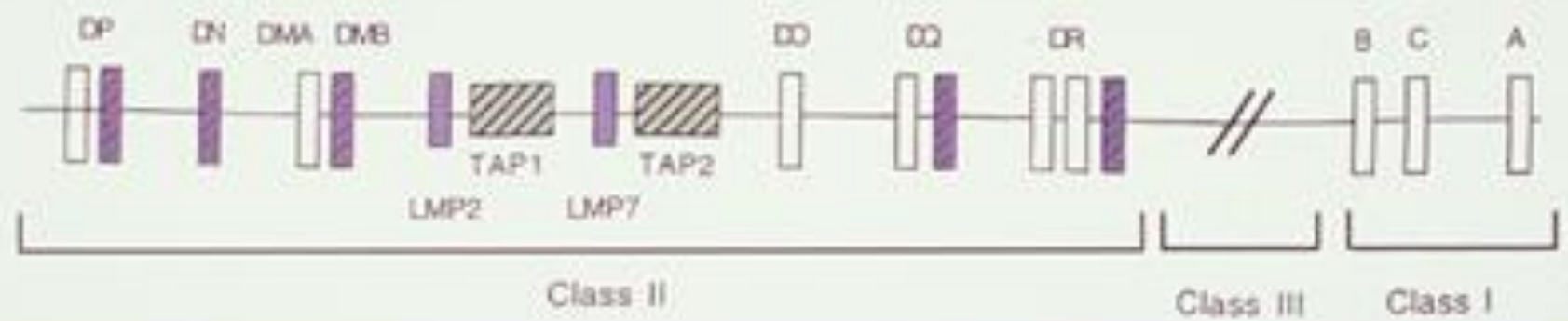
LAWS OF TRANSPLANTATION

Prehn & Main, 1958

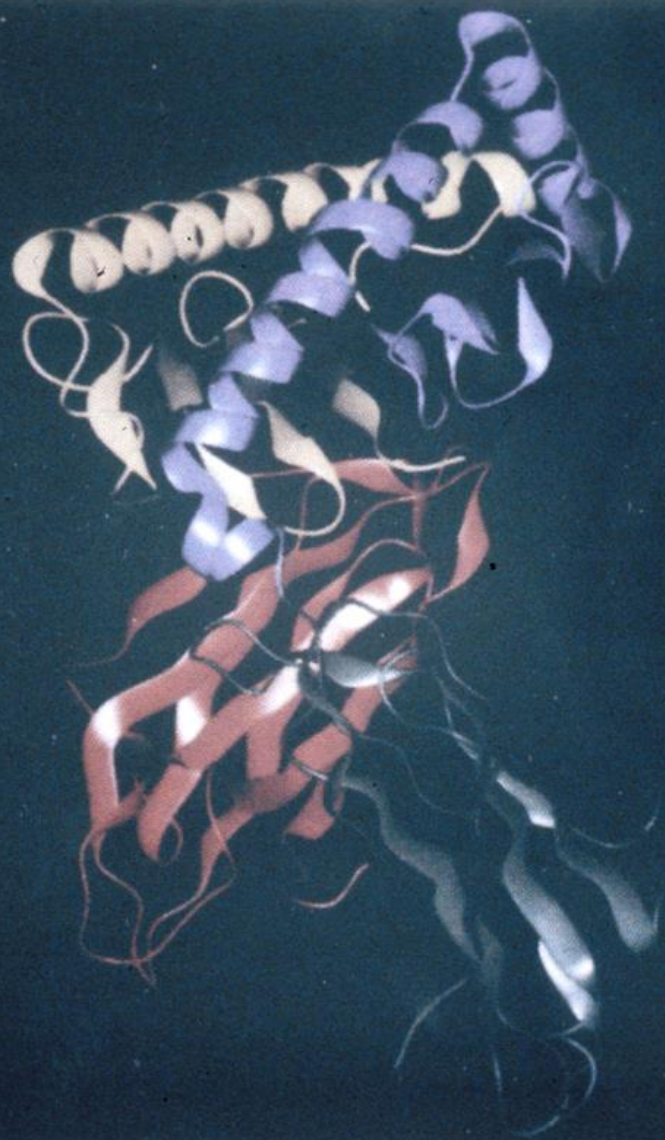




HUMAN MHC COMPLEX

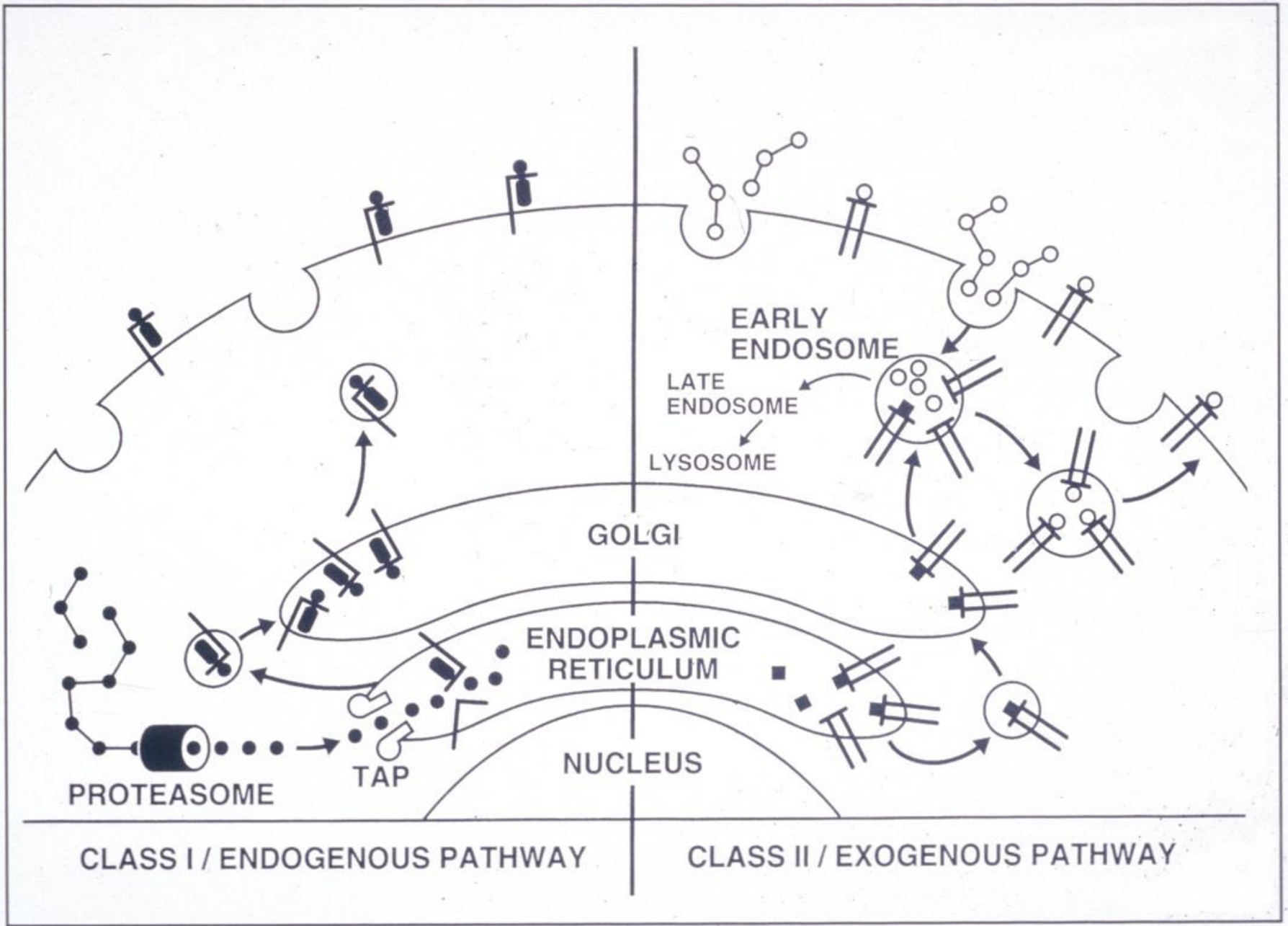


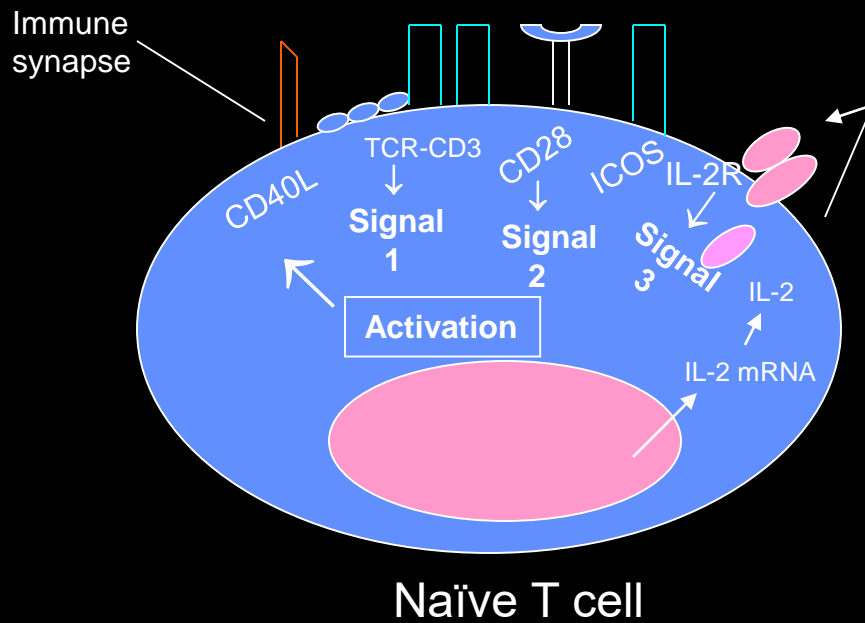
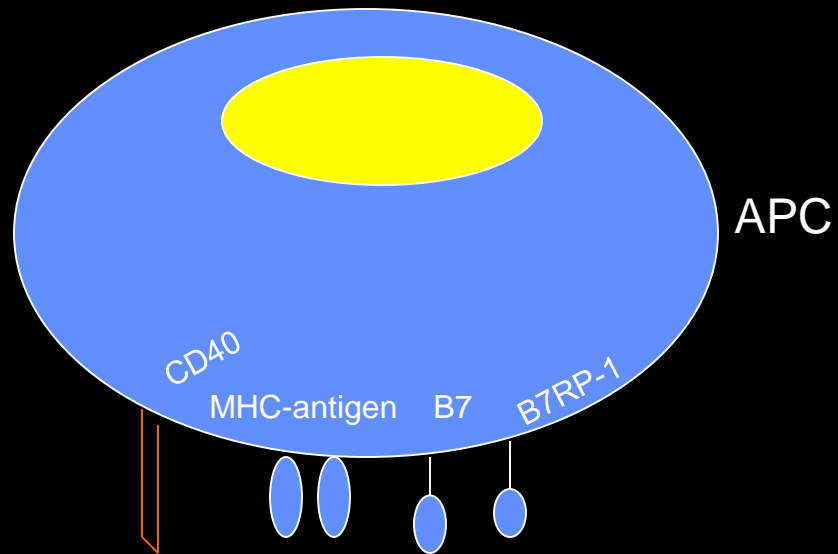
A

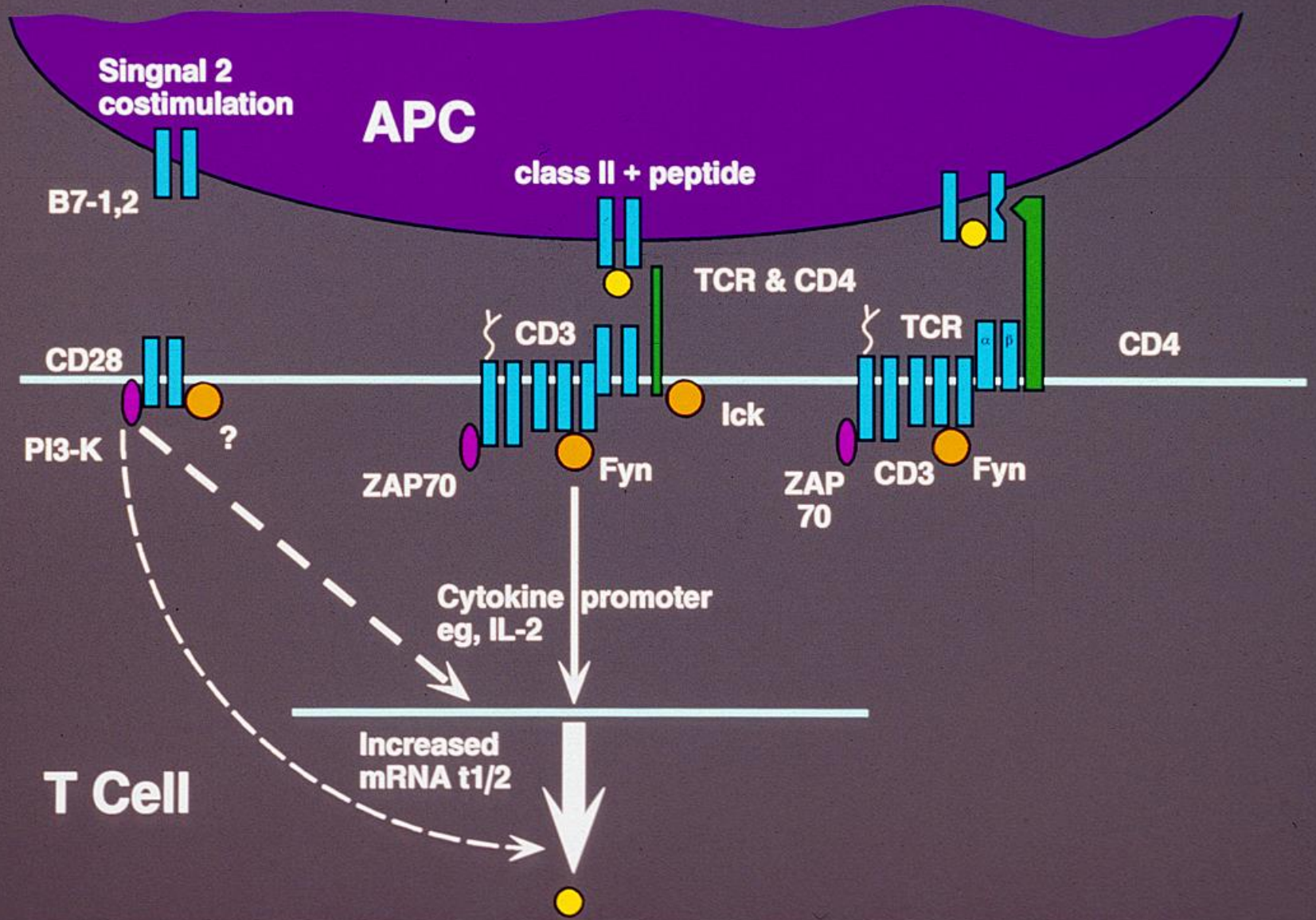


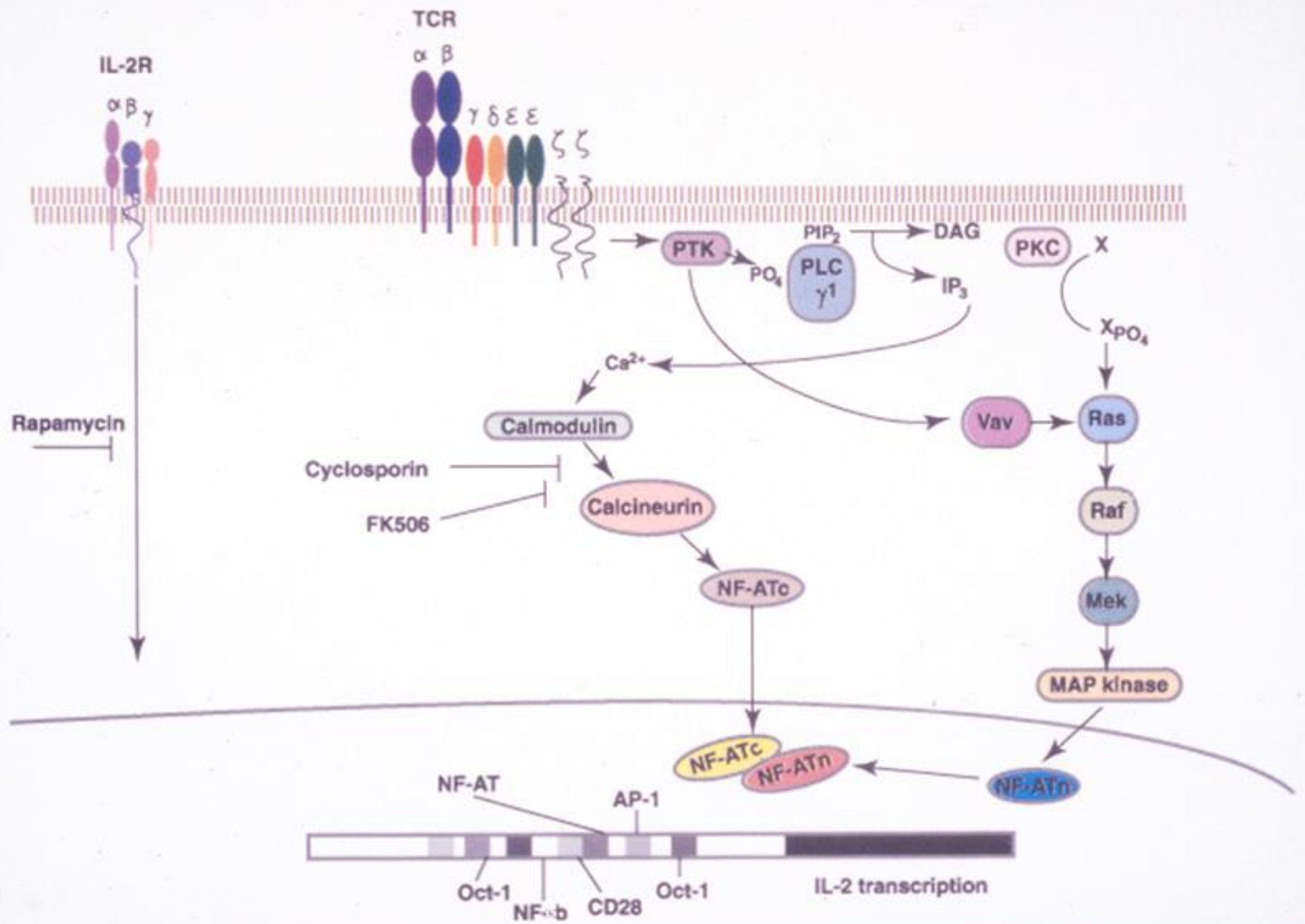
B

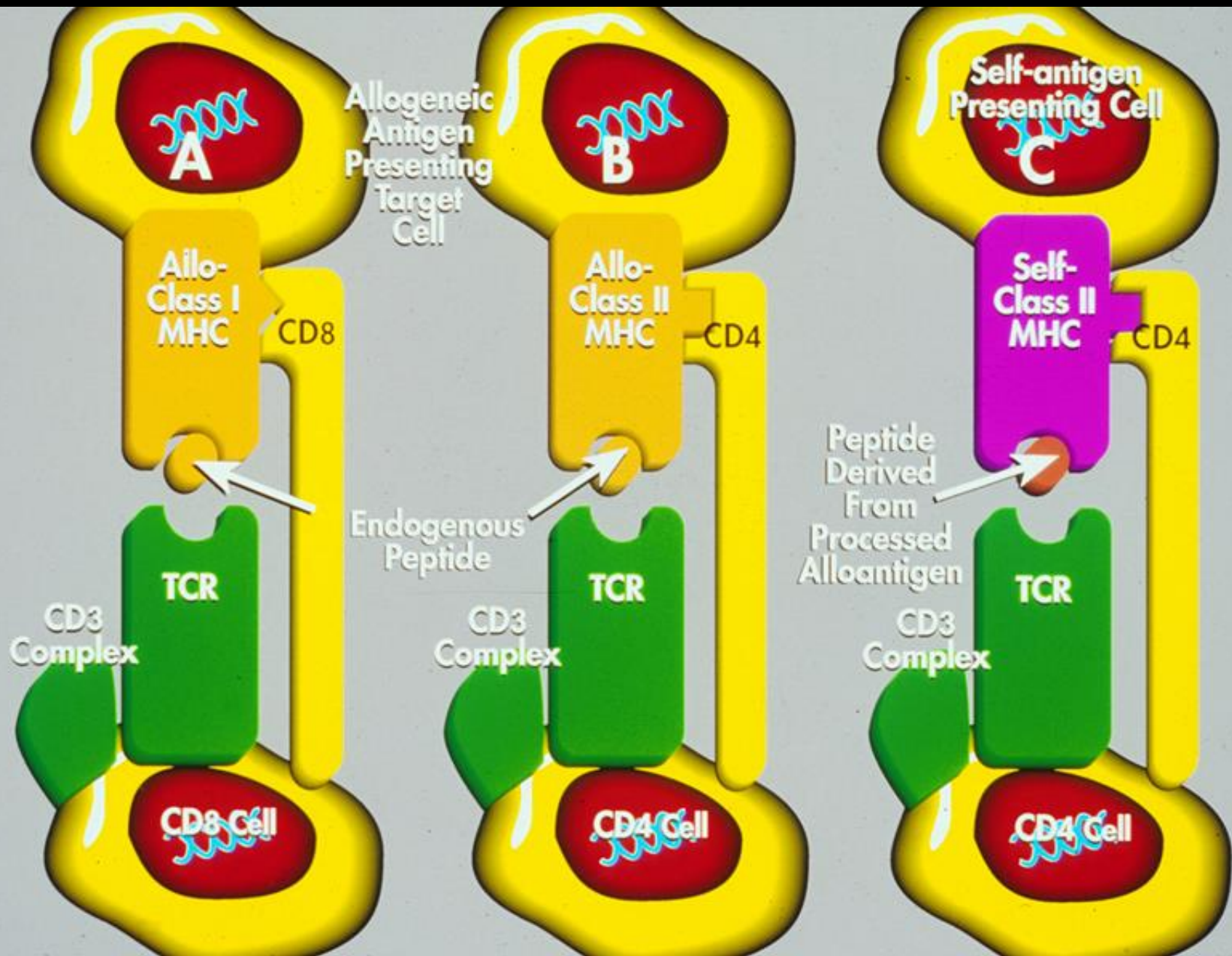






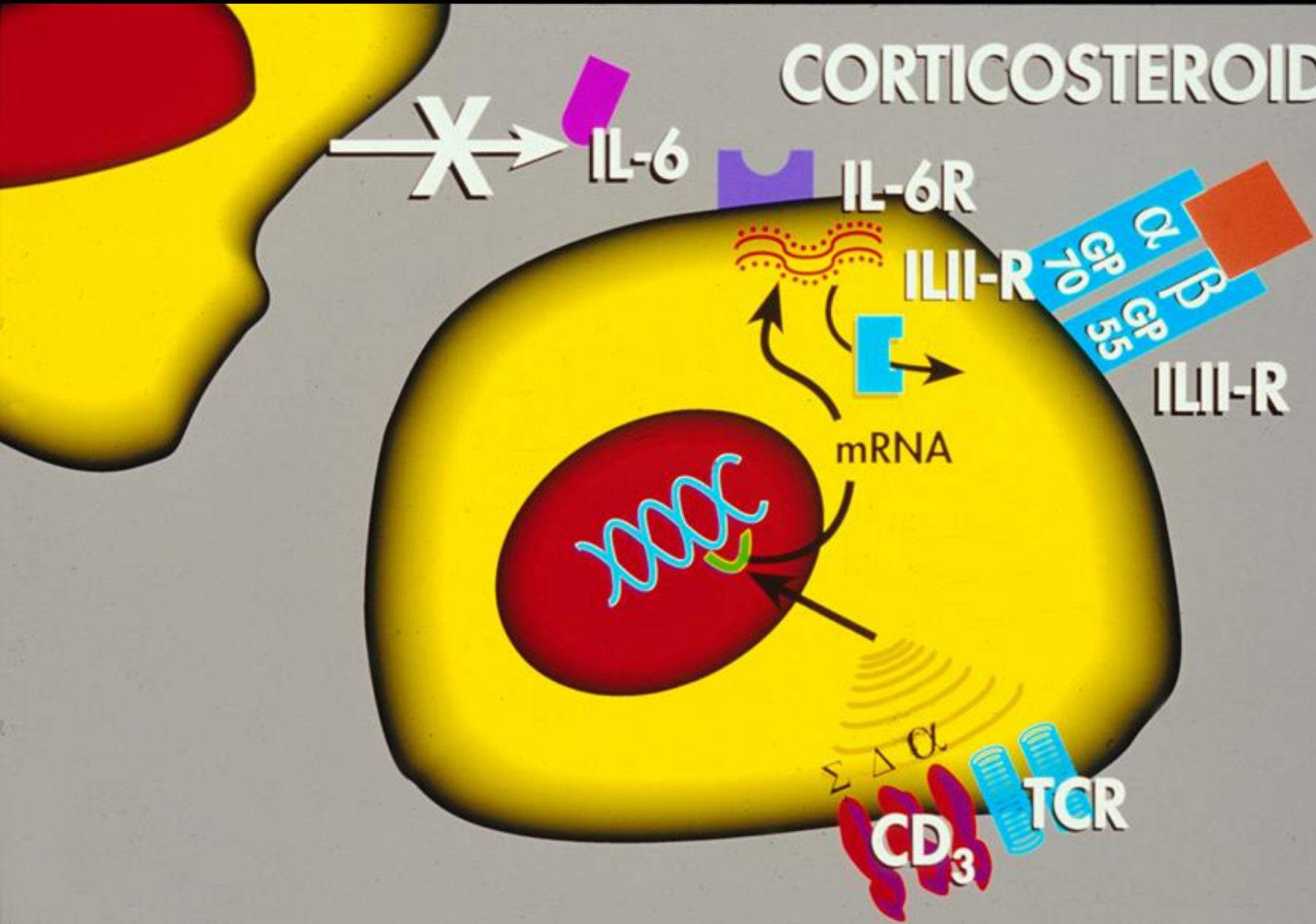


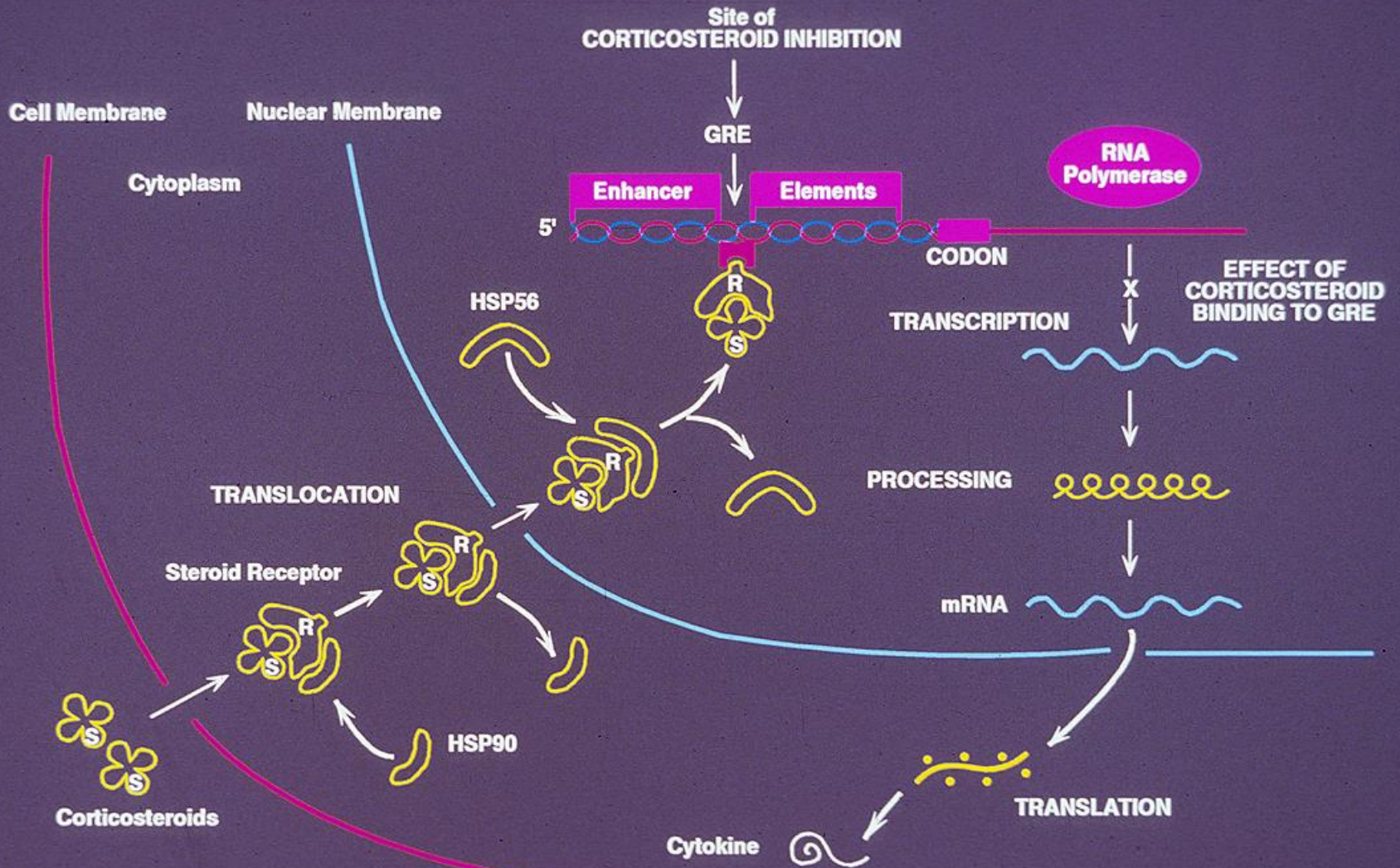




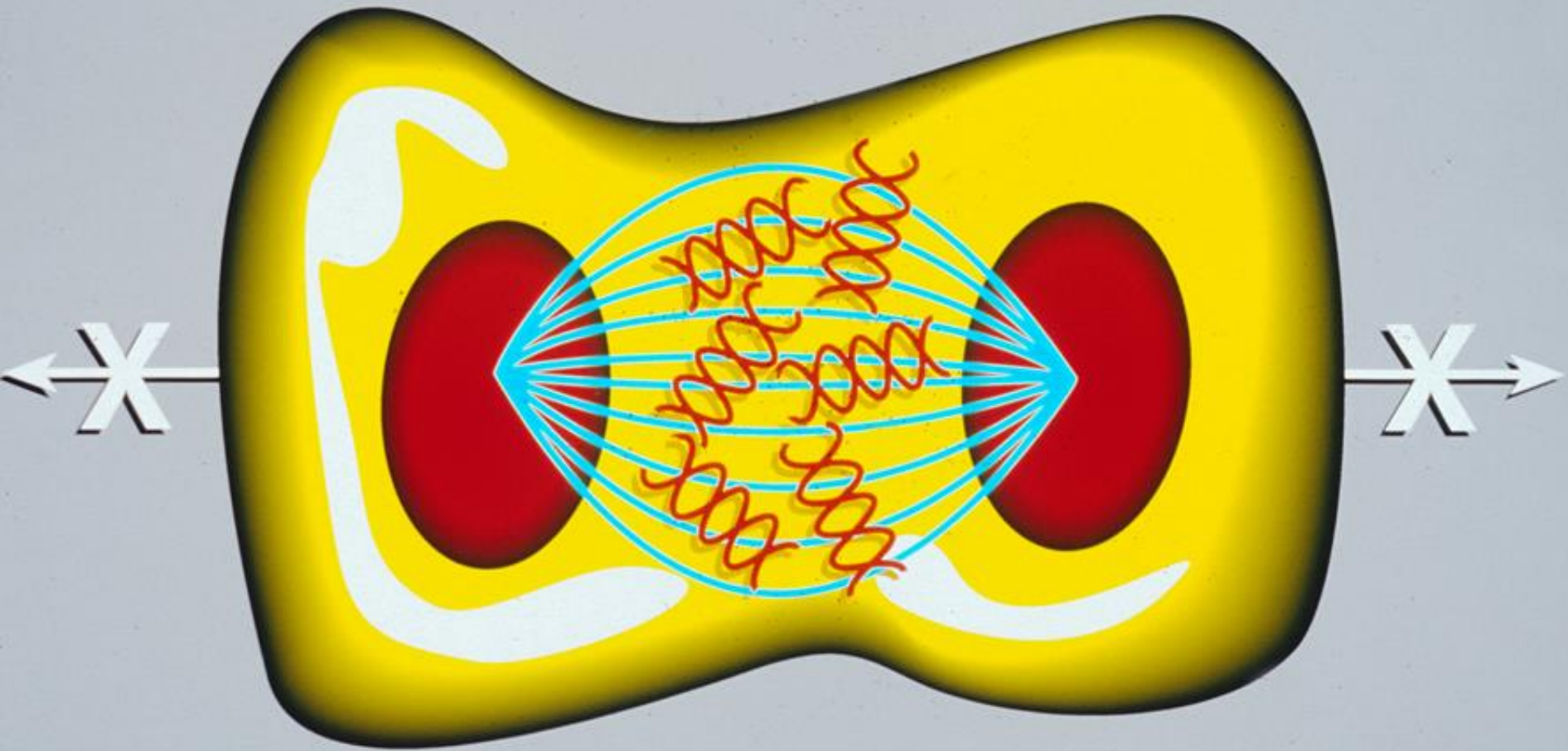
IMMUNOSUPPRESSANTS

CORTICOSTEROIDS

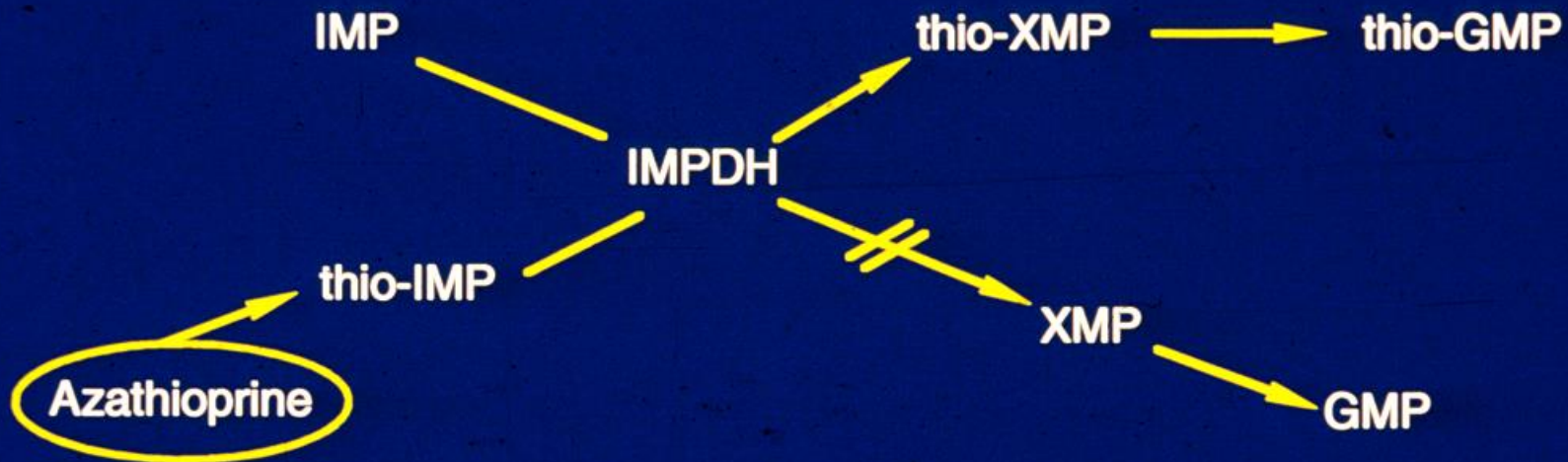




Antimetabolites - Azathioprine, Mycophenolate
Mofetil, Brequinar



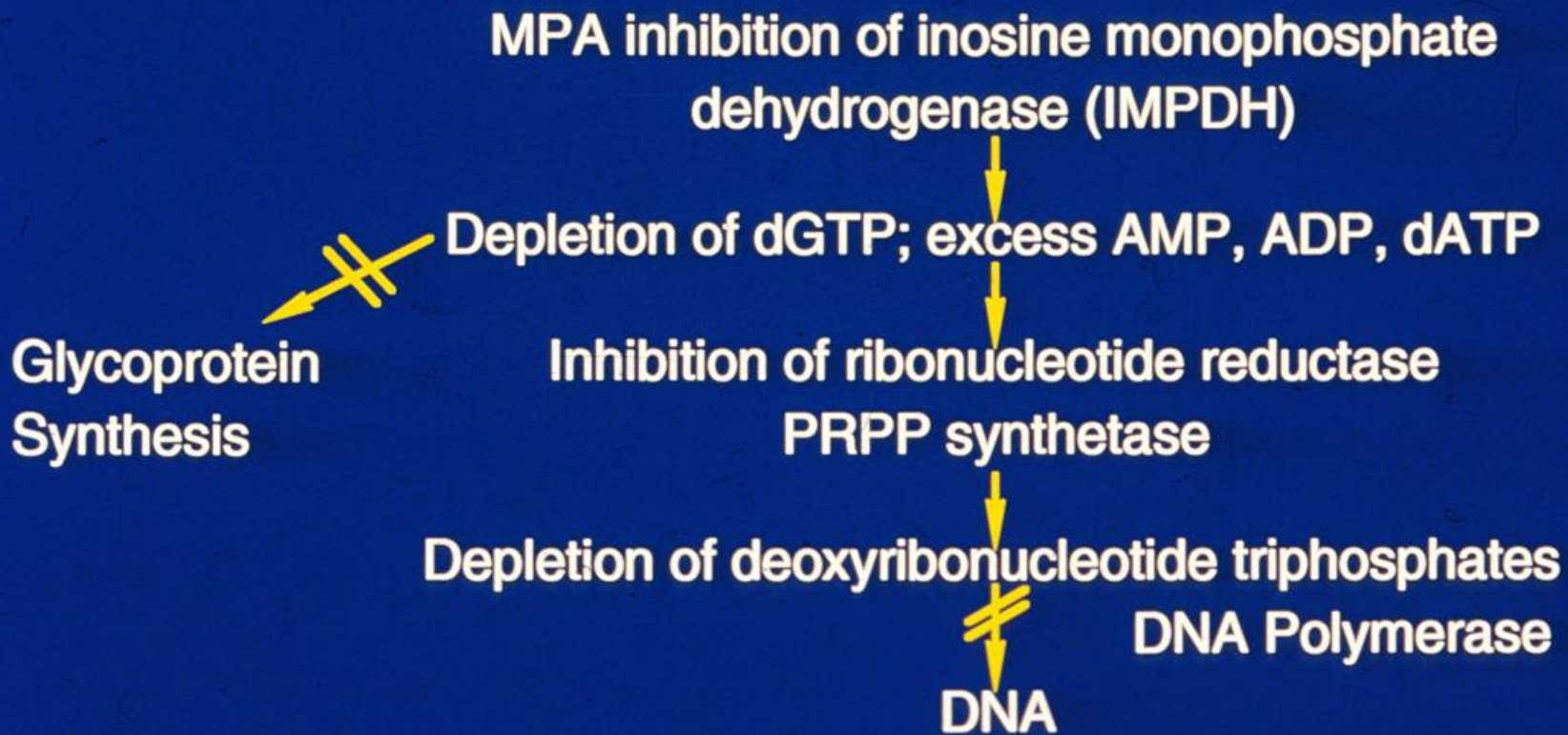
Nonselective Action of Azathioprine



Results:

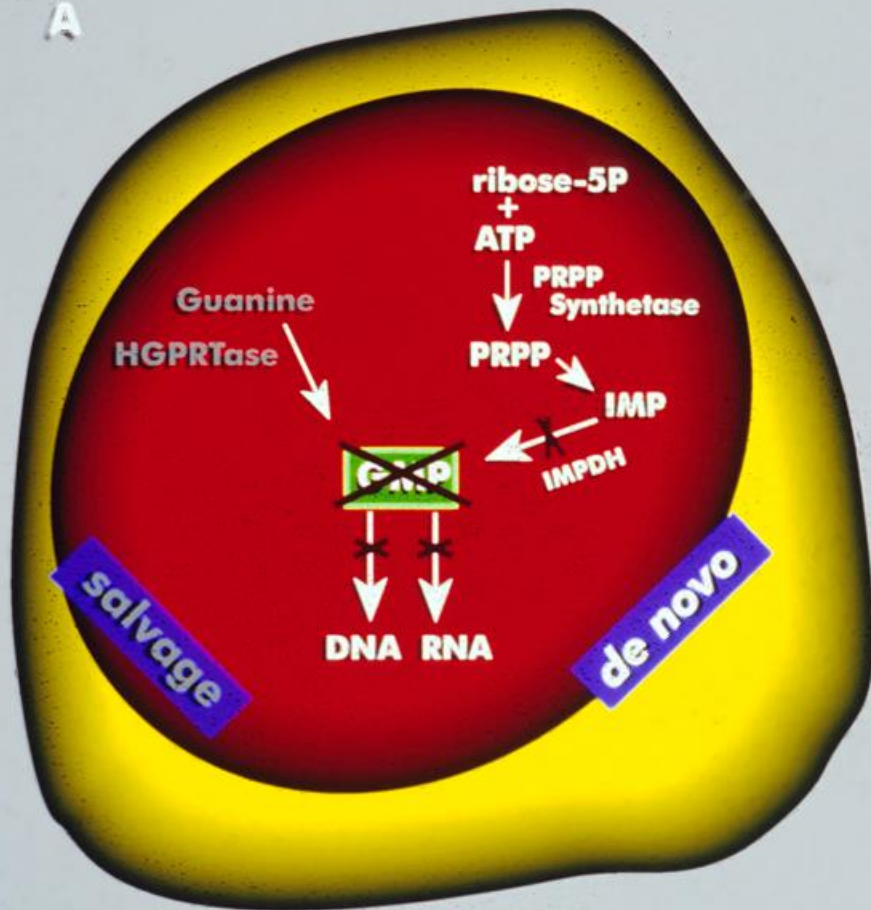
- 5'-phosphoribosylamine ↓
- XMP ↓ PRPP ↑ AMP ↑
- thio-dGTP incorporated into DNA ↑
 - DNA strand breaks
 - delayed cytotoxicity

Selective, Noncompetitive Inhibition of IMPDH by Mycophenolic Acid



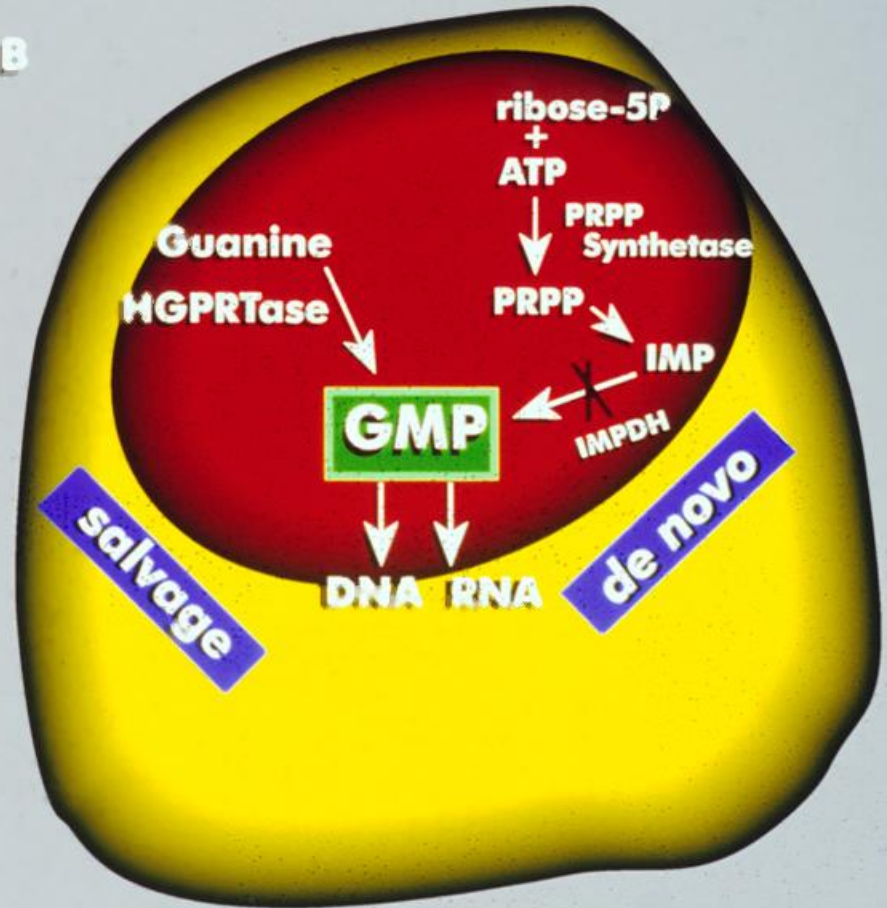
Mycophenolate Mofetil

A



Lymphocyte

B



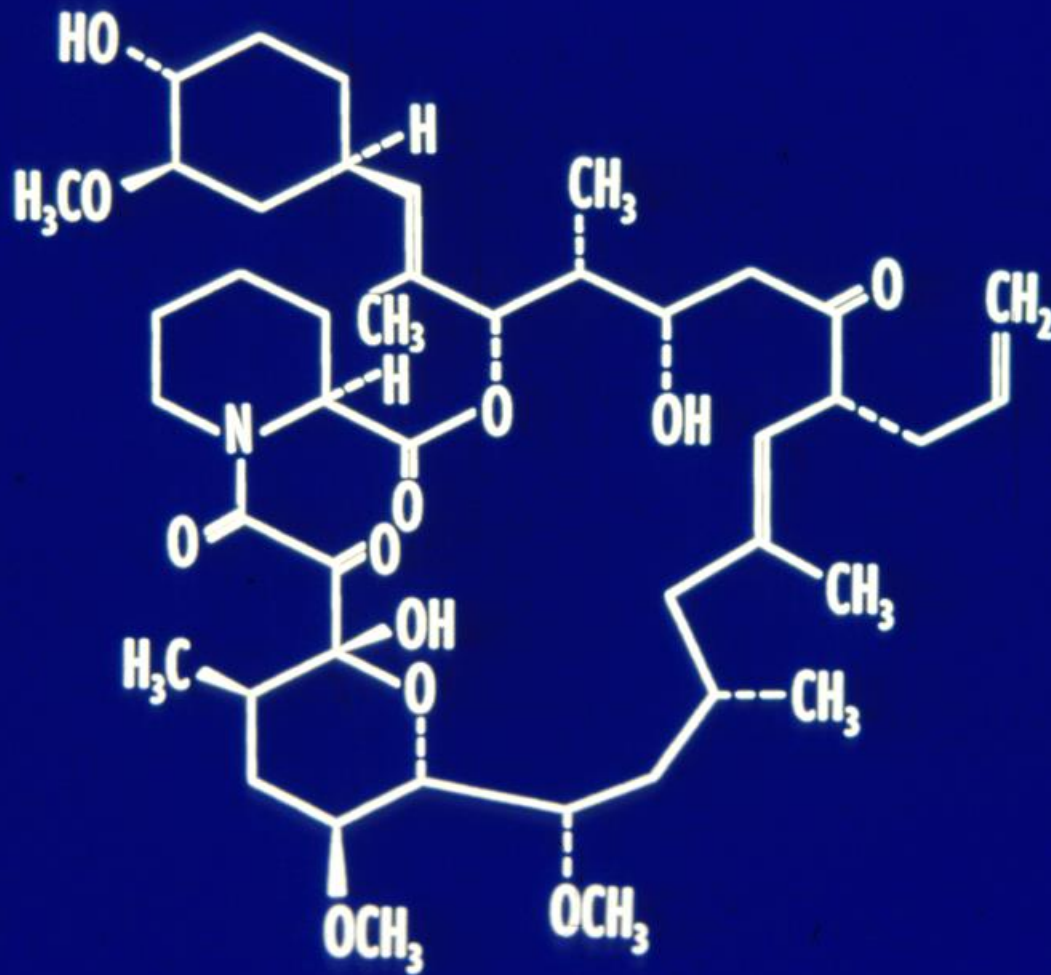
Parenchymal Cell

Immunophyllin Binding Agents

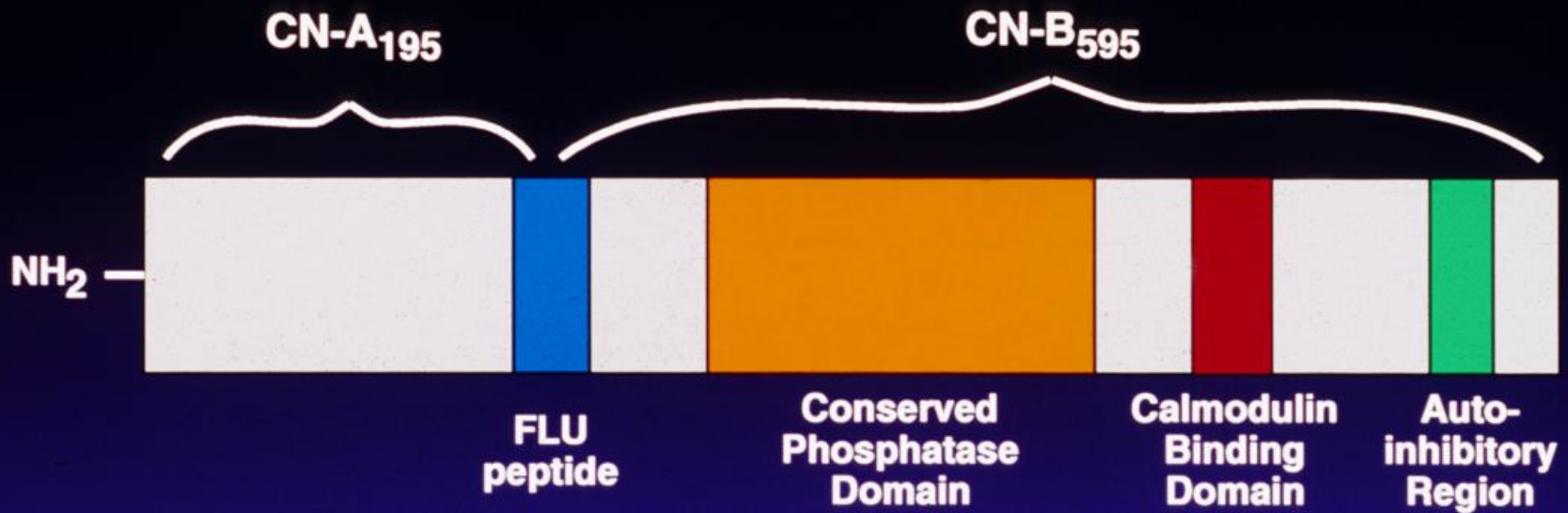
- 1. Cyclosporines (Sandimmune and Neoral)**
- 2. Tacrolimus (FK506, Prograf)**
- 3. Sirolimus (Rapamycin)**

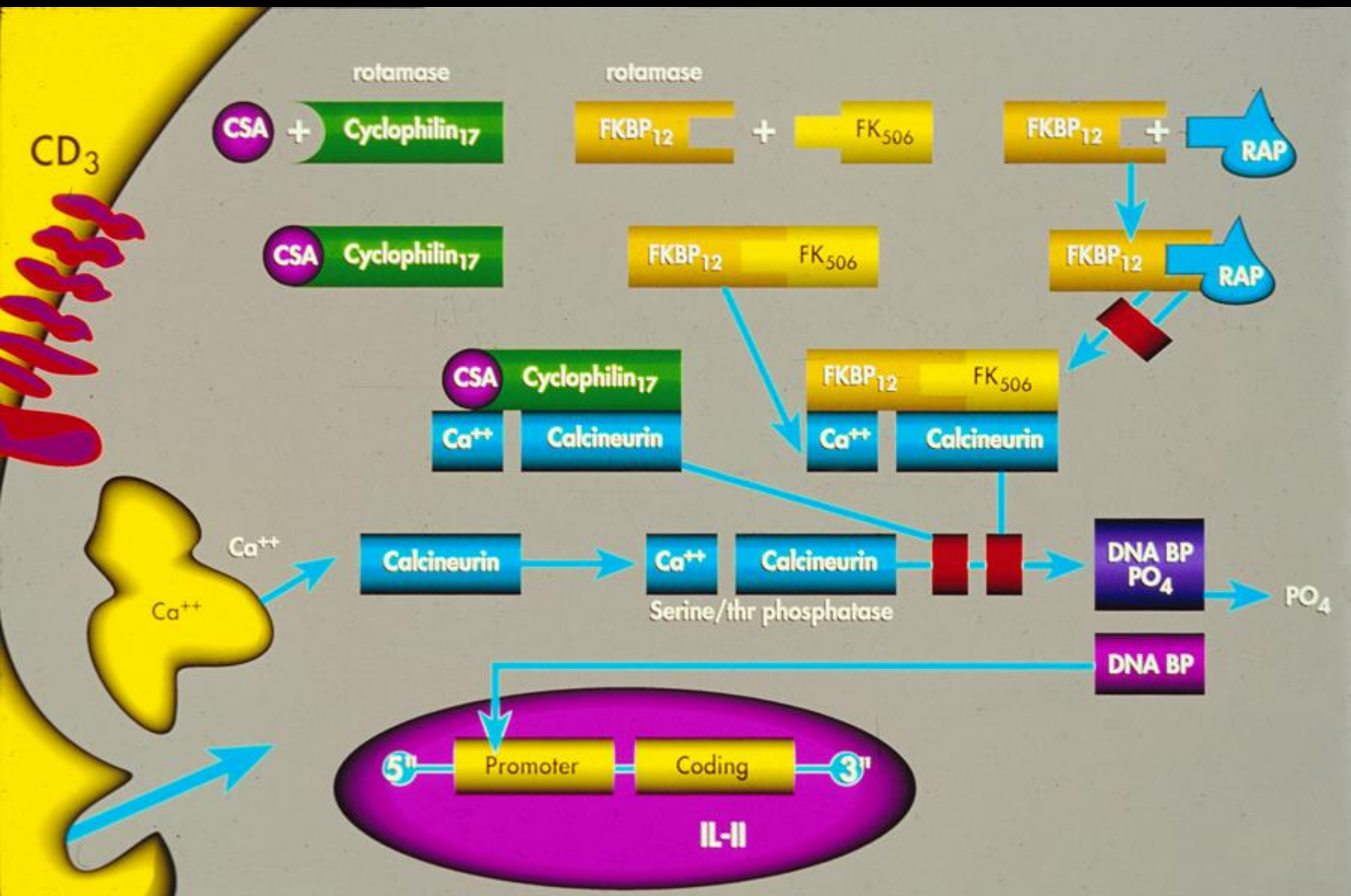


Tacrolimus (FK506)

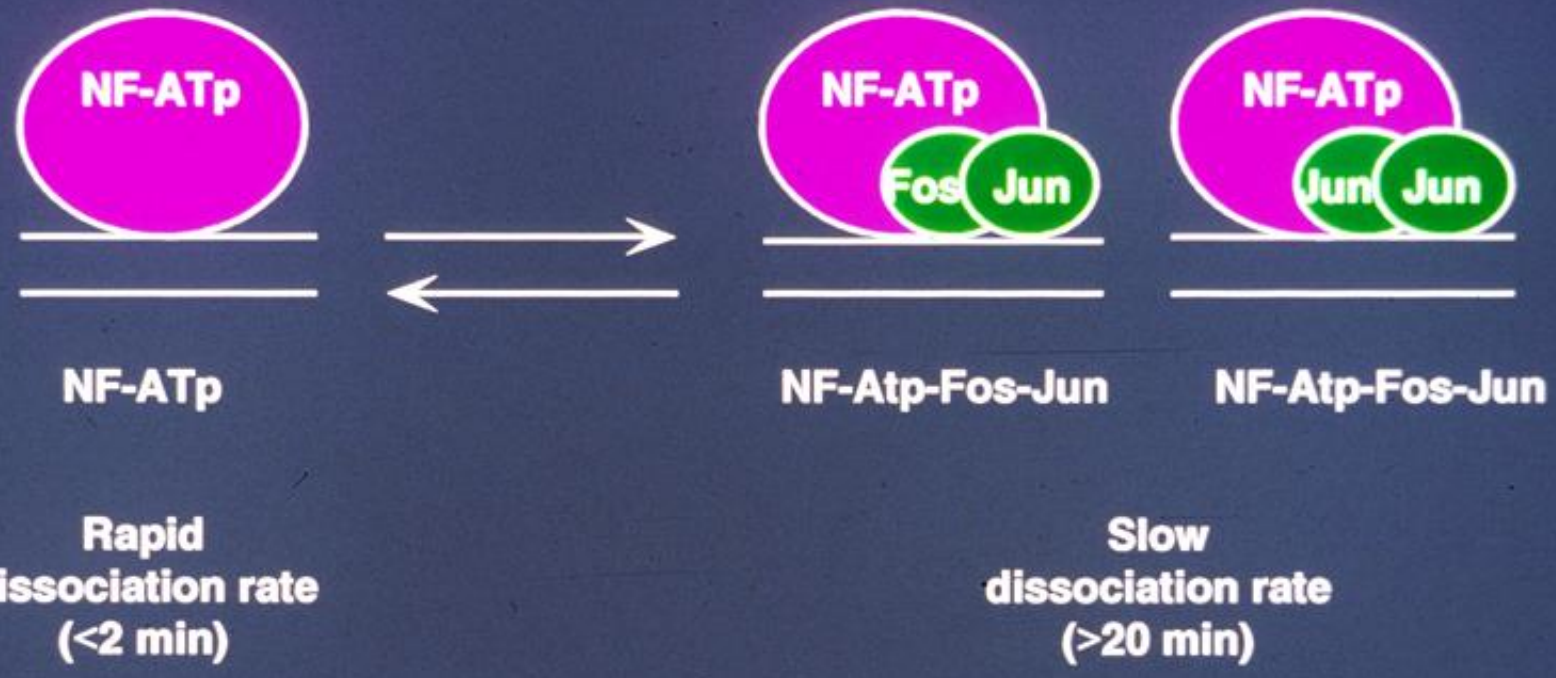


Structure of Calcineurin





(a)



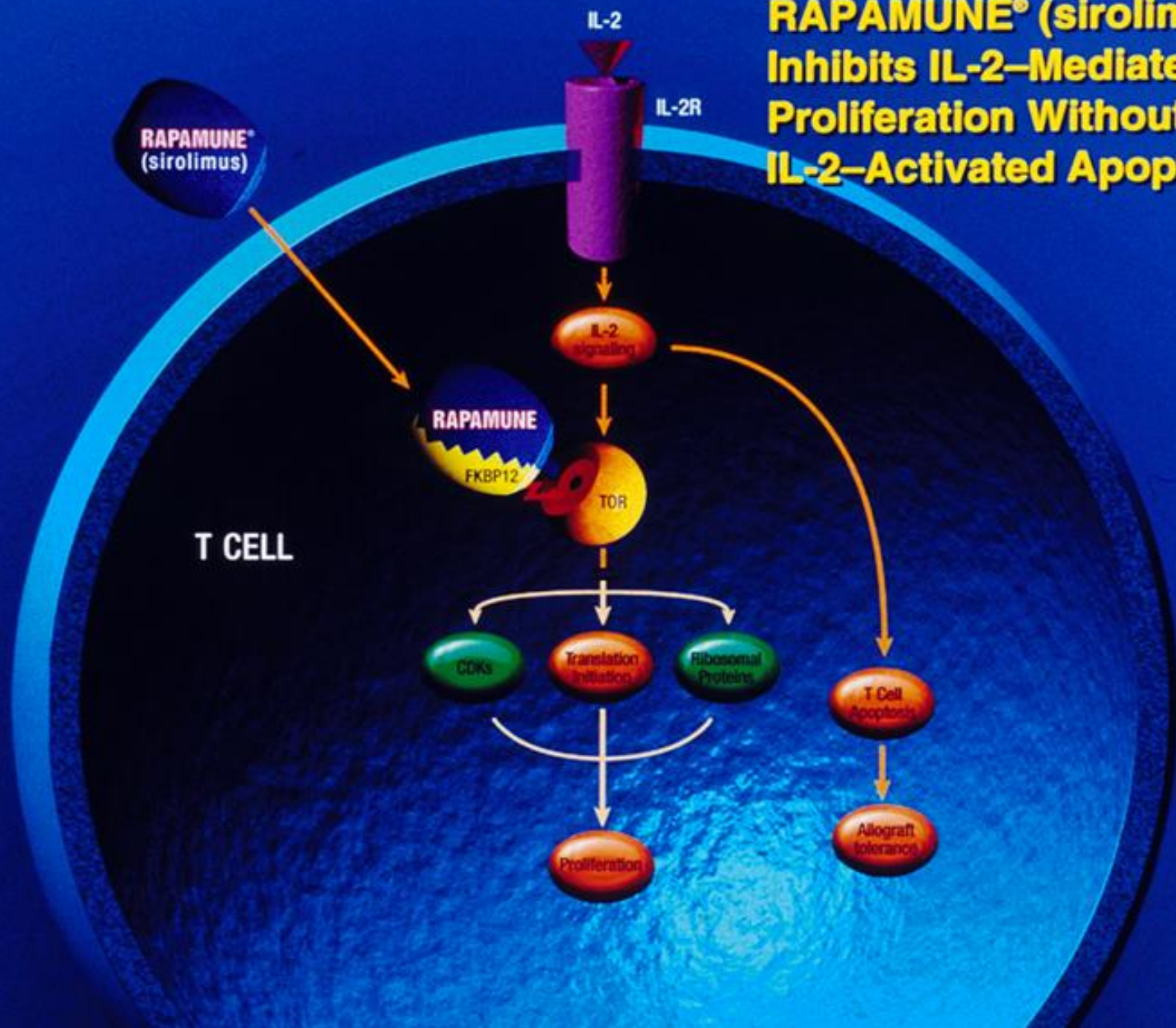
(b)

Distal murine NF-AT site

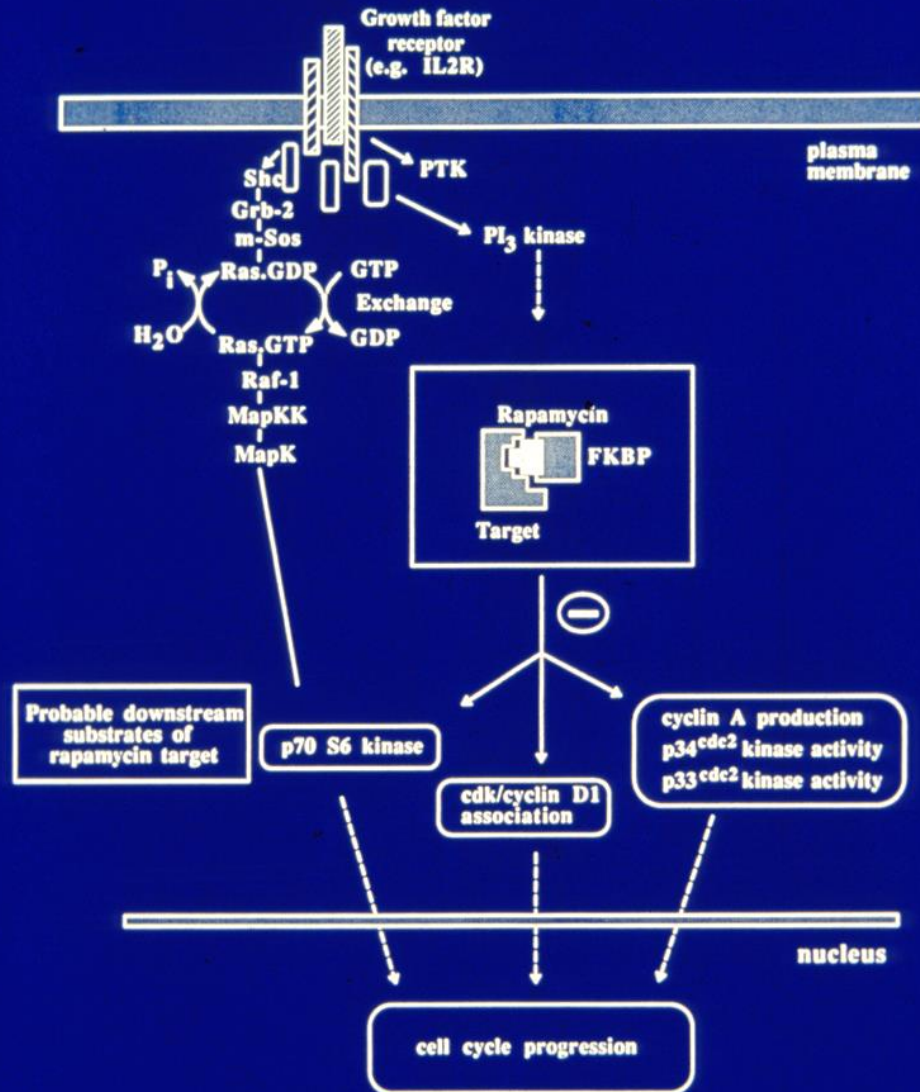
_____ _____
GCCCAAAGAGGAAAATTTGTTTCATACAG
 •• •

Anjana Rao, Immunology Today 1994:15

RAPAMUNE® (sirolimus) Inhibits IL-2-Mediated Cell Proliferation Without Altering IL-2-Activated Apoptosis



Mechanism of Action of Rapamycin

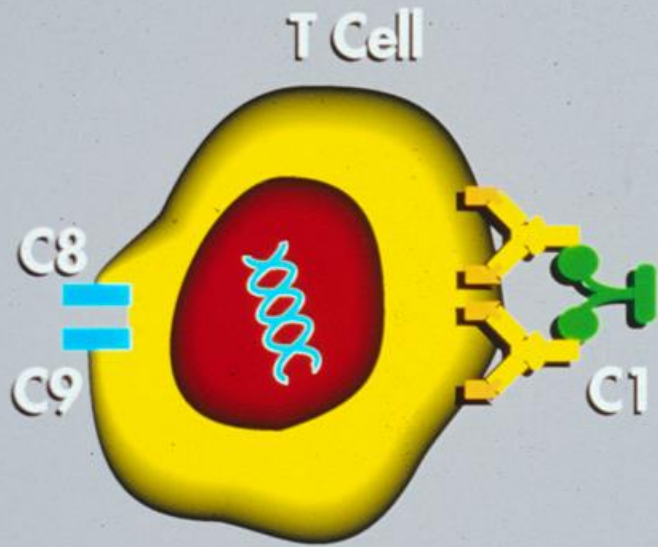


RAPAMUNE® (sirolimus) Has a Distinct Mechanism of Action

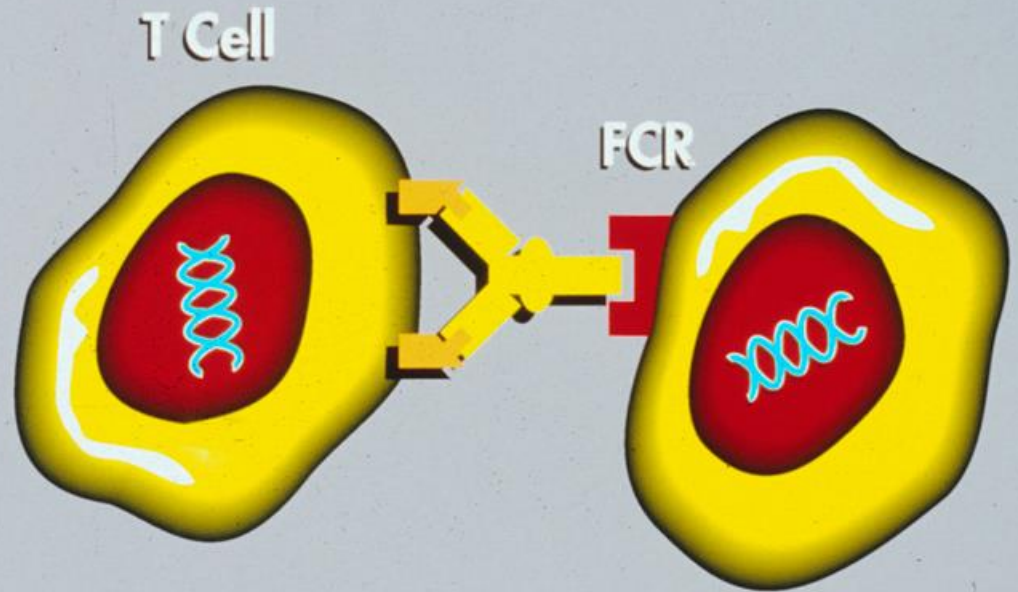
	Cyclosporine	RAPAMUNE
Binding protein	Cyclophilin	FKBP12
Effector protein	Calcineurin	mTOR
IL-2 message	Inhibited	–
IL-2 response	–	Inhibited
Cell-cycle effect	G₀-G₁	G₁-S

Galat A, et al. *Prog Biophys Mol Blo.* 1995;63:67-118. Wiederrecht G, et al. *Prog Cell Cycle Res.* 1995;1:53-71.
 Liu J, et al. *Cell.* 1991;66:807-815. Flanagan WM, et al. *Nature.* 1991;352:803-807.
 McCaffrey PG, et al. *J Biol Chem.* 1993;268:3747-3752.

Polyclonal Anti-T-Cell Antibodies

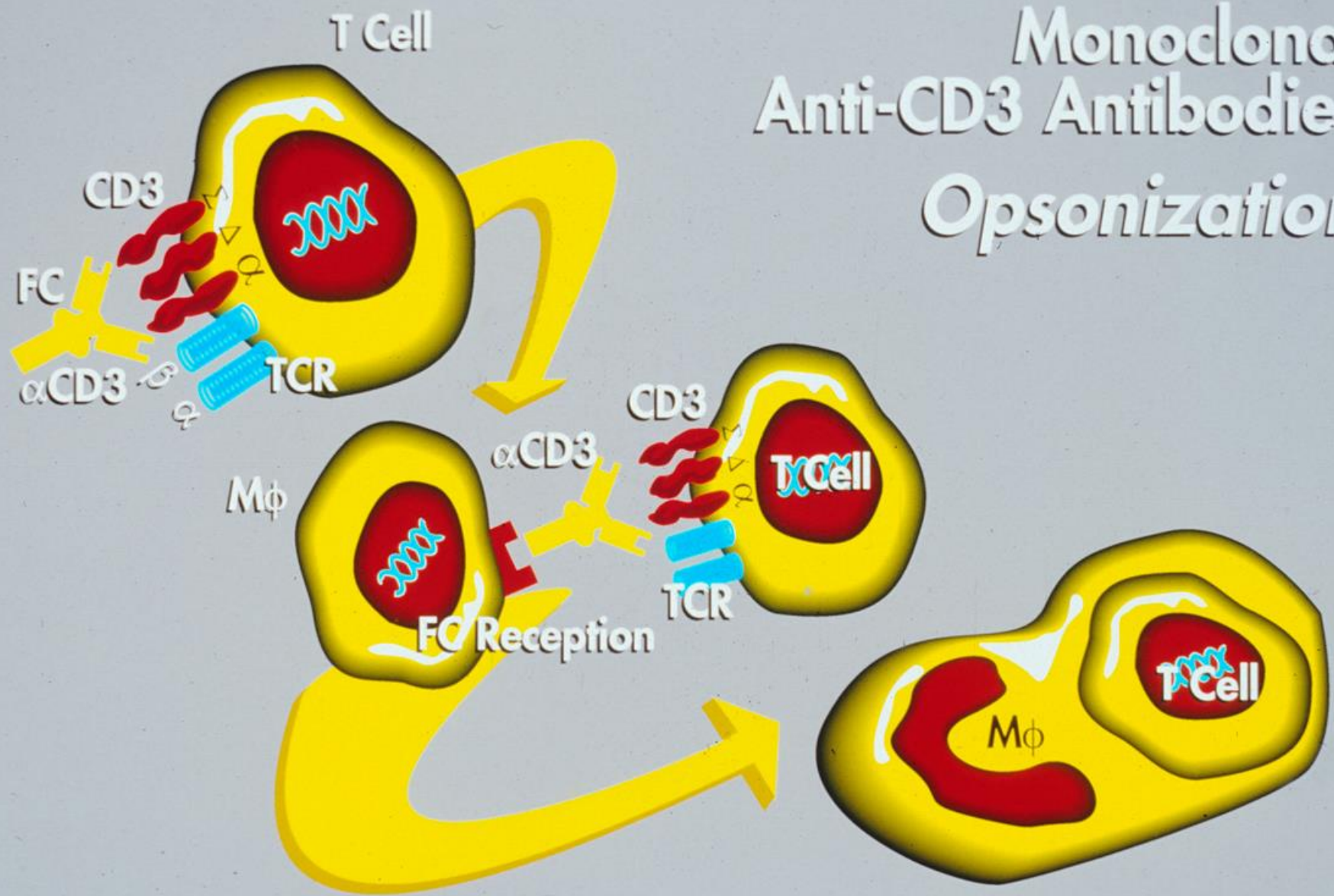


Complement-
Dependent Lysis



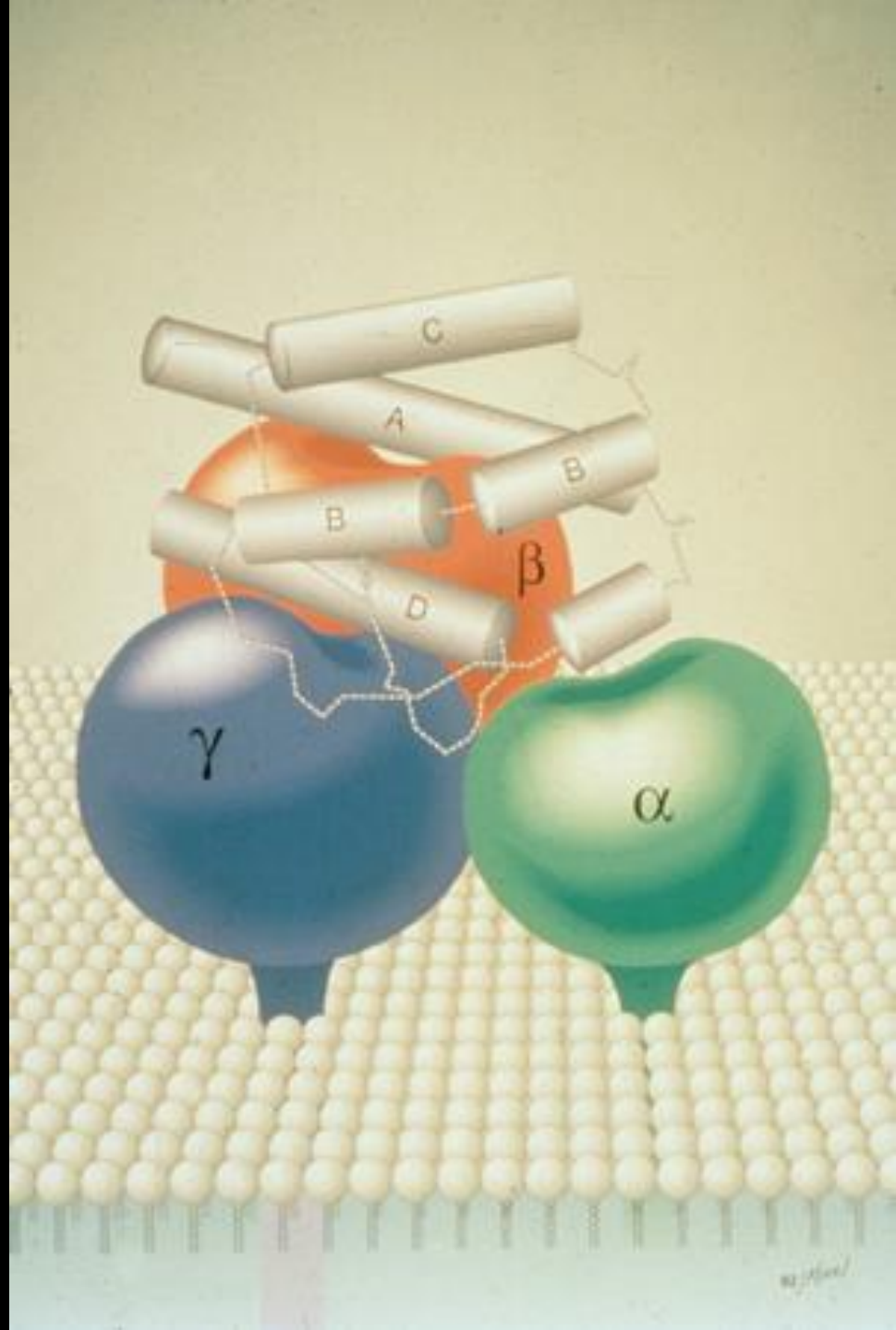
FC-Receptor-
Mediated Cell Lysis

Monoclonal Anti-CD3 Antibodies *Opsonization*

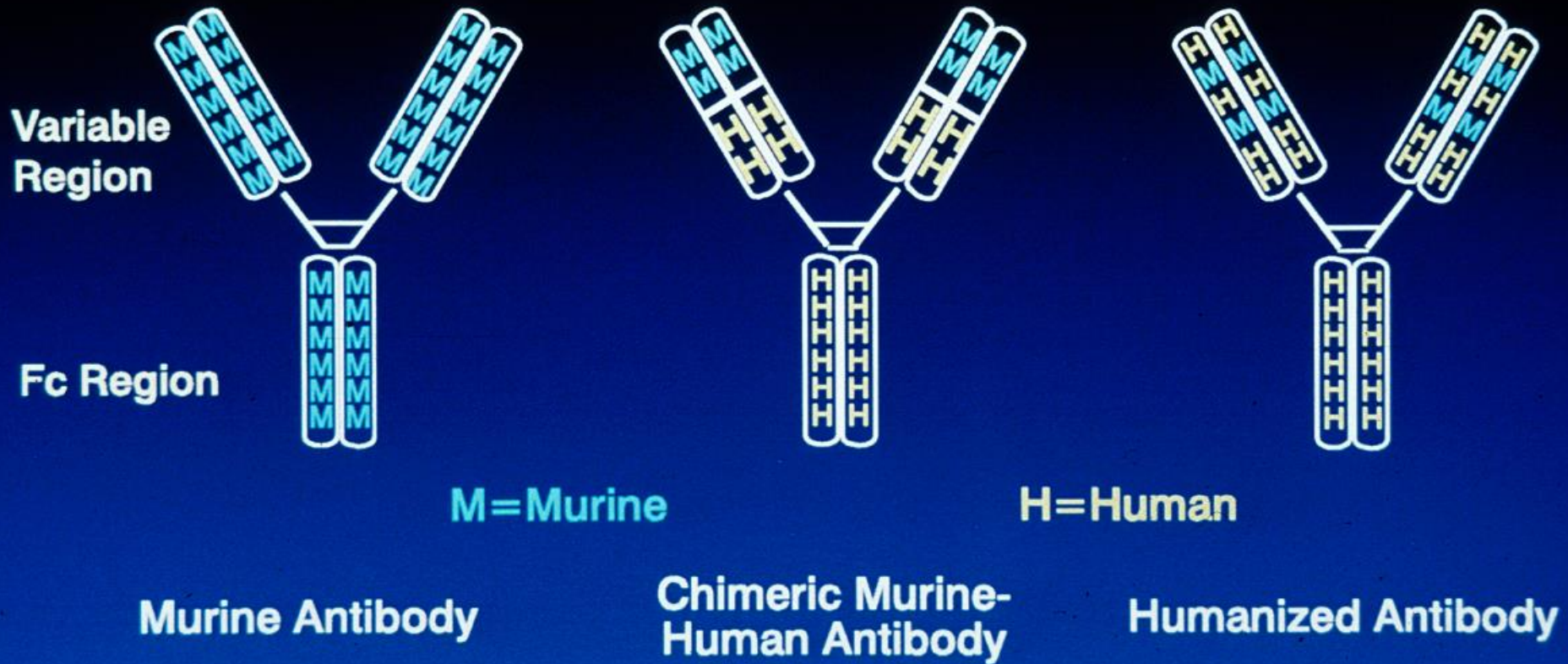


IL-2 RECEPTOR ANTIBODIES

- 1. TARGET: NONCONSTITUTIVE IL-2R,
MOSTLY β CHAIN**
- 2. IN ANIMALS HIGHLY CYTOTOXIC
AND PROLONGS GRAFTS**
- 3. IN MAN MODULATES RECEPTOR**
- 4. FRENCH STUDY: AS INDUCTION AGENT**
 - a. FEWER SIDE EFFECTS THAN P ON T CELL AB**
 - b. GRAFT SURVIVAL THE SAME**
 - c. TREND FOR MORE REJECTIONS**



Murine and Humanized Monoclonal Antibodies



CD 28 – CD 80/86 Pathway

- 1st studied reagent CTLA4Ig
 - fusion protein
 - extra cellular domain of CTLA4
 - Fc portion of human Ig
- Excellent pre clinical results but less spectacular non-human primate data

Sayegh and Turkha NEJM 338:1998

CD28 – CD80/86

- LEA 29Y (Belatacept)
 - Leucine 104 → Glutamate
 - Alanine 29 → Tyrosine
- 2nd generation CTLA4Ig
- Substitutions increase theoretic efficacy
 - 2 fold ↑ binding to CD 80
 - 4 fold ↑ binding to CD 86
 - 10 fold ↑ T cell function inhibition

FTY 720

Potential Advantages

- **Unique Action – Alteration of Lymphocyte Traffic**
- **Synergy With Calcineurin Inhibitors and Sirolimus Permitting Dose Reductions**
- **Side Effects Are Not Additive to Other I.S. Drugs**
- **Once Daily Dosing**
- **Minimal Drug-Drug Interactions**
- **Low Intra-subject Pharmacologic Variability**

FTY 720

- ❶ **Immunosuppressive *In Vitro***
- ❷ **Depletes T and B cells from peripheral blood**
- ❸ **Increases Lymphocyte homing to mesenteric nodes and Peyer's patches**

POSSIBLE SITES OF ACTION IN T CELLS OF NEW XENOBIOTIC IMMUNOSUPPRESSANTS

