Immunobiology of Immunosuppressant Agents (2011)

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GEORGE D. SNELL 1903

P. A. GORER 1907 - 1961


SIR PETER MEDAWAR 1915

Photo by Rico 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.

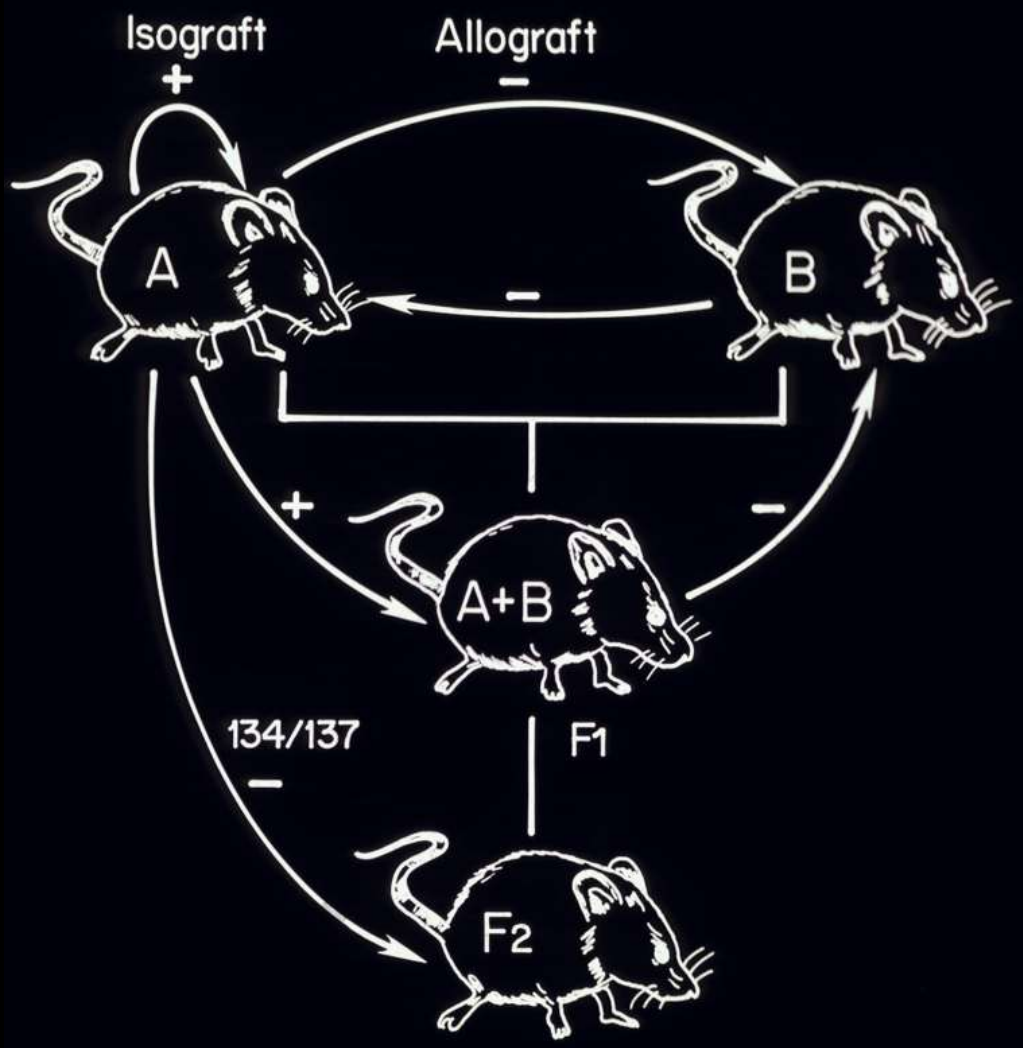
RENAL TRANSPLANT IN THE 20TH CENTURY

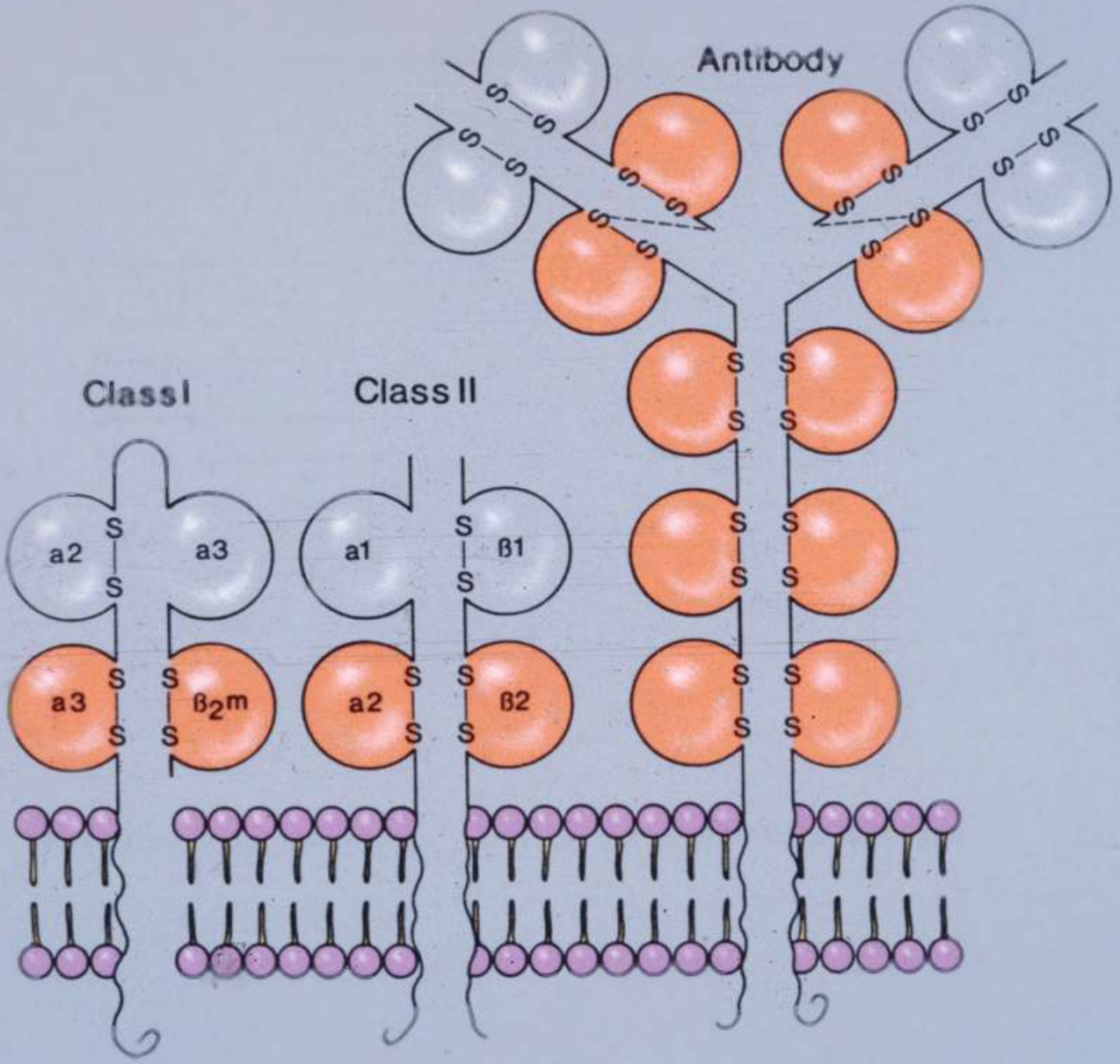
A HISTORY OF IMMUNOSUPPRESSIVE DRUGS

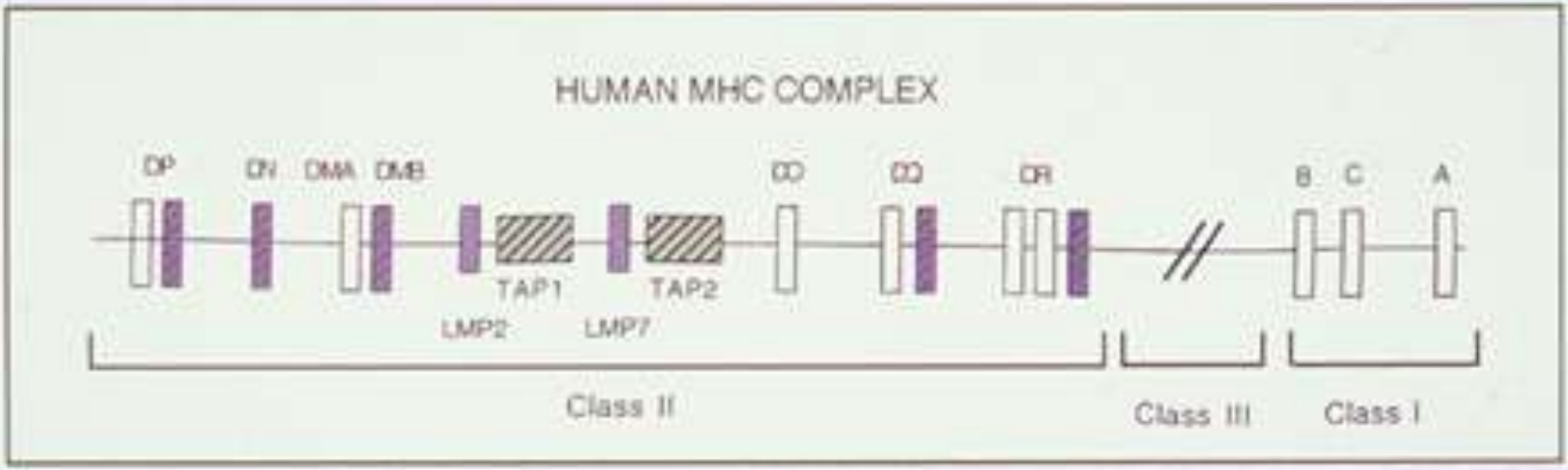
ERA 1	1953-63	THE EXPERIMENTAL PERIOD
ERA 2	1963-83	THE AZATHIOPRINE ERA-INCREASING PATIENT POPULATION FOR TRANSPLANT, WITH INCREASING PT SURVIVAL AT EXPENSE OF GRAFT SURVIVAL
ERA 3	1983-93	THE CYCLOSPORINE A ERA-MARKED IMPROVEMENT IN EARLY GRAFT SURVIVAL, ALL ORGANS ARE NOT CLINICALLY TRANSPLANTABLE,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

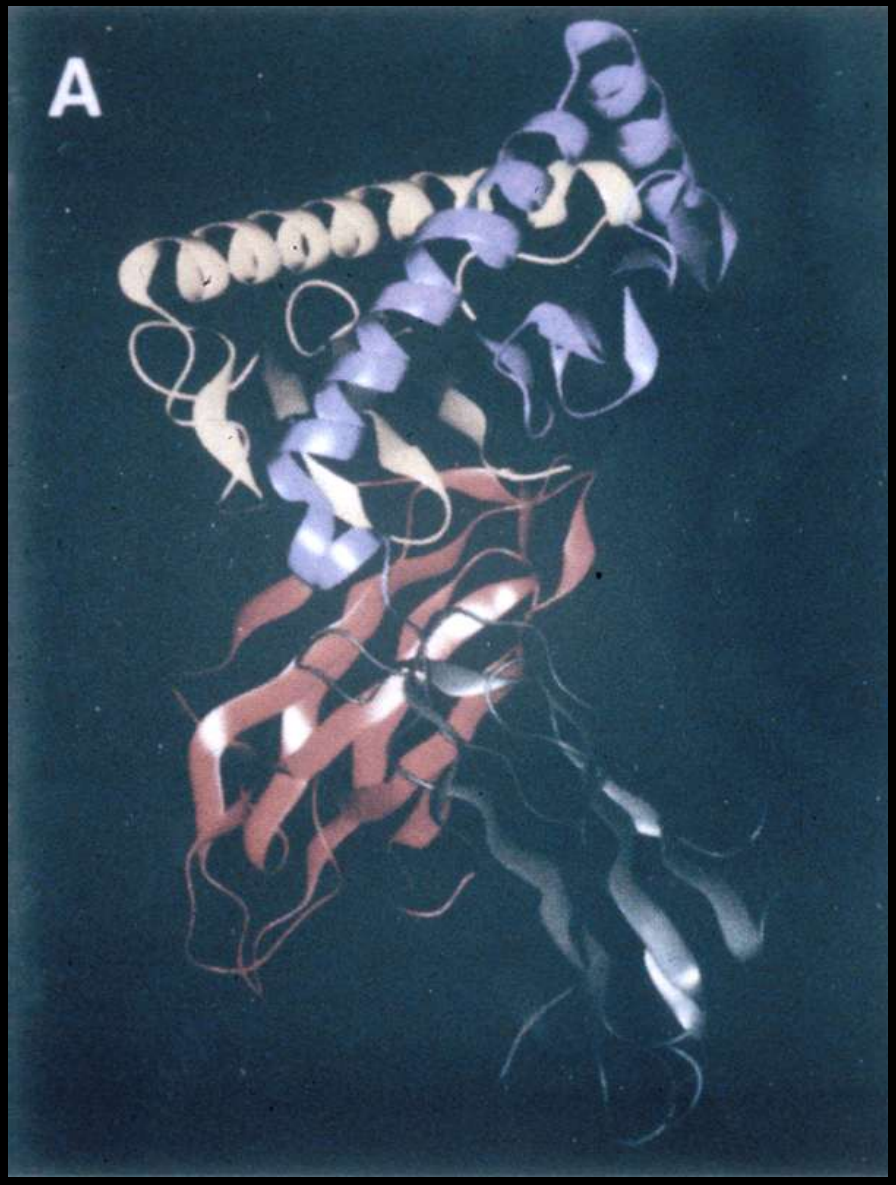
LAWS OF TRANSPLANTATION

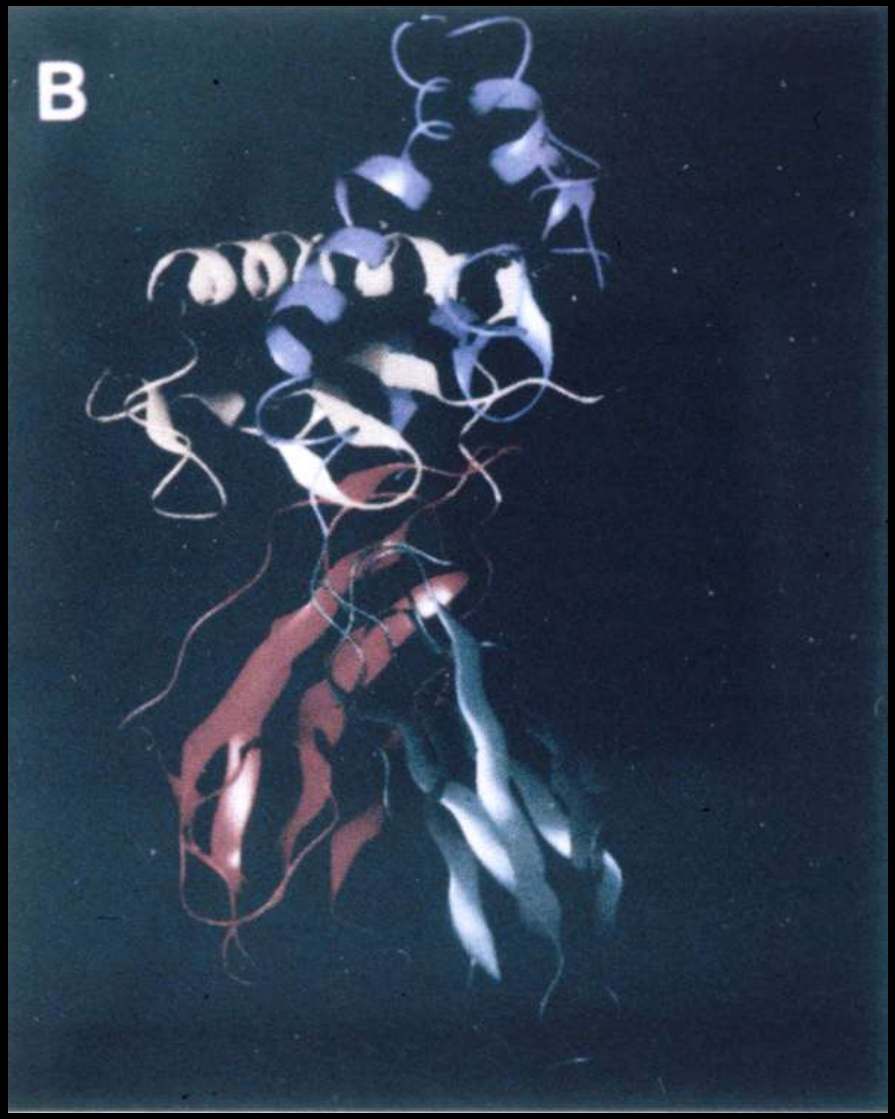
Prehn & Main, 1958

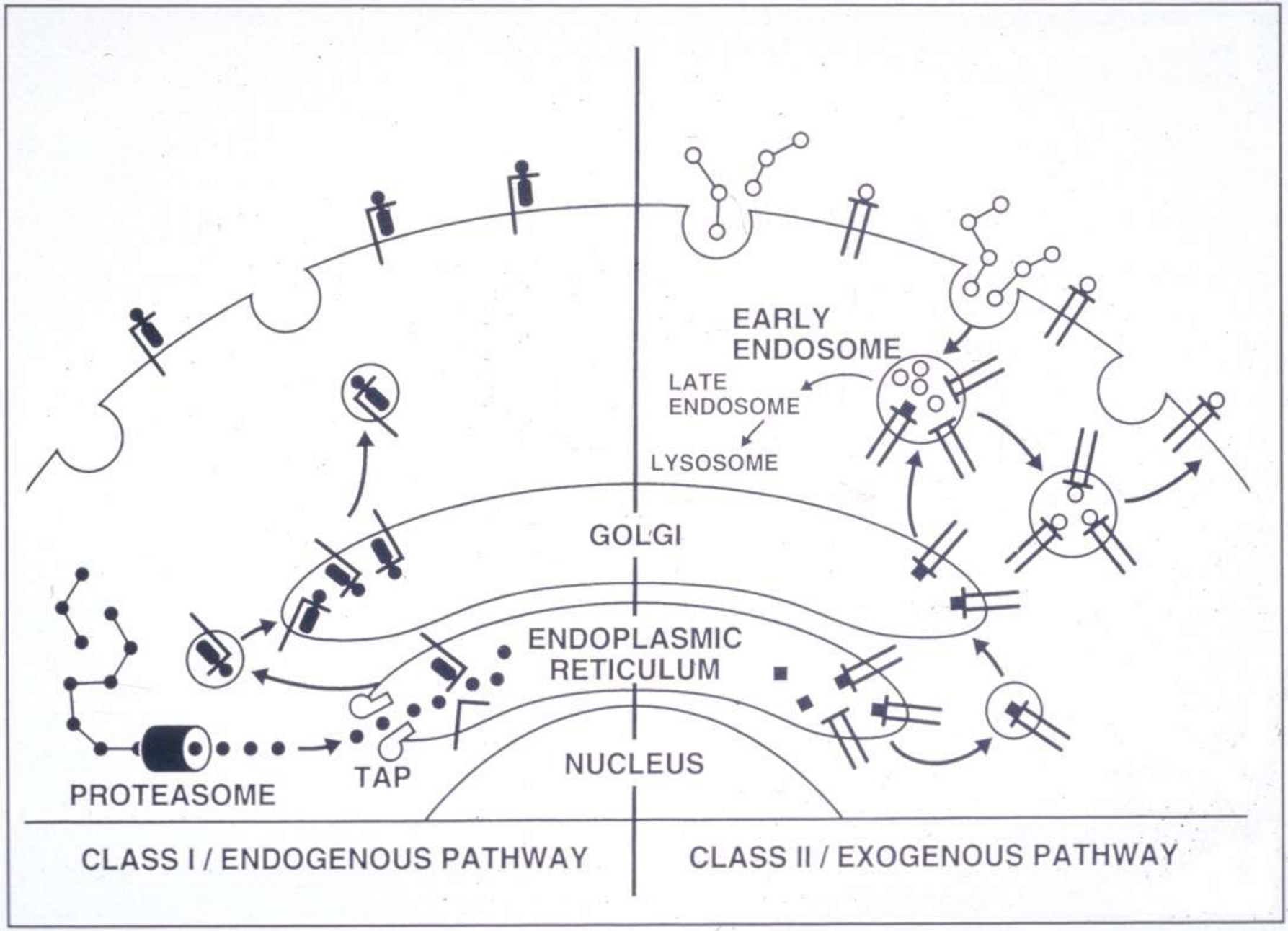


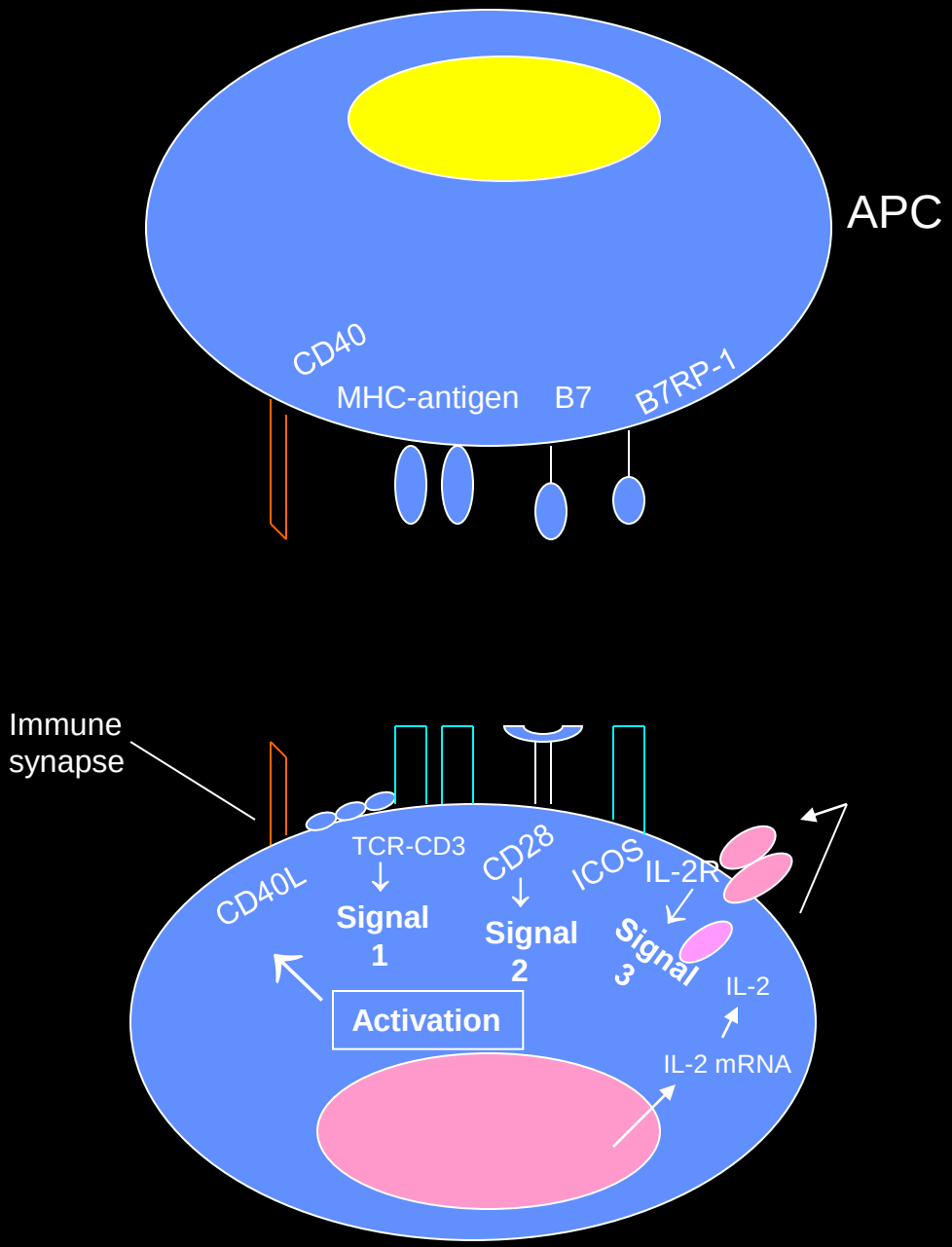

Antibody
Class I
Class II
a2
a3
a3
β_2m
a1
β1
a2
β2

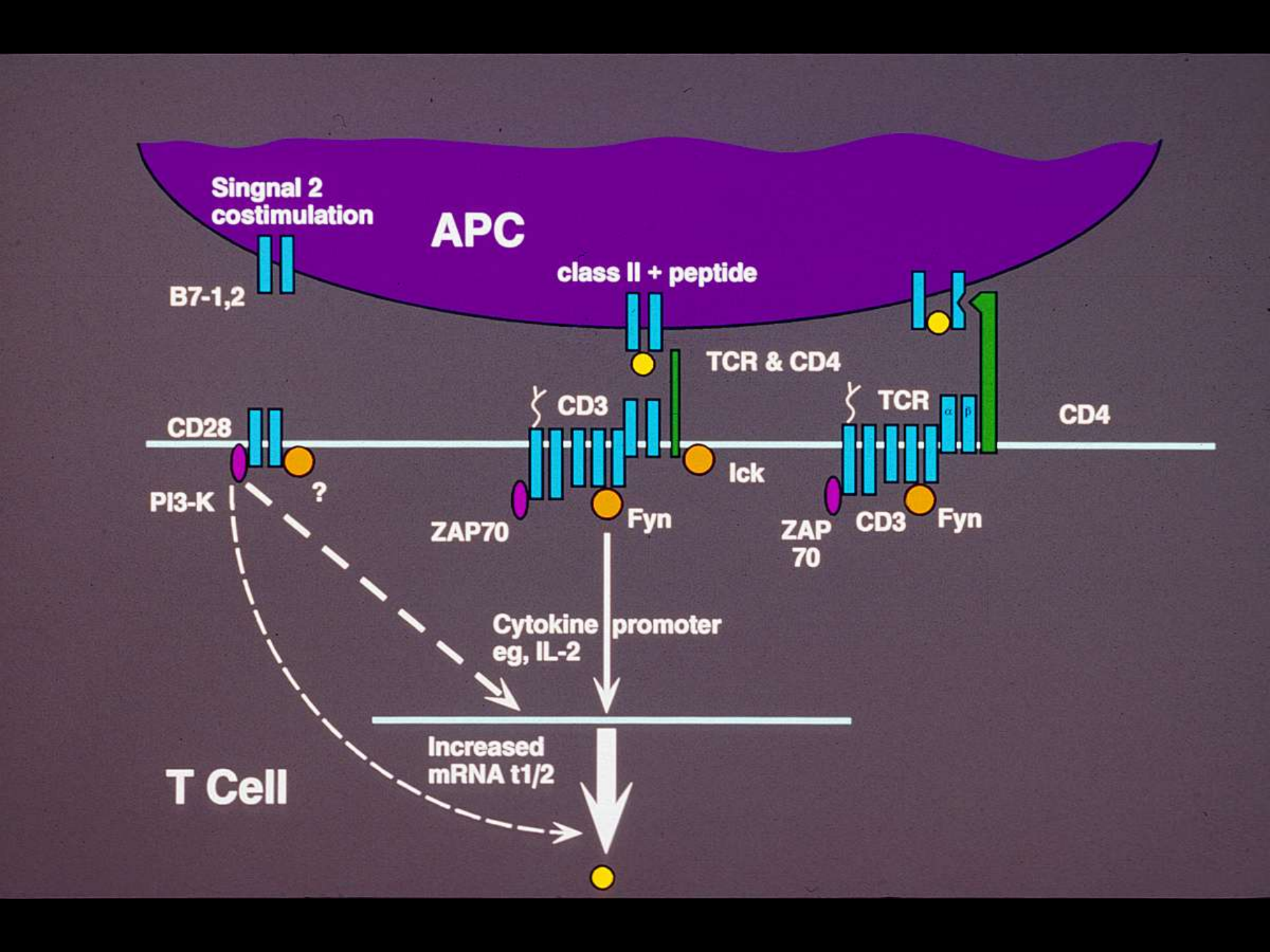

HUMAN MHC COMPLEX
DP
DN
DMA
DMB
TAP1
TAP2
LMP2
LMP7
DO
DQ
DR
B
C
A
Class II
Class III
Class I

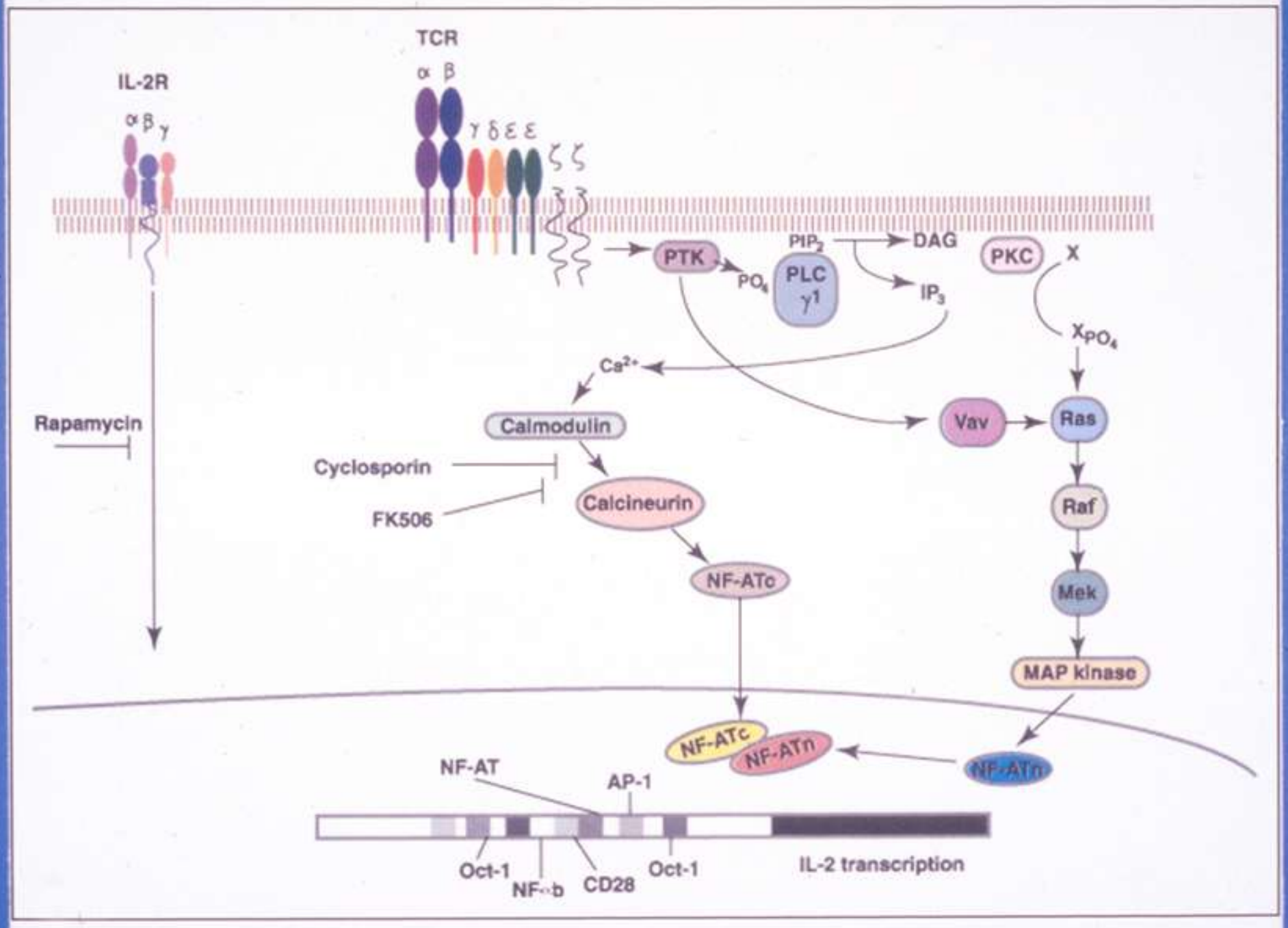

A

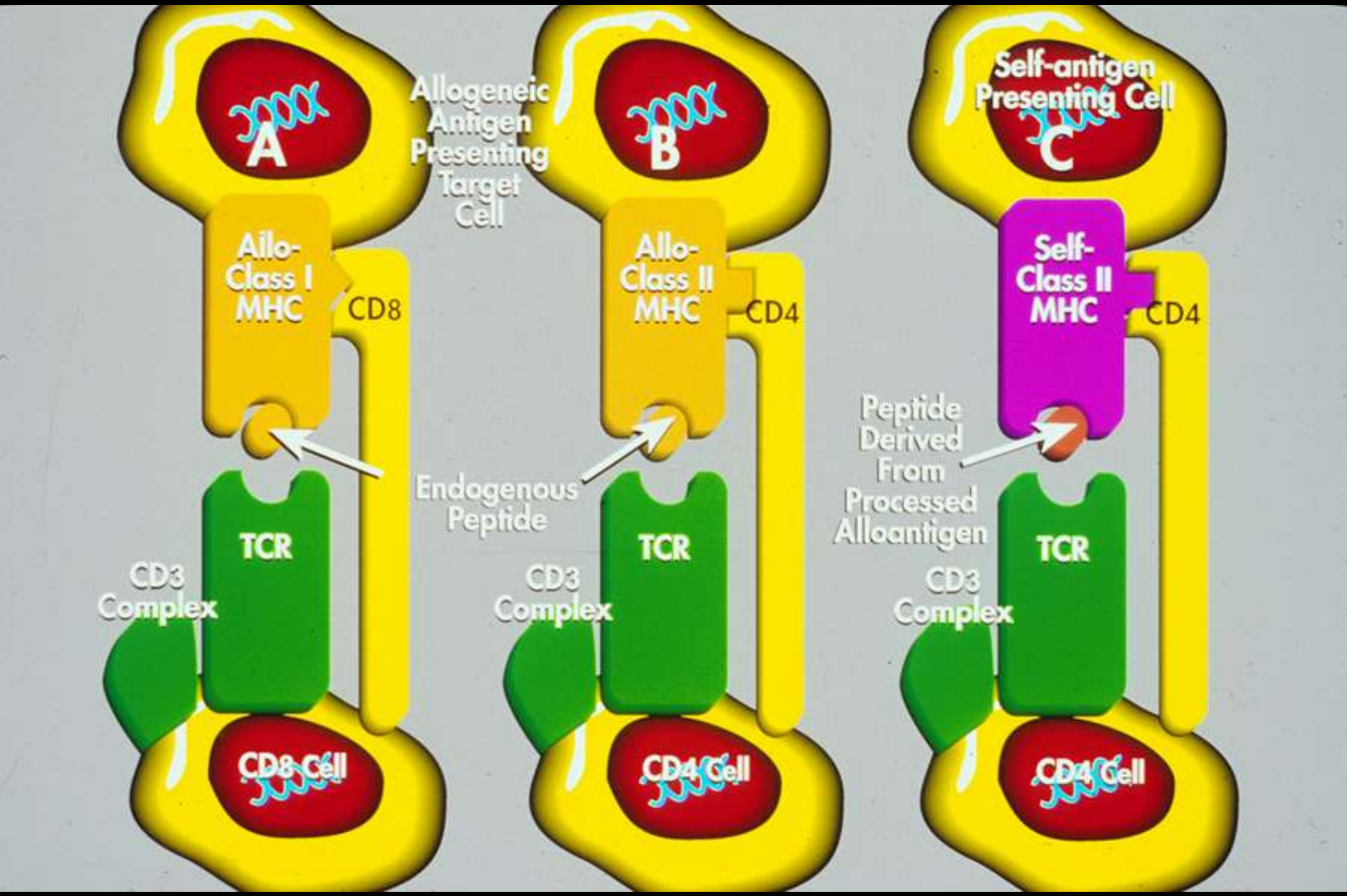

B


EARLY
ENDOSOME
LATE
ENDOSOME
LYSOSOME
GOLGI
ENDOPLASMIC
RETICULUM
NUCLEUS
TAP
PROTEASOME
CLASS I / ENDOGENOUS PATHWAY
CLASS II / EXOGENOUS PATHWAY

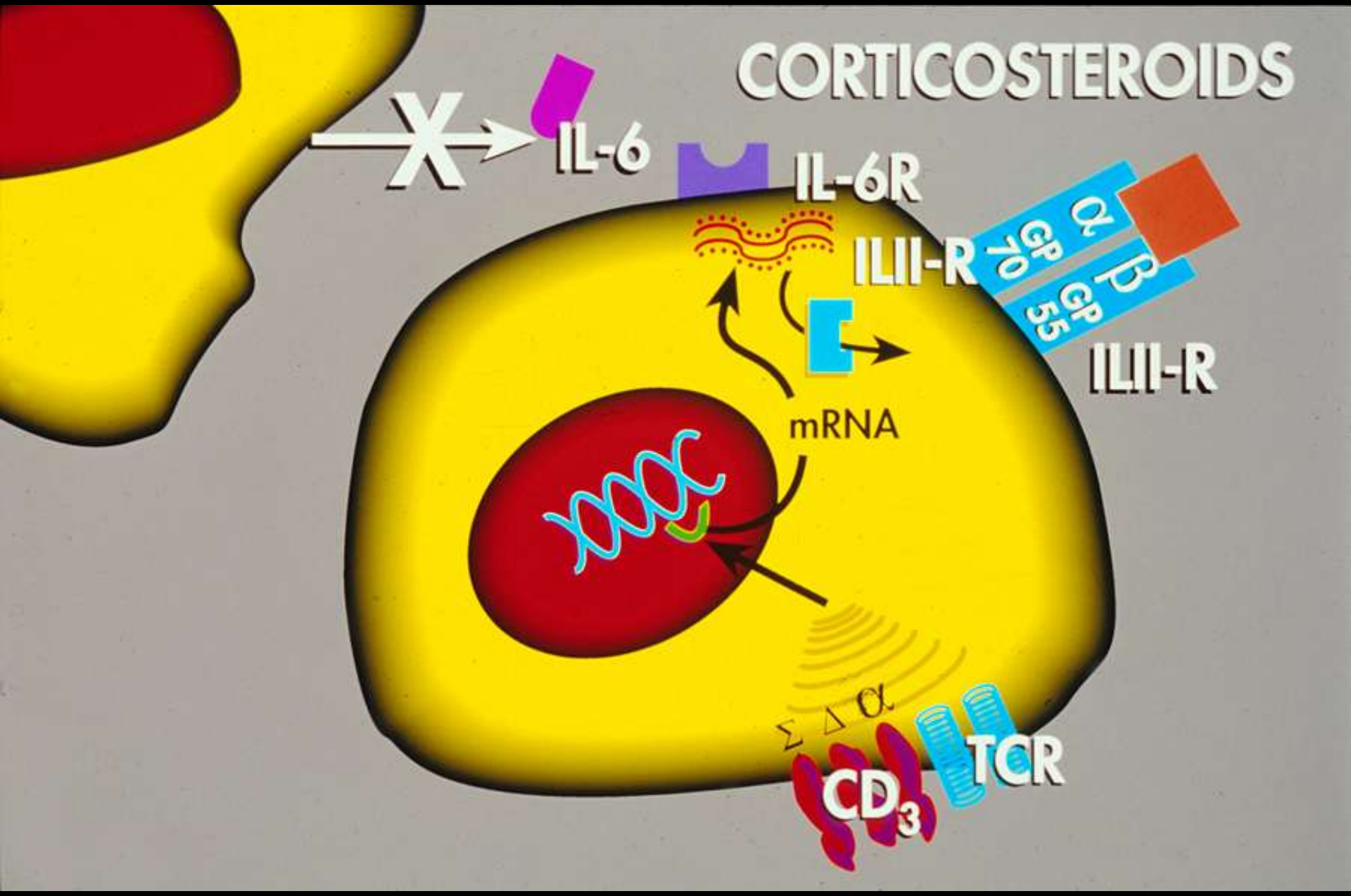

APC
CD40
MHC-antigen
B7
B7RP-1
Immune
synapse
CD40L
TCR-CD3
Signal
1
CD28
Signal
2
ICOS
IL-2R
Signal
3
Activation
IL-2
IL-2 mRNA
Naïve T cell

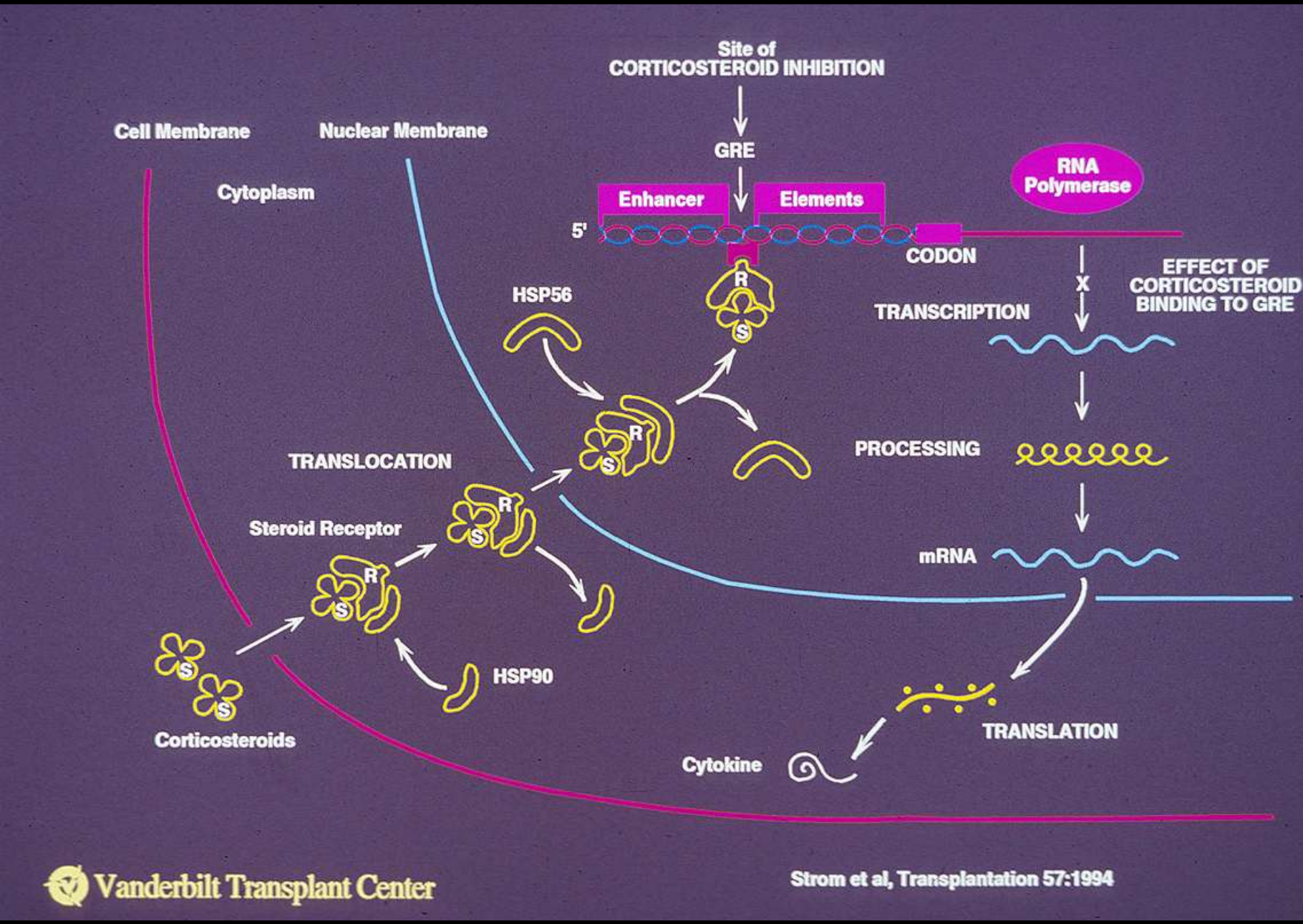

Singnal 2
costimulation
APC
B7-1,2
class II + peptide
TCR & CD4
CD3
TCR
CD4
CD28
Ick
PI3-K
?
ZAP70
Fyn
ZAP
70
CD3
Fyn
Cytokine promoter
eg, IL-2
Increased
mRNA t1/2
T Cell


TCR
α β
IL-2R
α β γ
γ δ ε ε
ζ ζ
PTK
PO4
PIP2
PLC γ1
DAG
IP3
PKC
X
XPO4
Ca2+
Rapamycin
Calmodulin
Vav
Ras
Cyclosporin
FK506
Calcineurin
Raf
NF-ATc
Mek
MAP kinase
NF-ATc
NF-ATn
NF-ATn
NF-AT
AP-1
Oct-1
NF-κb
CD28
Oct-1
IL-2 transcription


A
Allogeneic
Antigen
Presenting
Target
Cell
B
Self-antigen
Presenting Cell
C
Allo-
Class I
MHC
CD8
Allo-
Class II
MHC
CD4
Self-
Class II
MHC
CD4
Peptide
Derived
From
Processed
Alloantigen
Endogenous
Peptide
TCR
CD3
Complex
TCR
CD3
Complex
TCR
CD3
Complex
CD8 Cell
CD4 Cell
CD4 Cell

IMMUNOSUPPRESSANTS


CORTICOSTEROIDS
IL-6
IL-6R
ILII-R
α GP 70
β GP 55
ILII-R
mRNA
Σ Δ α
CD3
TCR



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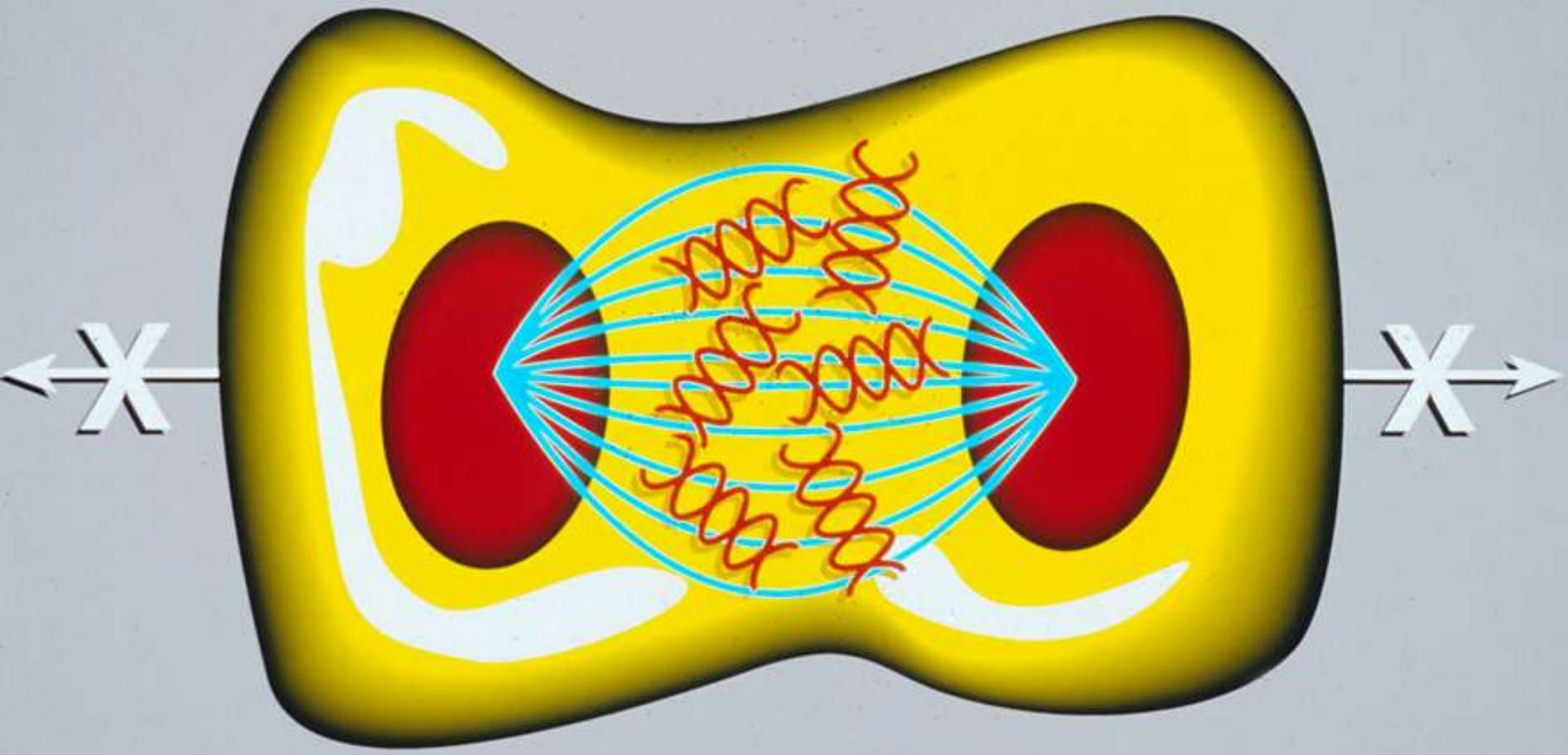
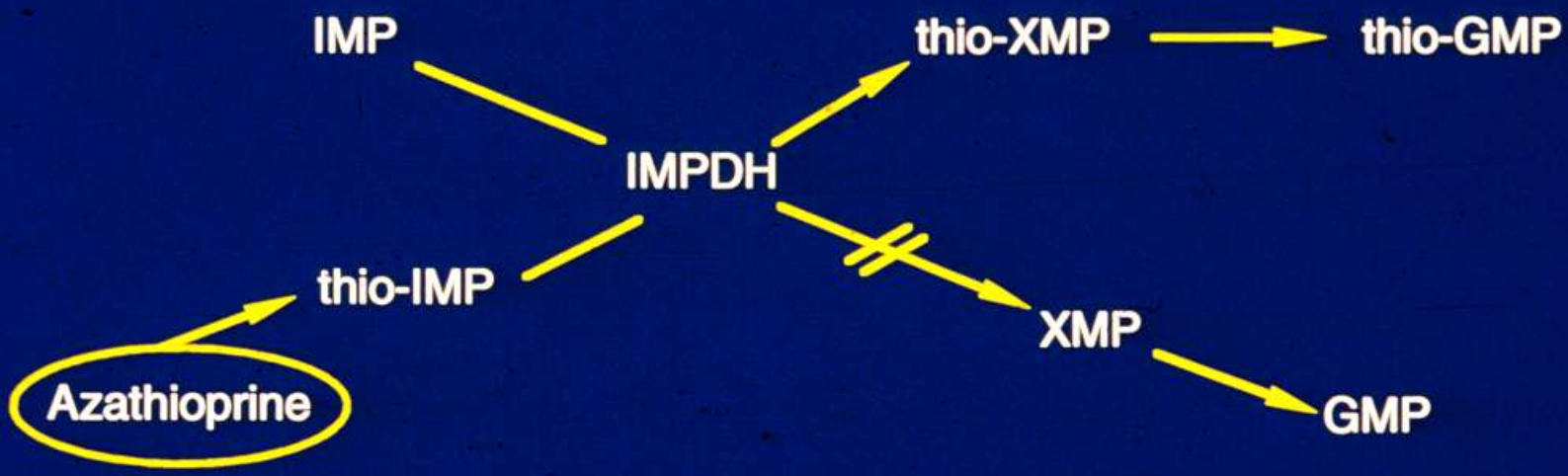
Strom et al, Transplantation 57:1994

Antimetabolites - Azathioprine, Mycophenolate Mofetil, Brequinar



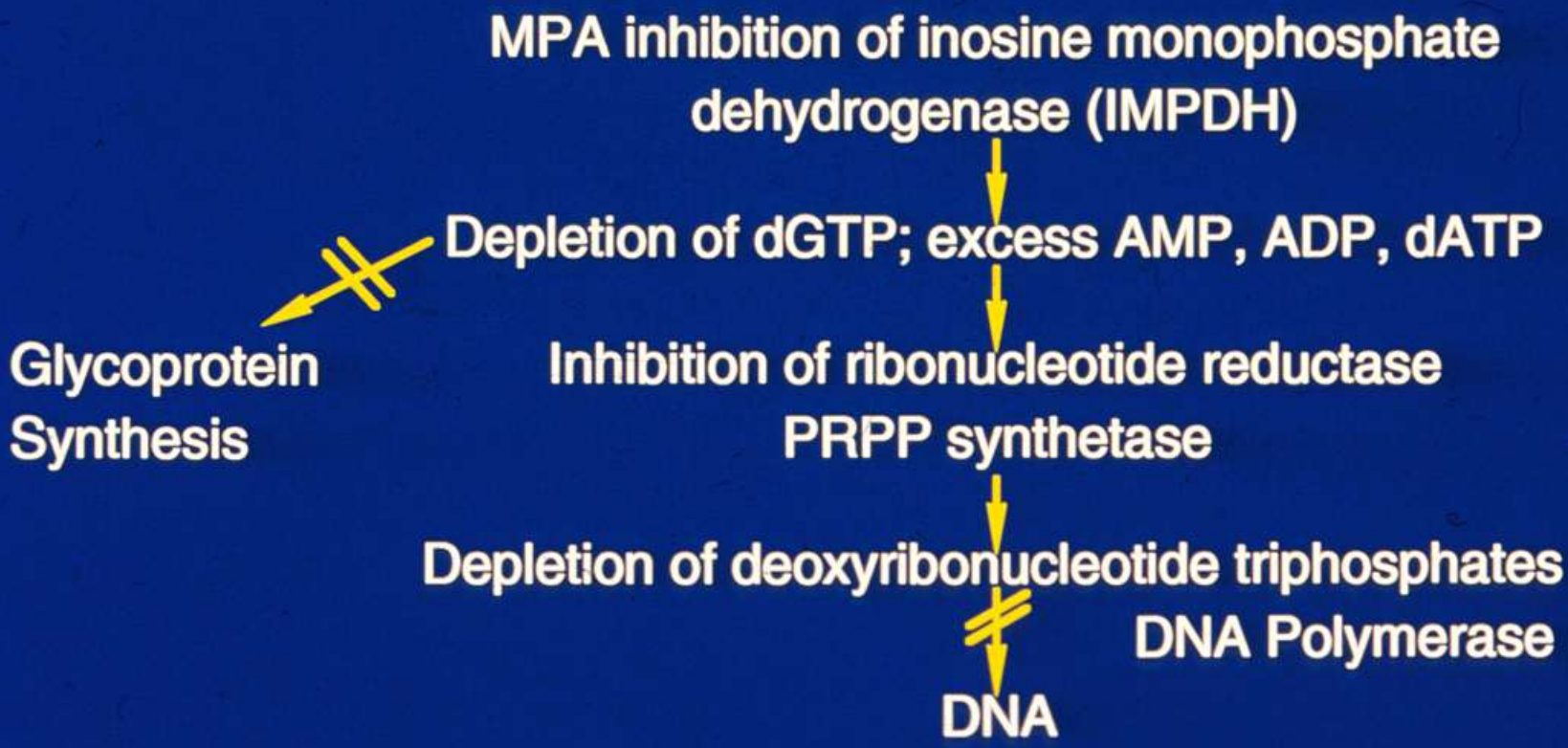
Nonselective Action of Azathioprine



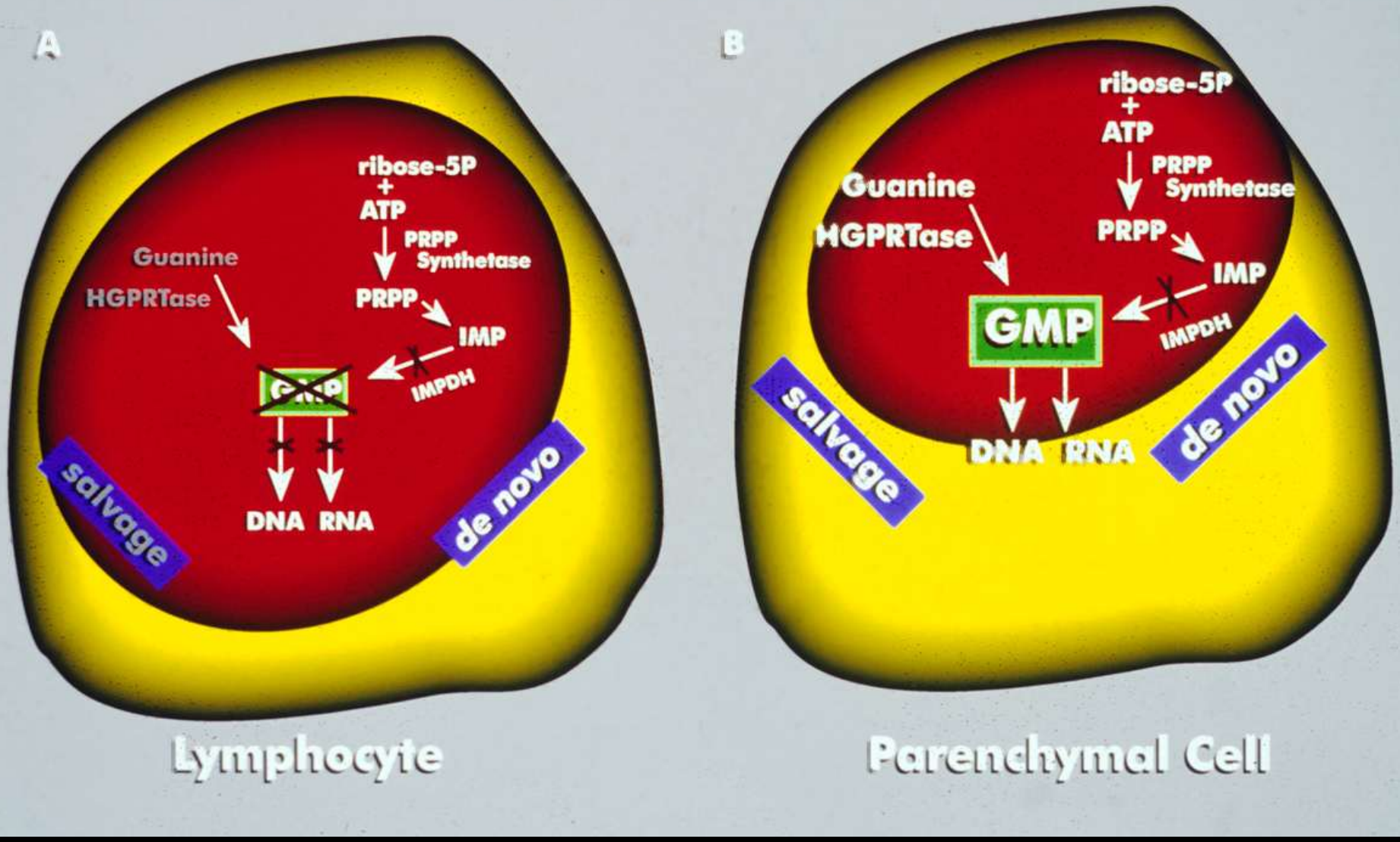
Results:

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

Selective, Noncompetitive Inhibition of IMPDH by Mycophenolic Acid



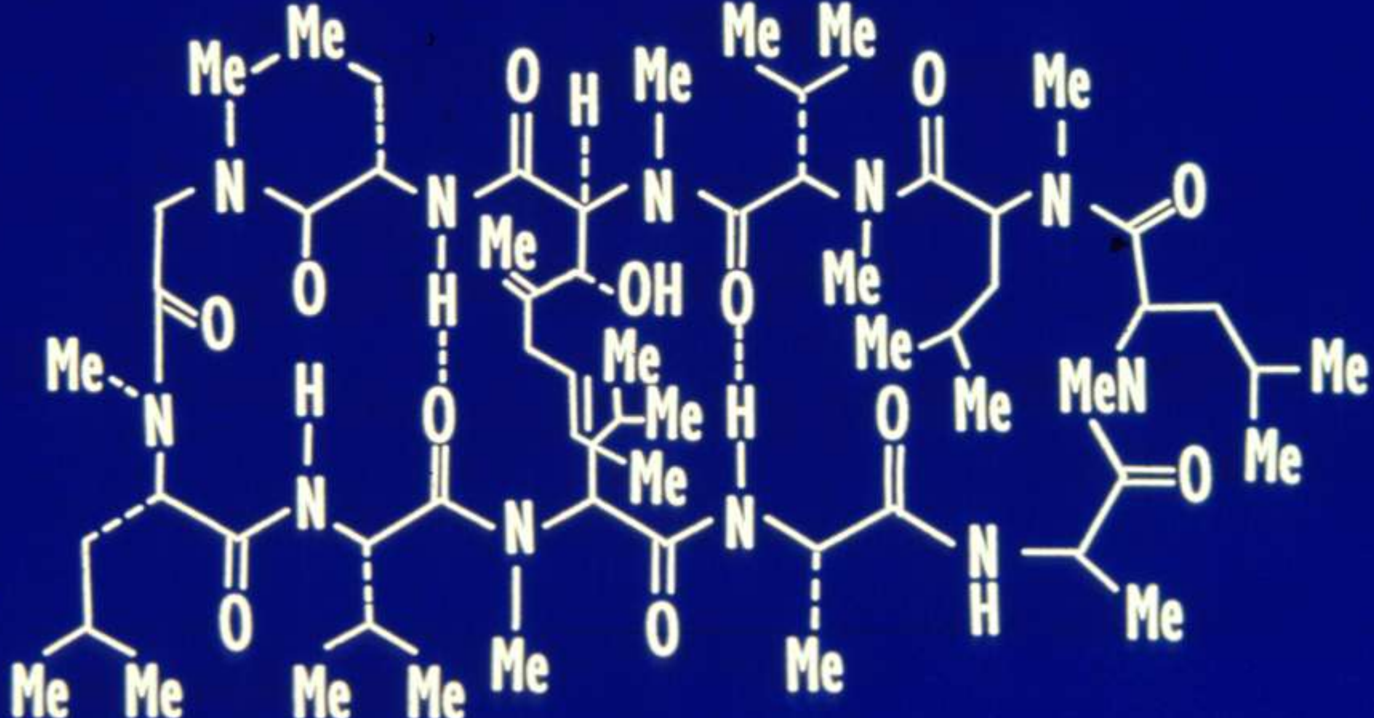
Mycophenolate Mofetil



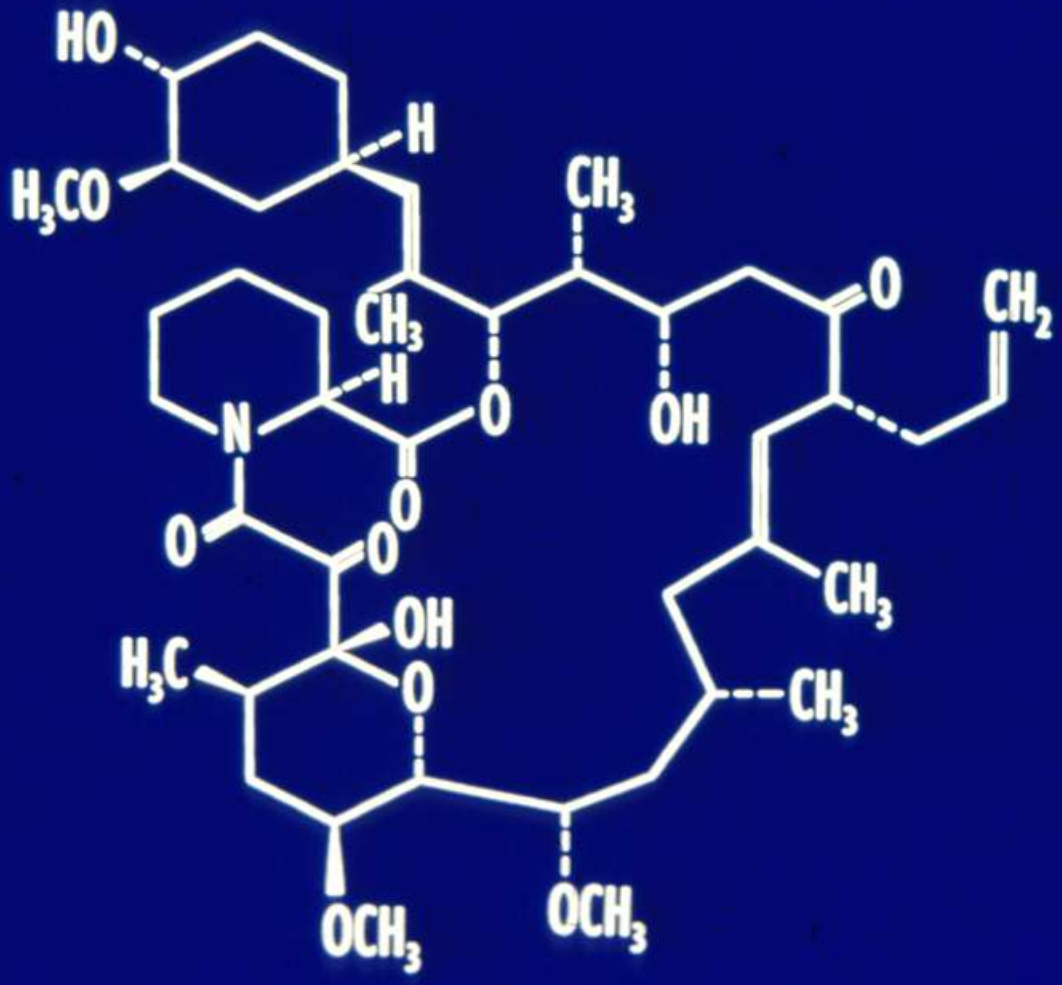
Immunophyllin Binding Agents

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

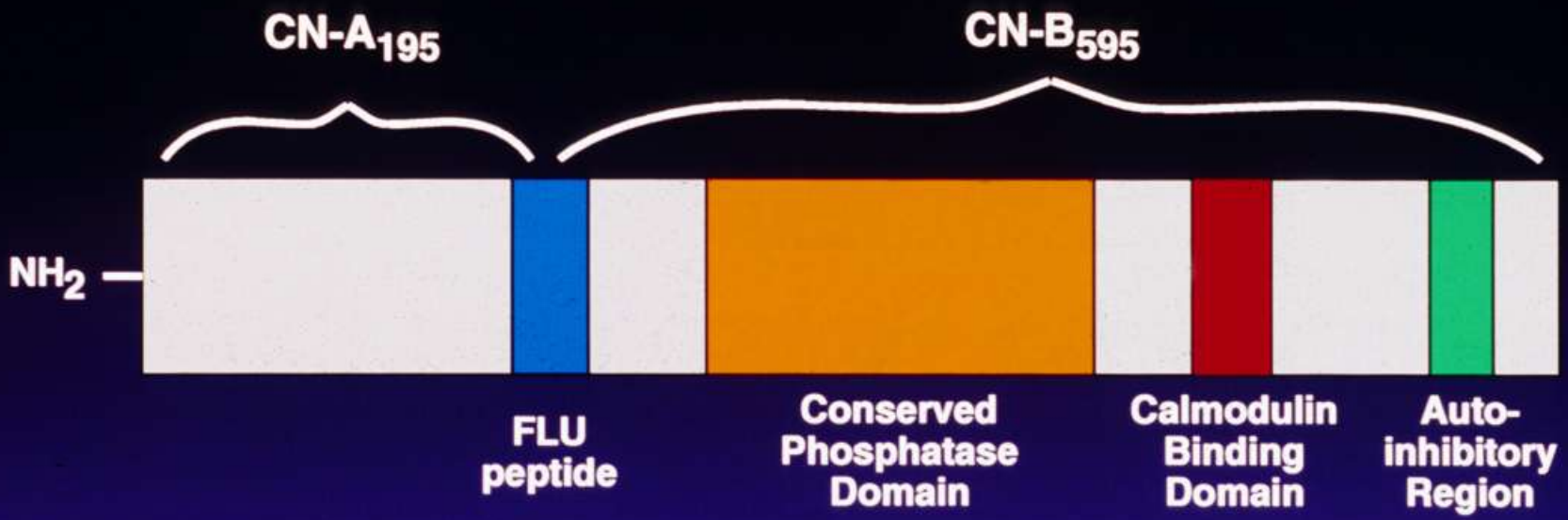
Cyclic undecapeptide cyclosporin A (CSA)



Tacrolimus (FK506)



Structure of Calcineurin



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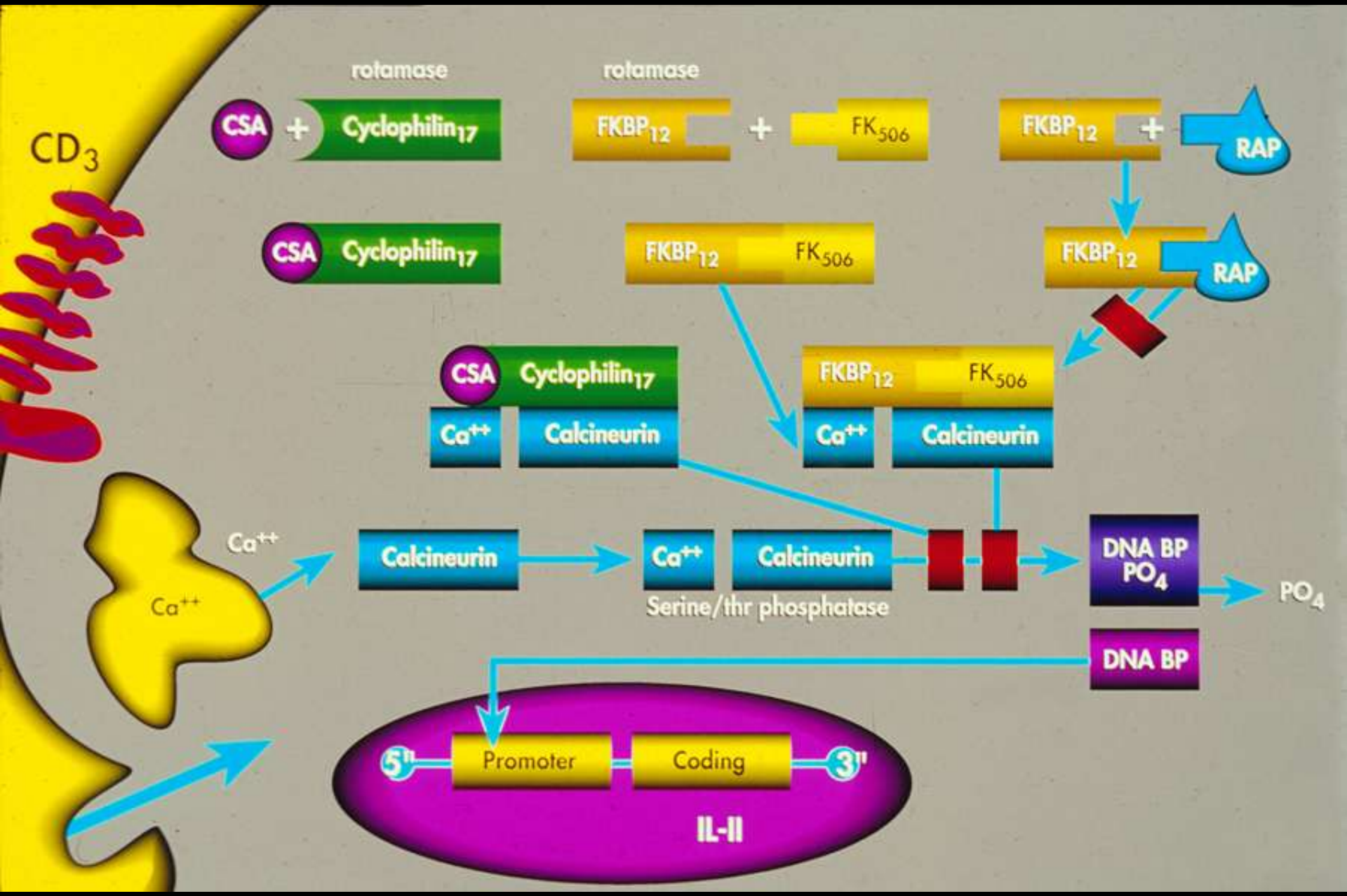
After Clipstone, Fiorentino, & Crabtree
J.Bio. Chem. 269:94


rotamase
rotamase
CSA
Cyclophilin17
FKBP12
FK506
FKBP12
RAP
CD3
CSA
Cyclophilin17
FKBP12
FK506
FKBP12
RAP
CSA
Cyclophilin17
Ca++
Calcineurin
FKBP12
FK506
Ca++
Calcineurin
Ca++
Ca++
Calcineurin
Ca++
Calcineurin
DNA BP
PO4
PO4
Serine/thr phosphatase
DNA BP
5'
Promoter
Coding
3'
IL-II

(a)

NF-ATp

NF-Atp-Fos-Jun

NF-Atp-Fos-Jun

Rapid
dissociation rate
(<2 min)

Slow
dissociation rate
(>20 min)

(b)

Distal murine NF-AT site

GCCCAAAGAGGAAAATTTGTTTCATACAG

Anjana Rao, Immunology Today 1994:15

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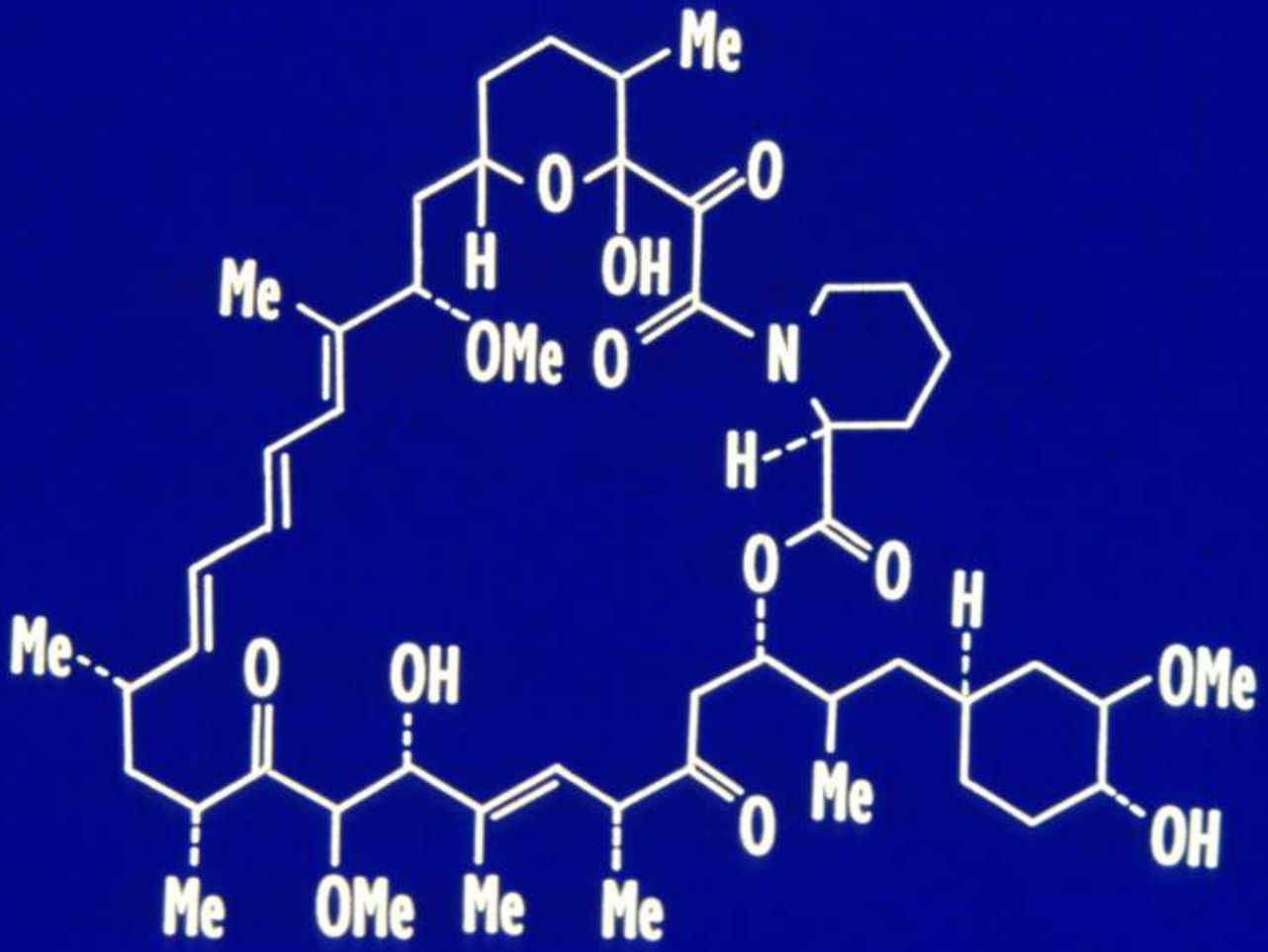
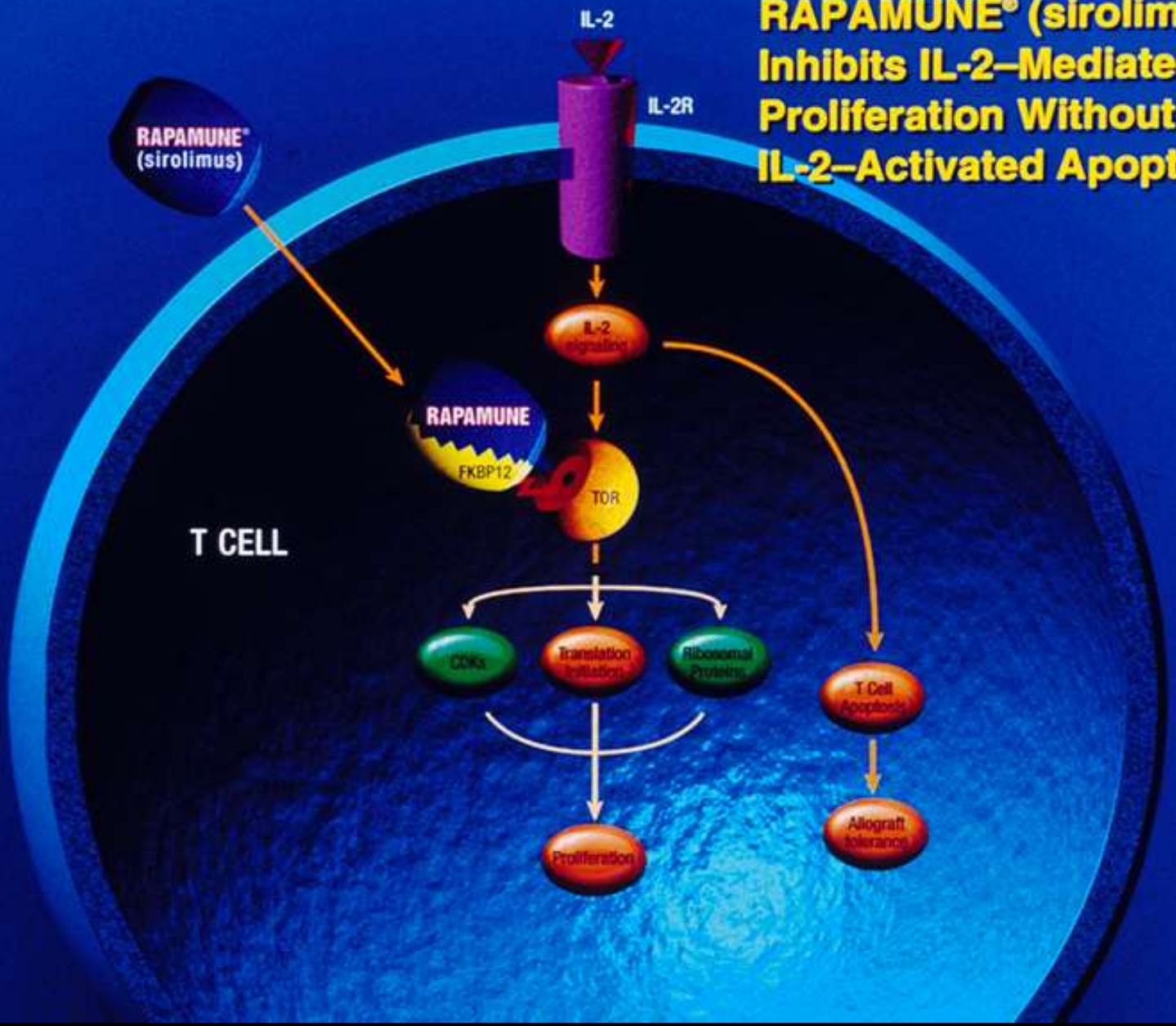
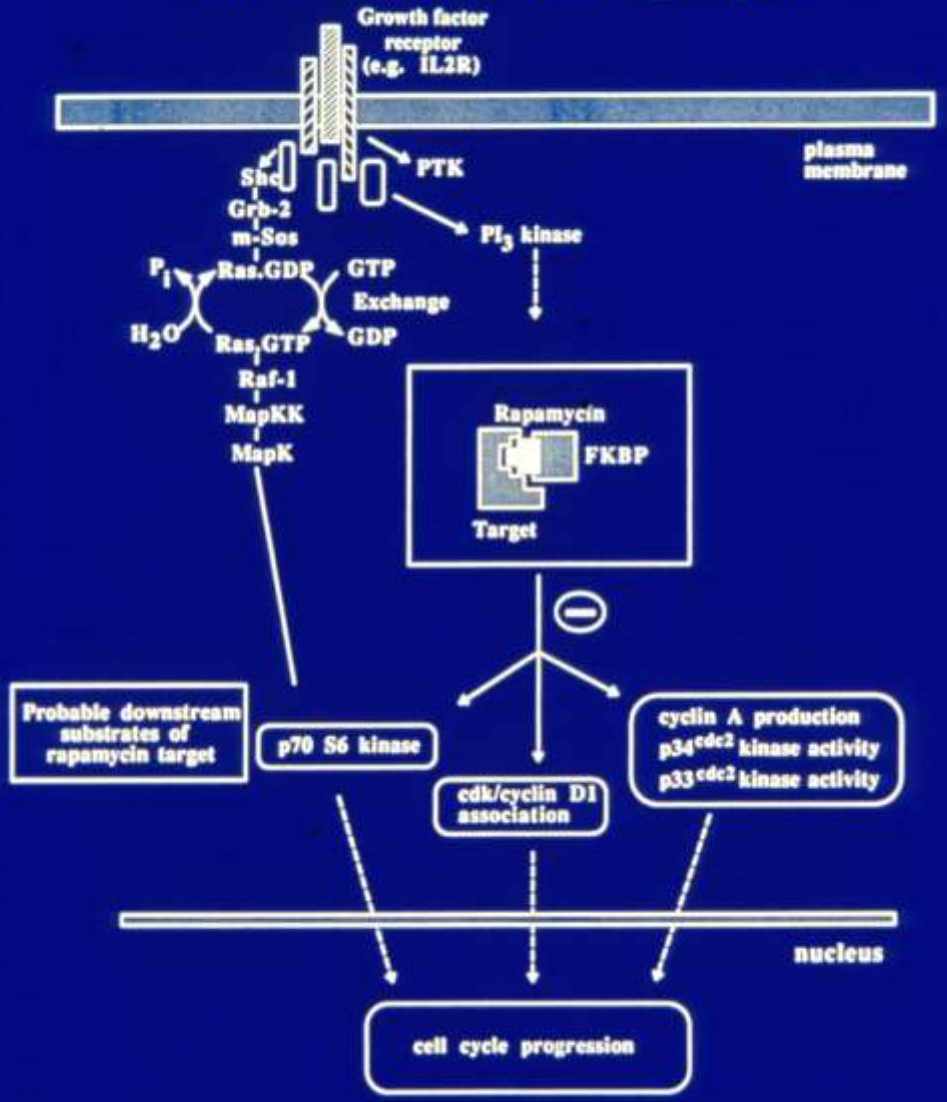
Rapamycin



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



Mechanism of Action of Rapamycin

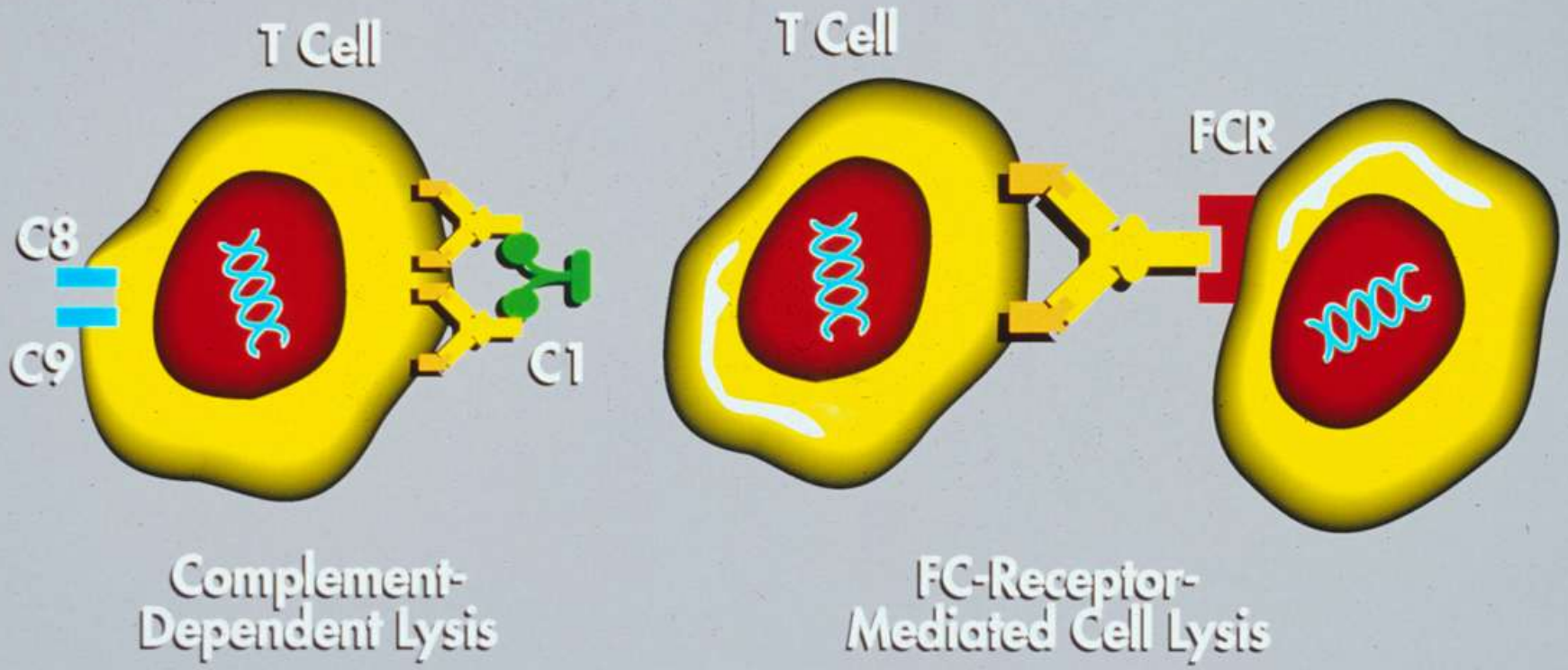


RAPAMUNE® (sirolimus) Has a Distinct Mechanism of Action

	Cyclosporine	RAPAMUNE
Binding protein	Cyclophilin	FKBP12
Effector protein	Calcineurin	mTOR
IL-2 message	Inhibited	–
IL-2 response	–	Inhibited
Cell-cycle effect	G_0-G_1	G_1-S

Galat A, et al. *Prog Biophys Mol Bio.* 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.

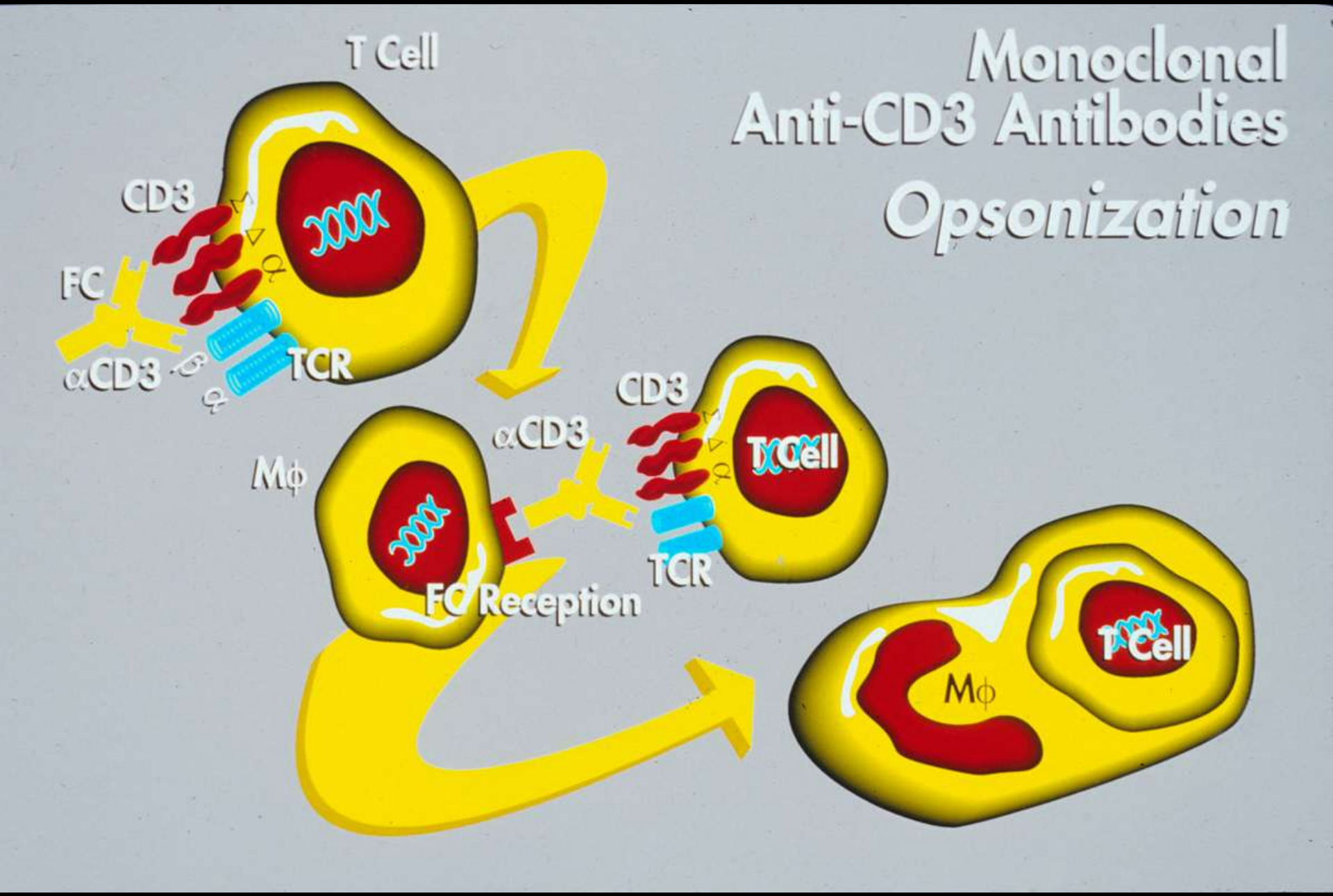
Polyclonal Anti–T-Cell Antibodies



SPECIFICITIES IN ANTIBODY PREPARATIONS

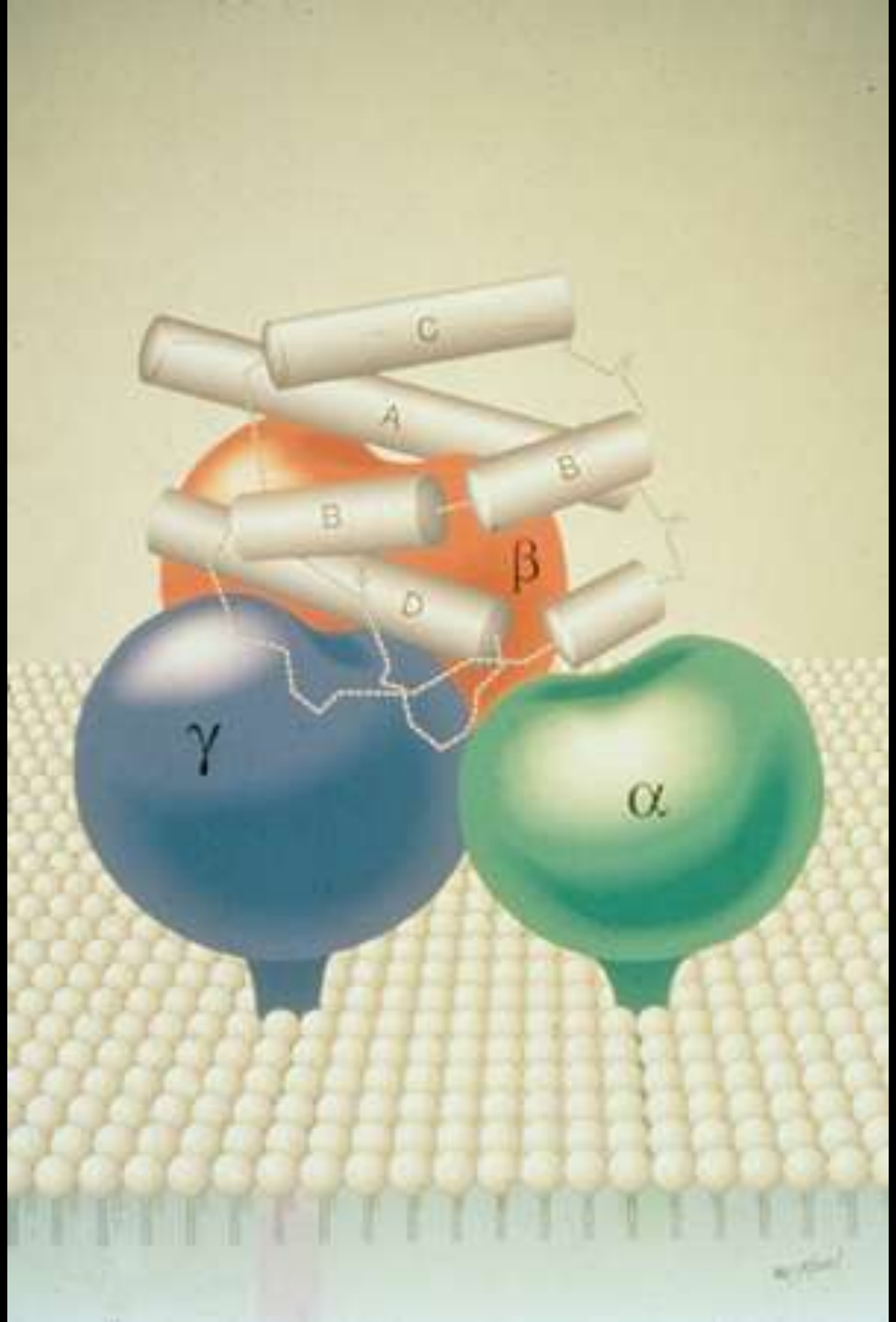
ANTIBODY	ANTIGEN TARGET
ATGAM	CD2, CD3, CD4, CD5, CD7 CD8, CD11a, CD18, CD45, TCR
OKT3	CD3
OKT4	CD4
ENLIMOMAB	ICAM-1
T10 B9	TCR
ANTI LFA-1	LFA-1
ANTI-TAC	IL2 Receptor

Source: Bourdage JS, Hamlin DM. Comparative polyclonal antithymocyte globulin and antilymphocyte/antilymphoblast globulin anti-cd antigen analysis by flow cytometry. *Transplantation*. April 27, 1995; 59(8).

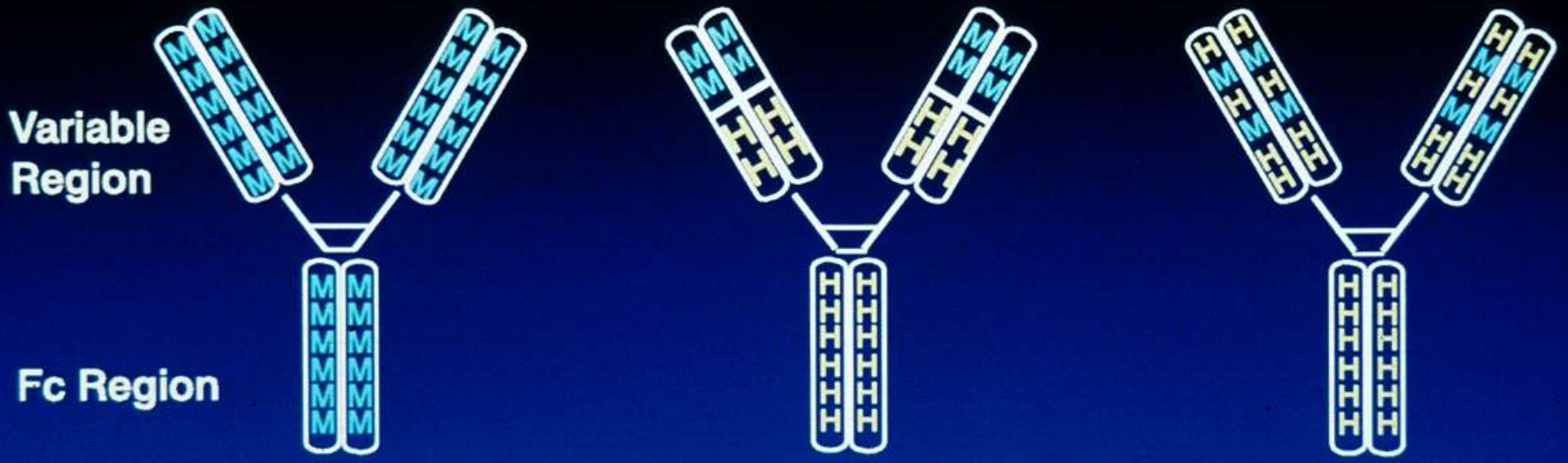

T Cell
Monoclonal
Anti-CD3 Antibodies
Opsonization
CD3
FC
αCD3
TCR
Mϕ
αCD3
CD3
T Cell
TCR
FC Reception
T Cell
Mϕ

IL-2 RECEPTOR ANTIBODIES

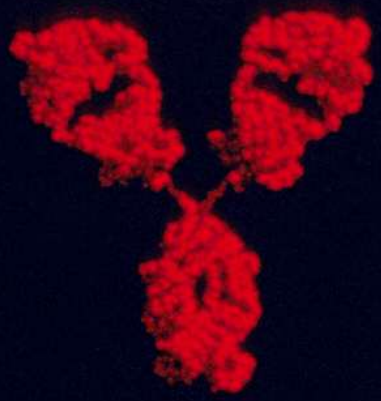
1. TARGET: NONCONSTITUTIVE IL-2R, MOSTLY β CHAIN
2. IN ANIMALS HIGHLY CYTOTOXIC AND PROLONGS GRAFTS
3. IN MAN MODULATES RECEPTOR
4. FRENCH STUDY: AS INDUCTION AGENT
   a. FEWER SIDE EFFECTS THAN P ON T CELL AB
   b. GRAFT SURVIVAL THE SAME
   c. TREND FOR MORE REJECTIONS


C
A
B
B
β
D
γ
α

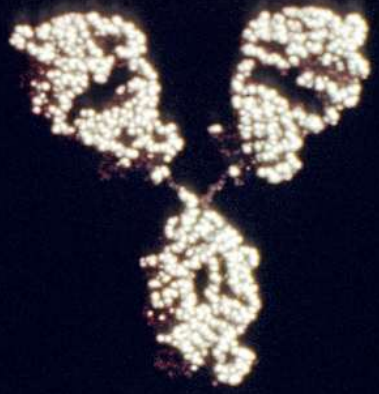
Murine and Humanized Monoclonal Antibodies



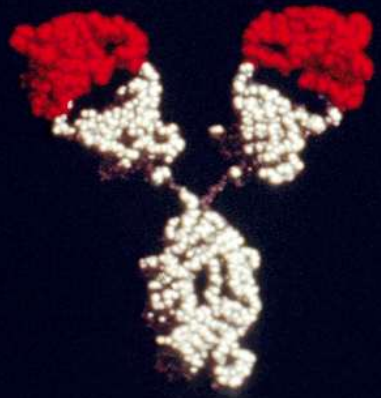
RECOMBINANT MONOCLONAL ANTIBODIES



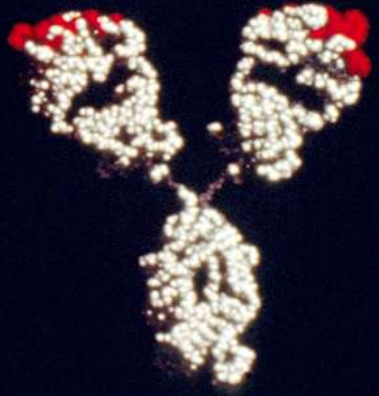
Mouse



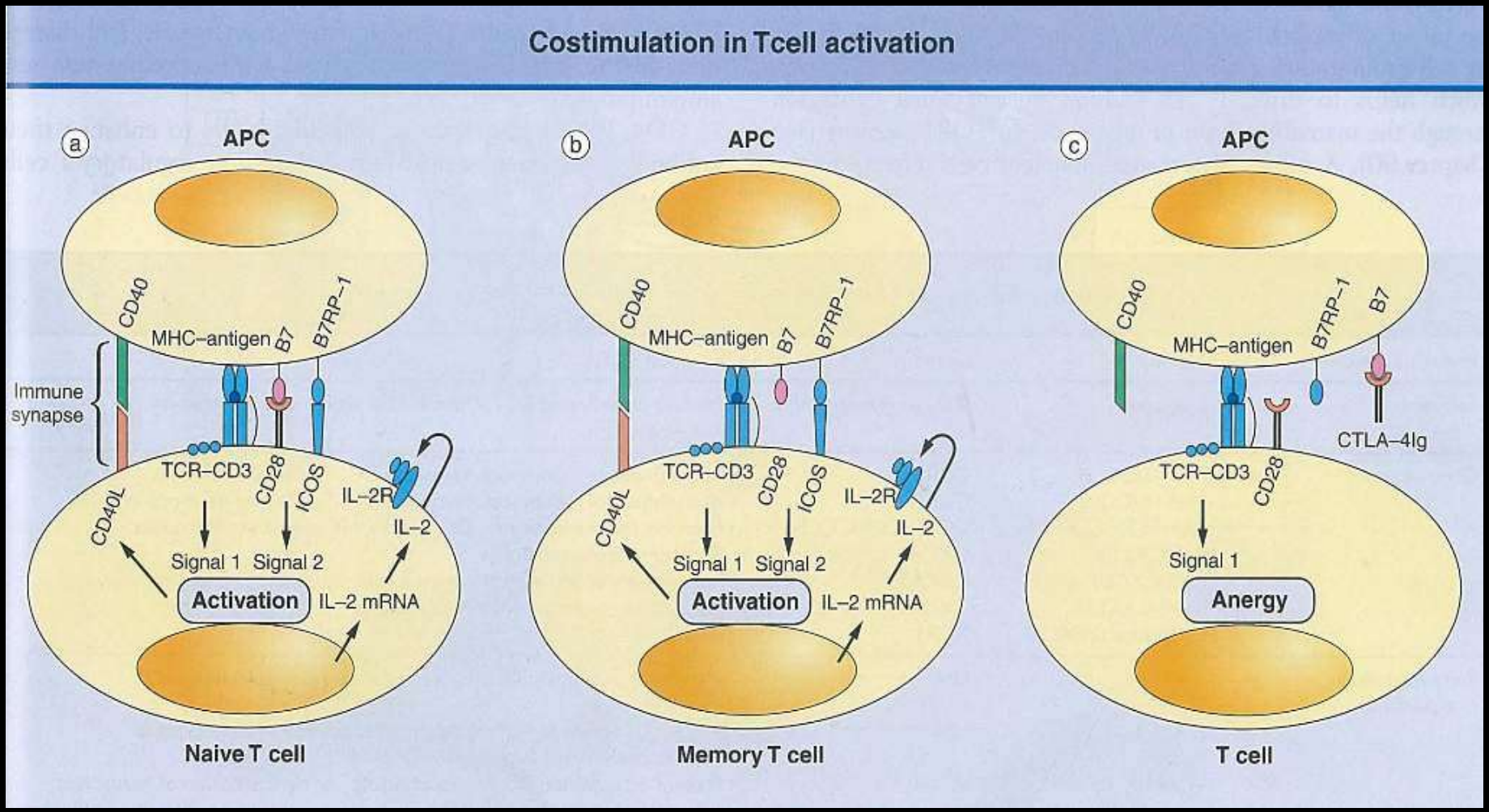
Human



Chimeric



Humanized


Costimulation in Tcell activation
a
APC
CD40
MHC–antigen
B7
B7RP–1
Immune synapse
TCR–CD3
CD28
ICOS
IL–2R
IL–2
CD40L
Signal 1
Signal 2
Activation
IL–2 mRNA
Naive T cell
b
APC
CD40
MHC–antigen
B7
B7RP–1
TCR–CD3
CD28
ICOS
IL–2R
IL–2
CD40L
Signal 1
Signal 2
Activation
IL–2 mRNA
Memory T cell
c
APC
CD40
MHC–antigen
B7RP–1
B7
CTLA–4Ig
TCR–CD3
CD28
Signal 1
Anergy
T cell

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

Larsen et al AJT 5:2005

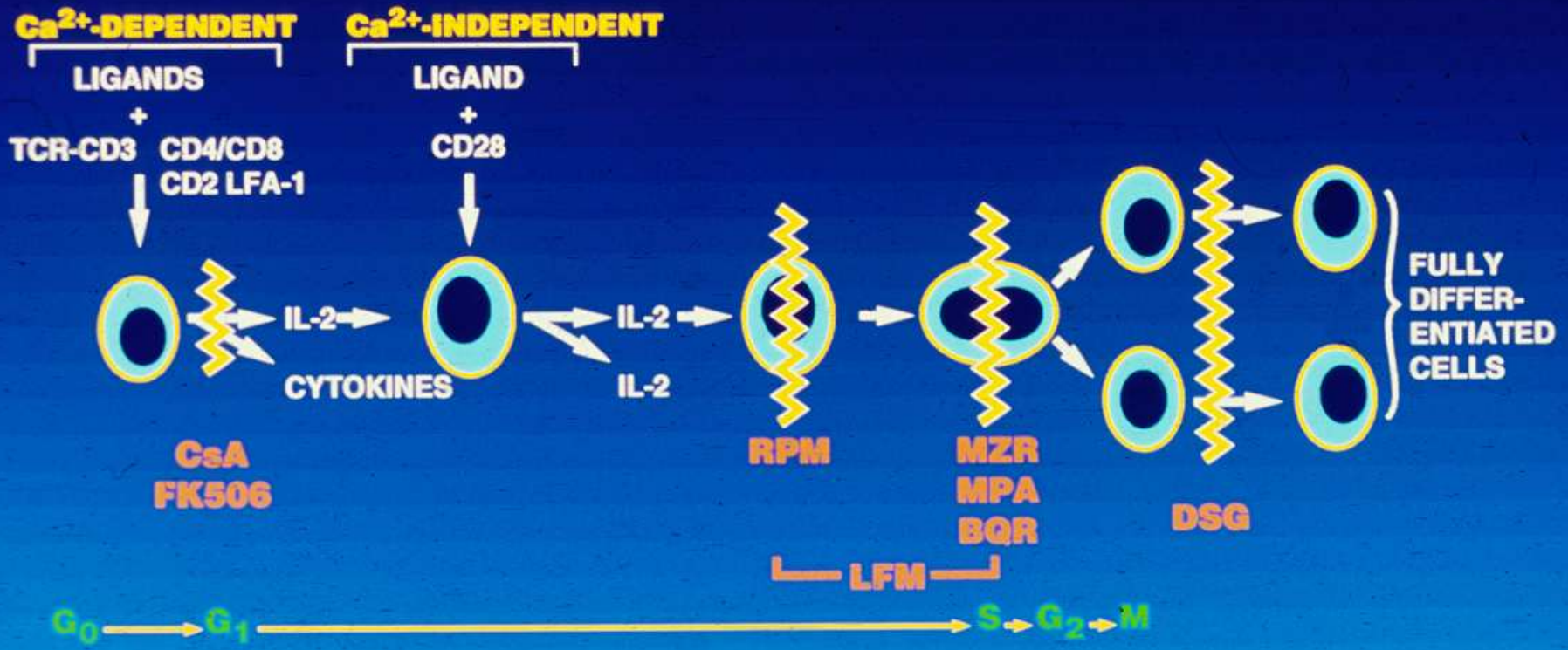
FTY 720
Potential Advantages

- 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

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

POSSIBLE SITES OF ACTION IN T CELLS OF NEW XENOBIOTIC IMMUNOSUPPRESSANTS



R.Morris '94