Causes of death, 2001:

Population:	6,122,210,000
Deaths:	56,554,000

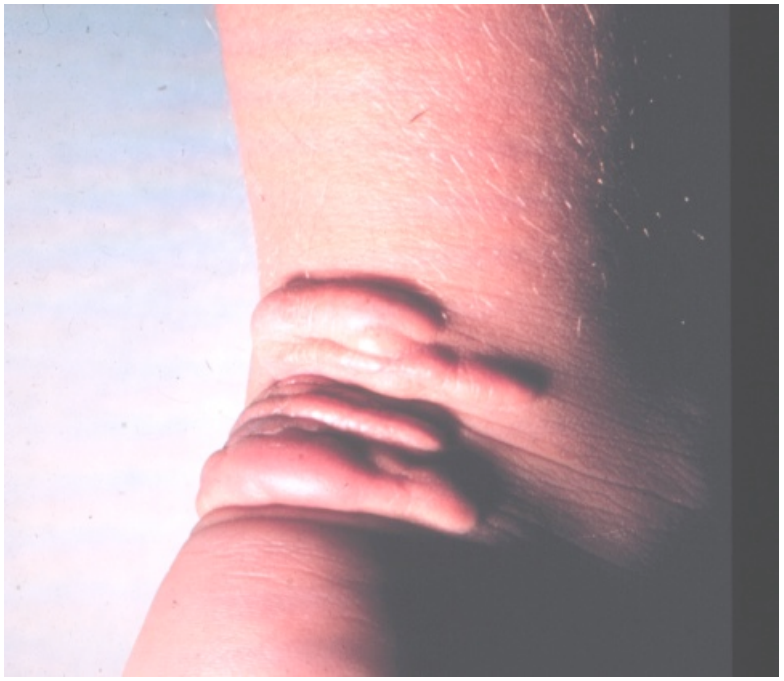
USA

6.	1.	**Infectious and parasitic diseases: 14.9 million**
1.	2.	**Heart diseases: 11.1 million**
2.	3.	**Cancers: 7.3 million**
3.	4.	**Stroke: 5.5 million**
4.	5.	**Respiratory diseases: 3.6 million**
5.	6.	**Accidents, fires, drowning, etc.: 3.5 million**
	7.	**Maternal and perinatal: 3.0 million**
	8.	**Violence (war, homicide, suicide): 1.6 million**

World Health Organization
World Health Report 2002

Atherosclerosis

Familial Hypercholesterolemia (FH)

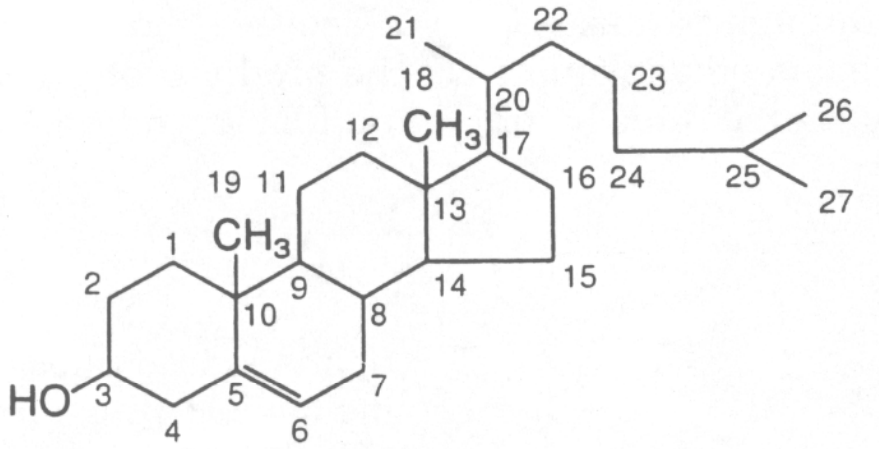


Xanthoma

Heterozygotes (1:500)
- 300-500 mg/dl plasma cholesterol
- Xanthomas in third decade
- Coronary heart disease in fourth decade
- Treat w/ statins and bile acid binding resins

Homozygotes (1:10^6)
- 500-1200 mg/dl plasma cholesterol
- Xanthomas at birth
- Death by MI before age 30
- Treat w/ plasma LDL apheresis

Cholesterol



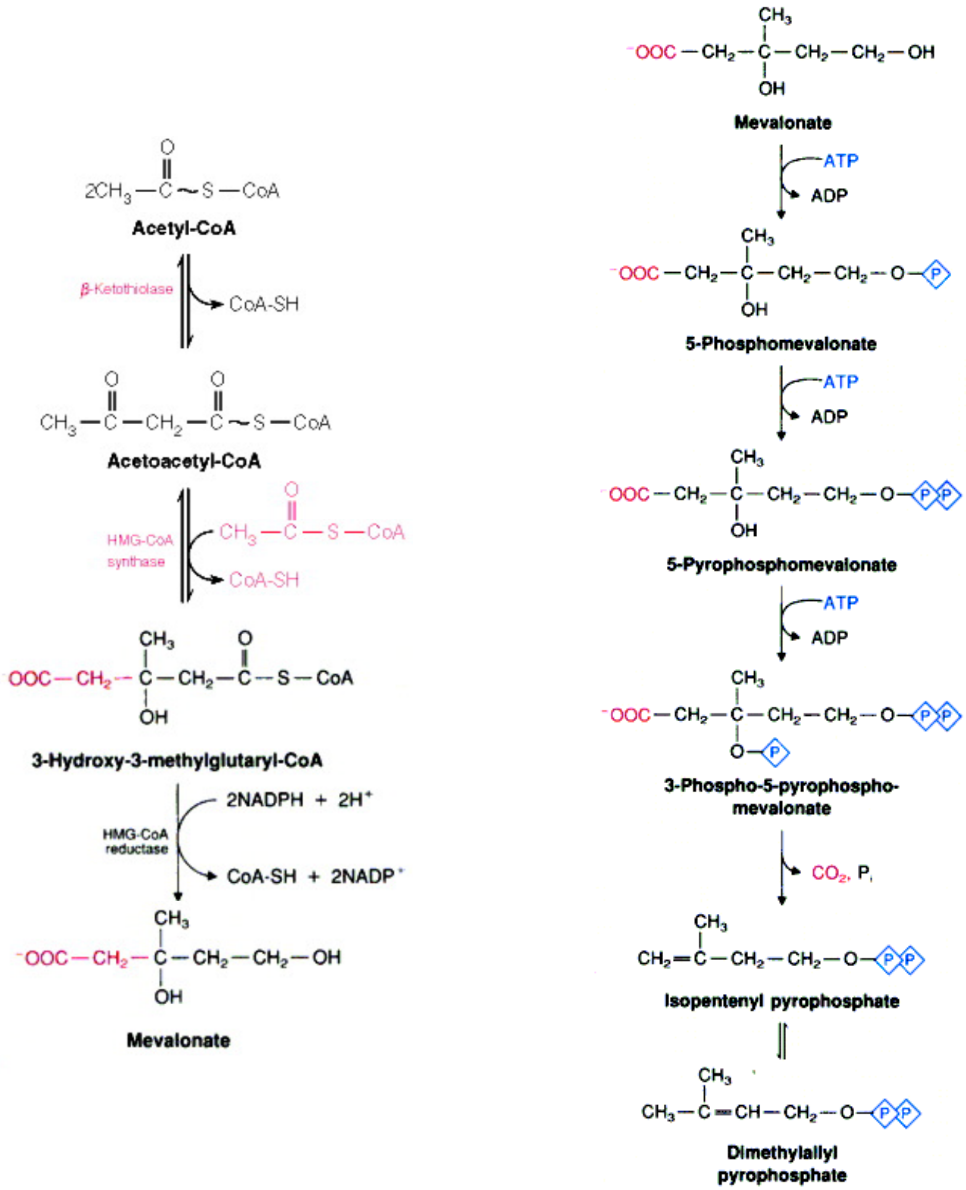
1) Acetyl-CoA → HMG-CoA → Mevalonate

2) Mevalonate (C_6) + 3ATP → Isopentenyl-PP_i (C_5 "isoprene") + CO_2 + 3ADP + P_i

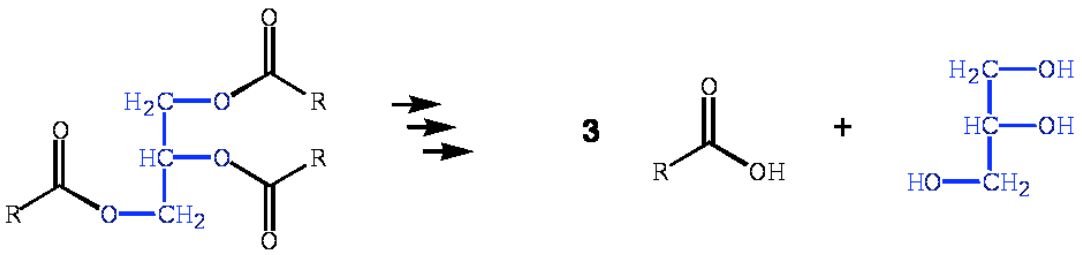
3) 6 Isoprene units (C_5) → Squalene (C_{30})

4) Squalene (C_{30}) → Cholesterol (C_{27})

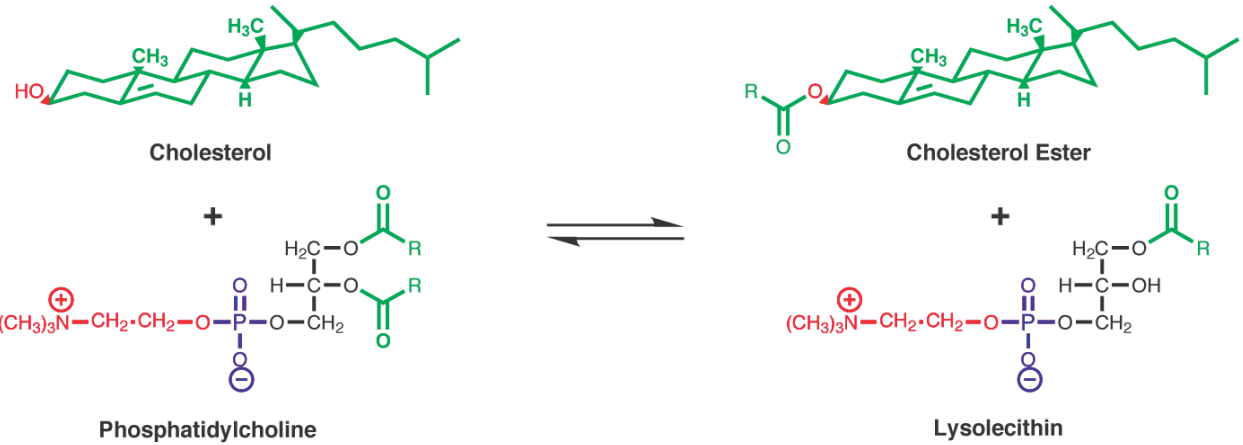
Isopentylpyrophosphate (MEV Pathway)



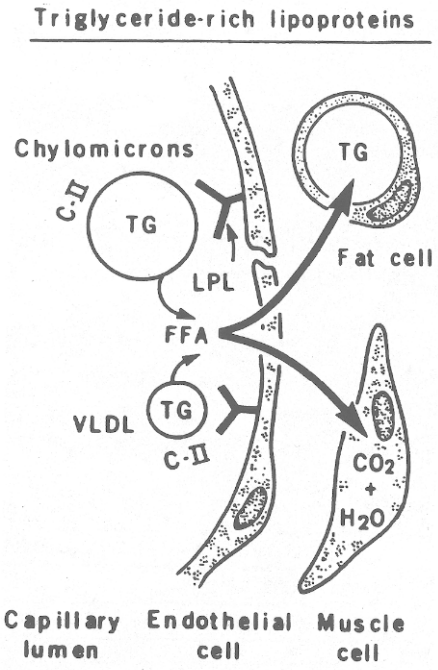
Lipid Trafficking Enzymes



Lipoprotein Lipase, LPL
(located on endothelium of muscle, adipose tissue)



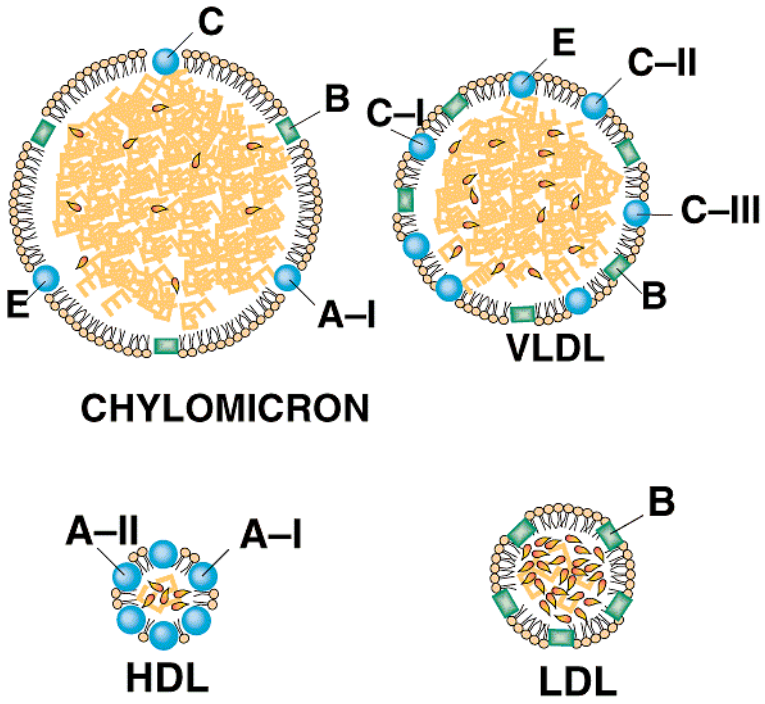
Lecithin:Cholesterol Acyltransferase (LCAT)
(located on HDL)



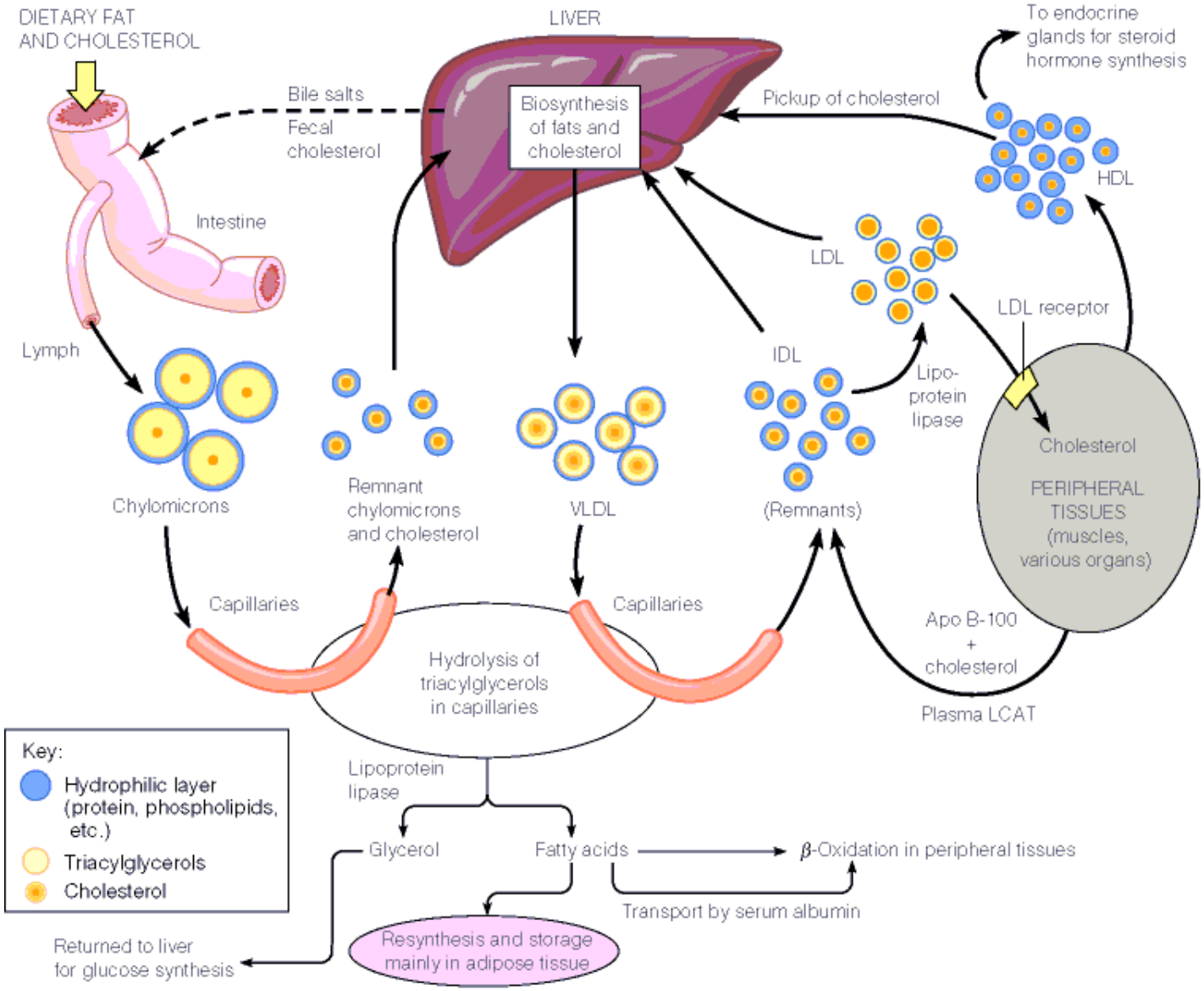
Also CETP

Lipoprotein Particles

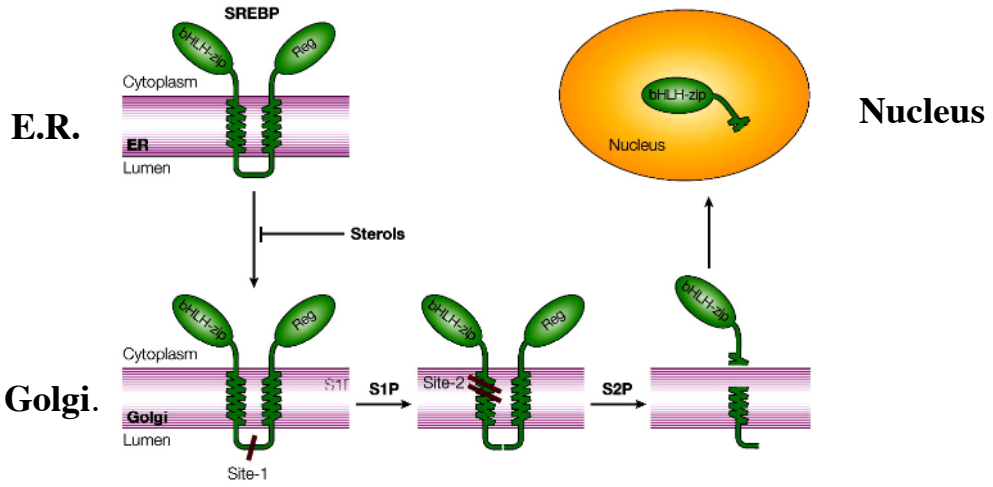
Apolipoprotein	M.W.	gL^{-1}	Comments
ApoA-I	28 kD	1.0-1.2	CMC, HDL
ApoA-II	17 kD	0.3-0.5	CMC, HDL
ApoA-IV	46 kD	0.15-0.16	CMC, HDL
ApoB-48	264 kD	0.03-0.05	CMC
ApoB-100	512 kD	0.7-1.0	VLDL, IDL, LDL; binds receptor
ApoC-I	7 kD	0.04-0.06	CMC, VLDL, HDL
ApoC-II	9 kD	0.03-0.05	CMC, VLDL, HDL; binds LPL
ApoC-III	9 kD	0.12-0.14	CMC, VLDL, HDL
ApoD	33 kD	0.06-0.07	HDL
ApoE	38 kD	0.03-0.05	CMC, VLDL, IDL, HDL; binds receptor



Lipoprotein Transport

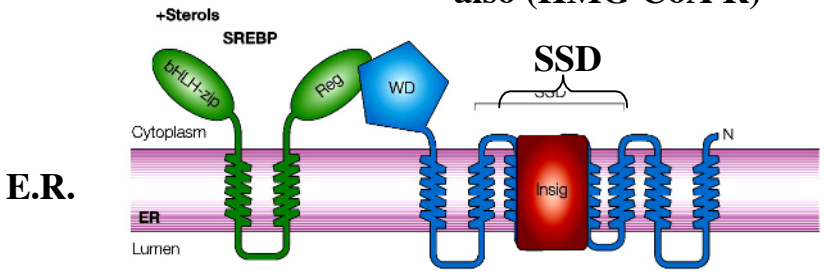


Sterol Regulation of Transcription by SREBP

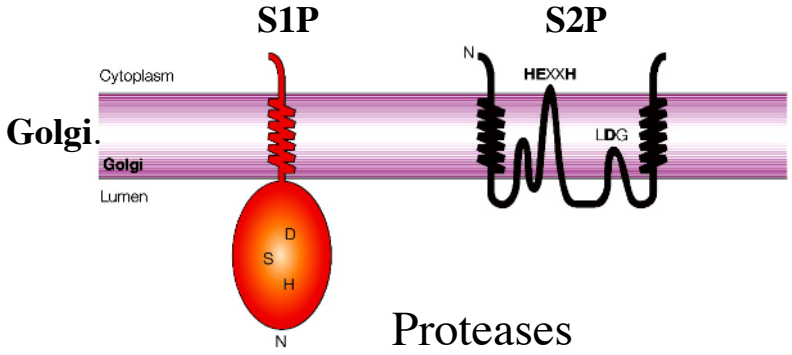


SREPB Transcription Factor Localization

SCAP/Insig proteins also (HMG CoA R)



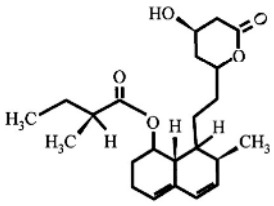
ER Retention



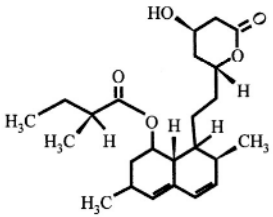
Proteases

The Statins

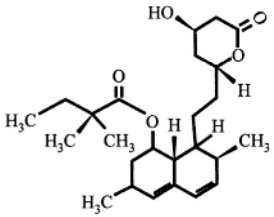
Fermentation-Derived Statins



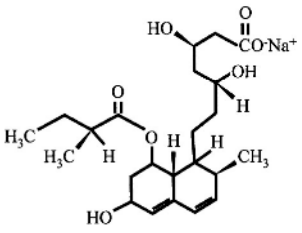
Mevastatin



Lovastatin

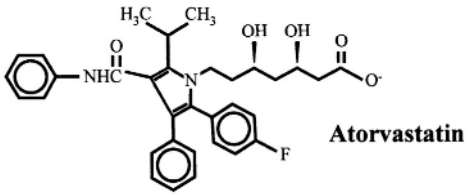


Simvastatin

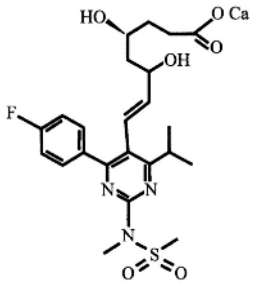


Pravastatin

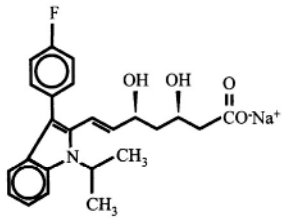
Synthetic Statins



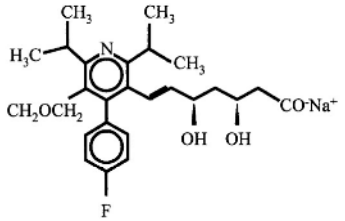
Atorvastatin



Rosuvastatin



Fluvastatin



Cerivastatin*

SHORT HISTORY

- 1976 Mevastatin from *Penicillinum citrinum*

- 1980 Mevinolin from *Aspergillus terreus*

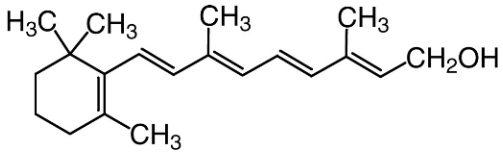
- 1987 FDA approves Lovastatin

- 1988 Lovastatin not effective in FH homozygotes

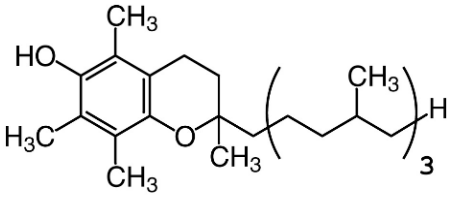
- 1995 Pravastatin decreases heart transplant rejection and mortality independently of lowering cholesterol levels

Isoprenoids in Humans

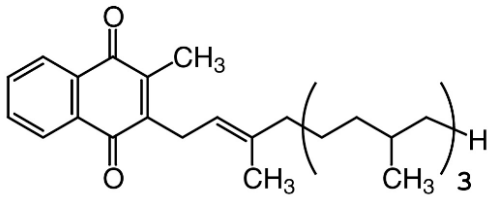
1. Steroids Hormones
2. Metabolites (Vit. A, E, K; co-Q; 25,000 terpenoids)



Vitamin A (*trans*-retinol)

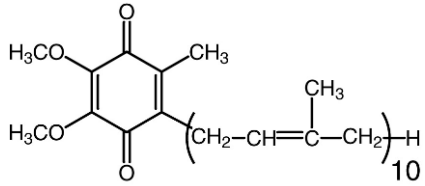


Vitamin E (α-tocopherol)

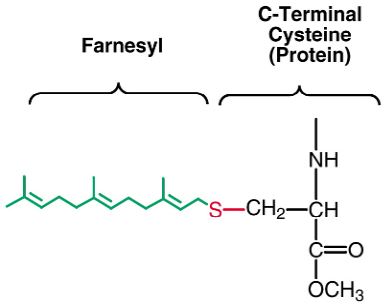


Vitamin K_1 (phytylmenaquinone)

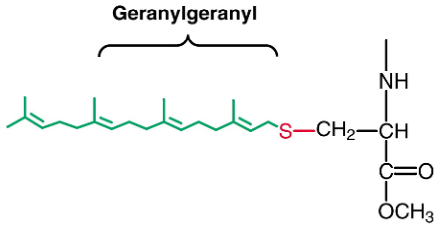
3. Isopentyl adenosine (tRNA)
4. Dolichol (N-linked glycosylation)
5. Protein Prenylation



Q, Ubiquinone

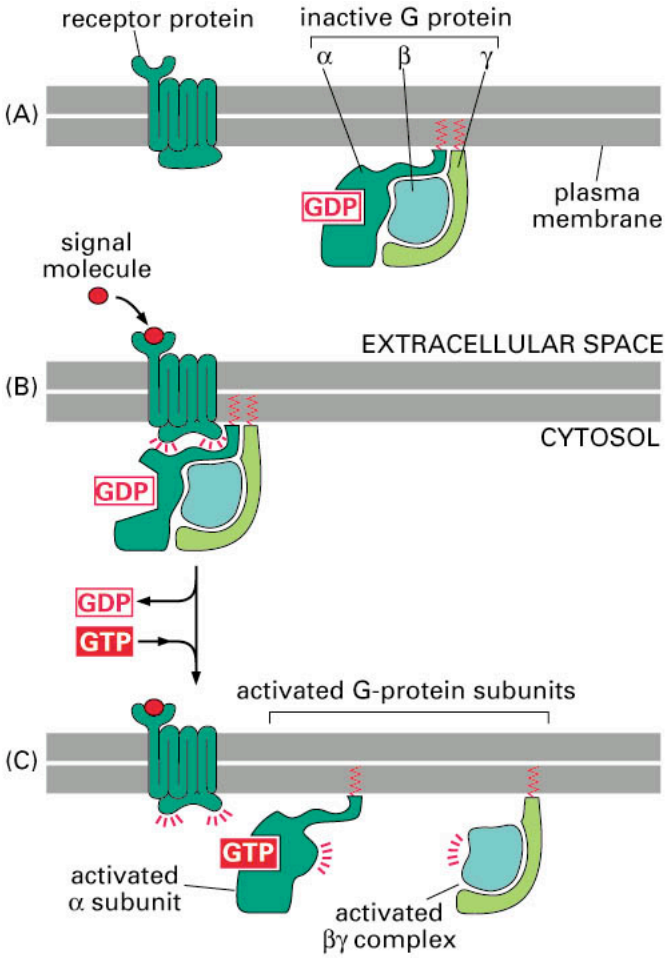


S-Farnesylcysteine

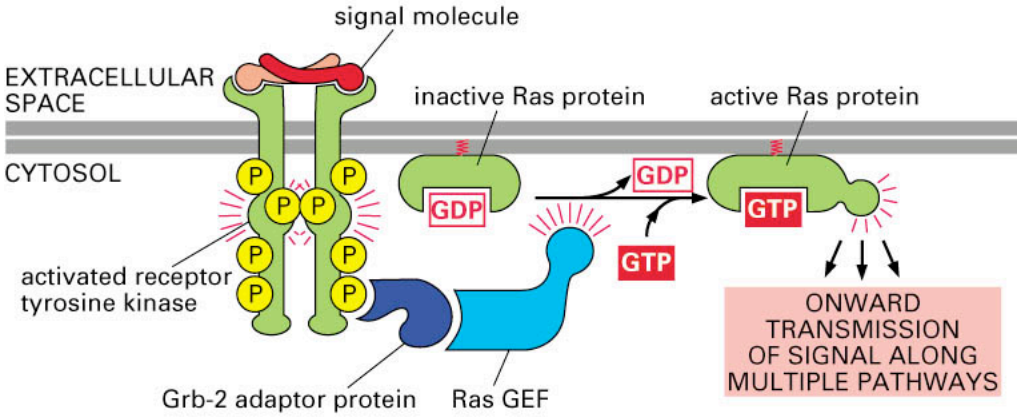


S-Geranylgeranylcysteine

Isoprenoids in G Protein Signaling



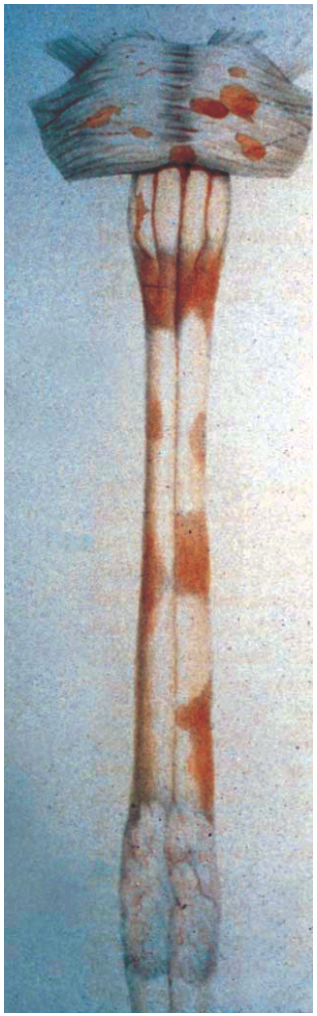
Heterotrimeric (GPCR's)



"Small" (RTK's)

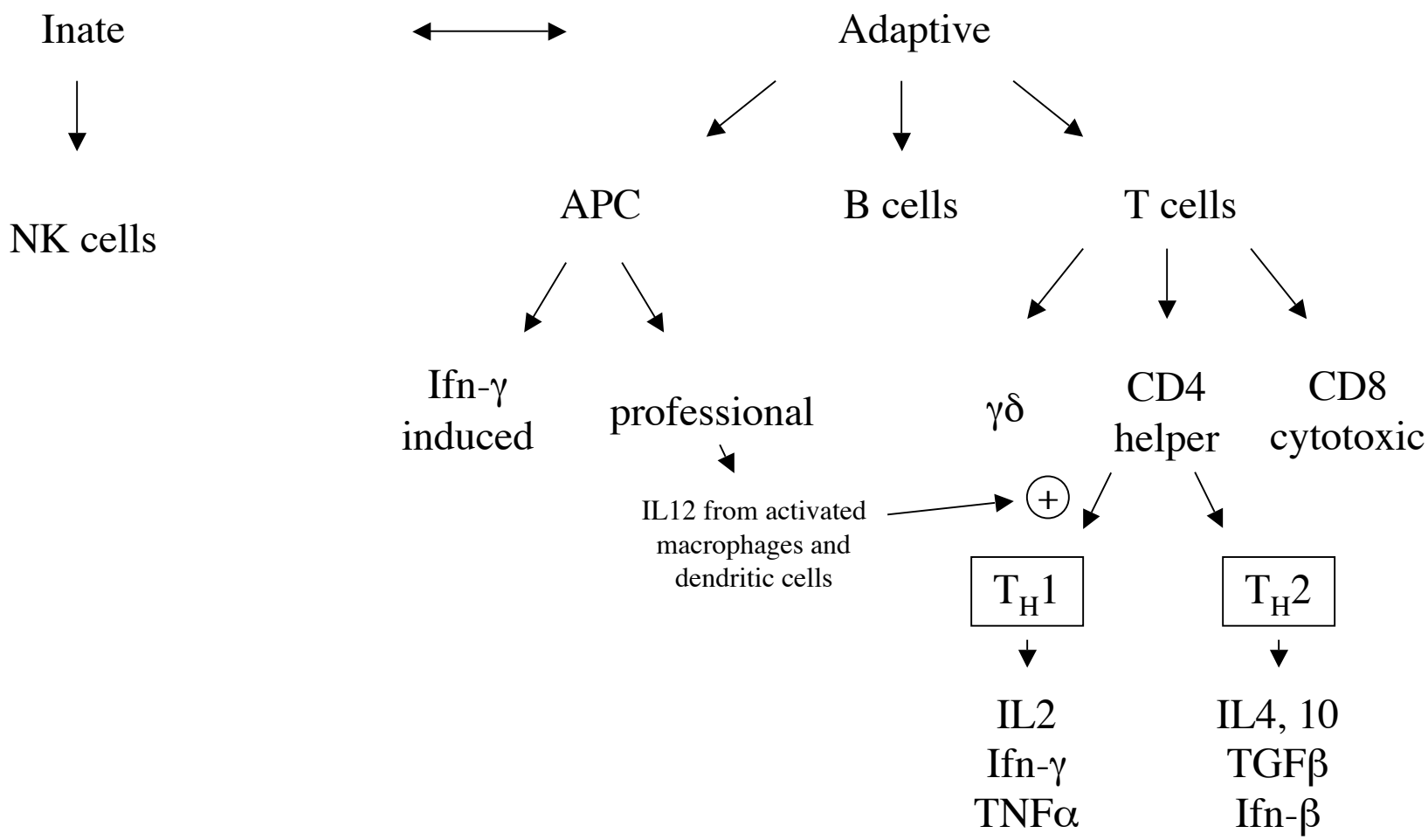
Multiple Sclerosis

- Effects up to one million worldwide
- 16,000 deaths in 2002 (0.03 %)
- Autoimmune attack of myelin in brain and spinal cord
- Progressive physical disability
- Current therapies include injected Ifn-β and copaxone (basic peptides)

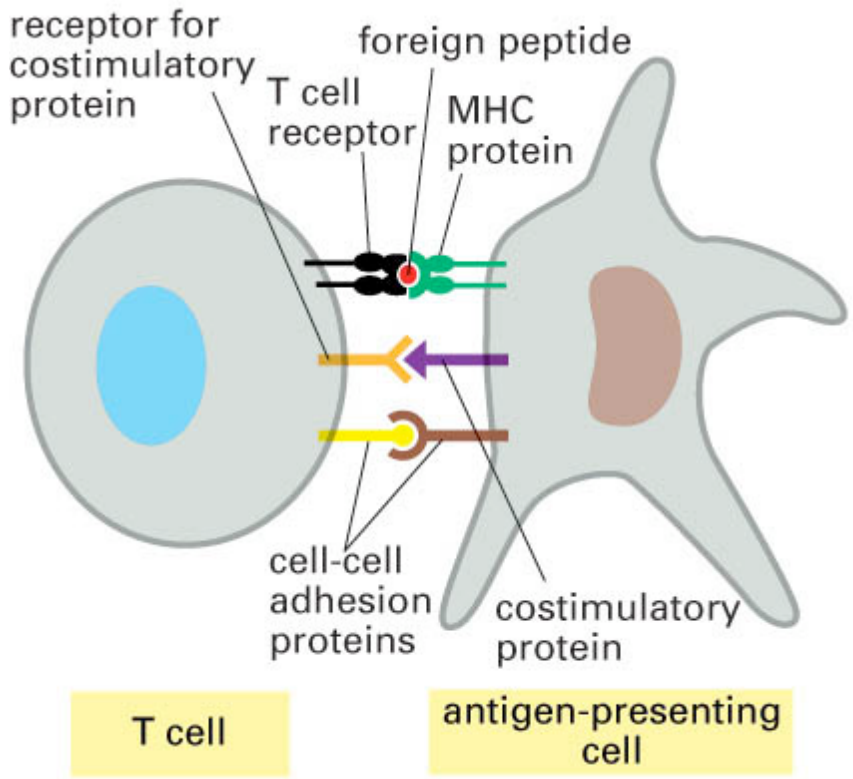


Lesions on cerebellum and spinal cord of an MS patient; Jean Cruvelhier circa 1860

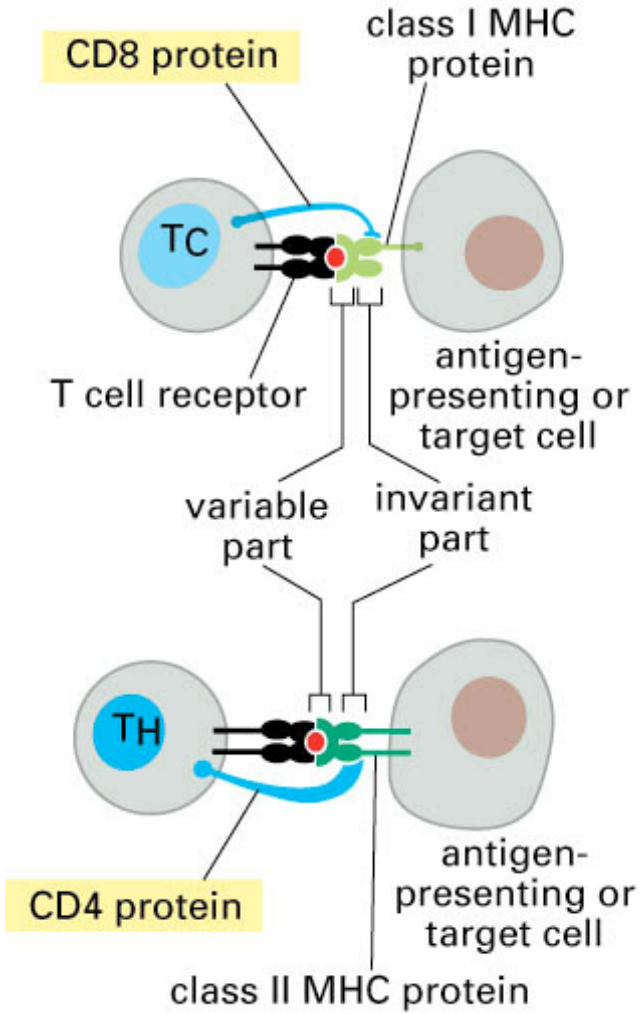
Immune System Overview



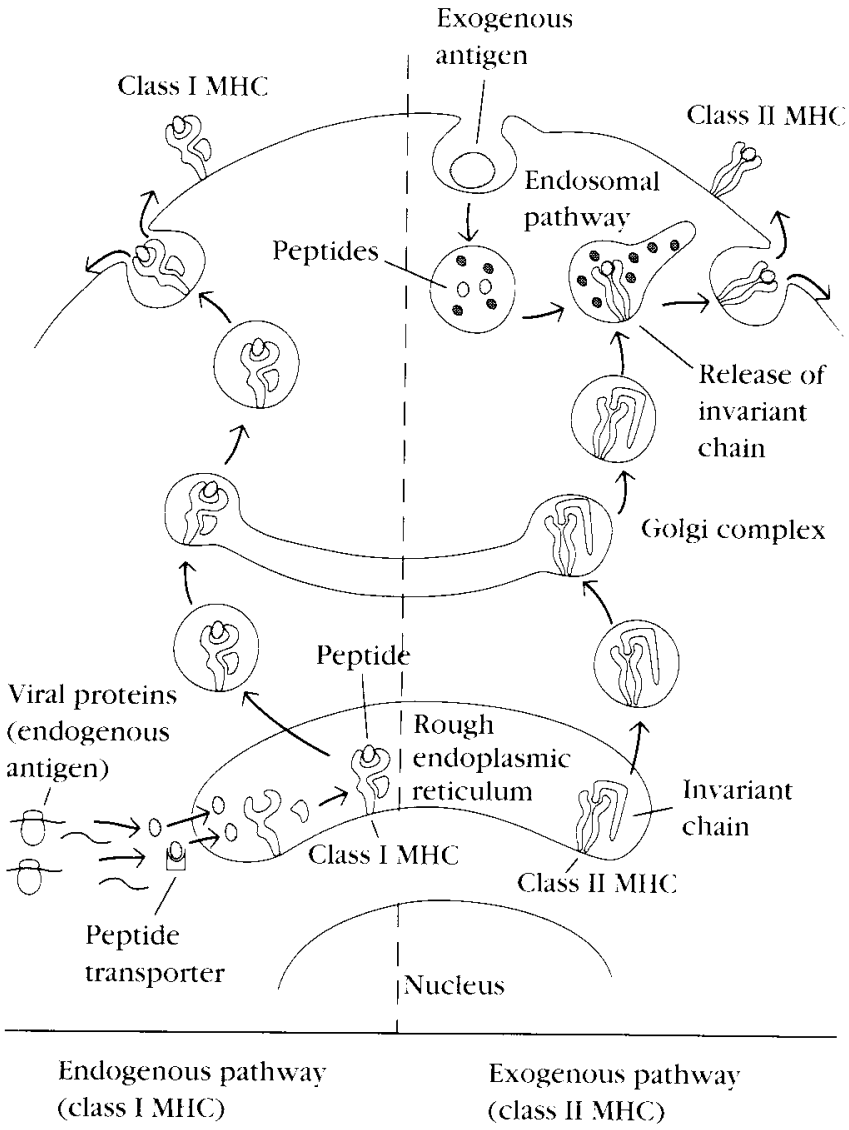
Cell Mediated Adaptive Immune Response



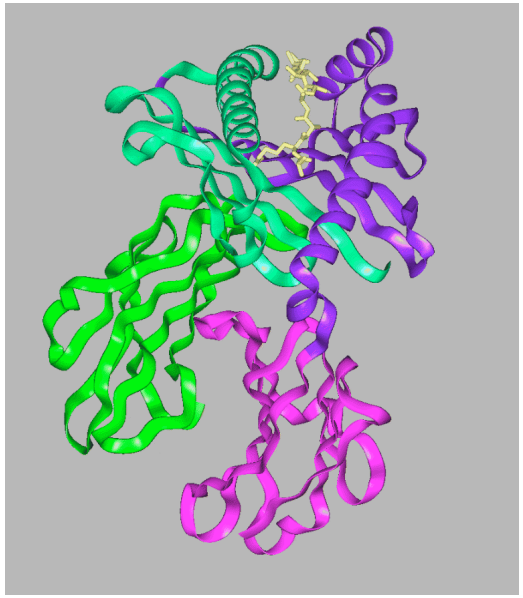
Tc/MHC1/CD8 versus Th/MHC2/CD4



MHC Antigen Presentation

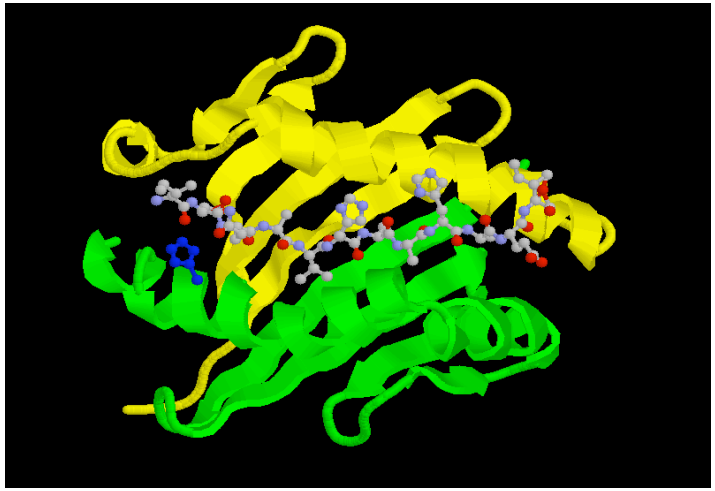


The MHC Molecules

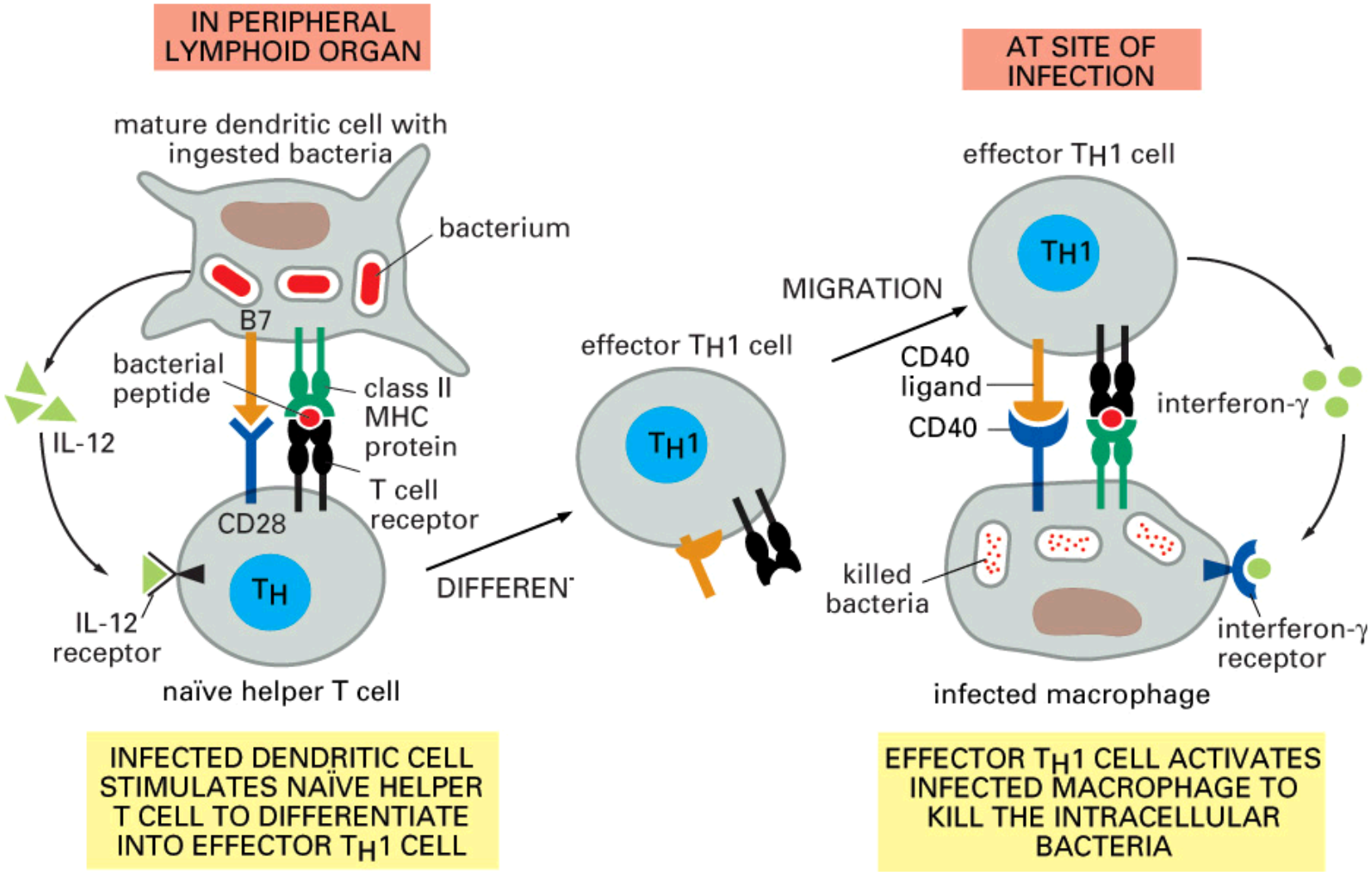


Class I

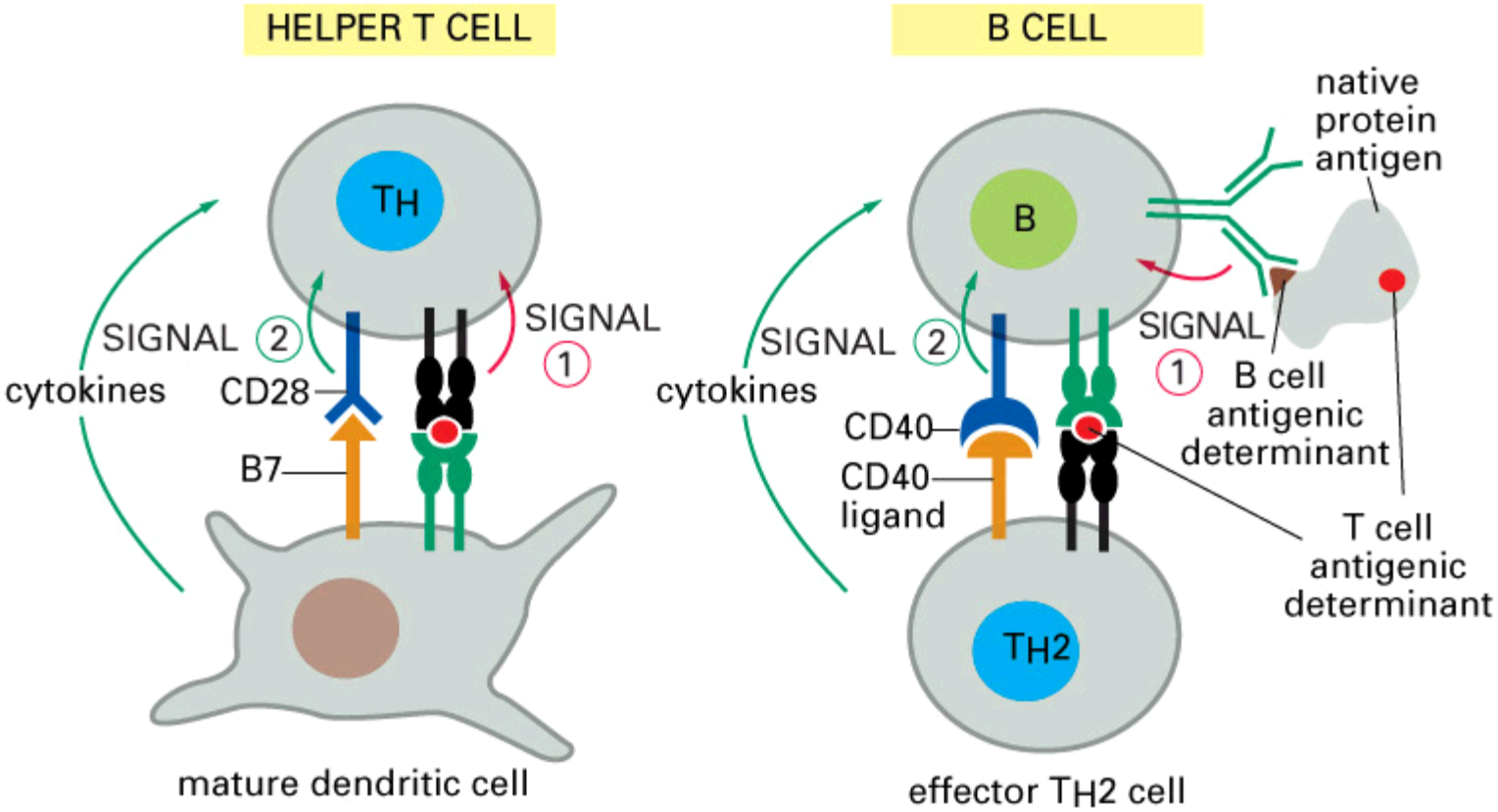
Class II



Th1 Helper Cells (macrophage/inflammatory)



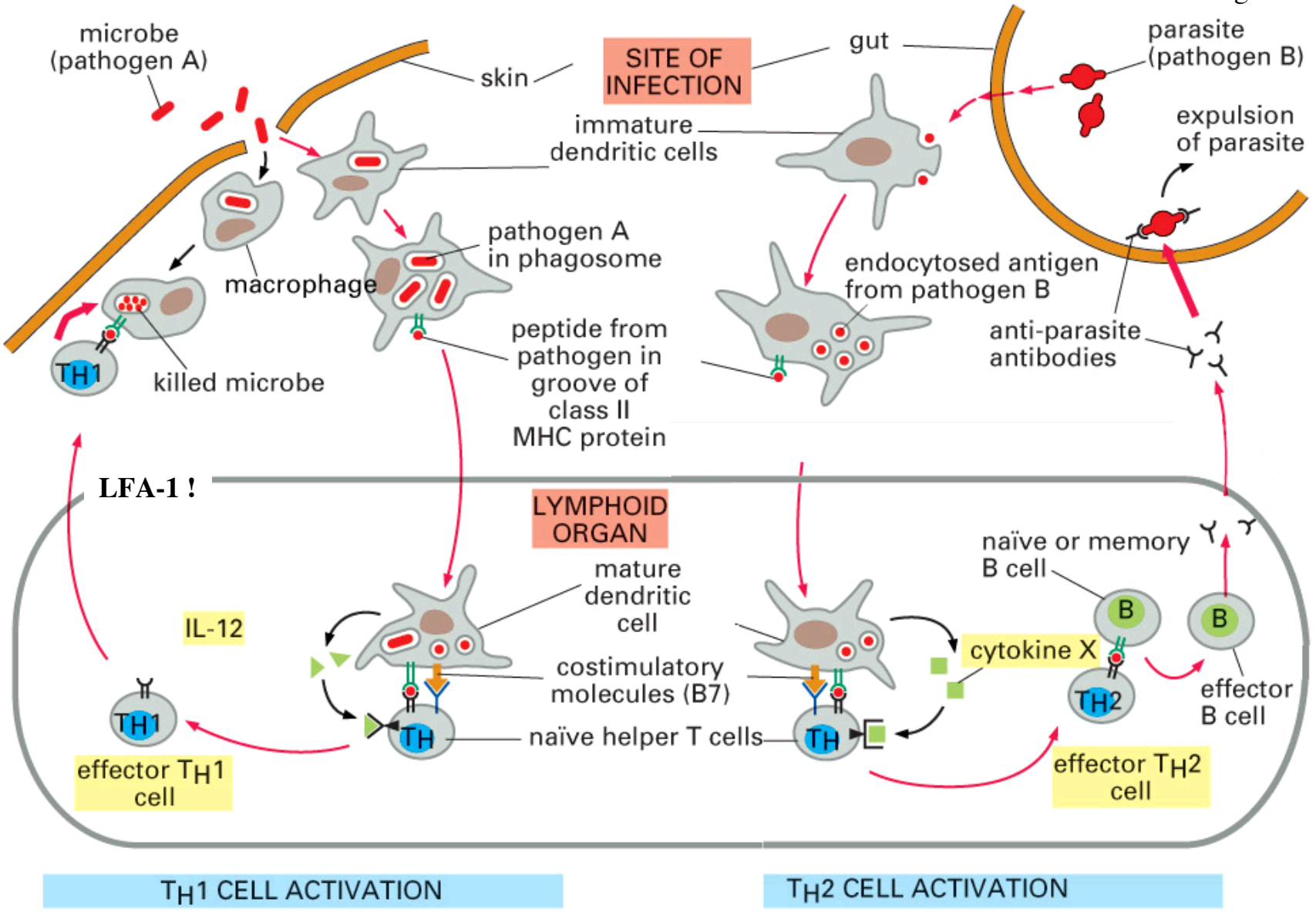
Th2 Helper Cells (B cell response)



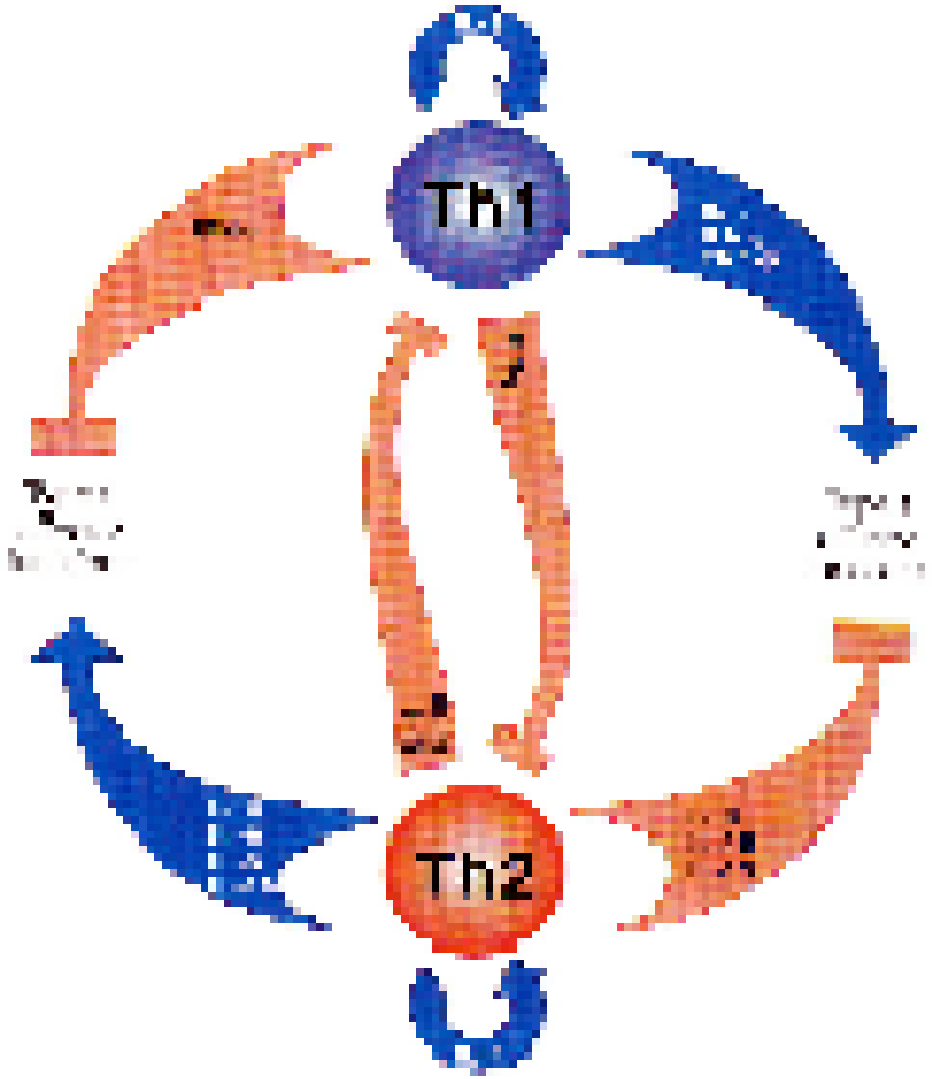
also mast cell degranulation and
eosinophil activation
high [antigen], nonprofessional

Th1 vs. Th2 Maturation

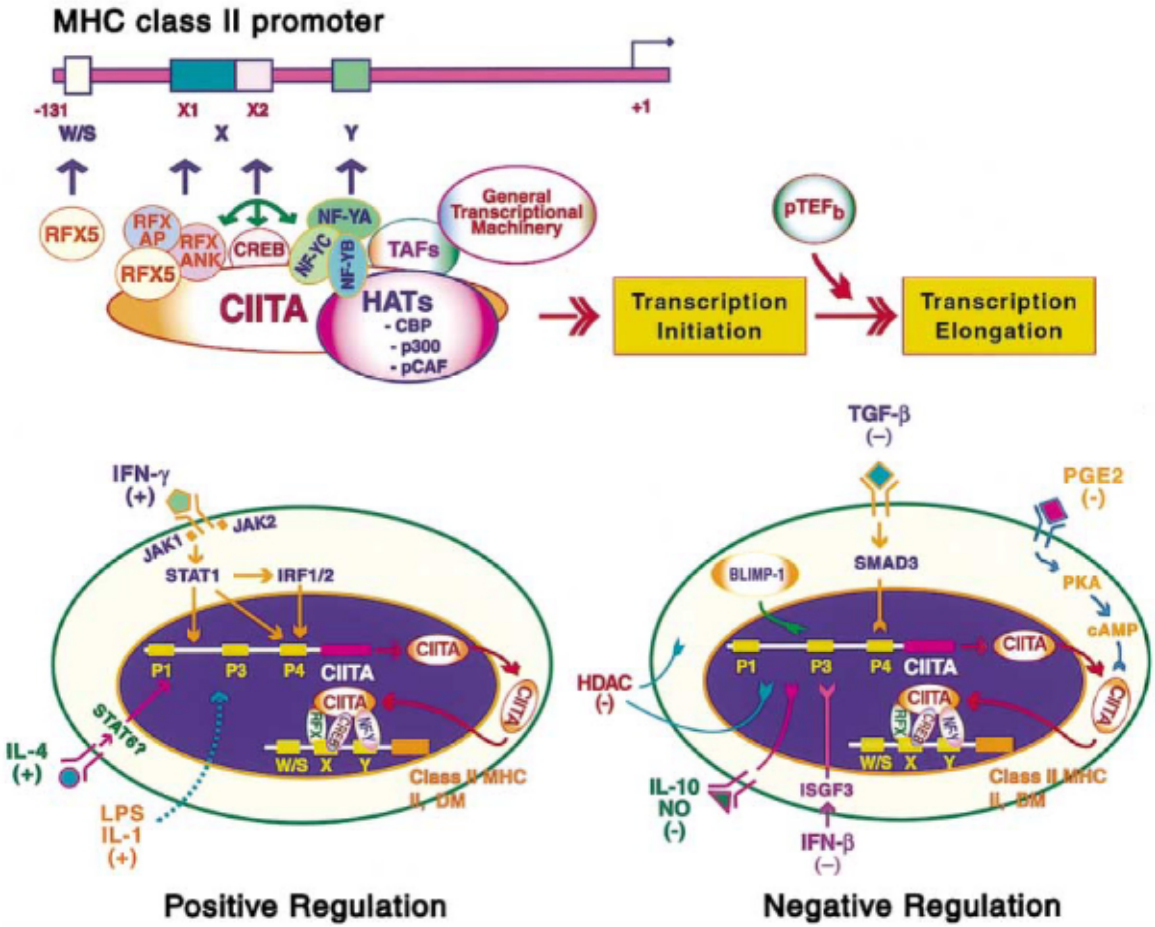
extracellular pathogens
e.g. helminths
also oral antigens



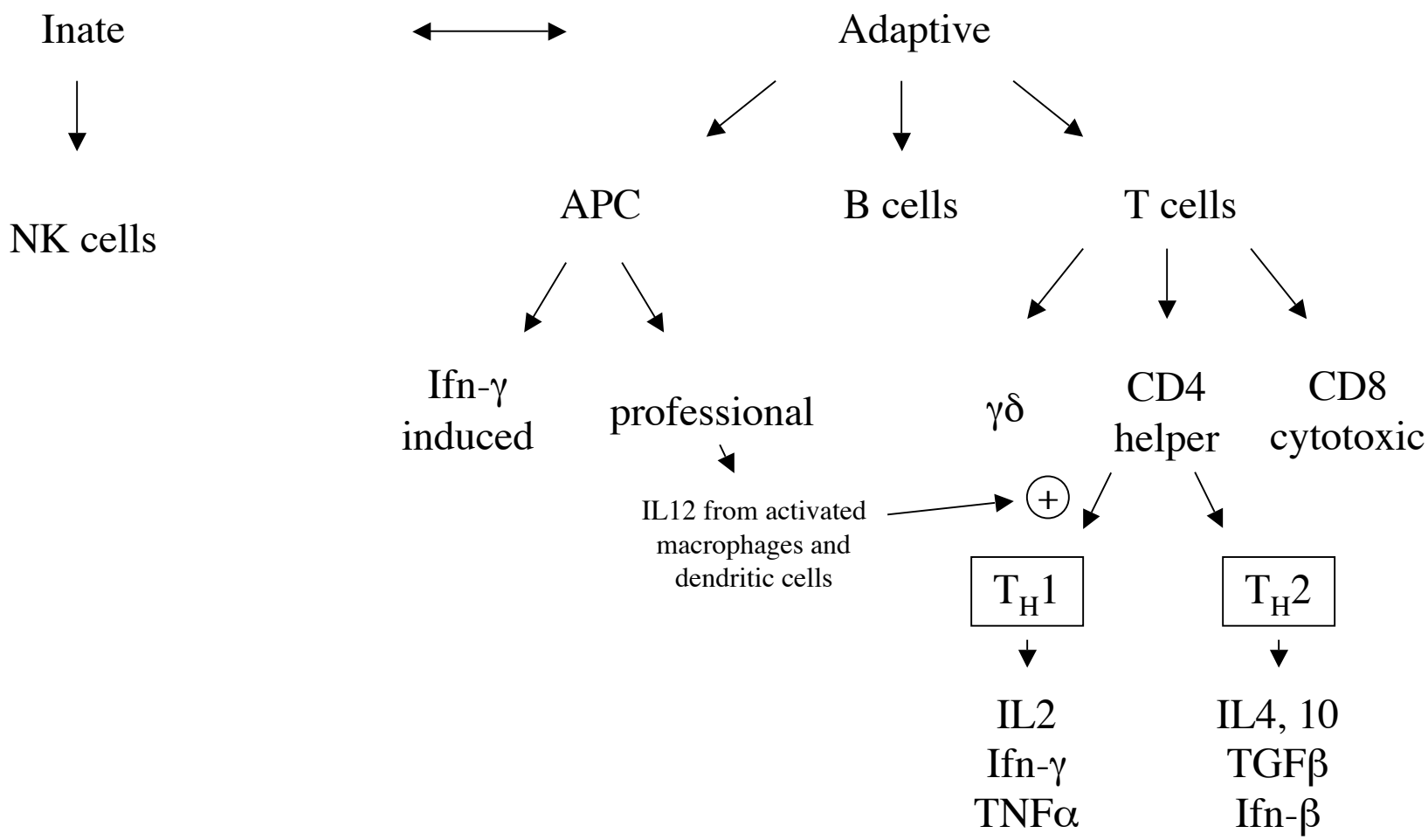
Th1 vs. Th2 Antagonism



MHC II Transcription by CIITA



Immune System Overview



How Do Statins Work?

Reported to:

- Decrease occurrence of AD by 70% in retrospective study
- Suppress MS (clinical trials)
- Block SMC proliferation/migration *in vitro*
- Modulate NF-κB Function *in vitro*
- Block IFN-γ induced MHCII expression *in vitro*
- Suppress expression/secretion of immunoinflammatory molecules *in vitro*
- Direct inhibition of LFA-1

Most *in vitro* effects reversed by mevalonate, *trans*F, *trans*GG, but not *cis*F, *cis*GG, squalene, isopentyl adenosine or ubiquinone

Youssef, S. *et al.* "The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease." *Nature* **420**: 78-84 (2002).

Soutschek J *et al.* "Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs." *Nature*. **432**(7014):173-8 (2004).

Uauy, R., Vega, G.L., Grundy, S.M. & Bilheimer, D.M. "Lovastatin therapy in receptor-negative homozygous familial hypercholesterolemia: lack of effect on low-density lipoprotein concentrations or turnover." *J Pediatr* **113**: 387-392 (1988).