CD4+ subsets

ADAPTIVE IMMUNE RESPONSE

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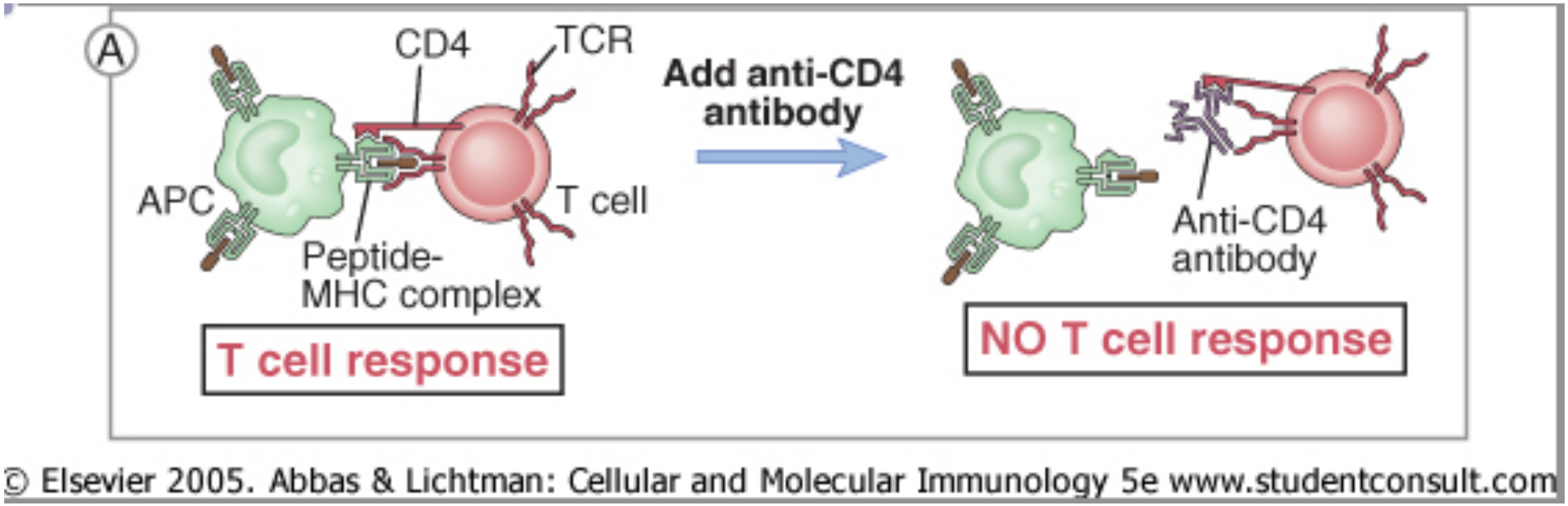
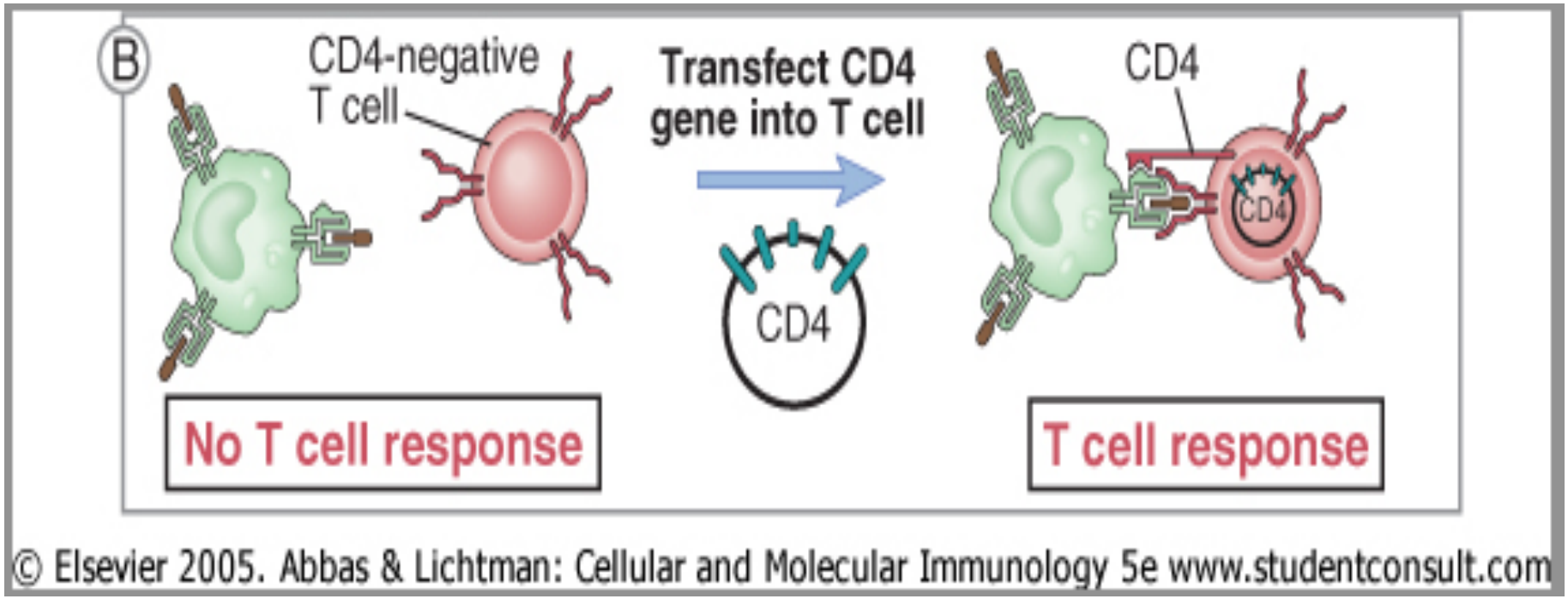
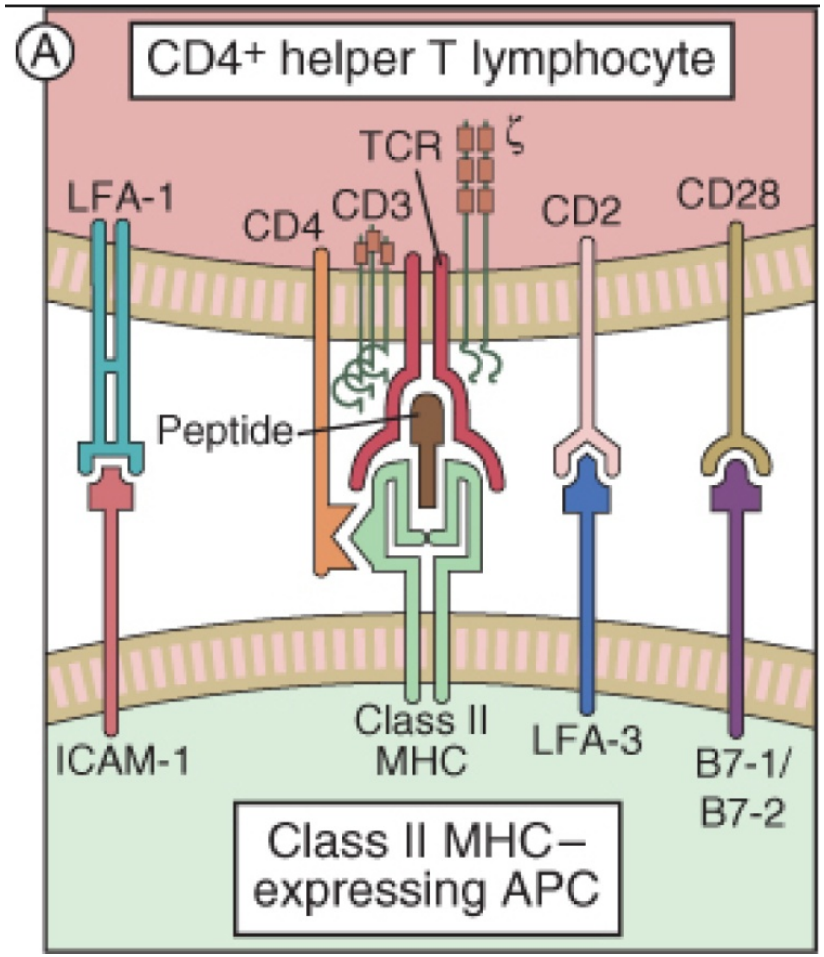
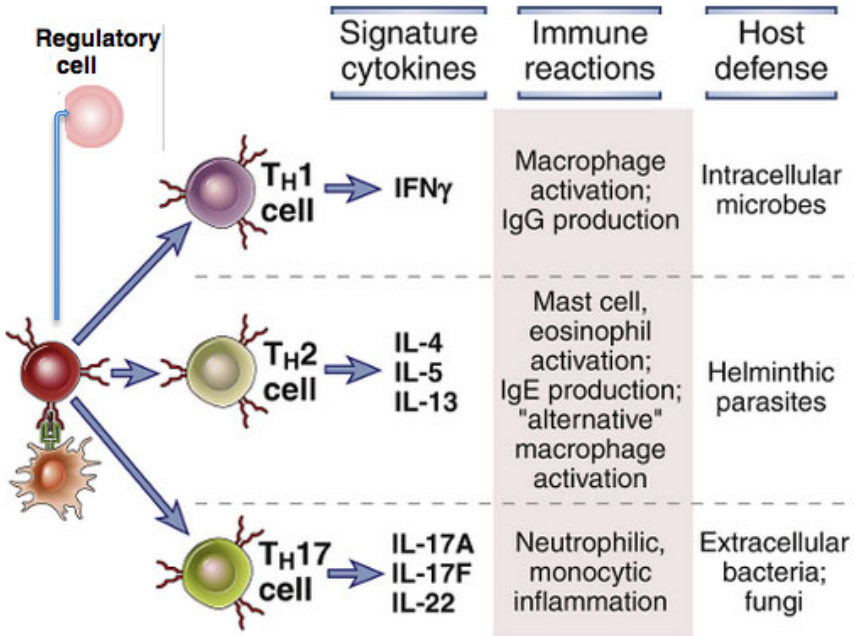
SAPIENZA
UNIVERSITÀ DI ROMA

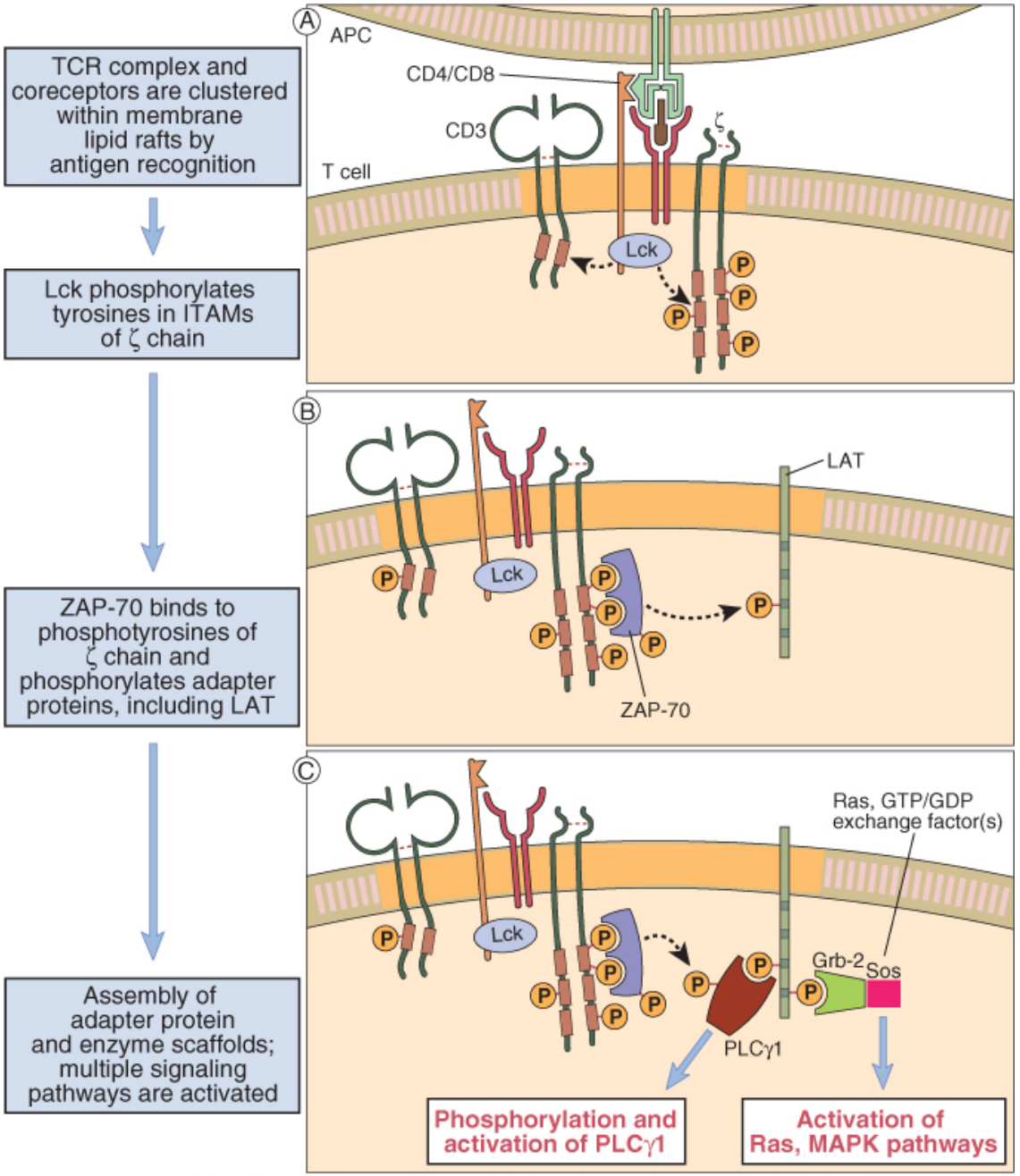




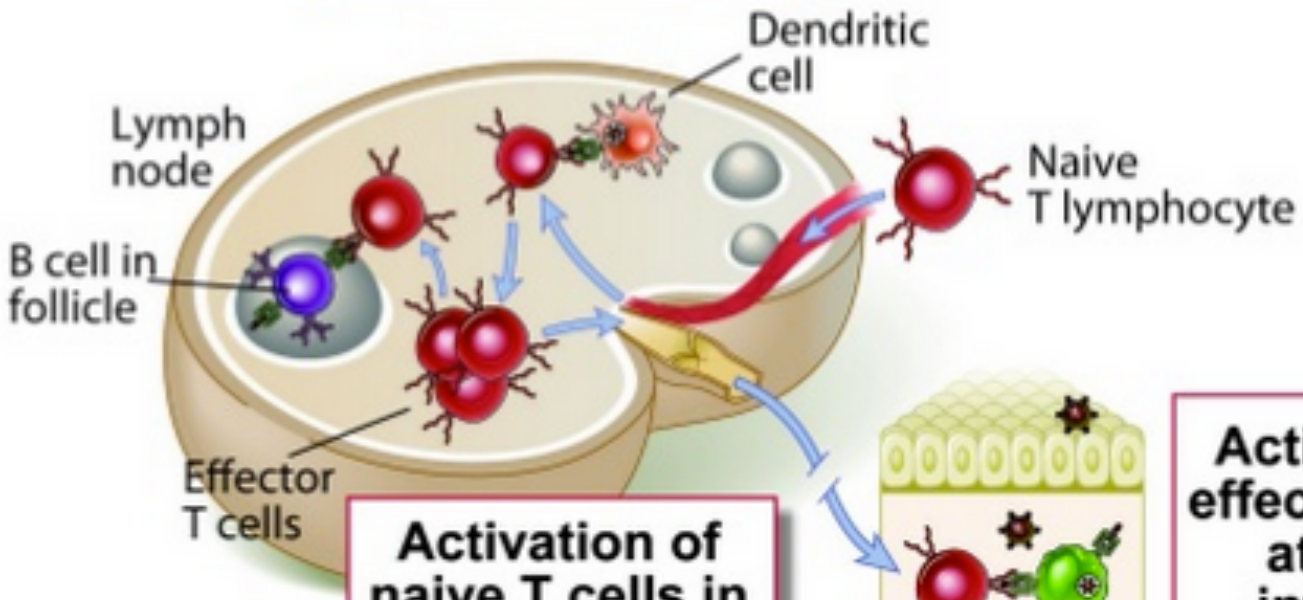
Different subsets of CD4+ cells







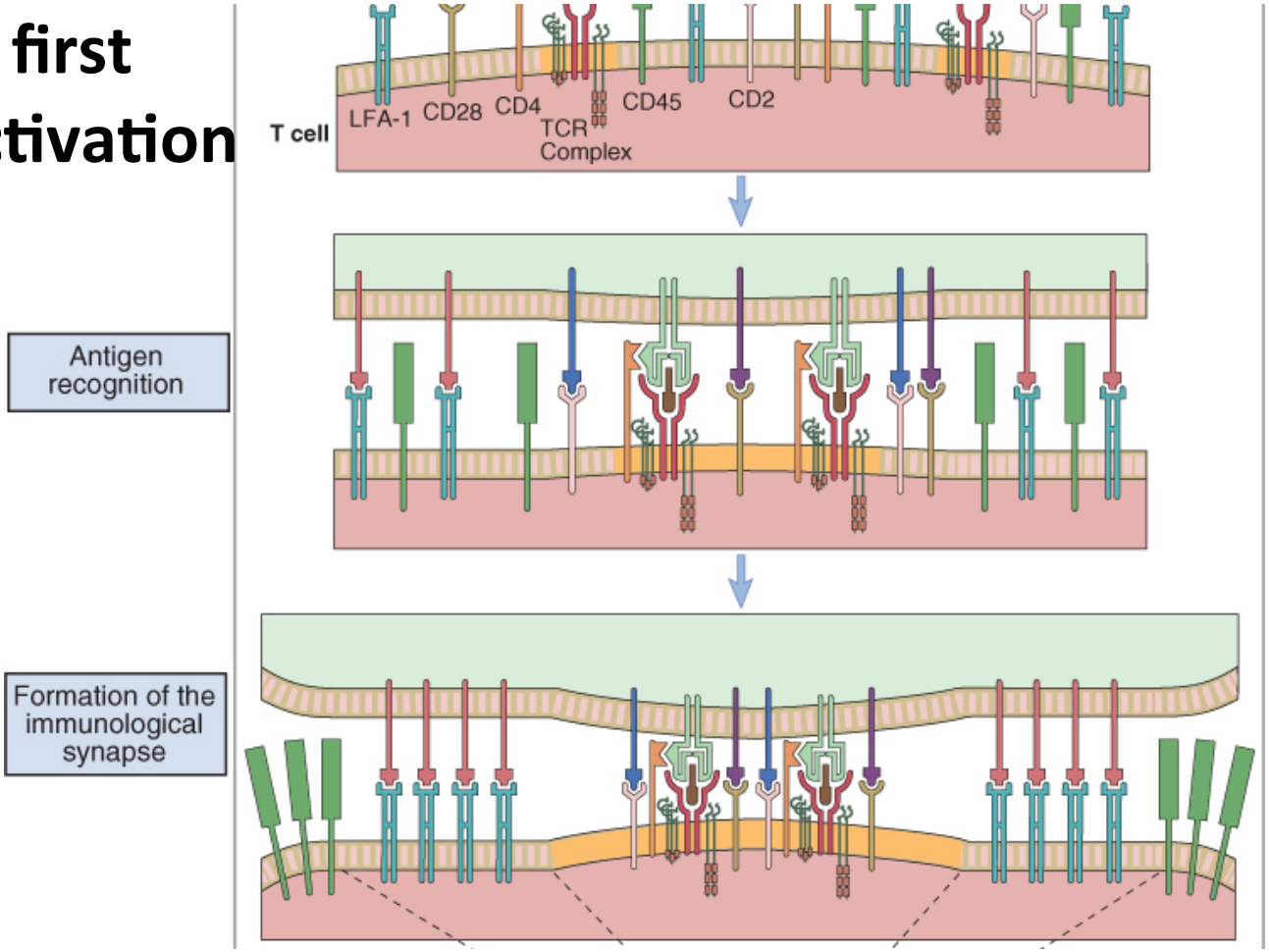
Niave T cells circulate through lymph nodes and find antigens



Activation of naive T cells in lymph node, development of effector cells

Activation of effector T cells at site of infection; eradication of microbe

IMMUNE SYNAPSES: first signal of activation



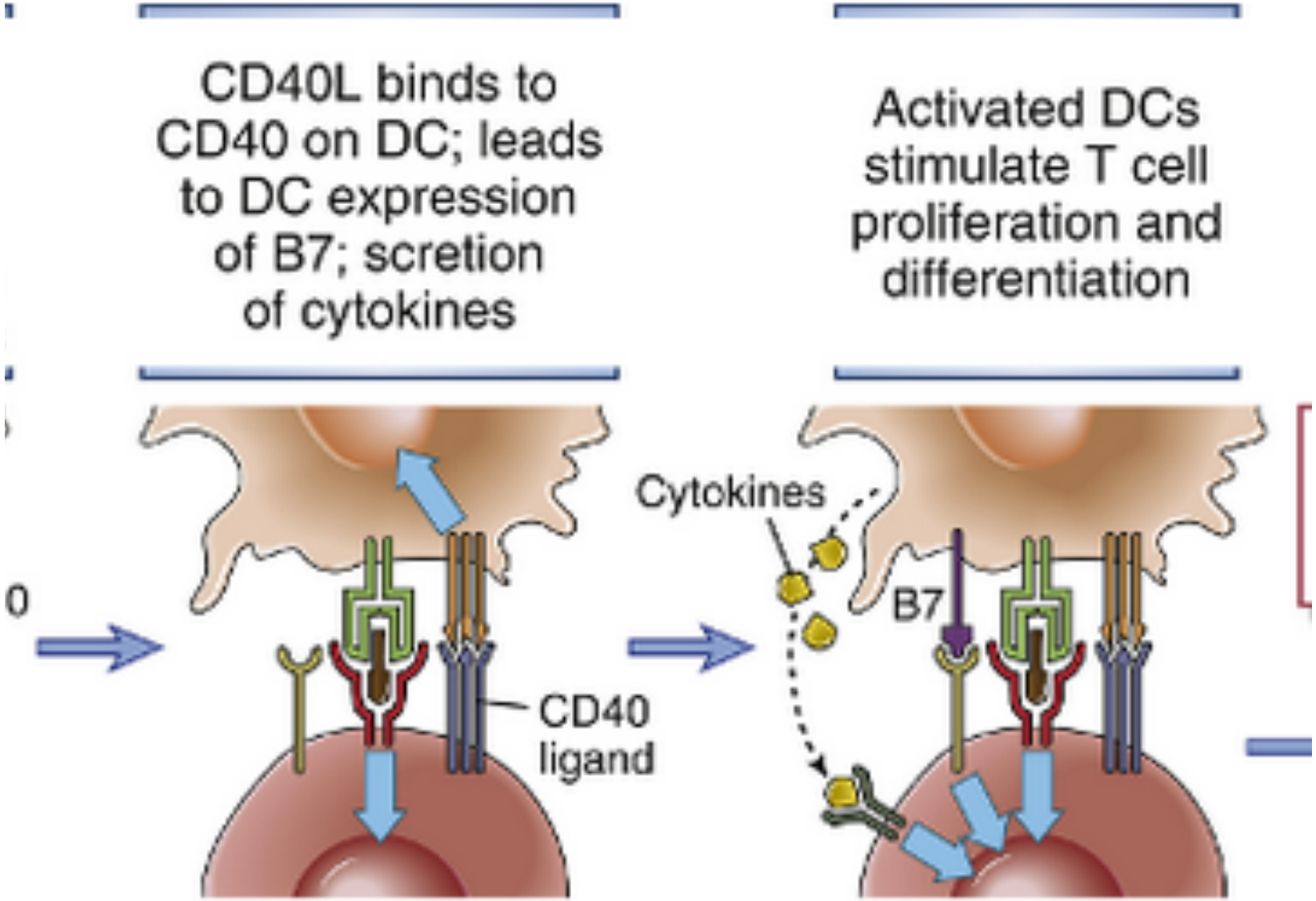
SupraMolecular Activation Cluster

Molecules in Immune synapses are: TCR complex (TCR AND CD3), co-receptor CD4 or CD8, co-activator receptors CD28, integrins.

The central part of the synapses is called central SMAC, the distance beetwen APC and T cell is 15nm.

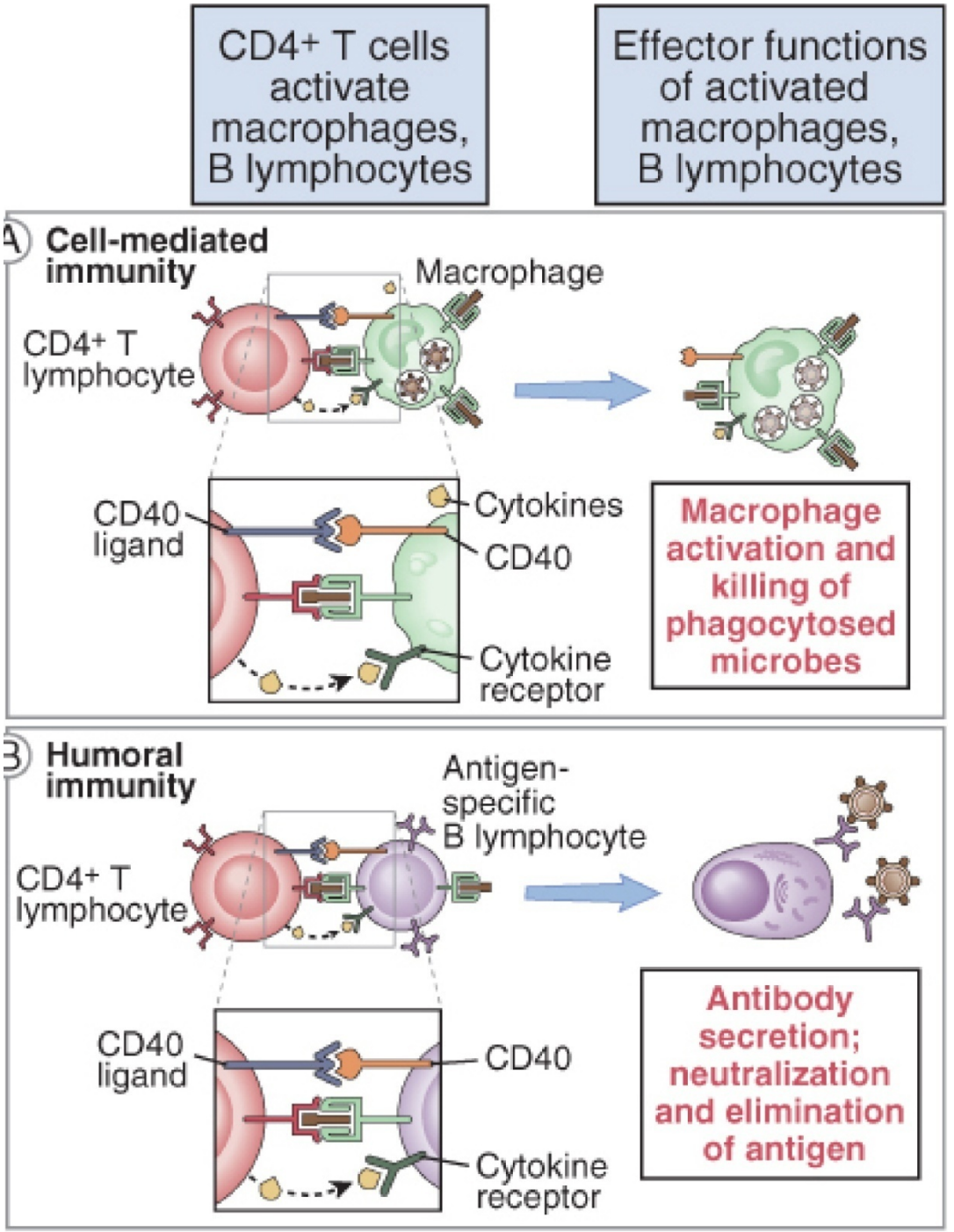
At the sides where integrins are, the distance is 40nm.

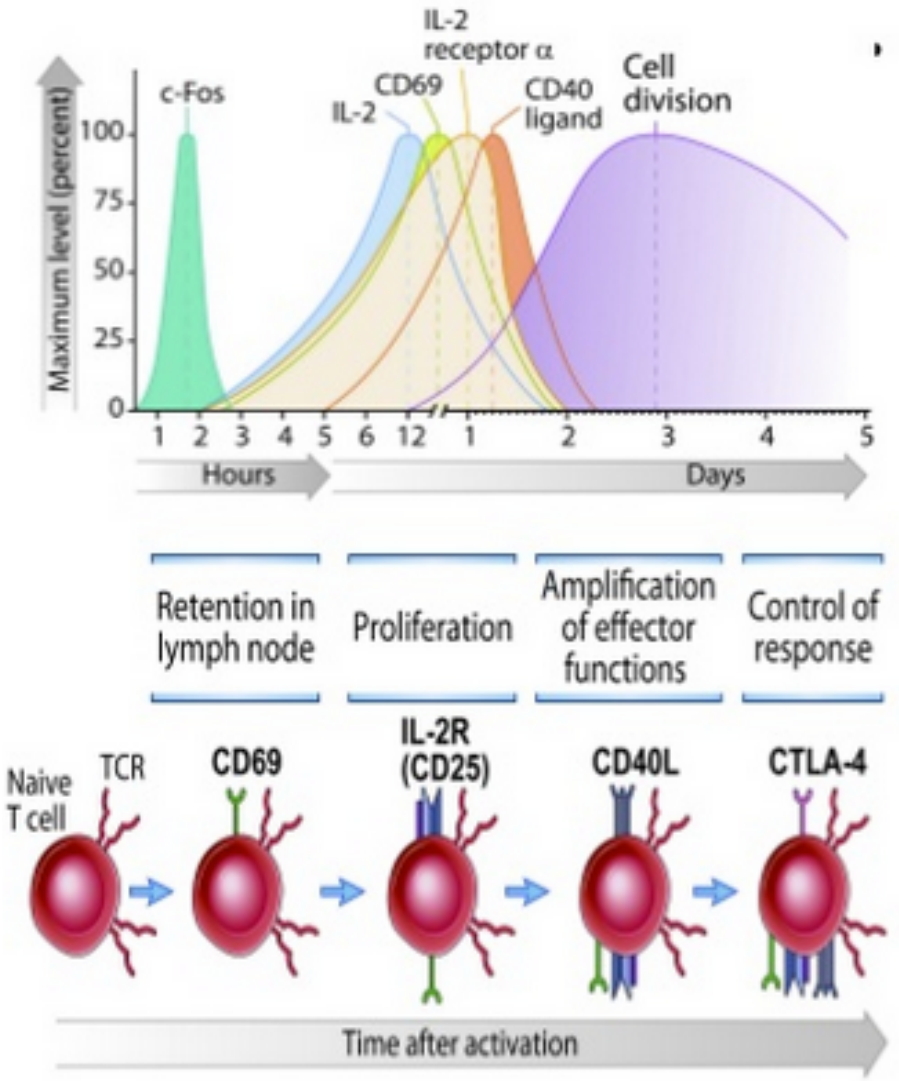
SECOND SIGNAL



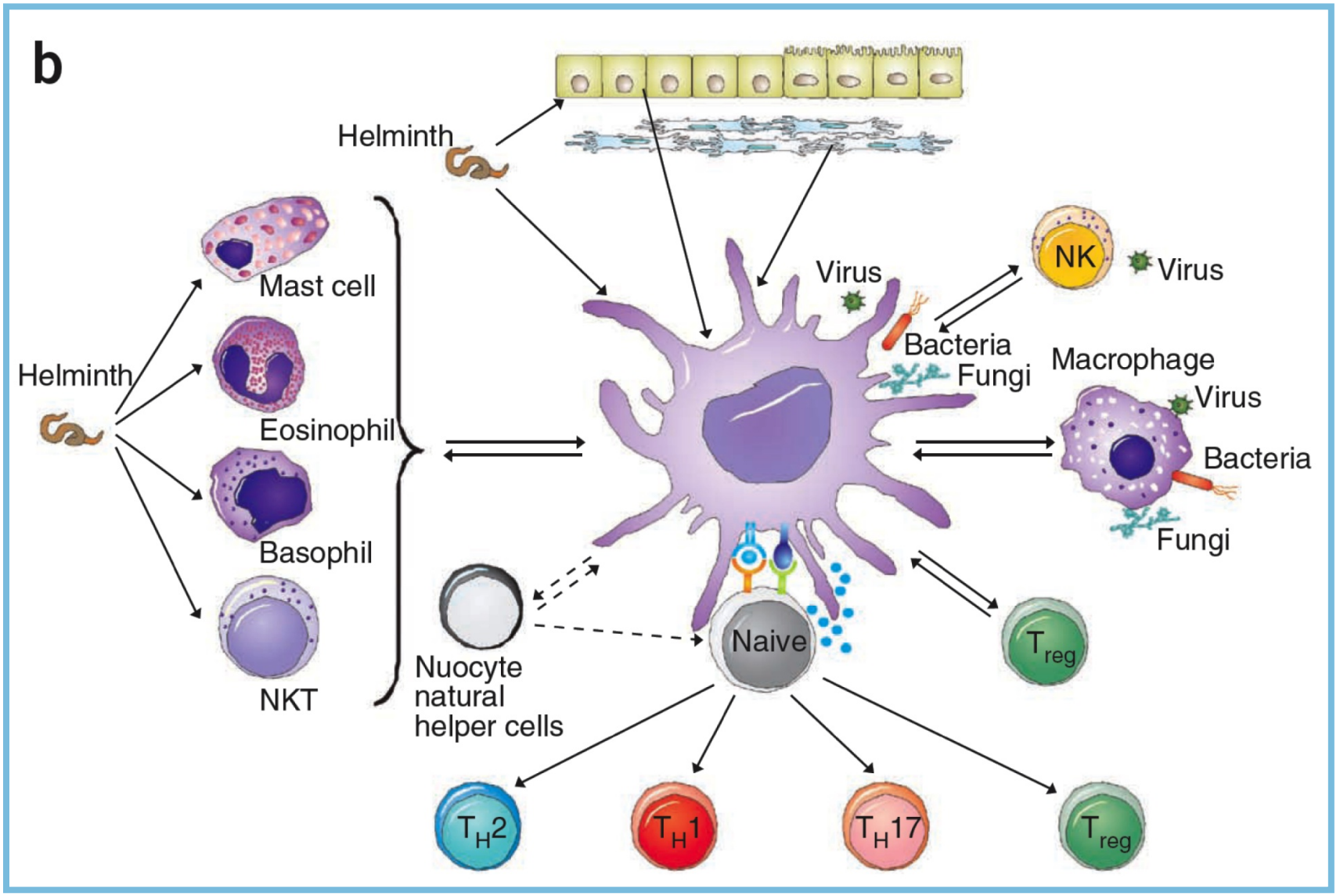
Helper T cells modulate cell functions through cytokine secretion and CD40-CD40L interaction

CD40L is induced on T cells by antigen recognition

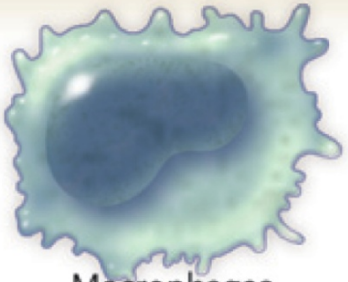
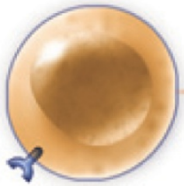
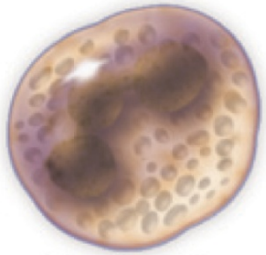
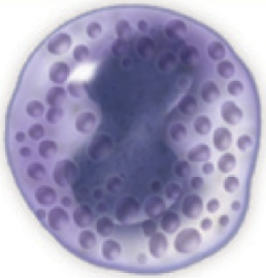



IL-2 receptor α
c-Fos
CD69
IL-2
CD40 ligand
Cell division
Maximum level (percent)
100
75
50
25
0
1 2 3 4 5 6 12 1 2 3 4 5
Hours
Days
Retention in lymph node
Proliferation
Amplification of effector functions
Control of response
Naive T cell
TCR
CD69
IL-2R (CD25)
CD40L
CTLA-4
Time after activation

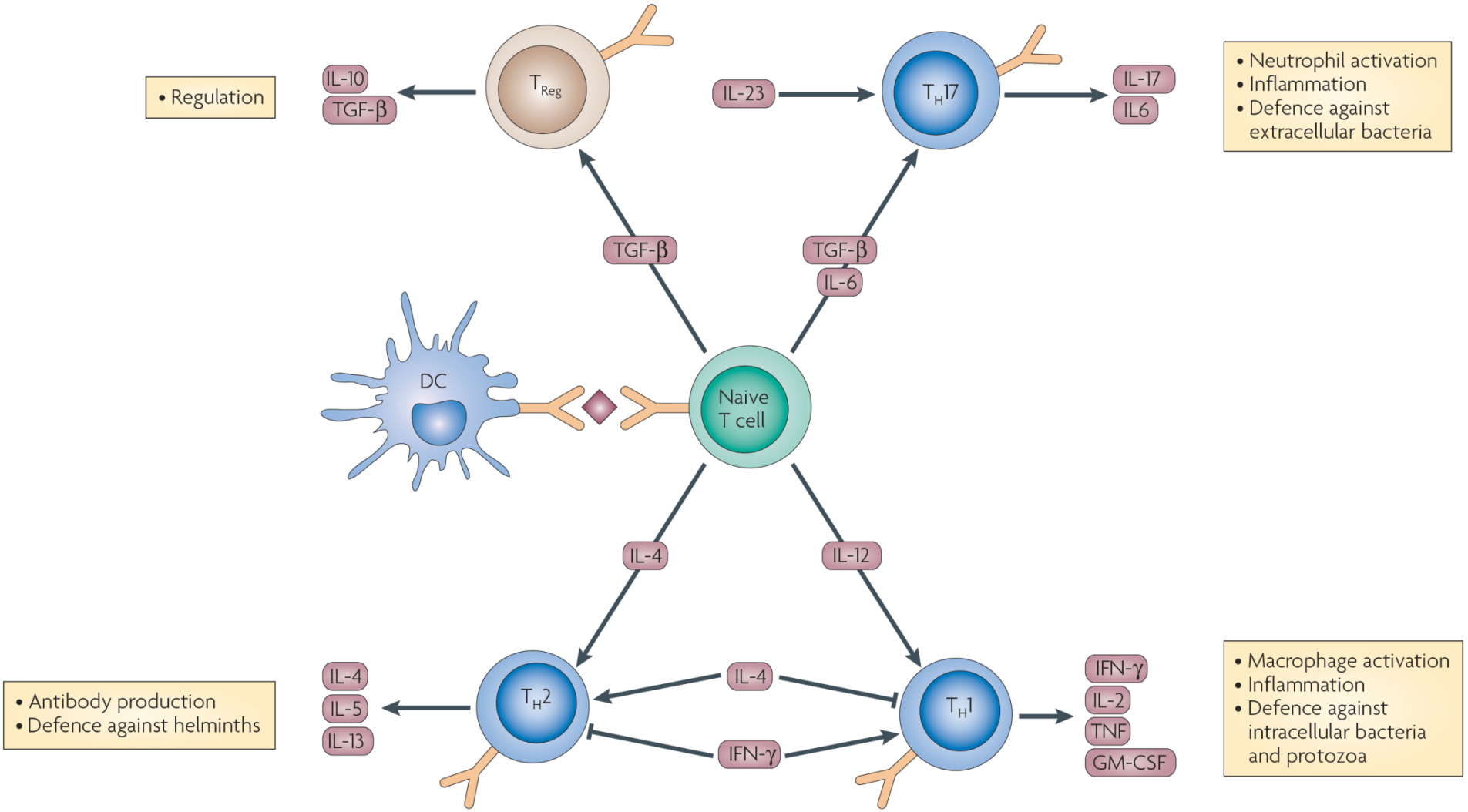
DCs can sense microbes directly but also indirectly (through immune cells and tissue cells), and integrate this information to orchestrate the response



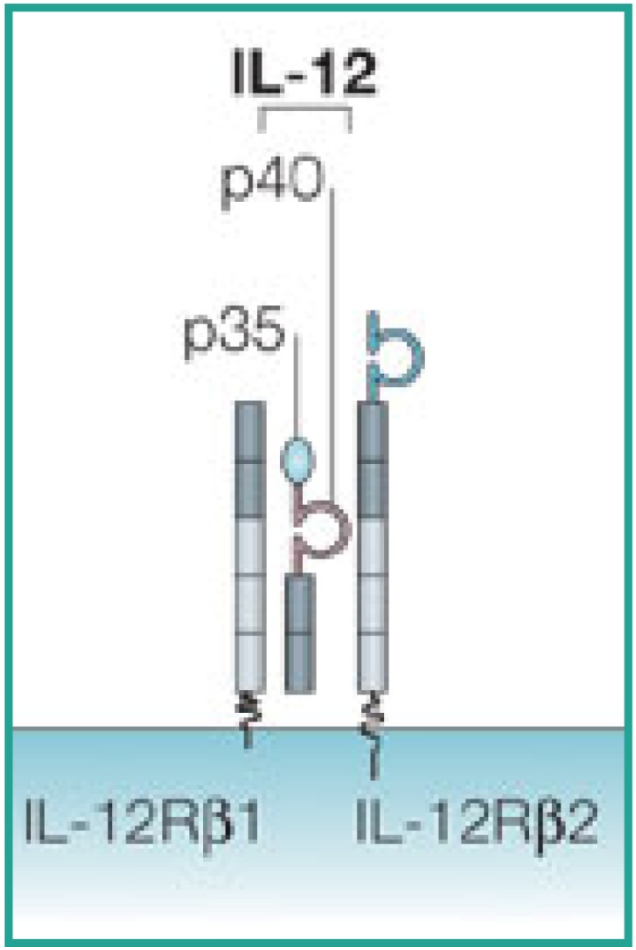
Helper T cell subgroups and effector functions

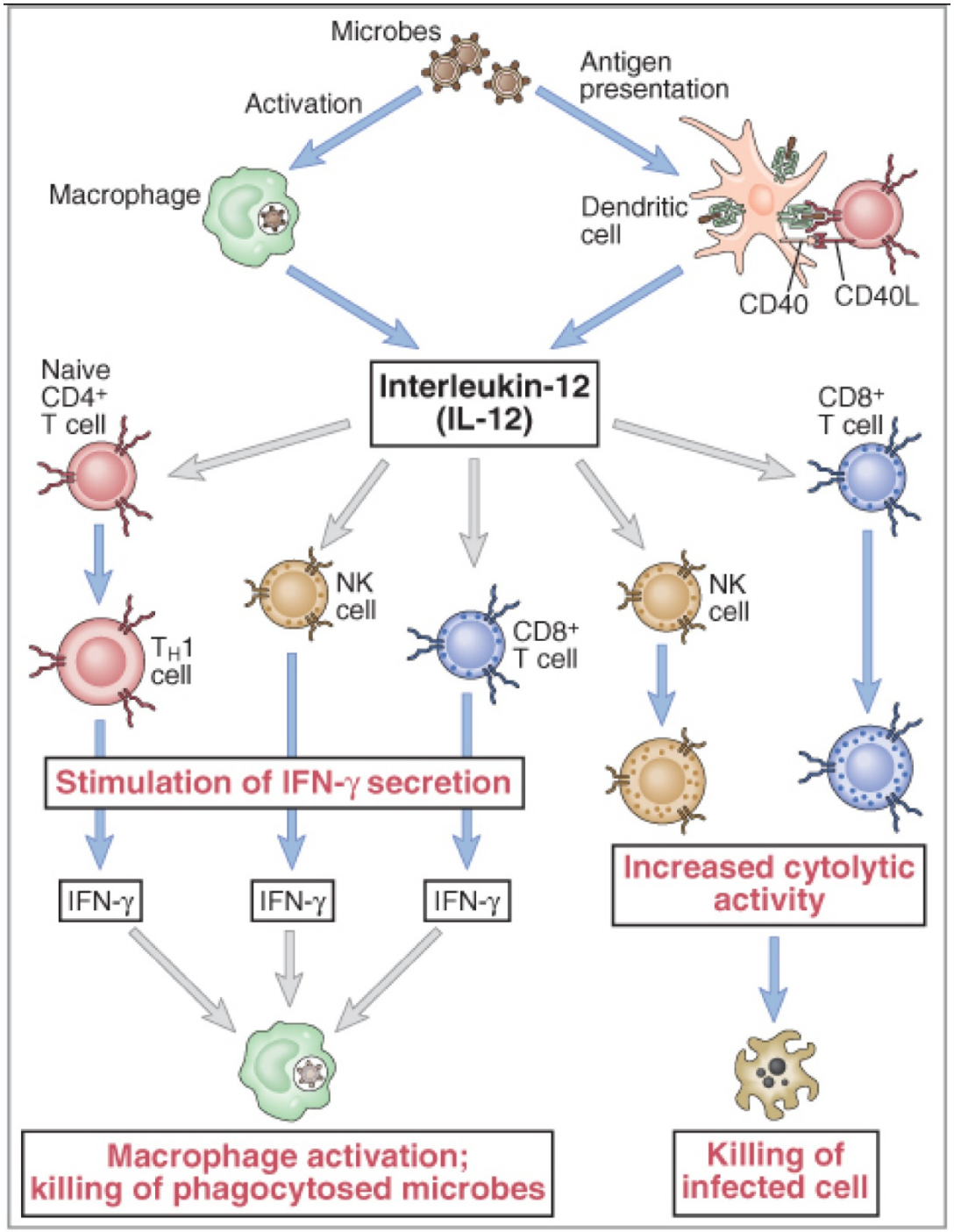
Th Group	Cell Products	Cell Target	Infectious Agents
Th1	 Interferon-γ Interleukin-2 Interleukin-12R	 Macrophages Dendritic cells	Intracellular bacteria Fungi Viruses
Th17	 Interleukin-17A Interleukin-17F Interleukin-21 Interleukin-22 Interleukin-23R	 Neutrophils	Extracellular bacteria Fungi
Th2	 Interleukin-4 Interleukin-13 Interleukin-5 Interleukin-4R	 Eosinophils Basophils	Parasites

Different subpopulations of CD4+ T cells

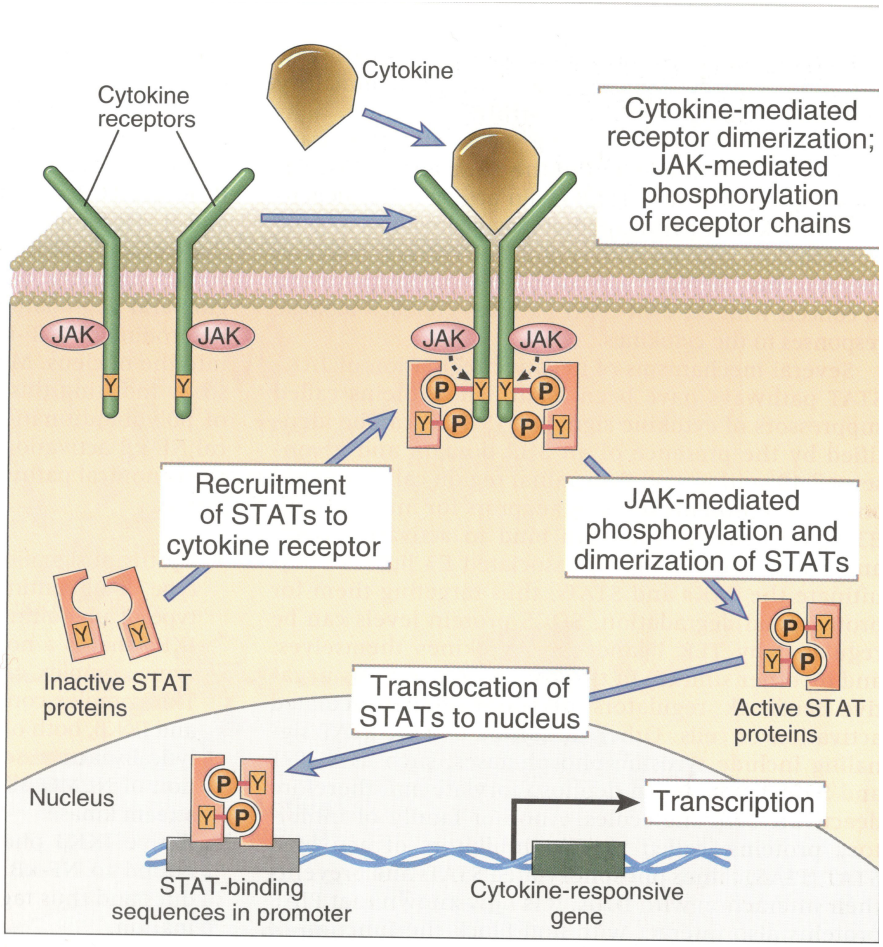


IL-12 is the major TH1-polarizing cytokine

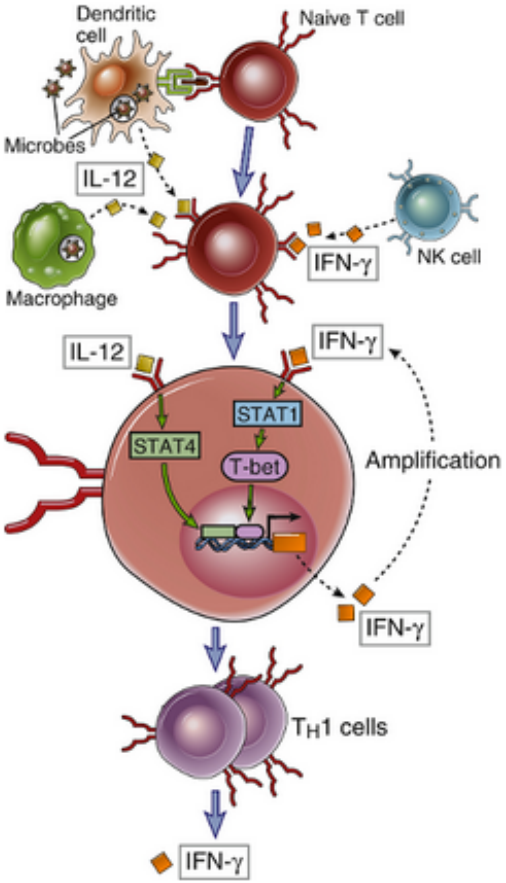


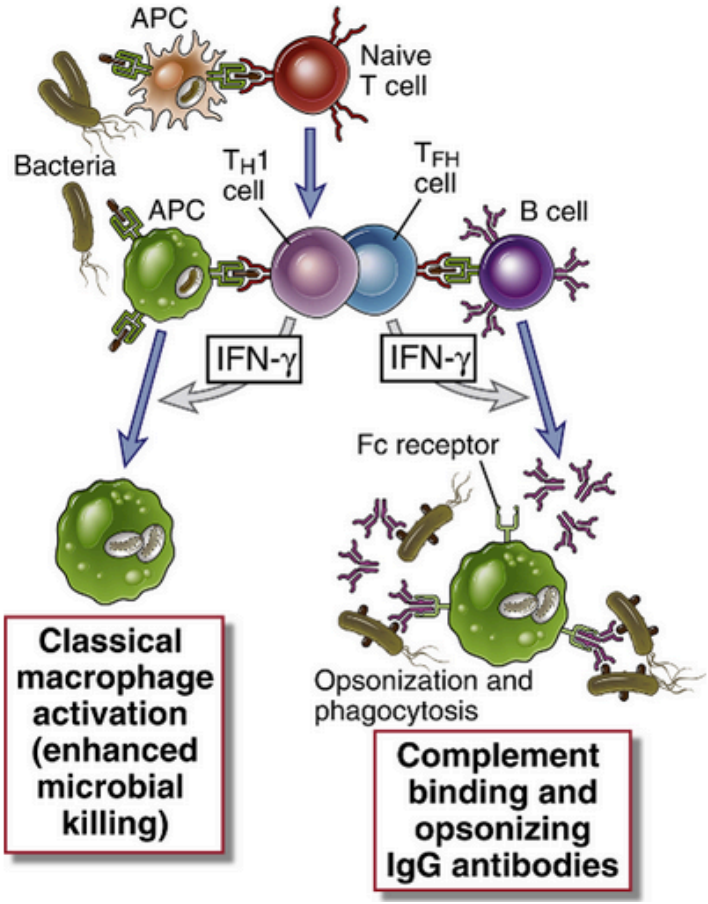


Transcription factors



TH1 SUBSET


Dendritic cell
Naive T cell
Microbes
IL-12
Macrophage
IFN-γ
NK cell
IL-12
IFN-γ
STAT1
STAT4
T-bet
Amplification
IFN-γ
TH1 cells
IFN-γ


APC
Naive T cell
Bacteria
TH1 cell
TFH cell
APC
B cell
IFN-γ
IFN-γ
Fc receptor
Classical macrophage activation (enhanced microbial killing)
Opsonization and phagocytosis
Complement binding and opsonizing IgG antibodies

Intracellular bacteria

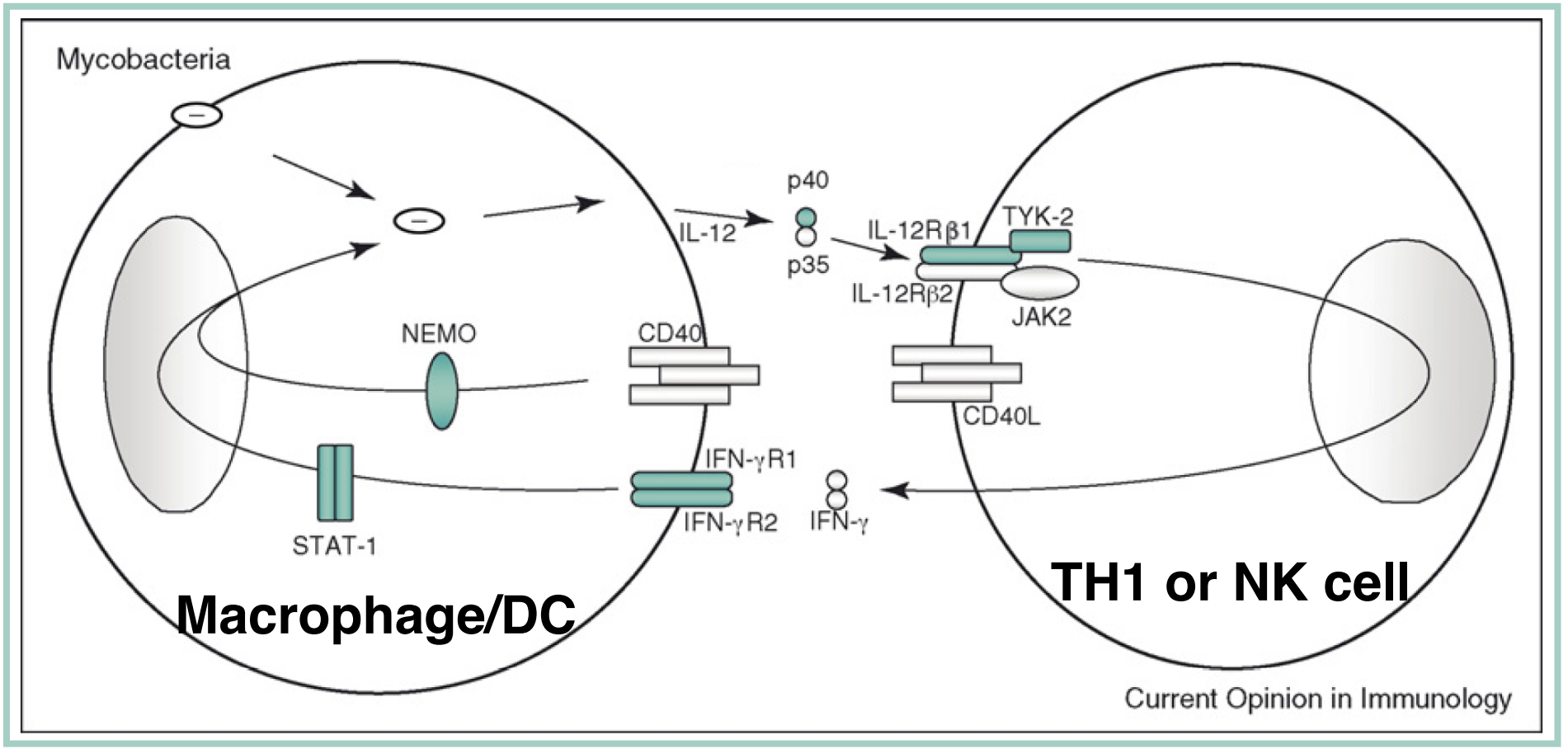
Facultative

- ***Legionella pneumophila***: It prefers intracellular environment of macrophages for growth. *Legionella*induce its own uptake and blocks lysosomal fusion by undefined mechanism.
- ***Listeria monocyotogenes***: Listeria quickly escapes the phagosome into the cytoplasm **before** phagosome-lysosome fusion.
- ***Salmonella*** : Very resistant to intracellular killing by phagocytic cells.
- **Invasive *Escherichia coli***
- ***Neisseria ,*** **Brucella, *Shigella***

Obligate

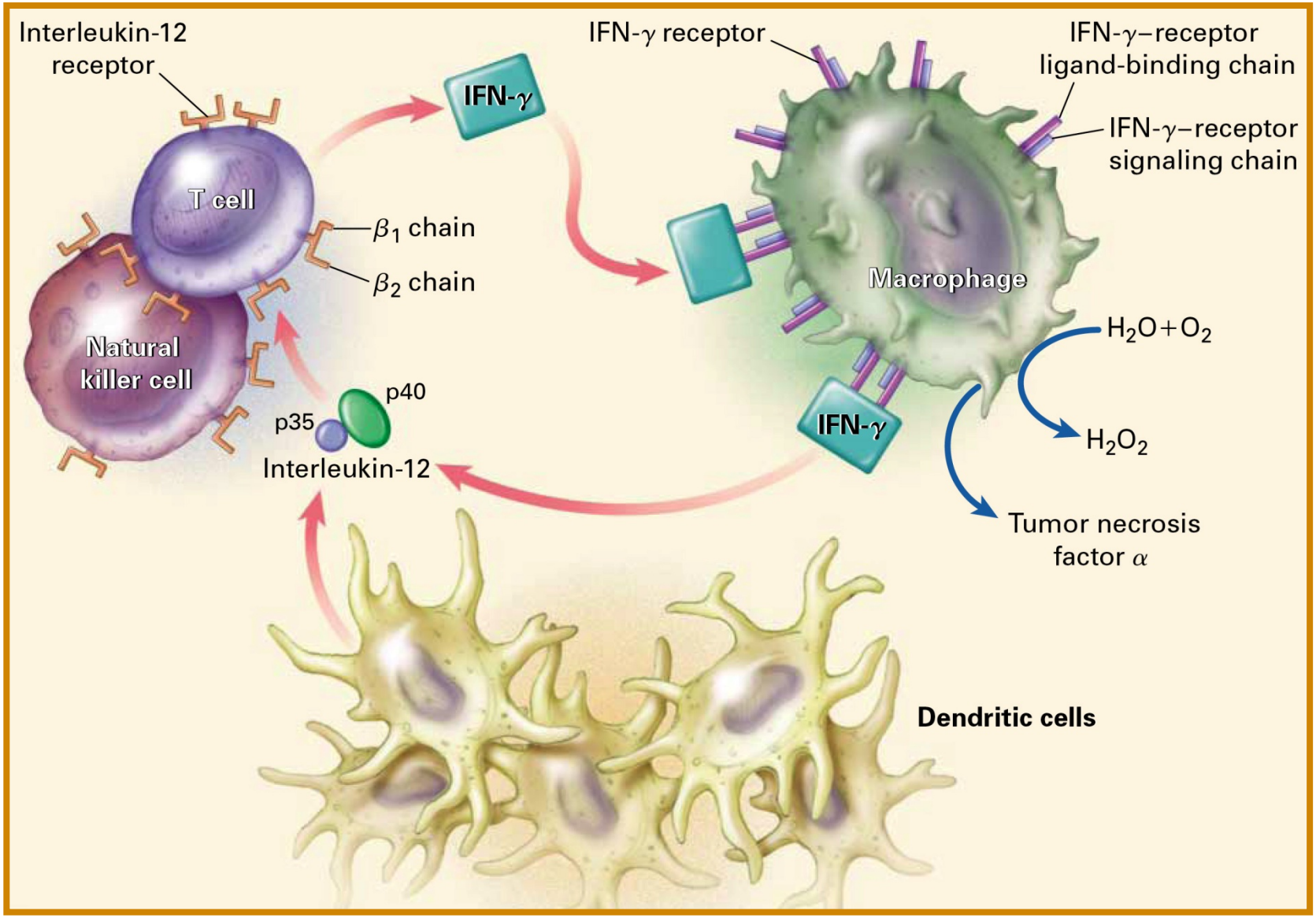
- ***Mycobacterium leprae***
- ***Mycobacterium tuberculosis***:inhibits phagosome-lysosome fusion.
- ***Coxiella burnetti*****:** metabolic activity greatly increased in the acidic environment of the phagolysosome.
- ***Ricekettsia, Toxoplasma, Cryptosporidium, Plasmodium, Leishmania, Babesia and Trypanosoma,***
- ***Pneumocystis jiroveci*** *is an obligate intracellular fungi.*
- ***Chlamydiae***

Genetic defects of the IL-12/IFN γ axis lead to susceptibility to some intracellular bacteria (mycobacteria, salmonella)

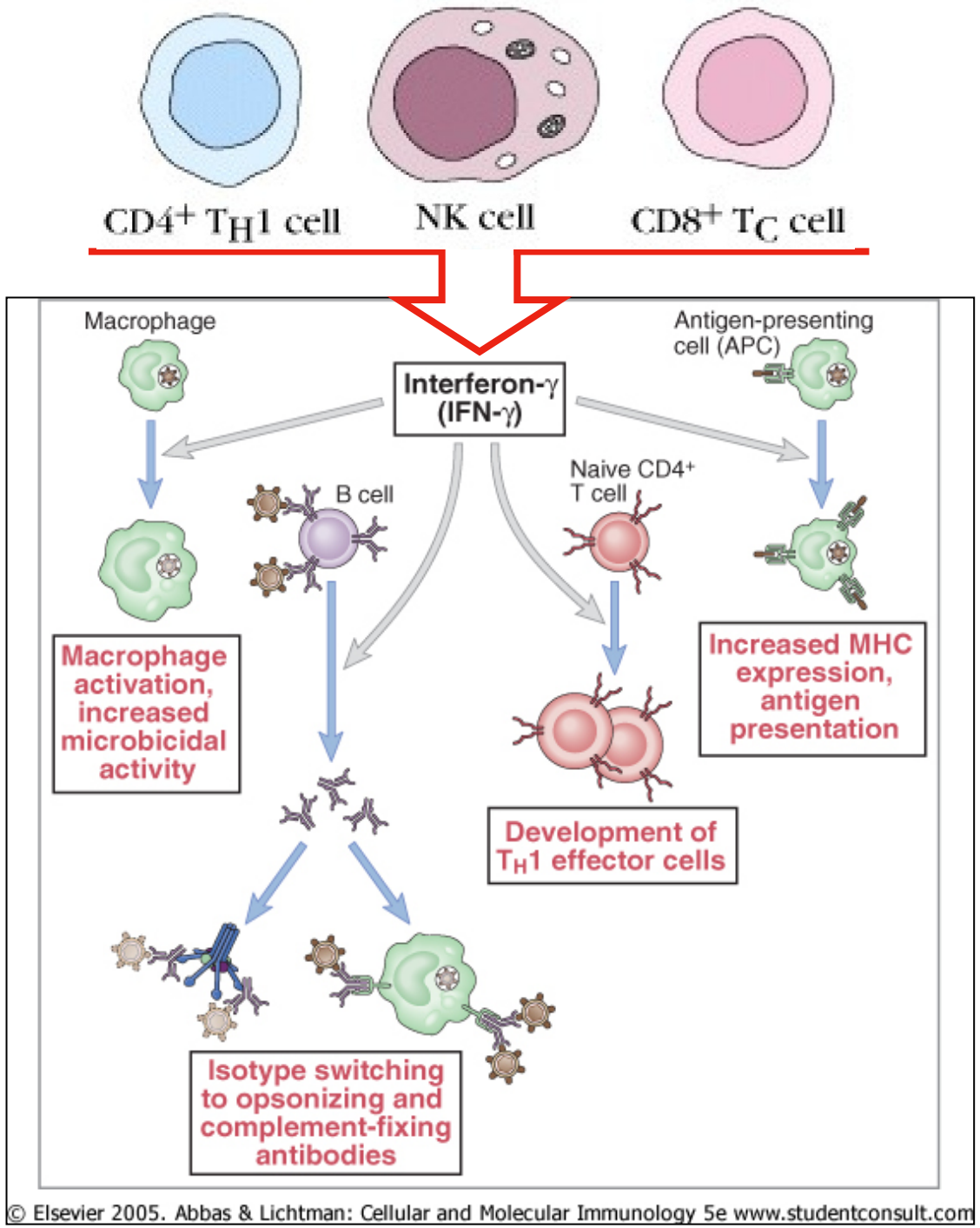


A selective immunodeficiency!

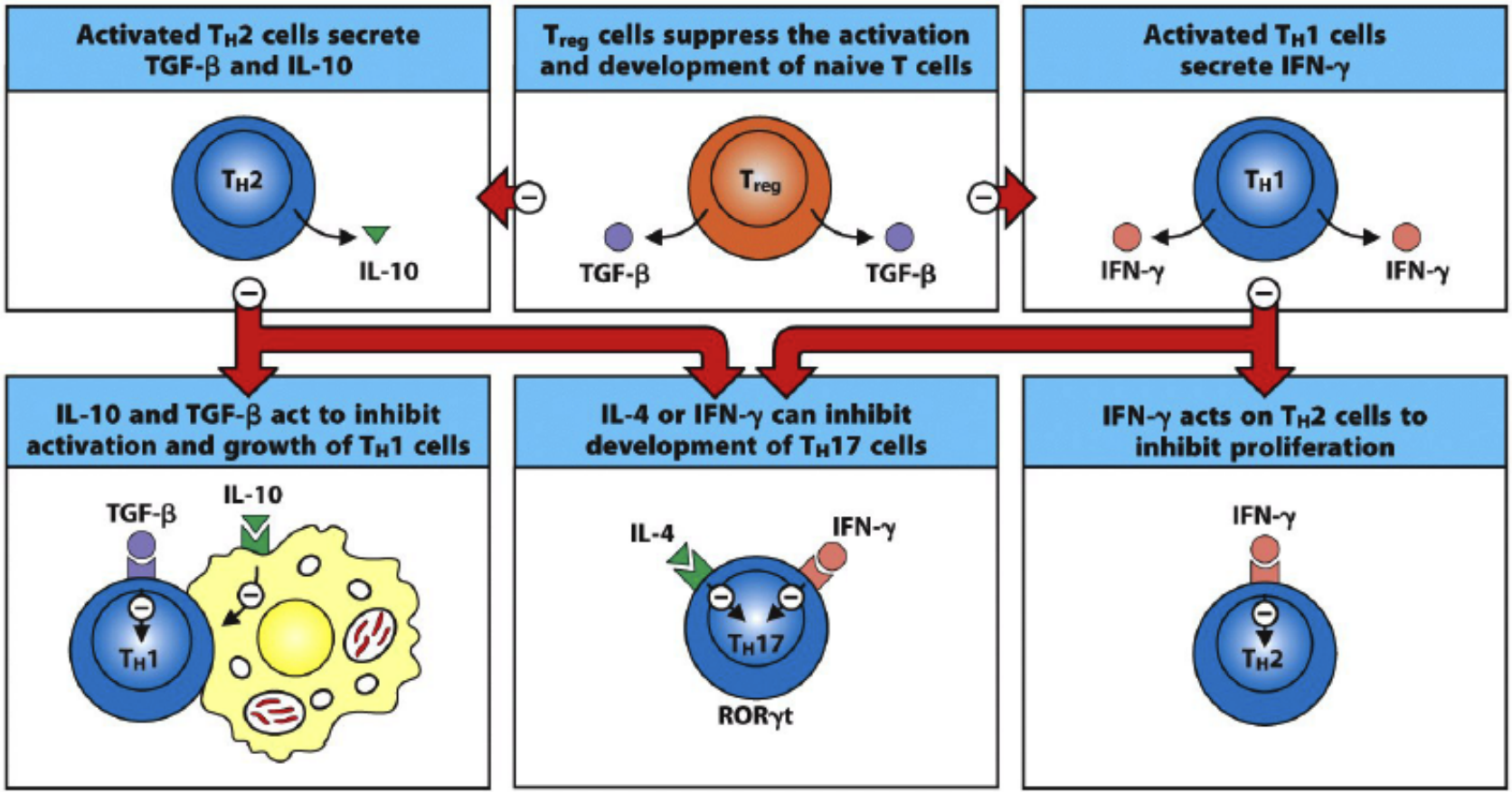
The IFN γ ⟺ IL-12 amplification loop



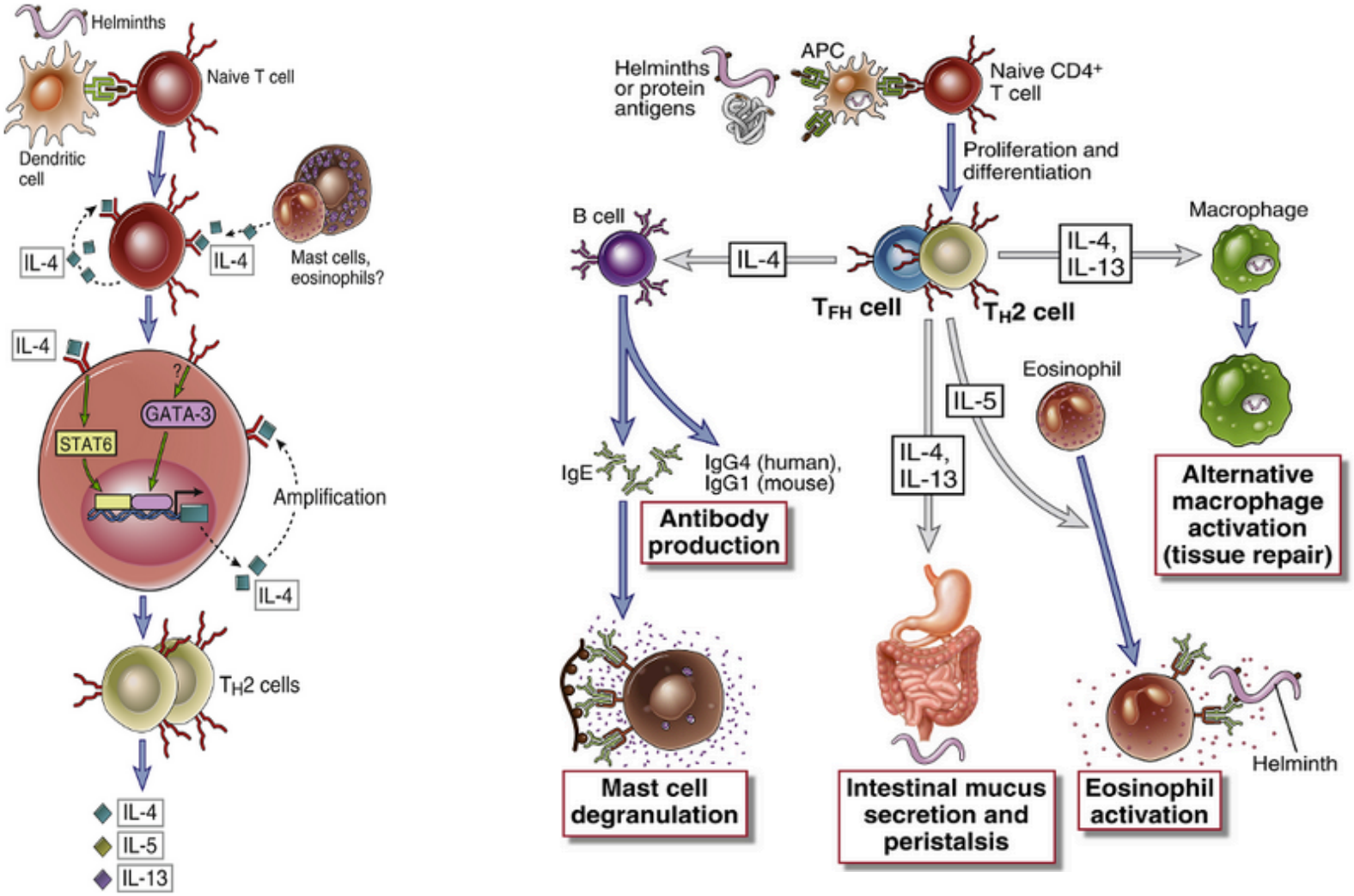
Functions of IFN γ



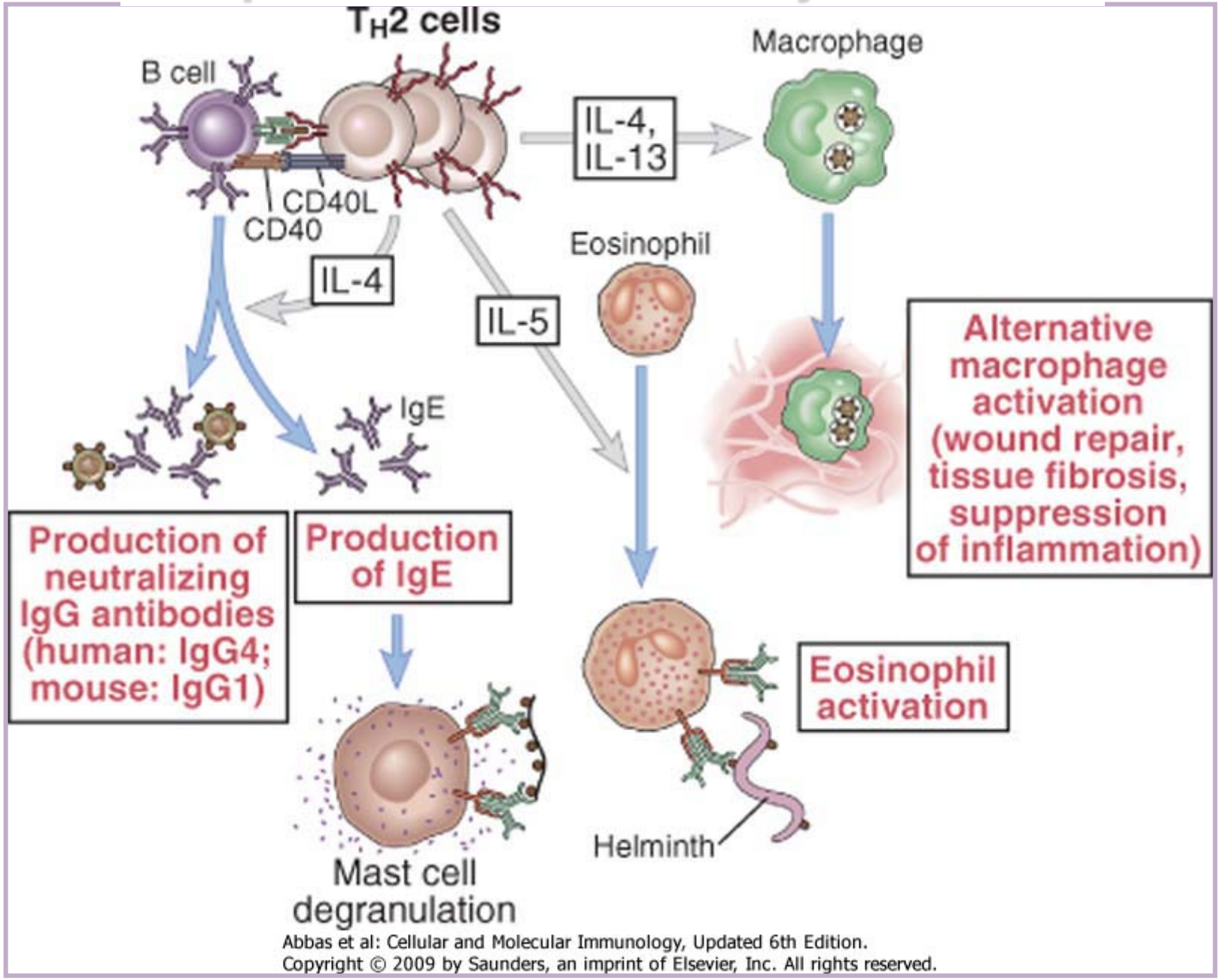
IFN-γ immunoregulatory functions



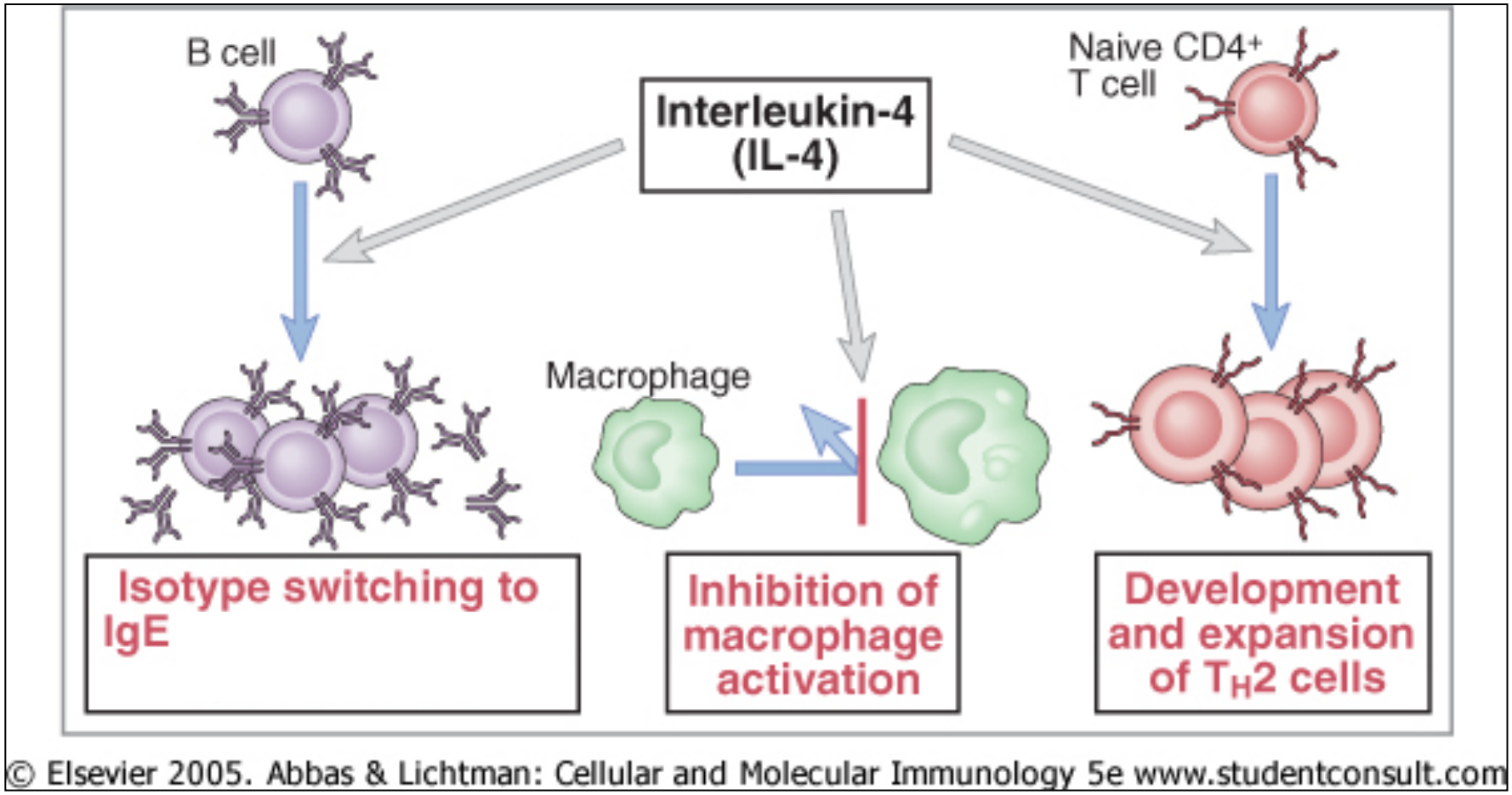
TH2 SUBSET


Helminths
Naive T cell
Dendritic cell
IL-4
IL-4
Mast cells, eosinophils?
IL-4
GATA-3
STAT6
Amplification
IL-4
TH2 cells
IL-4
IL-5
IL-13
Helminths or protein antigens
APC
Naive CD4+ T cell
Proliferation and differentiation
B cell
IL-4
TFH cell
TH2 cell
IL-4, IL-13
Macrophage
Eosinophil
IL-5
IL-4, IL-13
IgE
IgG4 (human), IgG1 (mouse)
Antibody production
Alternative macrophage activation (tissue repair)
Mast cell degranulation
Intestinal mucus secretion and peristalsis
Eosinophil activation
Helminth

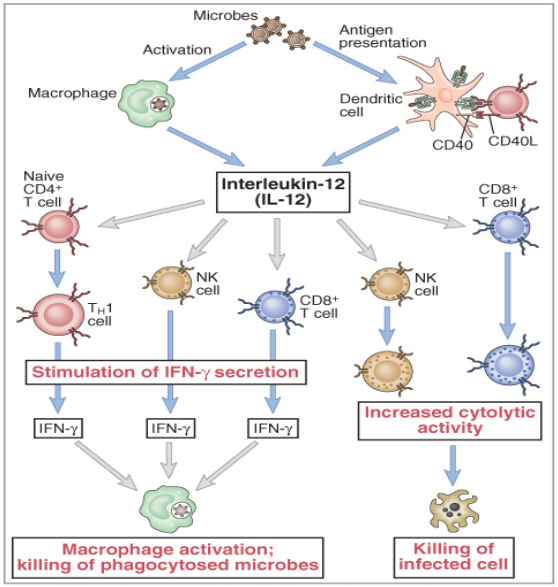
Response coordinated by TH2 cells

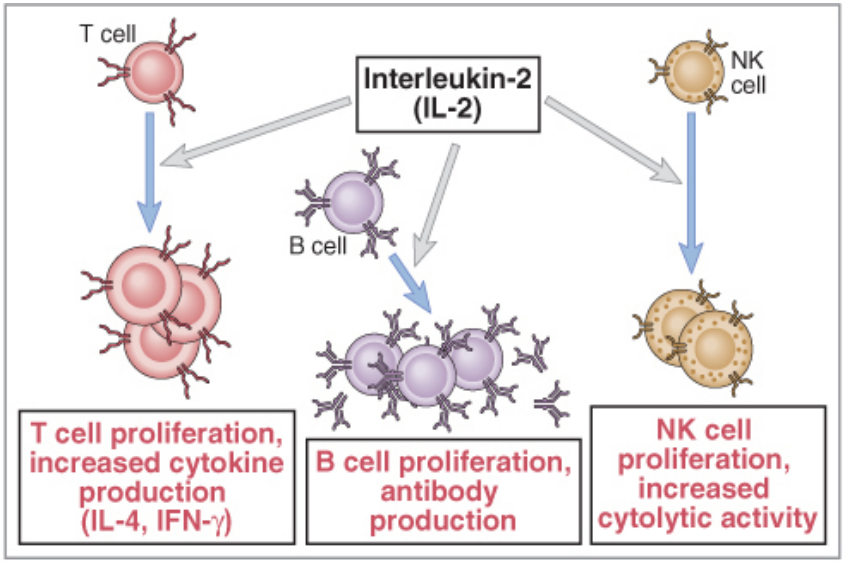


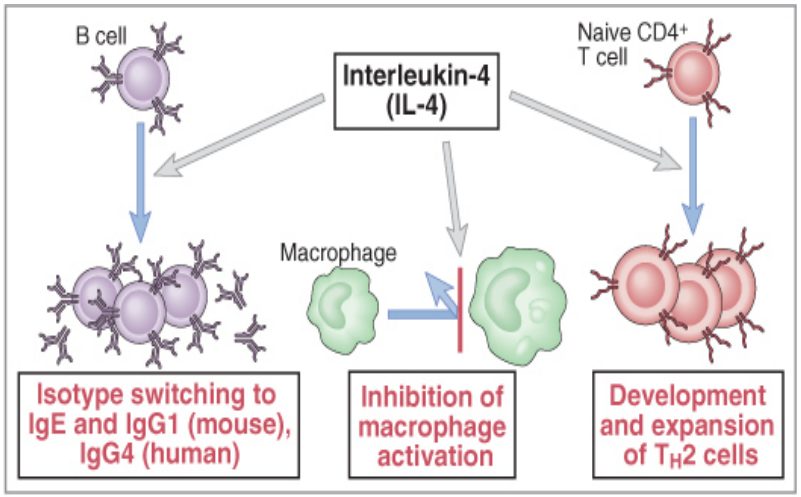
The main functions of IL-4

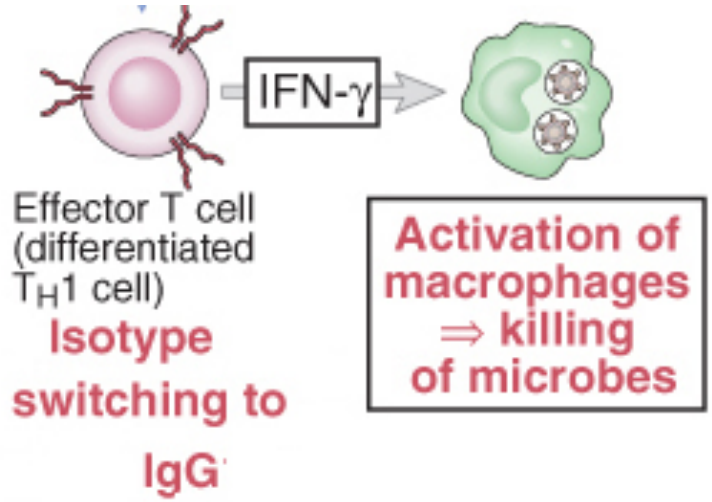


IL12,IL2,IL4 and IFNγ in brief

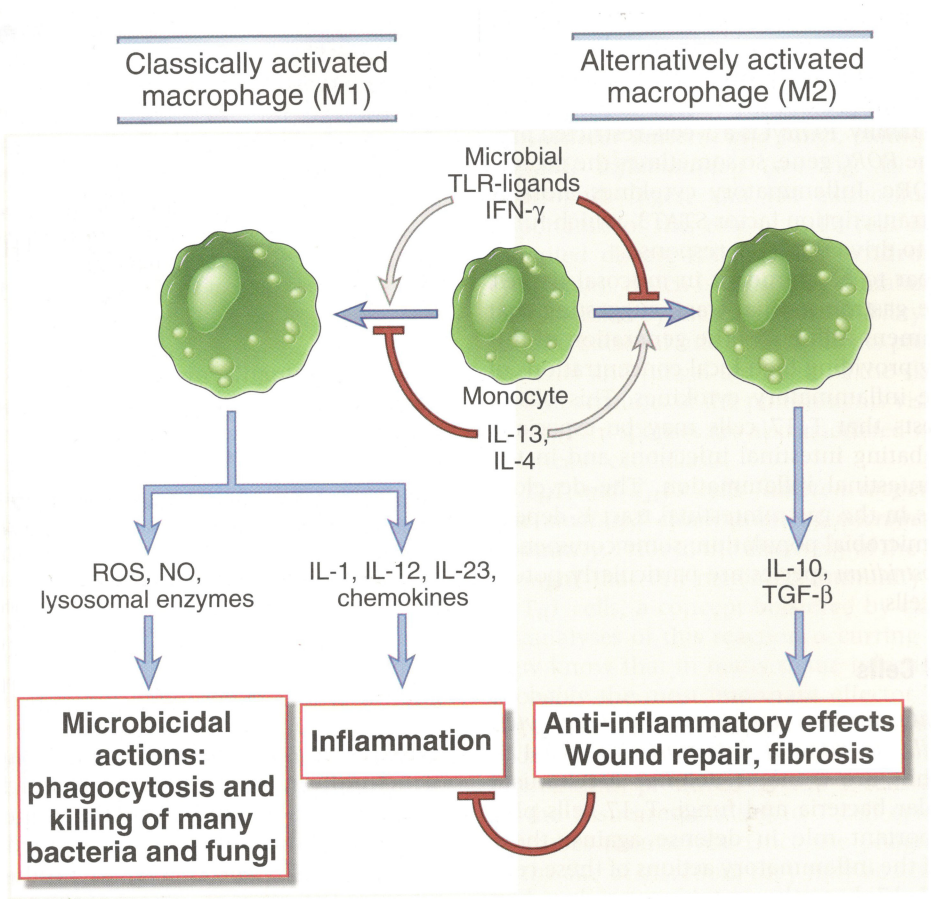




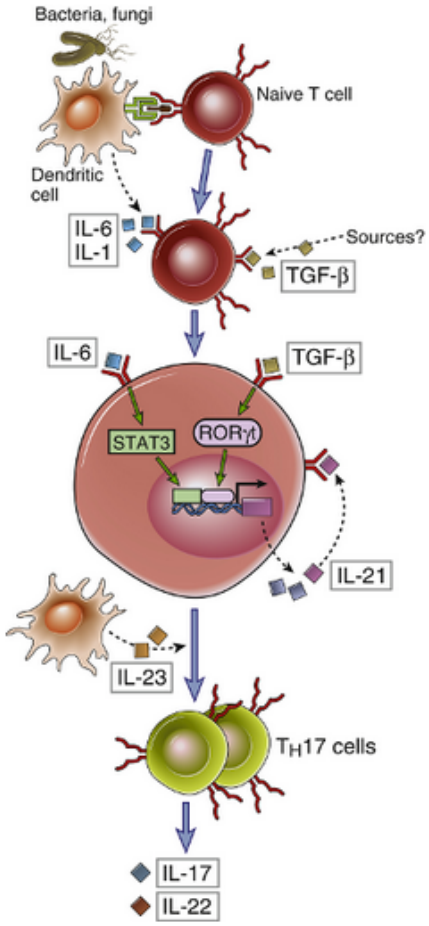


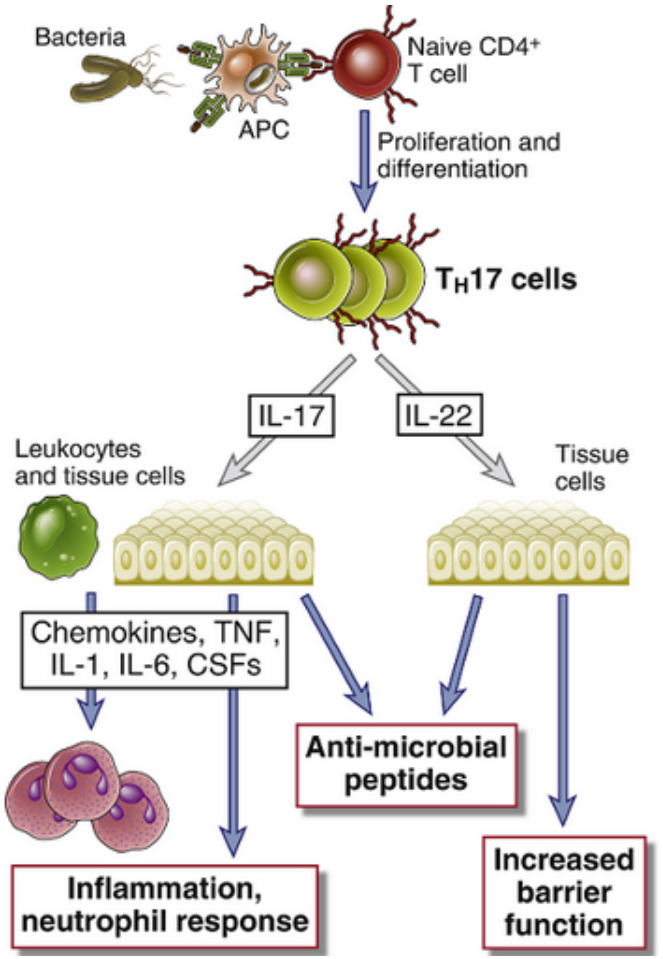


Macrophages



TH17 SUBSET


Bacteria, fungi
Naive T cell
Dendritic cell
IL-6
IL-1
Sources?
TGF-β
IL-6
TGF-β
STAT3
RORγt
IL-21
IL-23
TH17 cells
IL-17
IL-22

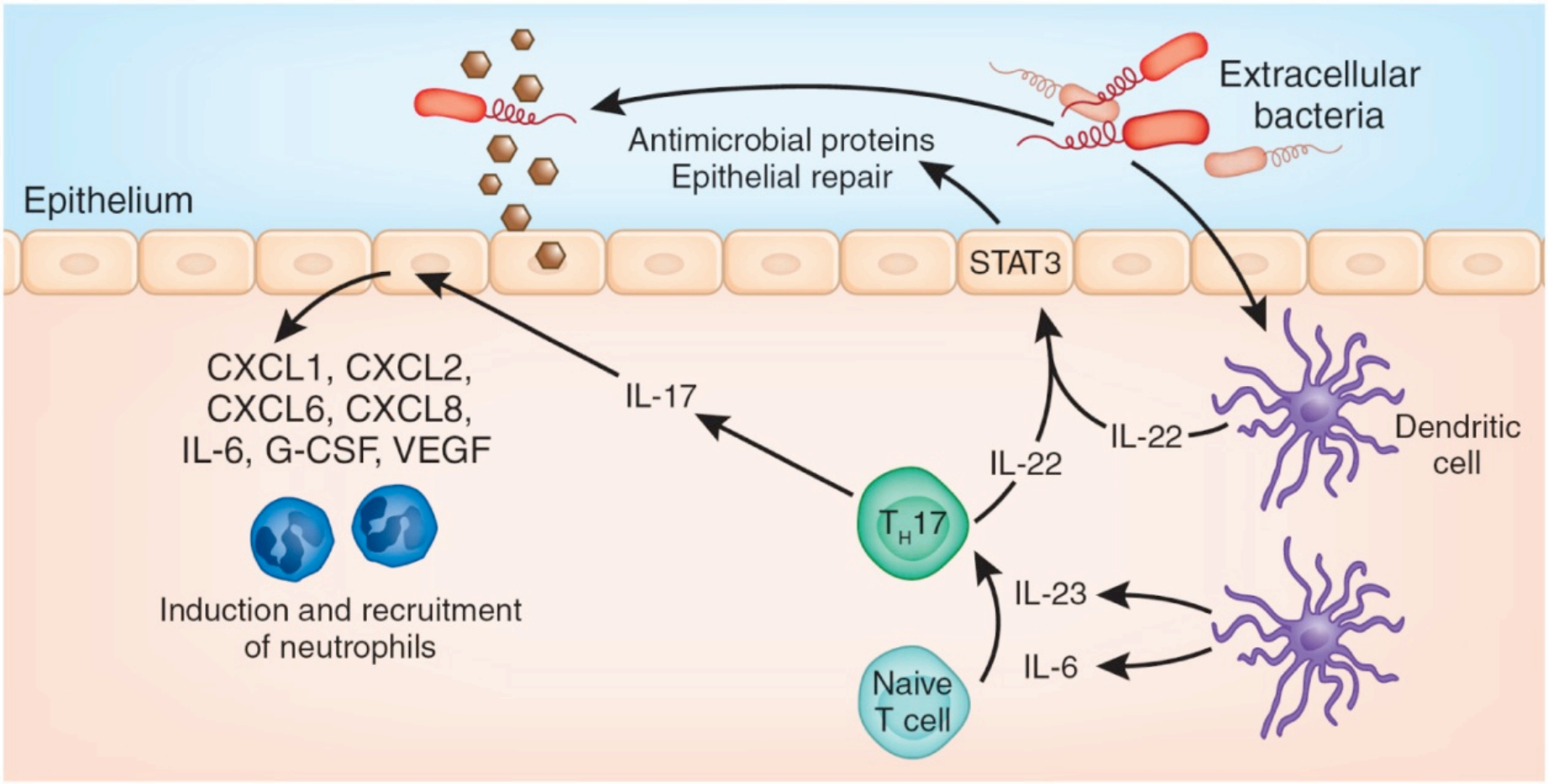

Bacteria
Naive CD4+ T cell
APC
Proliferation and differentiation
TH17 cells
IL-17
IL-22
Leukocytes and tissue cells
Tissue cells
Chemokines, TNF, IL-1, IL-6, CSFs
Anti-microbial peptides
Inflammation, neutrophil response
Increased barrier function

Extracellular bacteria

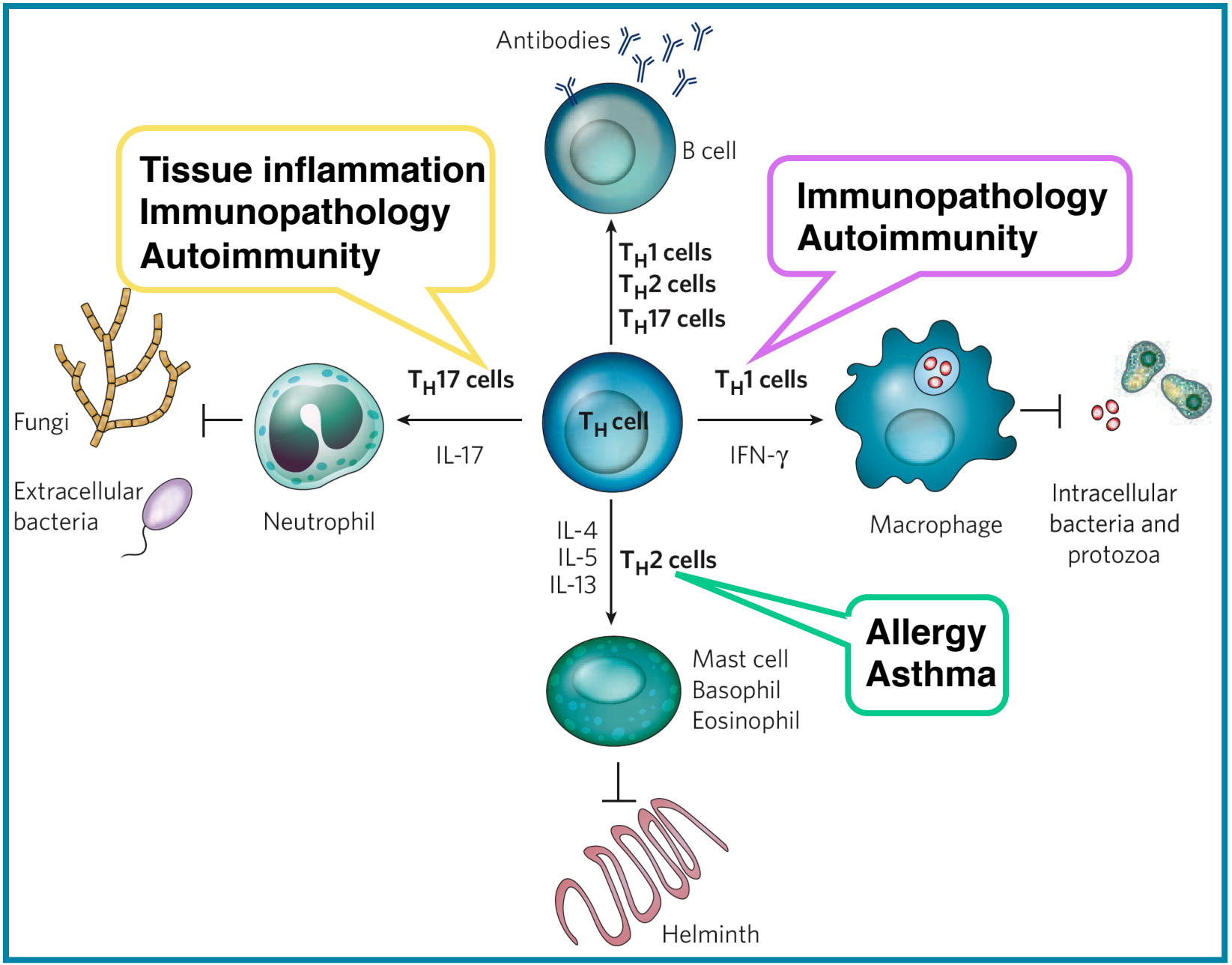
- **Predominantly extracellular bacteria are:**

- *1. Bacillus anthracis*
  2. Enterotoxigenic *Escherichia coli*
  3. *Haemophilus influenzae*
  4. *Mycoplasma*
  5. *Pseudomonas aeruginosa*
  6. *Staphylococcus aureus*
  7. *Streptococcus pyogenes*
  8. *Vibrio cholerae*

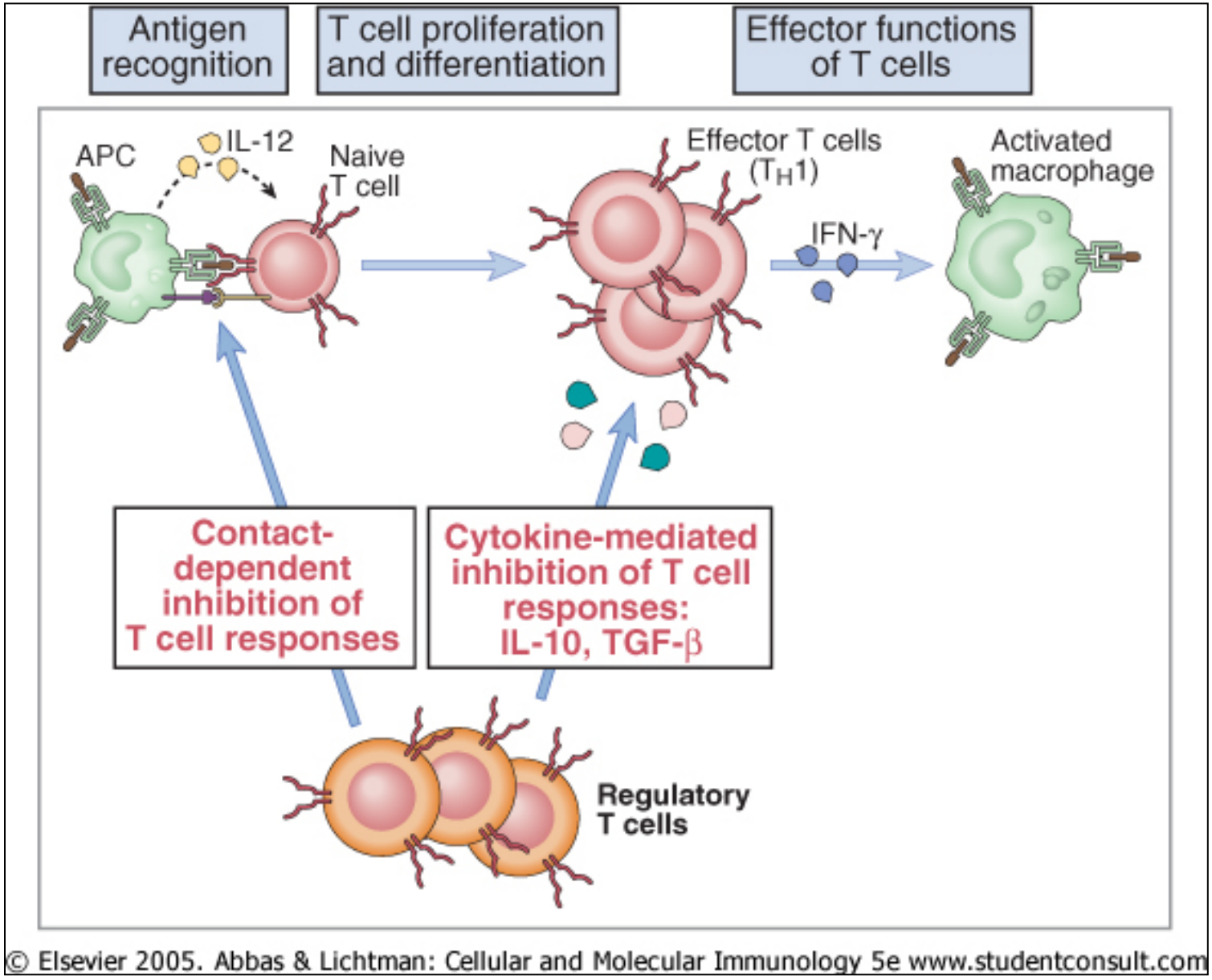
Functions of TH17-derived cytokines

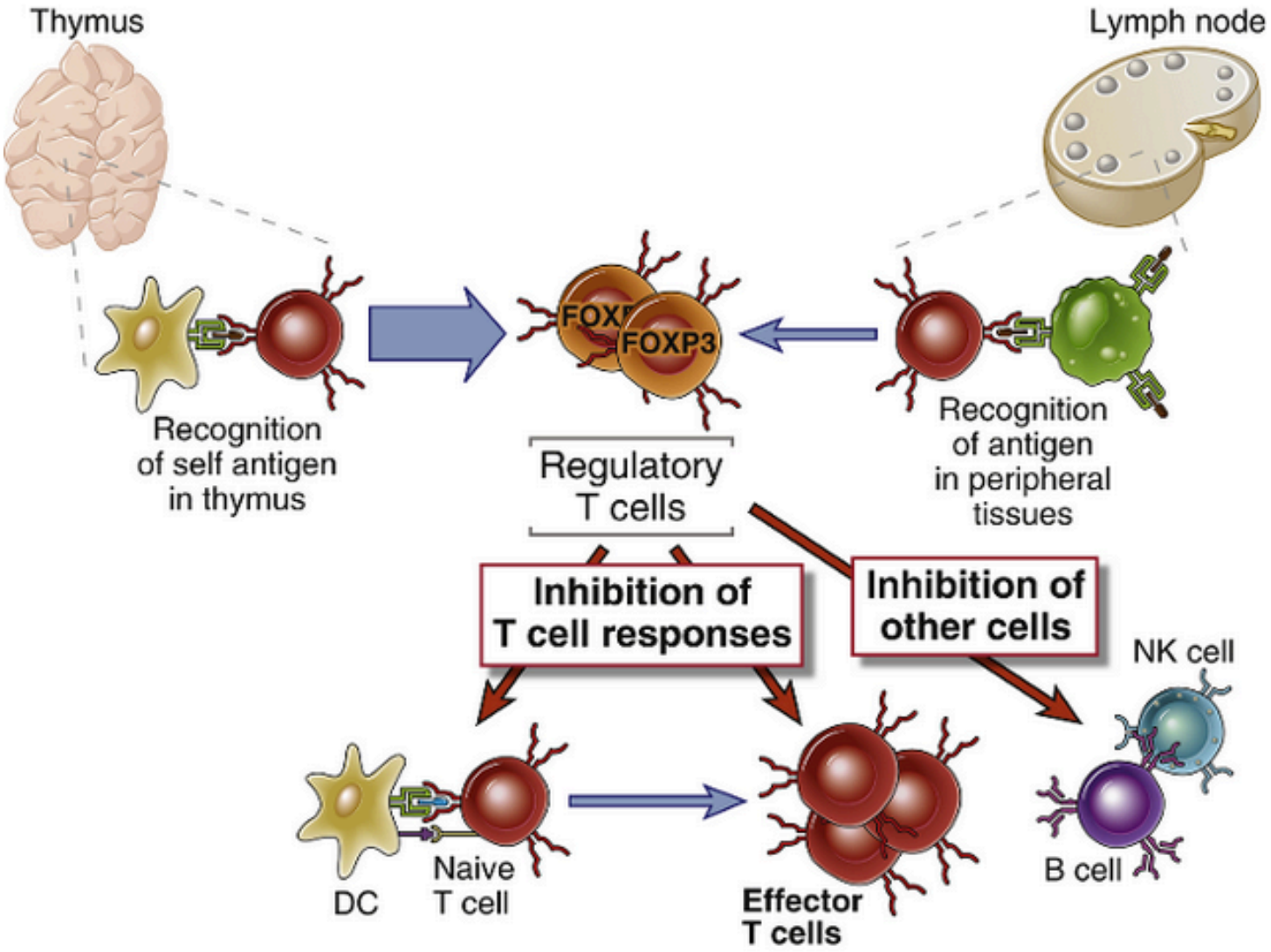


Effector Th cell lineage and pathogen class

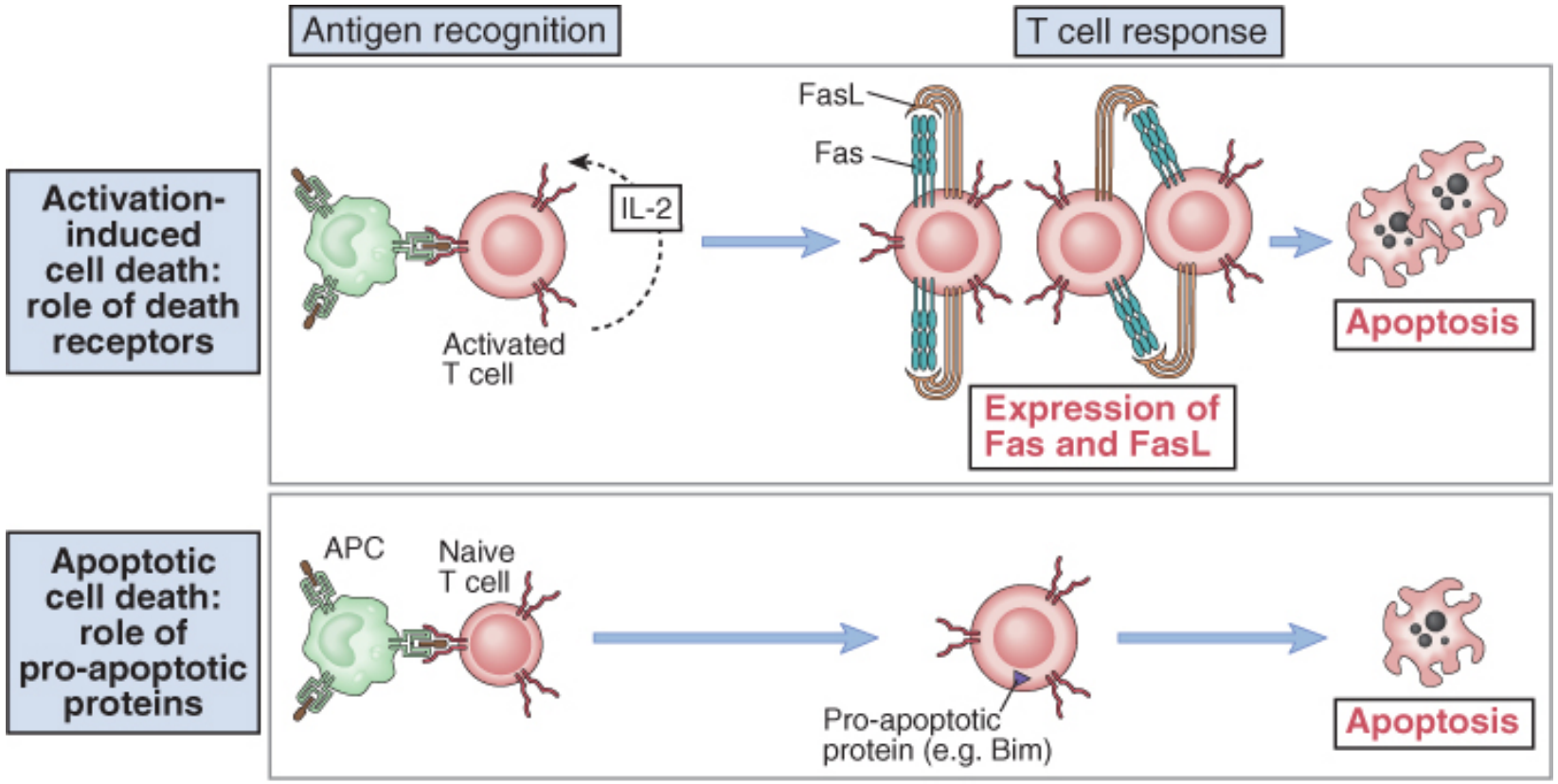


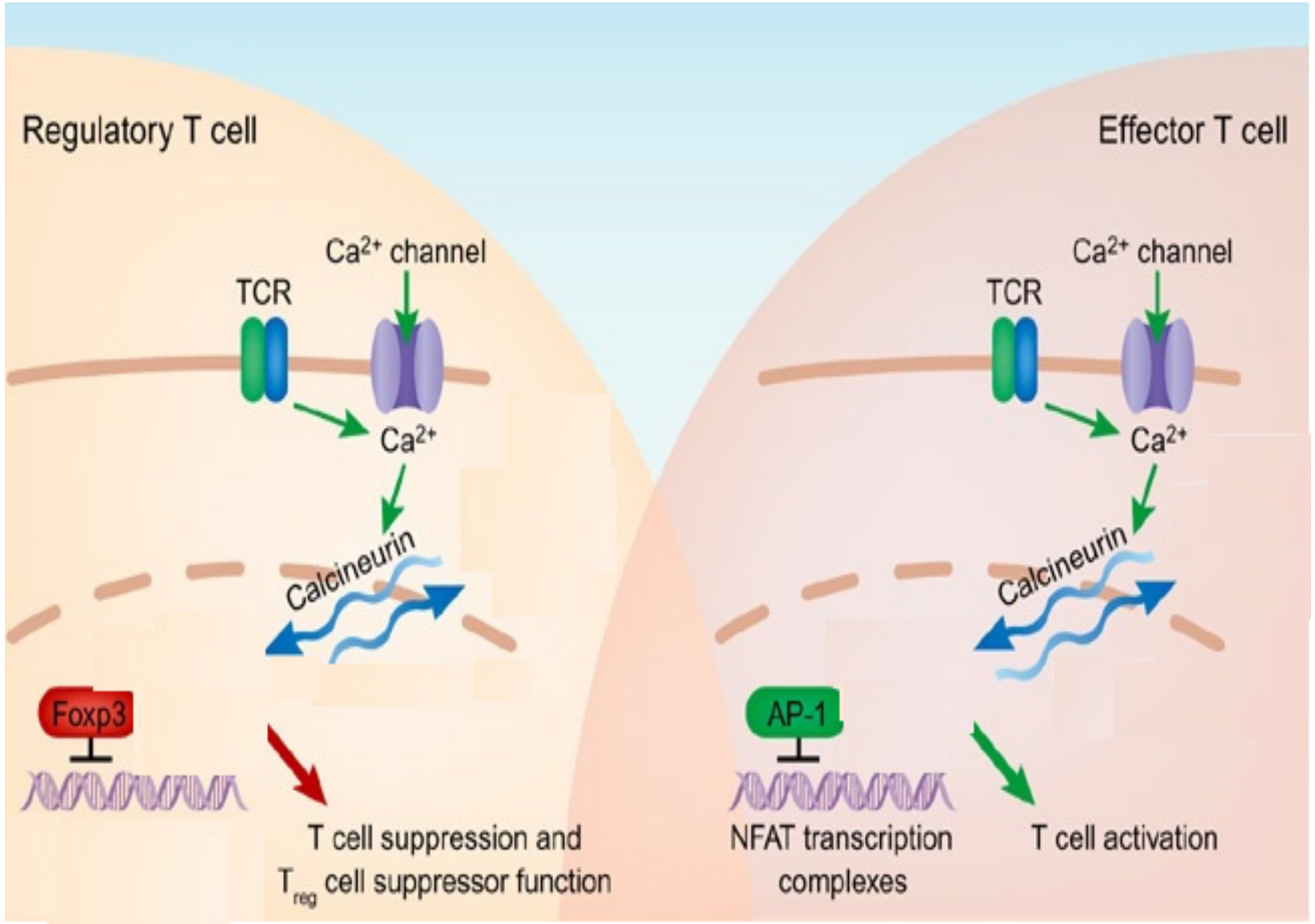
Regulatory CD4+ T cells suppress effector T cell activation




Thymus
Lymph node
FOXP3
Recognition
of self antigen
in thymus
Regulatory
T cells
Recognition
of antigen
in peripheral
tissues
Inhibition of
T cell responses
Inhibition of
other cells
NK cell
DC
Naive
T cell
Effector
T cells
B cell

FATE OF EFFECTOR T LYMPHOCYTES AFTER CELLULAR RESPONSE



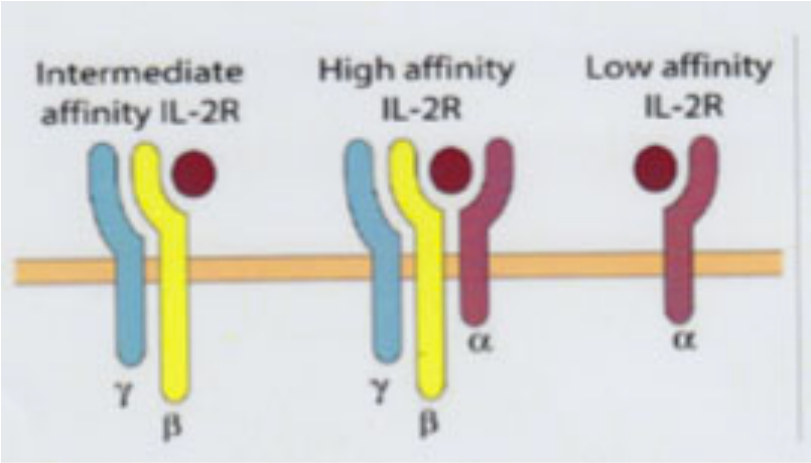

Regulatory T cell
Effector T cell
Ca2+ channel
TCR
Ca2+
Calcineurin
Foxp3
AP-1
T cell suppression and
Treg cell suppressor function
NFAT transcription
complexes
T cell activation

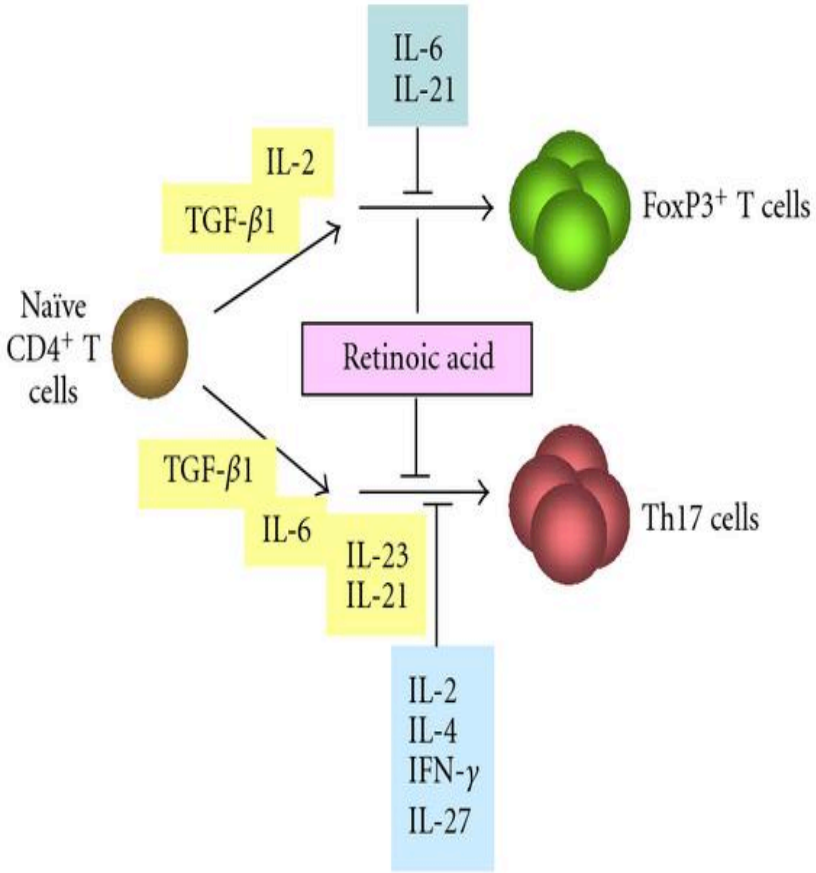
Mutations in FOXP3 gene

Mutations in Fox P3 gene cause IPEX syndrome (autoimmune disregulation and polyendocrine pathologies)

- Foxp3 positive cells express CD25

(IL2-r) at low or intermediate affinity





Reciprocal regulation of FoxP3+ T cells and Th17 cells by retinoic acid.

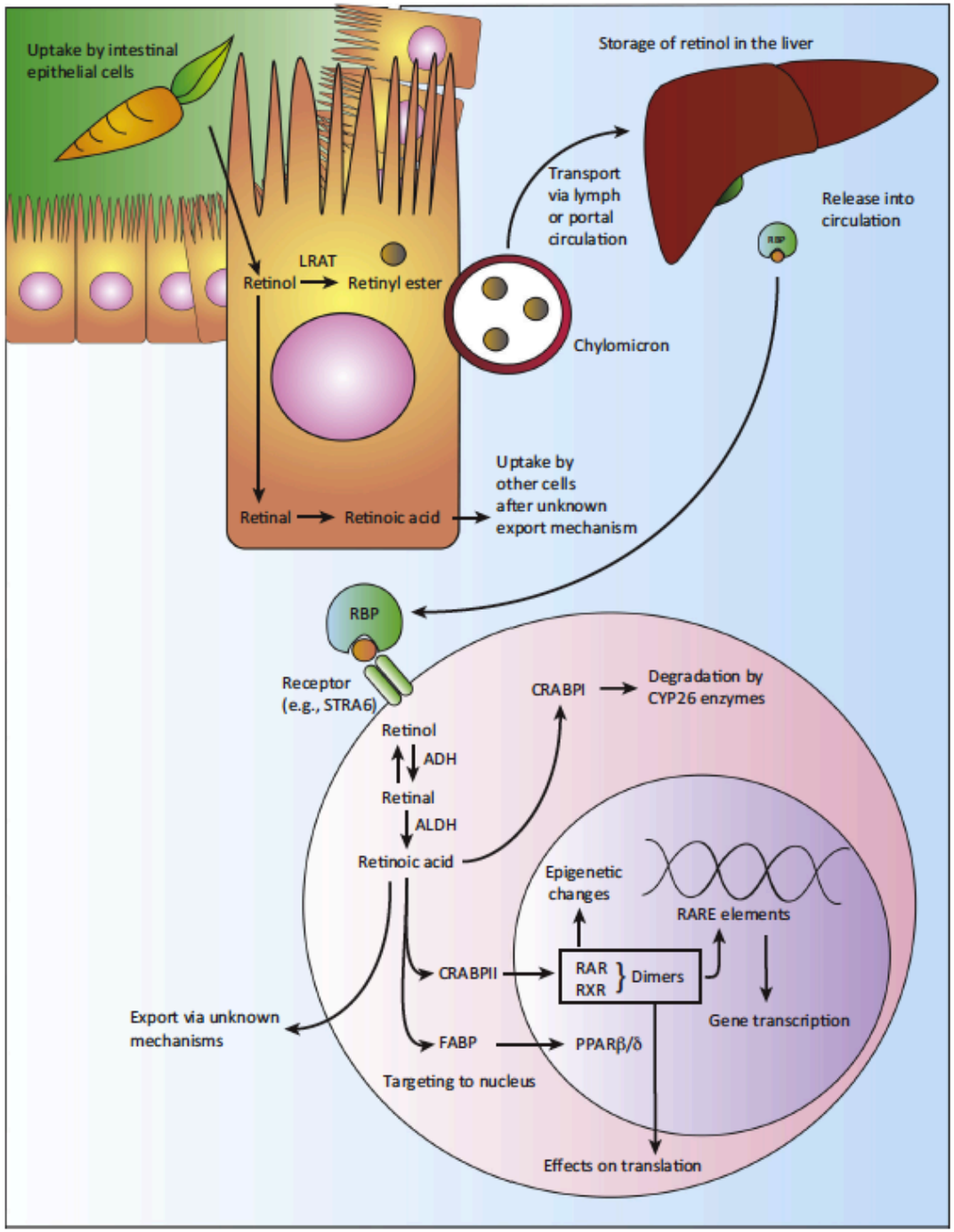
IL-2 and TGF-β 1 promote the generation of FoxP3+ T cells from naïve T cells.

IL-6 and TGF-β 1 promote the generation of Th17 cells.

IL-2 and the cytokines that promote T cell polarization into Th1 or Th2 cells (IL-4, IL-12, IFN-γ) suppress the generation of Th17 cells

IL-6 and IL-21 (pro-Th17 cells) suppress the generation of FoxP3+ Tcells.

Importantly, retinoic acid suppresses the generation of Th17 cells but promotes the induction of FoxP3+ T cells.

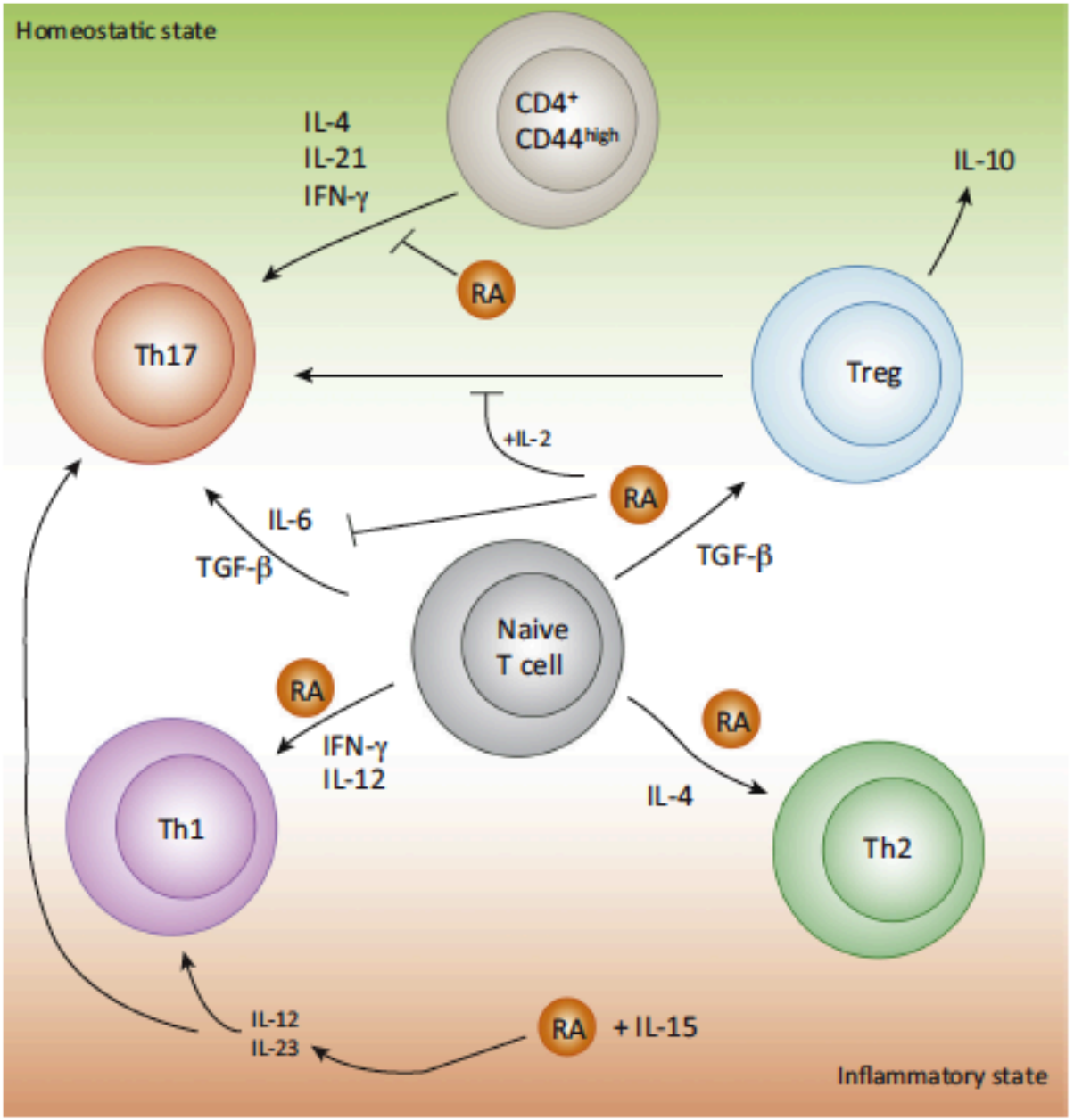


Trends in Immunology

Review

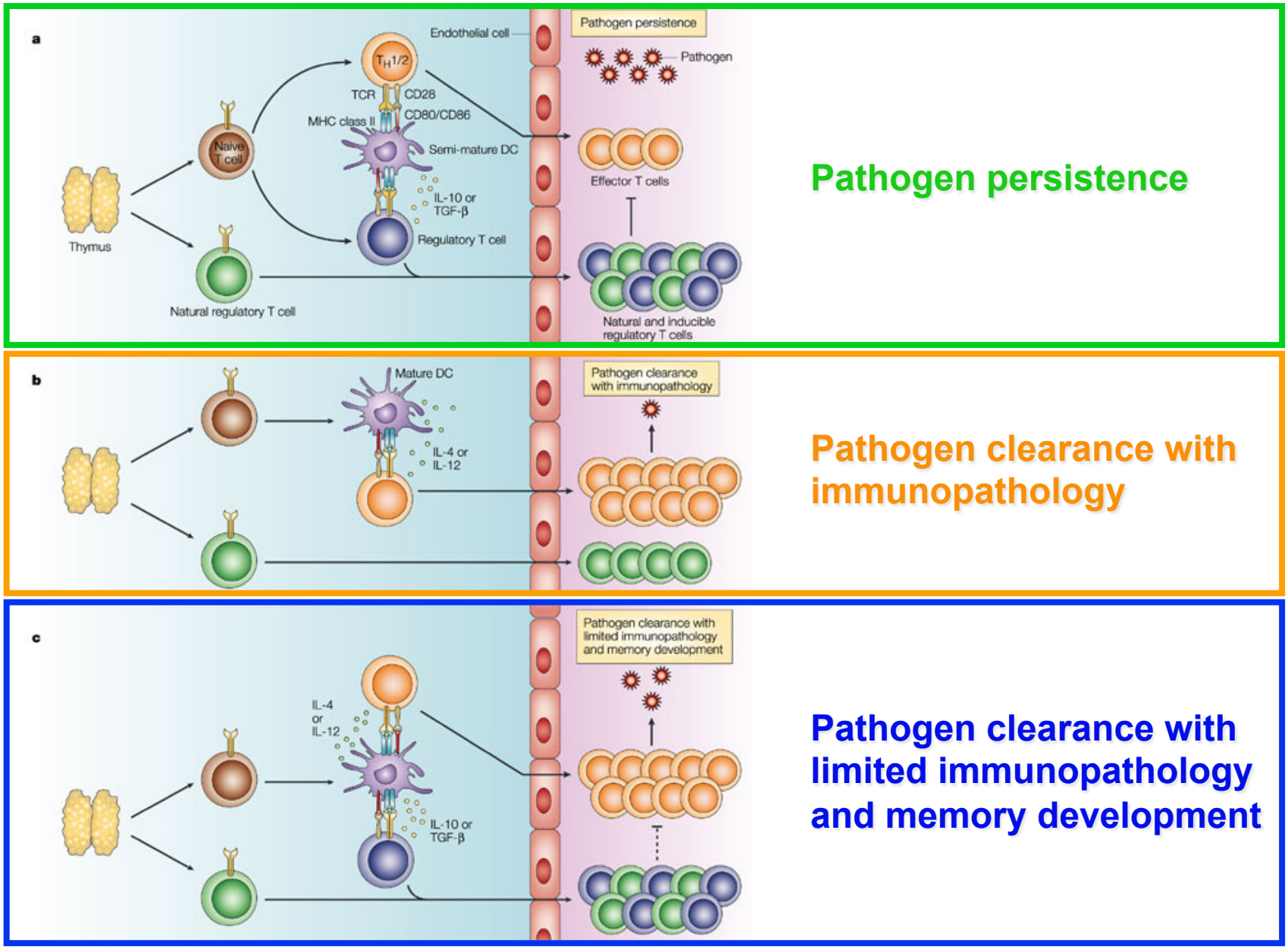
Retinoic Acid and Immune Homeostasis: A Balancing Act

Martje N. Erkelens[1] and Reina E. Mebius[1,*]

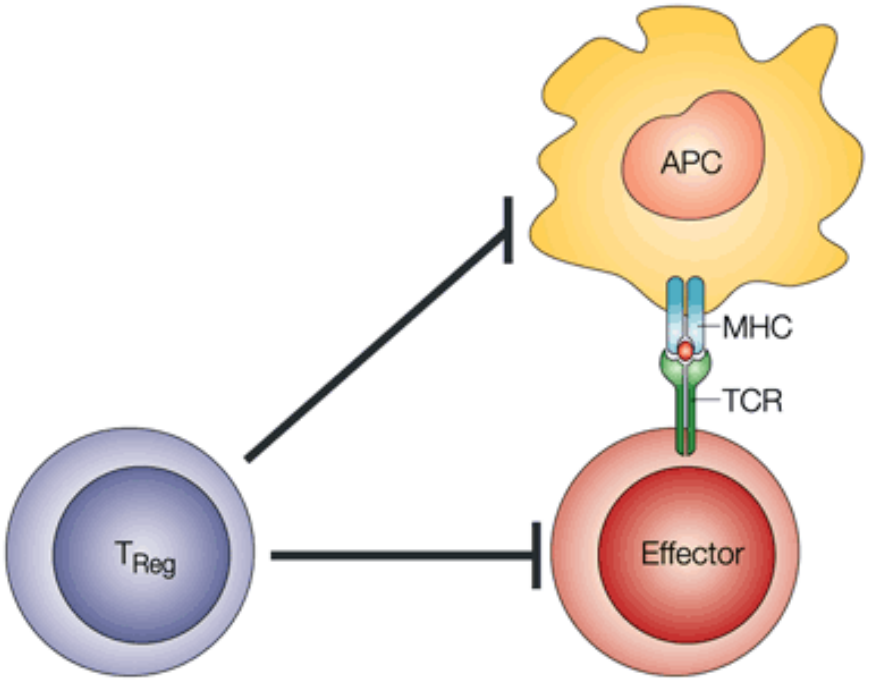


Trends in Immunology

Balancing effector and regulatory T cell responses



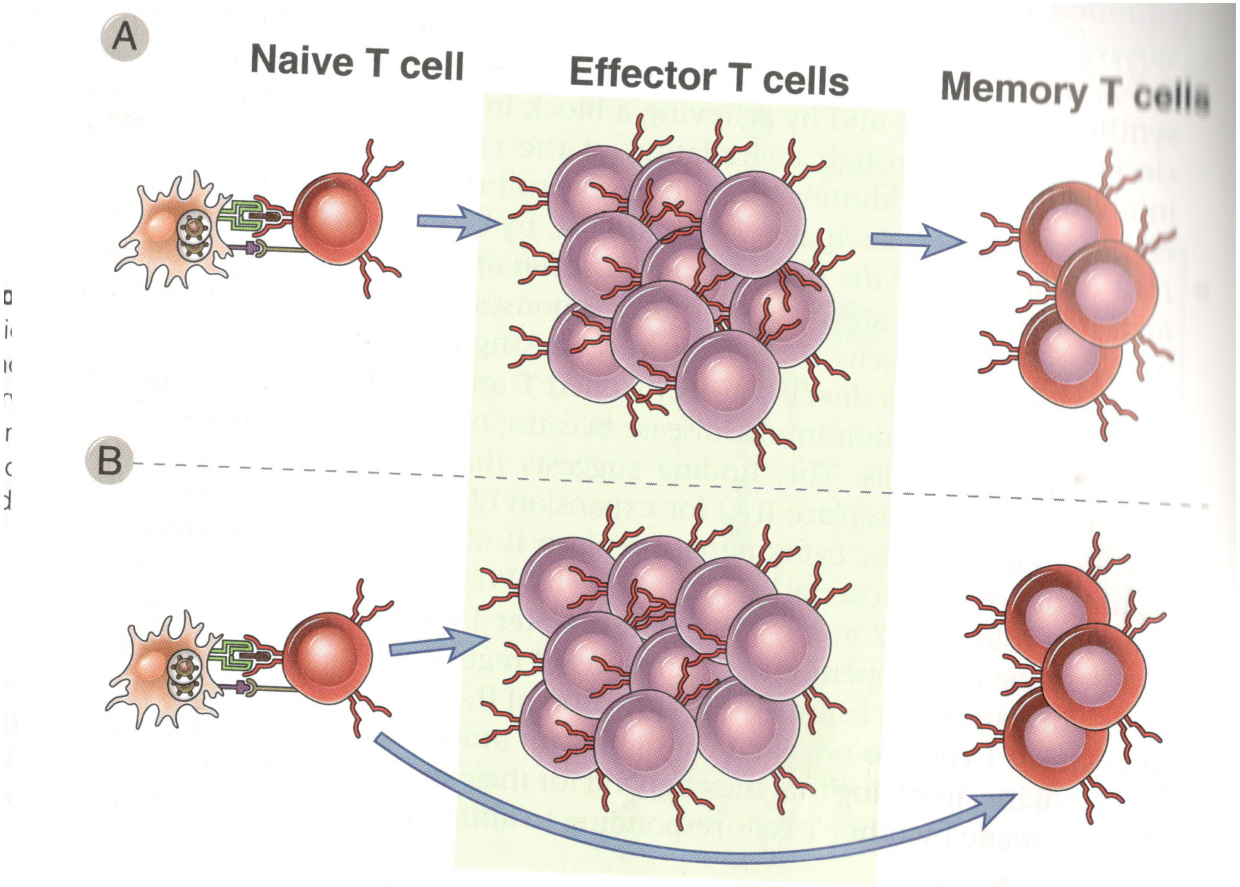
Regulatory T cells control immune responsiveness *in vivo*



Benefits:
- T-cell homeostasis
- prevents autoimmune disease
- tolerance after transplantation
- prevents GVHD
- prevents allergy
- prevents hypersensitivity

Detrimental effects:
- down-regulation of tumour immunity
- down-regulation of immunity to infection

T cell response

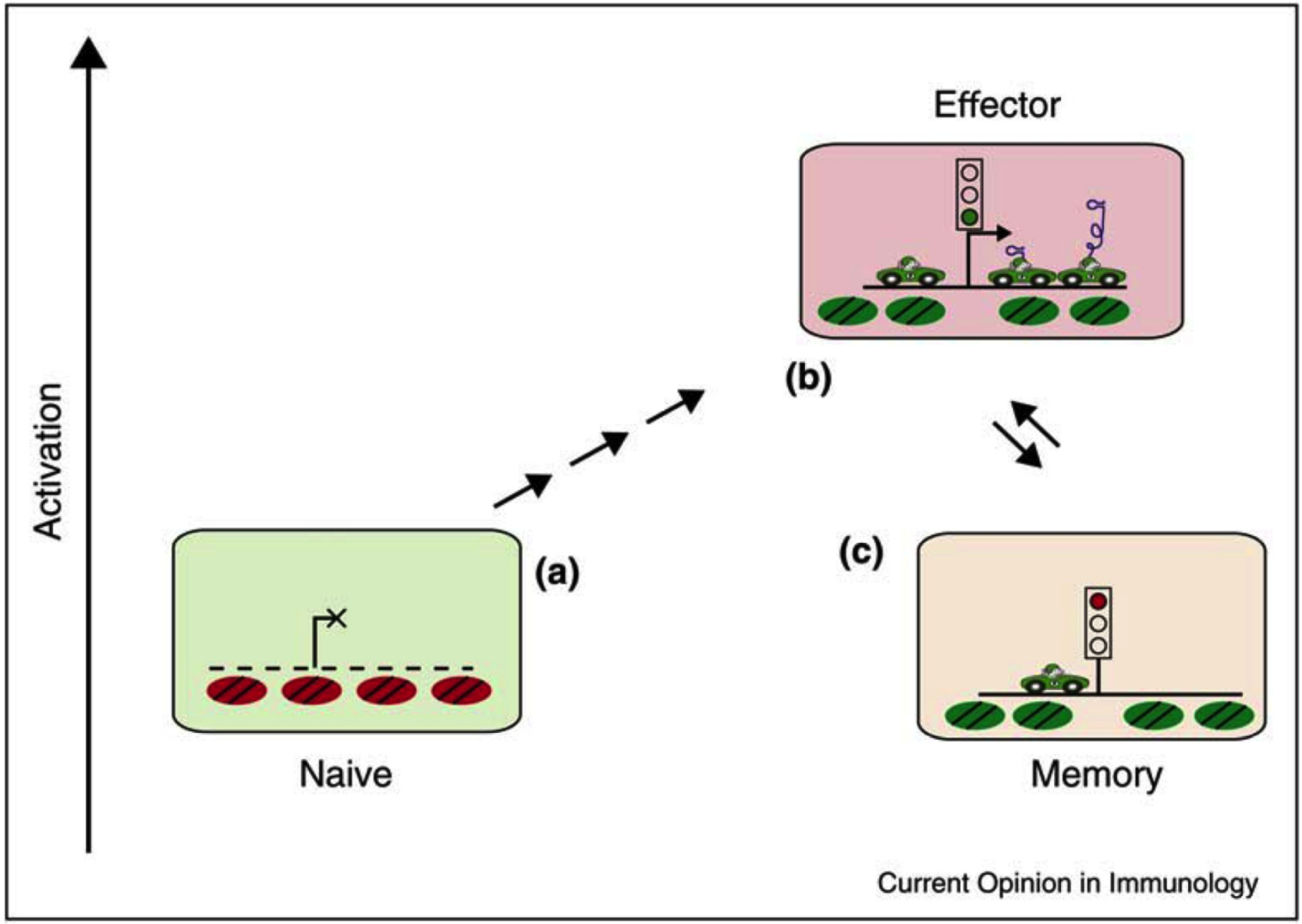


Memory T Lymphocytes

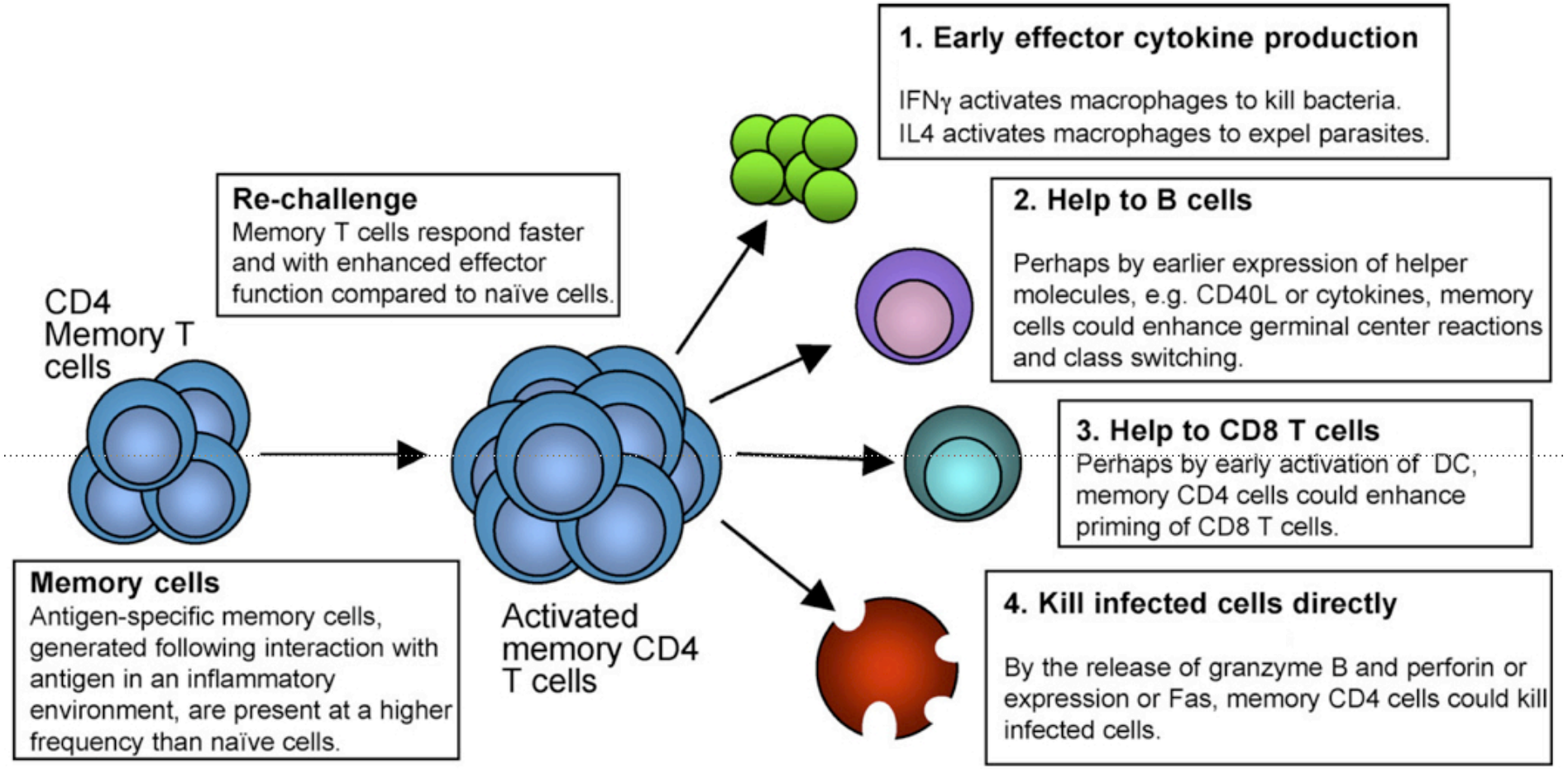
- **LONG TERM MEMORY**
- BNIP1 (transcription factor)
- CCR7 **Home in nodes**
- CD45RO+
- IL 7R
- CD4+ Respond to IL7
- CD8+ respond to IL7 and IL15

- **EFFECTOR MEMORY**
- **CD45 RO+**
- **CCR7 negative: home in tissues/mucosas**
- **Can be polarized TH1,TH2 and TH17 if commitment to become memory happened after polarization.**

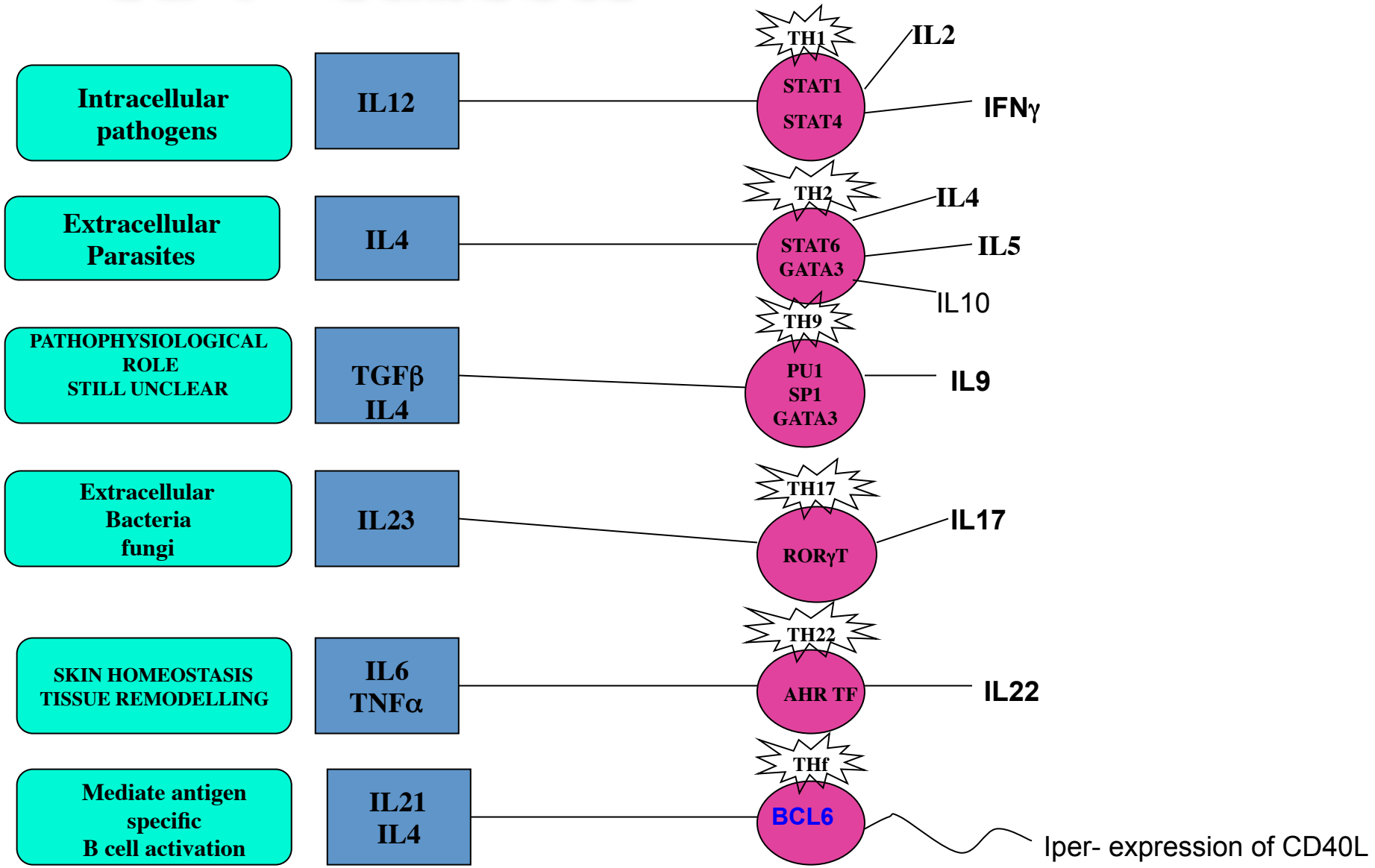
Immunological memory



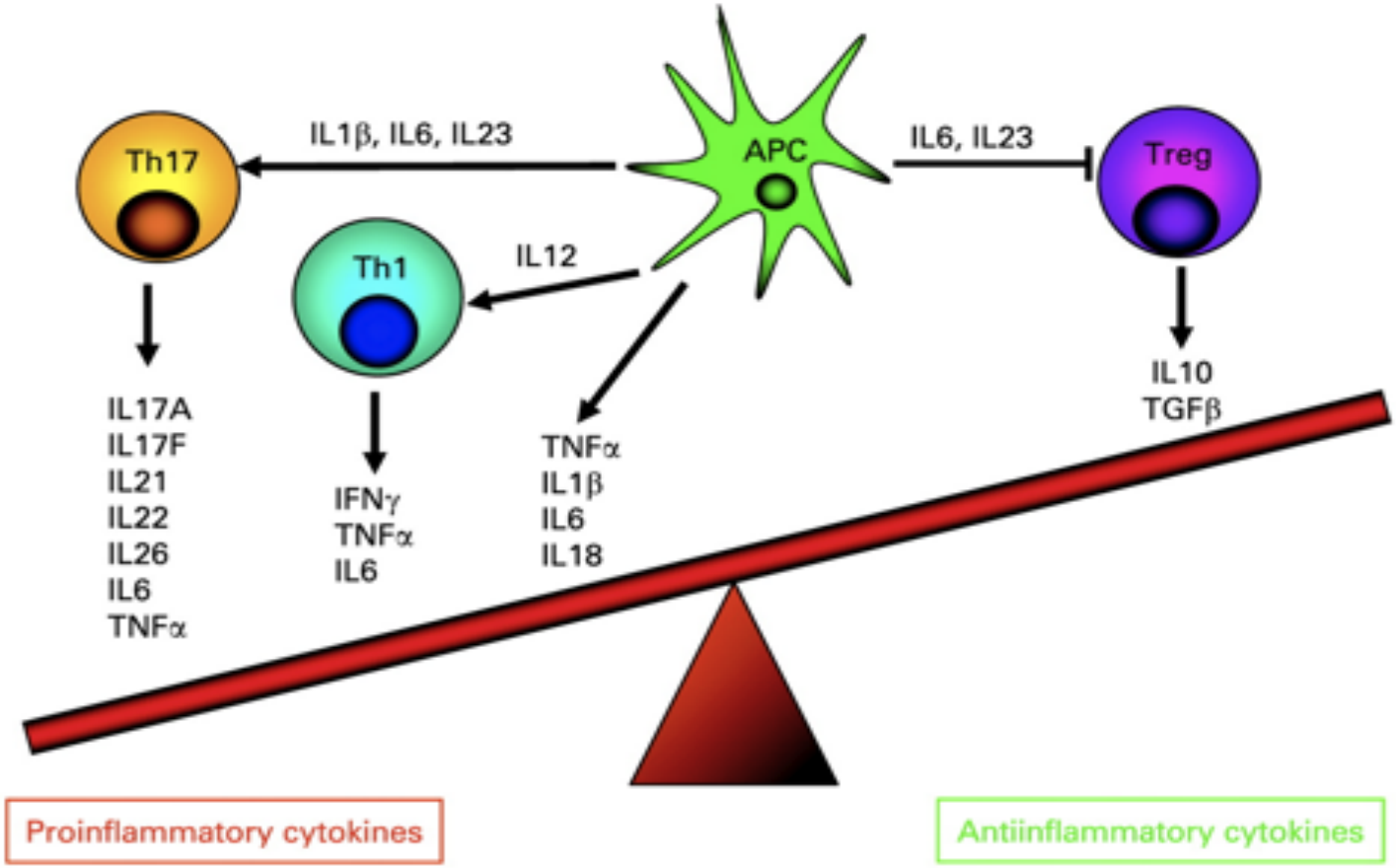
Memory CD4 T cells protect the host in a number of ways



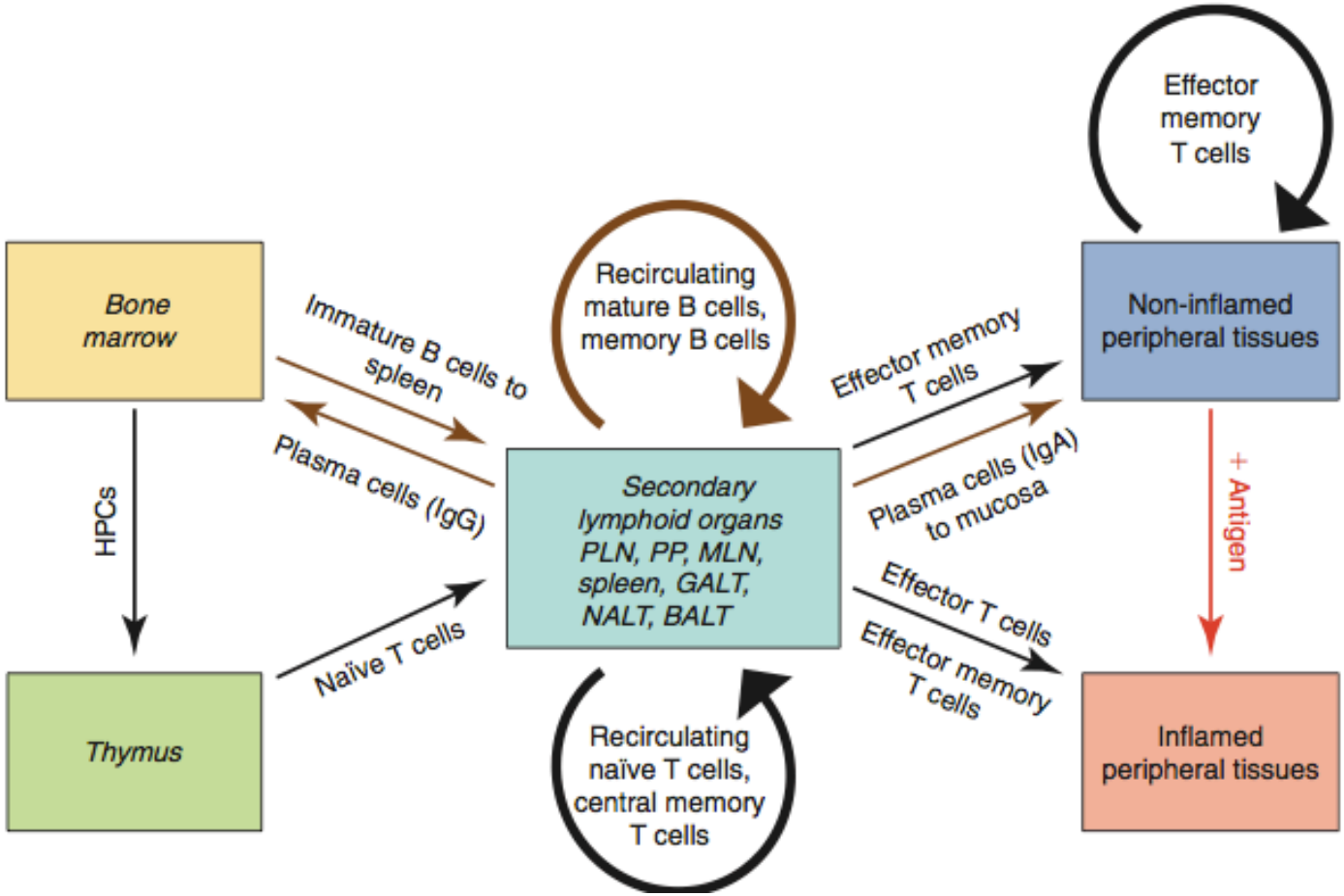
CD4+ subsets

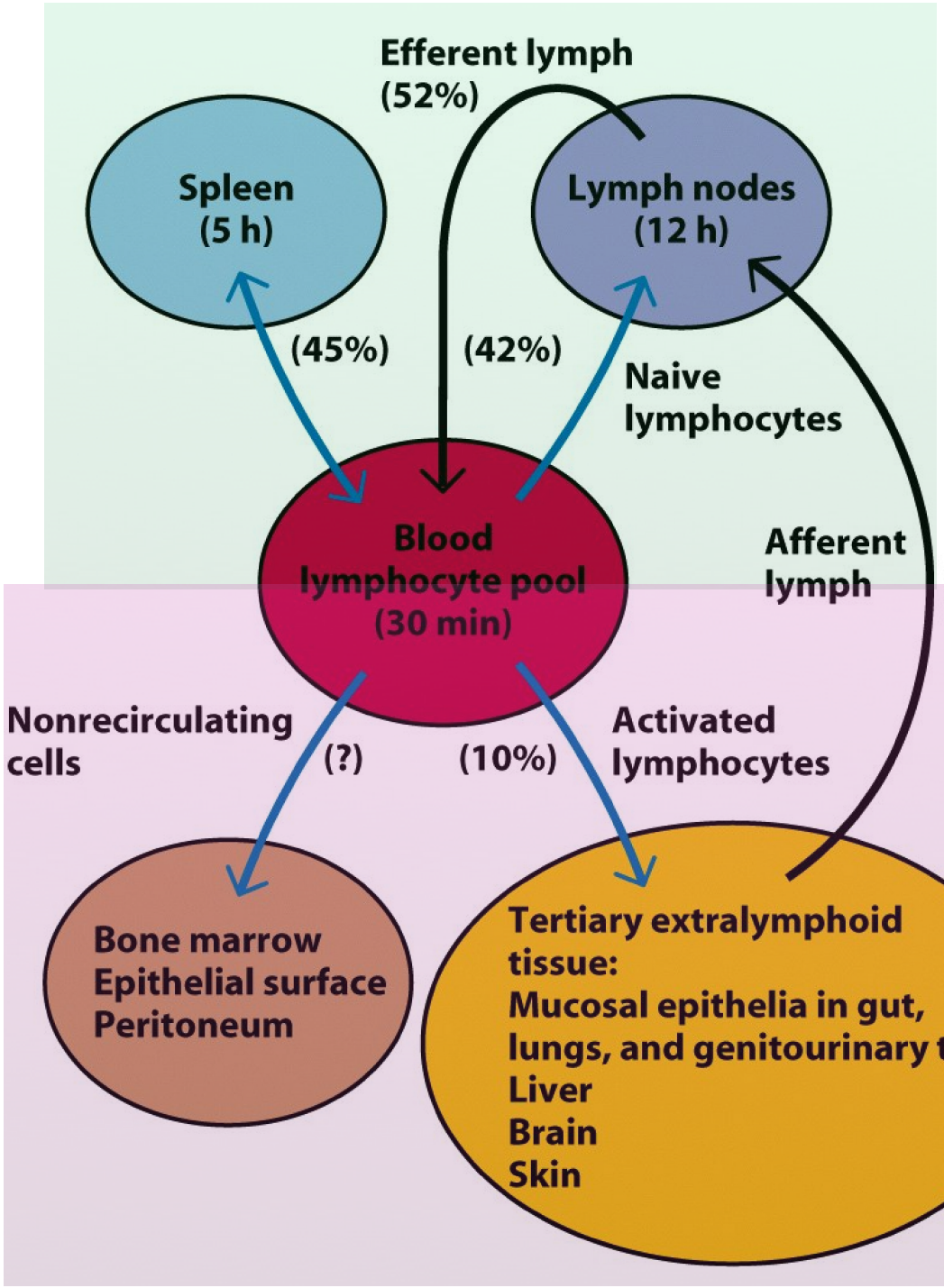

Intracellular pathogens
IL12
TH1
STAT1
STAT4
IL2
IFNγ
Extracellular Parasites
IL4
TH2
STAT6
GATA3
IL4
IL5
IL10
PATHOPHYSIOLOGICAL ROLE STILL UNCLEAR
TGFβ
IL4
TH9
PU1
SP1
GATA3
IL9
Extracellular Bacteria fungi
IL23
TH17
RORγT
IL17
SKIN HOMEOSTASIS TISSUE REMODELLING
IL6
TNFα
TH22
AHR TF
IL22
Mediate antigen specific B cell activation
IL21
IL4
THf
BCL6
Iper- expression of CD40L

Summary


Th17
IL1β, IL6, IL23
APC
IL6, IL23
Treg
Th1
IL12
IL17A
IL17F
IL21
IL22
IL26
IL6
TNFα
IFNγ
TNFα
IL6
TNFα
IL1β
IL6
IL18
IL10
TGFβ
Proinflammatory cytokines
Antiinflammatory cytokines

Routes of lymphocyte trafficking



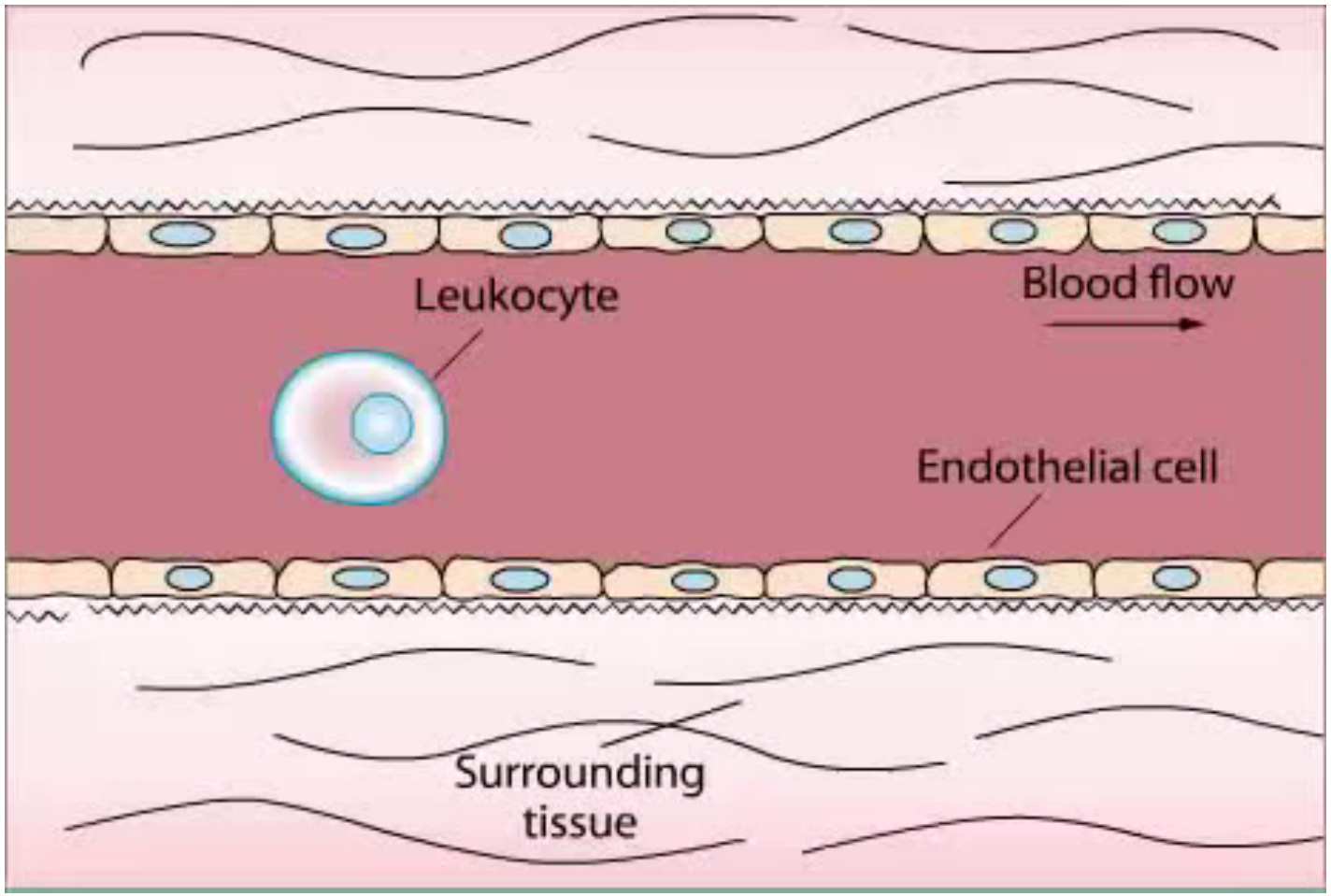


What does regulate lymphocyte trafficking?

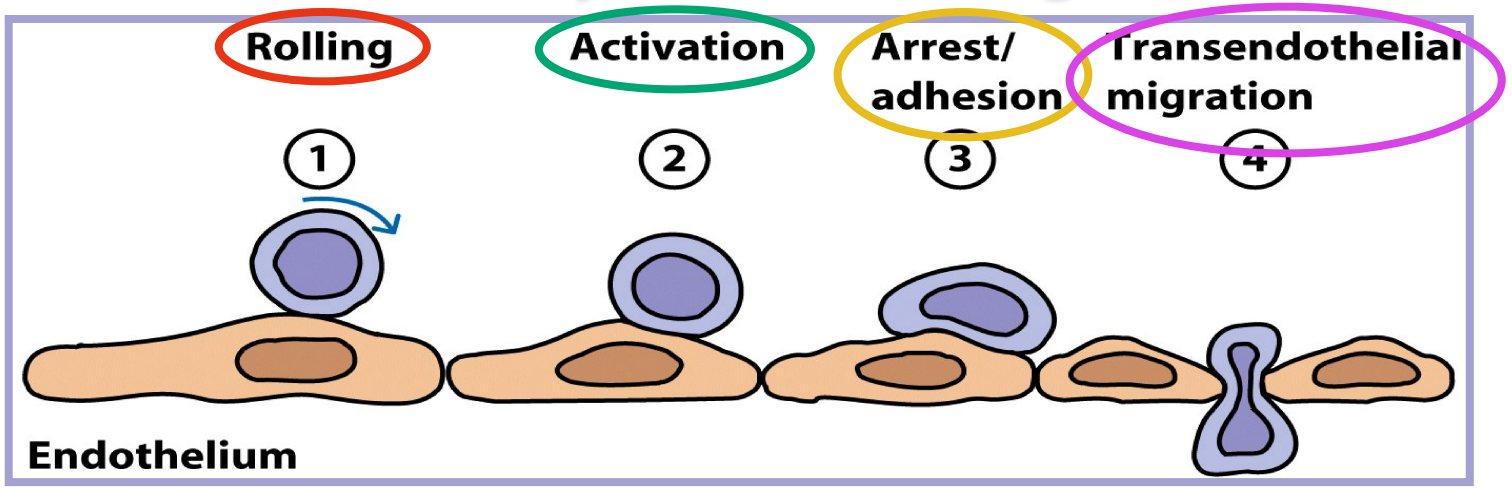
Naive lymphocytes recirculate between blood and peripheral lymphoid organs only

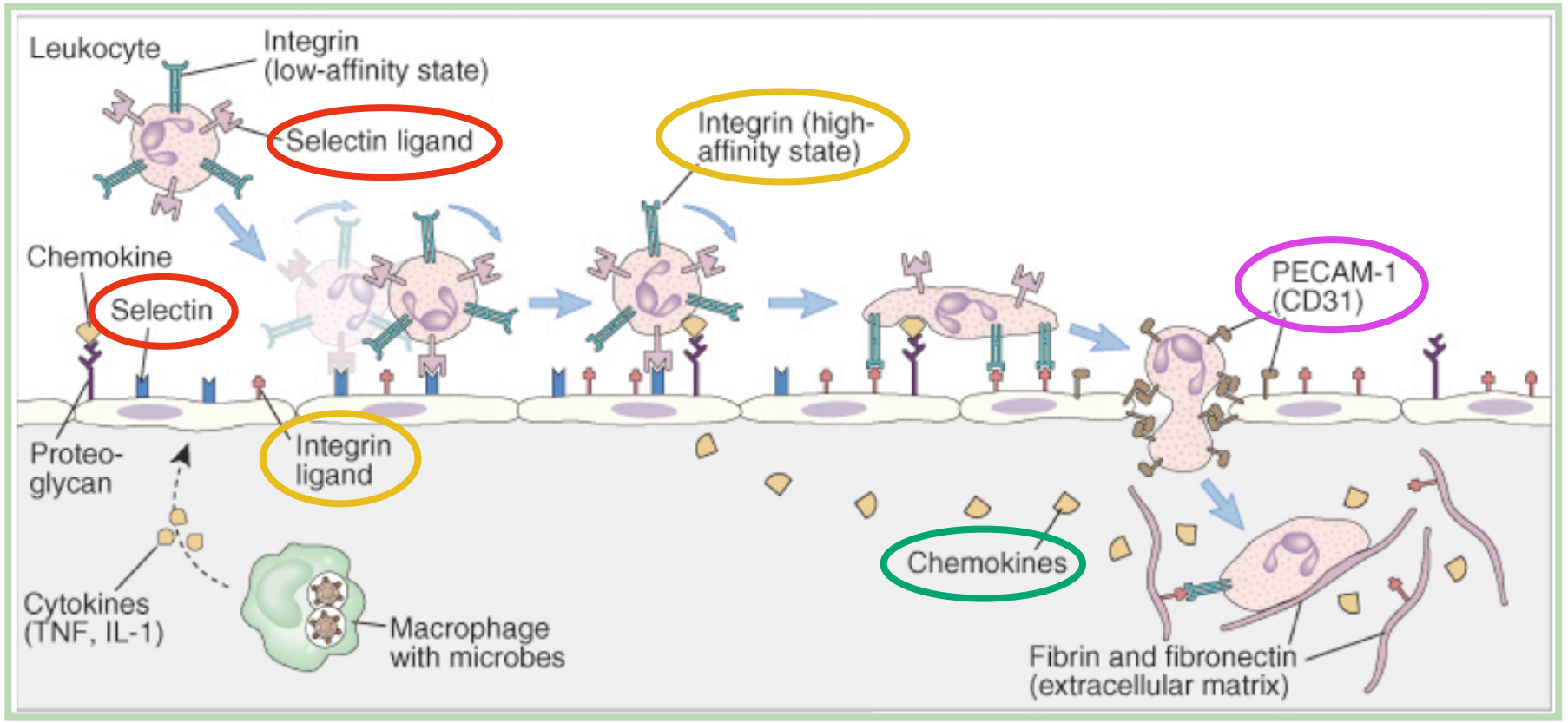
Activated lymphocytes traffic also to tissues

Should I stay or should I go?

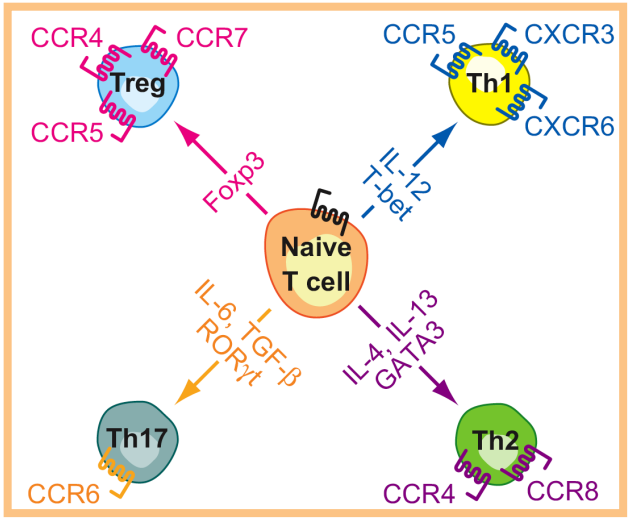


Should I stay or should I go?

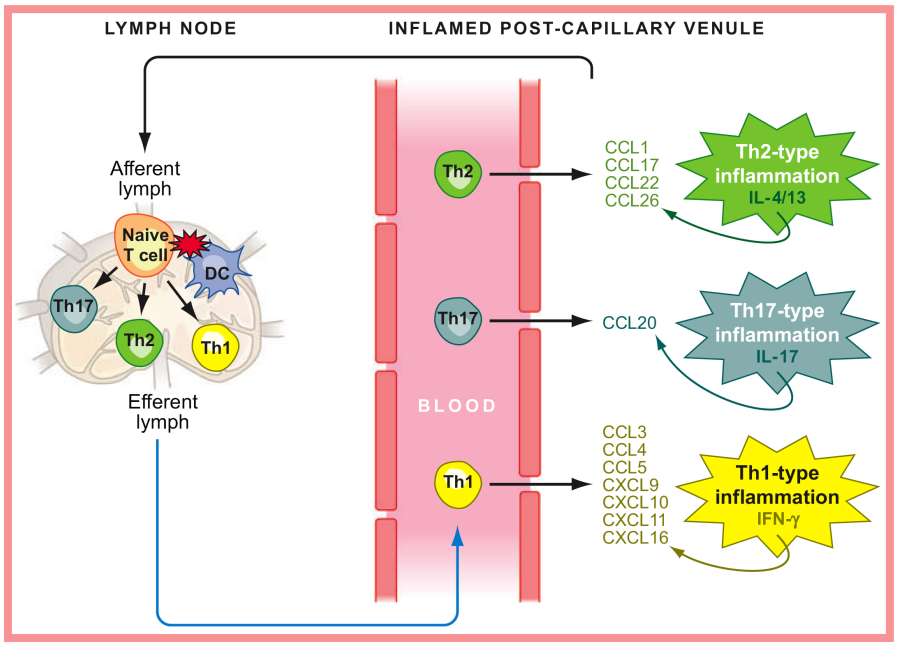




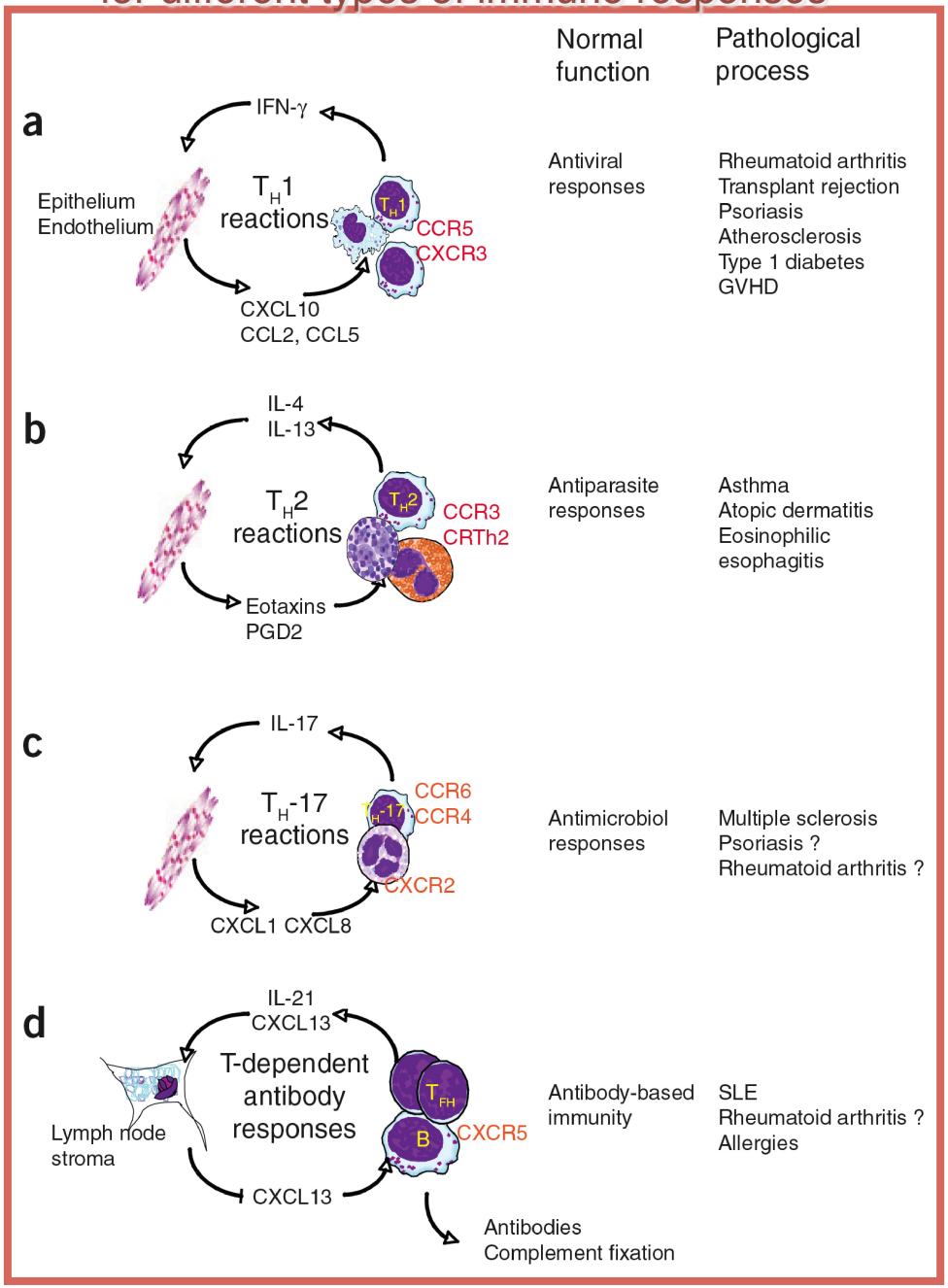
Distinct CD4+ T cell subsets express a different pattern of chemokine receptors….



…and are differentially recruited to the inflammatory site!



Chemoattractants, cytokines and leukocyte types for different types of immune responses



Inflammatory Disease	Infiltrate	Chemokine
Acute respiratory distress syndrome	Neutrophil	Interleukin-8; GRO-α, -β, -γ; ENA-78
Asthma	Eosinophil, T cell, monocyte, basophil	MCP-1, -4; MIP-1α; eotaxin; RANTES
Bacterial pneumonia	Neutrophil	Interleukin-8, ENA-78
Sarcoidosis	T cell, monocyte	IP-10
Glomerulonephritis	Monocyte, T cell, neutrophil	MCP-1, RANTES, IP-10
Rheumatoid arthritis	Monocyte, neutrophil	MIP-1α, MCP-1, interleukin-8, ENA-78
Osteoarthritis		MIP-1β
Atherosclerosis	T cell, monocyte	MCP-1, -4; IP-10
Inflammatory bowel disease	Monocyte, neutrophil, T cell, eosinophil	MCP-1, MIP-1α, eotaxin, IP-10, interleukin-8
Psoriasis	T cell, neutrophil	MCP-1, IP-10, MIG, GRO-β, interleukin-8
Bacterial meningitis	Neutrophil, monocyte	Interleukin-8; GRO-α; MCP-1; MIP-1α, -1β
Viral meningitis	T cell, monocyte	MCP-1, IP-10

Chemokine receptor antagonists in development

Chemokine Receptor	Clinical Indication
CCR1	Rheumatoid arthritis
	Multiple sclerosis
CCR2	Rheumatoid arthritis
	Type 2 diabetes
	Multiple sclerosis
CCR3	Allergic rhinitis and asthma
CCR5	HIV
CCR9	Inflammatory bowel disease
CXCR1, CXCR2	Chronic obstructive pulmonary disease
CXCR3	Psoriasis
CXCR4	Stem-cell mobilization

Role of chemokines and vasculature in various inflammatory diseases

Chronic inflammatory diseases associated with HEV-like vasculature

Disease	Affected organ	Plump endothelium	Mucin-like CAMs on endothelium*
Crohn's disease	Gut	+	+
Diabetes mellitus	Pancreas	+	+
Graves' disease	Thyroid	+	+
Hashimoto's thyroiditis	Thyroid	+	+
Rheumatoid arthritis	Synovium	+	+
Ulcerative colitis	Gut	+	+

*Includes GlyCAM-1, MAdCAM-1, and CD34.