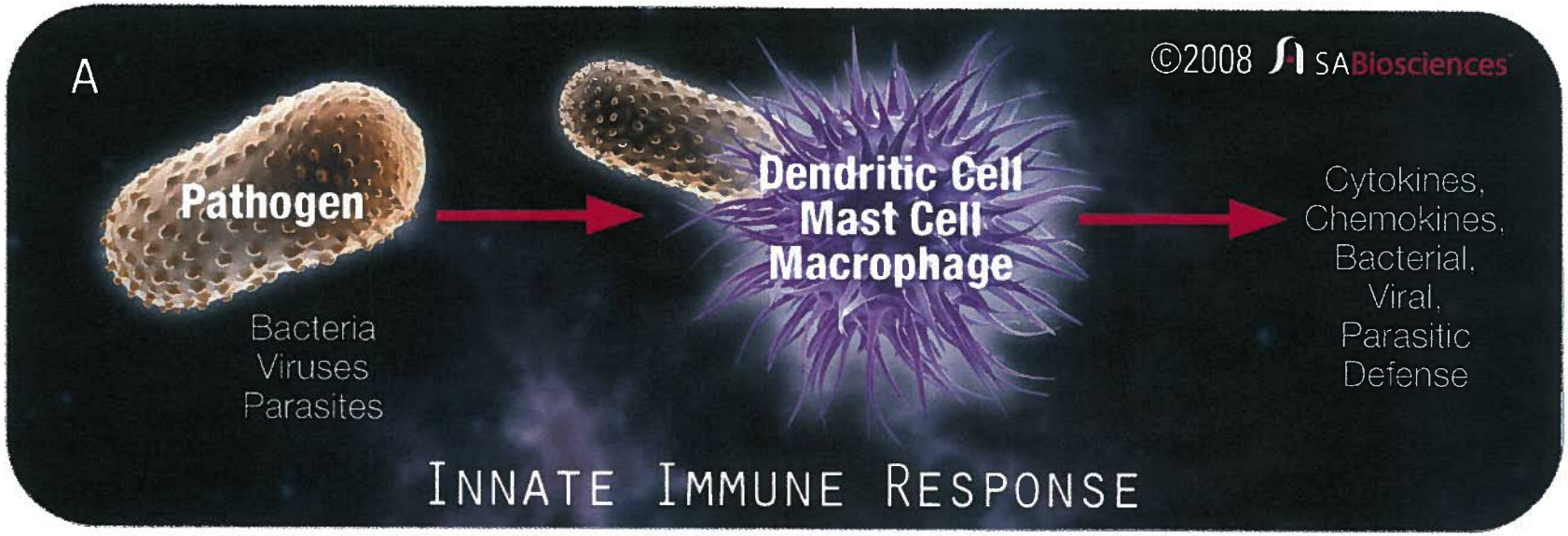

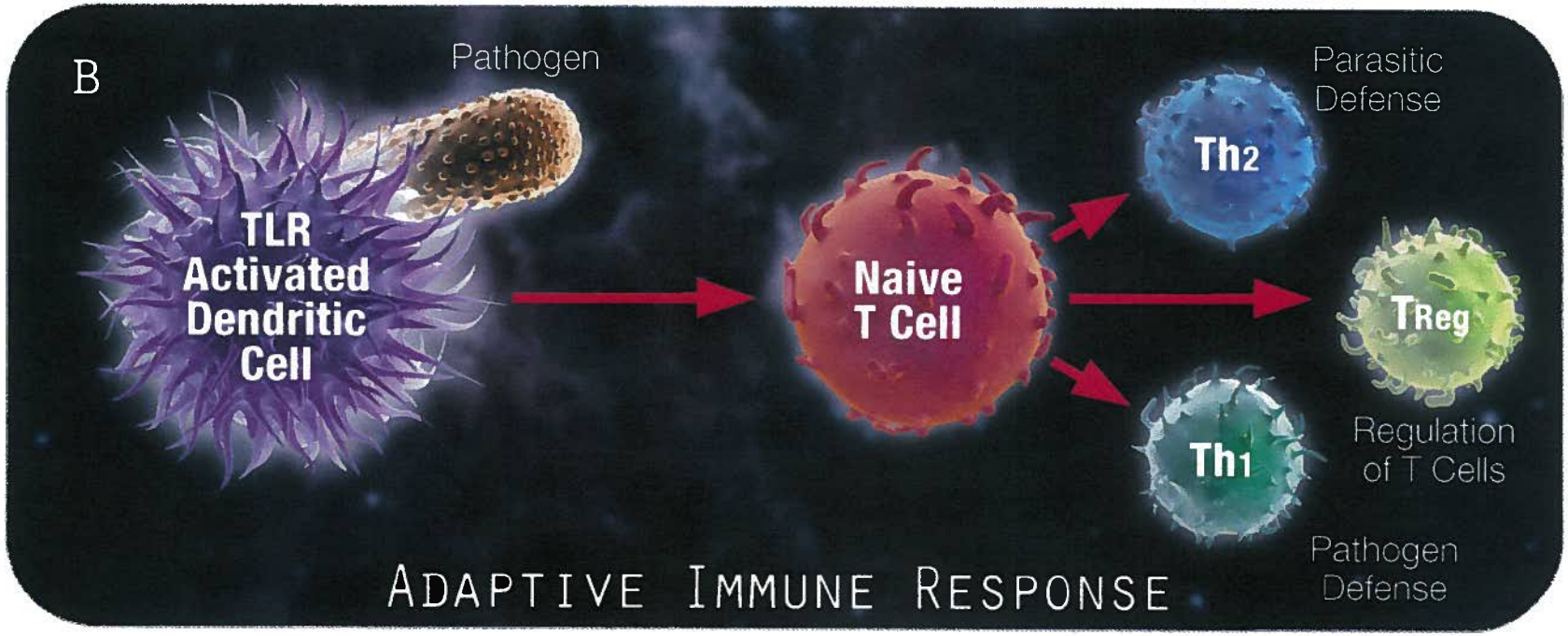

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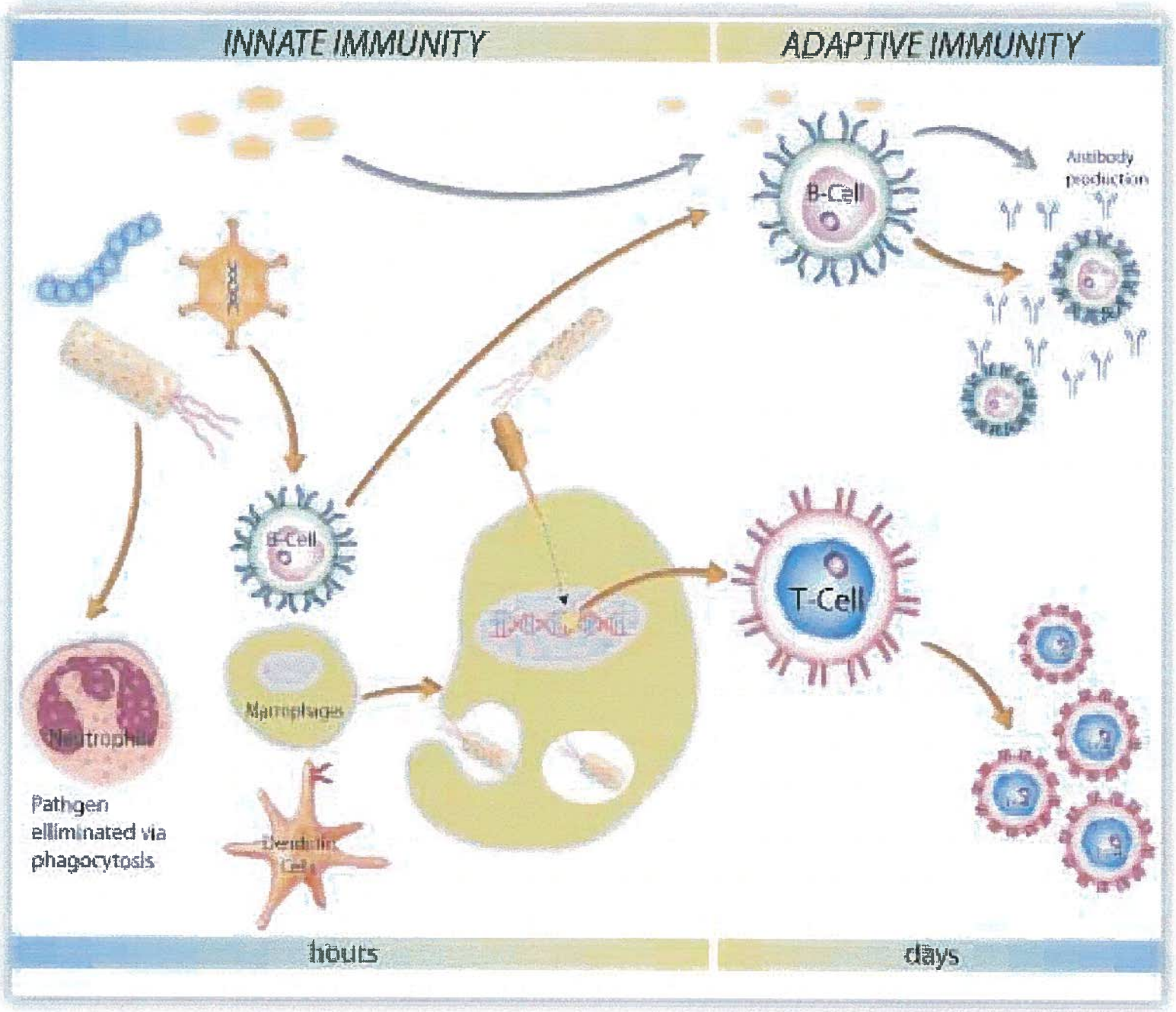


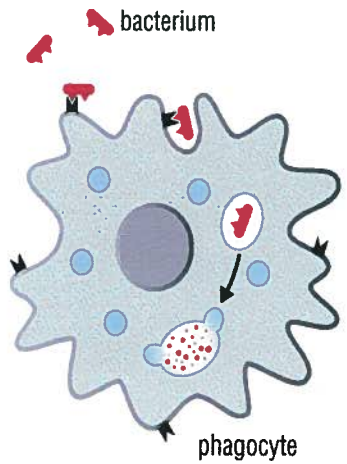
Slide courtesy of Caliper Life Sciences

Innate vs adaptive immunity

From **Immunity: The Immune Response in Infectious and Inflammatory Disease**
by DeFranco, Locksley and Robertson

Cellularists

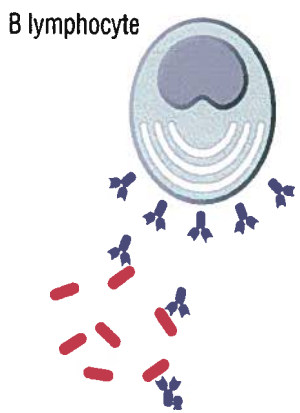
(a)



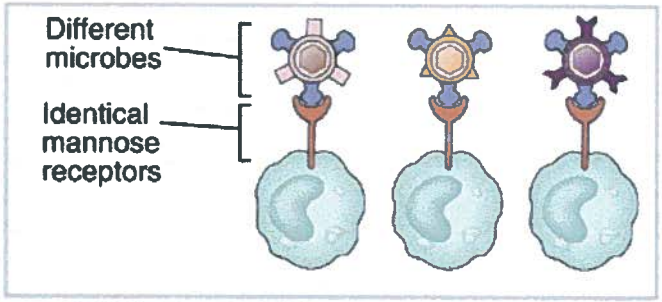
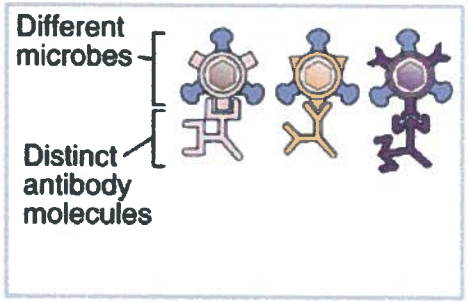
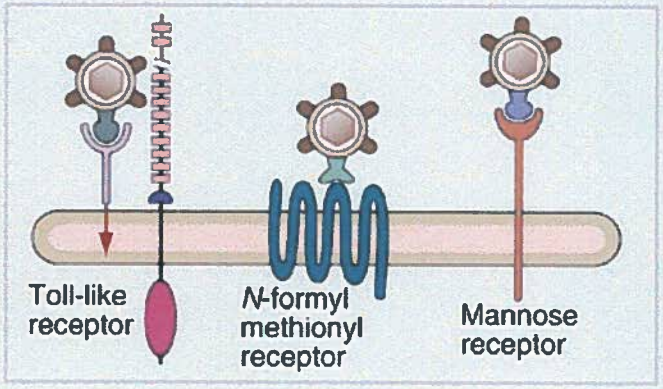
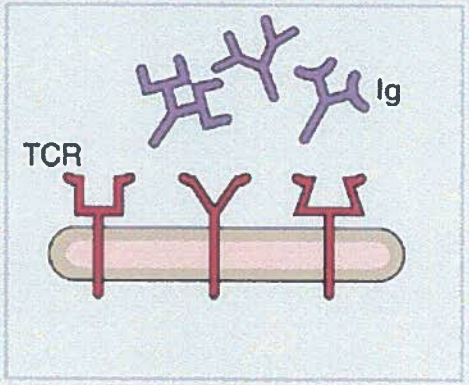
Ilya Ilyich Mechnikov
(1845-1916)
Nobel Prize 1908

Humoralists

(b)



Paul Ehrlich
(1854-1915)
Nobel Prize 1908

	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes ("molecular patterns") 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Receptors	Encoded in germline; limited diversity 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and nonself	Yes; host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on selection against self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

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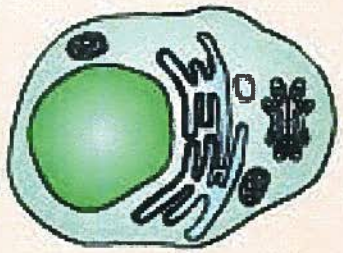
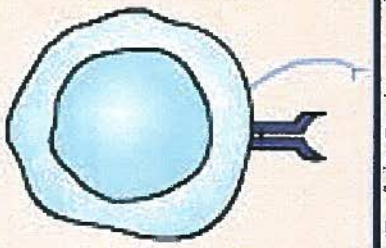
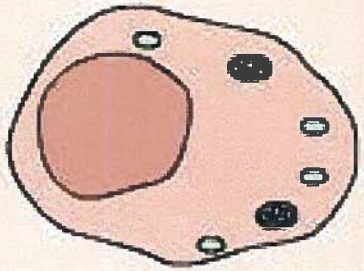
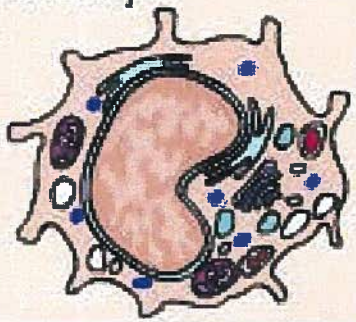
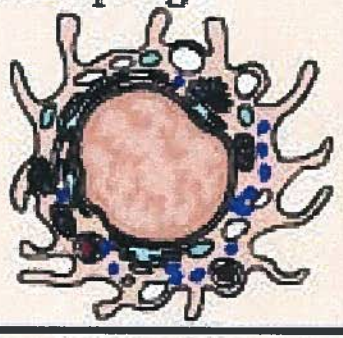
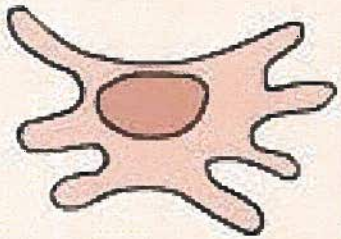
CELLS AND ORGANS OF IMMUNE SYSTEM

Cell Type	Precursor (factors)	Activity (cells/µL)
B cell 	Lymphoid stem cell (IL-7, IL-3); B progenitor (IL-4,IL-2, IL-5, IL-6).	Plasma cell: secretes antibodies. Memory cell: immunity. (Total lymphocytes: 2750 cells/µL or 20-40% of WBC.)
T cell 	Lymphoid stem cell; B progenitor (IL-4); Thymocyte (IL-7, IL-2, IL-4).	T helper cell (CD4+): secrete cytokines. Cytotoxic T lymphocyte (CD8+):Eliminate altered self-cells. Memory cell: long-term immunity.
Null cell 	Lymphoid stem?	Natural Killer (NK) cell: anti-tumor and anti-viral cytotoxic activity. (5-10% of lymphocytes in blood.)

Lymphocytes
Monocytes
Granulocytes
Organs

CELLS AND ORGANS OF IMMUNE SYSTEM

Cell Type	Precursor (factors)	Activity (cells/µL)
Monocyte 	Myeloid stem cell (IL-3, GM-CSF, IL-6); Granulocyte-monocyte progenitor (GM-CSF, M-CSF)	Circulate in bloodstream, migrate to tissue and differentiate into macrophages. (Average of 540 cells/µL, 1-6% of WBC.)
Macrophage 	Monocyte (see above).	Tissue macrophage: phagocytic; secrete hydrolytic enzymes, soluble factors, and cytotoxic proteins.
Dendritic cell 	Myeloid stem cell; Granulocyte-monocyte progenitor? Monocyte?	Potent antigen-presenting cell (no activation needed). Found in tissue; migrate to blood. (0.1% of WBC)

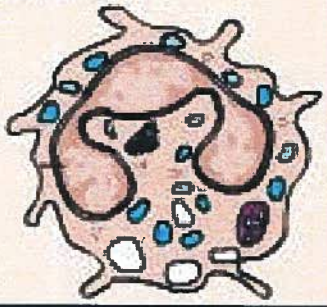
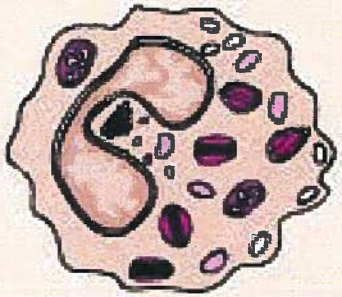
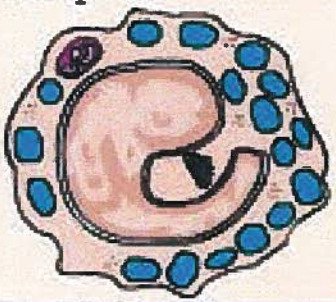
Lymphocytes

Monocytes

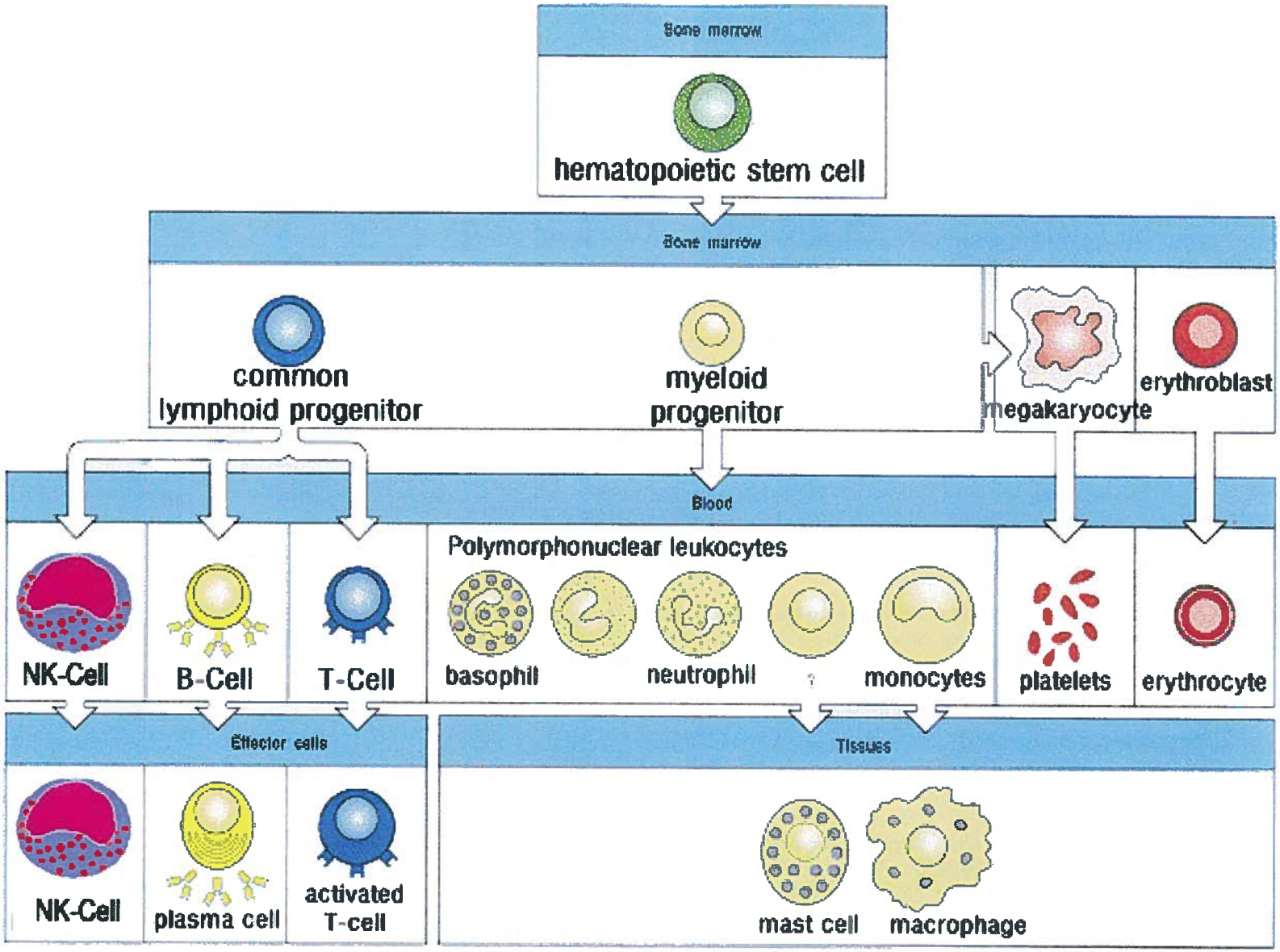
Granulocytes

Organs

CELLS AND ORGANS OF IMMUNE SYSTEM

Cell Type	Precursor (factors)	Activity (cells/µL)
Neutrophil 	Myeloid stem cell (IL-3, GM-CSF, IL-6); Granulocyte-monocyte progenitor (GM-CSF, G-CSF). Monocyte (IL-8).	Polymorphonuclear leukocyte (PMN): phagocytic. First response to inflamation; moves from blood into tissue through extravasation. (Average of 5400 cells/µL, or 50-70% of WBC.)
Eosinophil 	Myeloid stem cell (IL-3, GM-CSF); Eosinophil progenitor (GM-CSF, IL-5).	Migrate from blood into tissue. Anti-parasitic. Somewhat phagocytic. (Average of 275 cells/µL, or 1-3% of WBC.)
Basophil 	Myeloid stem cell (IL-3, GM-CSF); Basophil progenitor (GM-CSF, IL-4).	Along with MAST CELLS, releases active substances; major role in development of allergic response. Nonphagocytic. (Average of 35 cells/µL, or <1% of WBC.)

Lymphocytes
Monocytes
Granulocytes
Organs


Bone marrow
hematopoietic stem cell
Bone marrow
common
lymphoid progenitor
myeloid
progenitor
megakaryocyte
erythroblast
Blood
NK-Cell
B-Cell
T-Cell
Polymorphonuclear leukocytes
basophil
neutrophil
monocytes
platelets
erythrocyte
Effector cells
NK-Cell
plasma cell
activated
T-cell
Tissues
mast cell
macrophage

INNATE IMMUNITY

Innate Immunity Serves Three Important Functions

"Innate immunity is the initial response to microbes that prevents infection of the host and, in many instances, can eliminate the microbes."

"The effector mechanisms of innate immunity are often used to eliminate microbes even in adaptive immune responses."

"Innate immunity to microbes stimulates adaptive immune responses and can influence the nature of the adaptive responses to make them optimally effective against different types of microbes."

Abbas and Lichtman, 5th ed., p. 275-6

Innate Immune System

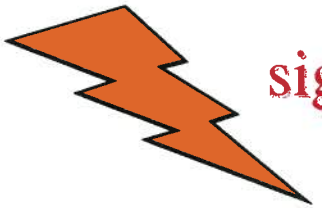
"External" Defenses	"Internal" Defenses
Mechanical	Complement
Chemical	Phagocytic Cells
Microbial	Non-phagocytic Cells

Innate Immunity depends upon:

Recognition of a: Pathogen-Associated Molecular Pattern (PAMP): conserved molecular motifs in microbes, *e.g.*, LPS, LP, mannose, etc.

By a: Pattern Recognition Receptor (PRR): host receptors that recognize PAMPs and enable signaling, e.g., CD14, TLRs, NODs, etc.

To induce:

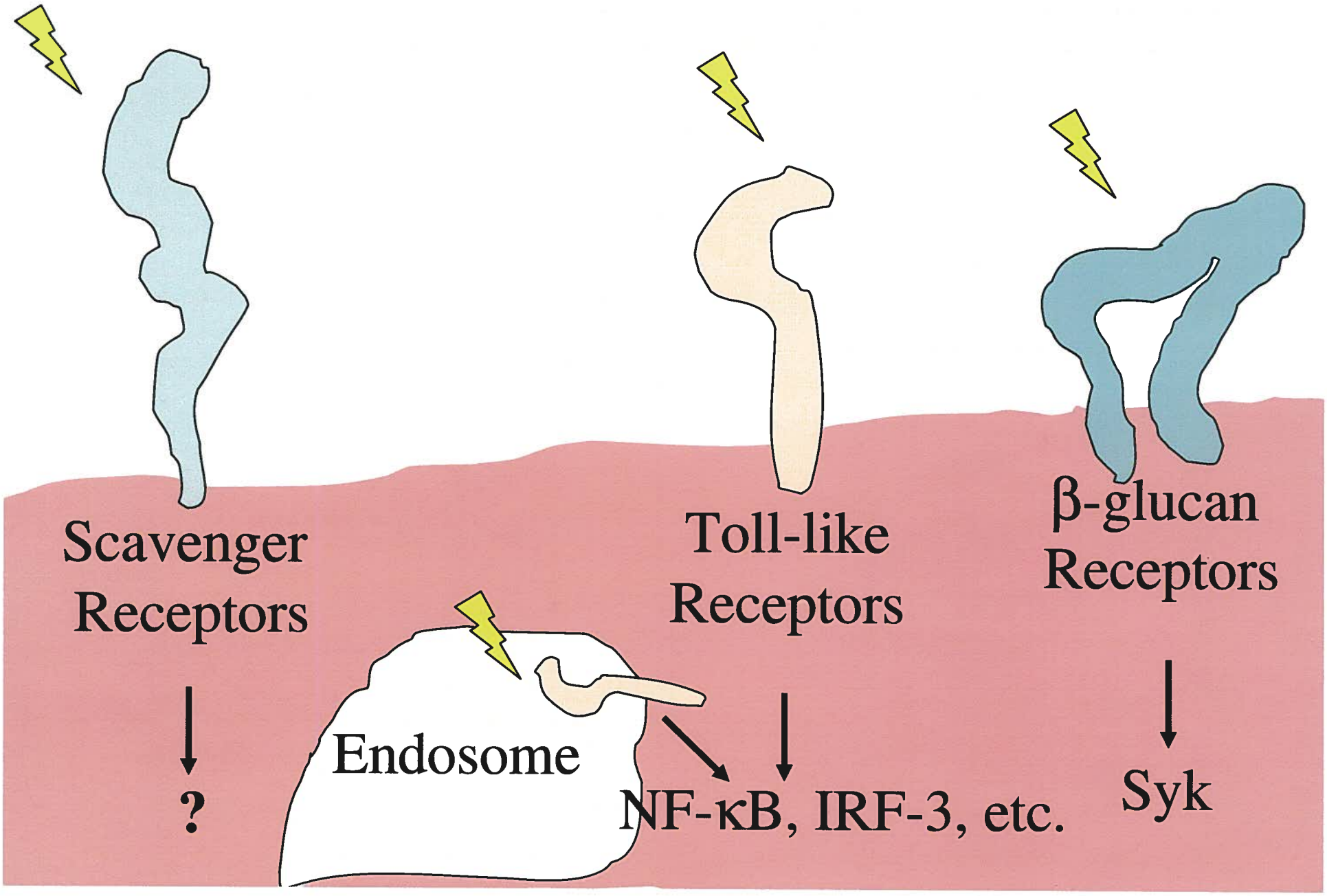


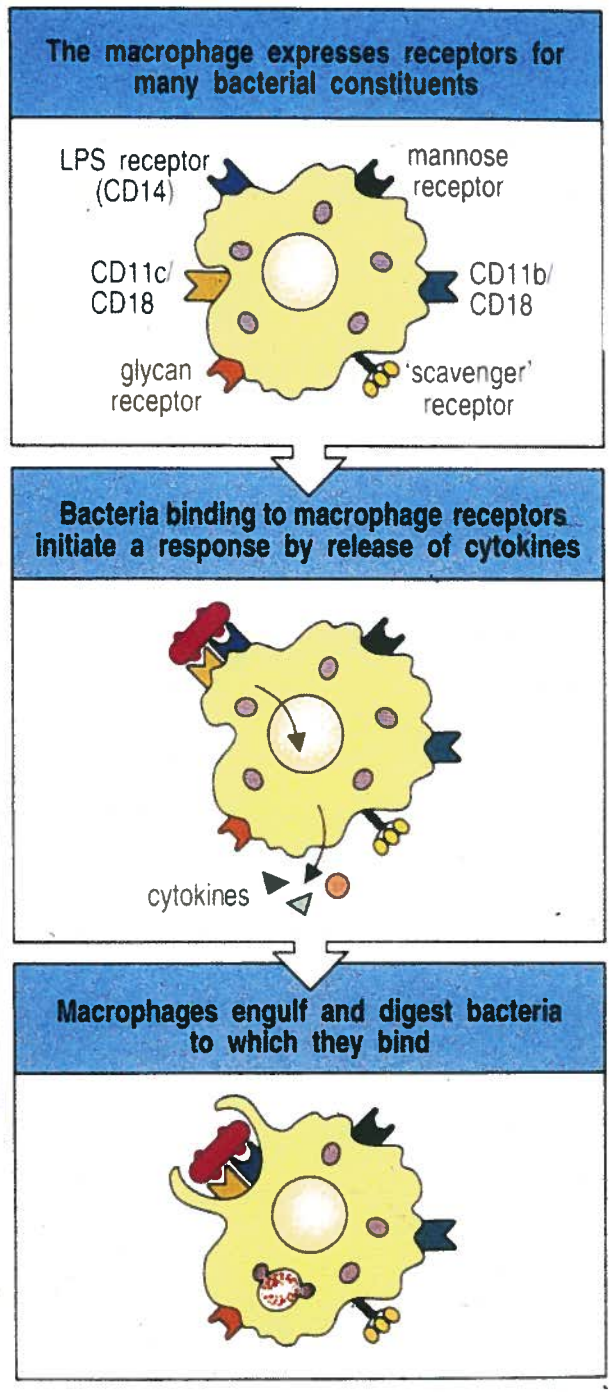
signal transduction

Changes in gene expression

Inflammation/destruction of microbes

PRRs: Pattern Recognition Receptors



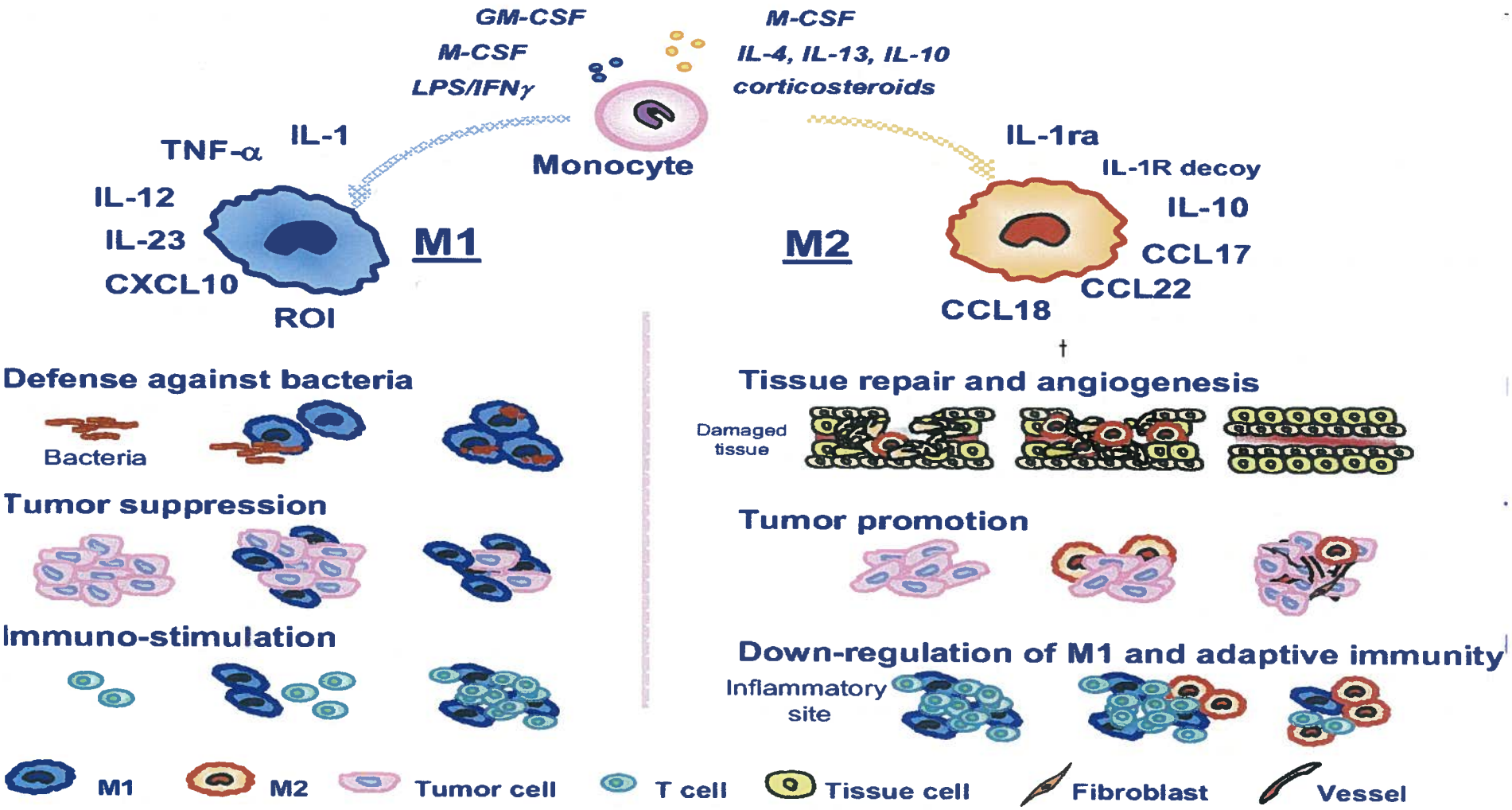


PRRs lead to recognition.

PRRs lead to signaling.

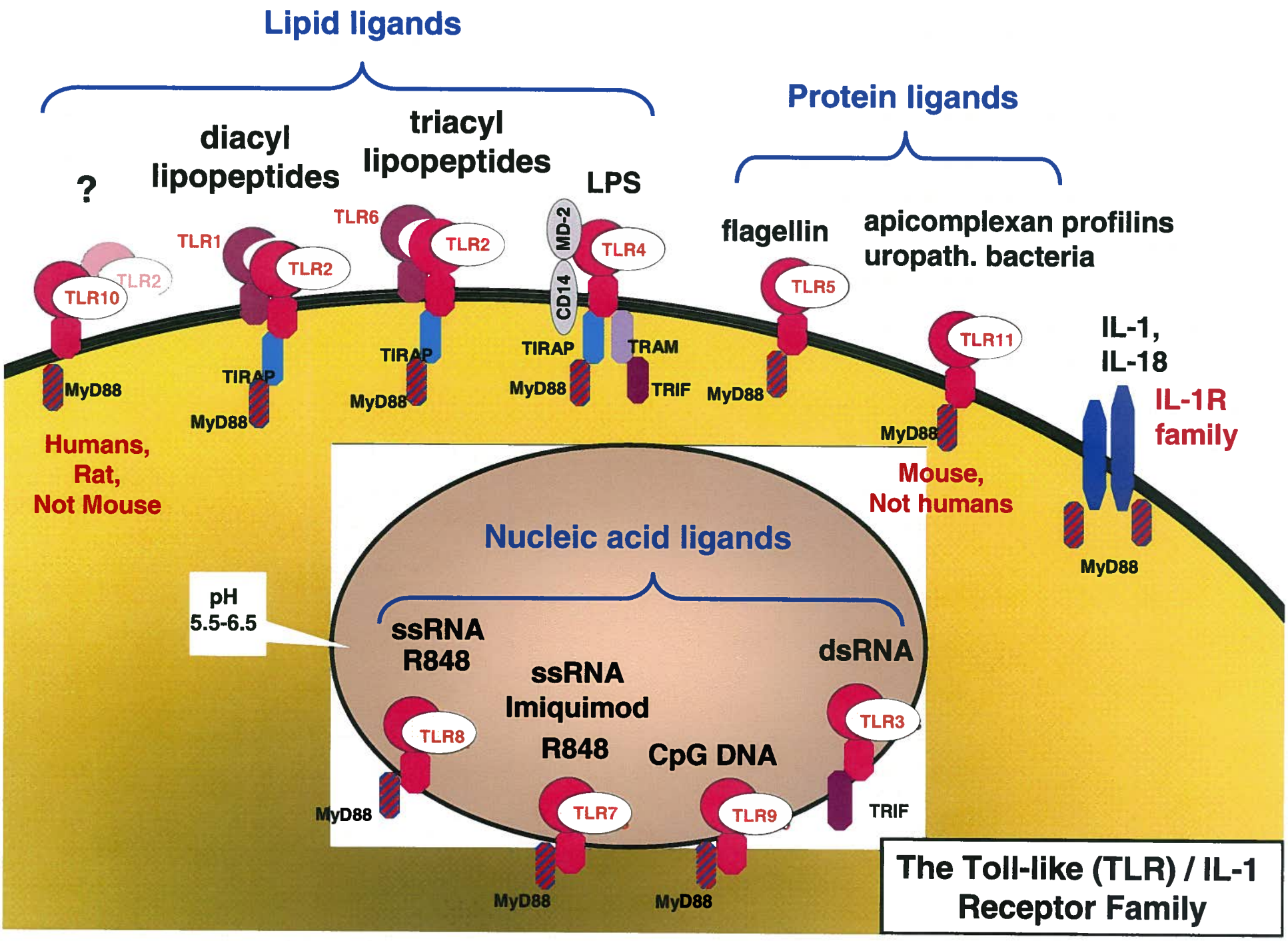
PRRs lead to uptake and killing of microbes intracellularly.

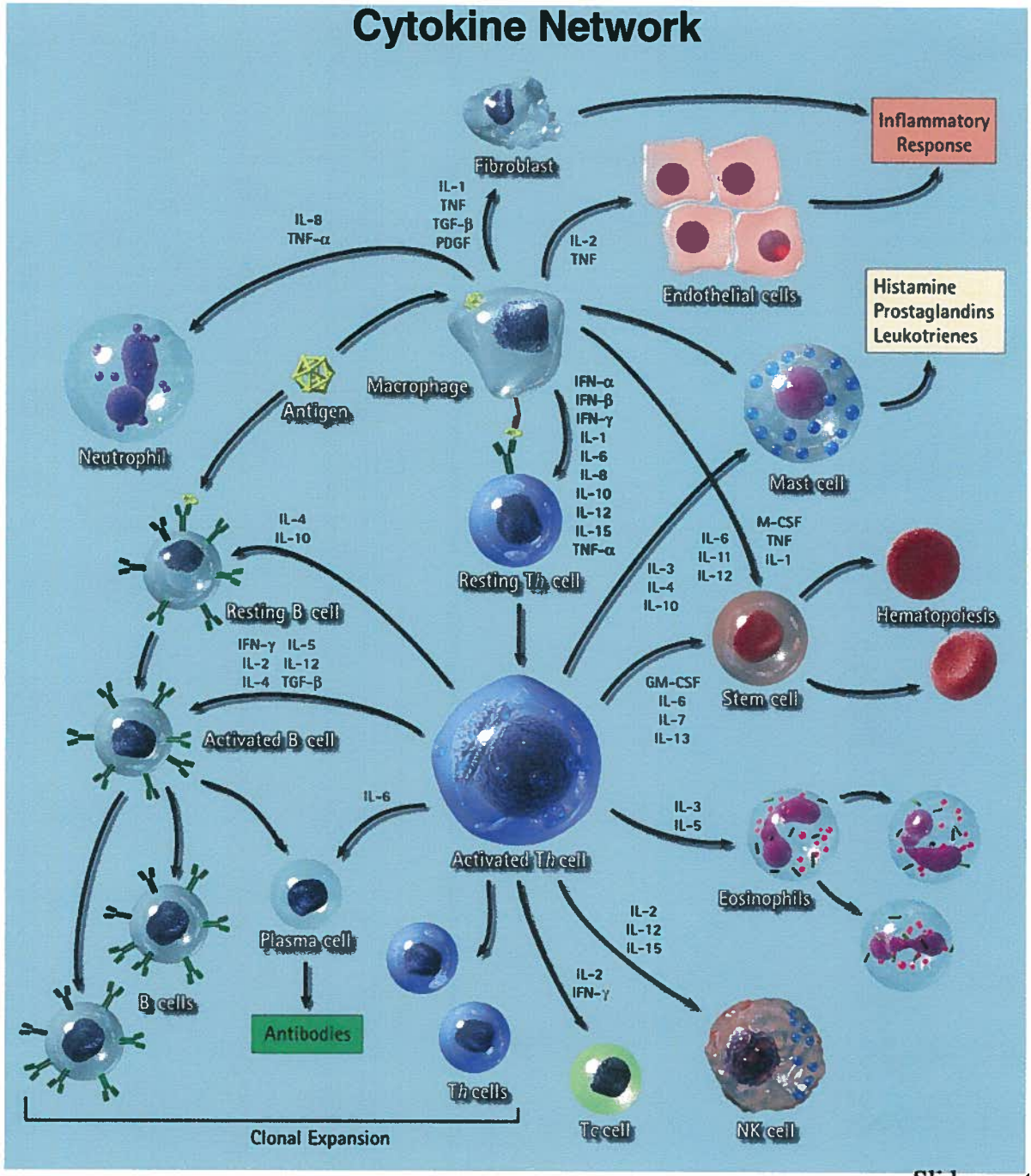
Polarization of macrophage function



G. Solinas, G. Germano, A. Mantovani and P. Allavena, *Journal of Leukocyte Biology*. 2009;86:1065-1073

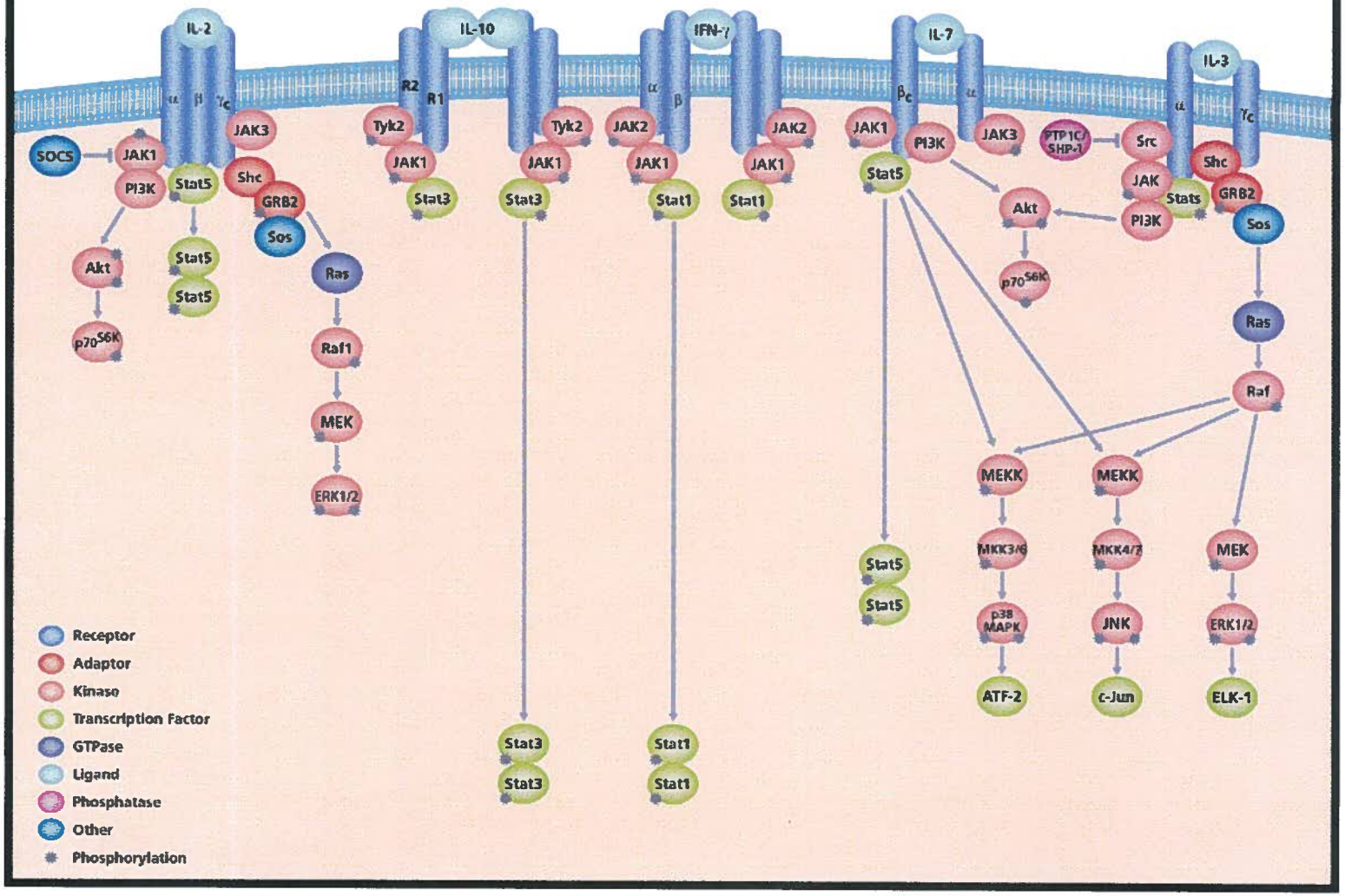
Signaling in the Innate Immune System


Lipid ligands
?
diacyl lipopeptides
triacyl lipopeptides
LPS
Protein ligands
flagellin
apicomplexan profilins
uropath. bacteria
TLR10
TLR2
TLR1
TLR2
TLR6
TLR2
MD-2
CD14
TLR4
TLR5
TLR11
IL-1,
IL-18
IL-1R family
MyD88
TIRAP
MyD88
TIRAP
MyD88
TIRAP
MyD88
TRAM
TRIF
MyD88
MyD88
Humans, Rat, Not Mouse
Mouse, Not humans
Nucleic acid ligands
pH 5.5-6.5
ssRNA R848
ssRNA Imiquimod R848
CpG DNA
dsRNA
TLR8
TLR7
TLR9
TLR3
MyD88
MyD88
MyD88
TRIF
The Toll-like (TLR) / IL-1 Receptor Family



Slide courtesy of EMD Biosciences

Cytokine Signaling

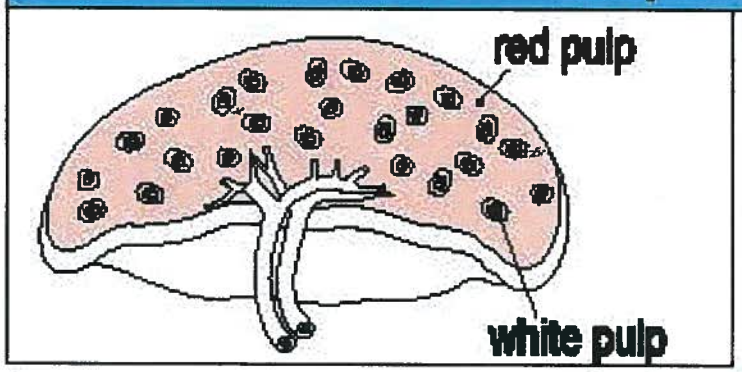


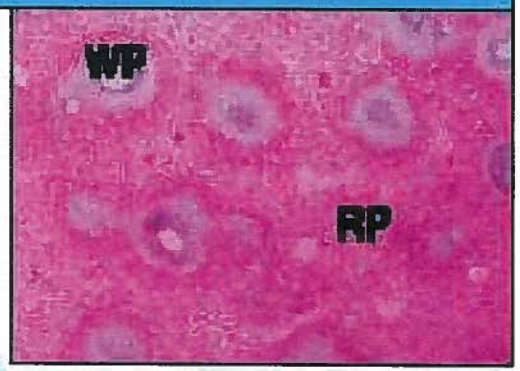
Courtesy and © Becton, Dickinson and Company

BD

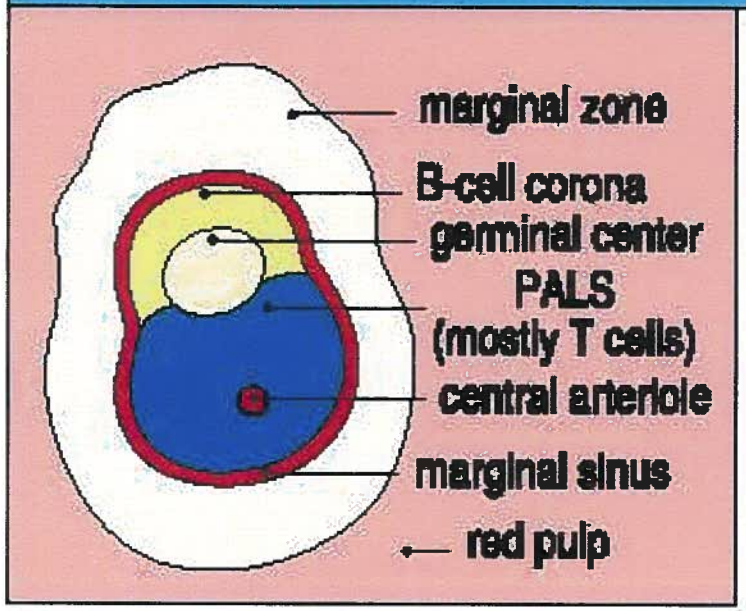
ADAPTIVE IMMUNITY

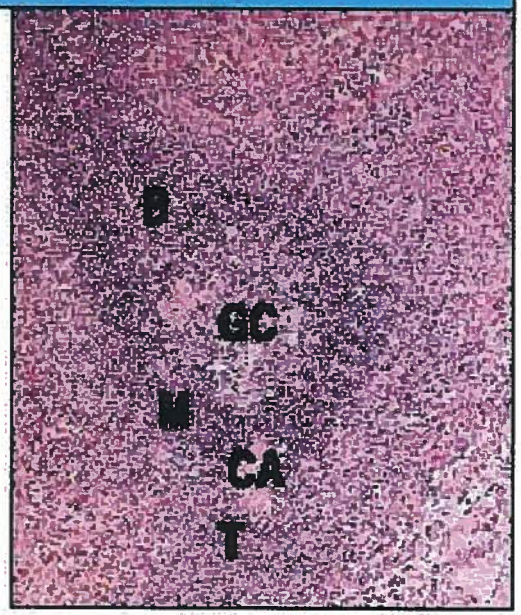
The spleen





Transverse section of white pulp of spleen





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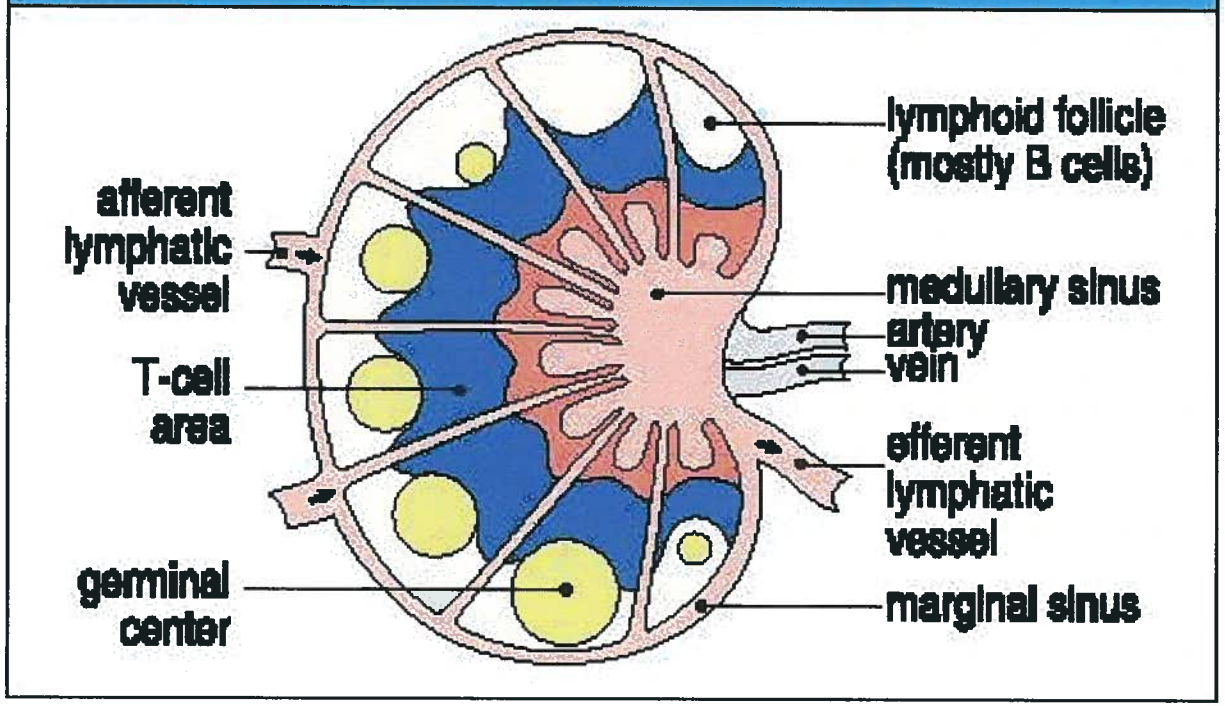
The lymph node



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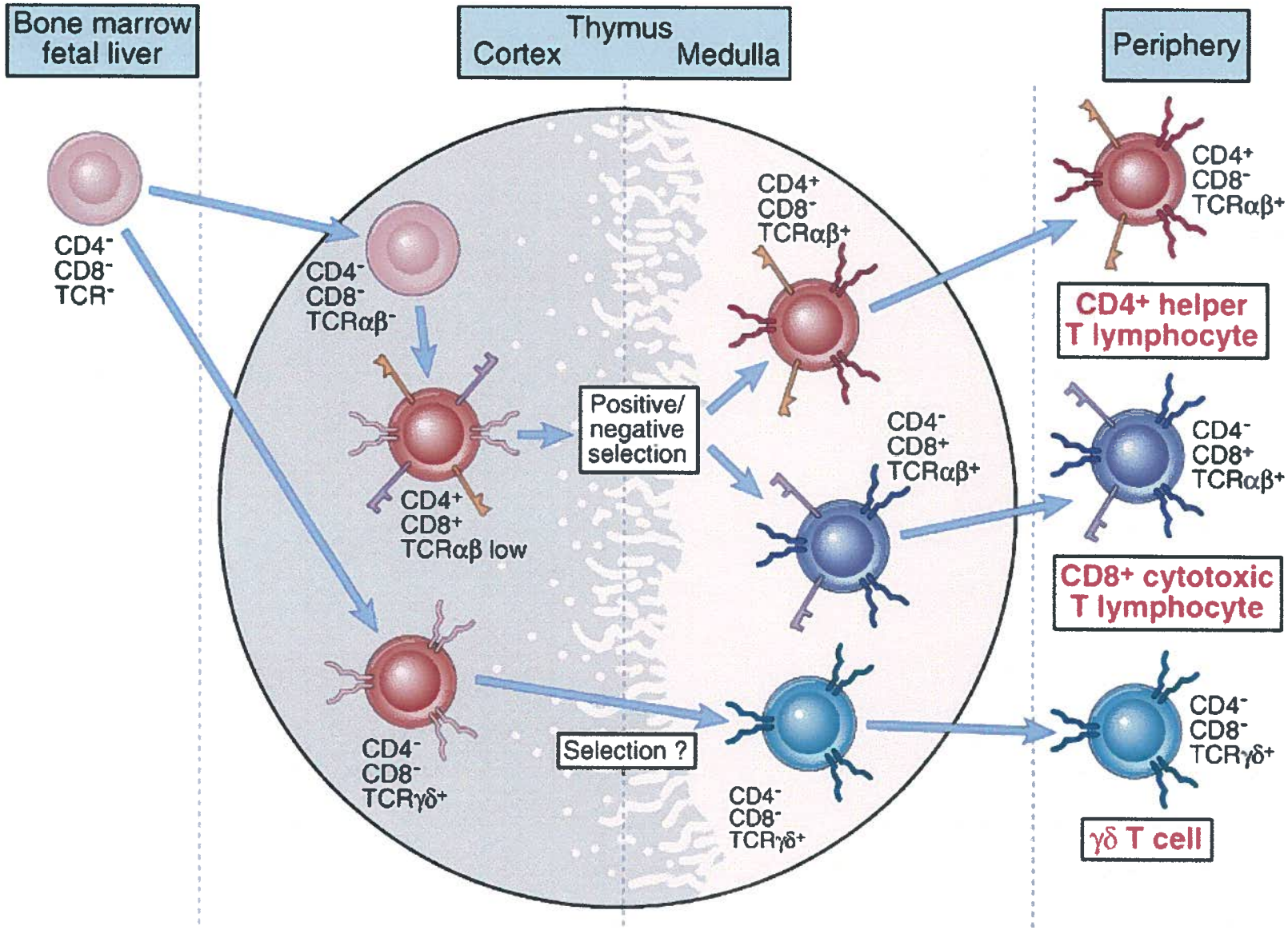
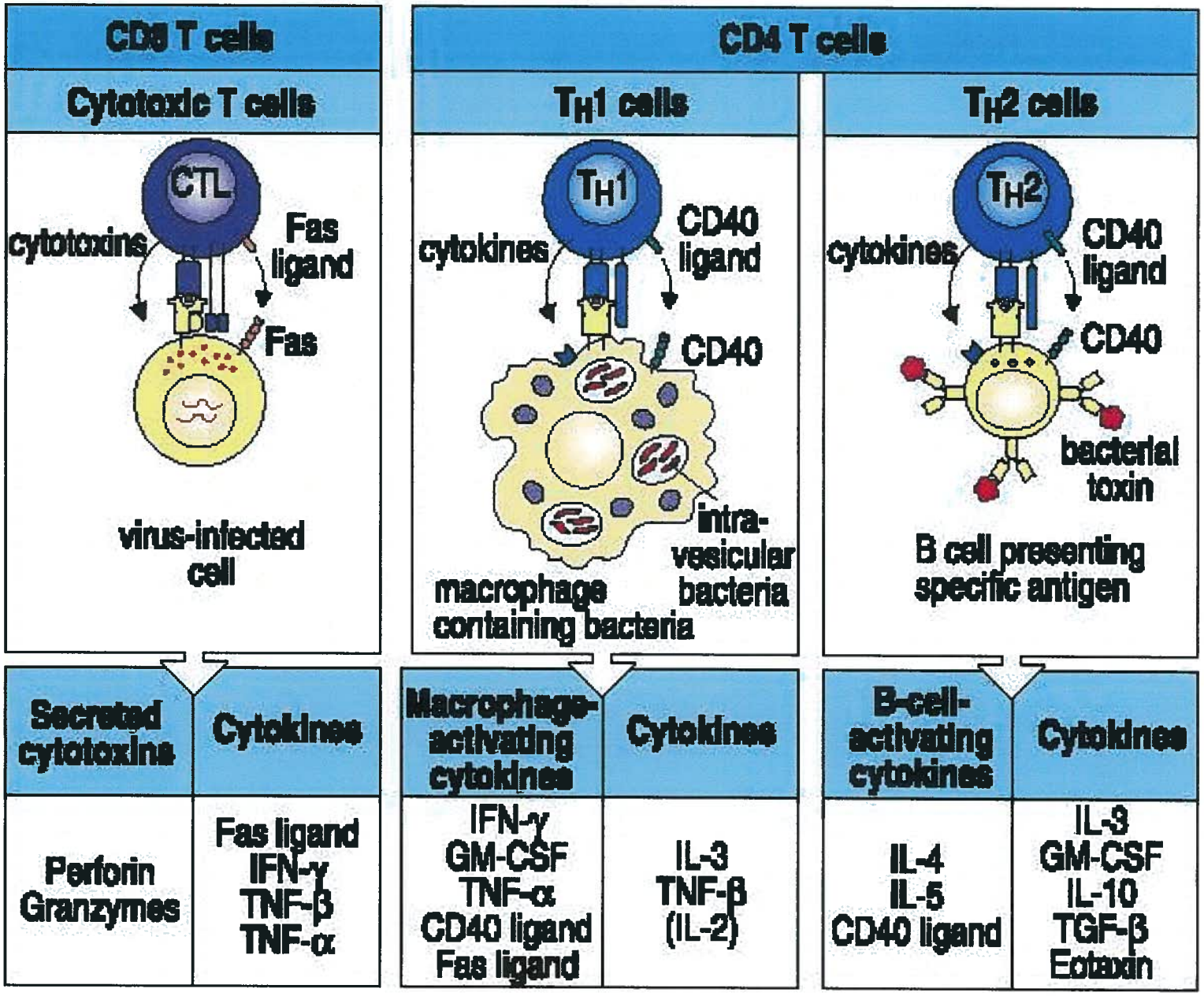
T Cells



© Elsevier. Abbas et al: Cellular and Molecular Immunology 6e - www.studentconsult.com



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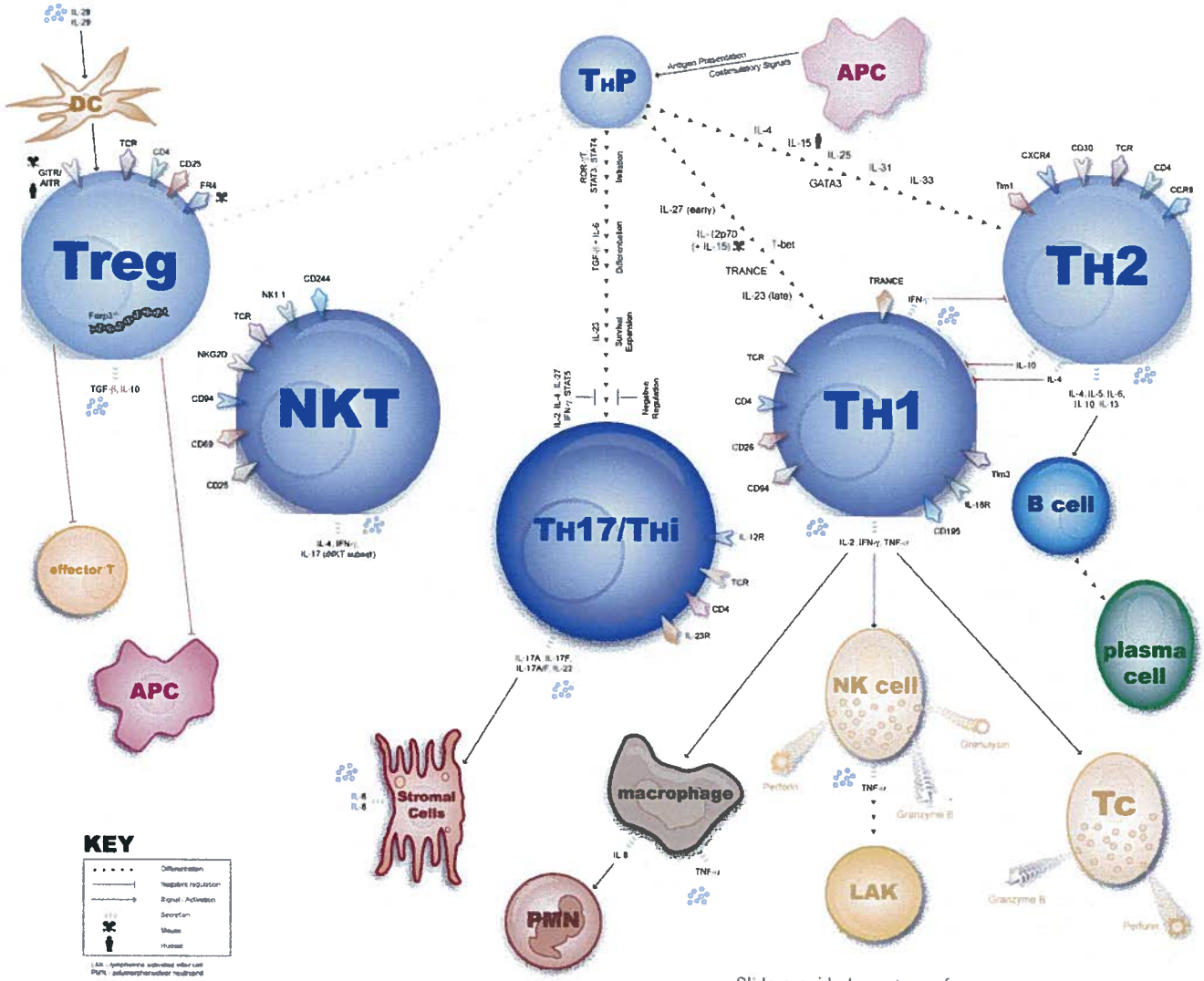
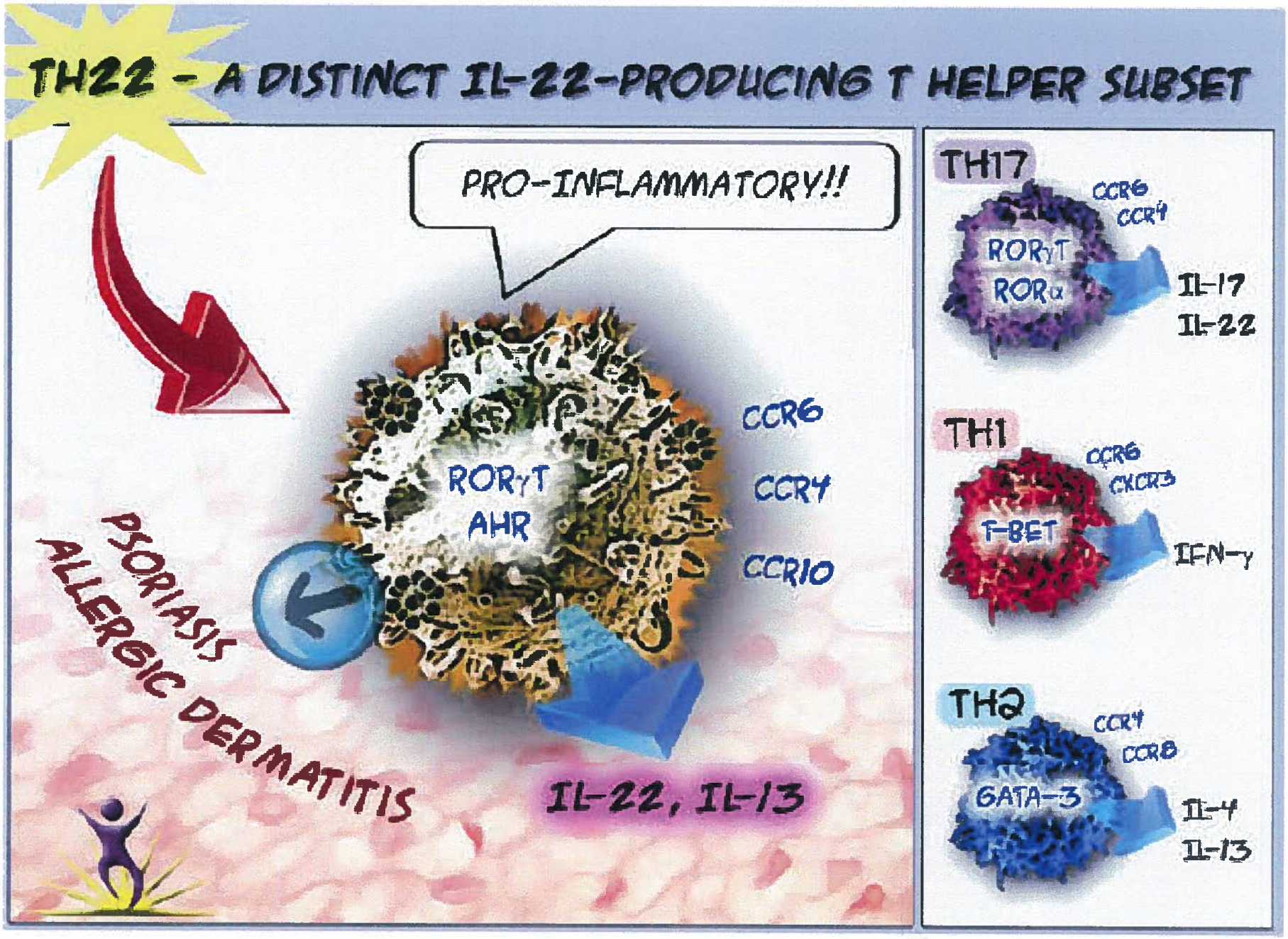
Functionally-Distinct T Cell Lineages: An Emerging Diversity



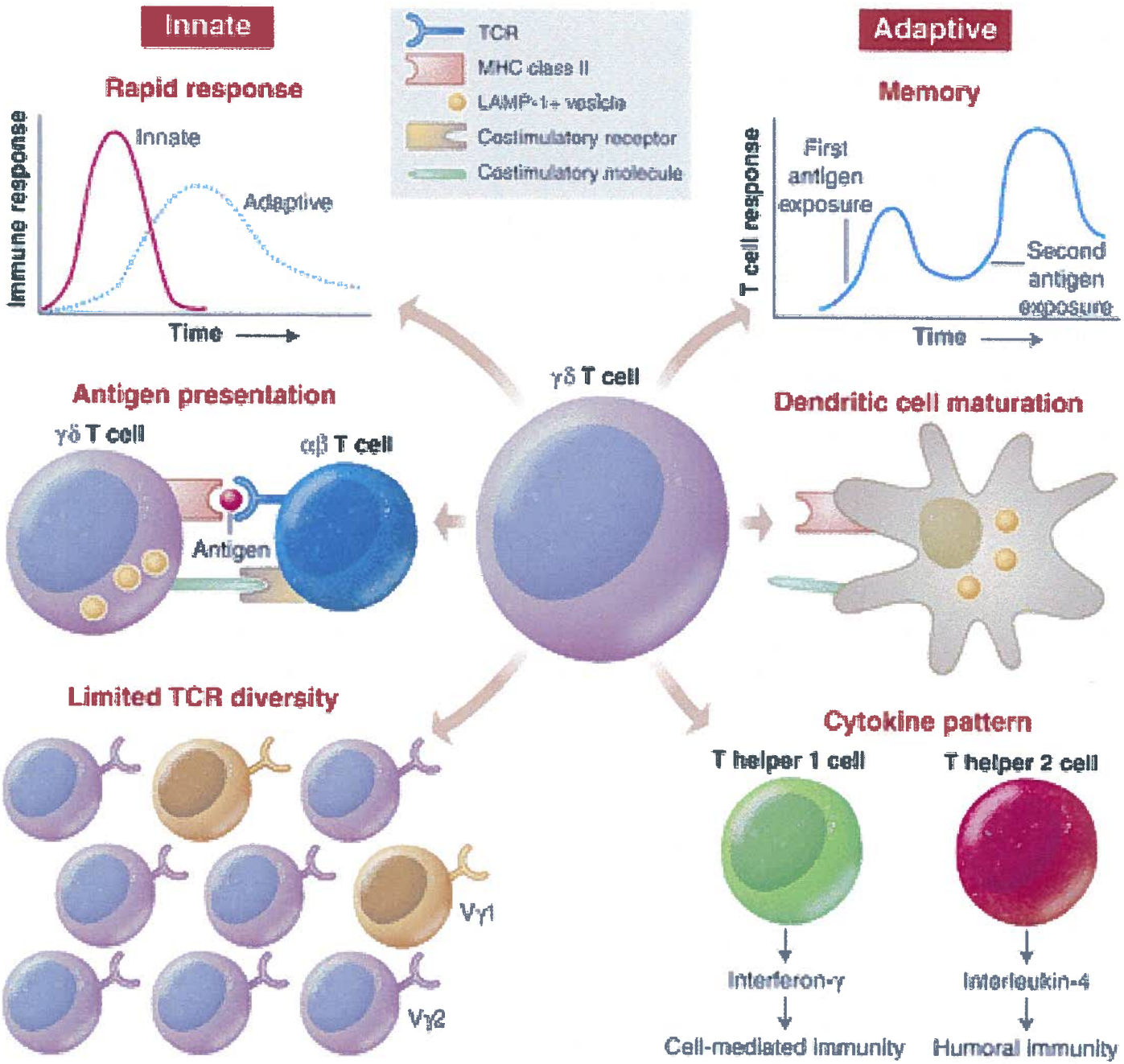
Slide provided courtesy of

full spectrum cell analysis
eBioscience™

www.ebioscience.com

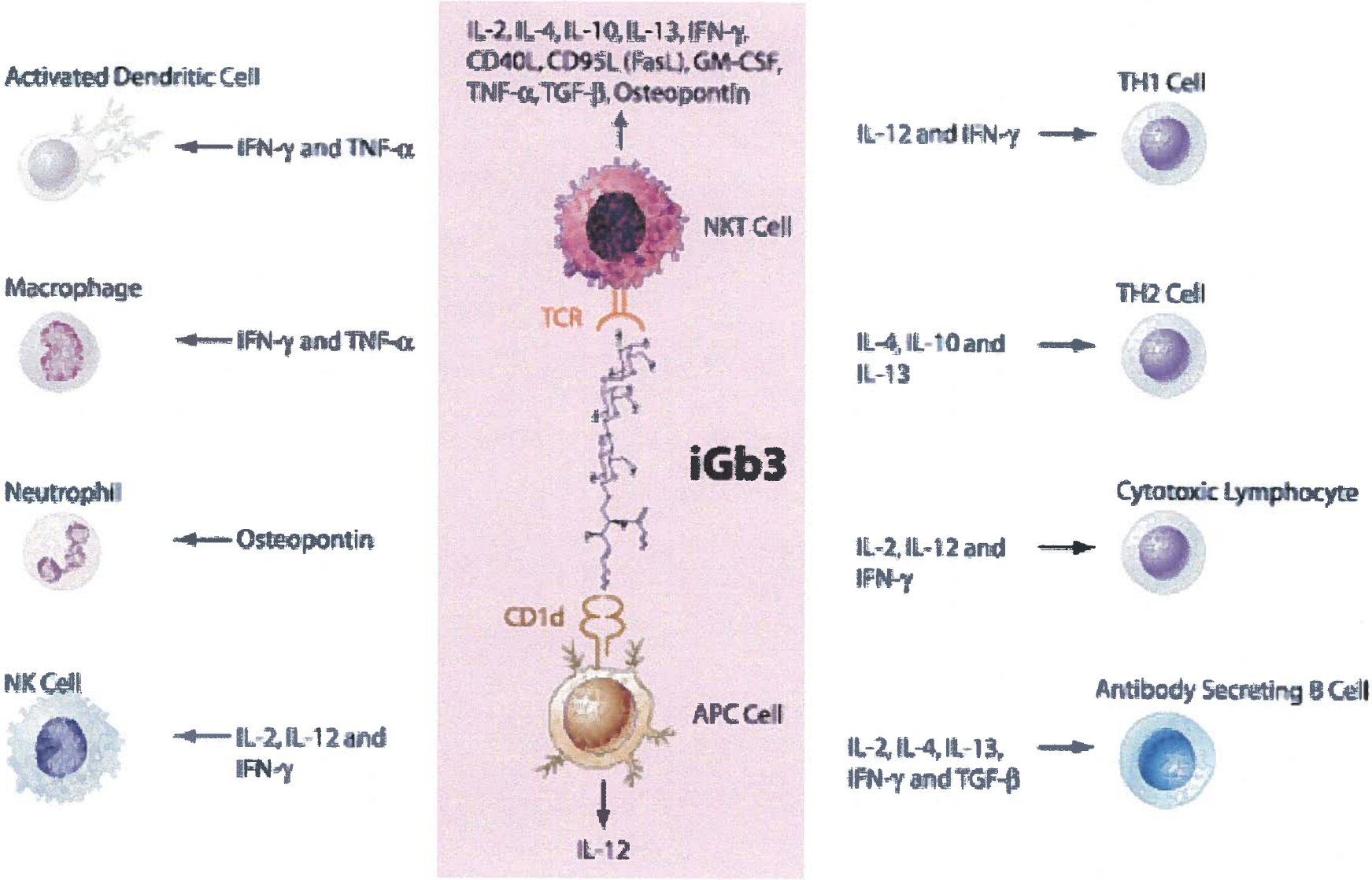


Slide Courtesy of BioLegend



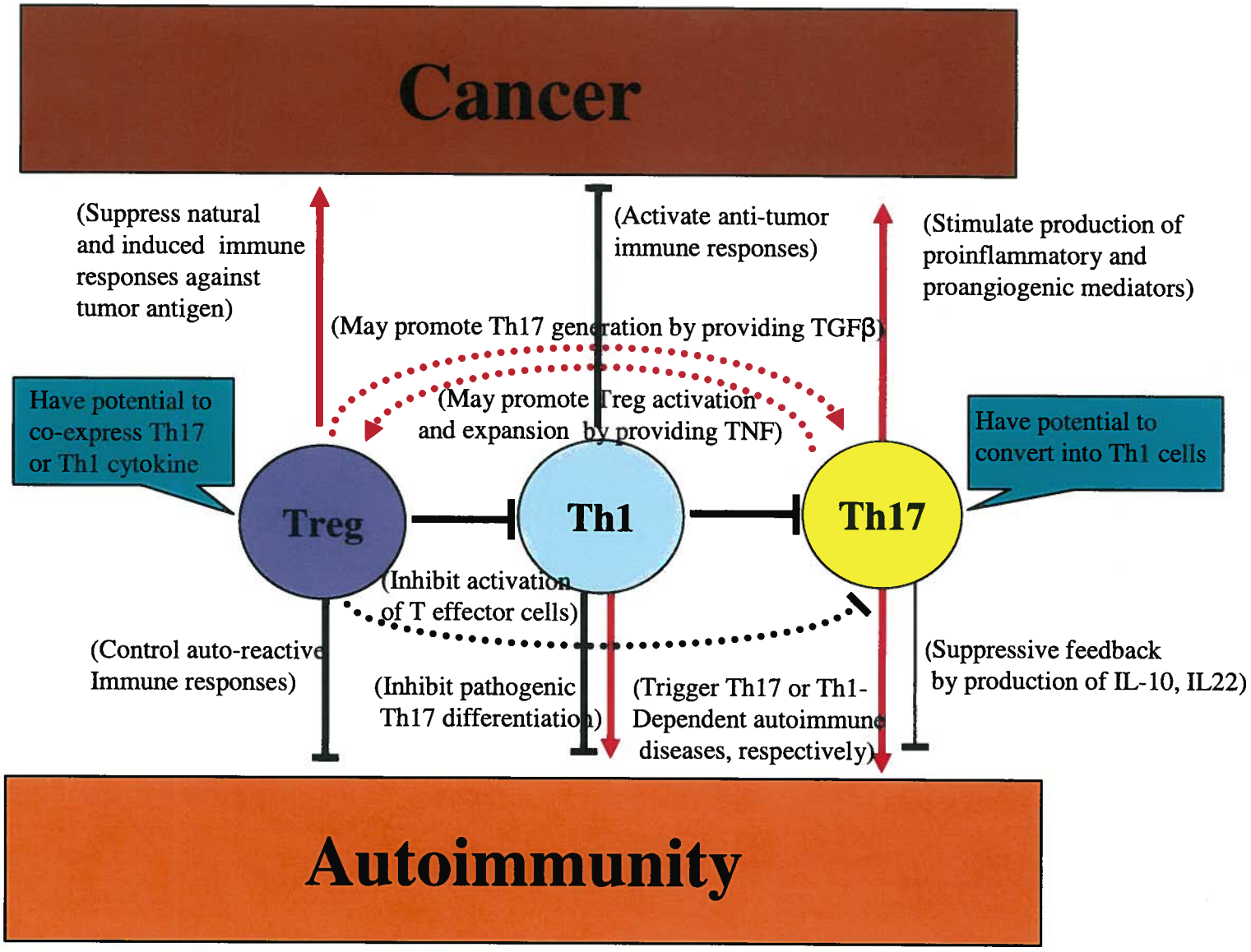
From RL Modlin, PA Sieling, Now Presenting: γδ T Cells, *Science* **309**, 252 (2005). Illustration by Preston Huey.

NKT Cell Activation



Slide courtesy of Alexis Biochemicals Corp.

Interactions and Effects of Th1, Th17 and Tregs in Cancer and Autoimmunity



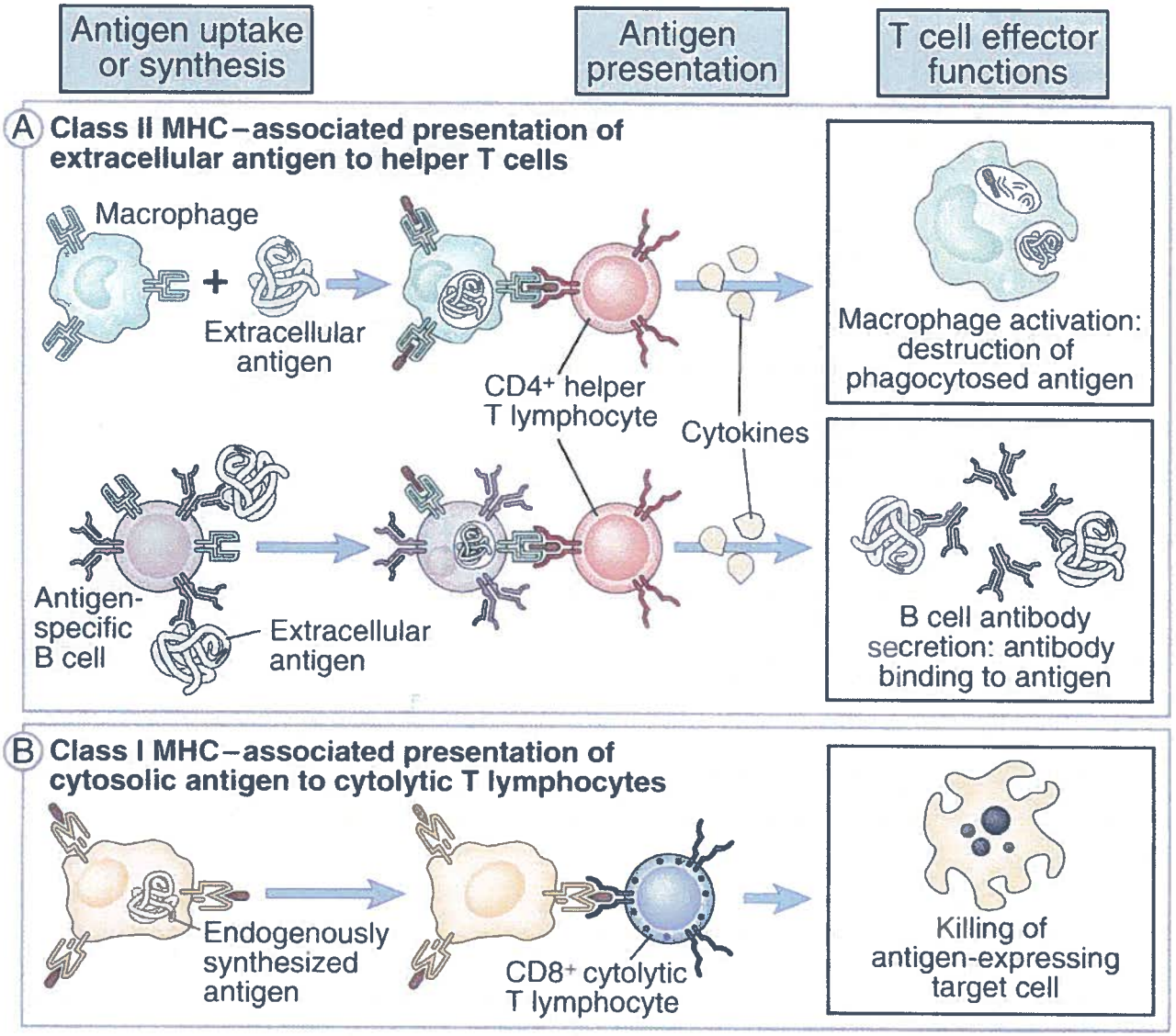


Figure 5–17 Presentation of extracellular and cytosolic antigens to different subsets of T cells.

A. Extracellular antigens are presented by macrophages or B lymphocytes to CD4+ helper T lymphocytes, which activate the macrophages or B cells and eliminate the extracellular antigens.

B. Cytosolic antigens are presented by nucleated cells to CD8+ CTLs, which kill (lyse) the antigen-expressing cells.

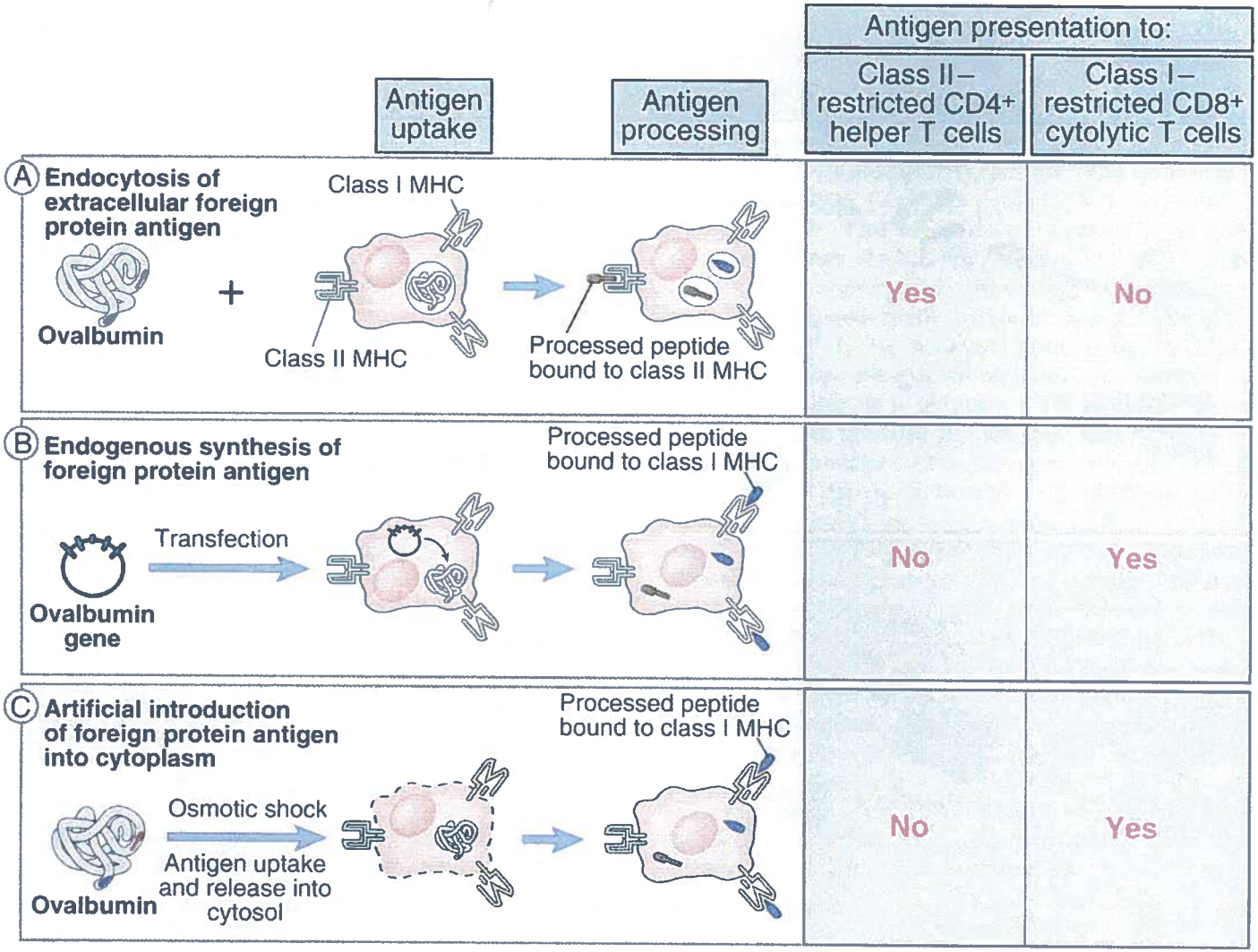
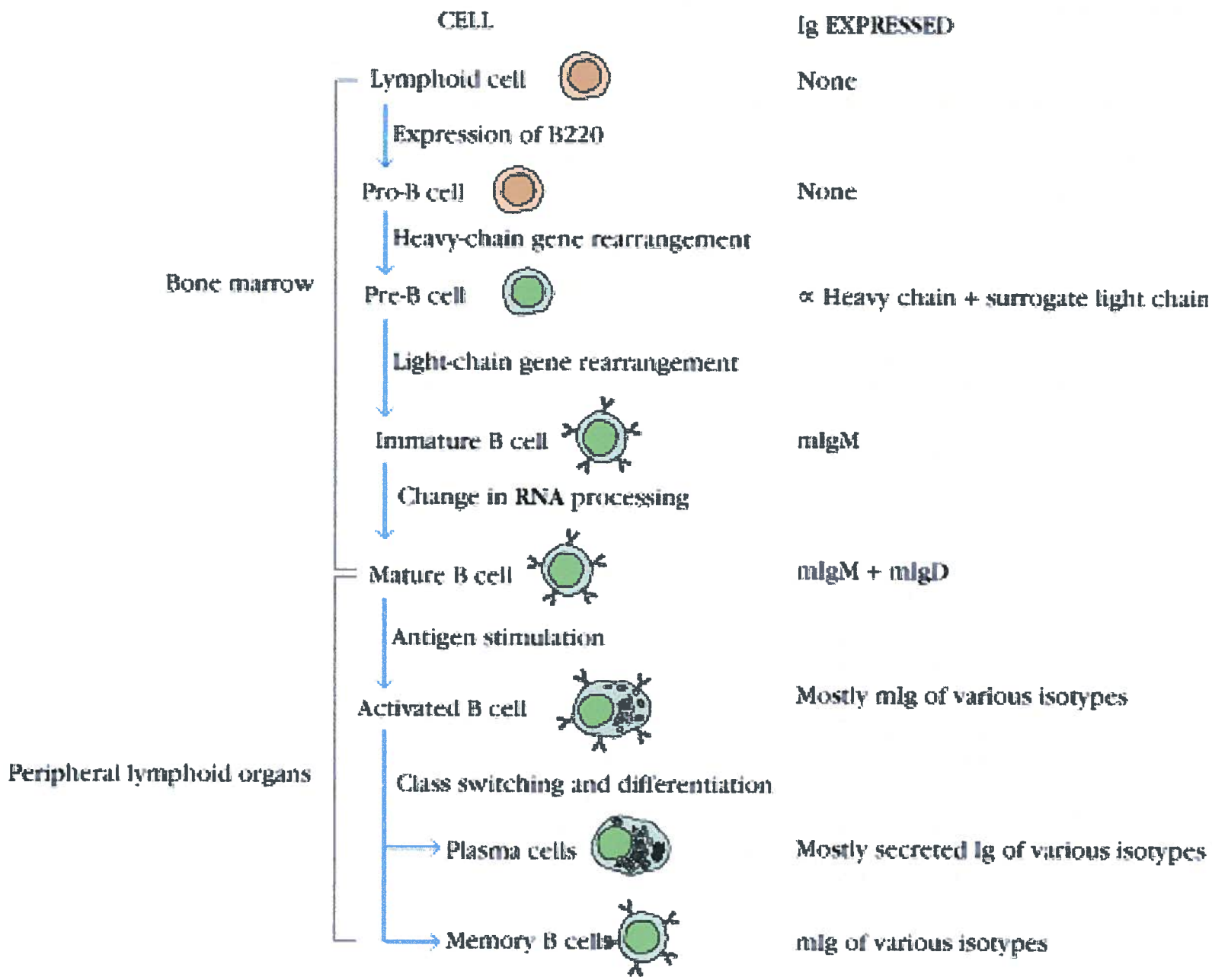
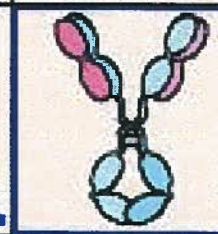
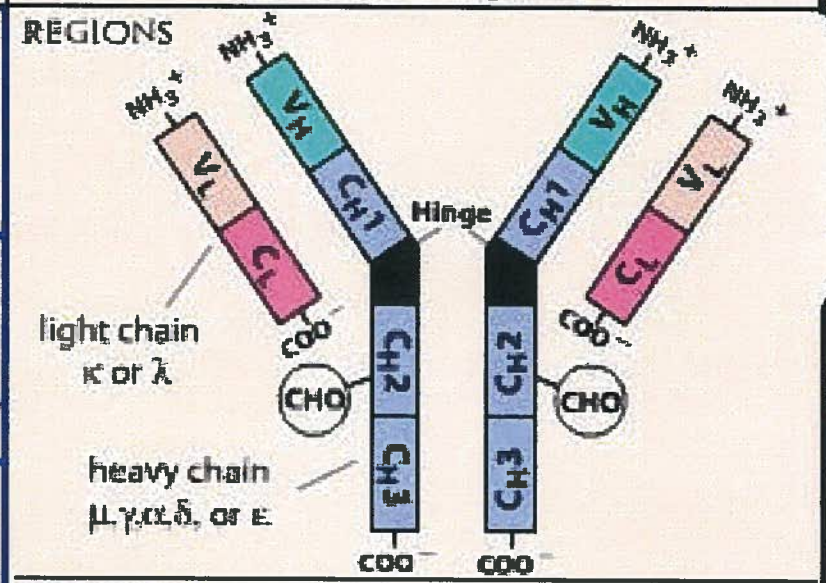
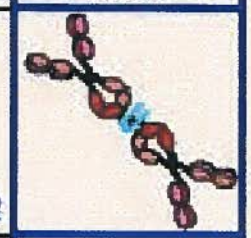
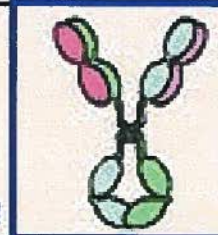
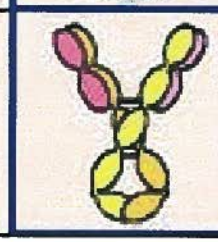


Figure 5–9 Presentation of extracellular and cytosolic antigens.
When a model protein ovalbumin is added as an extracellular antigen to an antigen-presenting cell that expresses both class I and class II MHC molecules, ovalbumin-derived peptides are presented only in association with class II molecules (A). When ovalbumin is synthesized intracellularly as a result of transfection of its gene (B), or when it is introduced into the cytoplasm through membranes made leaky by osmotic shock (C), ovalbumin-derived peptides are presented in association with class I MHC molecules. The measured response of class II–restricted helper T cells is cytokine secretion, and the measured response of class I–restricted CTLs is killing of the antigen-presenting cells.

B Cells


CELL
Ig EXPRESSED
Lymphoid cell
None
Expression of B220
Pro-B cell
None
Heavy-chain gene rearrangement
Bone marrow
Pre-B cell
α Heavy chain + surrogate light chain
Light-chain gene rearrangement
Immature B cell
mIgM
Change in RNA processing
Mature B cell
mIgM + mIgD
Antigen stimulation
Activated B cell
Mostly mIg of various isotypes
Peripheral lymphoid organs
Class switching and differentiation
Plasma cells
Mostly secreted Ig of various isotypes
Memory B cells
mIg of various isotypes

Ig Class	Structure	Schematic Diagrams
IgG structure		
IgA structure		
IgM structure		
IgE structure		
IgD		

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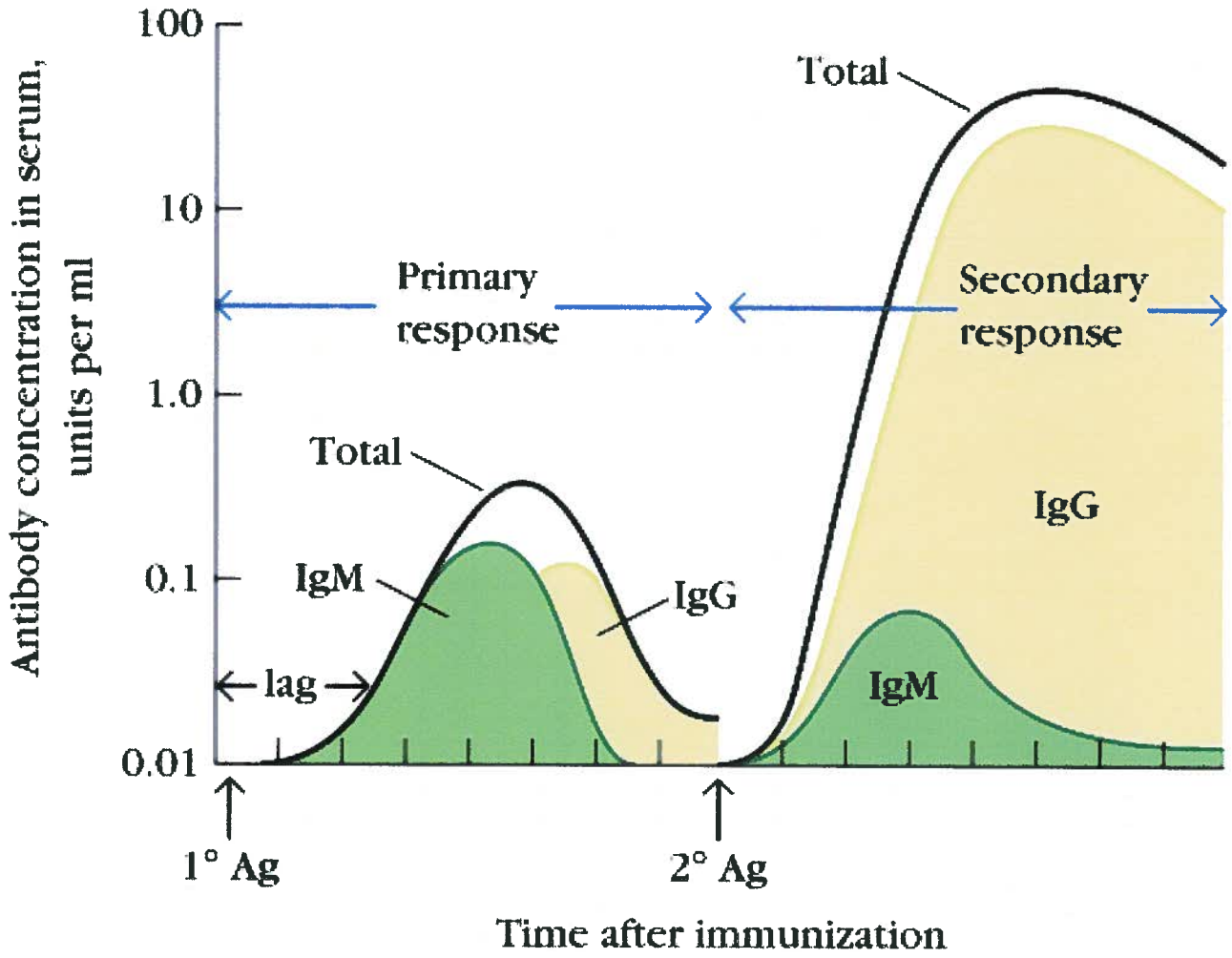

Antibody concentration in serum, units per ml
100
10
1.0
0.1
0.01
Primary response
Secondary response
Total
IgM
IgG
lag
Total
IgG
IgM
1° Ag
2° Ag
Time after immunization

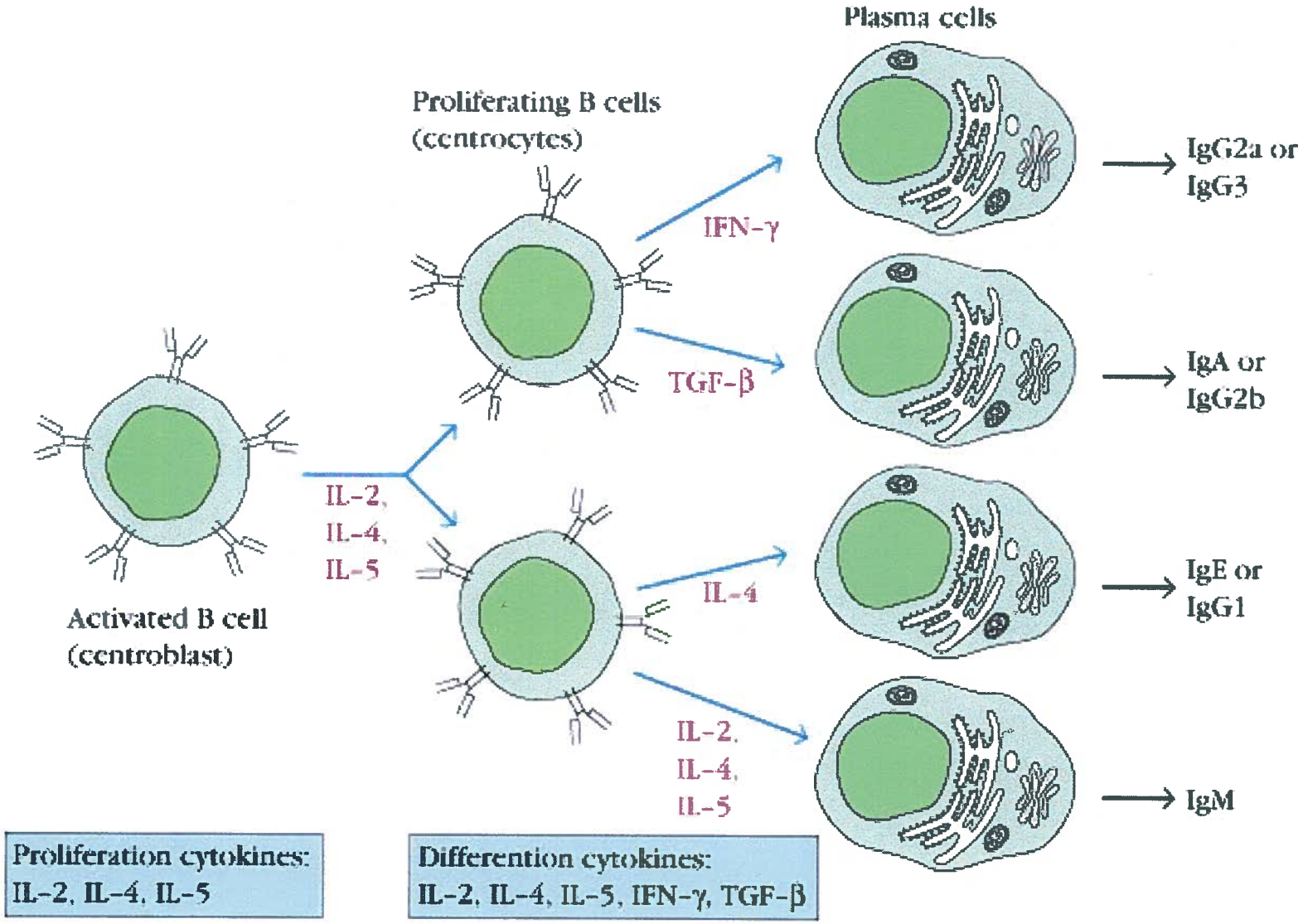

Plasma cells
Proliferating B cells
(centrocytes)
IFN-γ
TGF-β
IgG2a or
IgG3
IgA or
IgG2b
IL-2,
IL-4,
IL-5
IL-4
IgE or
IgG1
IL-2,
IL-4,
IL-5
IgM
Activated B cell
(centroblast)
Proliferation cytokines:
IL-2, IL-4, IL-5
Differention cytokines:
IL-2, IL-4, IL-5, IFN-γ, TGF-β

TABLE 11-4 COMPARISON OF PRIMARY AND SECONDARY ANTIBODY RESPONSES

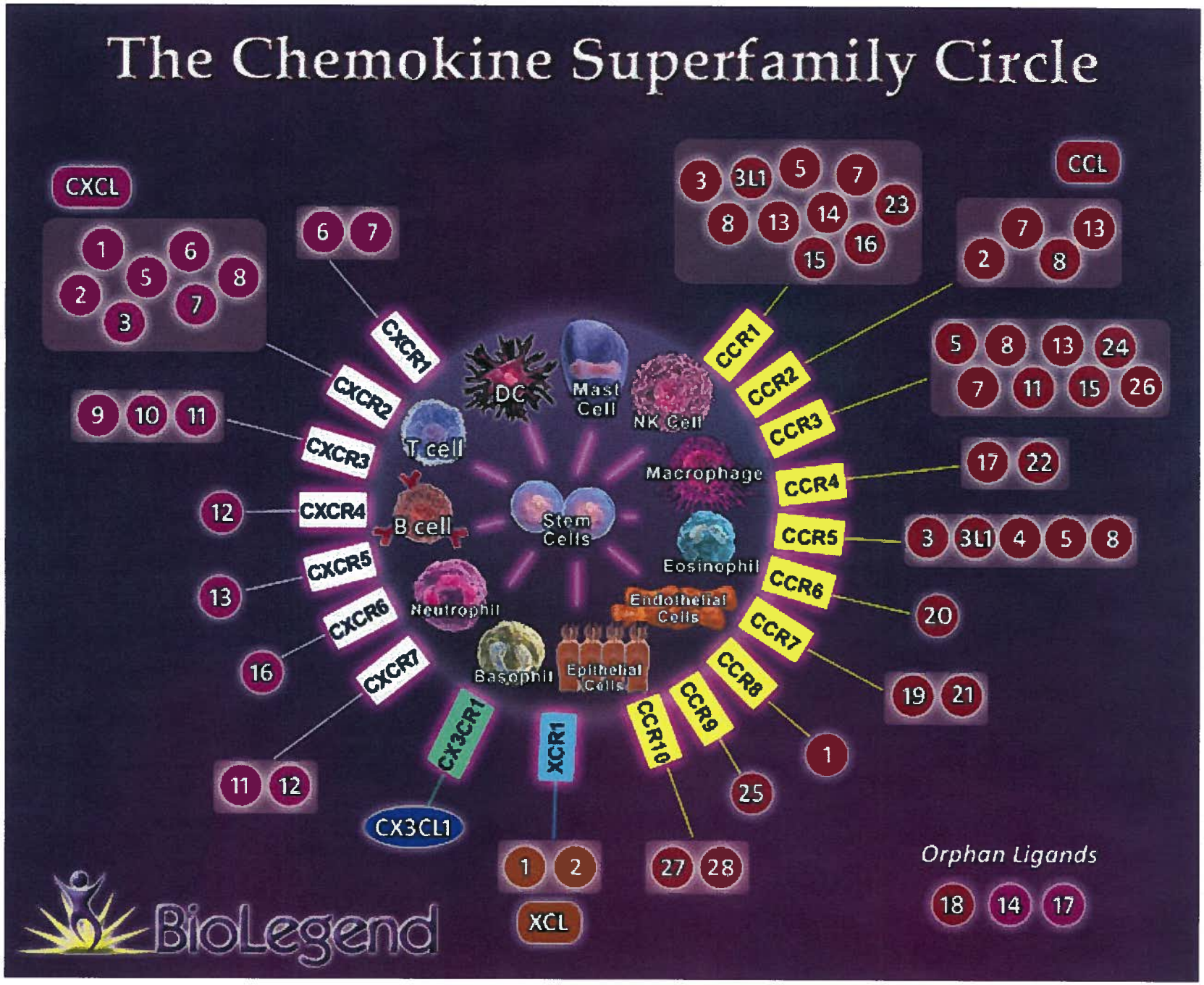
Property	Primary response	Secondary response
Responding B cell	Naive (virgin) B cell	Memory B cell
Lag period following antigen administration	Generally 4–7 days	Generally 1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000 times higher primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher

TABLE 11-7 COMPARISON OF NAIVE AND MEMORY B CELLS

Properties	Naive B cell	Memory B cell
Membrane markers		
Immunoglobulin	IgM, IgD	IgM, IgD(?), IgG, IgA, IgE
Complement receptor	Low	High
Anatomic location	Spleen	Bone marrow, lymph node, spleen
Life span	Short-lived	May be long-lived
Recirculation	Yes	Yes
Receptor affinity	Lower average affinity	Higher average affinity due to affinity maturation*
Adhesion molecules	Low ICAM-1	High ICAM-1

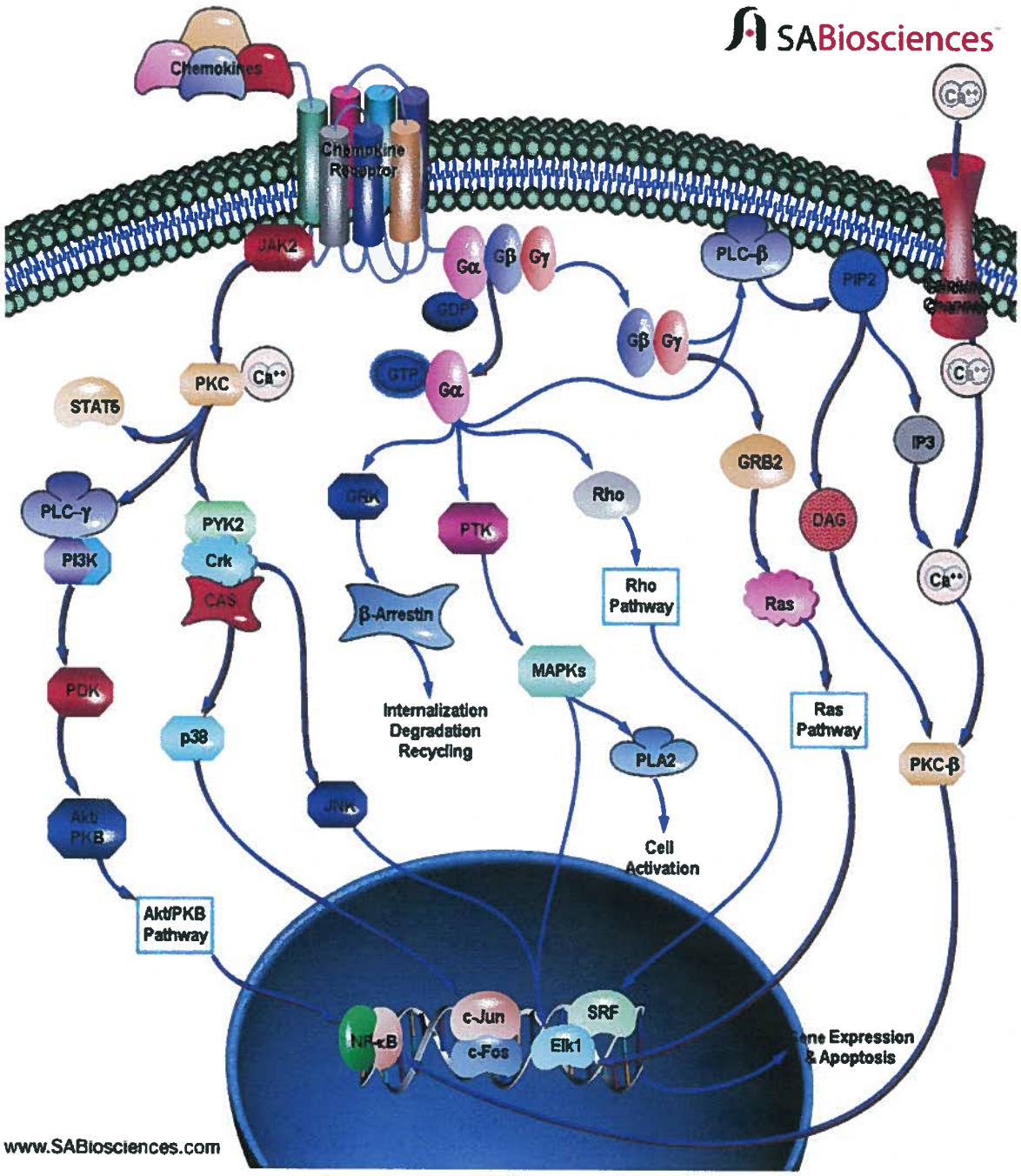
*Affinity maturation results from somatic mutation during proliferation of centroblasts and subsequent antigen selection of centrocytes bearing high-affinity mIg.

How do Immune Effector Cells get to where they are going?

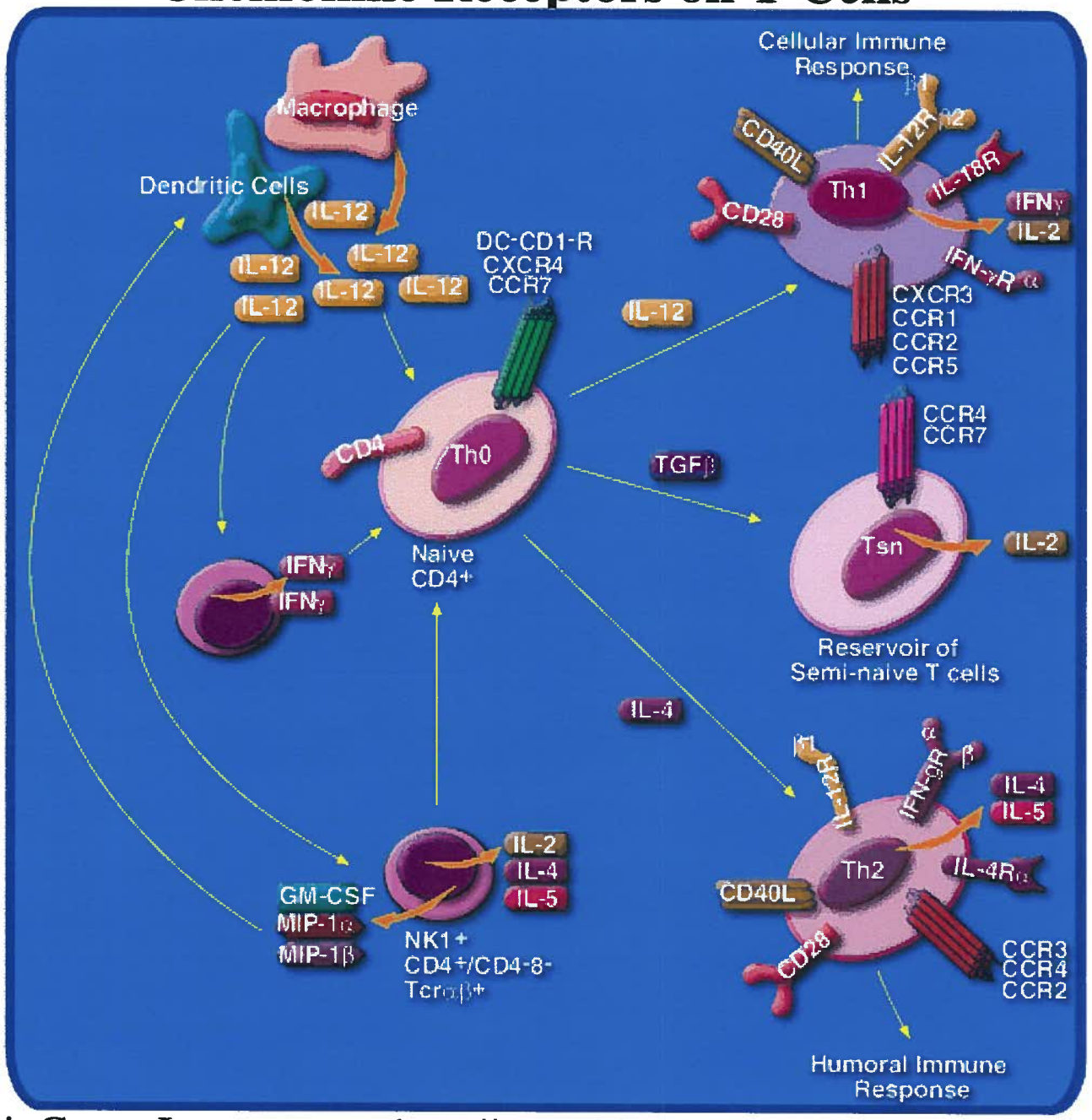


www.biolegend.com

Chemokine Signaling



Chemokine Receptors on T Cells



Courtesy of BioCarta, Inc http://www.biocarta.com/pathfiles/h_nktPathway.asp

How can I determine if specific immune effector subsets are involved in the effects/responses I am seeing?

Depletion of Immune Effector Subsets

Antibody	**Cell types depleted**
• CD4	CD4 T cells
• CD8	CD8 T cells
• CD25	Tregs, activated T cells
• asialoGM1	NK, some macrophages
• NK 1.1	NK, NKT (not in Balb/c mice)
• GR1	Granulocytes
• Ig	B cells
Liposomes	
• Chlordonate liposomes	Macrophages

I am working with
human tumor models,
Can I still use mice?

Immunodeficient Mice

For studies utilizing human xenografts, there are immunodeficient strains of mice available

Immune deficient mouse strains

Strain:	Deficiencies
• RAG/	T, B, NKT
• RAG/ IL2Rγ k/o	T, B, NK, NKT
• SCID	T, B, NKT (high NK)
• SCID/Beige	T, B, NK, NKT
• Nude	T, B cell function low, (high NK)
• Beige/Nude/XID (bnx)	T, B, NK (can be leaky)
• NOD/SCID	T, B, NK, NKT, macrophage (can drift)
• NOD/SCID/ B2M k/o	T, B, NK, NKT, Macrophage - absolute deficiencies. 4 month lifespan.
• Nude/NOD/SCID	T, B, NK, NKT - 2 year lifespan
• NOD/SCID/IL2Rγ k/o	T, B, NK, NKT

Conclusions

- **The immune system will affect all aspects of your mouse work**

- **The NIH has a very large immunology community: <u>TALK</u> to your fellow immunologists as you proceed with your studies**