Basis of Immunology and Immunophysiopathology of Infectious Diseases

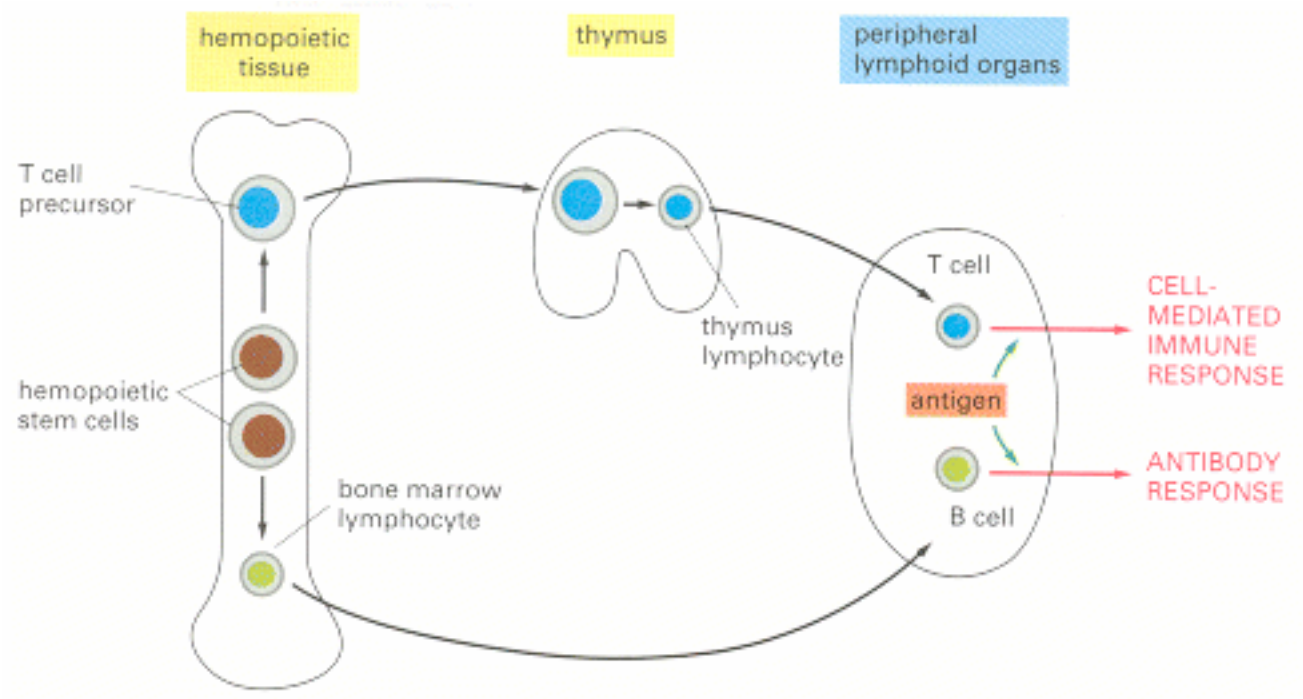
Jointly organized by
Institut Pasteur in Ho Chi Minh City and Institut Pasteur
with kind support from ANRS & Université Pierre et Marie Curie

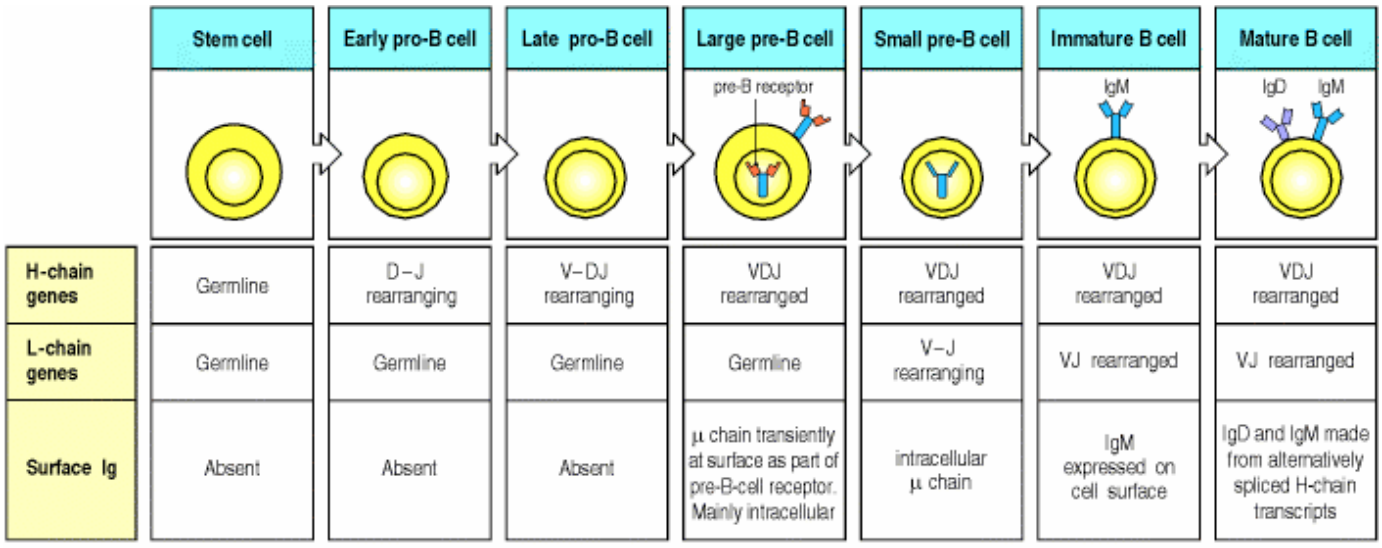
January 24 – February 5, 2005
at the Institut Pasteur in Ho Chi Minh City, Vietnam

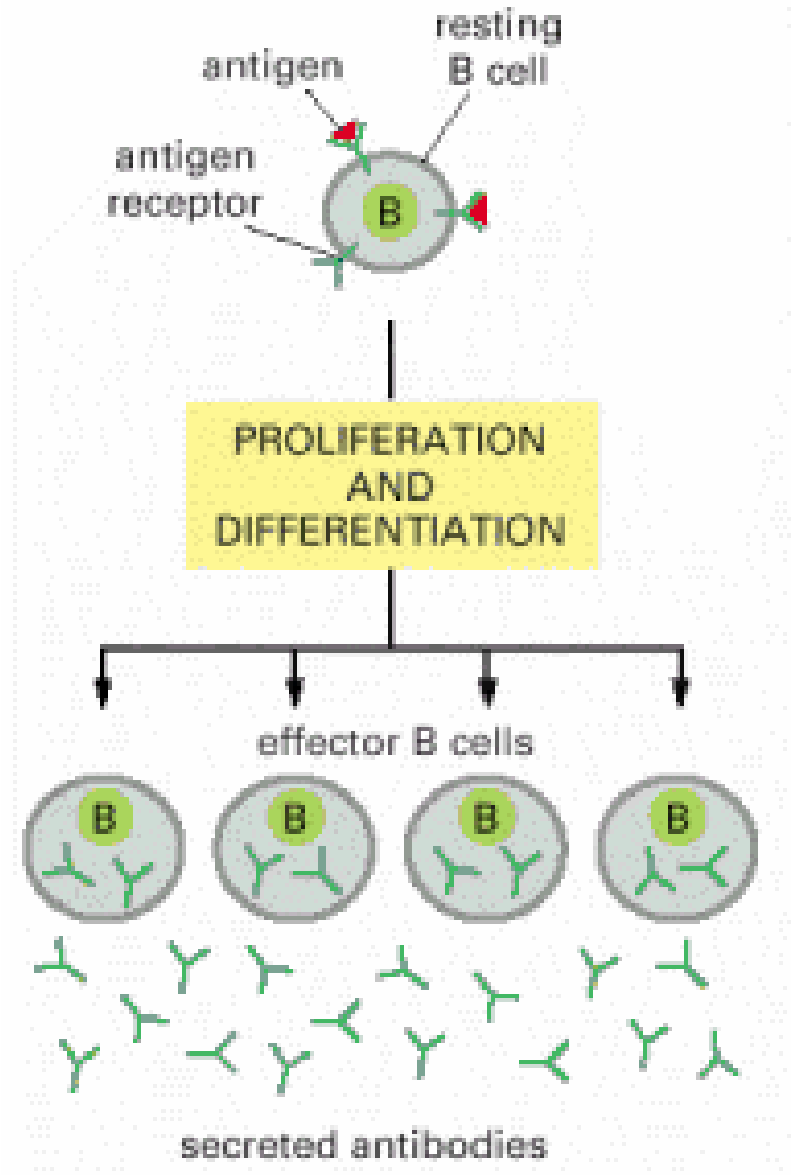
Lecture :
Activation of peripheral B lymphocytes

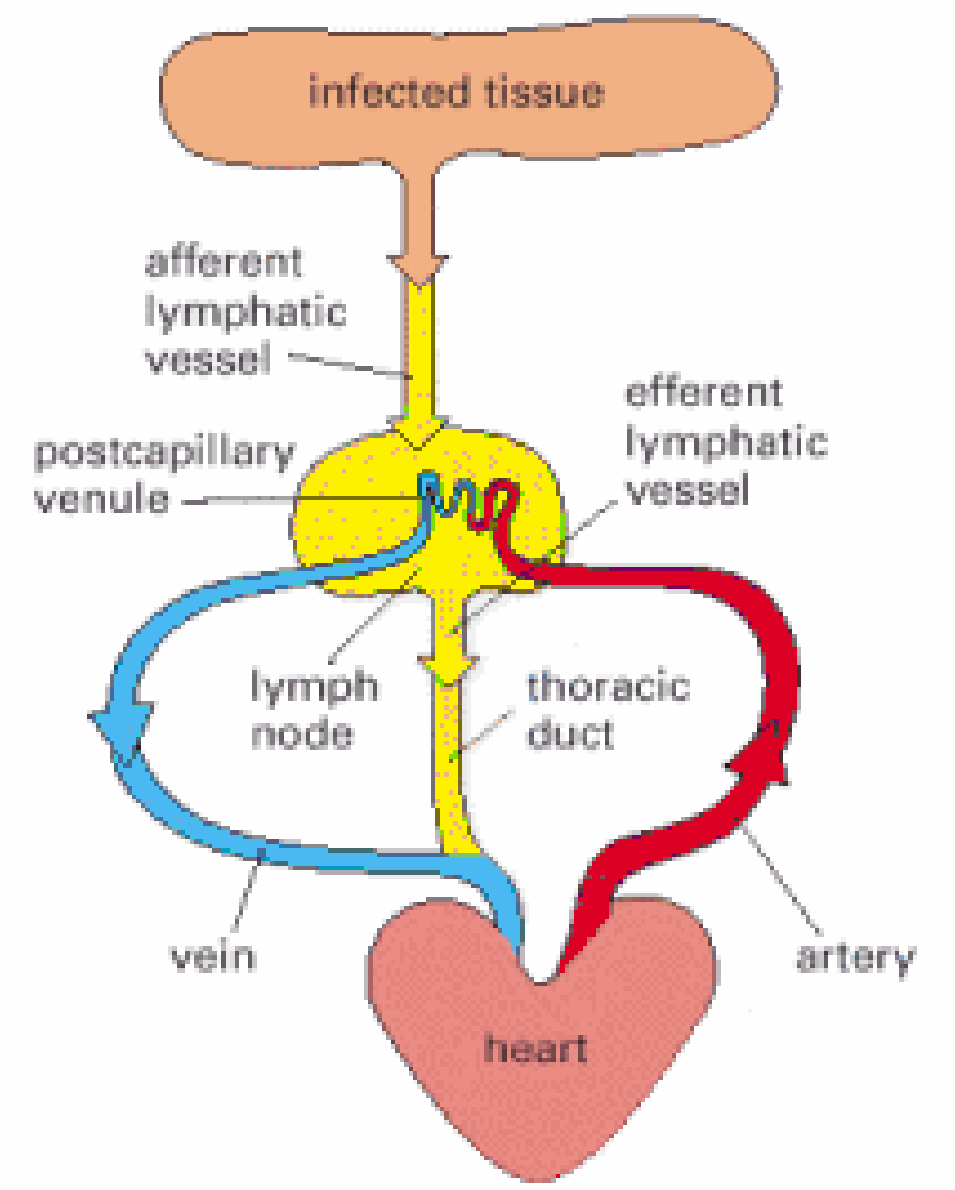
Prof. Pierre-André Cazenave

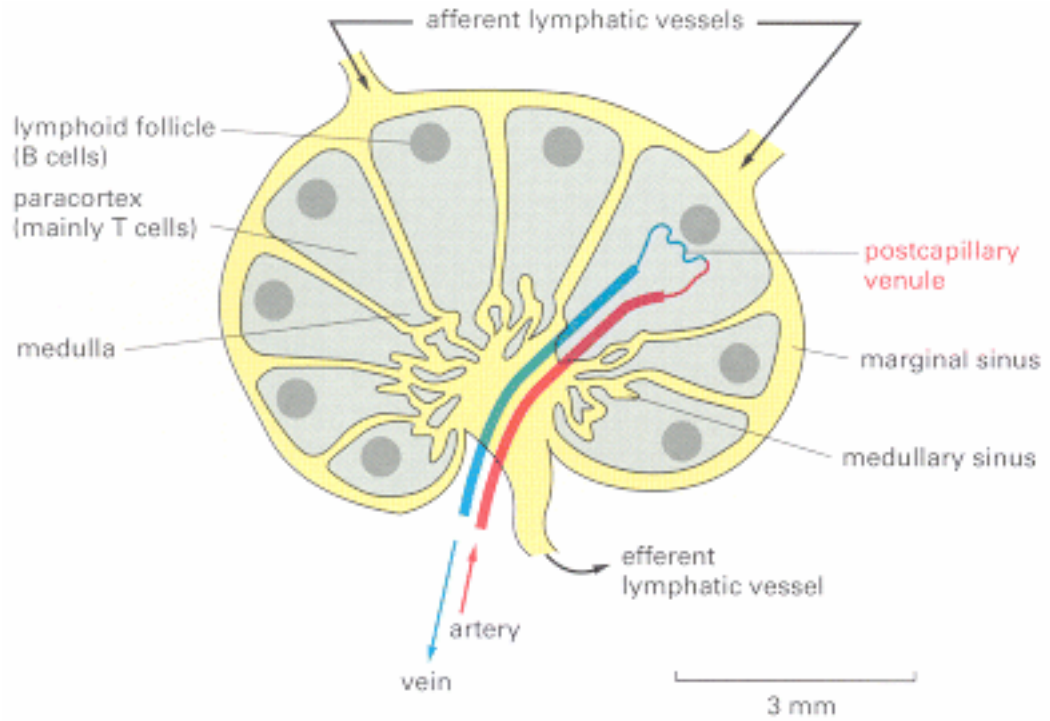
January 26, 2005

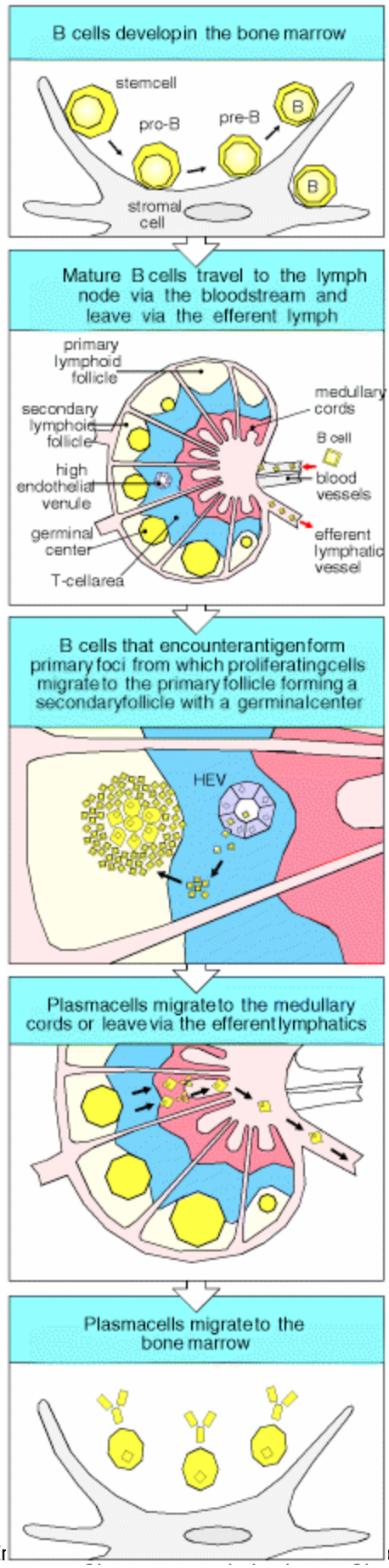

hemopoietic tissue
thymus
peripheral lymphoid organs
T cell precursor
hemopoietic stem cells
bone marrow lymphocyte
thymus lymphocyte
T cell
antigen
B cell
CELL-MEDIATED IMMUNE RESPONSE
ANTIBODY RESPONSE

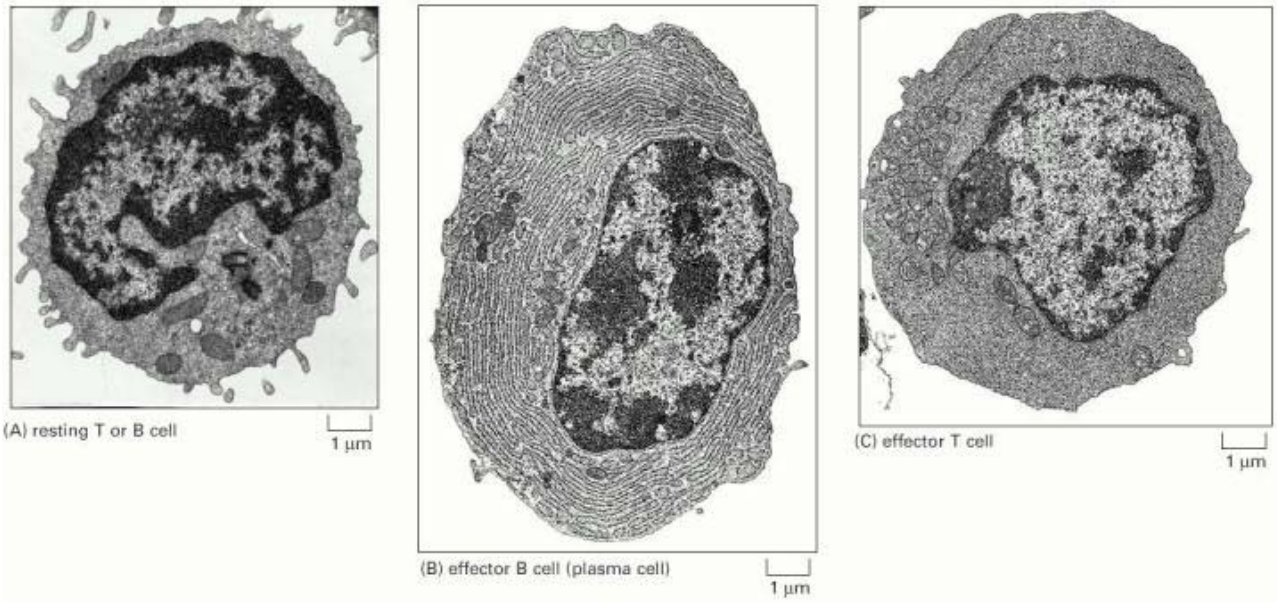

Stem cell
Early pro-B cell
Late pro-B cell
Large pre-B cell
Small pre-B cell
Immature B cell
Mature B cell
pre-B receptor
IgM
IgD
IgM
H-chain genes
Germline
D–J rearranging
V–DJ rearranging
VDJ rearranged
VDJ rearranged
VDJ rearranged
VDJ rearranged
L-chain genes
Germline
Germline
Germline
Germline
V–J rearranging
VJ rearranged
VJ rearranged
Surface Ig
Absent
Absent
Absent
μ chain transiently at surface as part of pre-B-cell receptor. Mainly intracellular
intracellular μ chain
IgM expressed on cell surface
IgD and IgM made from alternatively spliced H-chain transcripts

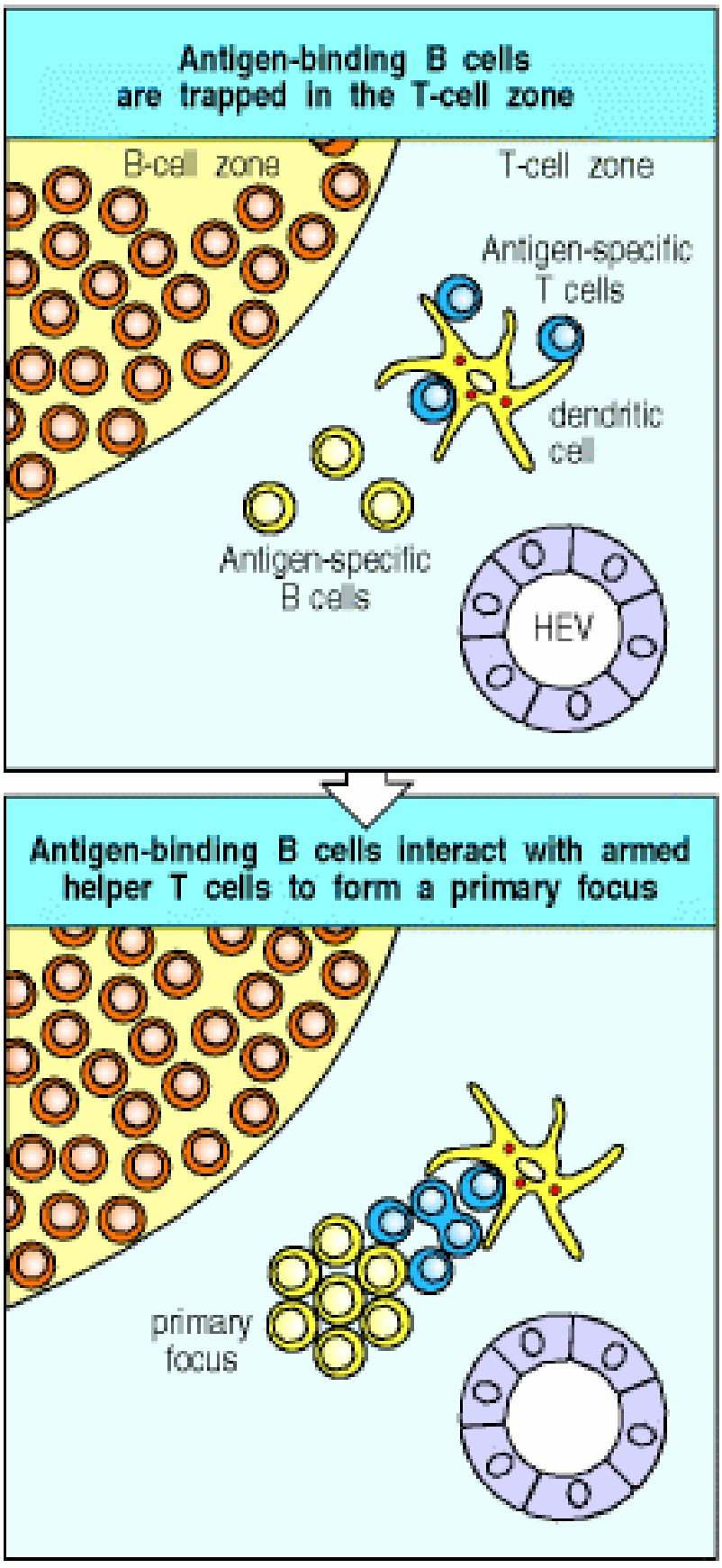

antigen
resting
B cell
antigen
receptor
B
PROLIFERATION
AND
DIFFERENTIATION
effector B cells
B
B
B
B
secreted antibodies


infected tissue
afferent lymphatic vessel
efferent lymphatic vessel
postcapillary venule
lymph node
thoracic duct
vein
artery
heart


afferent lymphatic vessels
lymphoid follicle
(B cells)
paracortex
(mainly T cells)
medulla
postcapillary
venule
marginal sinus
medullary sinus
efferent
lymphatic vessel
artery
vein
3 mm


B cells develop in the bone marrow
stem cell
pro-B
pre-B
B
B
stromal cell
Mature B cells travel to the lymph node via the bloodstream and leave via the efferent lymph
primary lymphoid follicle
secondary lymphoid follicle
high endothelial venule
germinal center
T-cell area
medullary cords
B cell
blood vessels
efferent lymphatic vessel
B cells that encounter antigen form primary foci from which proliferating cells migrate to the primary follicle forming a secondary follicle with a germinal center
HEV
Plasma cells migrate to the medullary cords or leave via the efferent lymphatics
Plasma cells migrate to the bone marrow


(A) resting T or B cell
1 μm
(B) effector B cell (plasma cell)
1 μm
(C) effector T cell
1 μm



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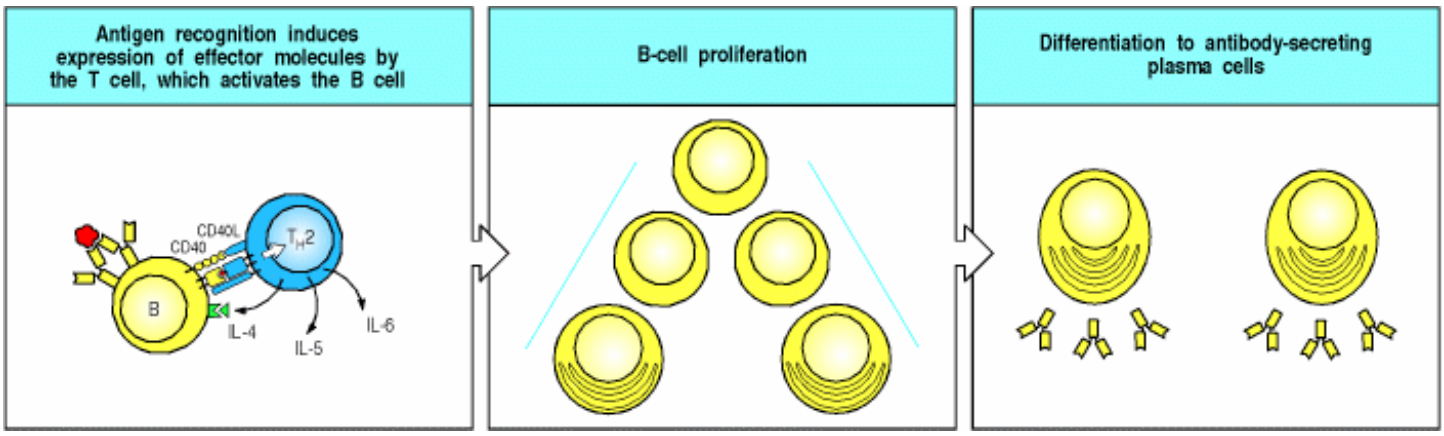
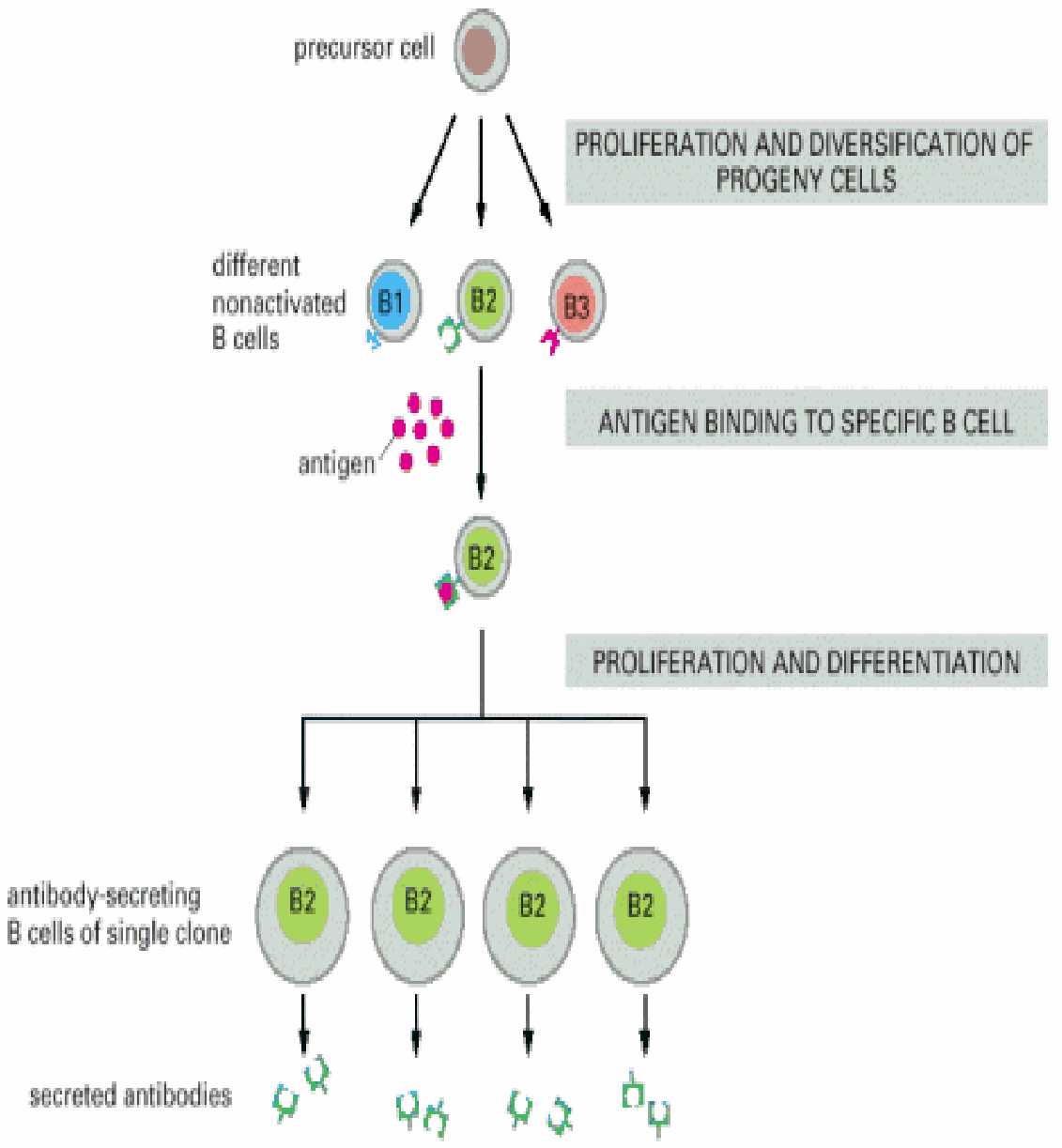
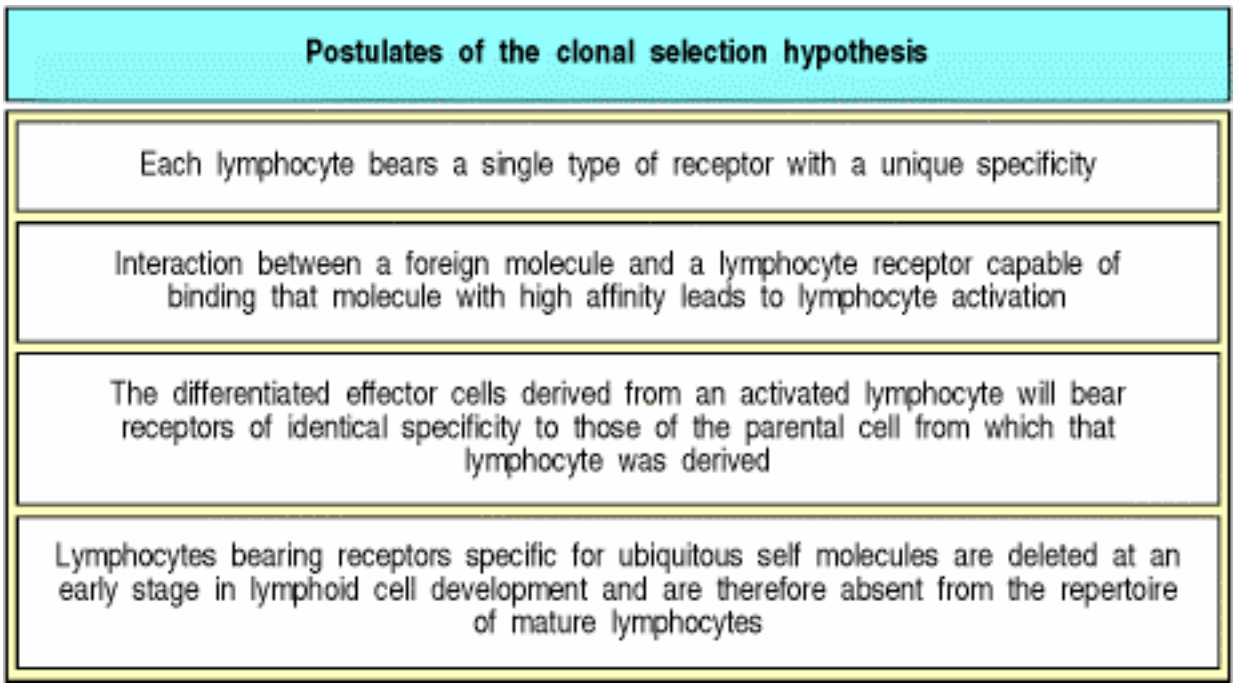
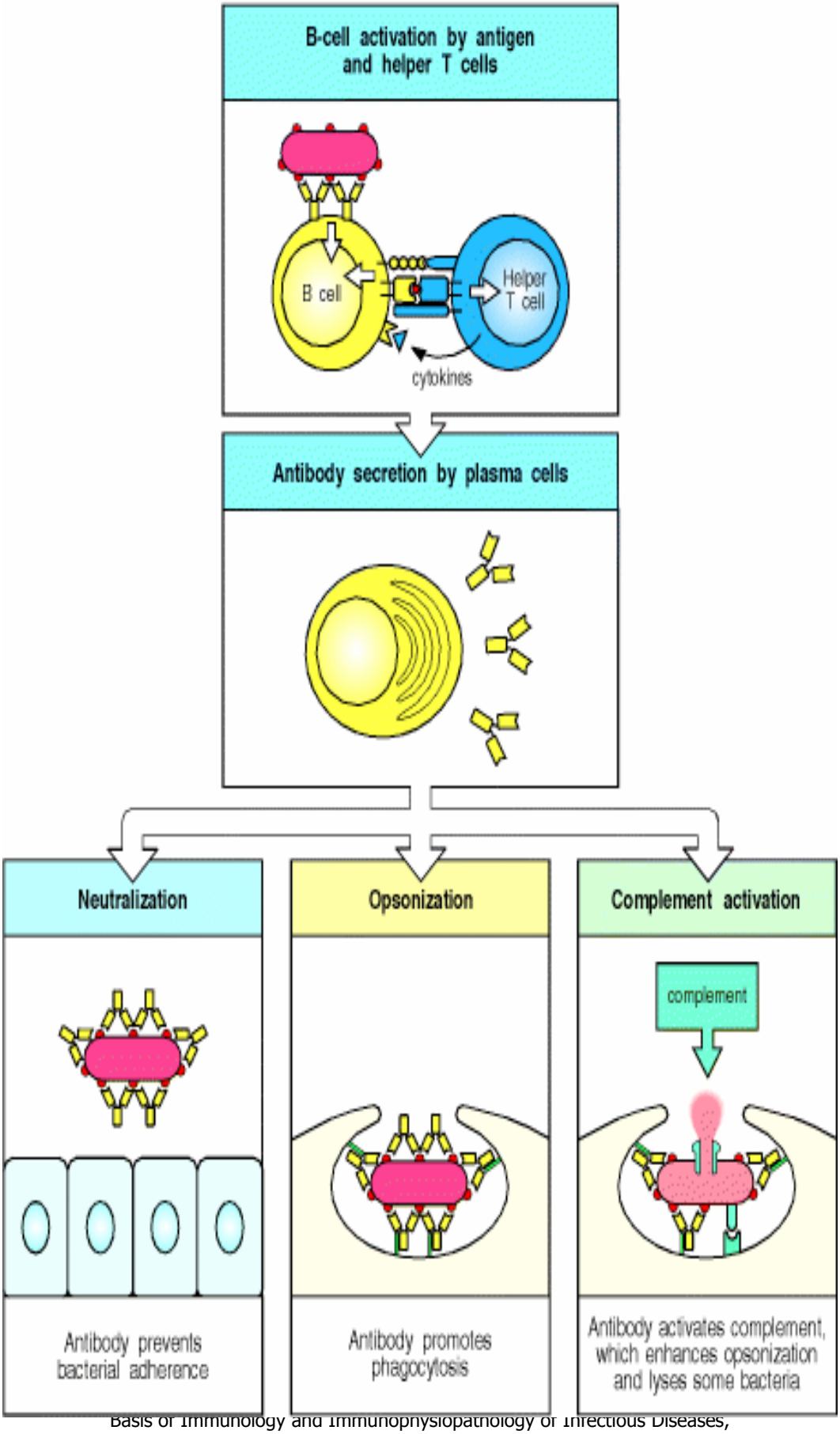
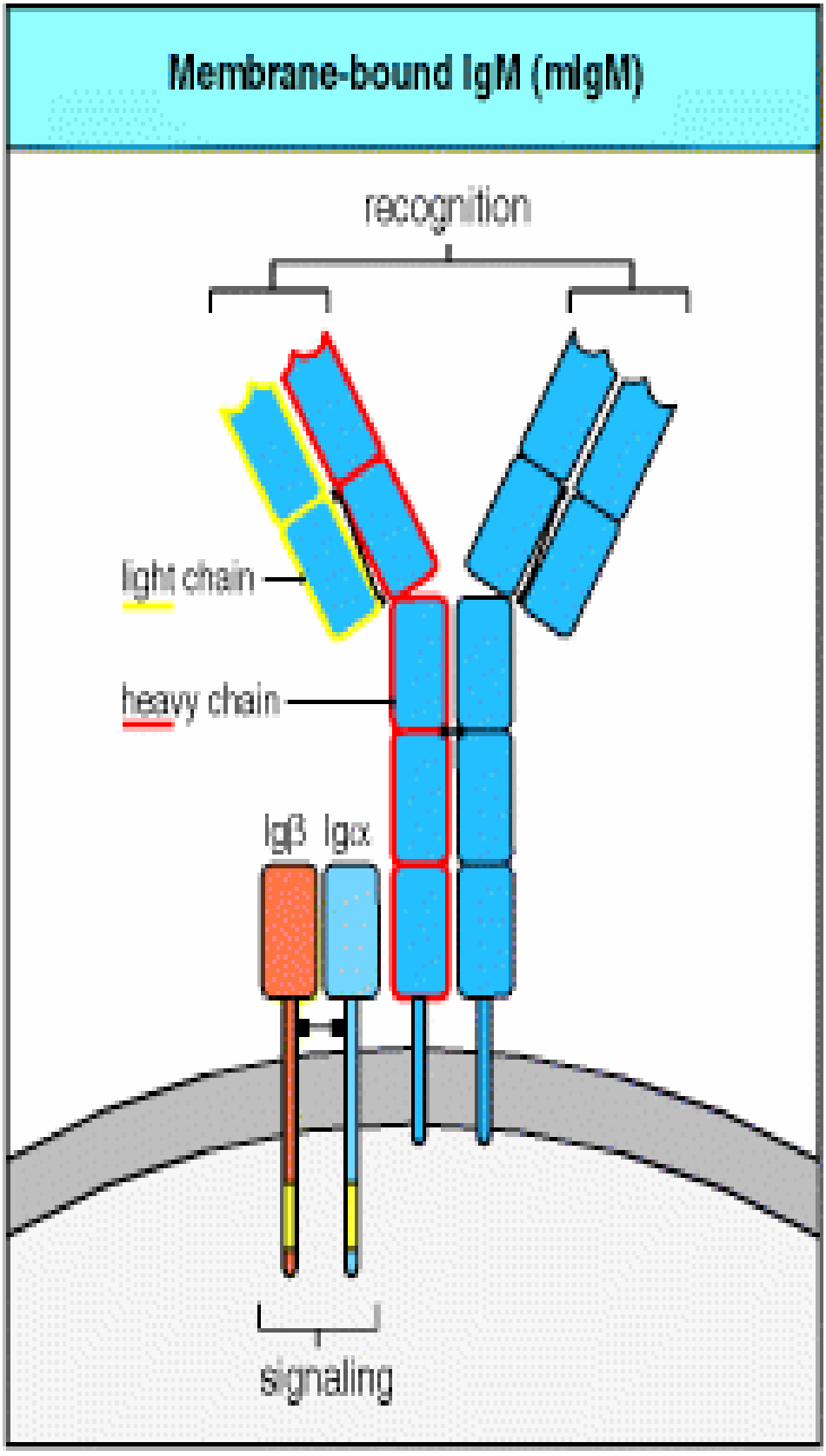
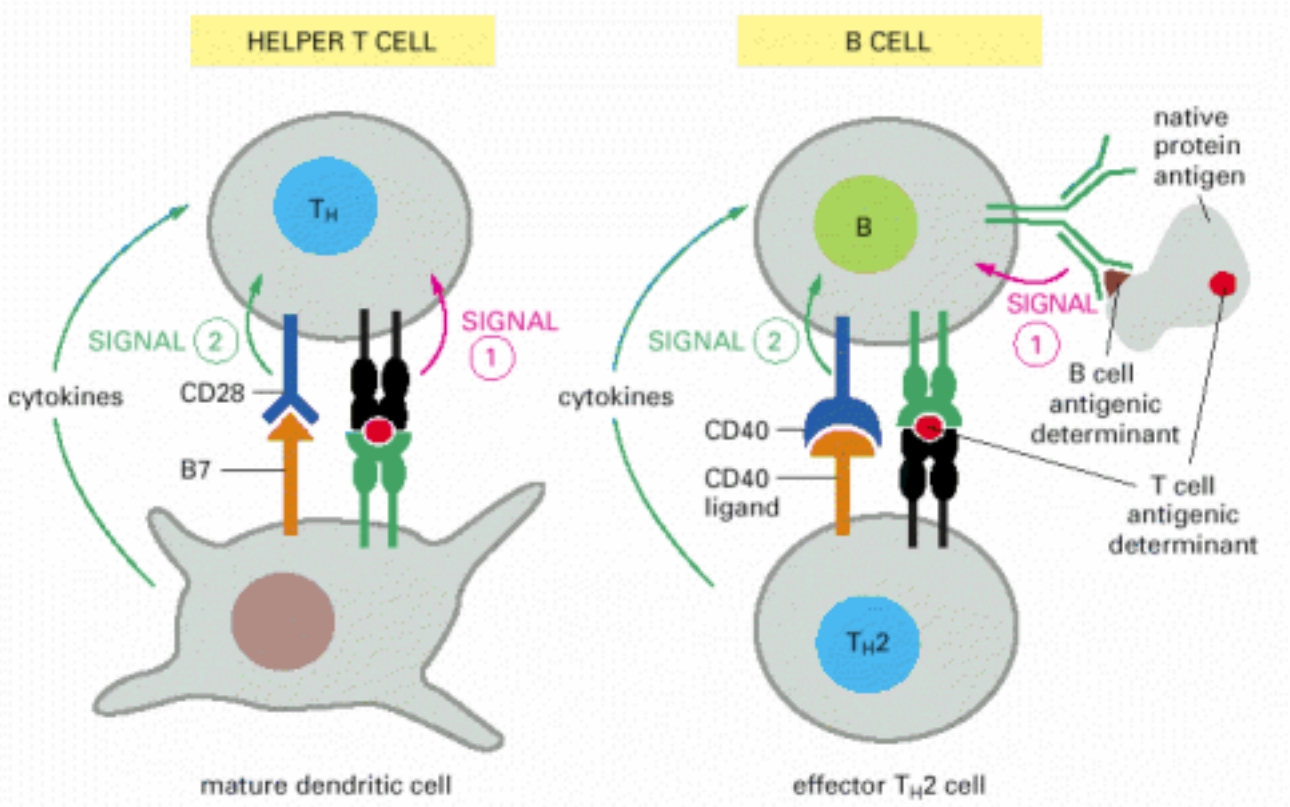

Antigen recognition induces expression of effector molecules by the T cell, which activates the B cell
B-cell proliferation
Differentiation to antibody-secreting plasma cells
CD40L
CD40
T_H2
B
IL-4
IL-5
IL-6

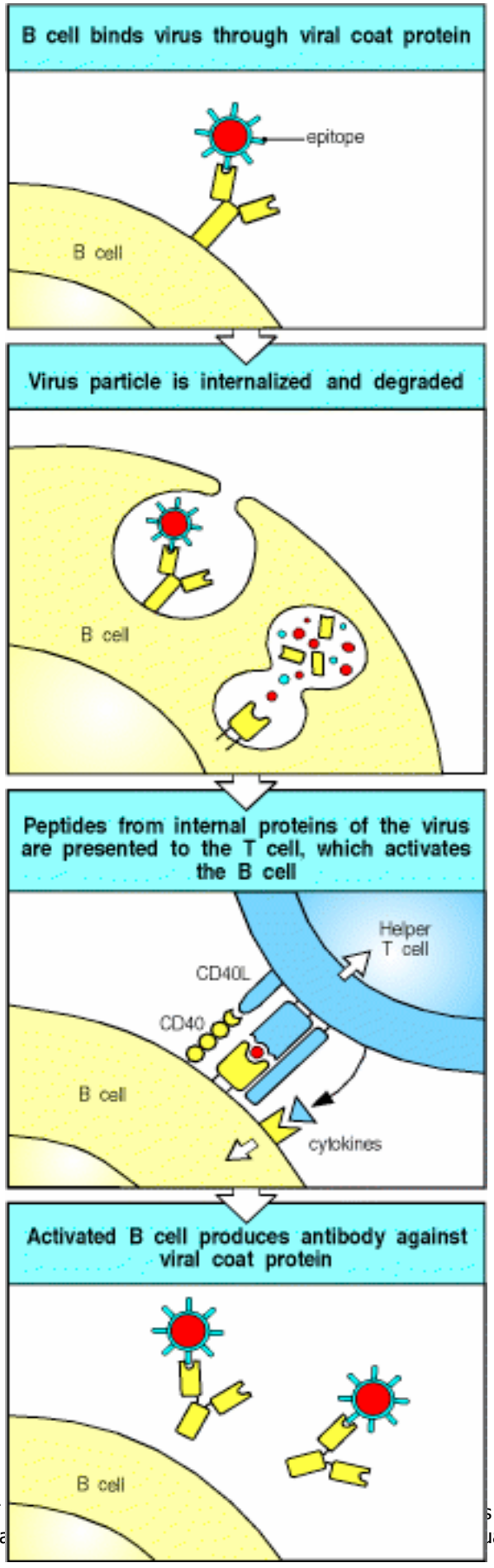

precursor cell
PROLIFERATION AND DIVERSIFICATION OF PROGENY CELLS
different nonactivated B cells
B1
B2
B3
antigen
ANTIGEN BINDING TO SPECIFIC B CELL
B2
PROLIFERATION AND DIFFERENTIATION
antibody-secreting B cells of single clone
B2
B2
B2
B2
secreted antibodies

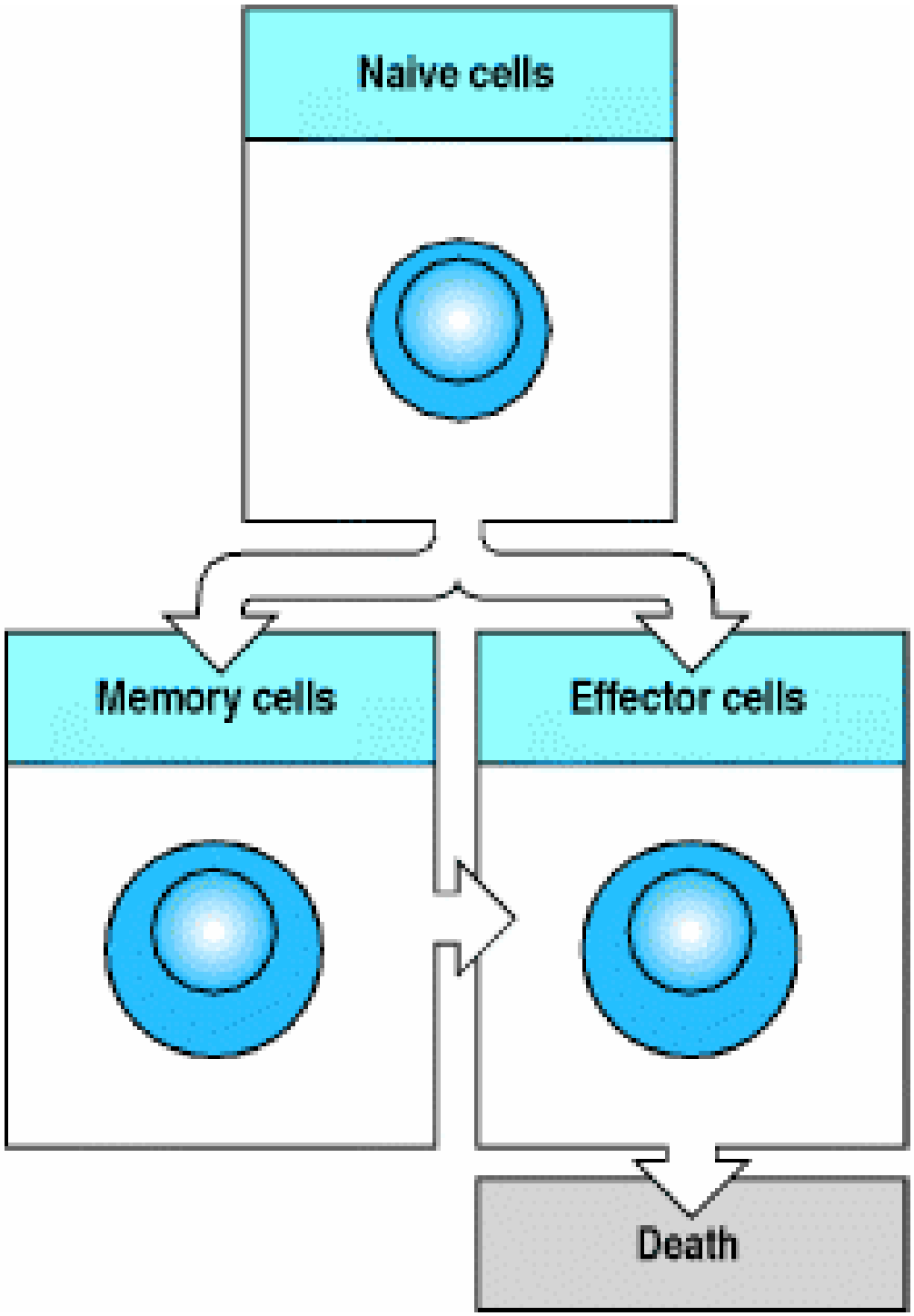

Postulates of the clonal selection hypothesis
Each lymphocyte bears a single type of receptor with a unique specificity
Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation
The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived
Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes

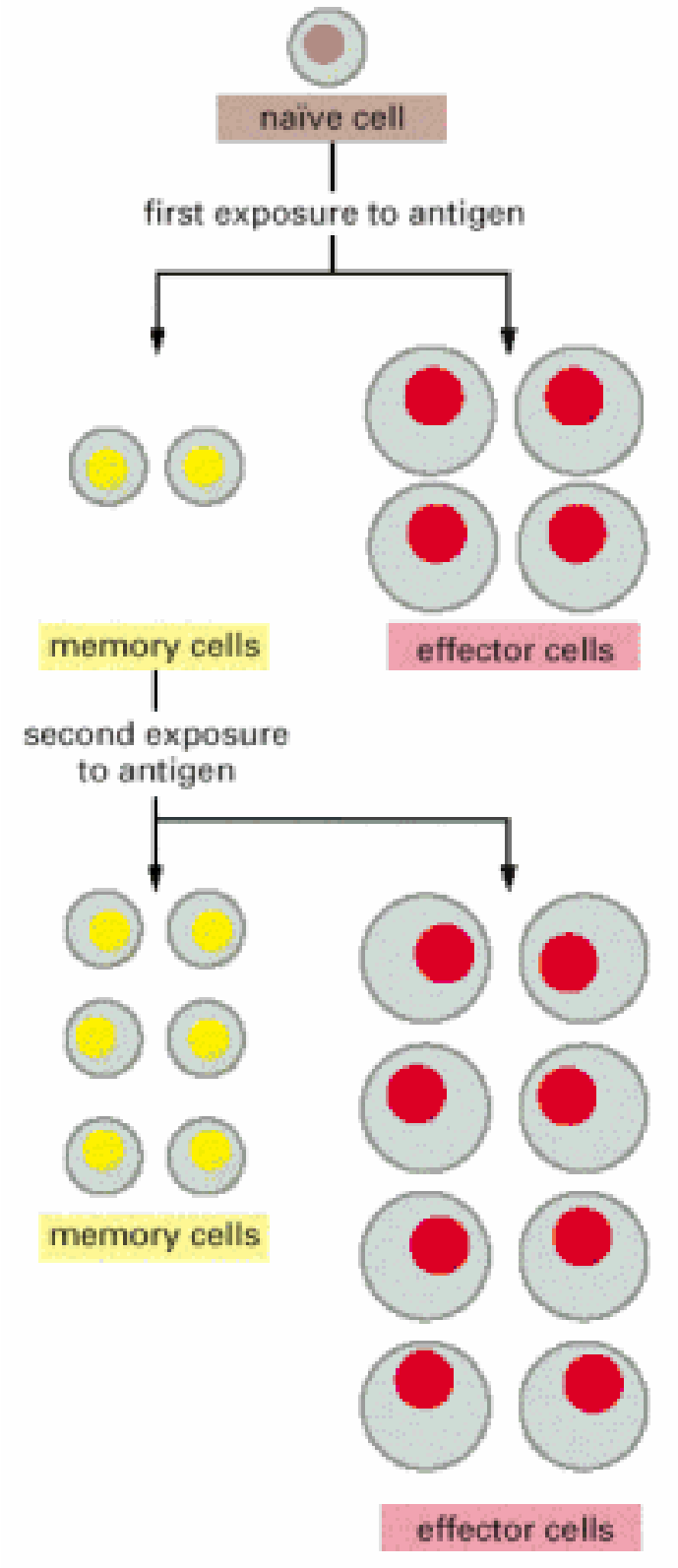

B-cell activation by antigen and helper T cells
B cell
Helper T cell
cytokines
Antibody secretion by plasma cells
Neutralization
Opsonization
Complement activation
complement
Antibody prevents bacterial adherence
Antibody promotes phagocytosis
Antibody activates complement, which enhances opsonization and lyses some bacteria


Membrane-bound IgM (mIgM)
recognition
light chain
heavy chain
Igβ Igα
signaling


HELPER T CELL
B CELL
T_H
B
native protein antigen
SIGNAL 2
SIGNAL 1
cytokines
CD28
B7
CD40
CD40 ligand
B cell antigenic determinant
T cell antigenic determinant
T_H2
mature dendritic cell
effector T_H2 cell

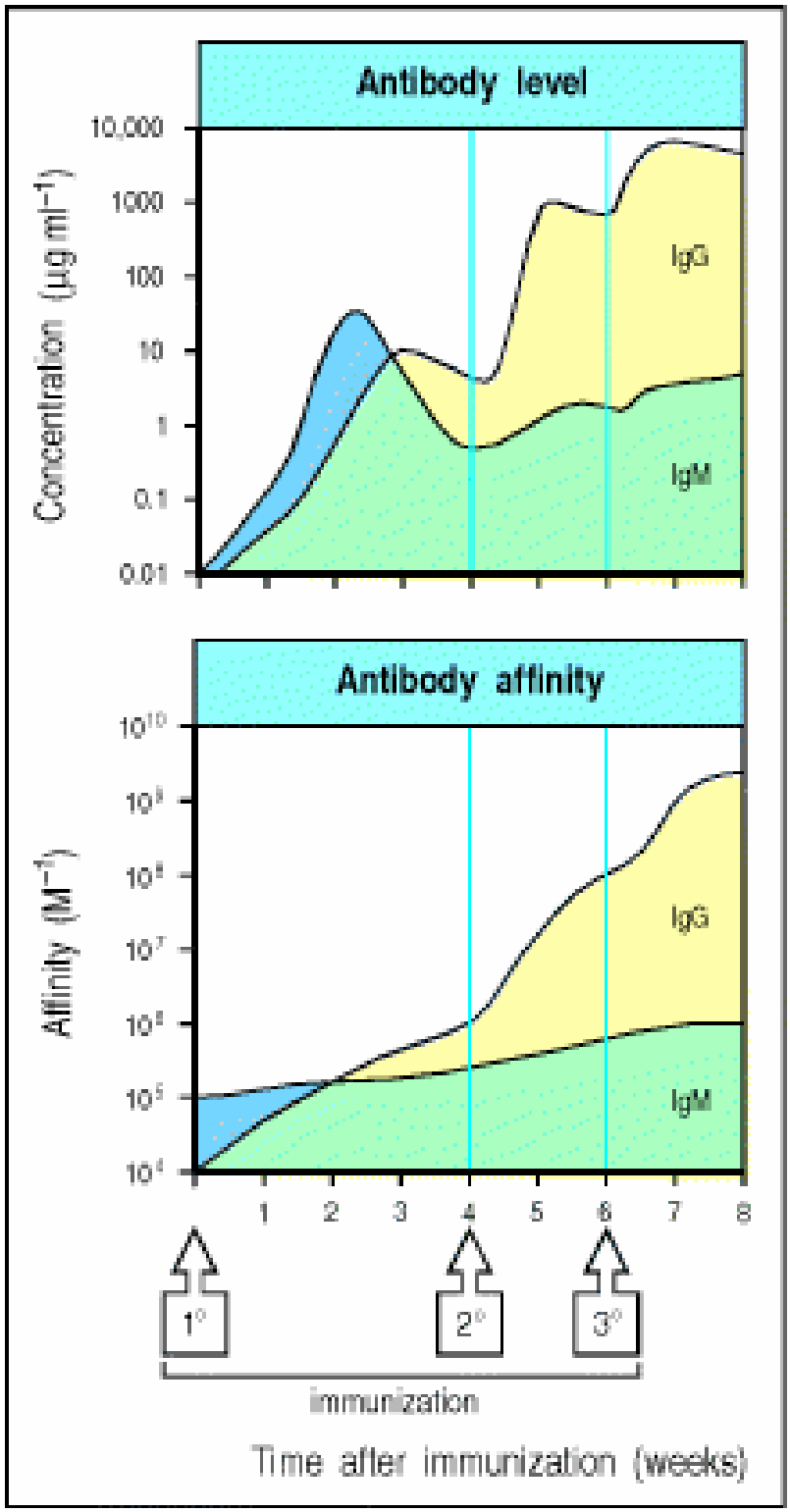

B cell binds virus through viral coat protein
epitope
B cell
Virus particle is internalized and degraded
B cell
Peptides from internal proteins of the virus are presented to the T cell, which activates the B cell
Helper T cell
CD40L
CD40
B cell
cytokines
Activated B cell produces antibody against viral coat protein
B cell

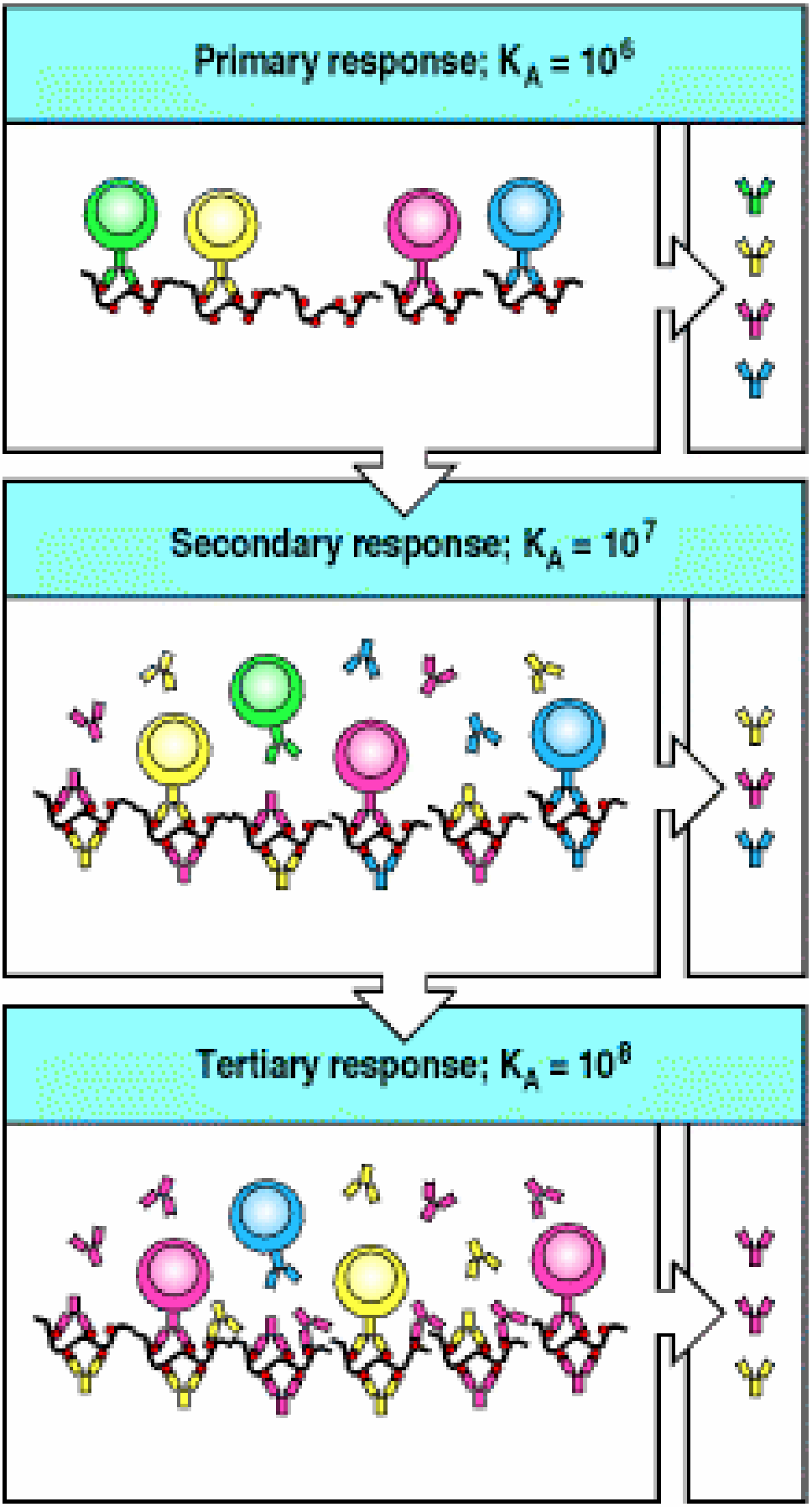

Naive cells
Memory cells
Effector cells
Death

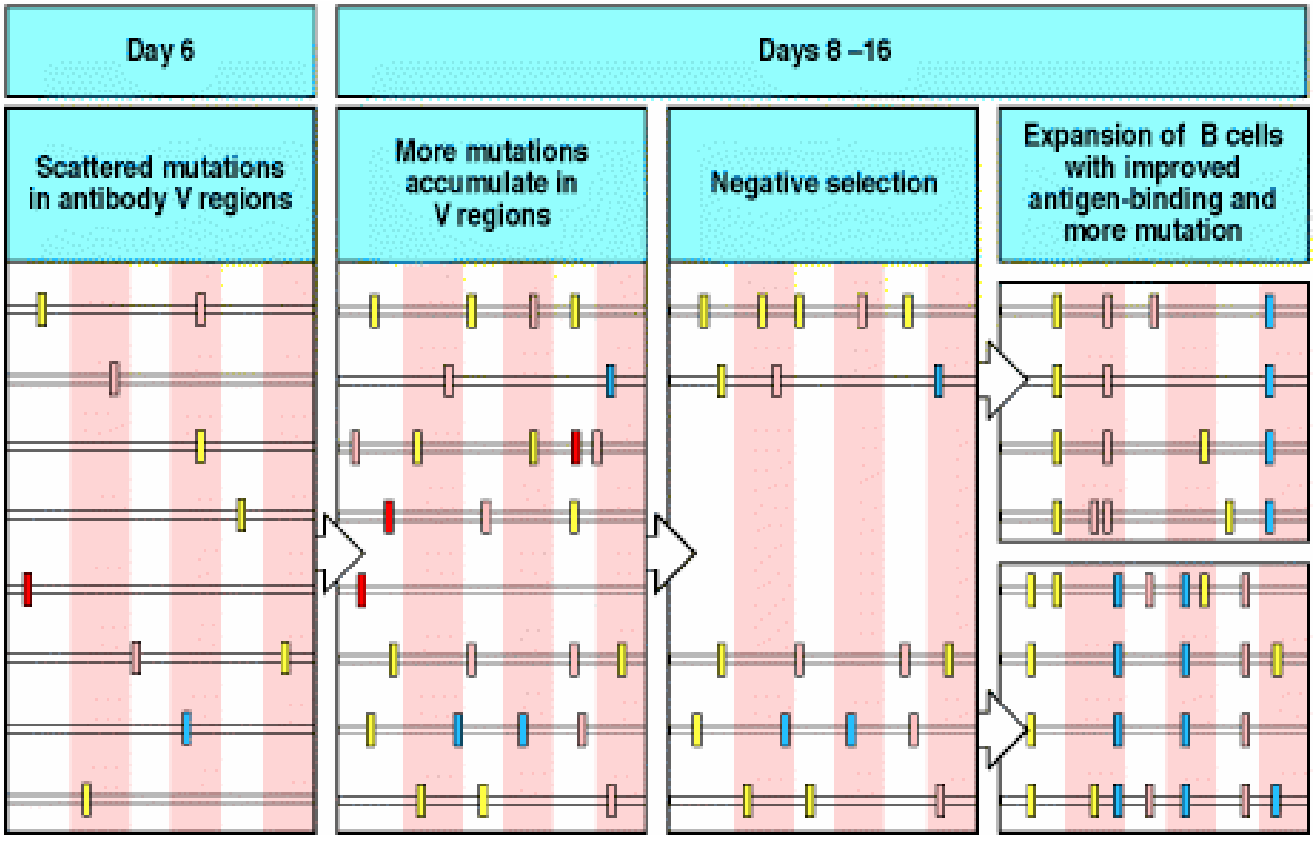

naïve cell
first exposure to antigen
memory cells
effector cells
second exposure
to antigen
memory cells
effector cells

	Property					
	Intrinsic			Inducible		
B-lineage cell	Surface Ig	Surface MHC class II	High-rate Ig secretion	Growth	Somatic hyper-mutation	Isotype switch
 Resting B cell	High	Yes	No	Yes	Yes	Yes
 Plasma cell	Low	No	Yes	No	No	No

	Source of B cells	
	Unimmunized donor Primary response	Immunized donor Secondary response
Frequency of specific B cells	$1:10^4 - 1:10^5$	$1:10^3$
Isotype of antibody produced	IgM > IgG	IgG, IgA
Affinity of antibody	Low	High
Somatic hypermutation	Low	High

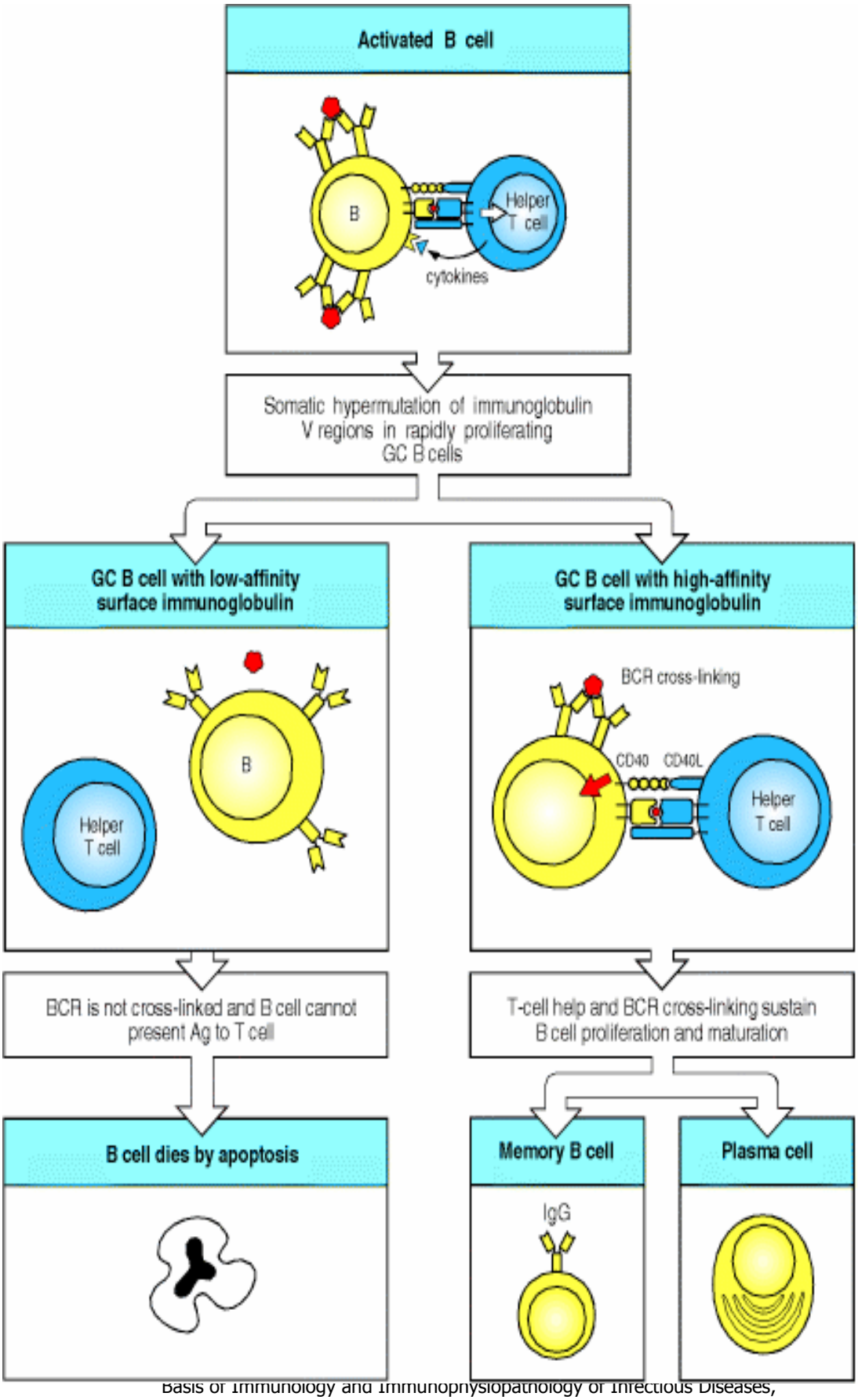

Antibody level
10,000
1000
100
10
1
0.1
0.01
Concentration (µg ml⁻¹)
IgG
IgM
Antibody affinity
Affinity (M⁻¹)
IgG
IgM
1
2
3
4
5
6
7
8
1°
2°
3°
immunization
Time after immunization (weeks)

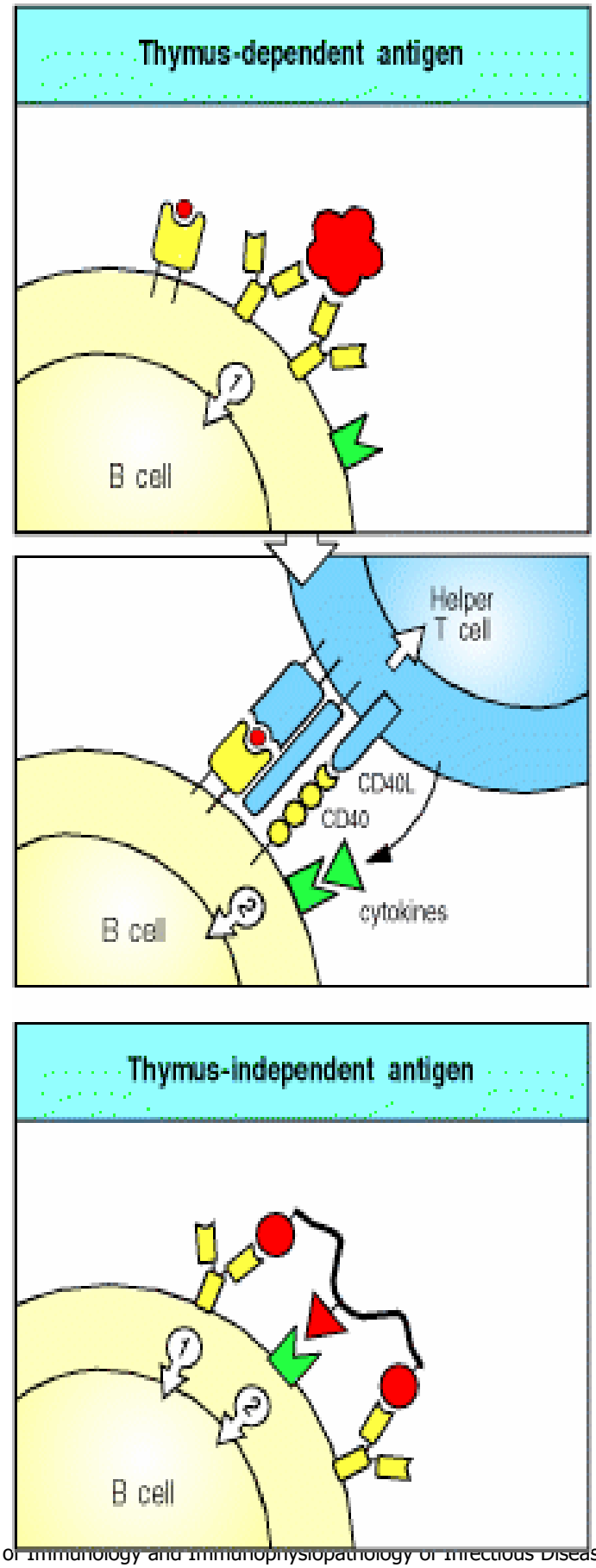

Primary response; $K_A = 10^6$
Secondary response; $K_A = 10^7$
Tertiary response; $K_A = 10^8$

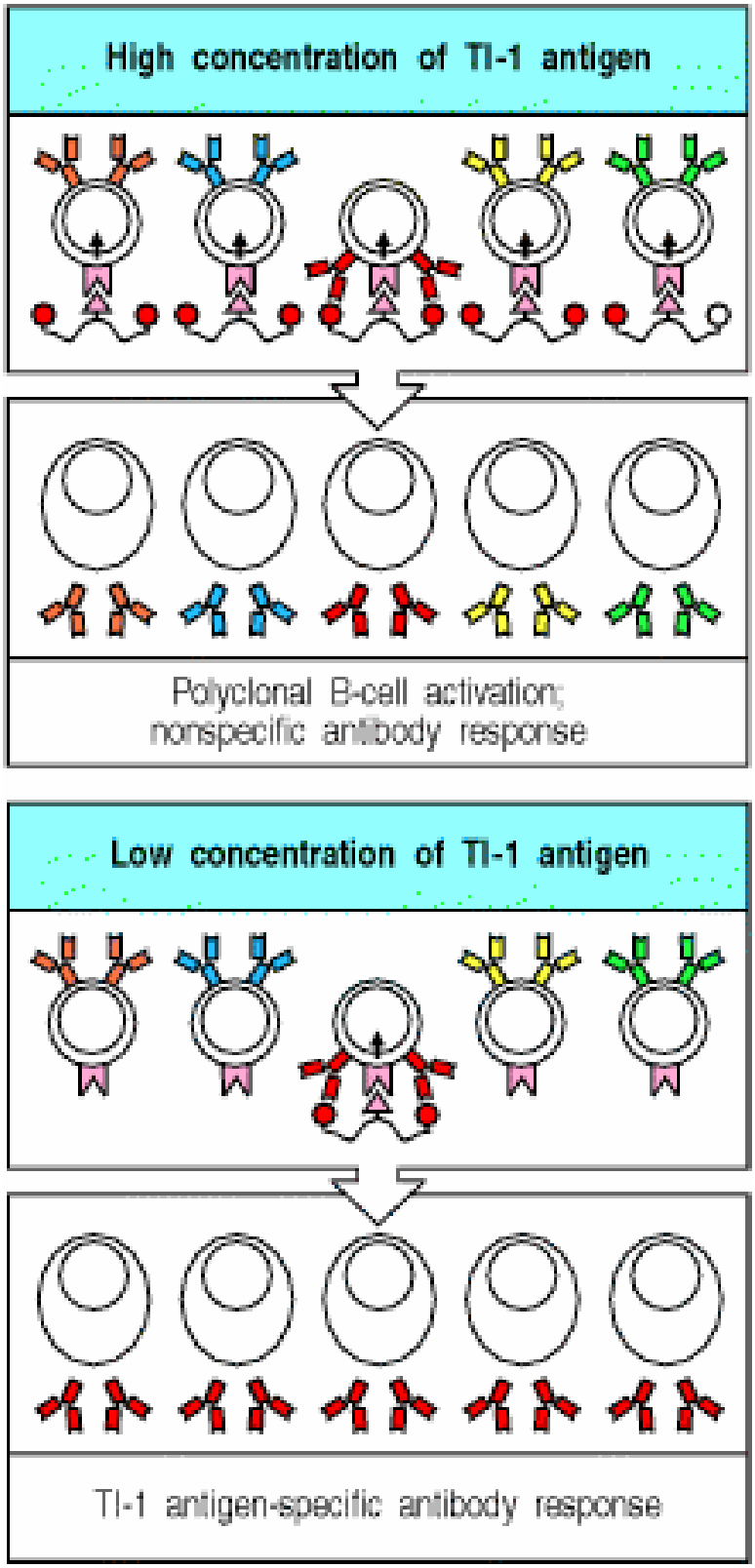

Day 6
Days 8 –16
Scattered mutations in antibody V regions
More mutations accumulate in V regions
Negative selection
Expansion of B cells with improved antigen-binding and more mutation

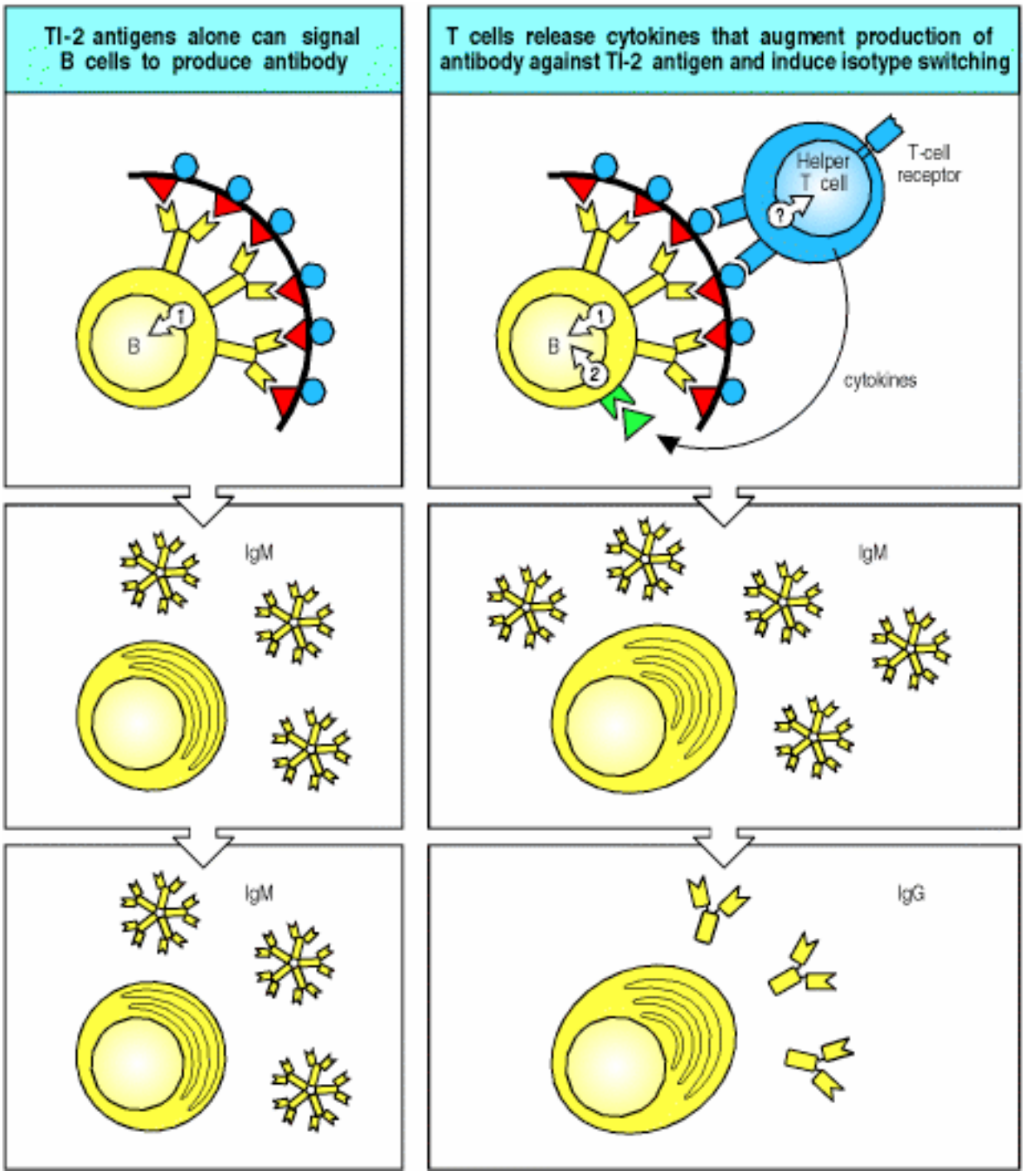
Role of cytokines in regulating Ig isotype expression

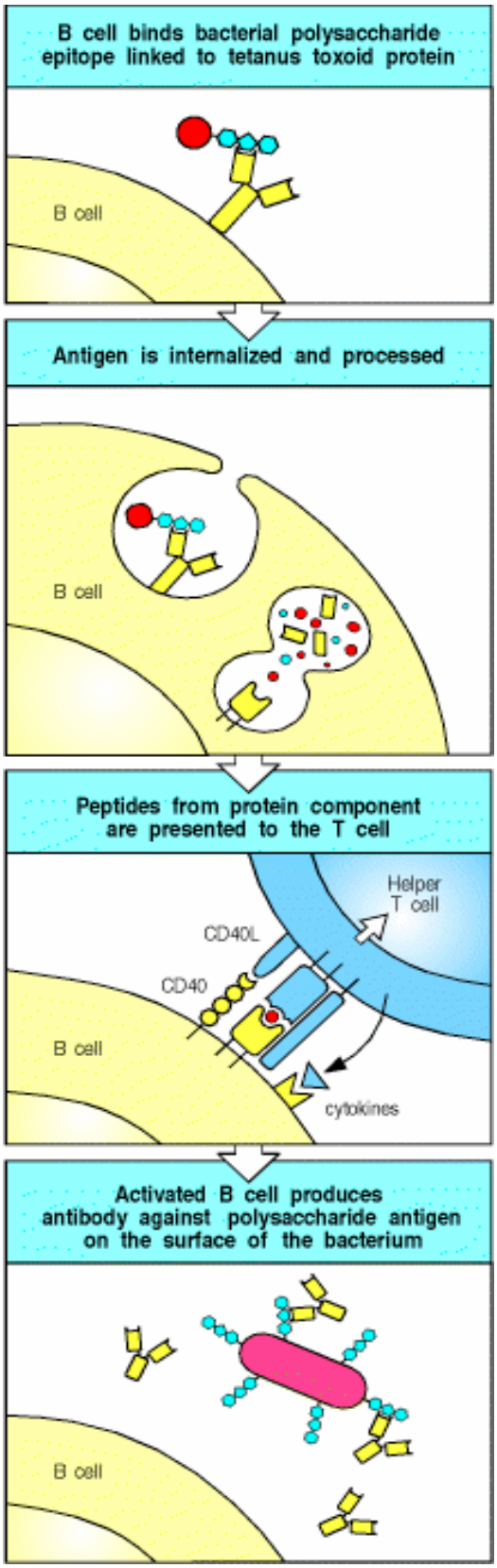
Cytokines	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN-γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF-β	Inhibits	Inhibits		Induces			Induces


Activated B cell
B
Helper T cell
cytokines
Somatic hypermutation of immunoglobulin V regions in rapidly proliferating GC B cells
GC B cell with low-affinity surface immunoglobulin
B
Helper T cell
GC B cell with high-affinity surface immunoglobulin
BCR cross-linking
CD40
CD40L
Helper T cell
BCR is not cross-linked and B cell cannot present Ag to T cell
T-cell help and BCR cross-linking sustain B cell proliferation and maturation
B cell dies by apoptosis
Memory B cell
IgG
Plasma cell


Thymus-dependent antigen
B cell
Helper
T cell
CD40L
CD40
cytokines
B cell
Thymus-independent antigen
B cell


High concentration of TI-1 antigen
Polyclonal B-cell activation;
nonspecific antibody response
Low concentration of TI-1 antigen
TI-1 antigen-specific antibody response


TI-2 antigens alone can signal B cells to produce antibody
T cells release cytokines that augment production of antibody against TI-2 antigen and induce isotype switching
B
1
Helper T cell
T-cell receptor
?
2
cytokines
IgM
IgG


B cell binds bacterial polysaccharide epitope linked to tetanus toxoid protein
B cell
Antigen is internalized and processed
B cell
Peptides from protein component are presented to the T cell
Helper T cell
CD40L
CD40
B cell
cytokines
Activated B cell produces antibody against polysaccharide antigen on the surface of the bacterium
B cell