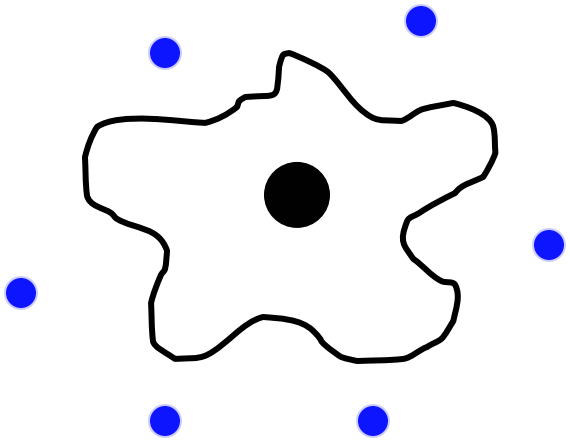
THE EFFECTOR FUNCTIONS OF ANTIBODIES

Catherine Fridman

BMC423 2008

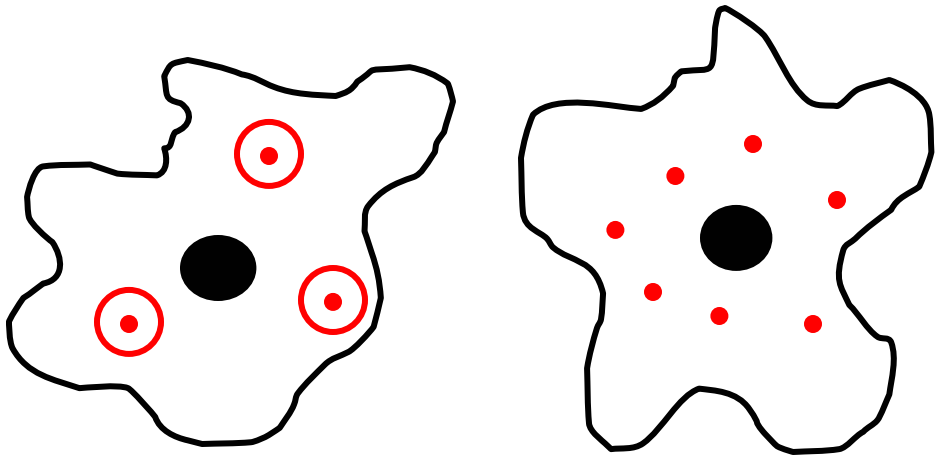
TWO CLASSES OF PATHOGENS

EXTRACELLULAR



BACTERIA:
Streptococcus, Staphylococcus, Neisseria, Salmonella
PARASITES
Plasmodium, Trypanosoma, Toxoplasma

INTRACELLULAR



VESICULAR
BACTERIA:
Mycobacteria, Chlamydia, Shigella, Legionella
PARASITES:
Leishmania, Schistosome

CYTOSOLIC
VIRUSES

HUMORAL IMMUNITYAND CELLULAR IMMUNITY

HUMORAL IMMUNITY (ANTIBODIES AND COMPLEMENT) IS USED TO FIGHT AGAINST **EXTRACELLULAR BACTERIA**

CELLULAR IMMUNITY IS USED TO FIGHT AGAINST **INTRACELLULAR MICROBES** (CTL/VIRUSES; TH/INTRACELLULAR BACTERIA)

Emil von Behring, Nobel prize of physiology or medicine in 1901

He discovered that the sera from animals vaccinated with « attenuated » diphteria contained substances, antibodies that protected other animals from living organisms

The first successfull treatment of a child occured in 1891

THE EFFECTOR FUNCTIONS OF ANTIBODIES

I-Antibodies, definitions, structure and isotypes

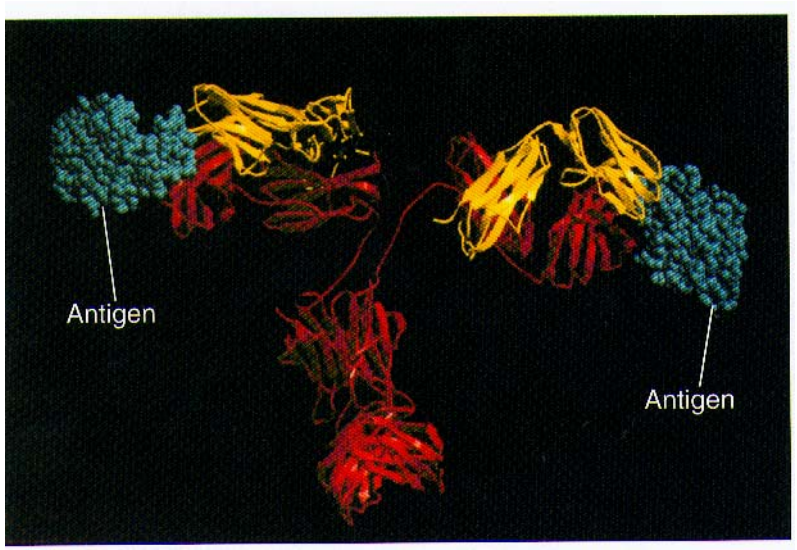
II-Effector functions of antibodies

1-Complement activation

2-FcR dependent functions :
-via the Fc gamma R : `
Internalization
cytotoxicity
cell activation
inhibition of cell activation
-via the Fc epsilon R

III-Transport function via FcRn and PolyIgR

ANTIBODIES ARE BIFUNCTIONNAL MOLECULES



Immunology, 7th edition, D.Male et al., Mosby, Elsevier

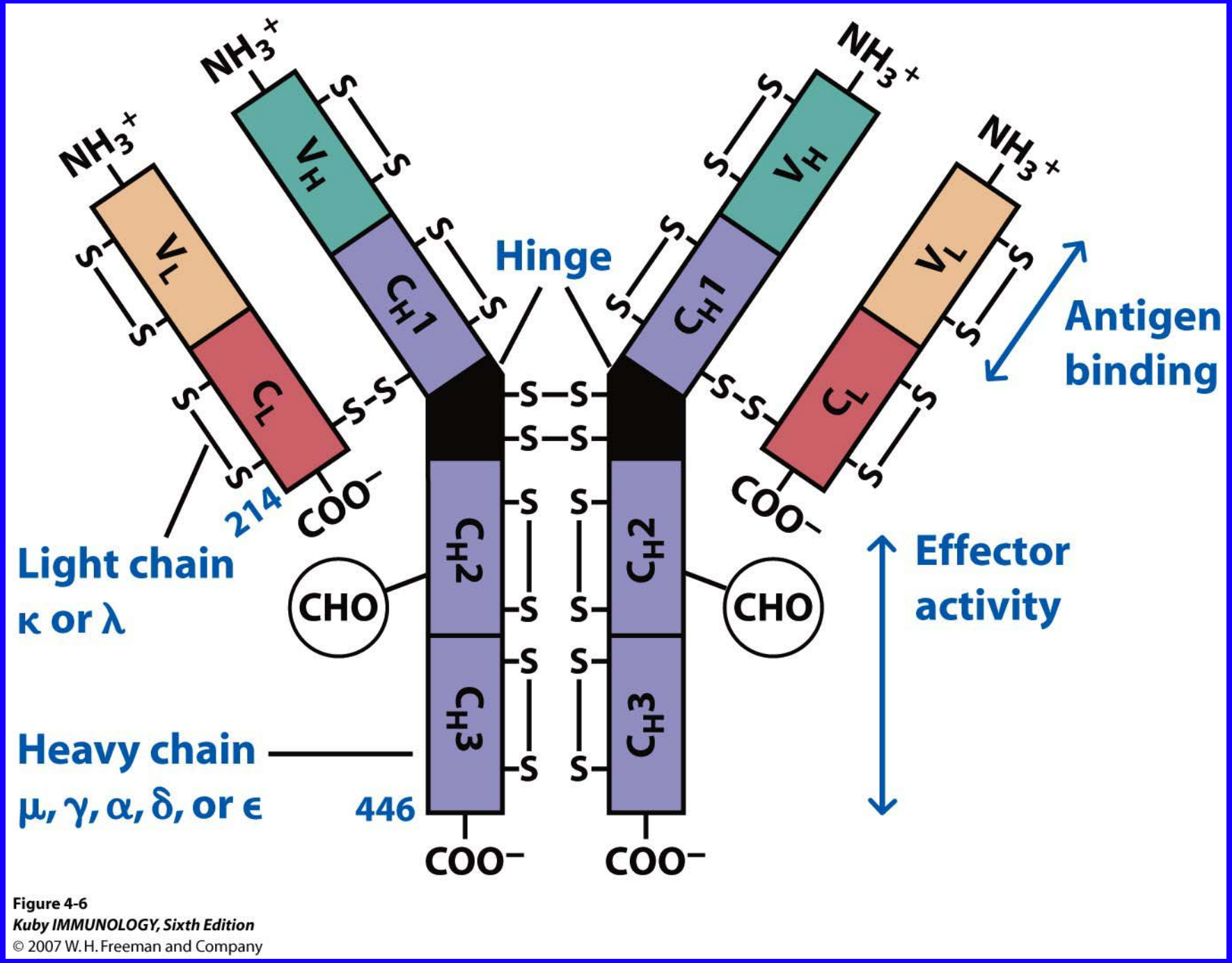
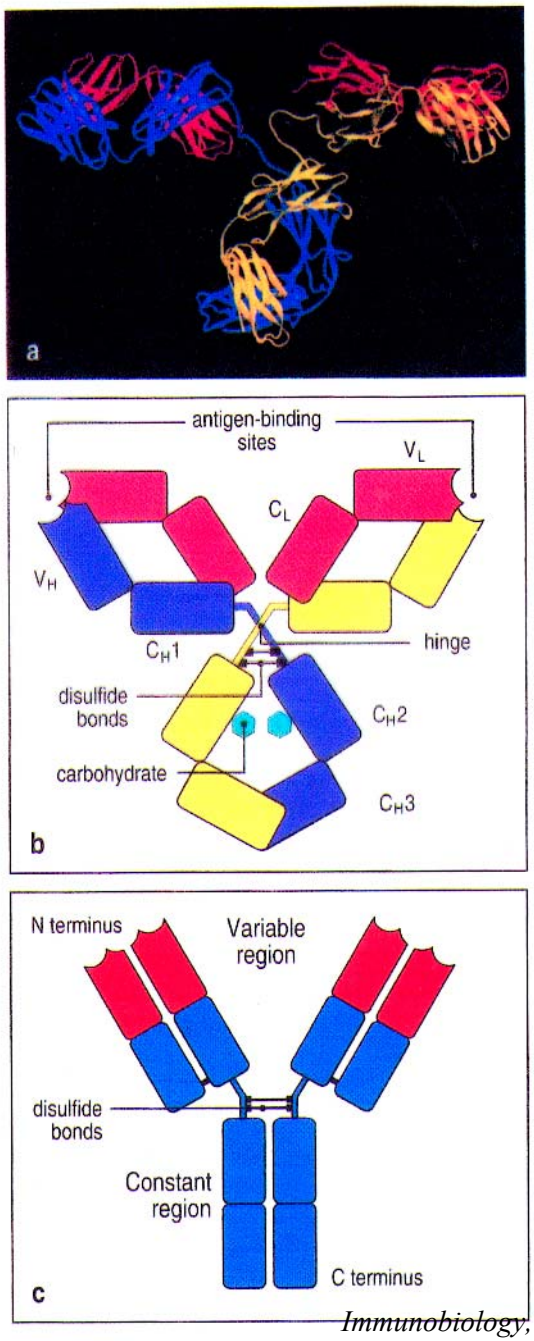


Figure 4-6
Kuby IMMUNOLOGY, Sixth Edition



Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

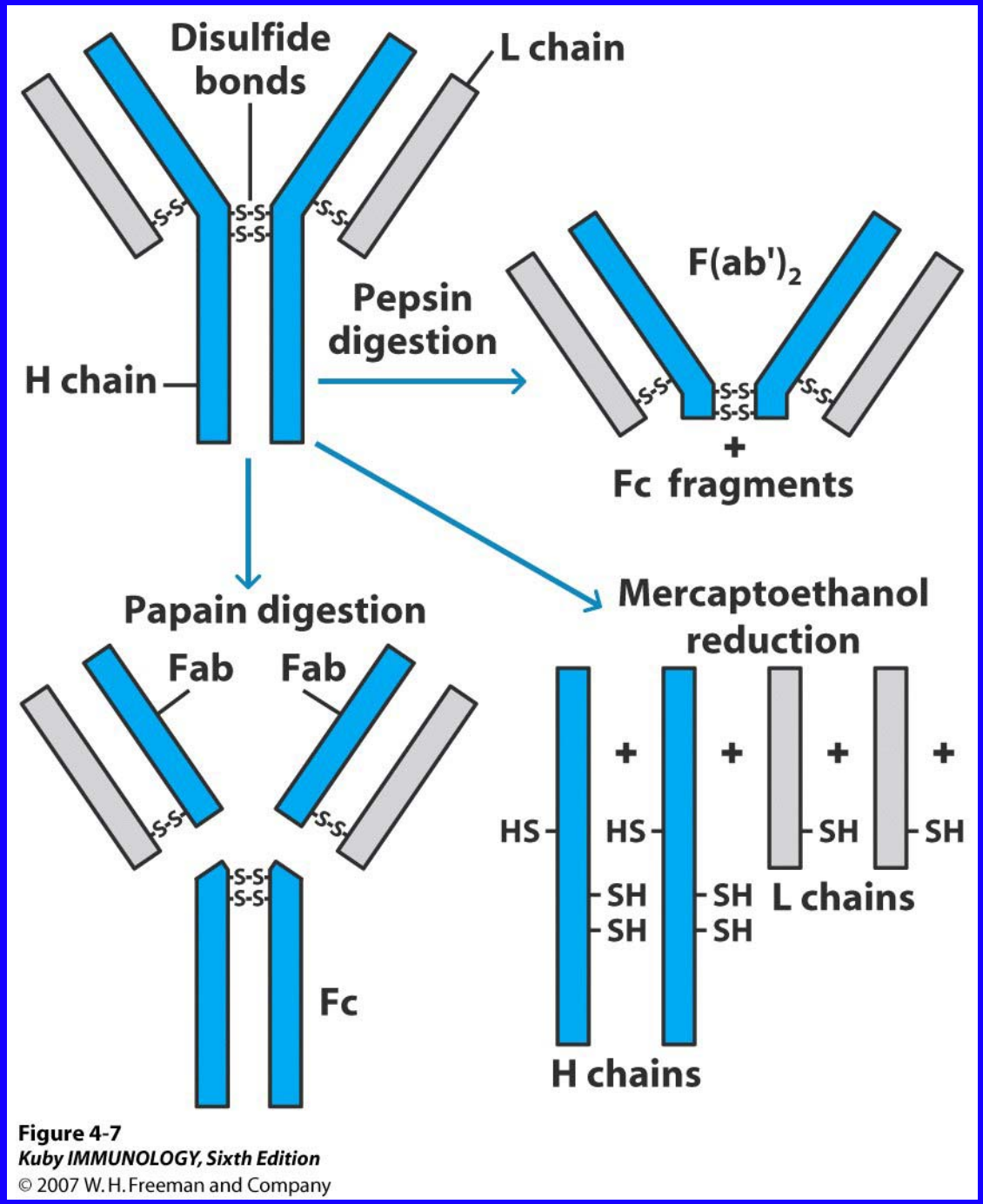


Figure 4-7
Kuby IMMUNOLOGY, Sixth Edition

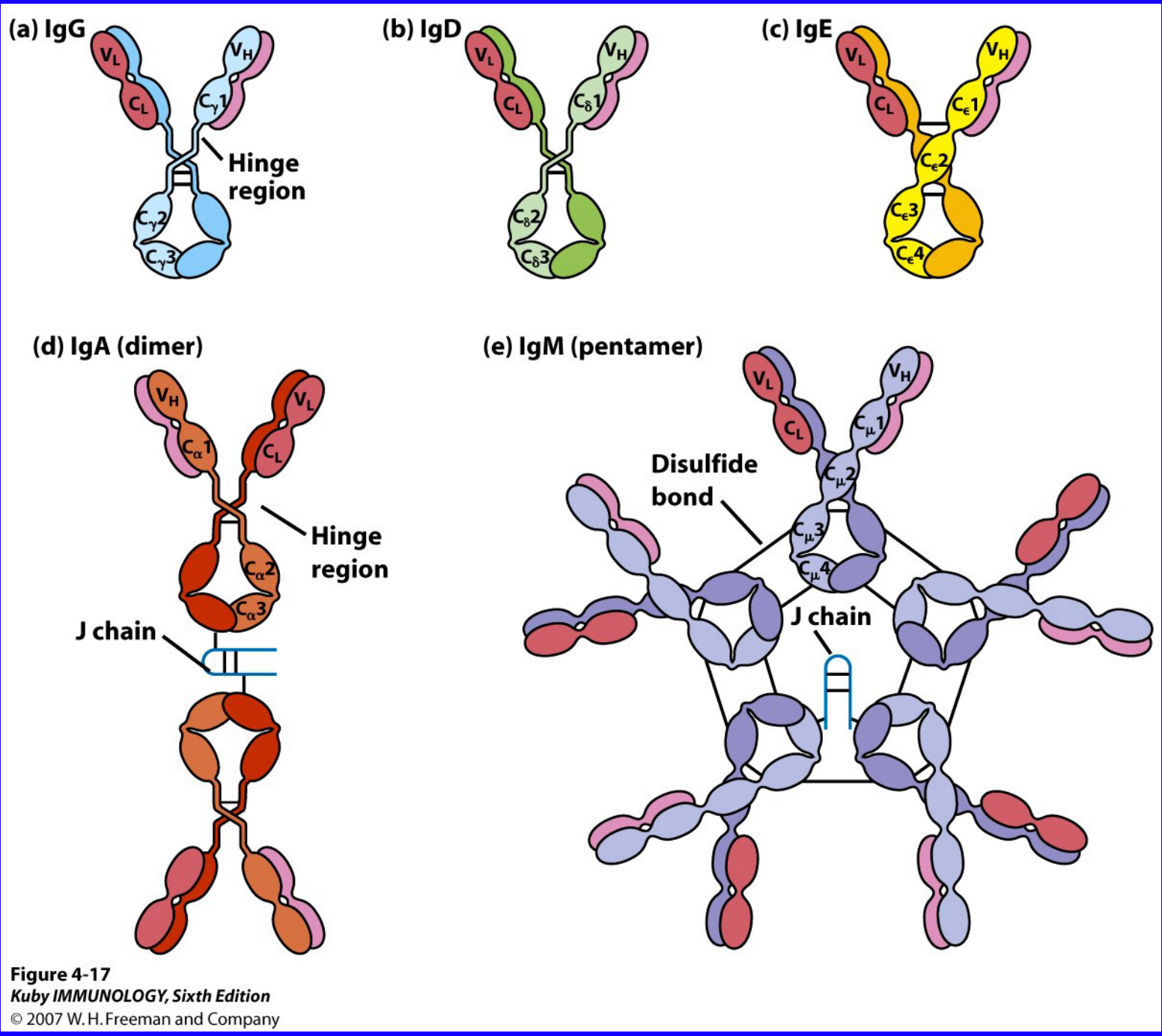


Figure 4-17
Kuby IMMUNOLOGY, Sixth Edition

TABLE 4-3 Chain composition of the five immunoglobulin classes in humans

Class*	Heavy chain	Subclasses	Light chain	Molecular formula
IgG	γ	$\gamma 1, \gamma 2, \gamma 3, \gamma 4$	κ or λ	$\gamma_2\kappa_2$ $\gamma_2\lambda_2$
IgM	μ	None	κ or λ	$(\mu_2\kappa_2)_n$ $(\mu_2\lambda_2)_n$ $n = 1$ or 5
IgA	α	$\alpha 1, \alpha 2$	κ or λ	$(\alpha_2\kappa_2)_n$ $(\alpha_2\lambda_2)_n$ $n = 1, 2, 3,$ or 4
IgE	ϵ	None	κ or λ	$\epsilon_2\kappa_2$ $\epsilon_2\lambda_2$
IgD	δ	None	κ or λ	$\delta_2\kappa_2$ $\delta_2\lambda_2$

*See Figure 4-1 for general structures of five antibody classes.

Table 4-3
Kuby IMMUNOLOGY, Sixth Edition

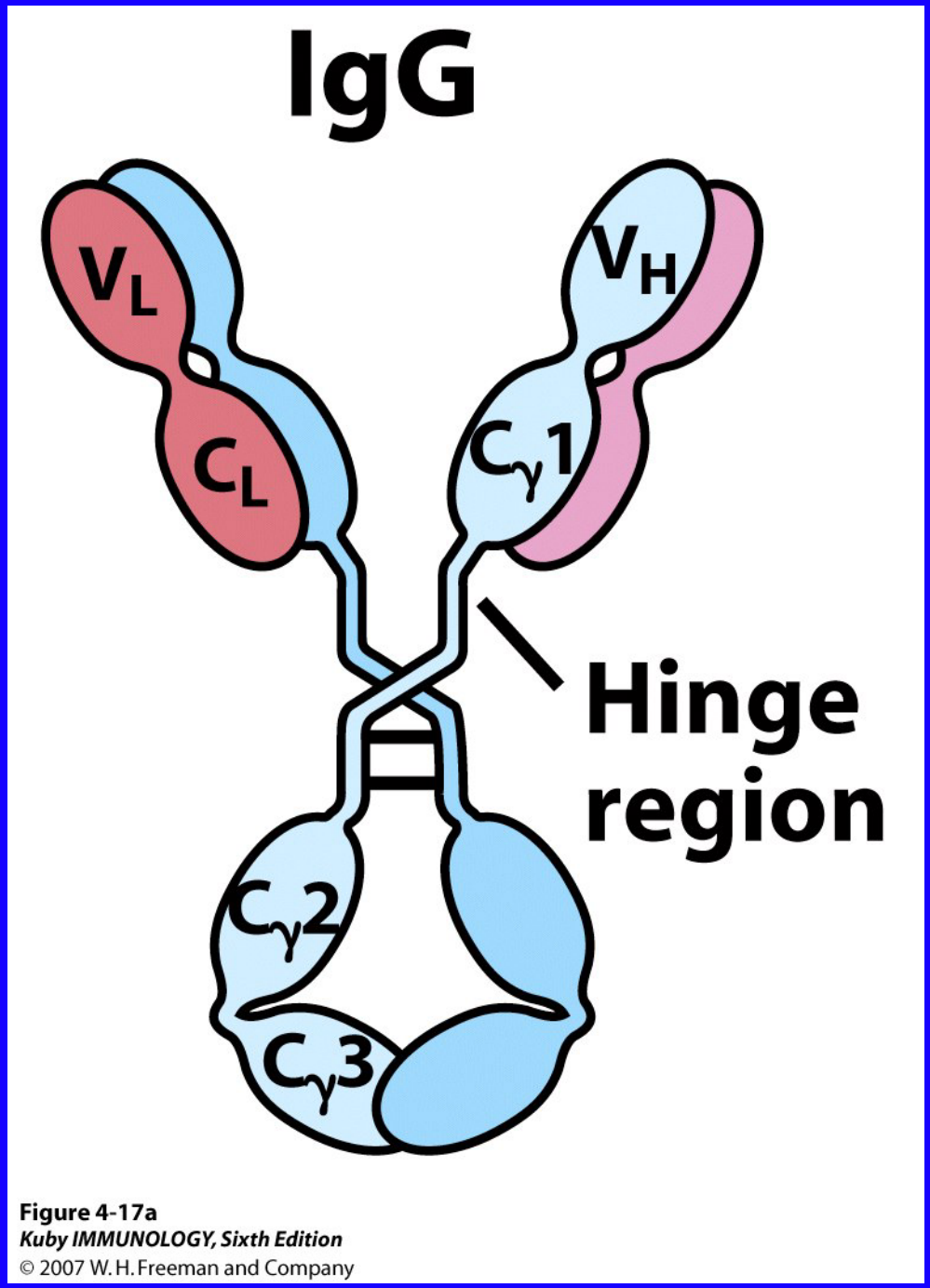


Figure 4-17a
Kuby IMMUNOLOGY, Sixth Edition

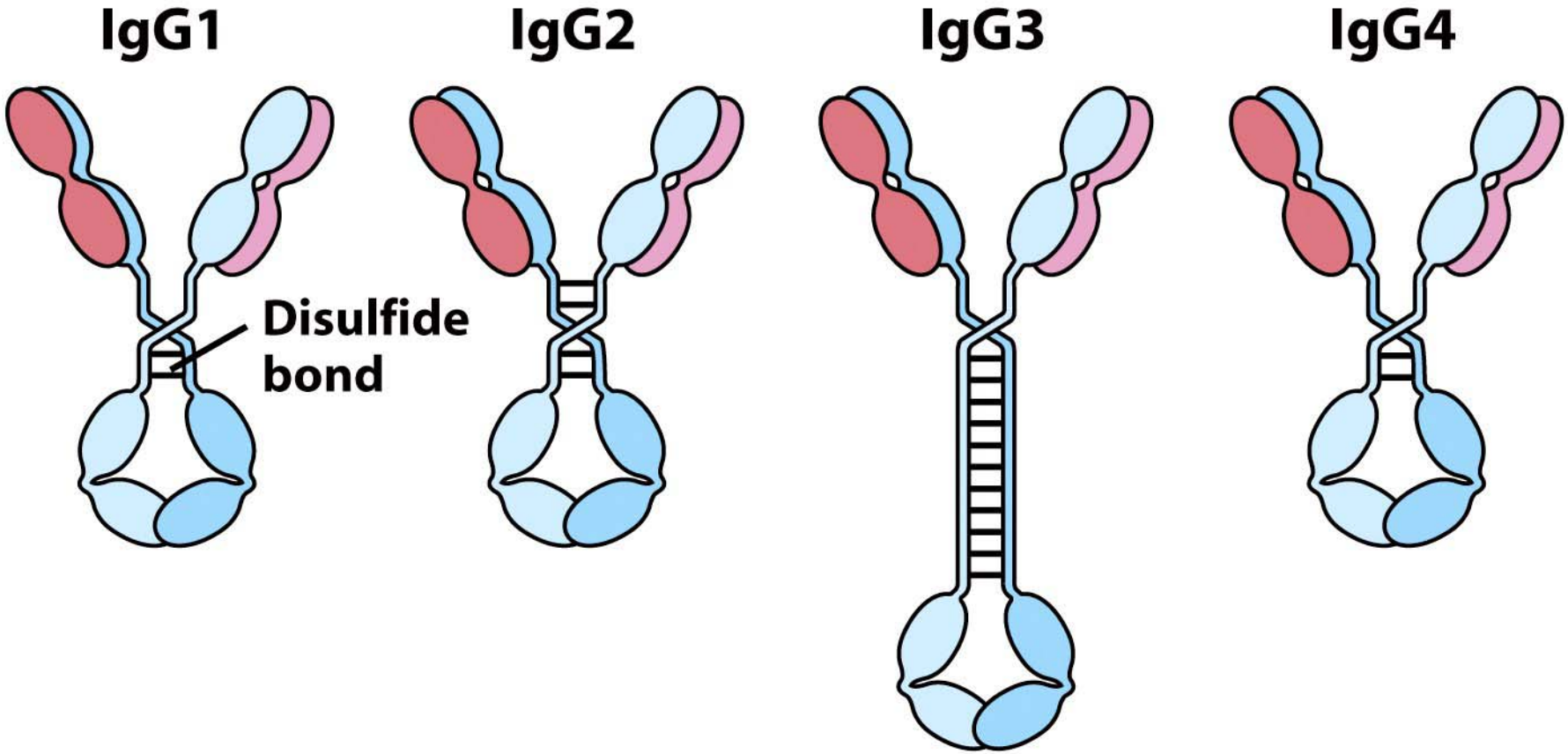


Figure 4-18
Kuby IMMUNOLOGY, Sixth Edition

IMMUNOGLOBULINS A

- PRESENT IN MUCOSAL TISSUES
- TWO ISOTYPES IgA1 et IgA2
- MONOMERS IN BLOOD (IgA1/IgA2 = 4)
- DIMERS IN MUCUS (IgA1/IgA2 = 3:2)

Structure of secretory IgA

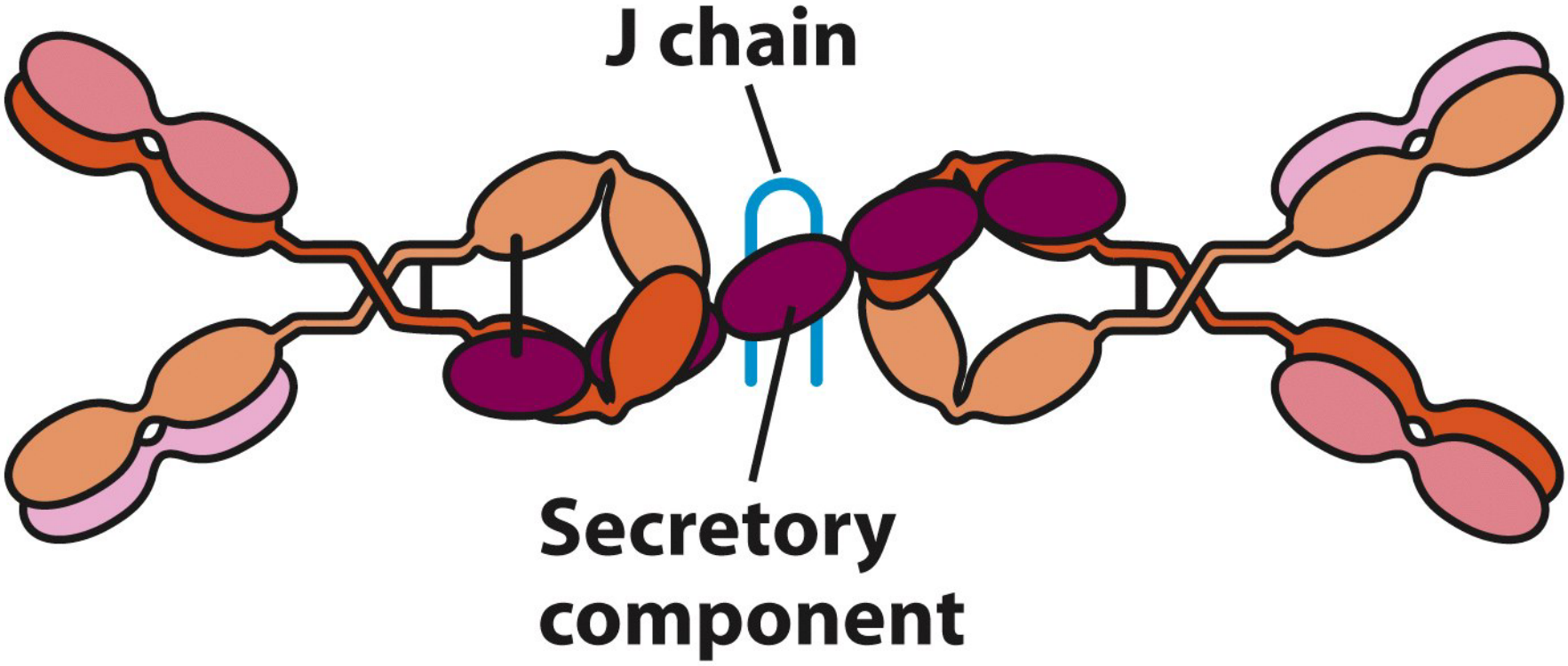


Figure 4-19a
Kuby IMMUNOLOGY, Sixth Edition

Isotypic determinants

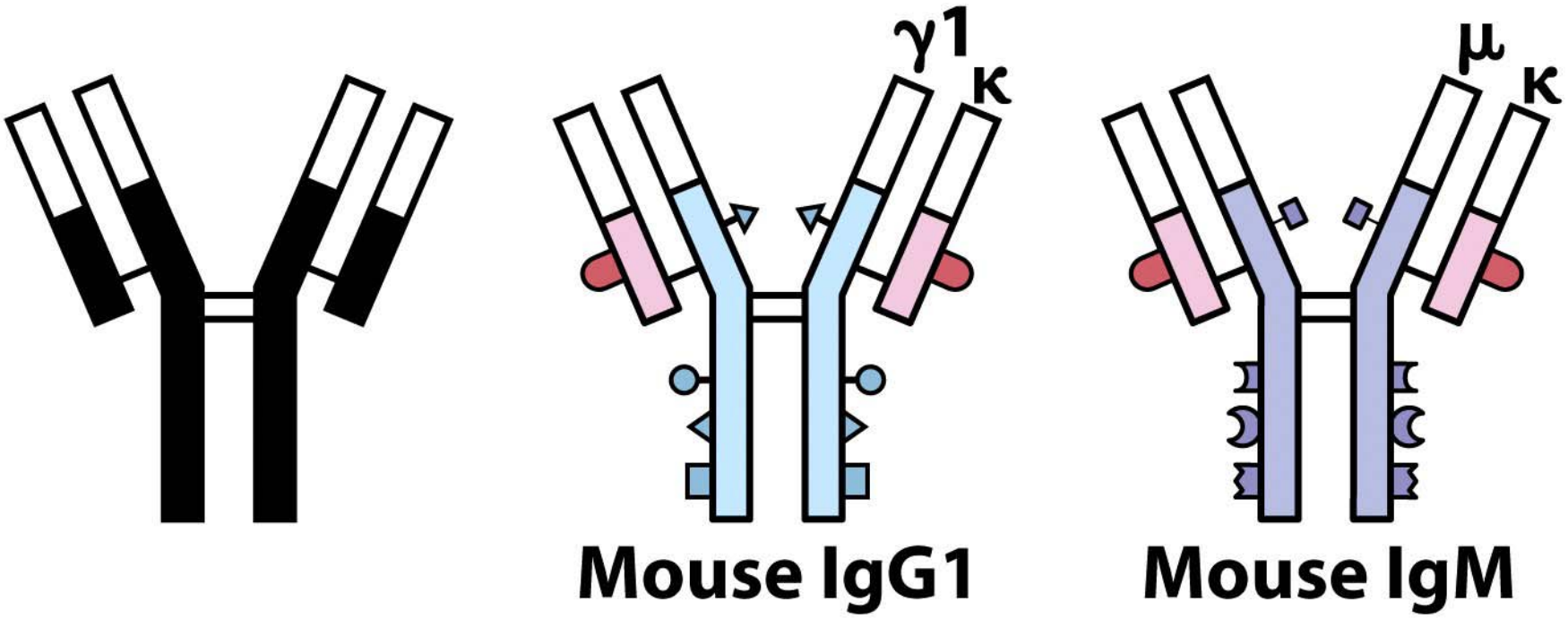
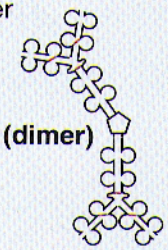
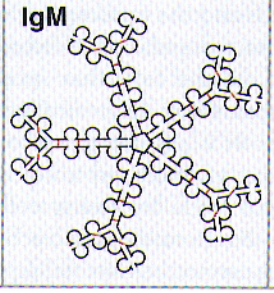
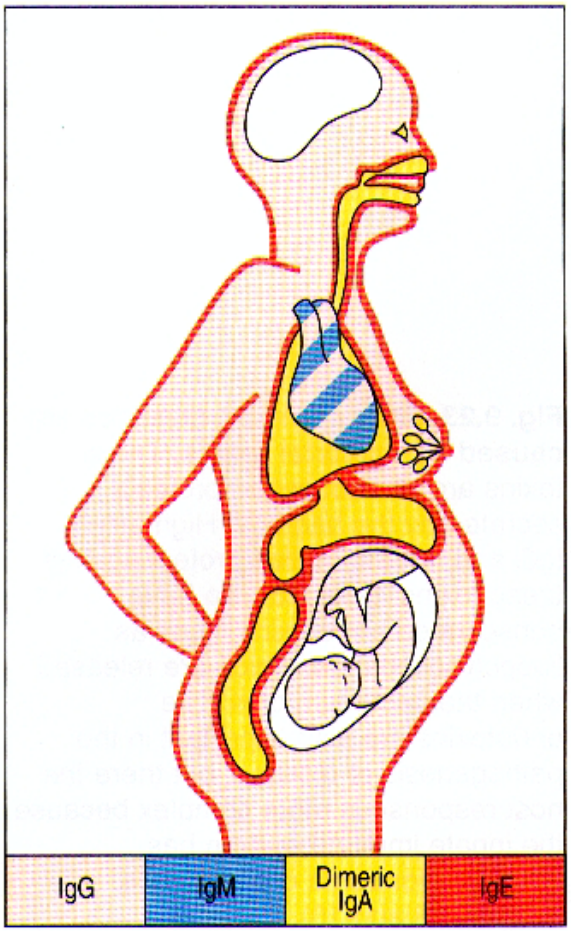


Figure 4-21a
Kuby IMMUNOLOGY, Sixth Edition

Isotype of antibody	Subtypes	H chain	Serum concentr. (mg/mL)	Serum half-life (days)	Secreted form	Functions
IgA	IgA1,2	α(1 or 2)	3.5	6	Monomer,dimer, trimer 	Mucosal immunity, neonatal passive immunity
IgD	None	δ	Trace	3	None	Naive B cell antigen receptor
IgE	None	ε	0.05	2	Monomer 	Mast cell activation (immediate hypersensitivity)
IgG	IgG1-4	γ (1,2,3 or 4)	13.5	23	Monomer 	Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None	μ	1.5	5	Pentamer 	Naive B cell antigen receptor, complement activation

Basic Immunology, 2nd edition, Abbas and Lichtman, Saunders Elsevier ed

Ig isotypes have an heterogeneous distribution in the body



Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

Isotypes have different functionnal activities

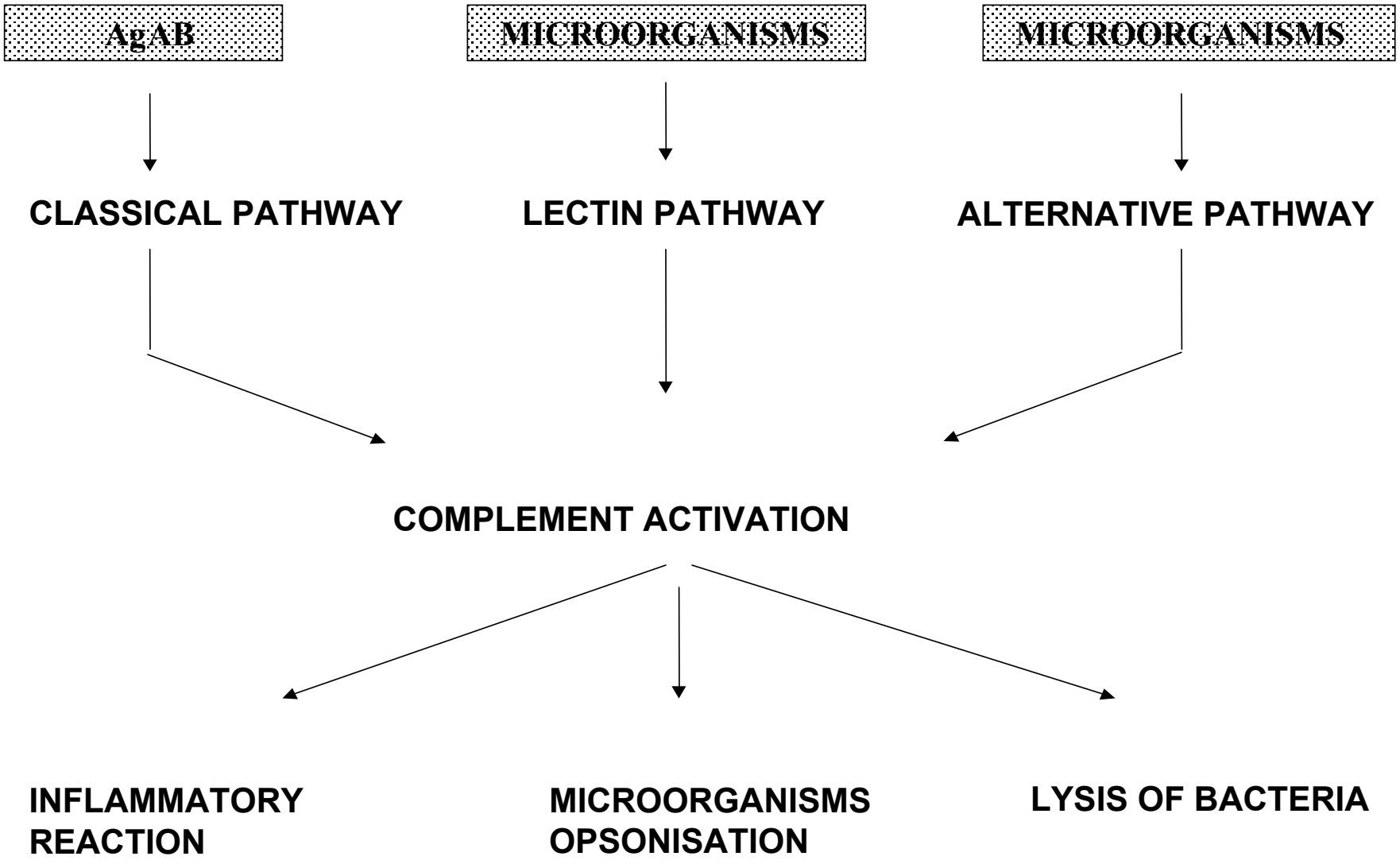
Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	+	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–

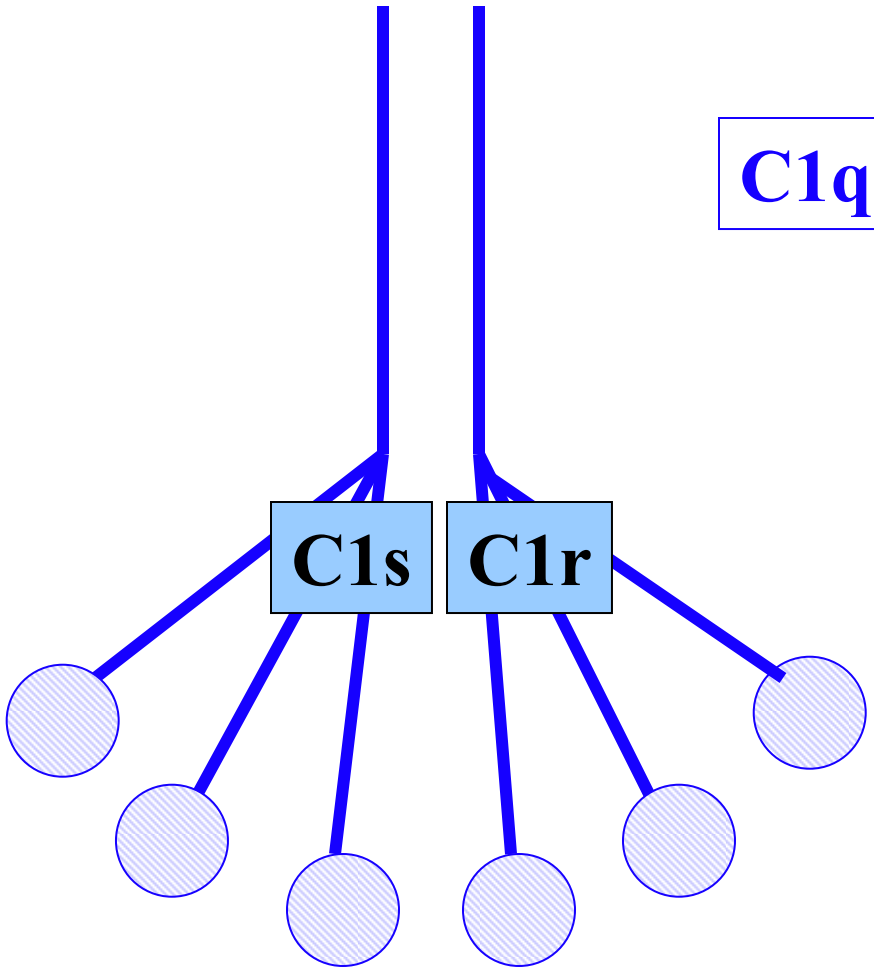
Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	3×10^{-5}

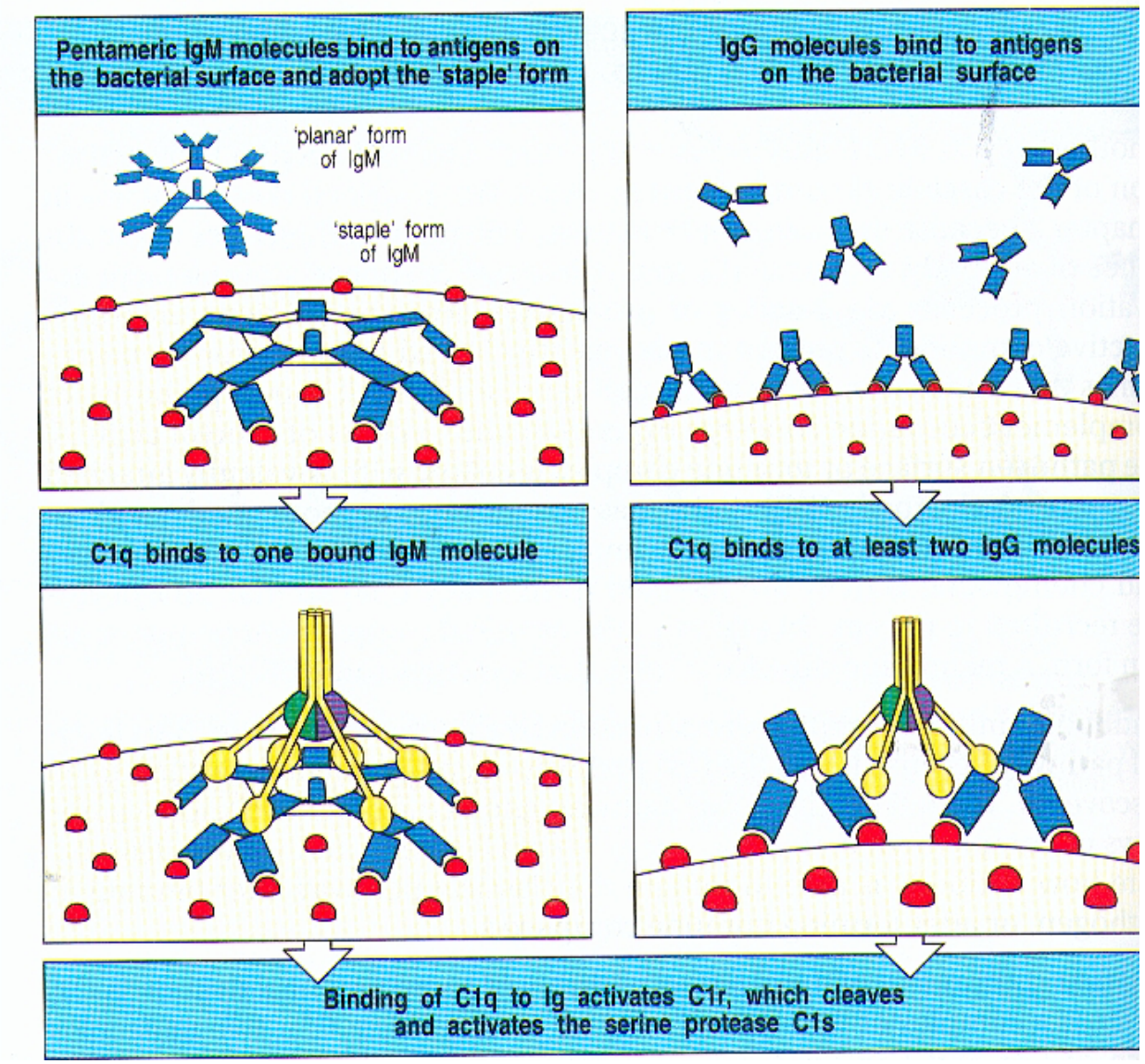
Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

FUNCTIONS OF ANTIBODIES

IgM	PRESENT IN BODY FLUIDS DEFENSES AGAINST INFECTION AND CANCER
IgG	PRESENT IN BODY FLUIDS AND TISSUES, DEFENSES AGAINST INFECTION AND CANCER
IgA	PRESENT IN MUCOSAL SURFACES, NEUTRALIZATION OF PATHOGENS
IgE	PRESENT IN TISSUES AND ON VASCULAR ENDOTHELIUM, ALLERGY, DEFENSES AGAINST HELMINTHS

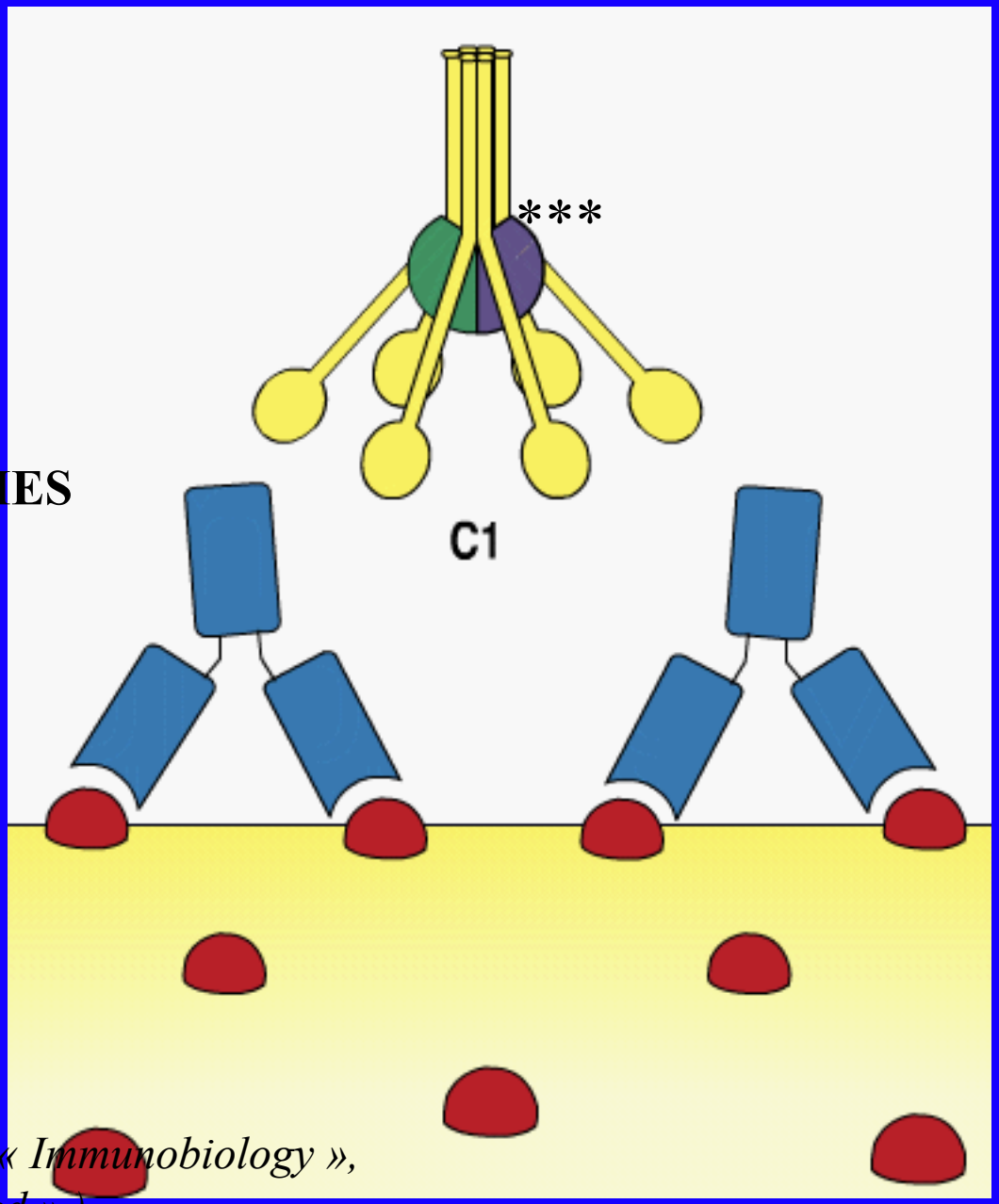

AgAB
MICROORGANISMS
MICROORGANISMS
CLASSICAL PATHWAY
LECTIN PATHWAY
ALTERNATIVE PATHWAY
COMPLEMENT ACTIVATION
INFLAMMATORY REACTION
MICROORGANISMS OPSONISATION
LYSIS OF BACTERIA


C1q
C1s
C1r

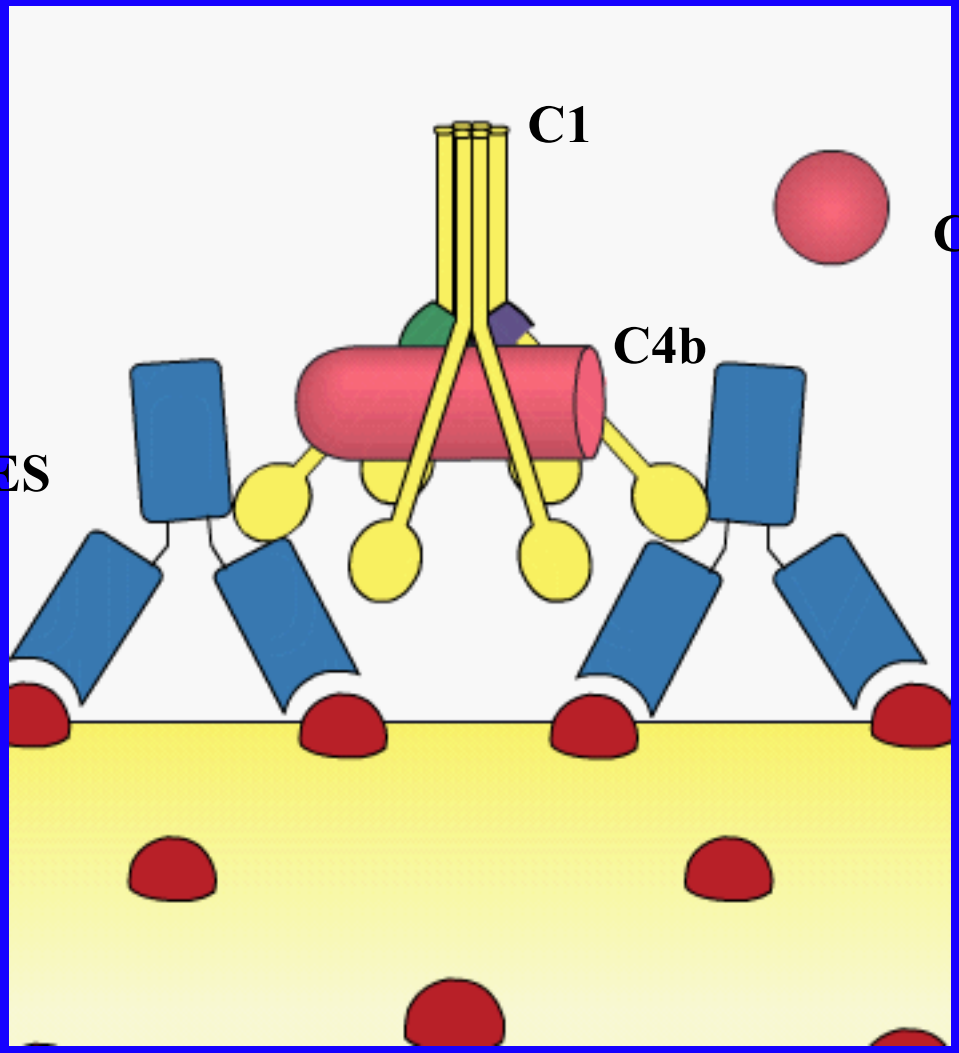


Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone

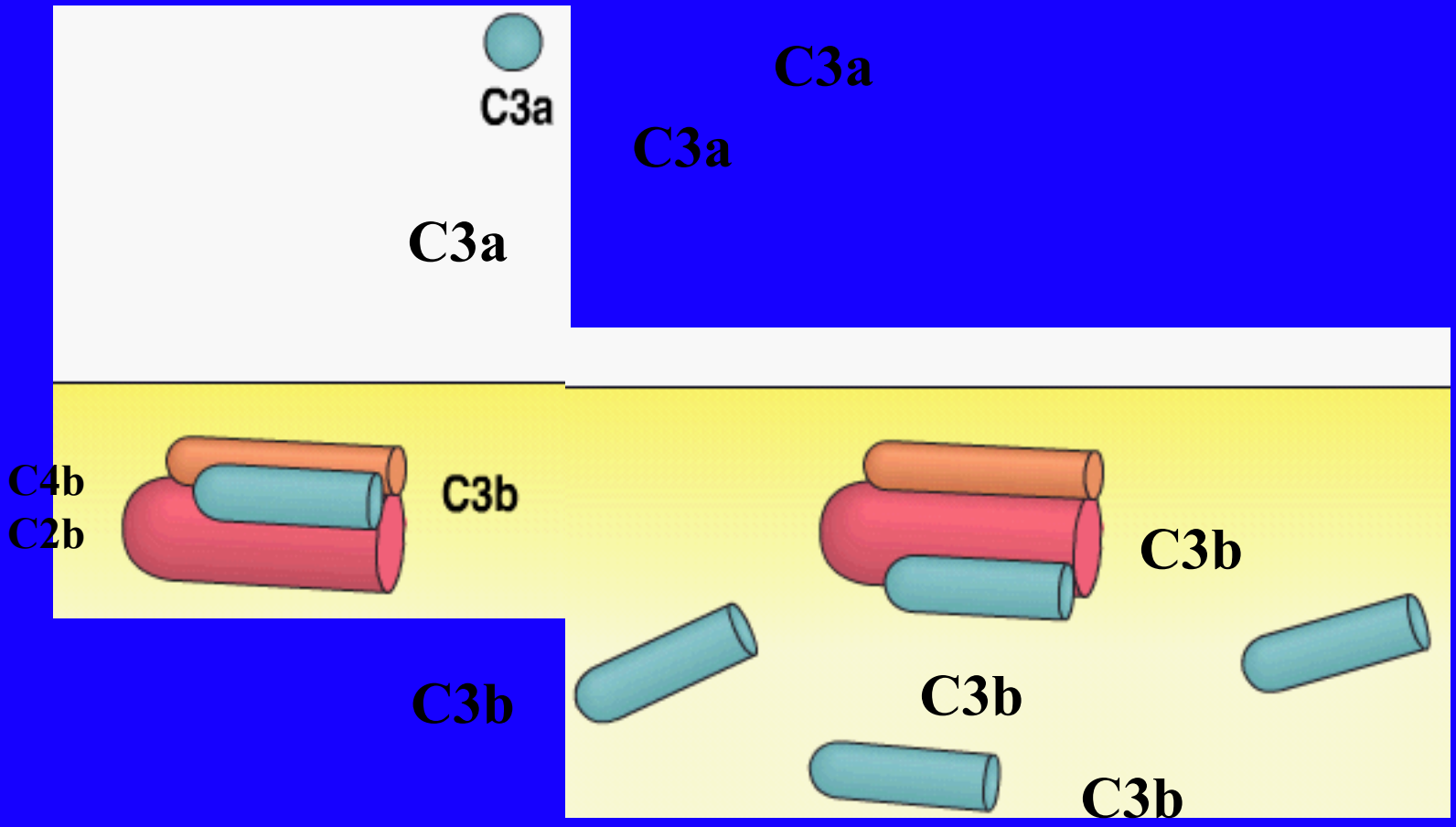
ANTIBODIES



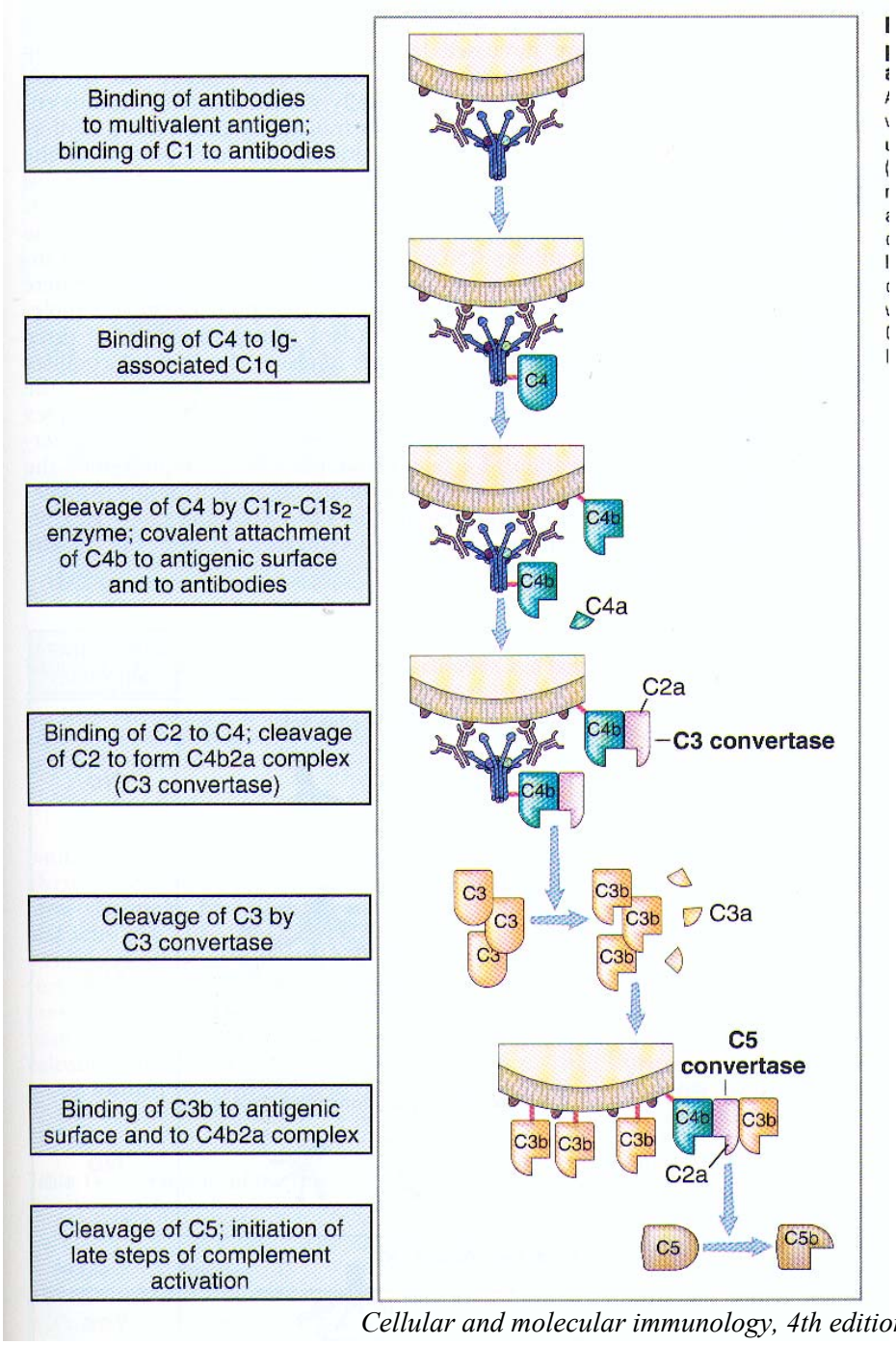
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



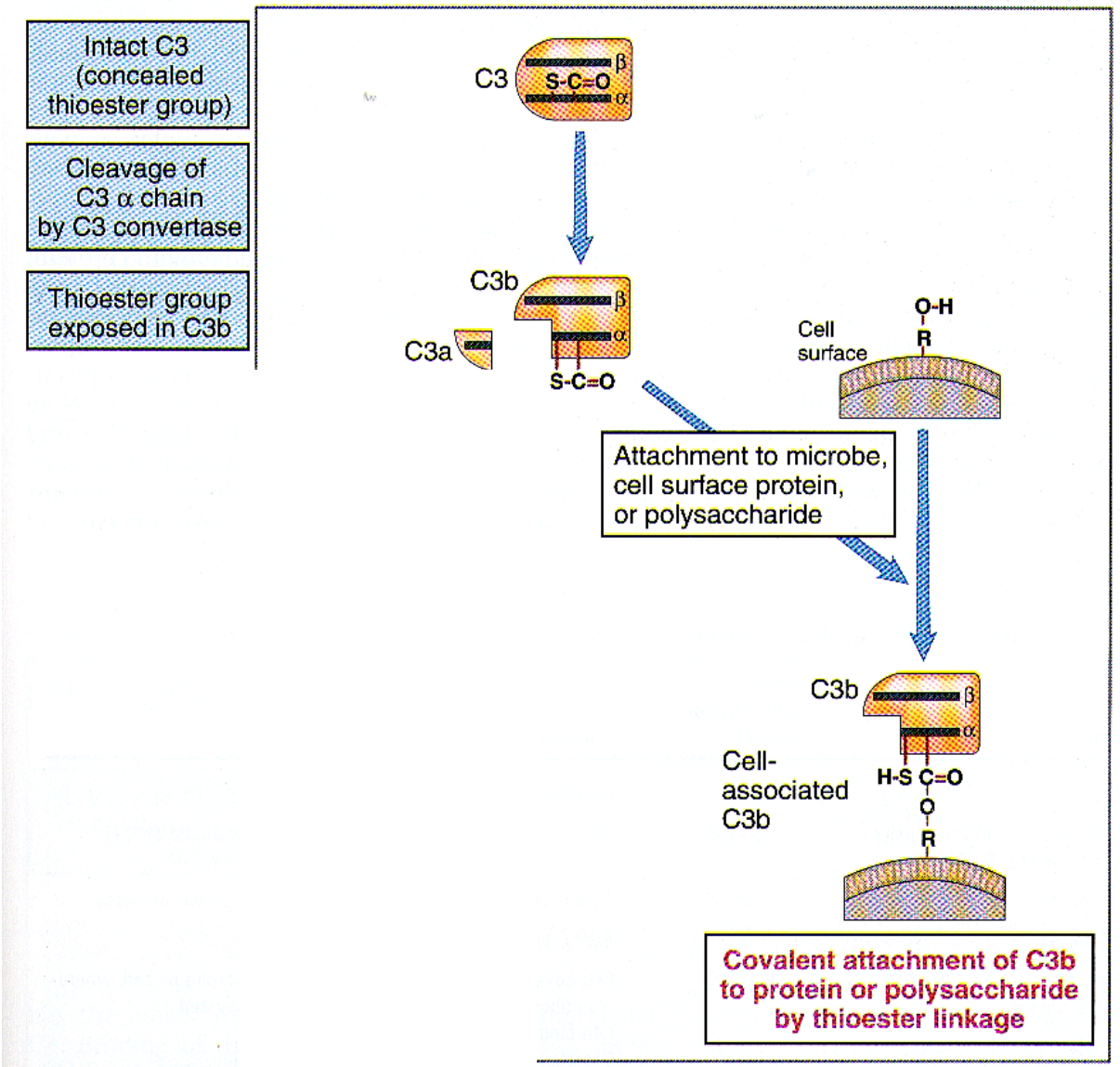
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



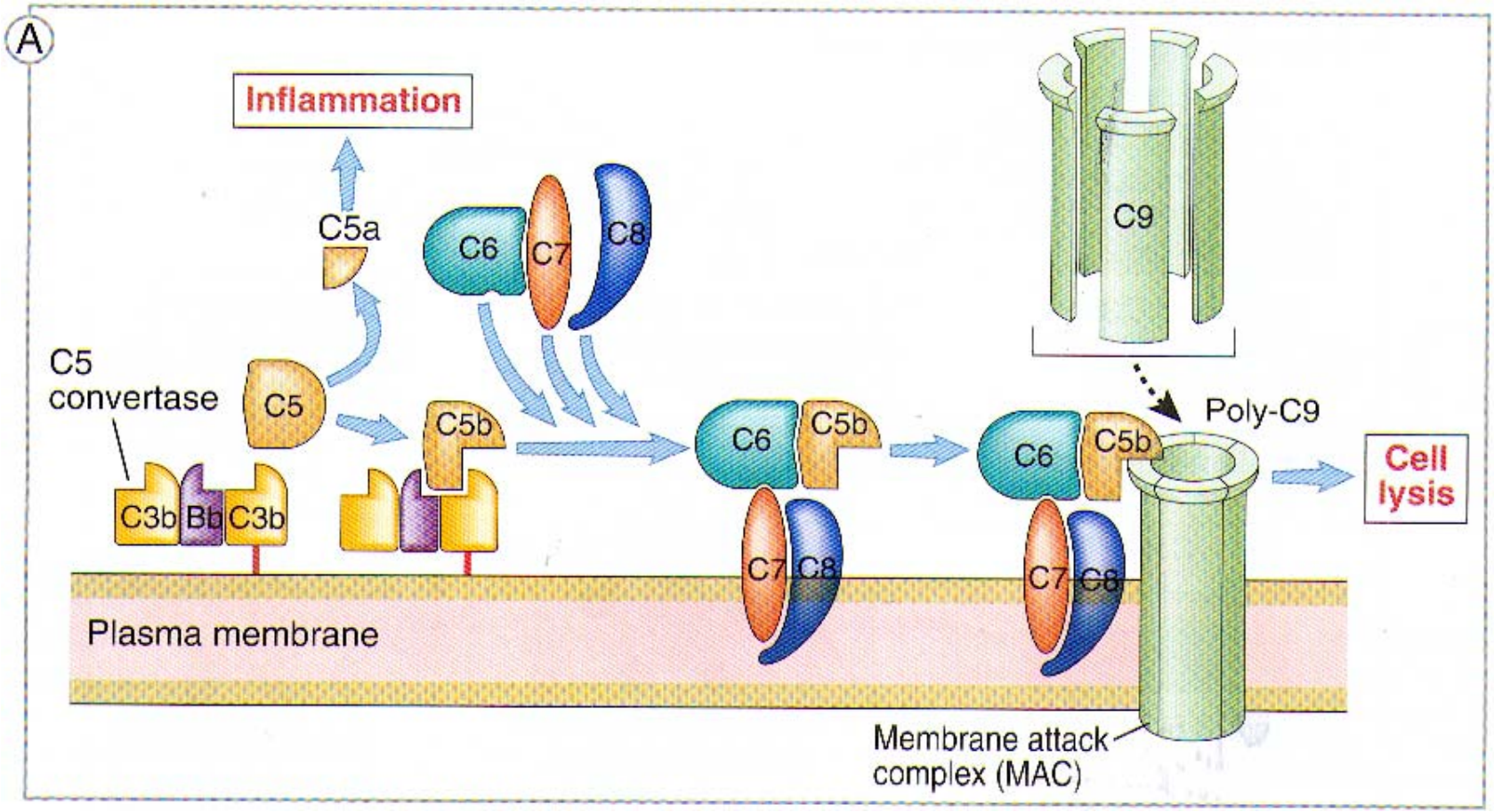
(from Janeway et al, « Immunobiology », 5th edition Garland ed »)



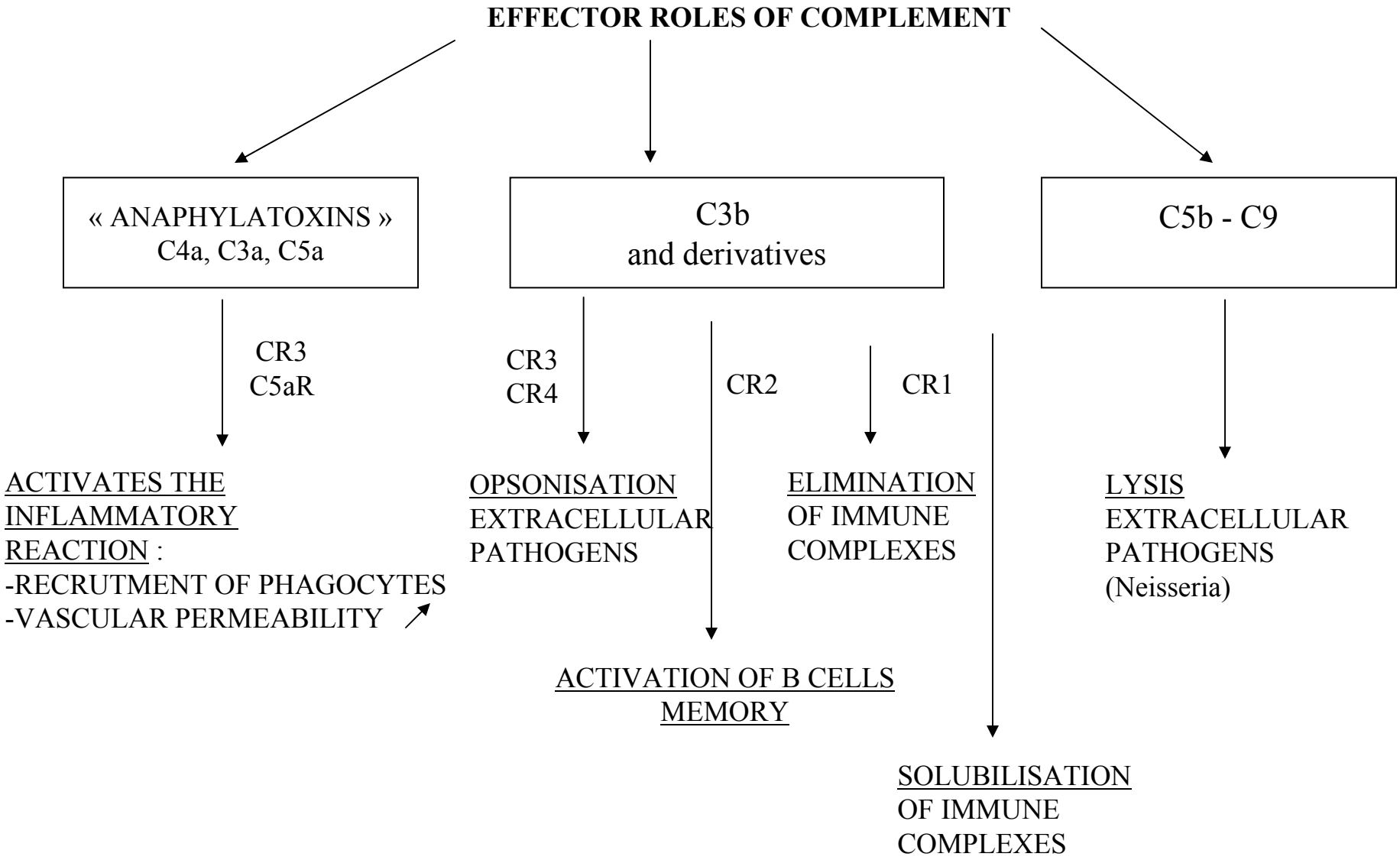
Cellular and molecular immunology, 4th edition, A.K. Abbas et al., Saunders ed



Cellular and molecular immunology, 4th edition, A.K. Abbas et al., Saunders ed



Basic Immunology, 2nd edition, Abbas and Lichtman, Saunders Elsevier ed

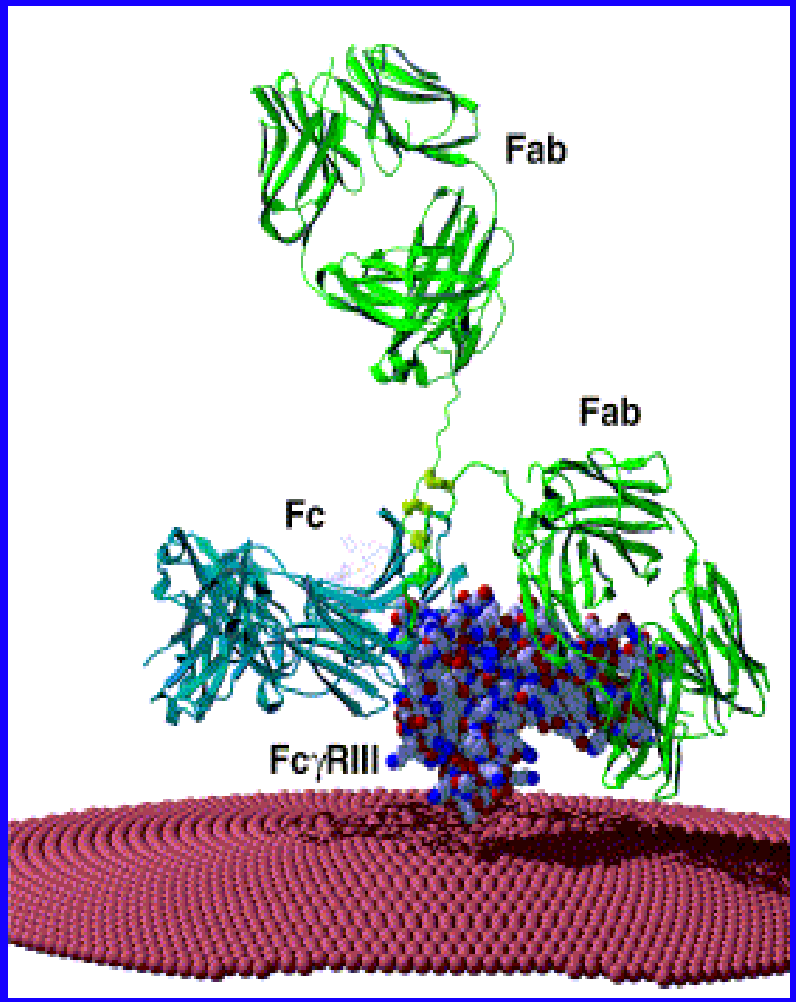

EFFECTOR ROLES OF COMPLEMENT
« ANAPHYLATOXINS »
C4a, C3a, C5a
C3b
and derivatives
C5b - C9
CR3
C5aR
CR3
CR4
CR2
CR1
ACTIVATES THE INFLAMMATORY REACTION :
-RECRUTMENT OF PHAGOCYTES
-VASCULAR PERMEABILITY
OPSONISATION
EXTRACELLULAR PATHOGENS
ELIMINATION
OF IMMUNE
COMPLEXES
LYSIS
EXTRACELLULAR
PATHOGENS
(Neisseria)
ACTIVATION OF B CELLS
MEMORY
SOLUBILISATION
OF IMMUNE
COMPLEXES

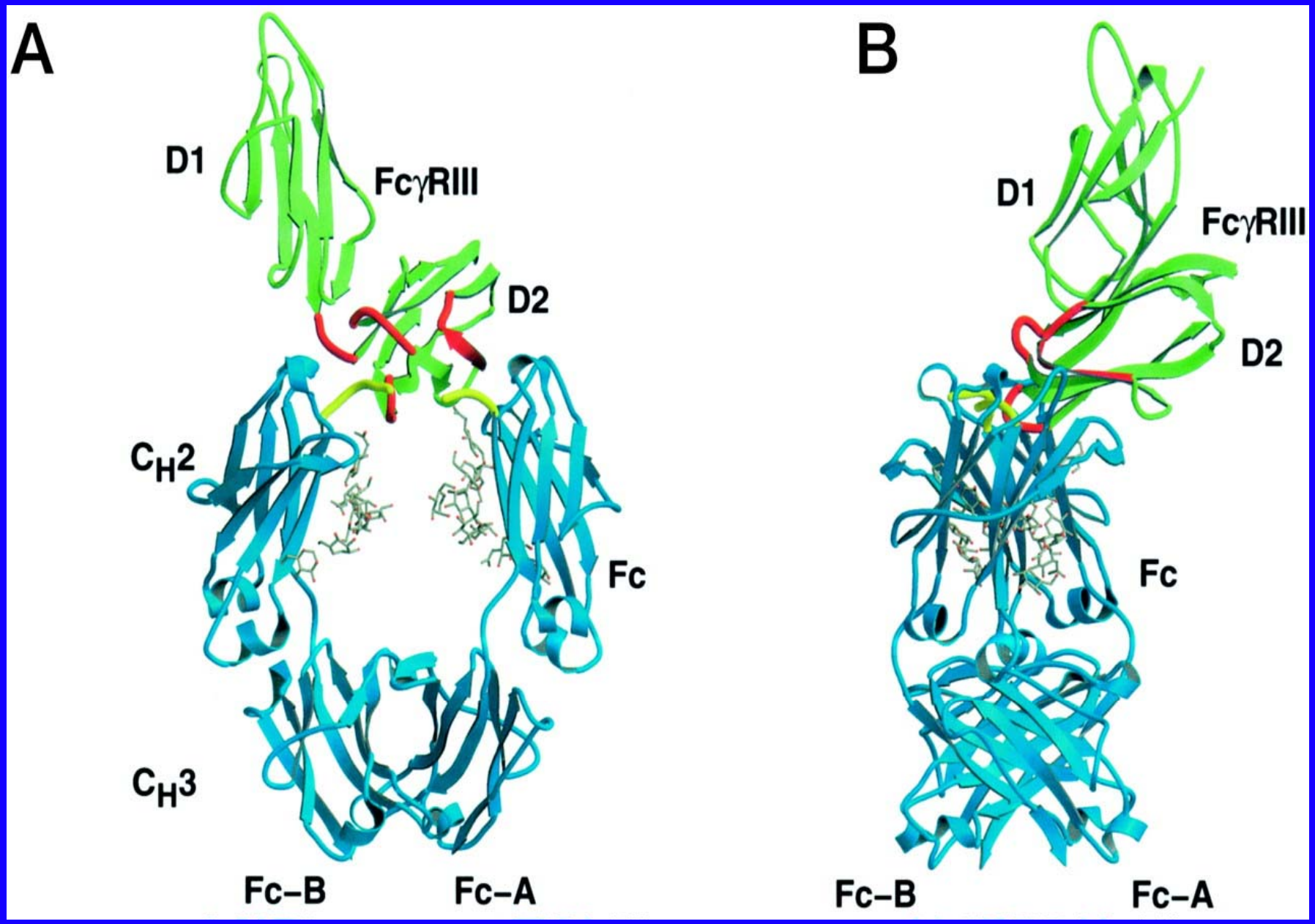
OTHER FUNCTIONS OF ANTIBODIES

CLASS	FcR TYPE	FcR for TRANSPORT OF Ig
IgM	-	PolylgR
IgG	RFcγ	RFcn
IgA	RFcα	PolylgR
IgE	RFcε	-
IgD	-	-

BIOLOGICAL ACTIVITIES OF Ag-Ab (IgG) COMPLEXES

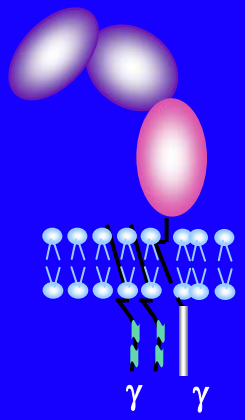
- **Internalization**
  - **Phagocytosis**
  - **Endocytosis**
- **Cell activation :**
  - **Release of mediators**
  - **Perforin and granzyme release (ADCC)**
  - **Cytokine secretion**
- **Inhibition of Cell activation**


Fab
Fab
Fc
FcγRIII


A
D1
FcγRIII
D2
C_H2
Fc
C_H3
Fc–B
Fc–A
B
D1
FcγRIII
D2
Fc
Fc–B
Fc–A

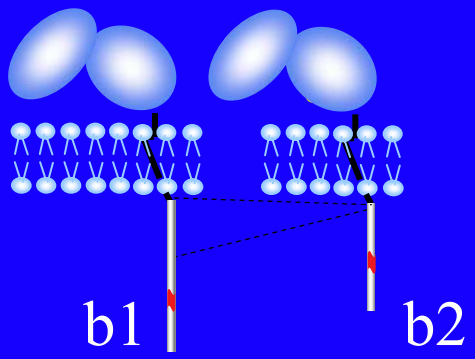
MOUSE FcγR

FcγRI



Macrophages
Neutrophils

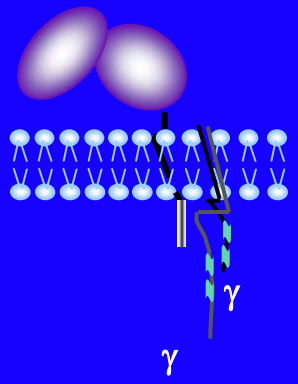
FcγRIIb



B cells
Mast cells

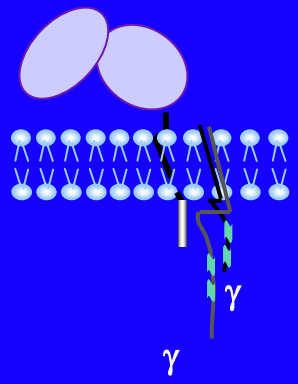
Macrophages
Dendritic cells

FcγRIII



NK cells
Monocytes
Mast cells

FcγRIV

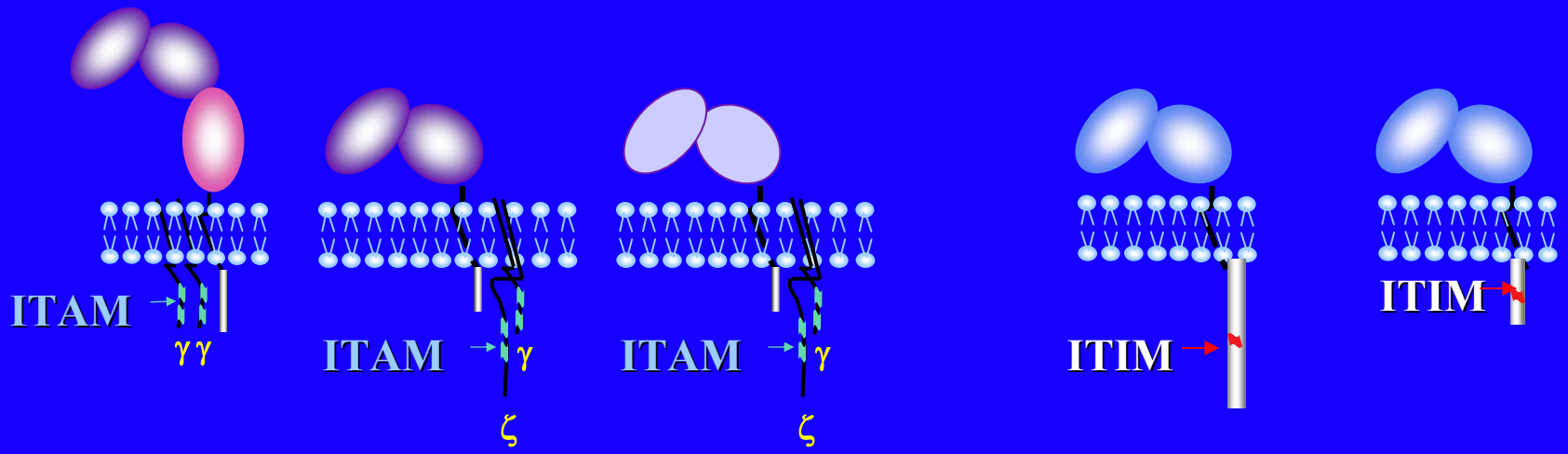


Monocytes
Dendritic cells
Neutrophils

ACTIVATING RECEPTORS

INHIBITORY RECEPTORS

FcγRI **FcγRIII** **FcγRIV** **FcγRIIb1** **FcγRIIb2**



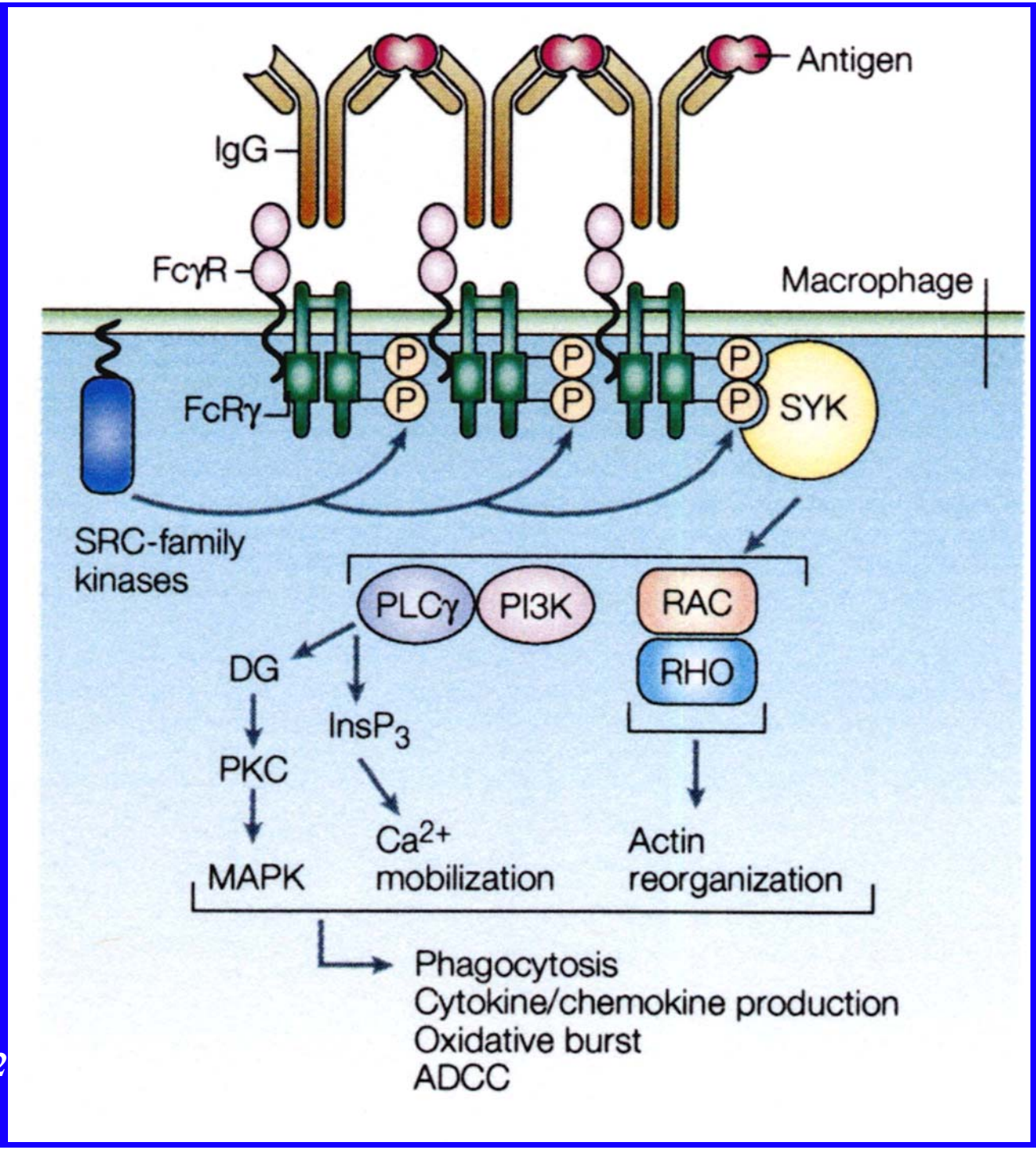
« Immunoreceptor tyrosine activation motif »

(YxxL)(X)n(YxxL)

« Immunoreceptor tyrosine inhibition motif »

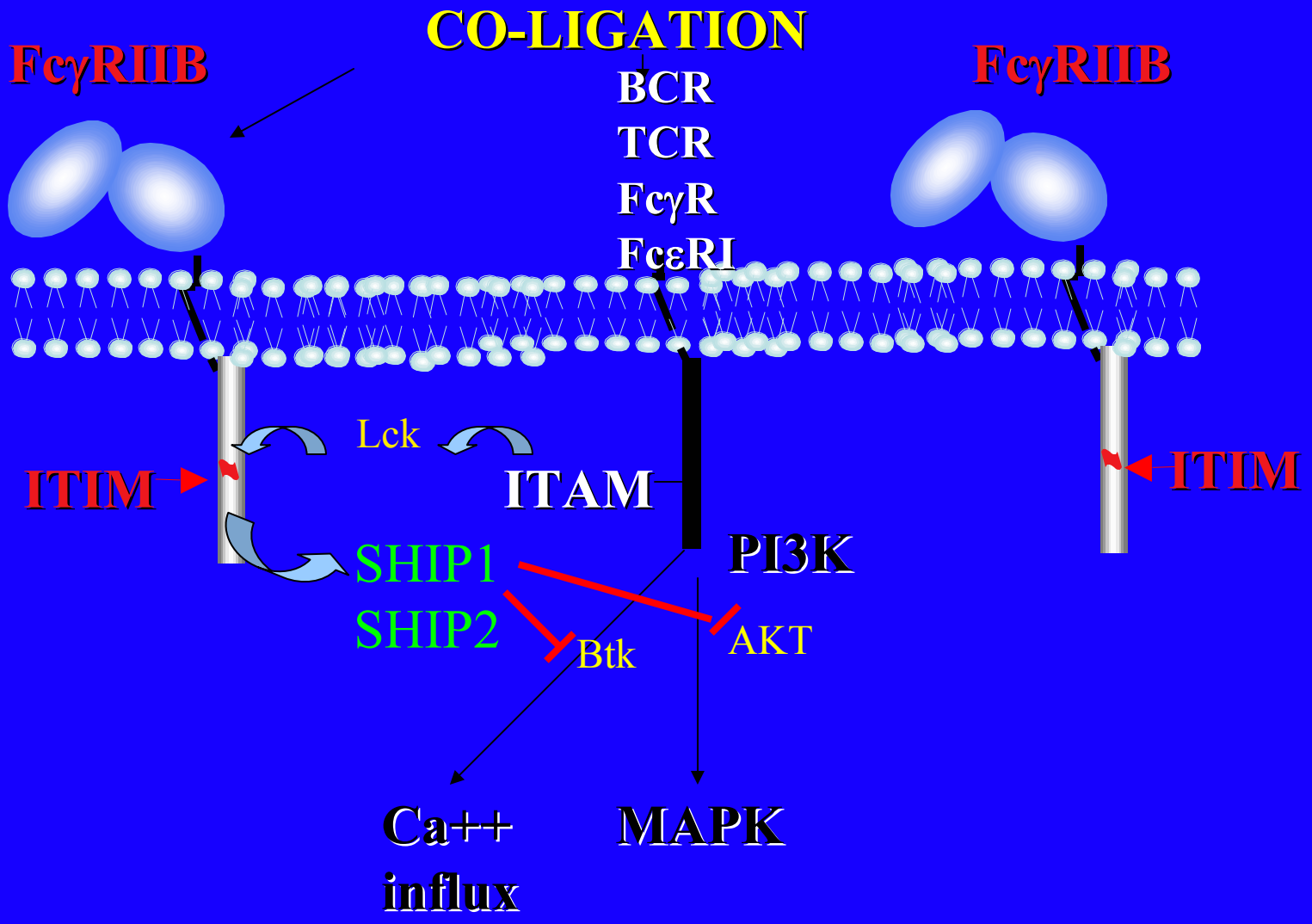
ITYSLL

ACTIVATING RECEPTORS

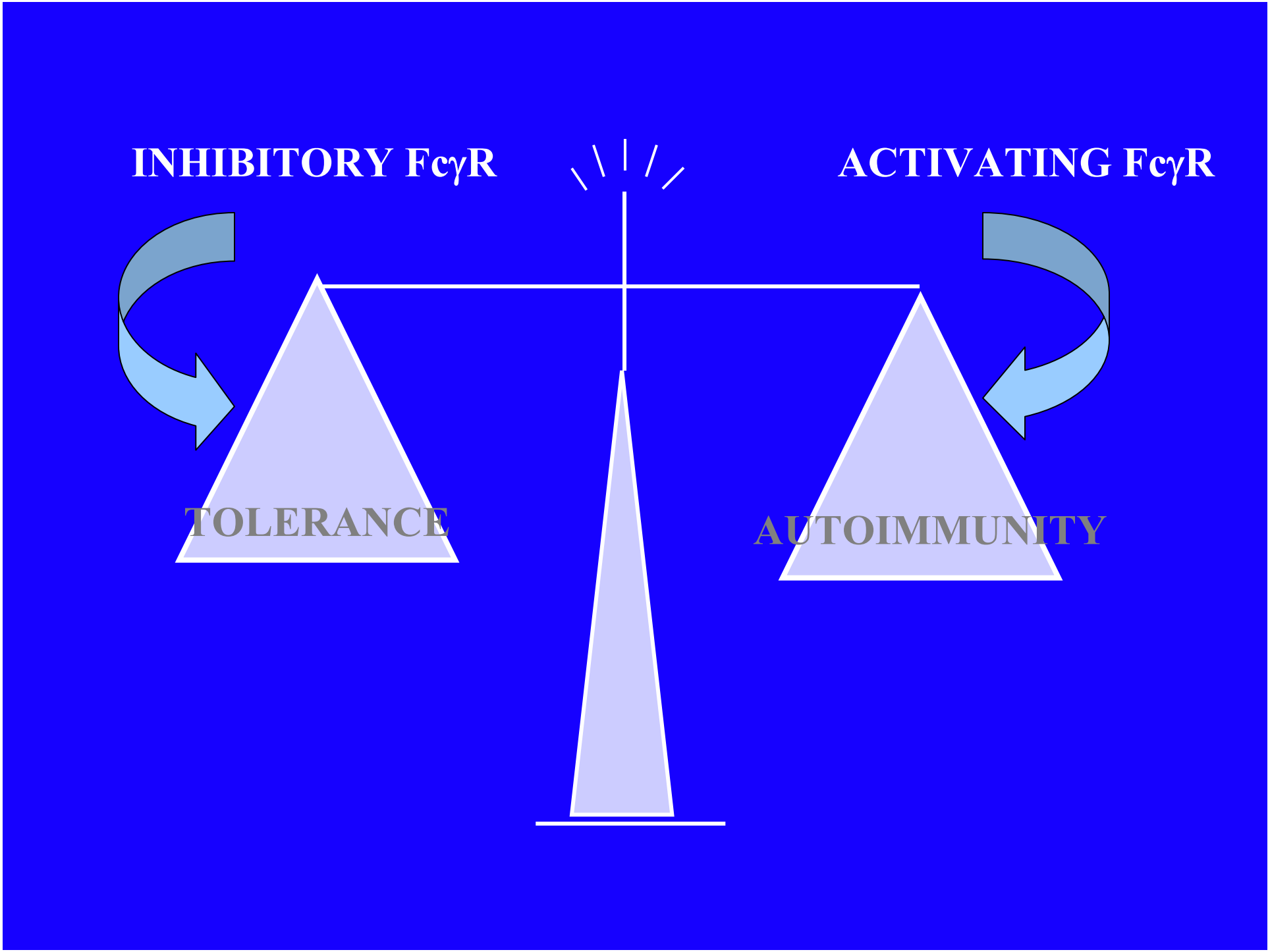


T. Takaï, Nature Rev 2002

INHIBITORY FcγRECEPTORS : DOWN REGULATE ITAM-DEPENDENT RESPONSES



MICE DEFICIENT IN	HYPERSENSITIVITY REACTIONS (II,III) ARTHUS REACTION	AUTOIMMUNE DISEASES (IgG DEPENDENT)
ACTIVATING FcγR	IMPAIRED	RESISTANT
INHIBITORY FcγR	ENHANCED	INCREASED SUSCEPTIBILITY


INHIBITORY FcγR
ACTIVATING FcγR
TOLERANCE
AUTOIMMUNITY

FcγR POLYMORPHISMS IN HUMAN AUTOIMMUNE DISEASES

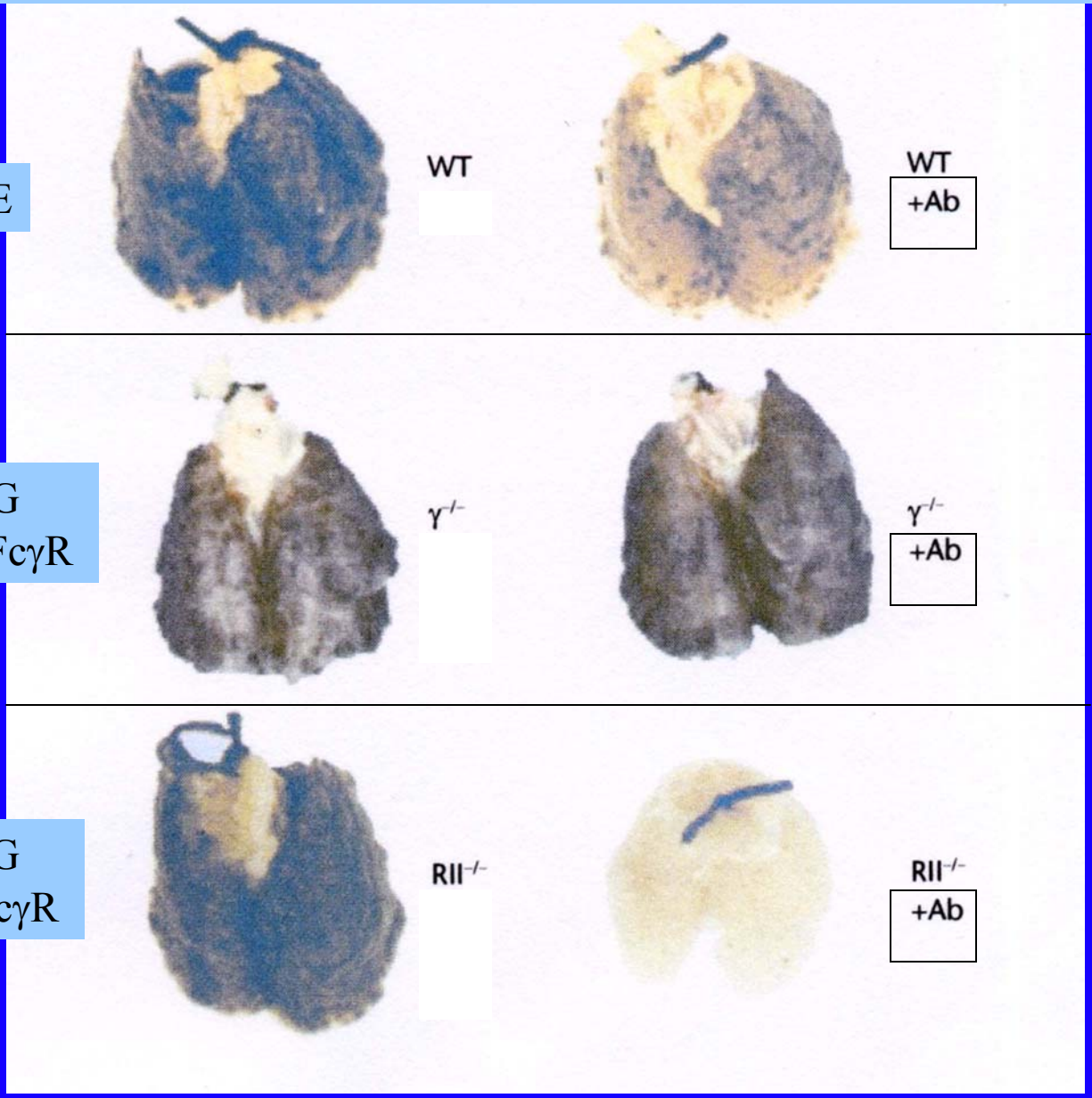
INCREASED SUSCEPTIBILITY TO	FcγRIIa	FcγRIIB	FcγRIIIA	FcγRIIIB
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	131 Arg	232 Thr* and promoter	158 Phe NA2	
RHEUMATOID ARTHRITIS (RA)			158 Phe	
WEGENER GRANULOMATOSIS				NA1
GUILLAIN BARRE SYNDROME	131Arg			NA2
MULTIPLE SCLEROSIS	131 Arg			NA2

Fcγ RECEPTORS CONTROL ANTIBODY THERAPY TO METASTATIC MELANOMA

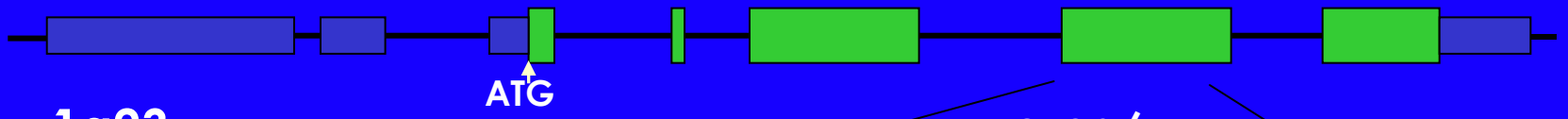
NORMAL MICE

MICE LACKING ACTIVATING FcγR

MICE LACKING INHIBITORY FcγR



FCGR3A Gene

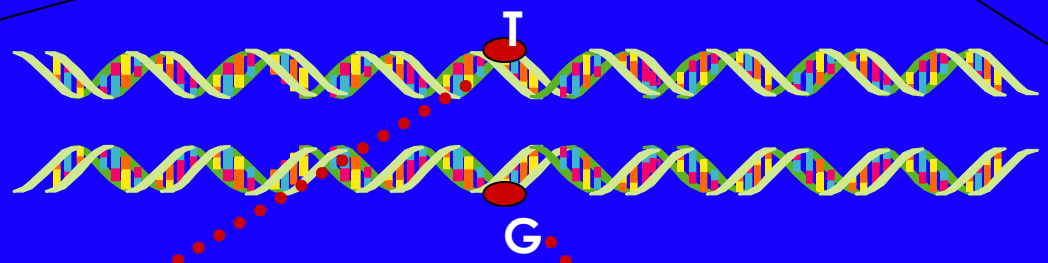


1q23

exon 6

allele +4985T: 0,6

allele +4985G: 0,4

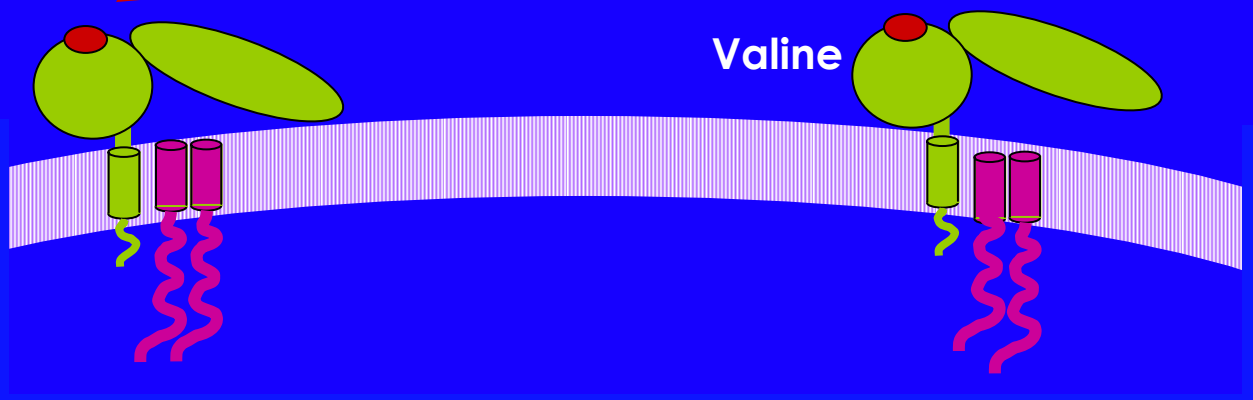


FcγRIIIa-158F

FcγRIIIa-158V

Phenylalanine

Valine

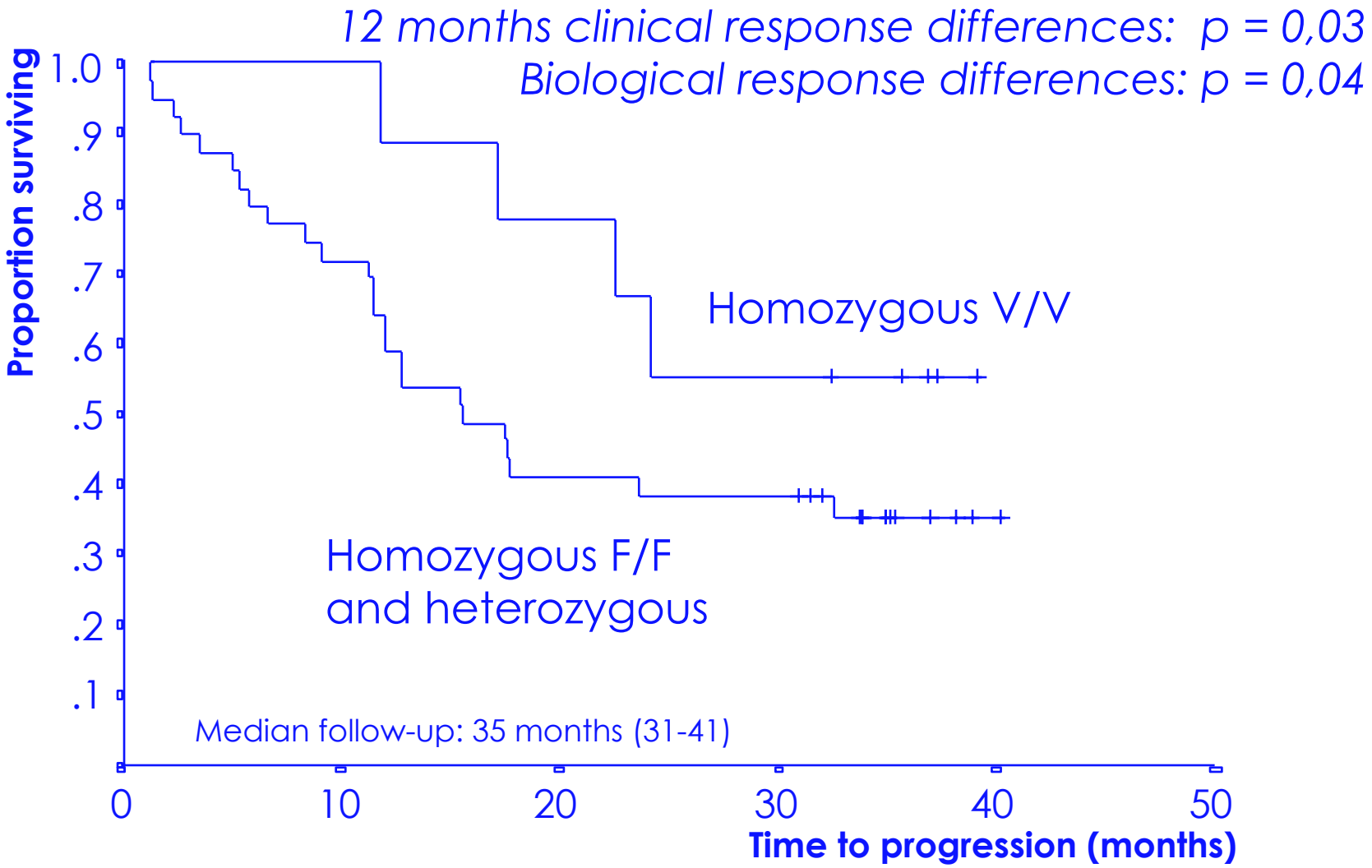


Homozygous 158F/F: ~ 35 %

Heterozygous: ~ 50 %

Homozygous 158V/V: ~ 15 %

Cartron et al., Blood 2002



EFFECTOR FUNCTIONS OF IgE

FcεRI: High-affinity IgE receptor

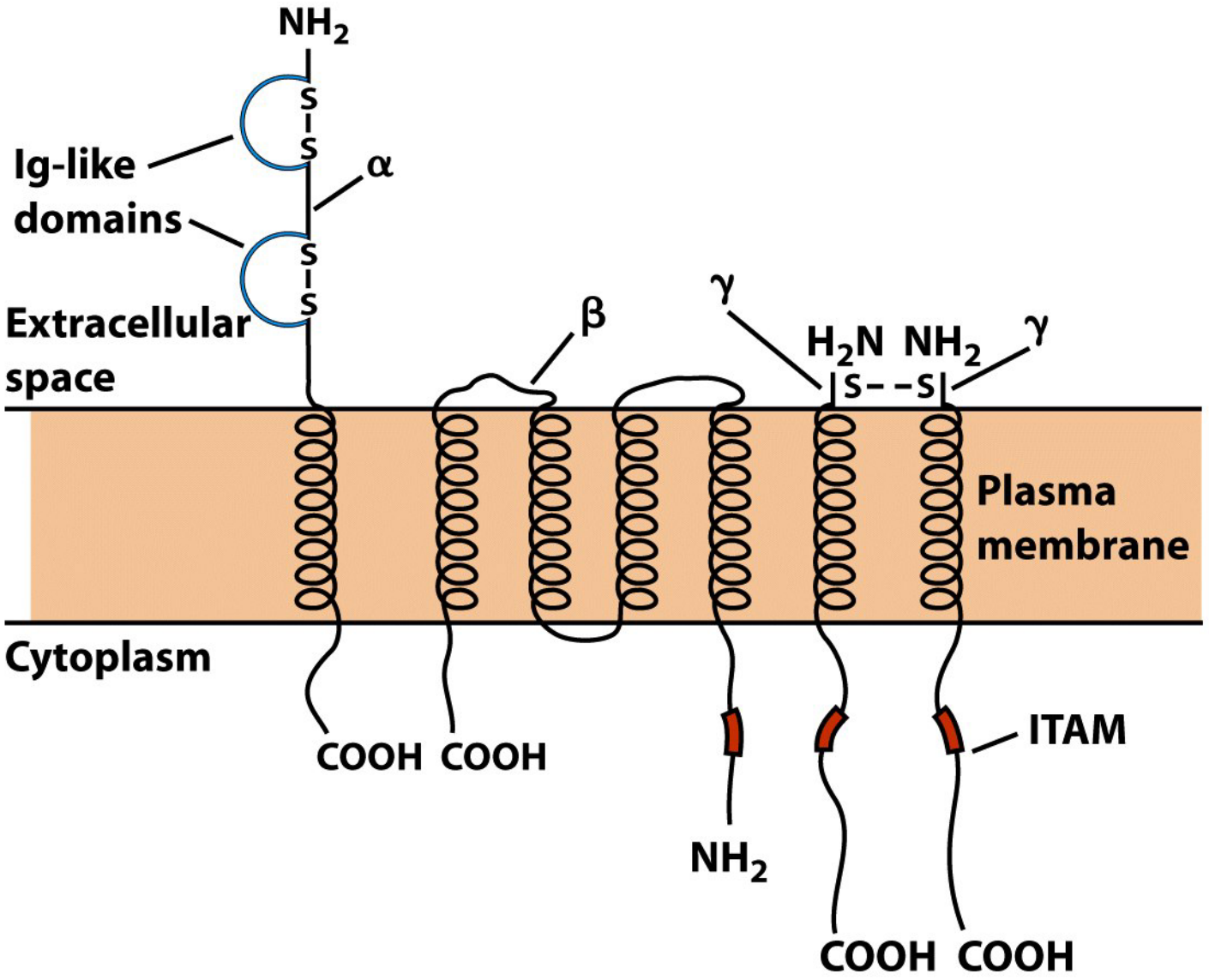


Figure 15-4a
Kuby IMMUNOLOGY, Sixth Edition

Allergen cross-linkage of cell-bound IgE

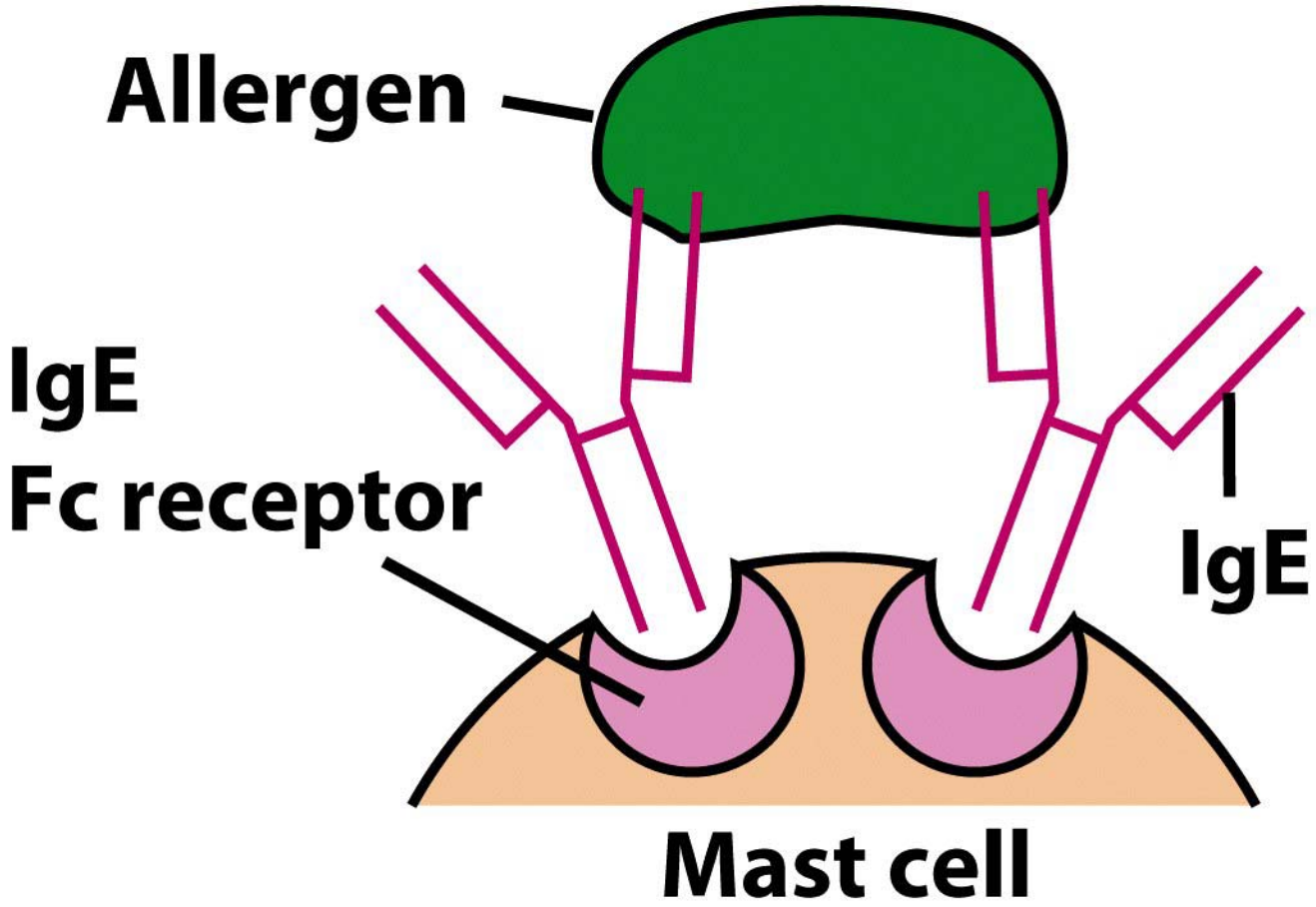


Figure 15-5a
Kuby IMMUNOLOGY, Sixth Edition

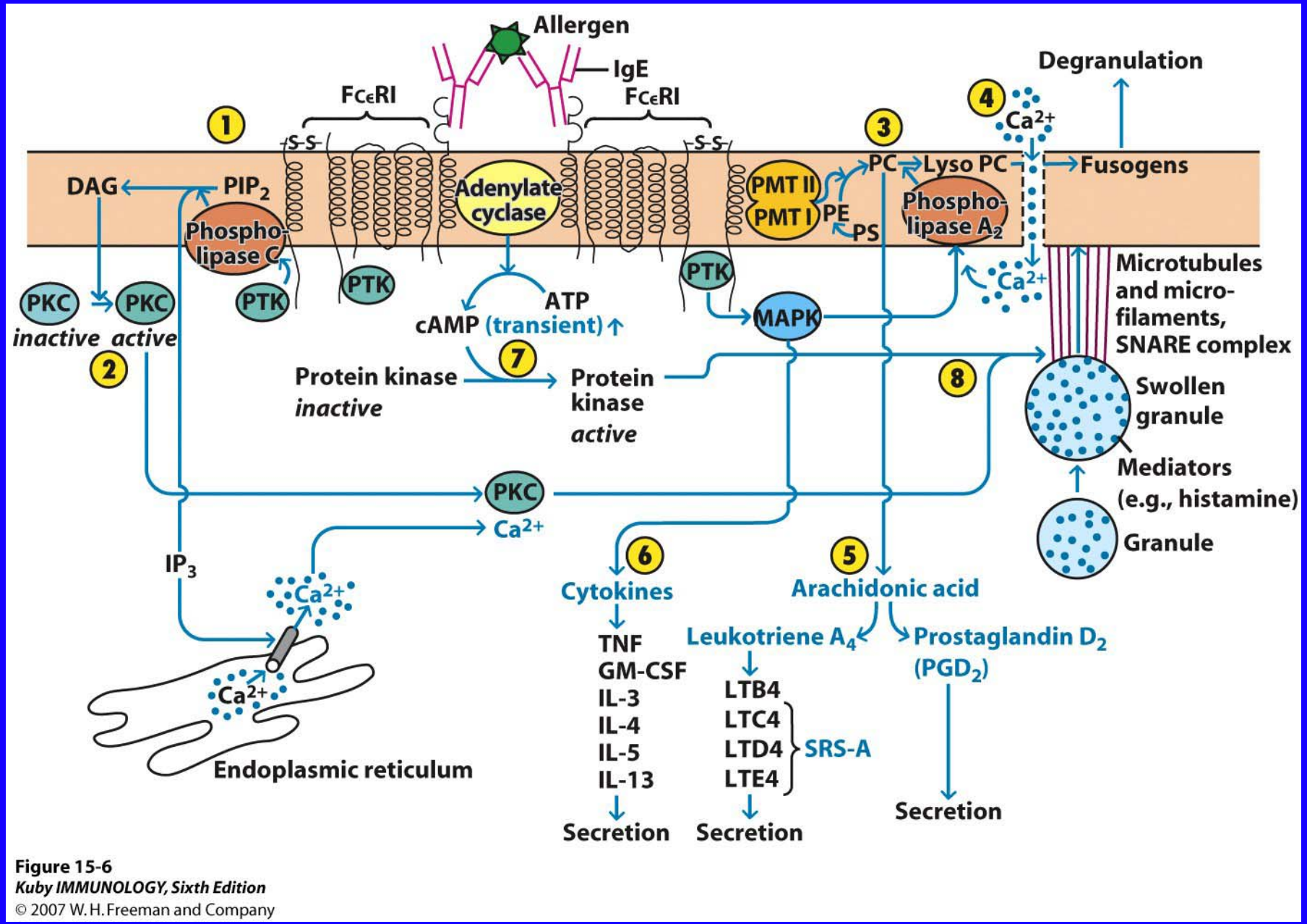


Figure 15-6
Kuby IMMUNOLOGY, Sixth Edition

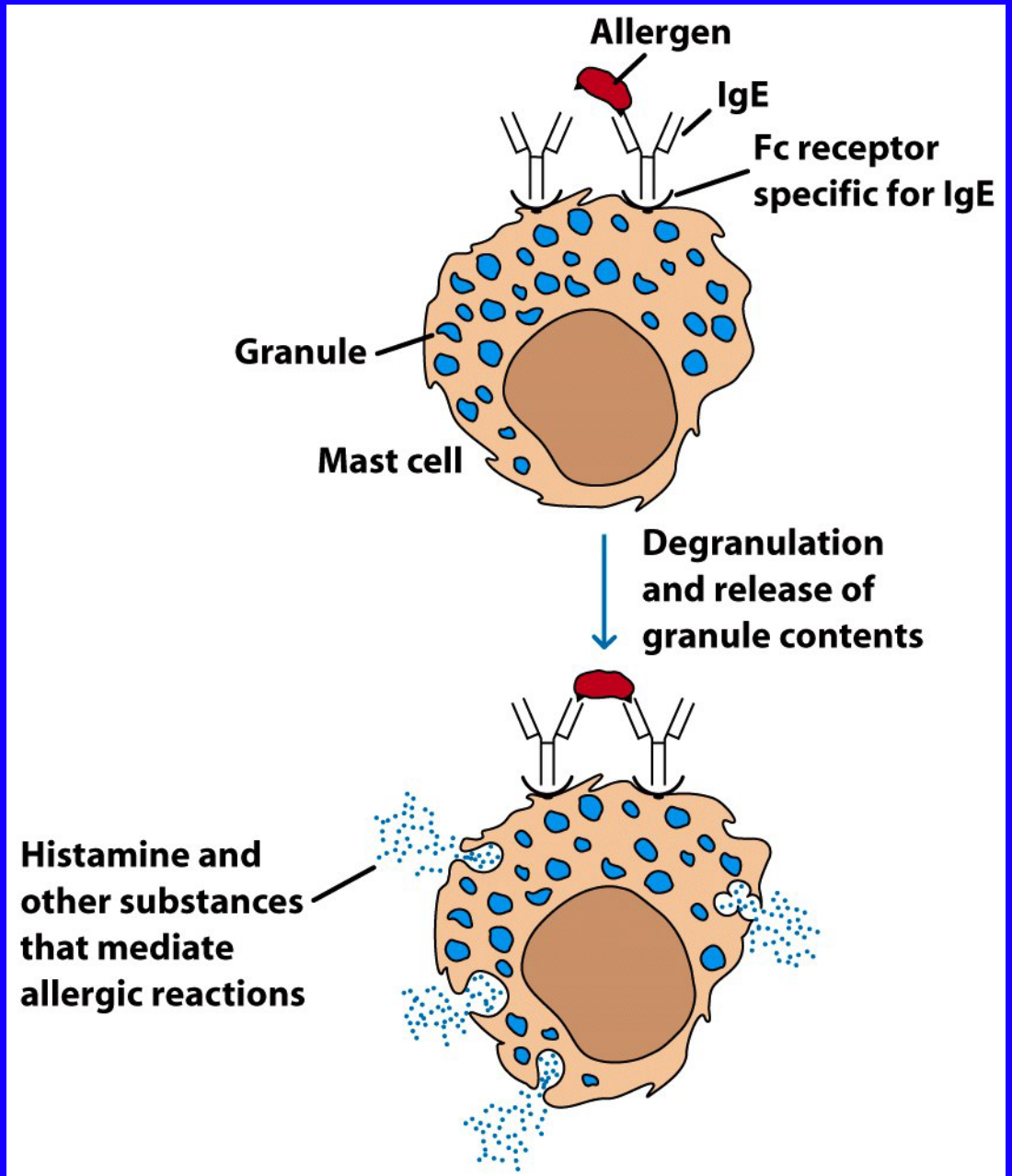


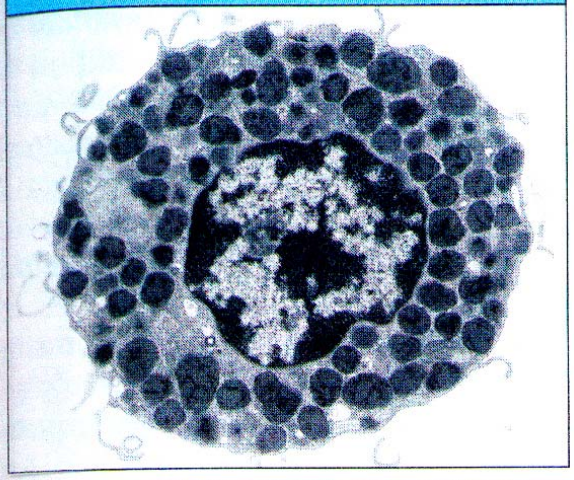
Figure 4-20
Kuby IMMUNOLOGY, Sixth Edition

TABLE 15-3 Principal mediators involved in type I hypersensitivity

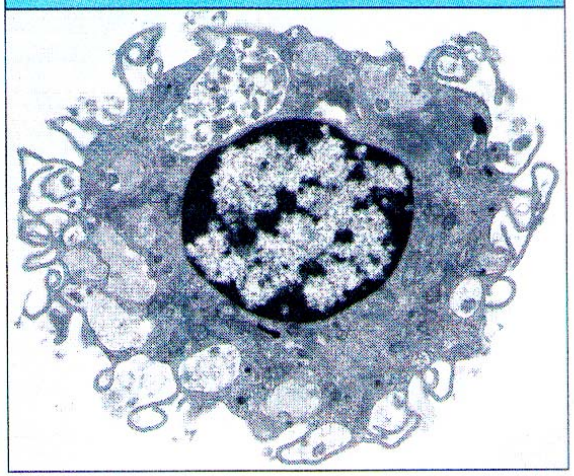
Mediator	Effects
	PRIMARY
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products
	SECONDARY
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Table 15-3
Kuby IMMUNOLOGY, Sixth Edition

Resting mast cell



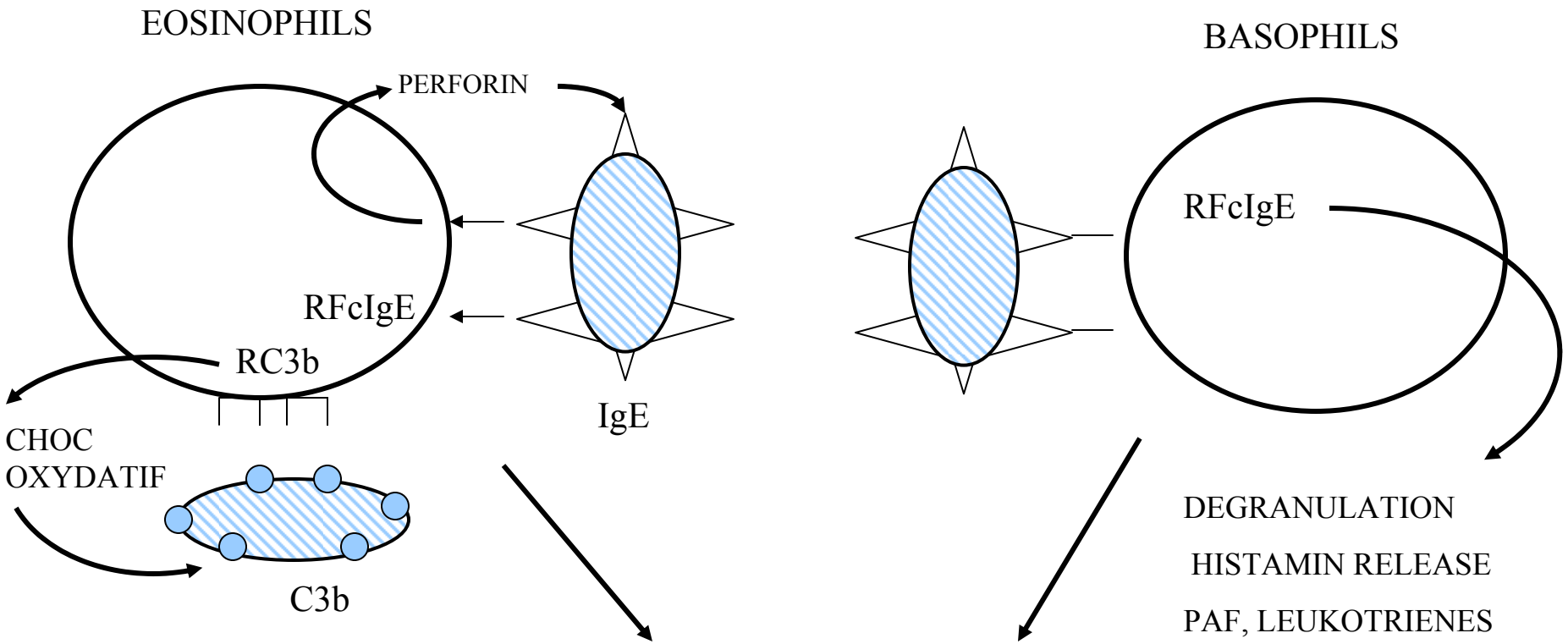
Activated mast cell



Resting mast cell contains granules containing histamine and other inflammatory mediators

Multivalent antigen cross-links bound IgE antibody, causing release of granule contents

ADCC AGAINST HELMINTHS



KILLS PARASITE
+ INFLAMMATORY REACTION

CF04

TRANSPORT FUNCTIONS OF ANTIBODIES

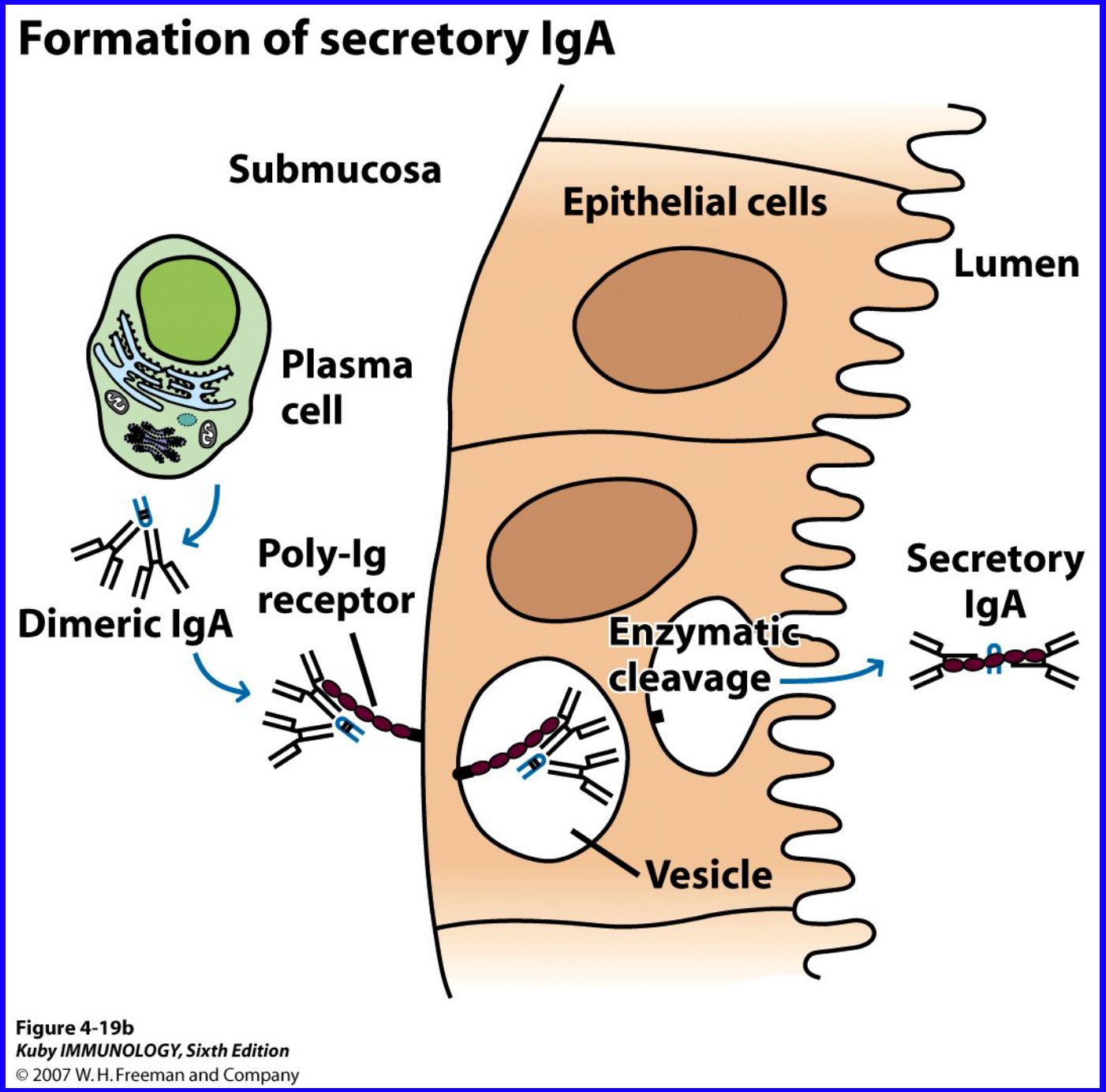
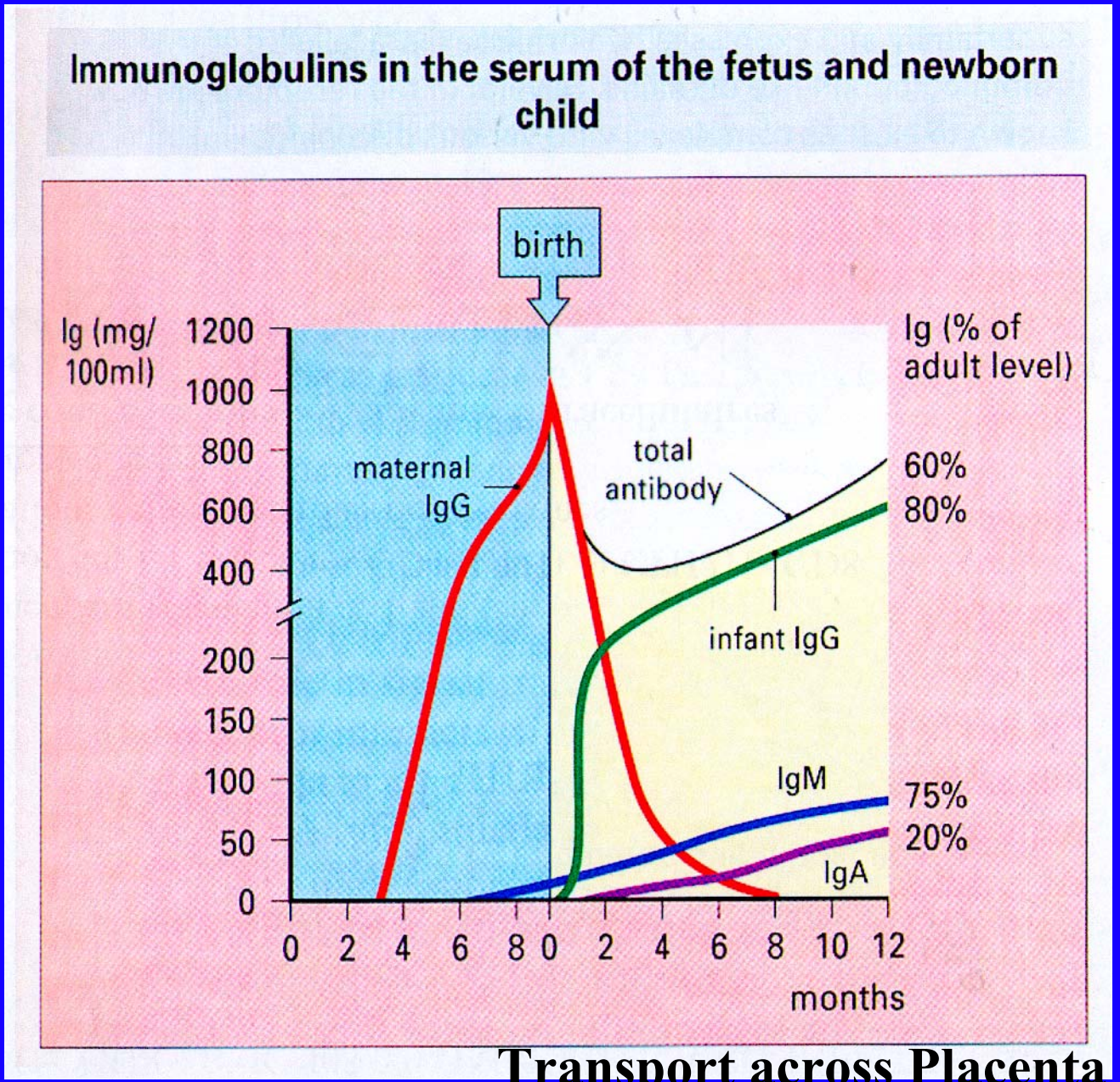


Figure 4-19b
Kuby IMMUNOLOGY, Sixth Edition



Transport across Placenta

Immunobiology, 6th edition,, C.Janeway et al., Churchill, Livingstone