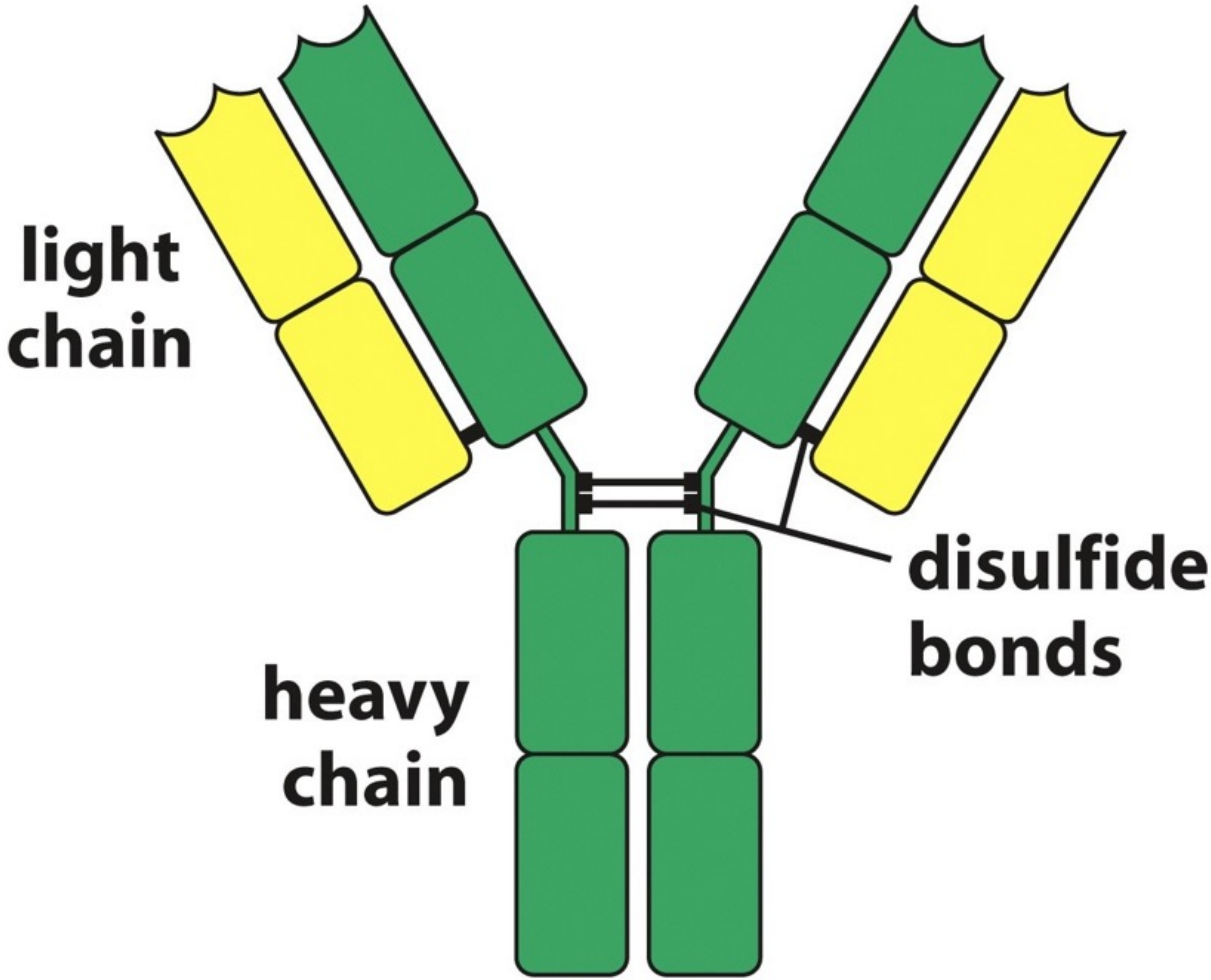


Figure 4.2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

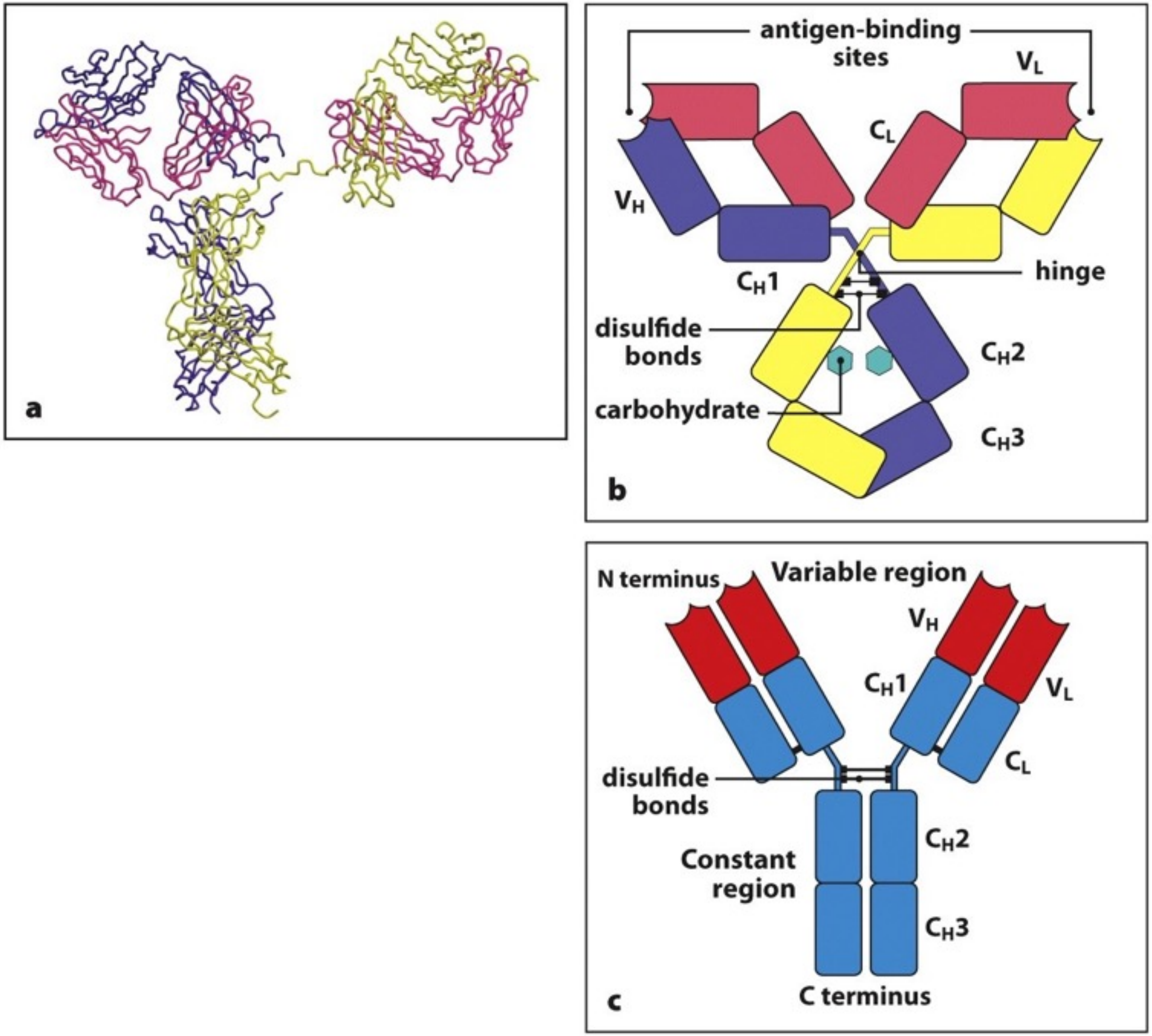


Figure 4.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

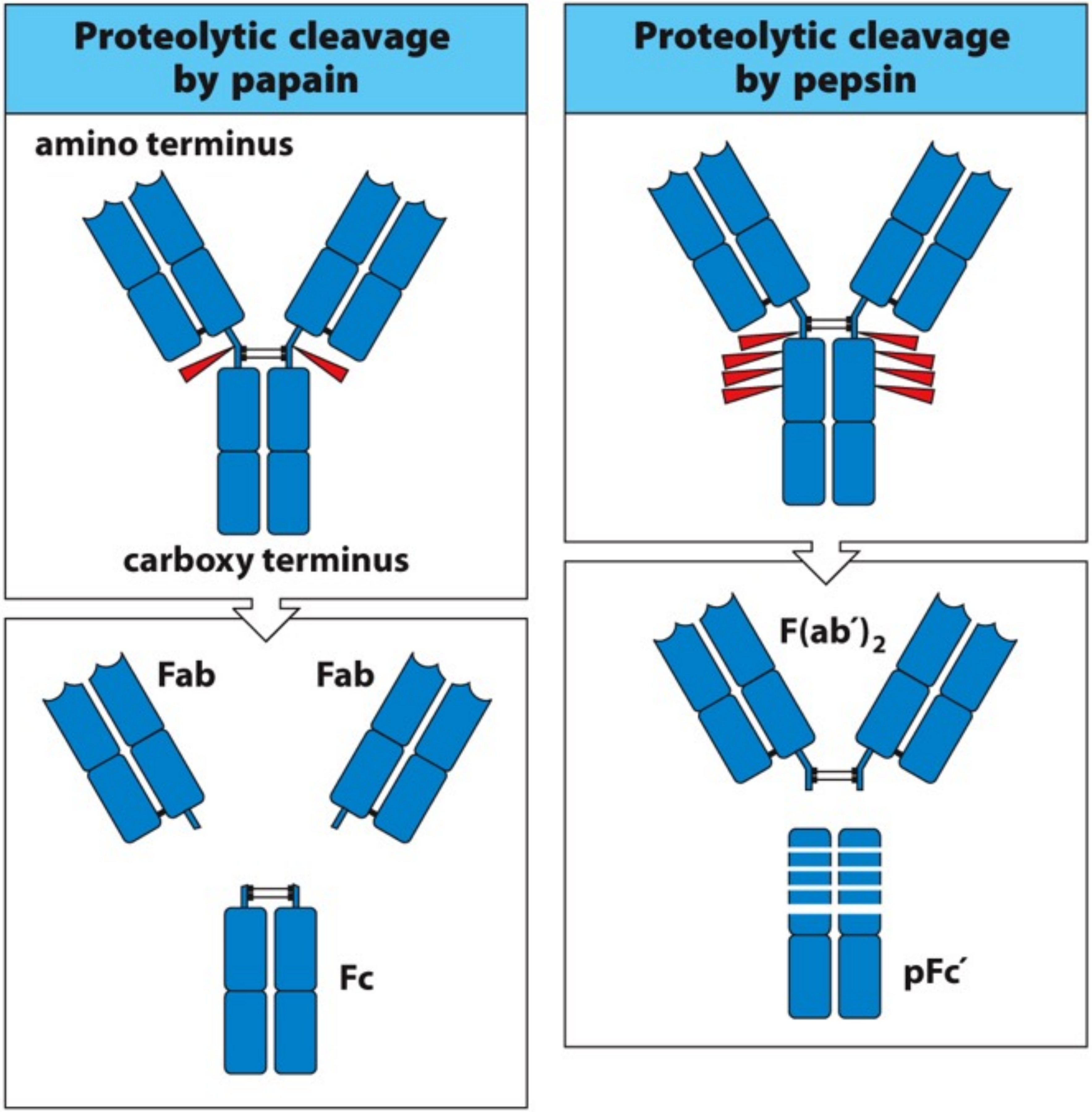


Figure 4.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

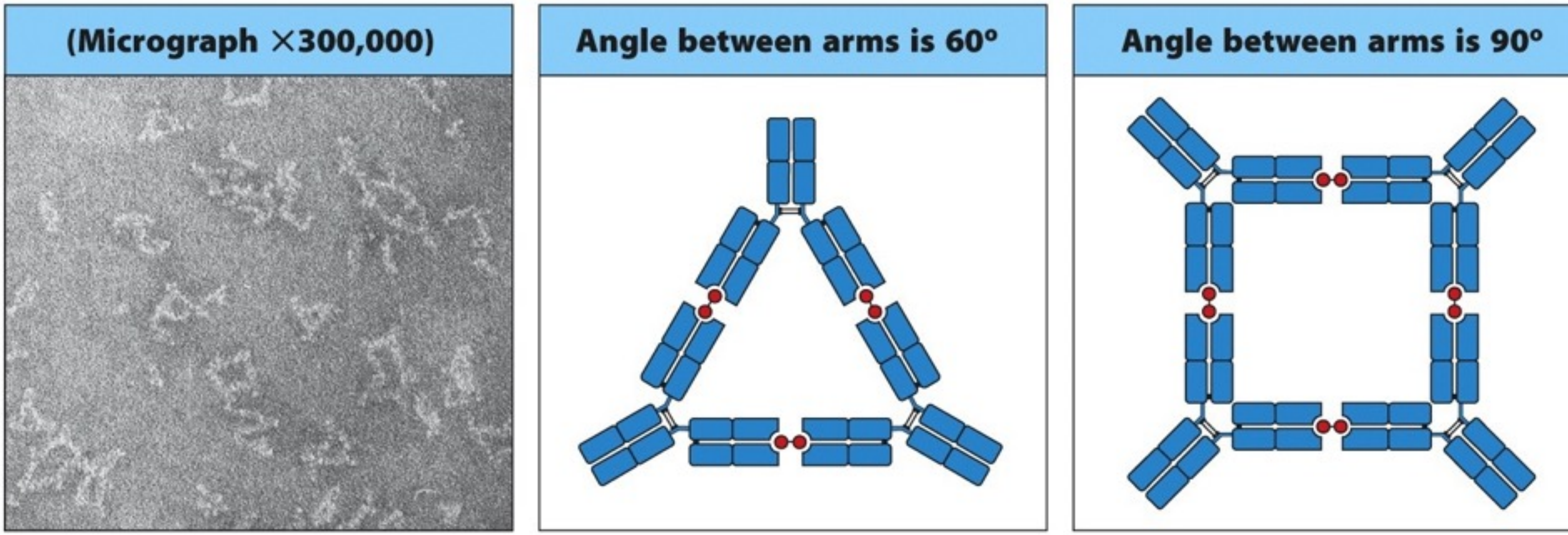


Figure 4.4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

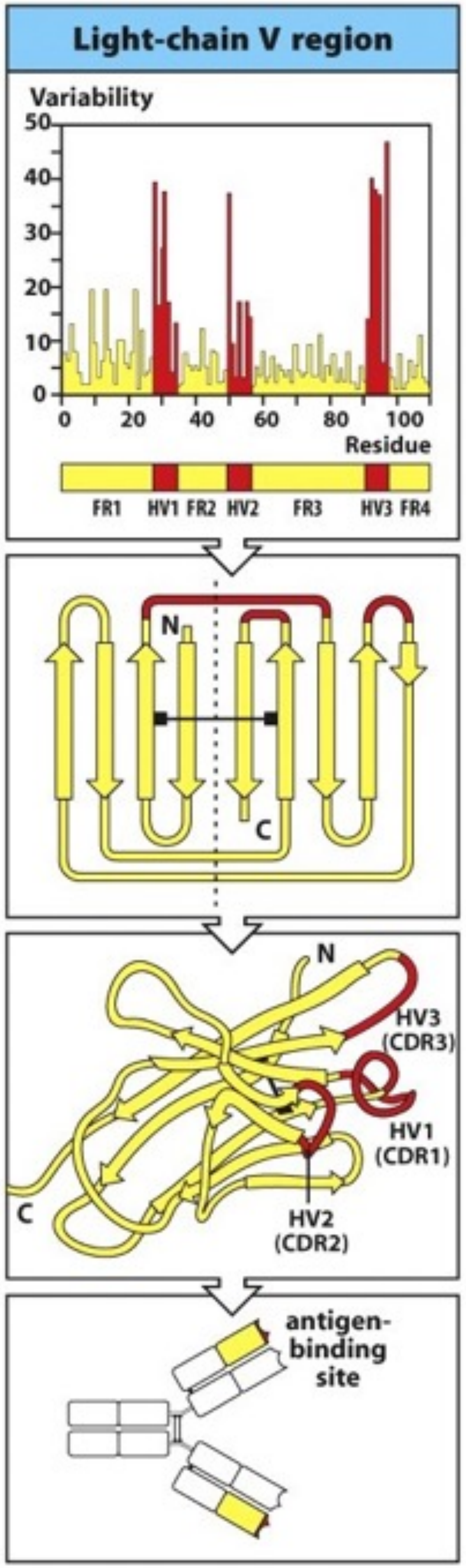


Figure 4.7 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

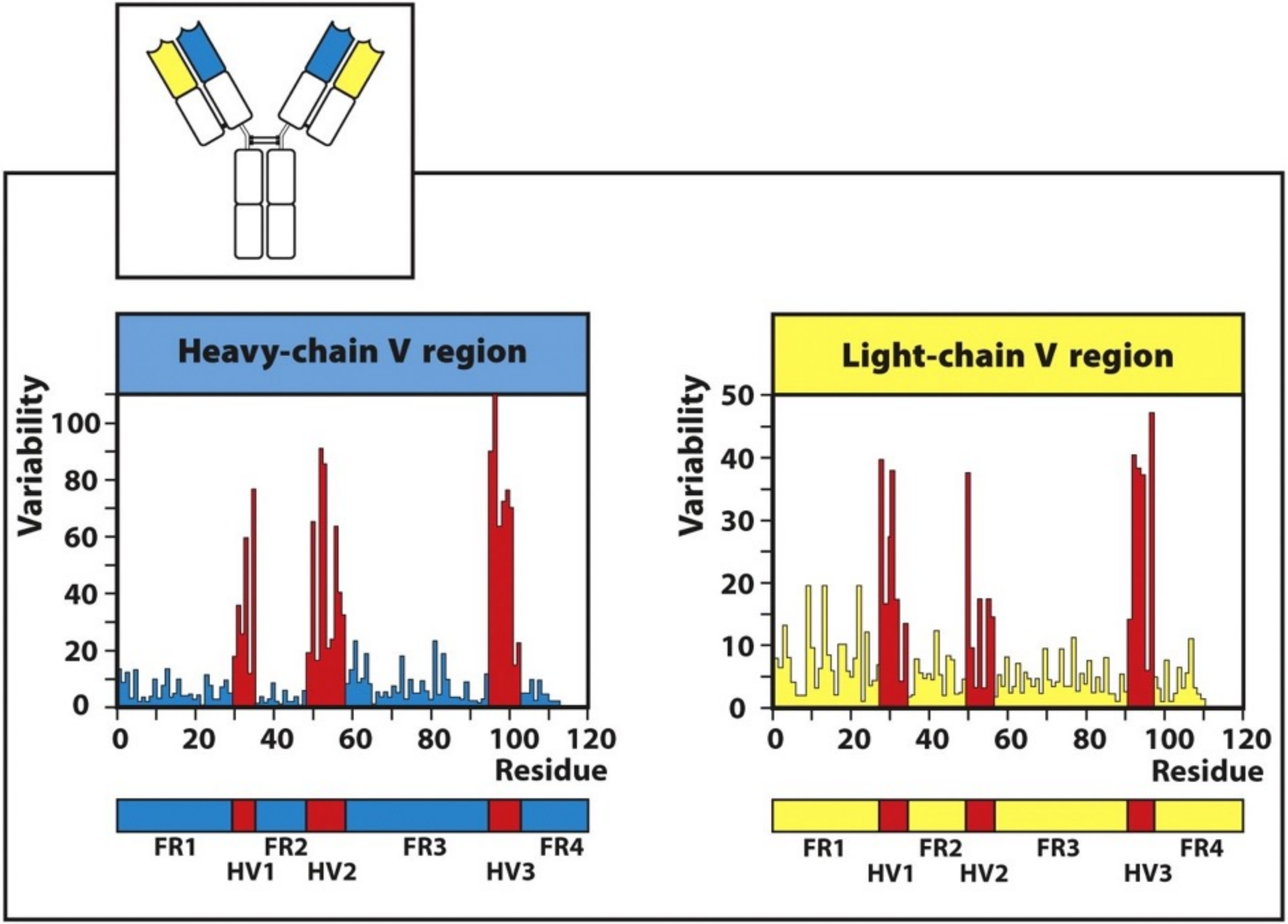


Figure 4.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

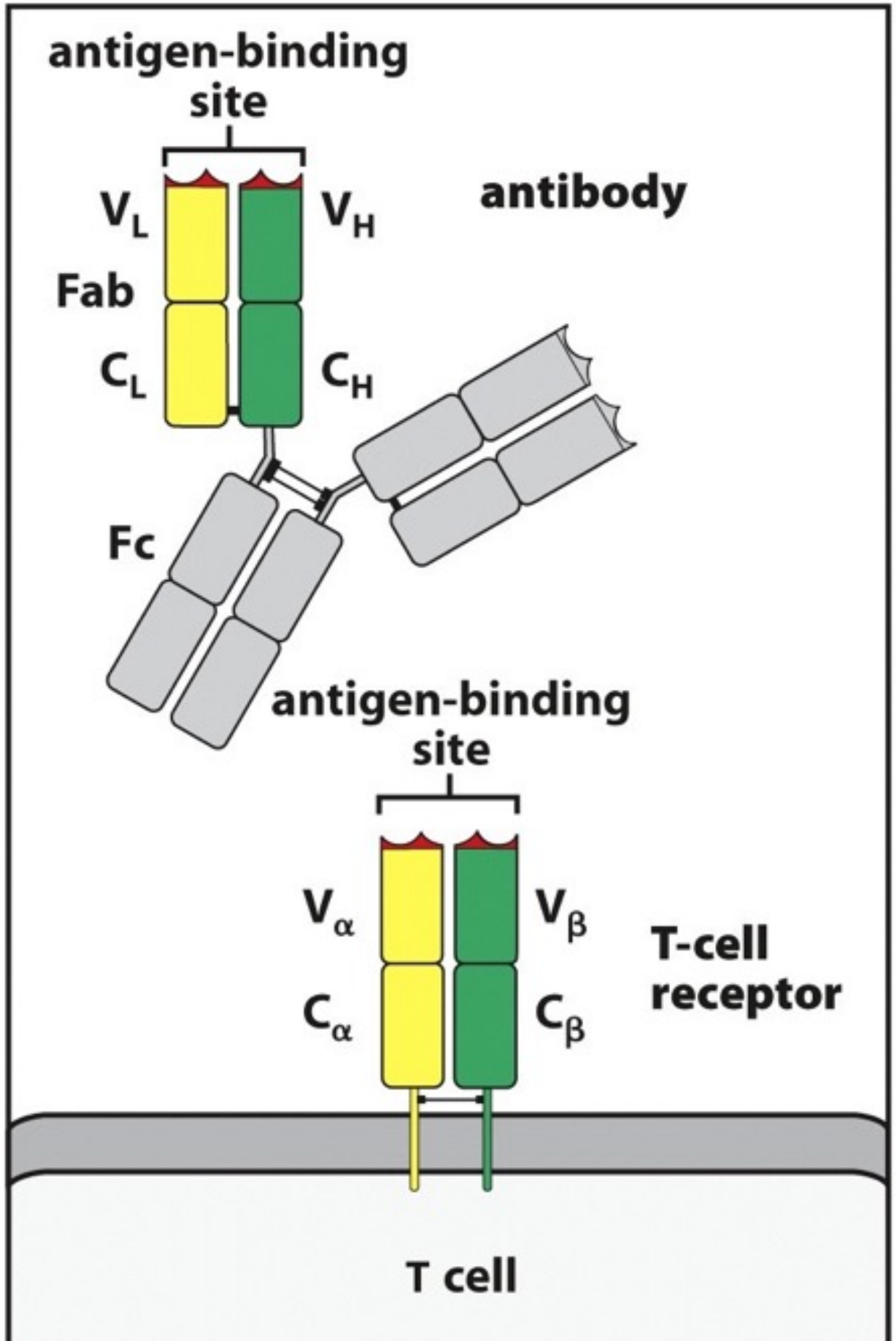


Figure 4.11 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

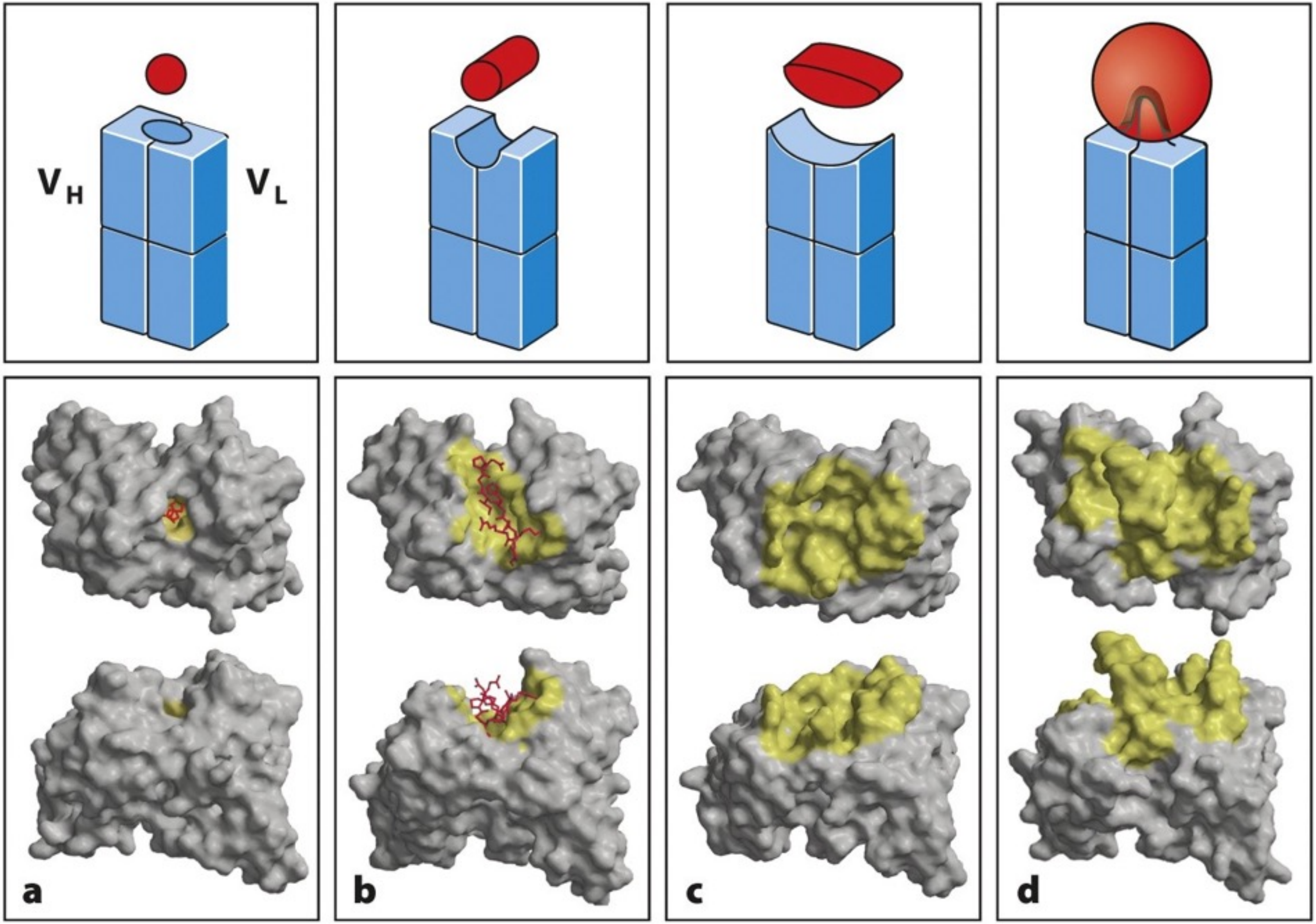


Figure 4.8 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

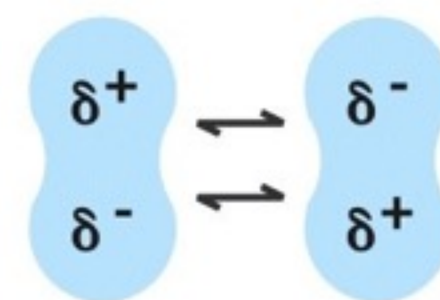
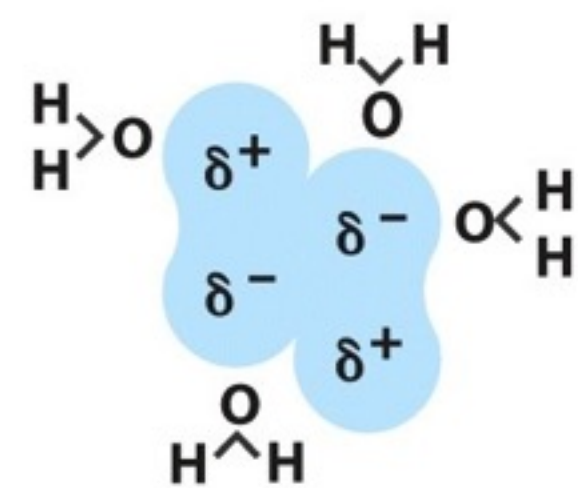
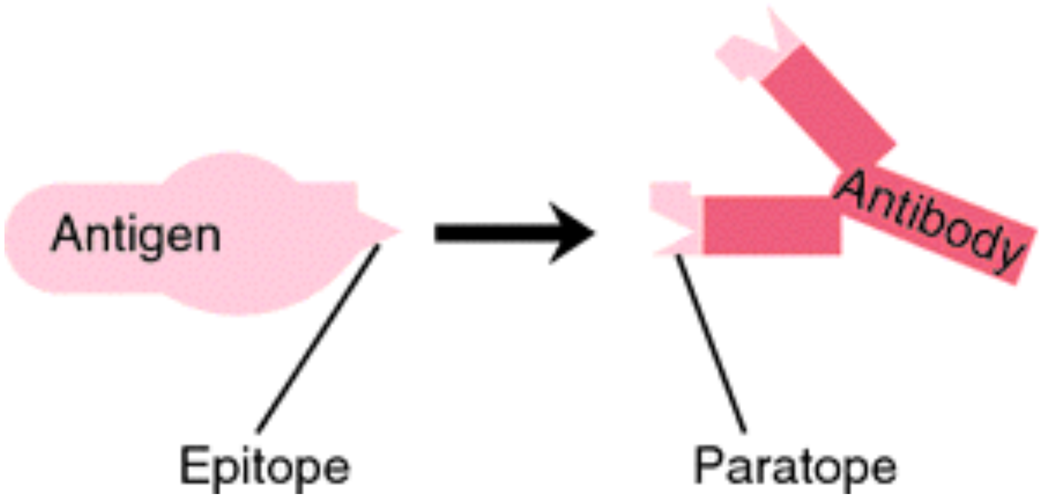
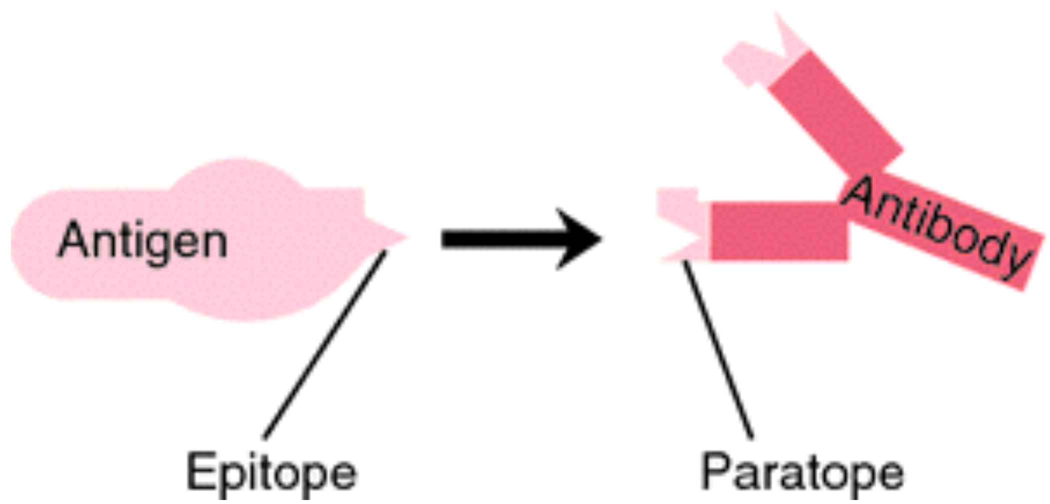
Noncovalent forces	Origin	
Electrostatic forces	Attraction between opposite charges	$-NH_3^{\oplus}$ $\;{}^{\ominus}OOC-$
Hydrogen bonds	Hydrogen shared between electronegative atoms (N,O)	$>N^{\delta-} - H^{\delta+} - - O^{\delta-} = C<$
Van der Waals forces	Fluctuations in electron clouds around molecules polarize neighboring atoms oppositely	
Hydrophobic forces	Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces	

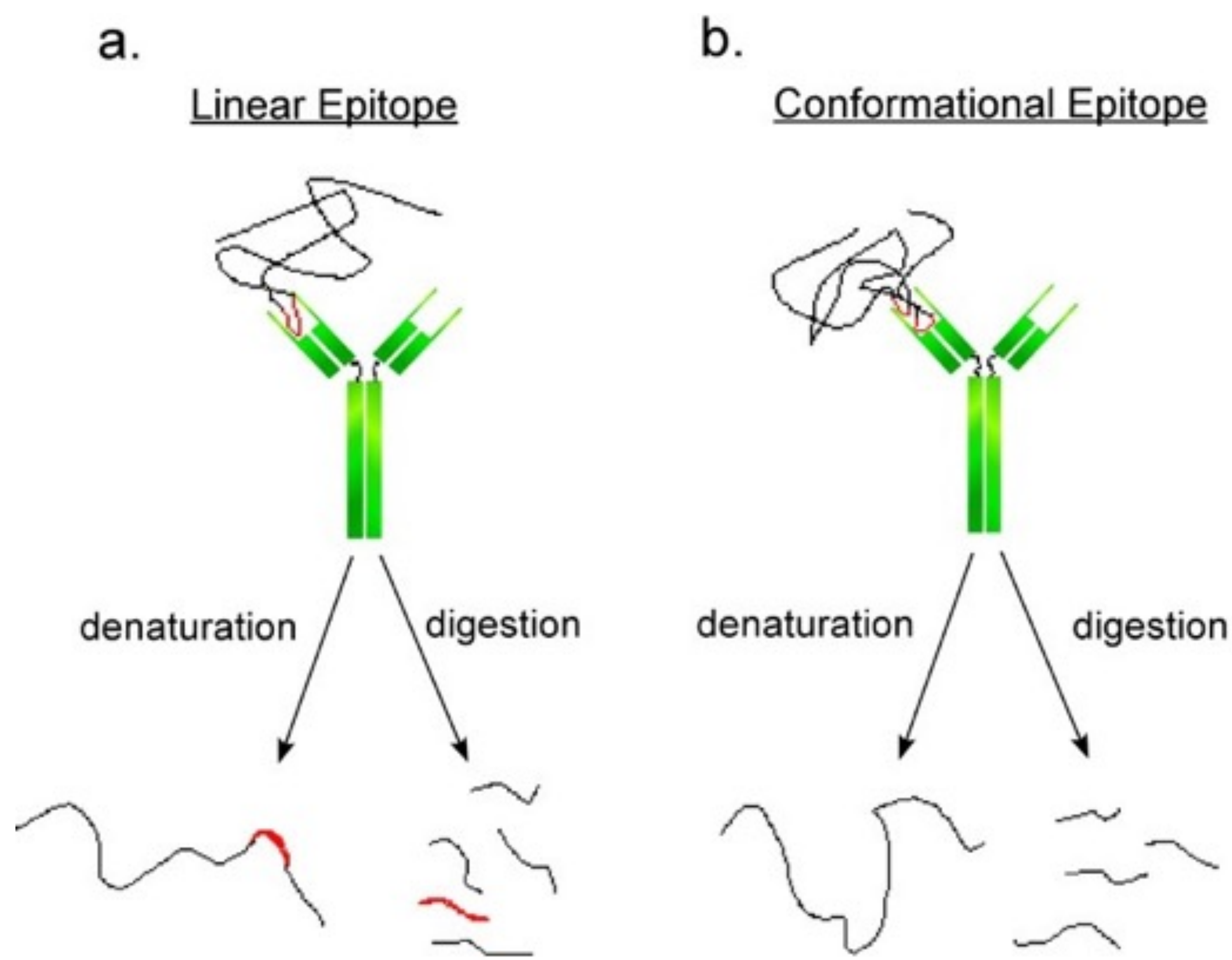
Figure 4.9 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

EPÍTOPO



EPÍTOPO
linear x conformacional





ISOTIPOS

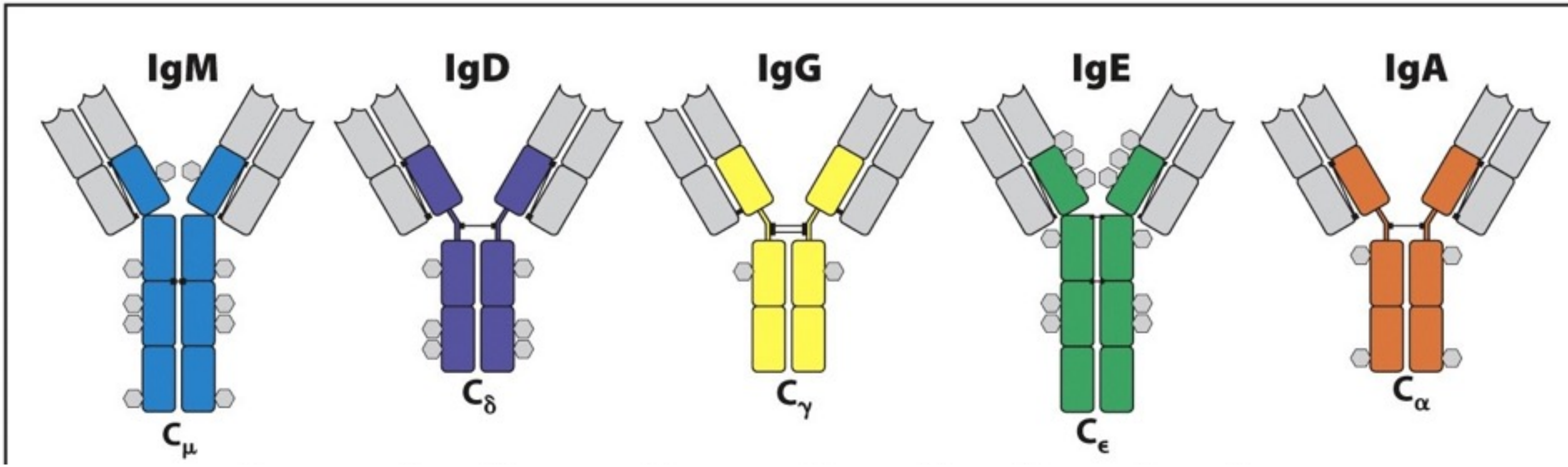


Figure 5.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

	Immunoglobulin								
	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Heavy chain	γ_1	γ_2	γ_3	γ_4	μ	α_1	α_2	δ	ϵ
Molecular weight (kDa)	146	146	165	146	970	160	160	184	188
Serum level (mean adult mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.03	5×10^{-5}
Half-life in serum (days)	21	20	7	21	10	6	6	3	2
Classical pathway of complement activation	++	+	+++	−	++++	−	−	−	−
Alternative pathway of complement activation	−	−	−	−	−	+	−	−	−
Placental transfer	+++	+	++	−/+	−	−	−	−	−
Binding to macrophage and phagocyte Fc receptors	+	−	+	−/+	−	+	+	−	+
High-affinity binding to mast cells and basophils	−	−	−	−	−	−	−	−	+++
Reactivity with staphylococcal Protein A	+	+	−/+	+	−	−	−	−	−

Figure 5.15 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

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}

Figure 10.21 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Neutralização

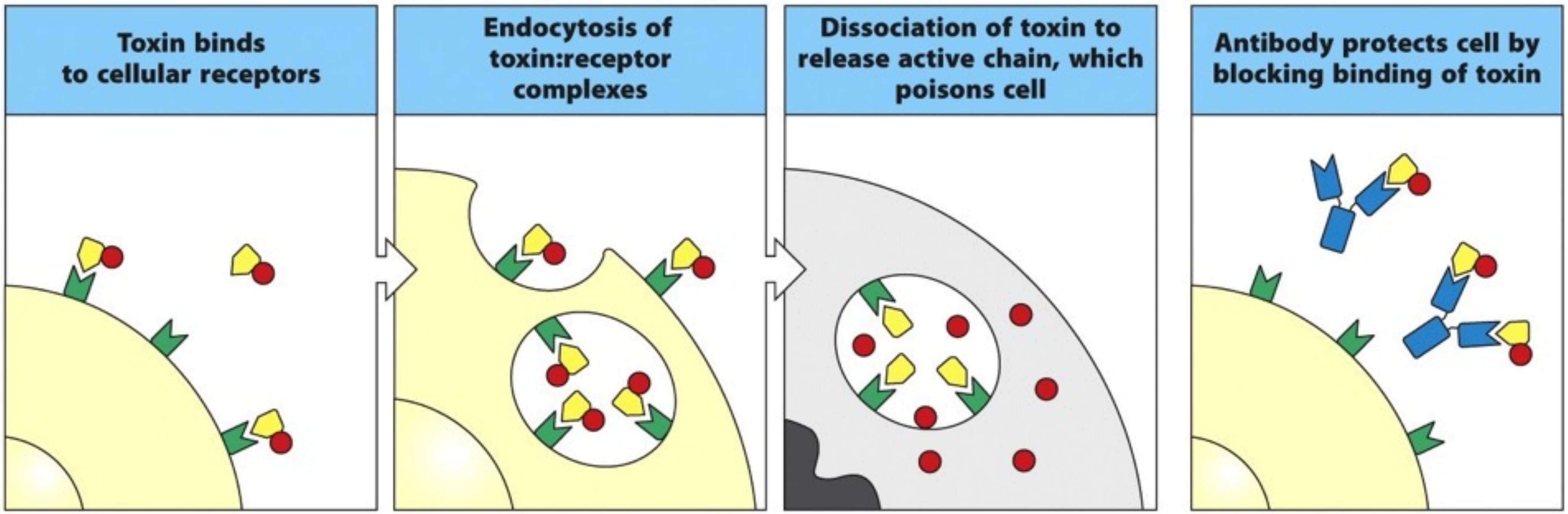


Figure 10.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Disease	Organism	Toxin	Effects *in vivo*
Tetanus	*Clostridium tetani*	Tetanus toxin	Blocks inhibitory neuron action, leading to chronic muscle contraction
Diphtheria	*Corynebacterium diphtheriae*	Diphtheria toxin	Inhibits protein synthesis, leading to epithelial cell damage and myocarditis
Gas gangrene	*Clostridium perfringens*	Clostridial toxin	Phospholipase activation, leading to cell death
Cholera	*Vibrio cholerae*	Cholera toxin	Activates adenylate cyclase, elevates cAMP in cells, leading to changes in intestinal epithelial cells that cause loss of water and electrolytes
Anthrax	*Bacillus anthracis*	Anthrax toxic complex	Increases vascular permeability, leading to edema, hemorrhage, and circulatory collapse
Botulism	*Clostridium botulinum*	Botulinum toxin	Blocks release of acetylcholine, leading to paralysis
Whooping cough	*Bordetella pertussis*	Pertussis toxin	ADP-ribosylation of G proteins, leading to lymphoproliferation
		Tracheal cytotoxin	Inhibits cilia and causes epithelial cell loss
Scarlet fever	*Streptococcus pyogenes*	Erythrogenic toxin	Vasodilation, leading to scarlet fever rash
		Leukocidin Streptolysins	Kill phagocytes, allowing bacterial survival
Food poisoning	*Staphylococcus aureus*	Staphylococcal enterotoxin	Acts on intestinal neurons to induce vomiting. Also a potent T-cell mitogen (SE superantigen)
Toxic-shock syndrome	*Staphylococcus aureus*	Toxic-shock syndrome toxin	Causes hypotension and skin loss. Also a potent T-cell mitogen (TSST-1 superantigen)

Figure 10.25 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Neutralização

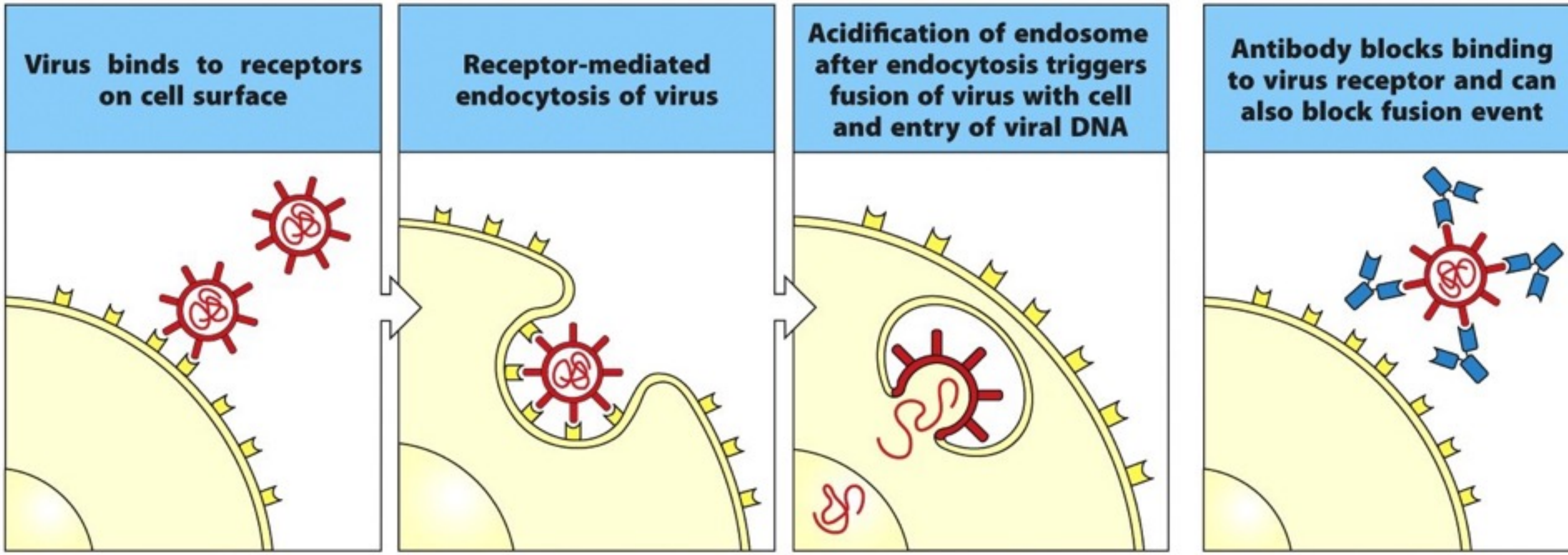


Figure 10.27 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Neutralização

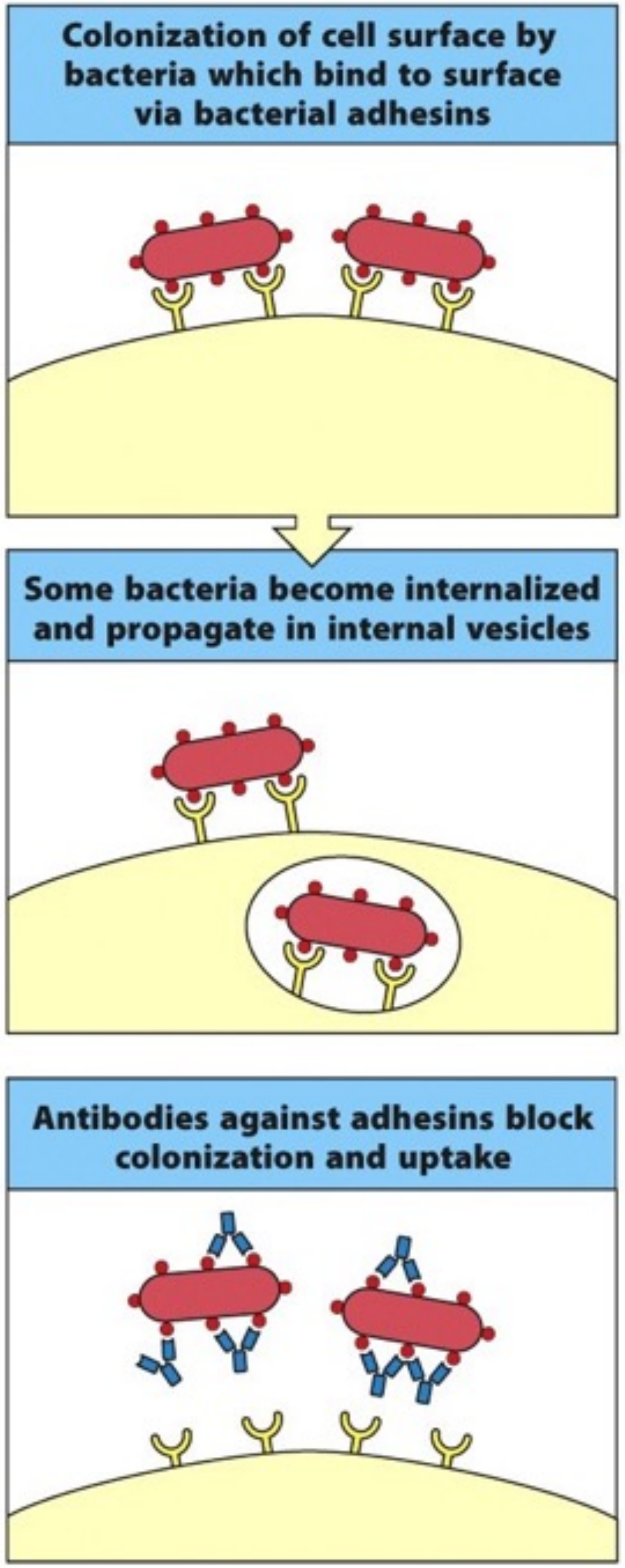


Figure 10.28 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Opsonização

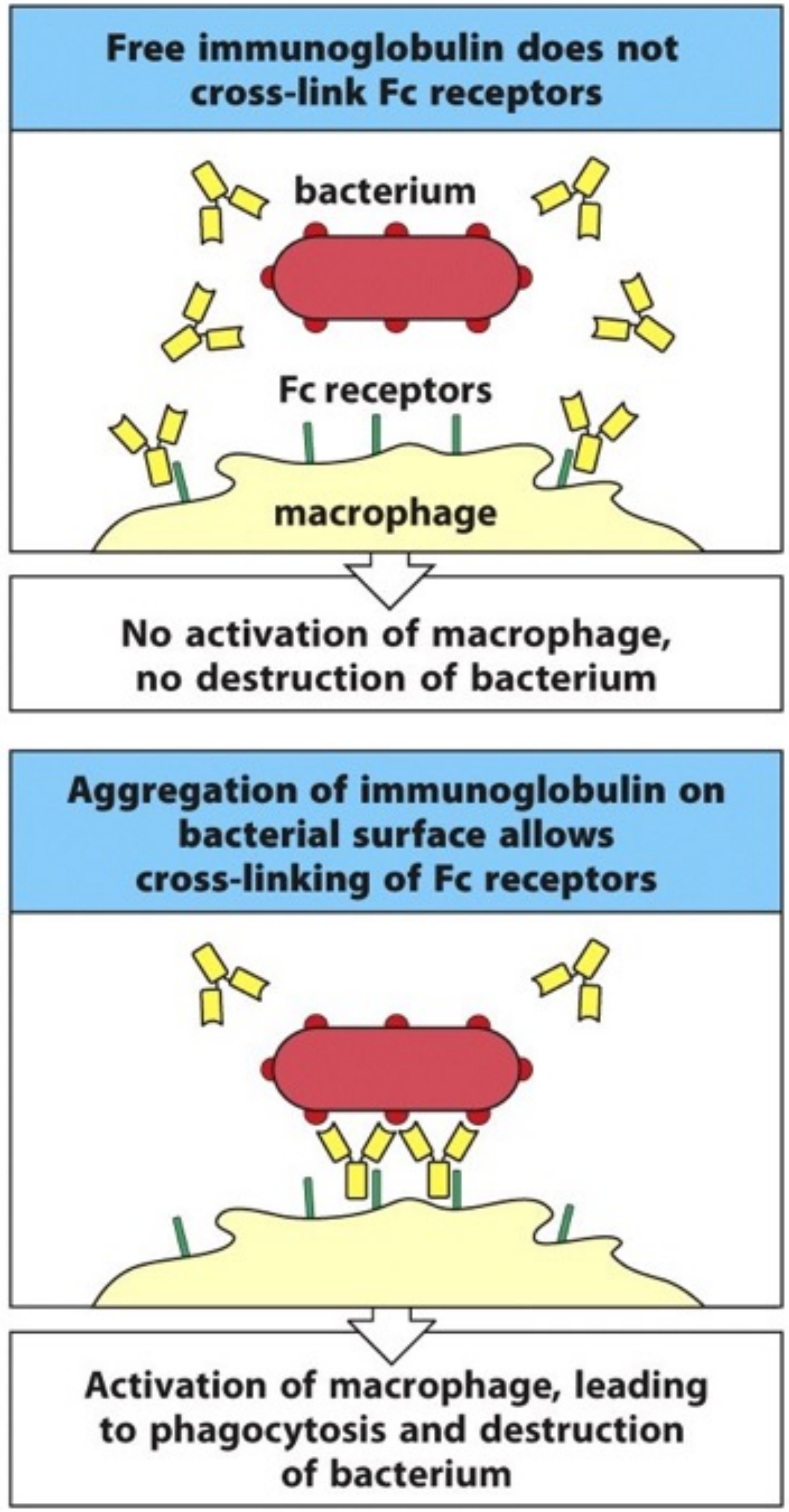


Figure 10.34 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

ADCC
Antibody-Dependent Cell Cytotoxicity

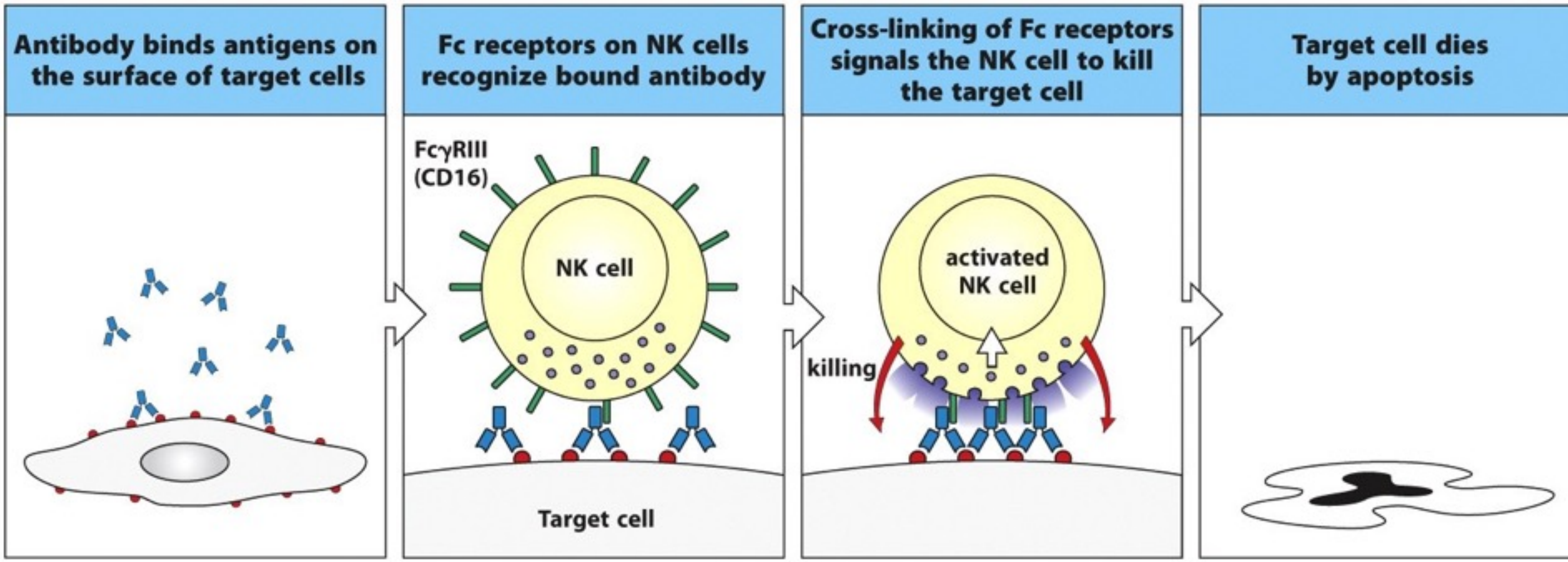


Figure 10.36 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

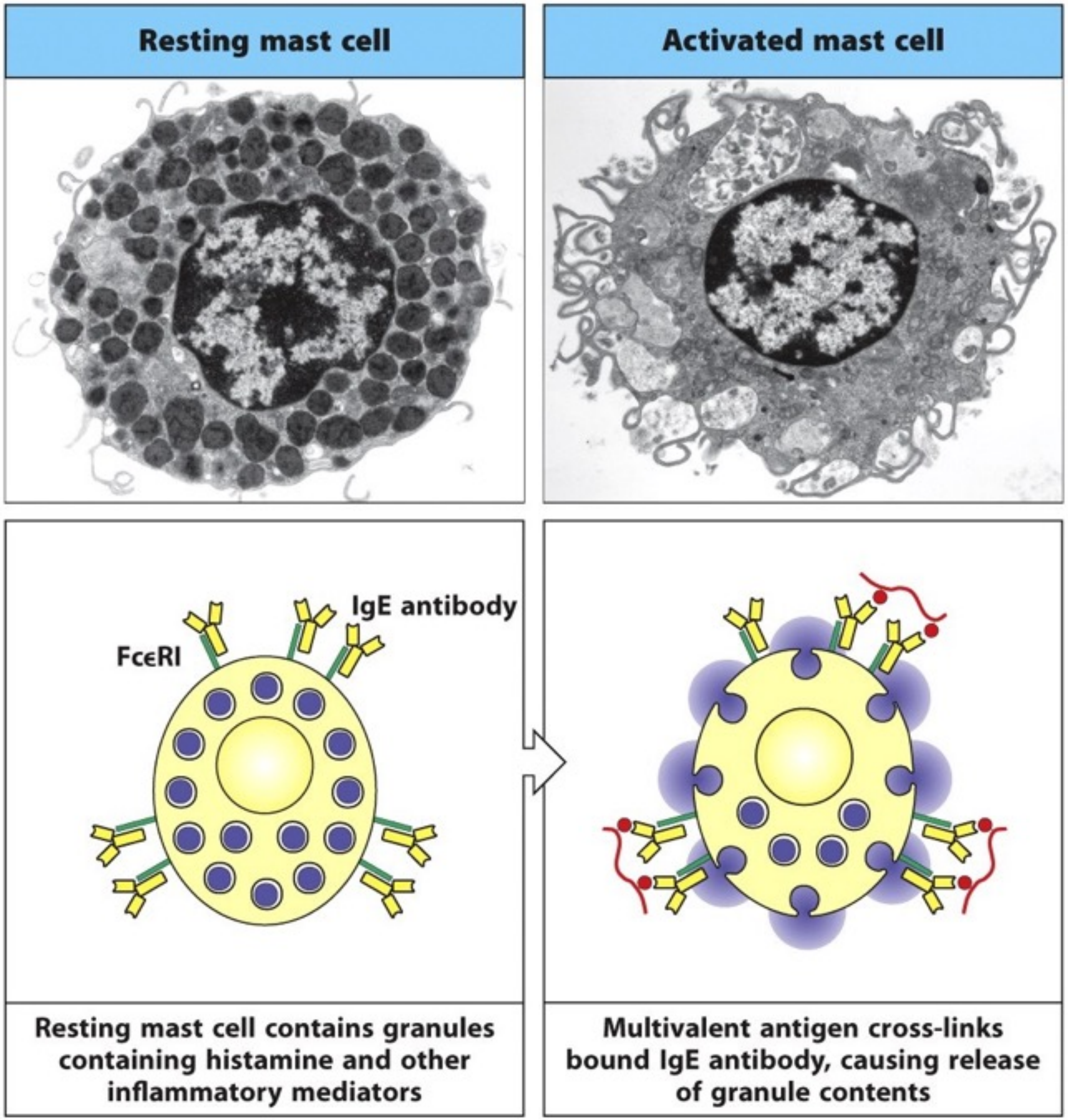


Figure 10.37 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Degranulação de Mastócitos

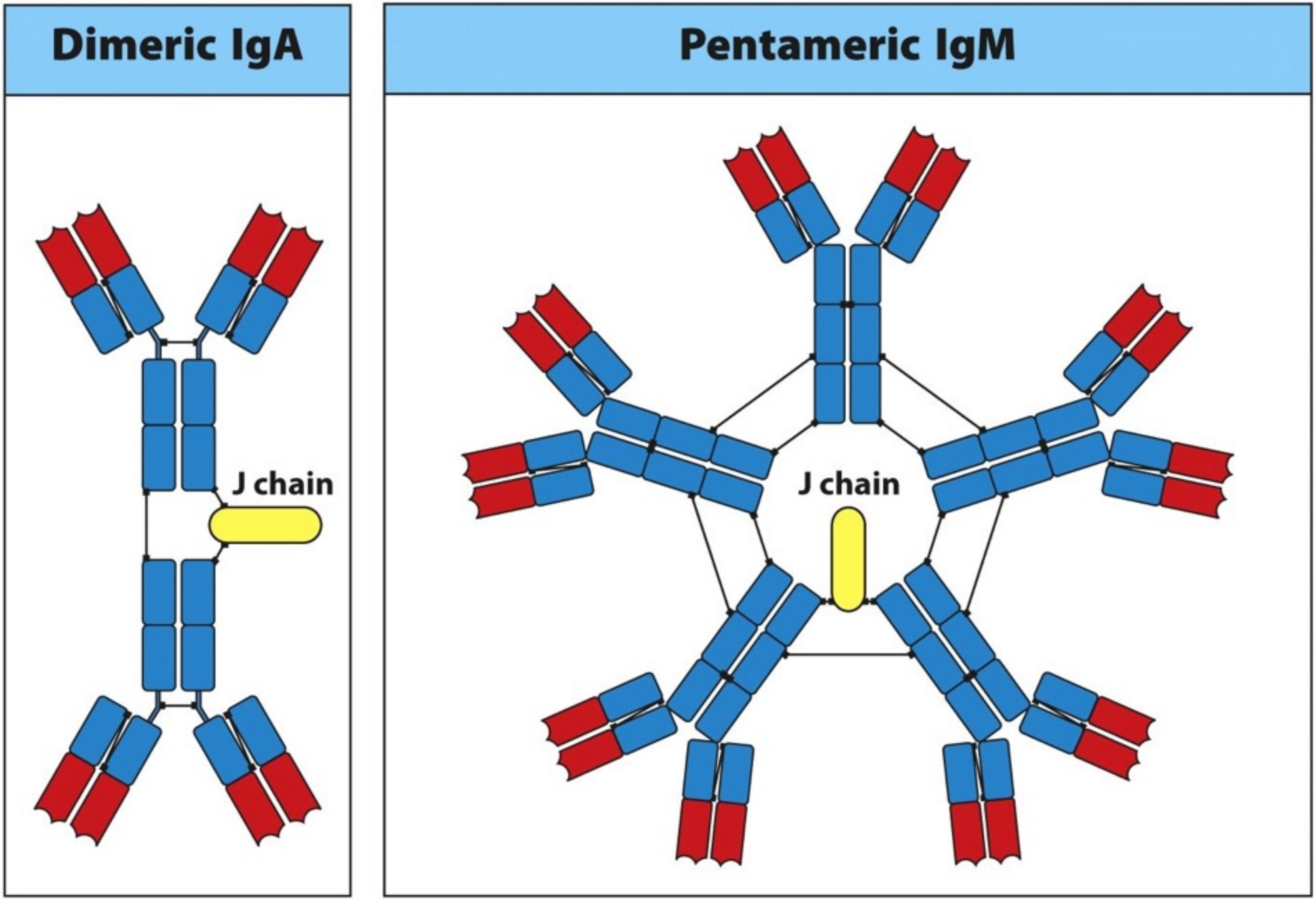
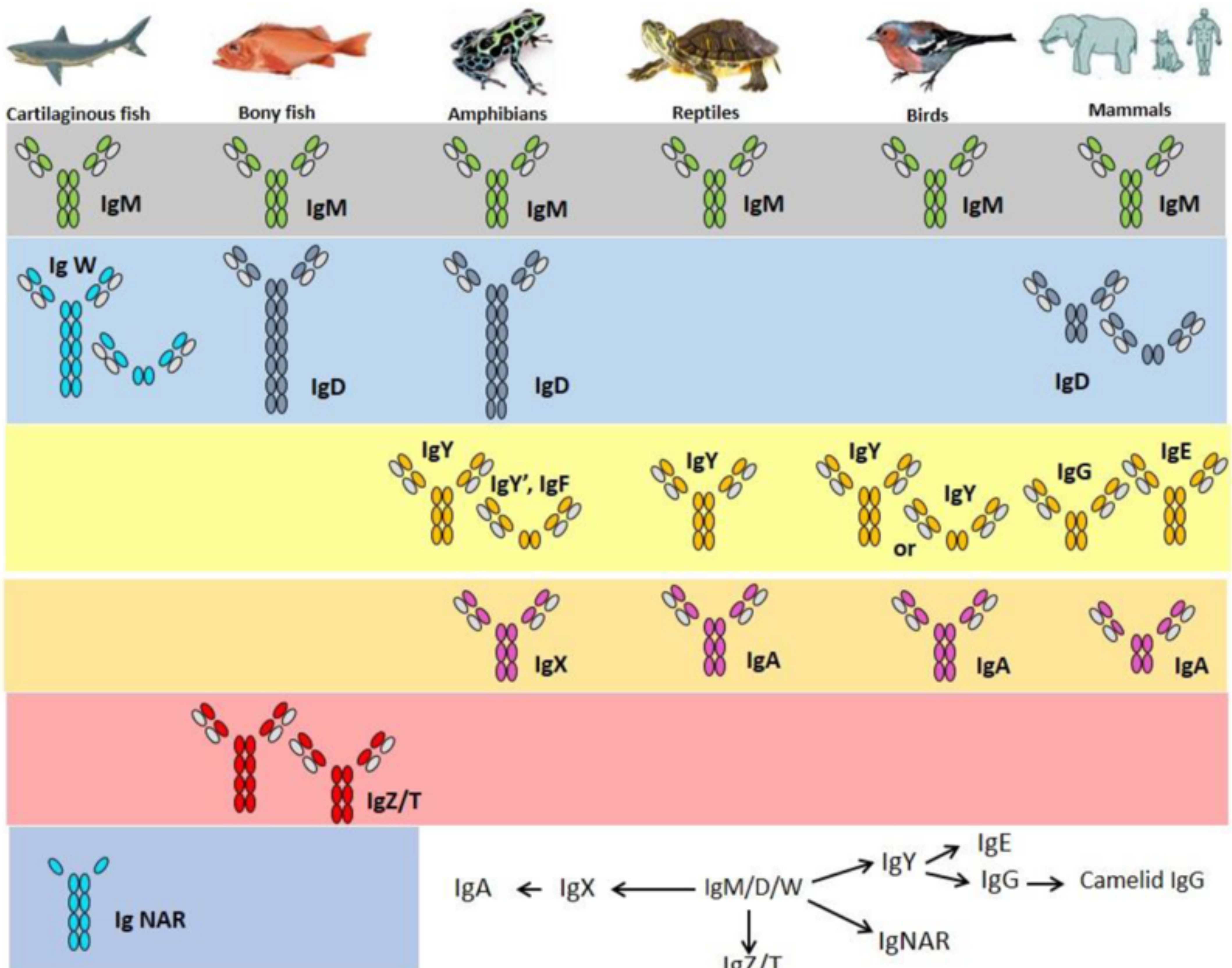


Figure 5.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

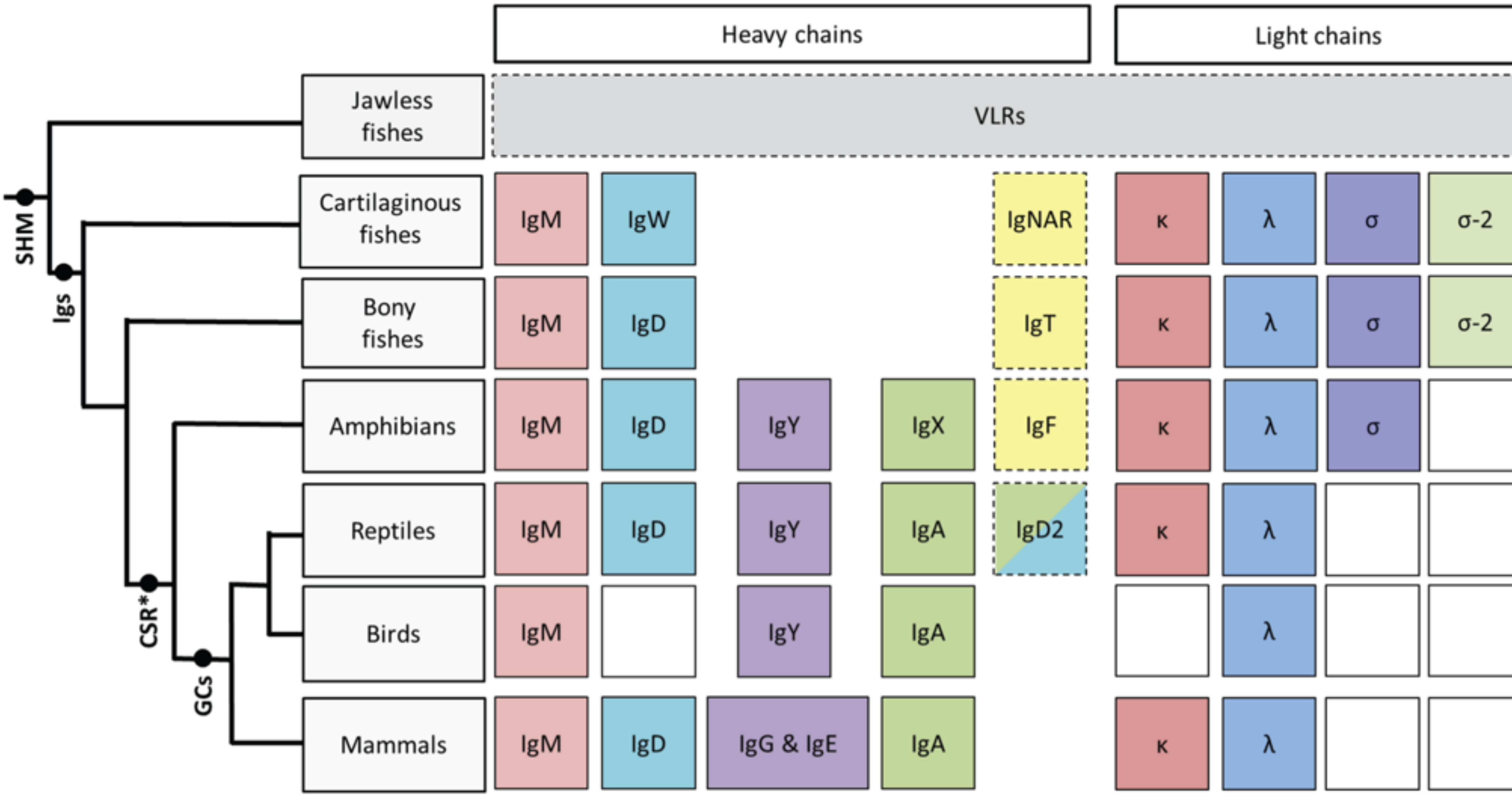


Biology **2016**, *5*(4), 45; doi:10.3390/biology5040045

Review

Fish Immunoglobulins

Sara Mashoof [1] and Michael F. Criscitiello [1,2,*]



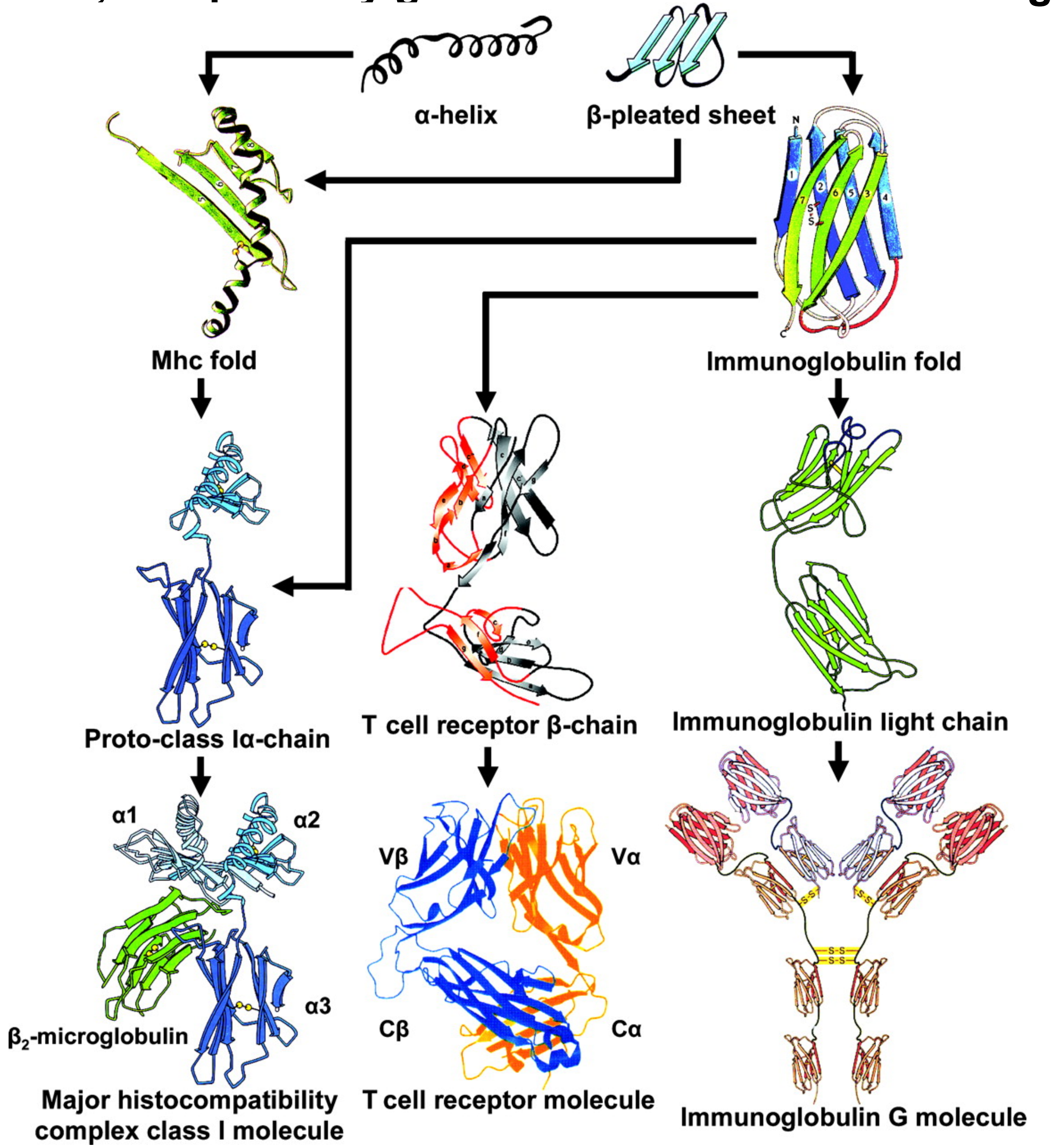
Biomolecules **2014**, *4*(4), 1045-1069; doi:10.3390/biom4041045

Review

The Immunoglobulins of Cold-Blooded Vertebrates

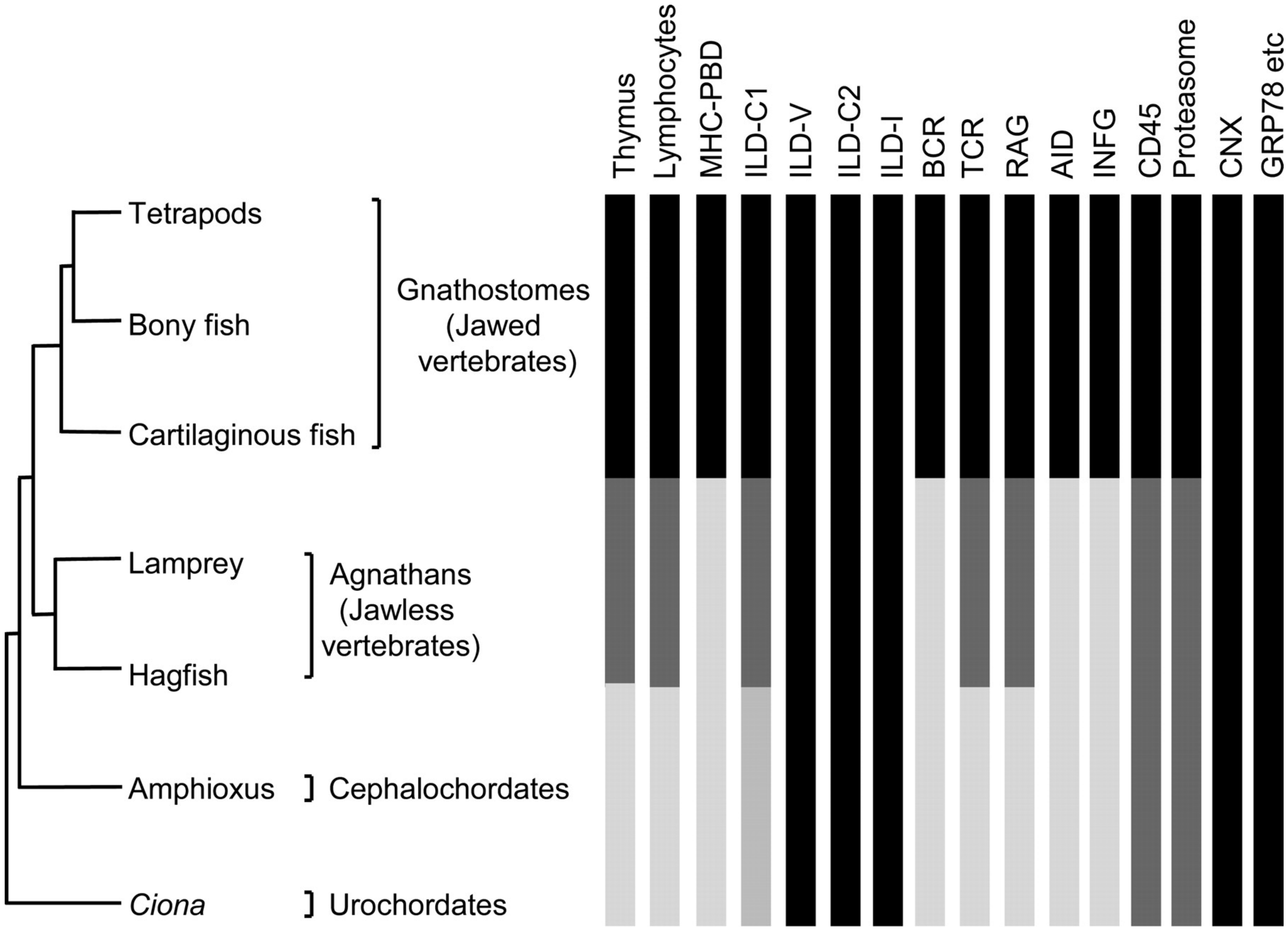
Rita Pettinello and Helen Dooley *

Hypothetical scenario for the emergence of the MHC, TCR, and BCR molecules by gradual evolution, which encompassed modification of preexisting domains, joining together of different domains, and possibly generation of new domain designs.



Jan Klein, and Nikolas Nikolaidis PNAS 2005;102:169-174

Emergence of the organs, cells, and molecules of the AIS during the evolution of chordates.

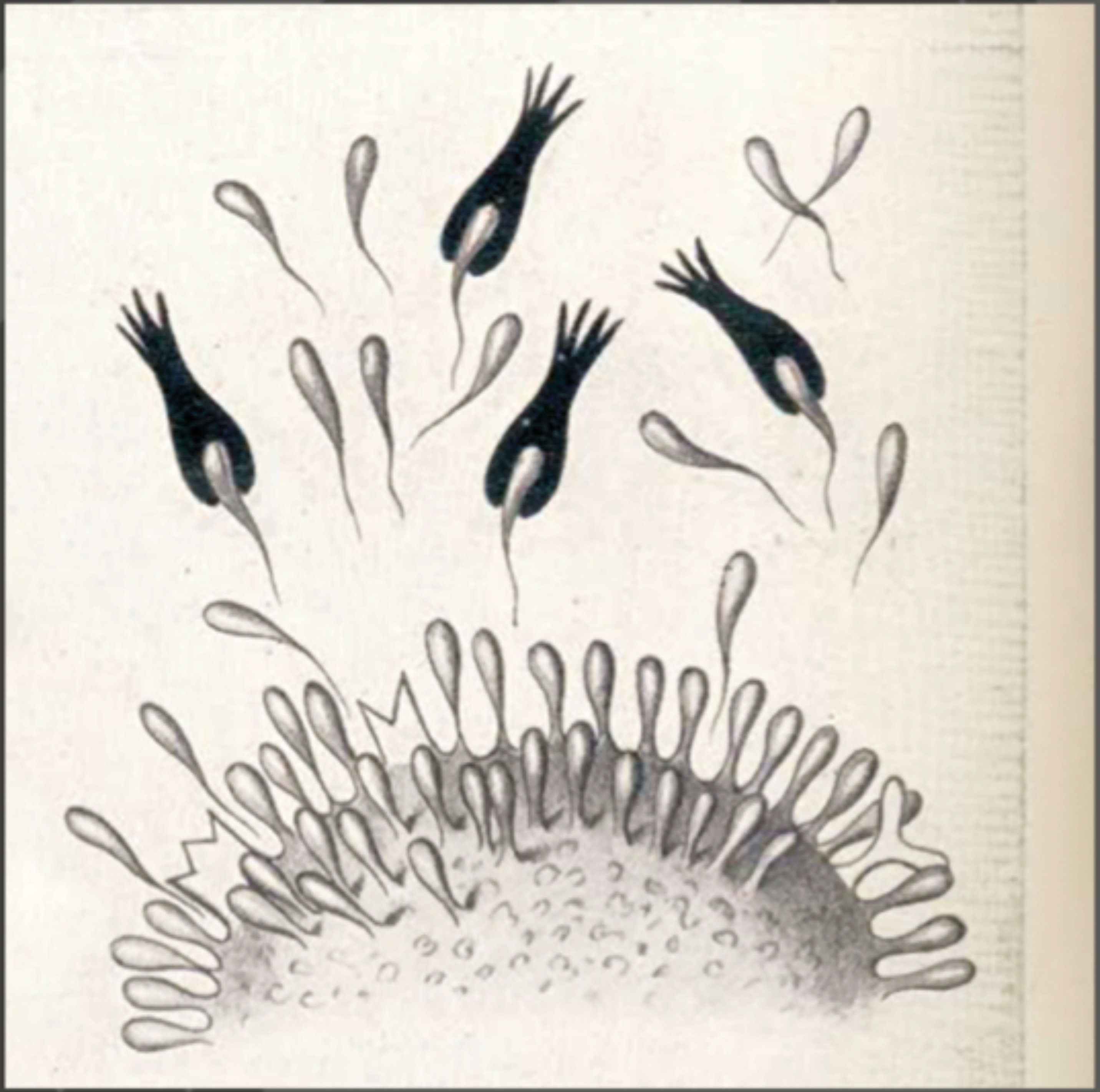


Jan Klein, and Nikolas Nikolaidis PNAS 2005;102:169-174

1890 / MILESTONE 1

FIRST DESCRIPTION OF ANTI-SERA

FIND OUT MORE



Adapted from: Ehrlich, P. Croonian lecture: on immunity with special reference to cell life. *Proc. Royal Soc. Lond.* **66**, 424–448 (1900). Courtesy of Stefan H.E. Kaufmann.

1900 / MILESTONE 2

EHRLICH'S 'SIDE-CHAIN' MODEL

FIND OUT MORE

1901

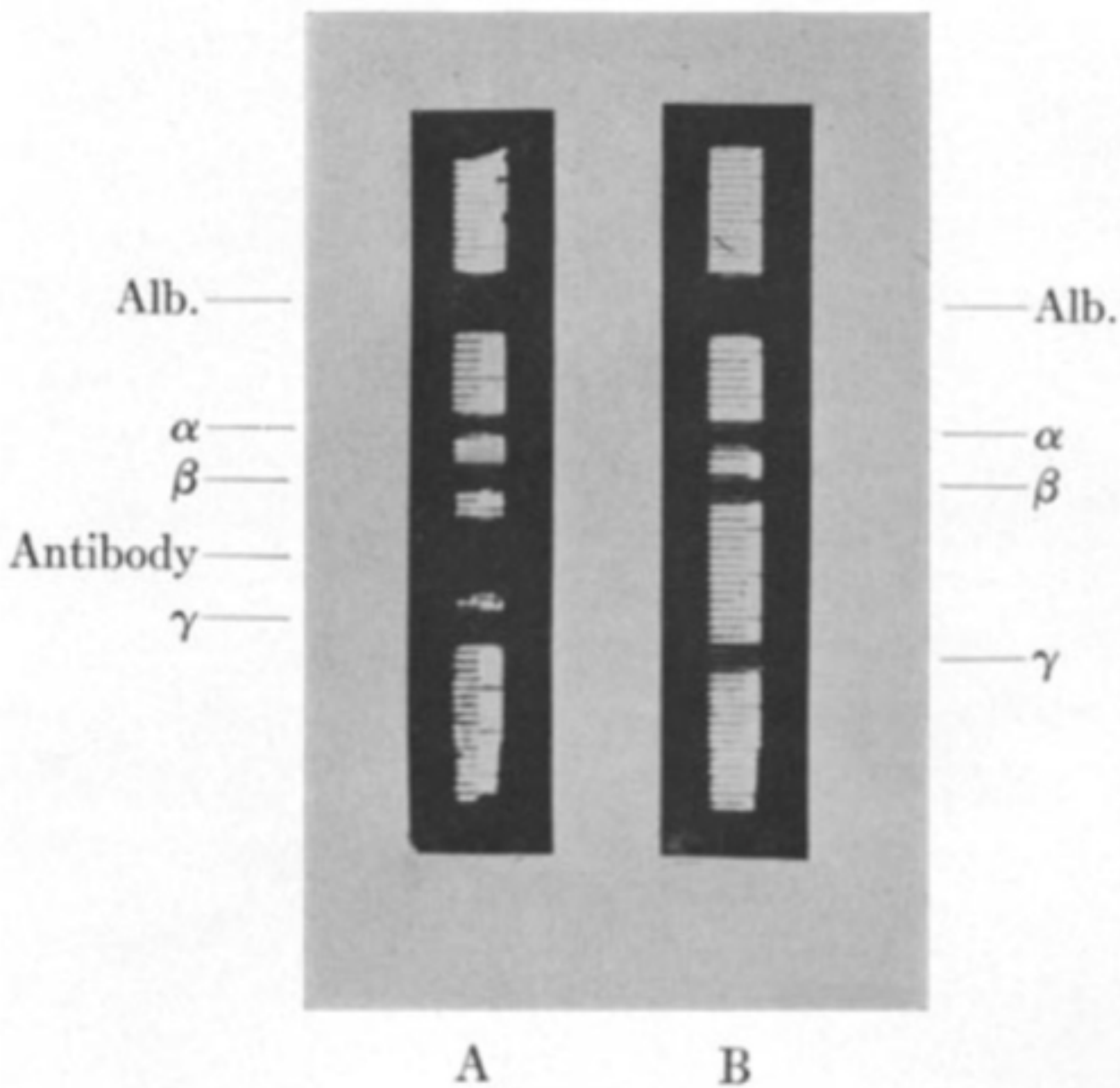
NOBEL PRIZE: EMIL VON BEHRING

for '...the development of serum therapy'

1908

NOBEL PRIZE: PAUL EHRLICH

'…in recognition of… work on immunity'



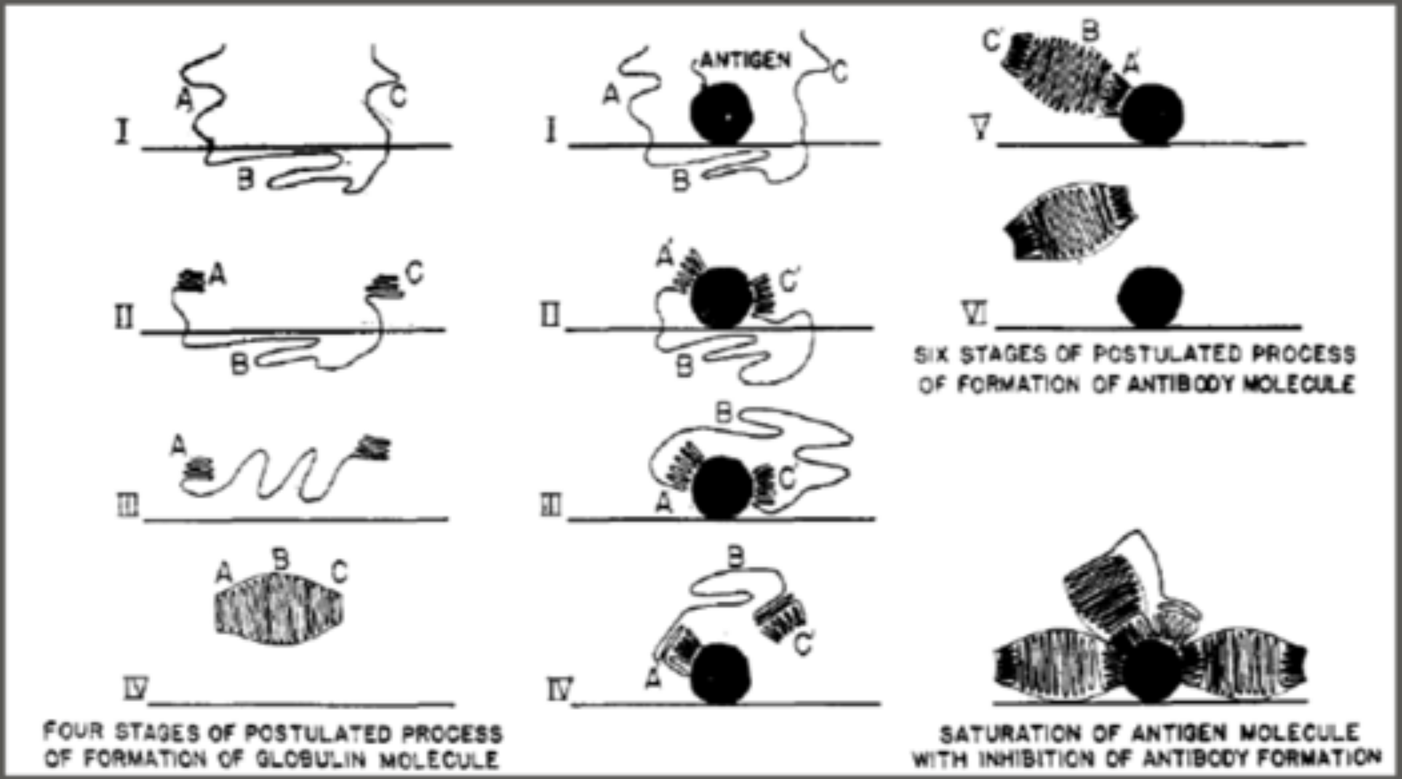
1935

ANTIBODIES ARE GAMMA-GLOBULINS

Arne Tiselius and Elvin A. Kabat use electrophoresis to separate serum components to demonstrate that antibodies are γ-globulins.

FURTHER READING

Tiselius, A. & Kabat, E.A. *J. Exp. Med.* **69**, 119–131 (1939)



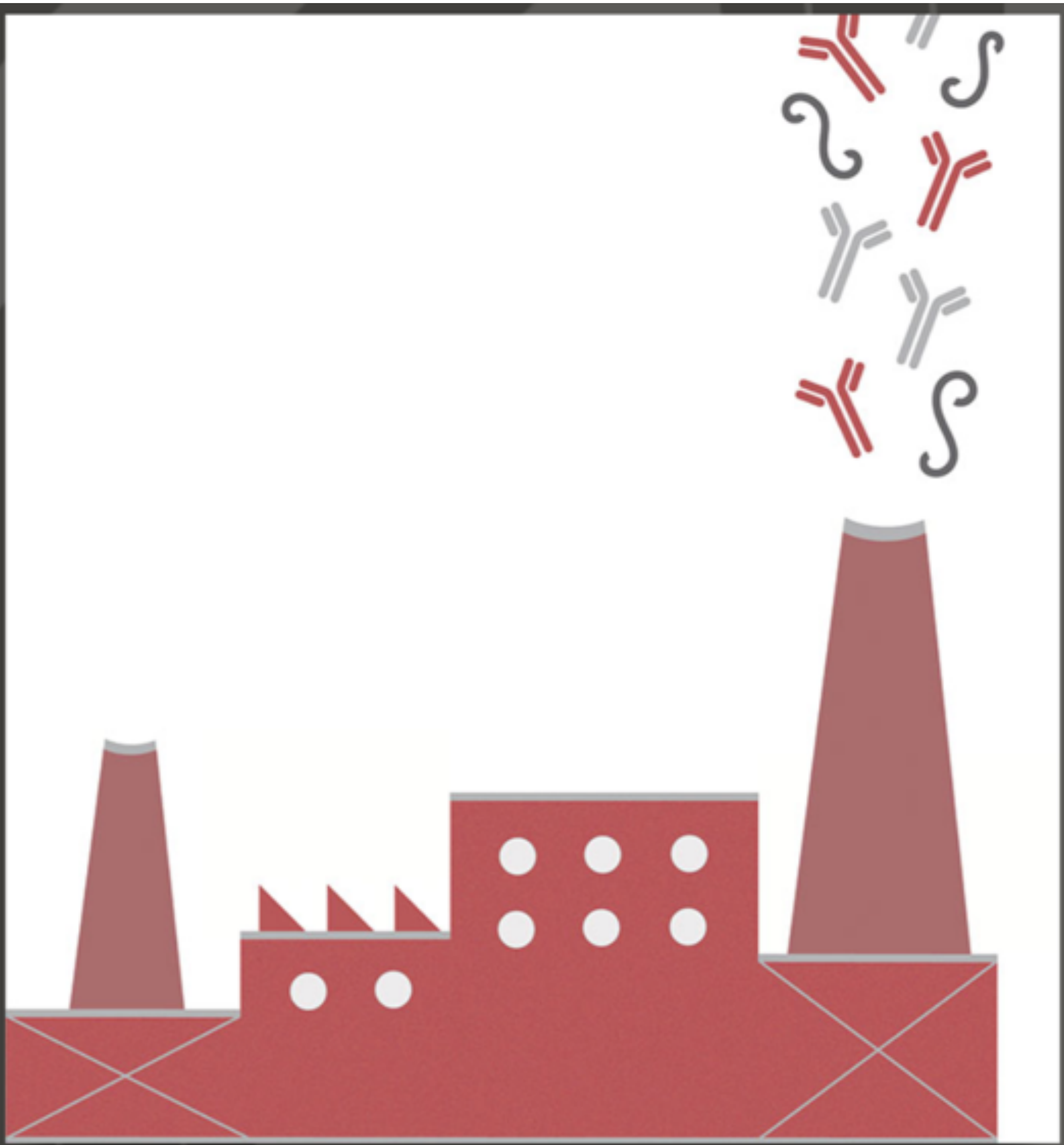
Reprinted with permission from Pauling, L. A. Theory of the Structure and Process of Formation of Antibodies. *J. Am. Soc. Chem.* **62**, 2643-2657 (1940). Copyright American Chemical Society

1940

INSTRUCTIONAL MODEL

Linus Pauling proposes a revolutionary model to describe generation of antibody diversity.

FIND OUT MORE

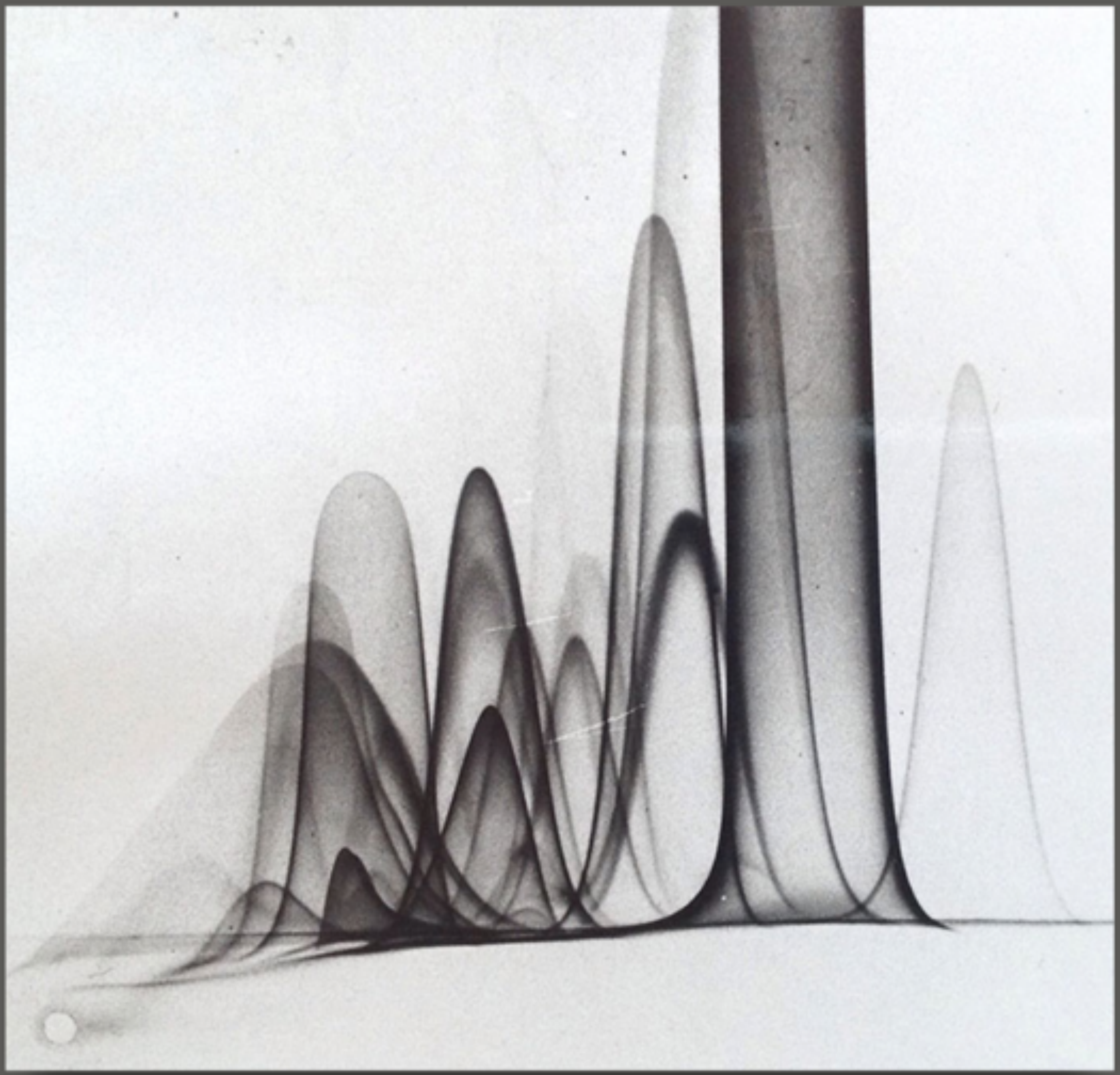


1943 / MILESTONE 3

VACCINATION-PLASMA CELL-ANTIBODY LINK

A series of landmark papers in the 1940s and 1950s identified plasma cells as the 'antibody-producing factories' of the immune system. It was later shown that plasma cells develop from B cells and that this process requires help from T cells.

FIND OUT MORE

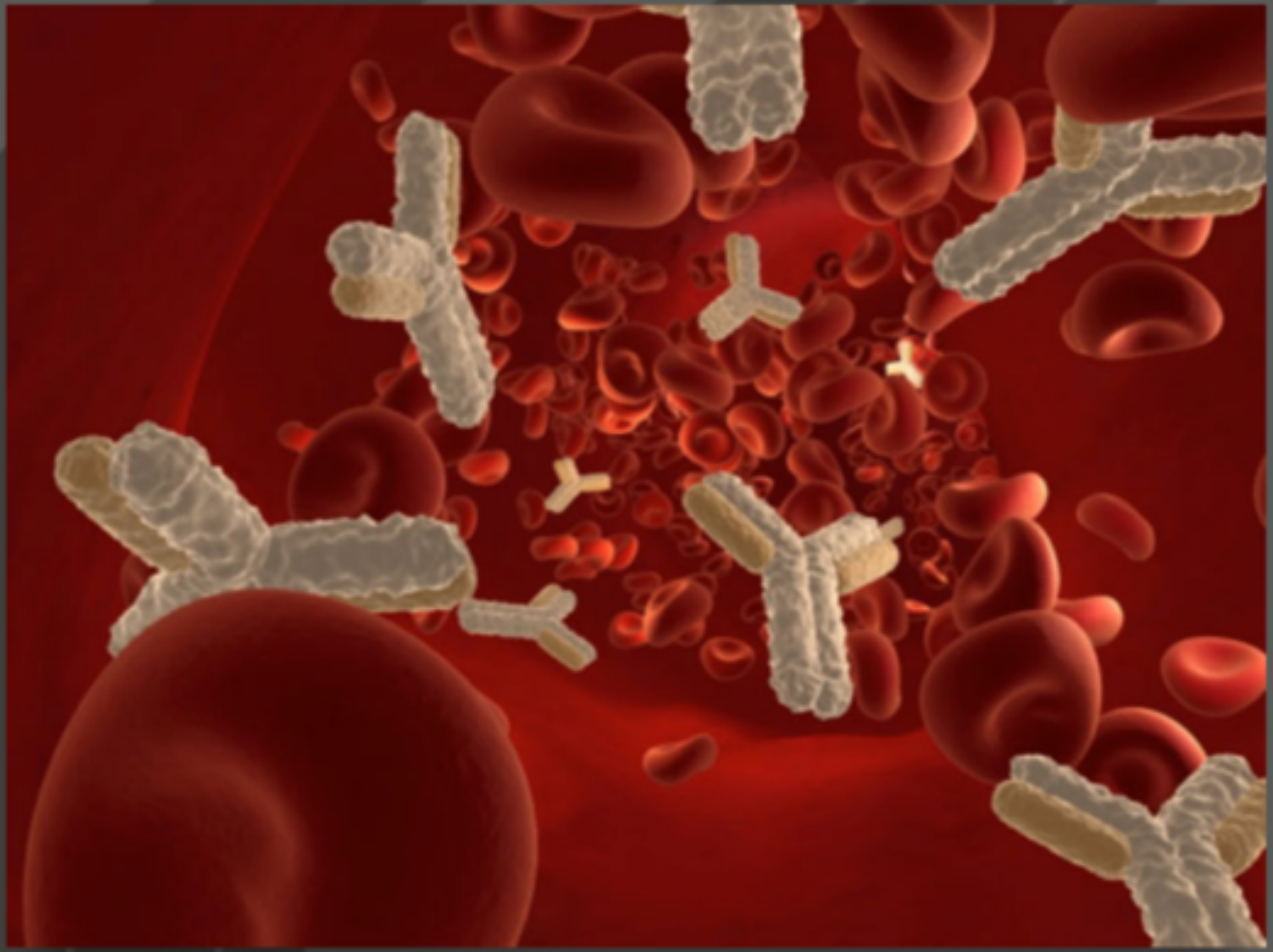


1945 / MILESTONE 4

COOMBS TEST

Antibodies are used routinely in a vast number of laboratory and clinical applications – the Coombs test was one of the earliest.

FIND OUT MORE



1947

PLASMA CELLS PRODUCE ANTIBODIES

Astrid Fagraeus demonstrates that plasma cells isolated from rabbits immunized with *Salmonella* produce antibodies *in vitro*.

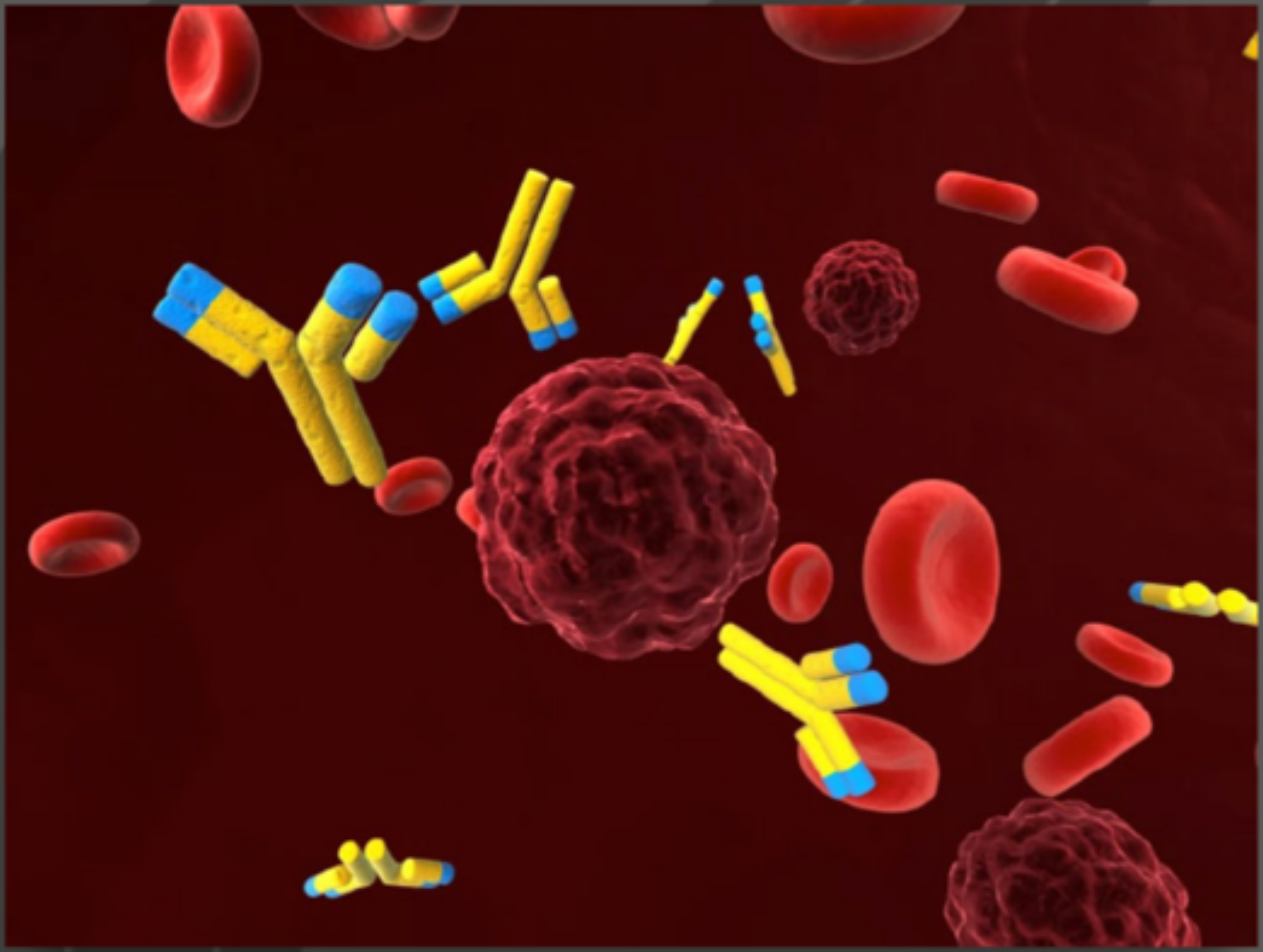
FURTHER READING

Fagraeus, A. *Nature* **159**, 499 (1947).
Fagraeus, A. *J. Immunol.* **58**, 1–13 (1948).

1957 / MILESTONE 5

BURNET'S CLONAL SELECTION MODEL

FIND OUT MORE



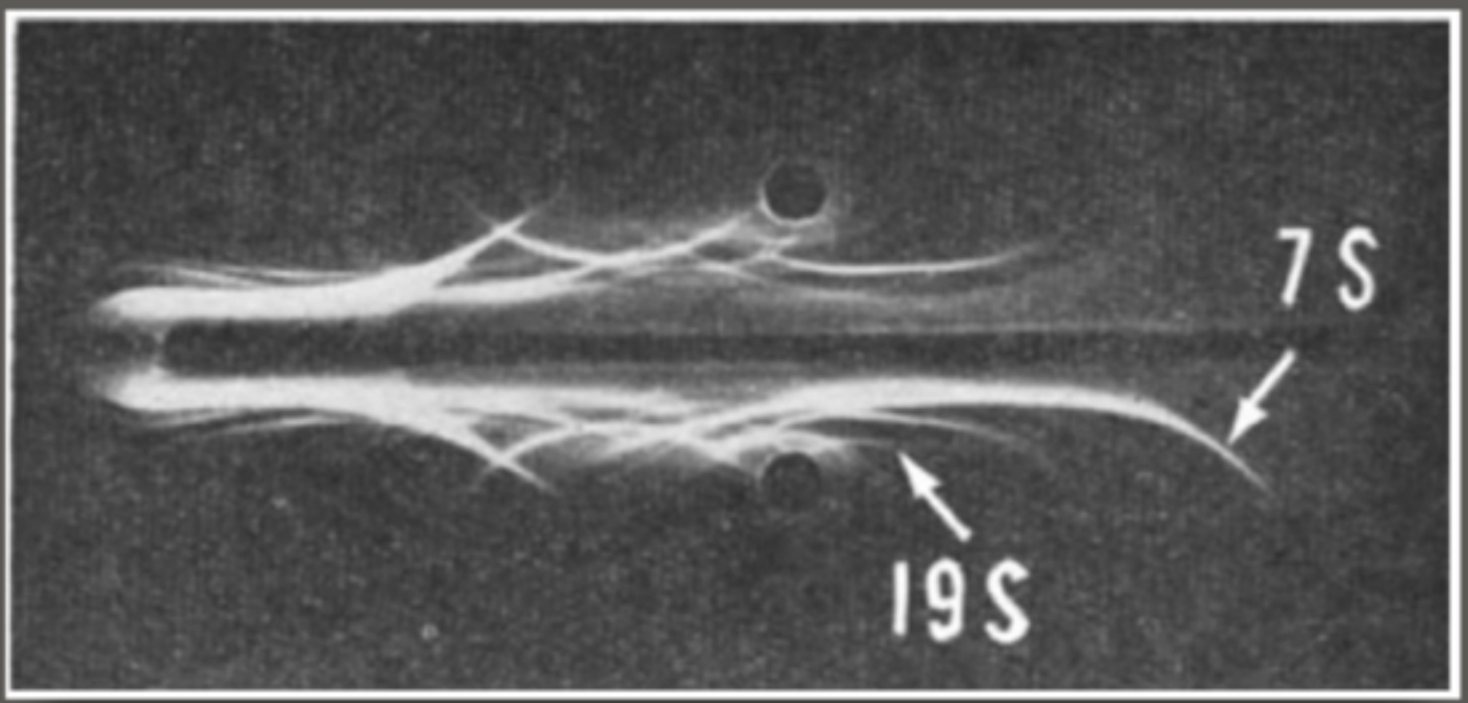
1958

ONE CELL-ONE ANTIBODY

Gustav Nossal and Joshua Lederberg isolate single plasma cells in oil droplets and demonstrate that they only ever produce antibodies of one antigen specificity.

FURTHER READING

Nossal, G.J.V. & Lederberg, J. *Nature* **181**, 1419–1420 (1958)
Nossal, G.J.V. *Nat. Immunol*. **8**, 1015–1017 (2007)



1965

DEFINITION OF B CELL AND T CELL LINEAGES

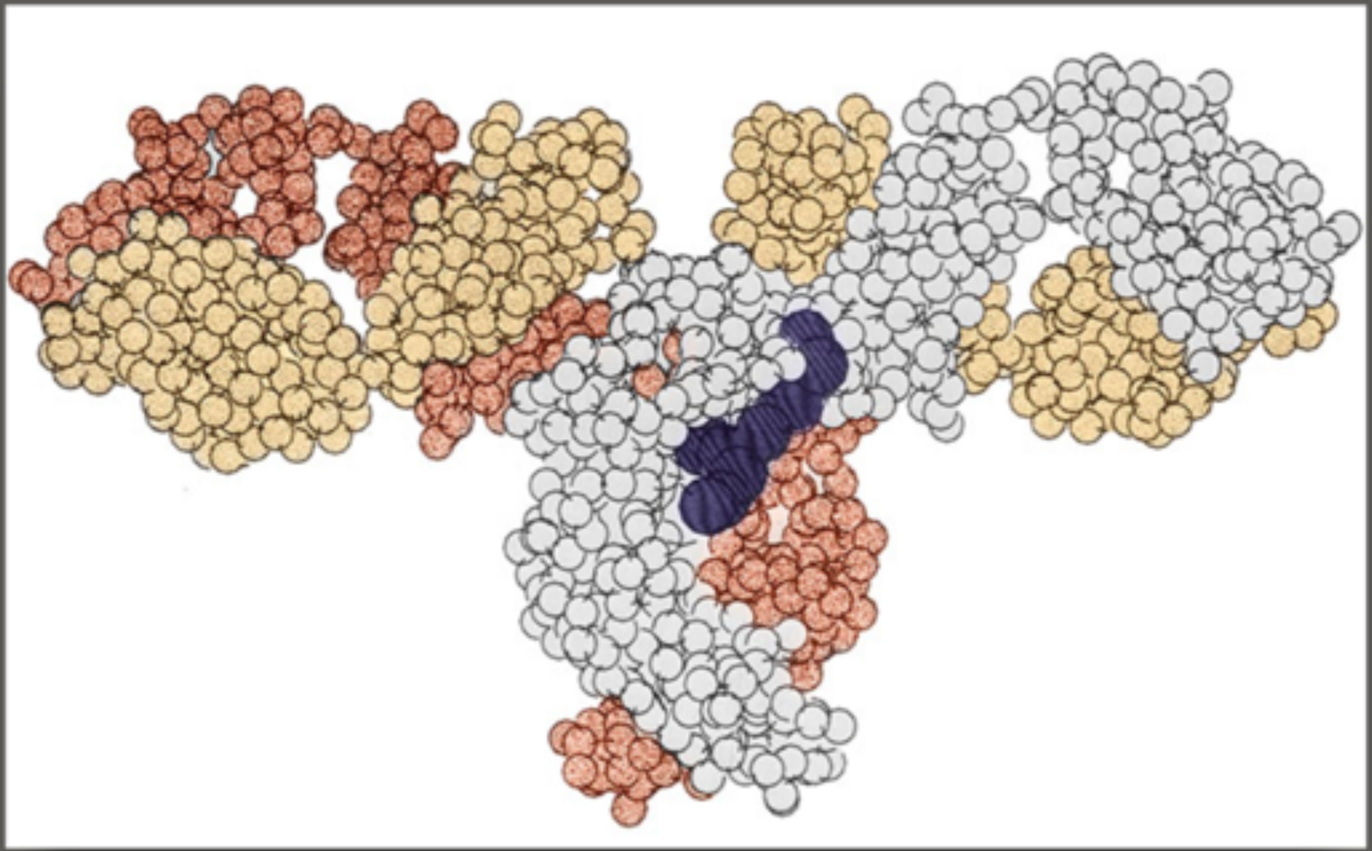
FIND OUT MORE

1966 / MILESTONE 6

IDENTIFICATION OF IMMUNOGLOBULIN E

Immunoglobulin E was the final human antibody type to be discovered and has a central role in allergy.

FIND OUT MORE

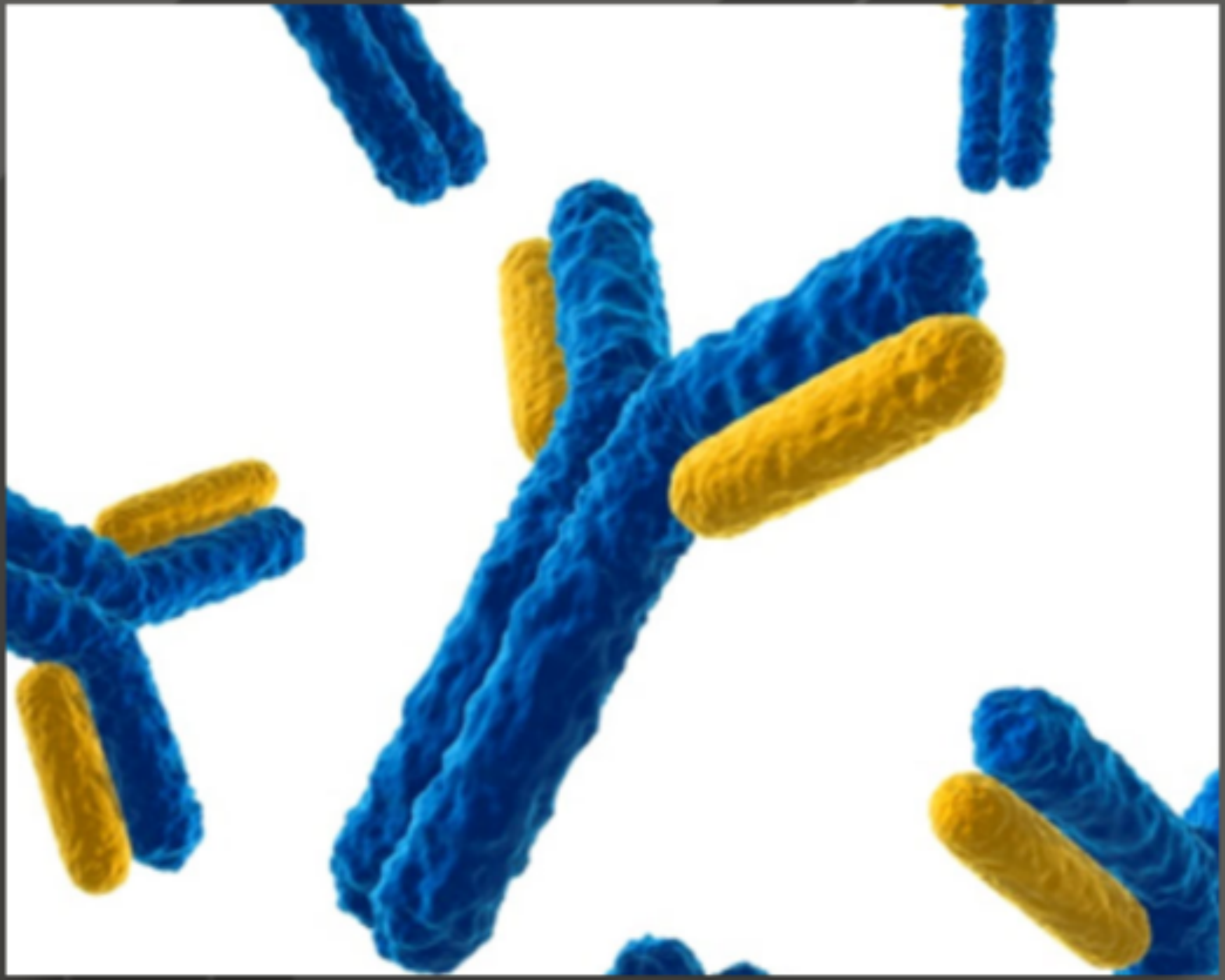


Silverton *et al. Proc. Natl. Acad. Sci. USA.* 74, 5140–5144 (1977). Modified and reproduced with permission from *Proceedings of the National Academy of Sciences USA*.

1969 / MILESTONE 7

COVALENT STRUCTURE OF AN ENTIRE IMMUNOGLOBULIN

FIND OUT MORE



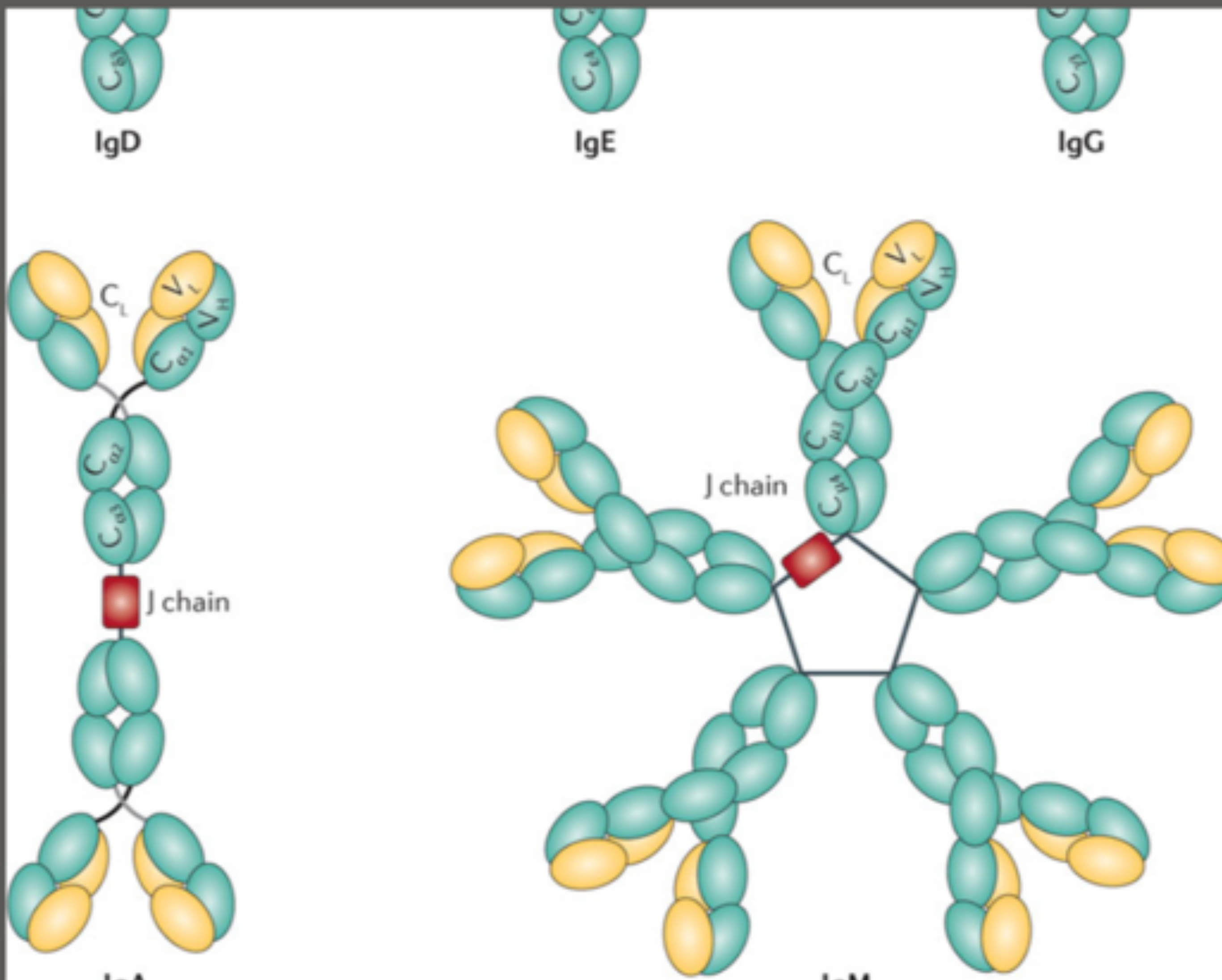
1970

IMMUNOGLOBULIN LIGHT CHAIN SEQUENCE.

Tai Te Wu and Elvin A. Kabat sequence the immunoglobulin light chain and in so doing identify the hypervariable complementarity determining regions.

FURTHER READING

Wu, T. T. & Kabat, E. A. *J. Exp. Med.* **132**, 211–250 (1970)



1970 / MILESTONE 8

GENETIC BASIS OF IMMUNOGLOBULIN CLASS SWITCHING

Alfred Nisonoff and colleagues present the first experimental evidence for antibody class-switching of IgM to IgG.

FIND OUT MORE

1972

NOBEL PRIZE: EDELMAN AND PORTER

"…for their discoveries concerning the chemical structure of antibodies"

César Milstein and Georges Köhler together in 1984, the year they were awarded the Nobel Prize in physiology or medicine, jointly with Niels Jerne. Photo reproduced courtesy of Celia Milstein and the MRC Laboratory of Molecular Biology, Cambridge, UK.

1975 / MILESTONE 9

MONOCLONAL ANTIBODIES

Georges Köhler and César Milstein fuse myeloma cells with B cells, thereby generating immortal hybridomas that secrete antibodies of a single specificity.

WATCH VIDEO

FIND OUT MORE

7 Oct 1976

NRDC

National Research Development Corporation
PO box 236 Kingsgate House 66/74 Victoria Street London SW1 E 6SL
Telephone 01-828 3400 Telegrams Nardec London SW1 Telex 23580

Your ref

Our ref EJT/AED

7th October 1976.

Mr. L.D. Hamlyn,
Medical Research Council,
20 Park Crescent,
London, W1N 4AL.

Dear Jimmy,

Continuous Cultures of Fused Cells

We have now had an opportunity to study the paper by Kohler and Milstein to which you referred in your letter of 24th September addressed to Ron Homer.

Although the authors suggest that the cultures which they have developed, or rather similar cultures, could be valuable for medical and industrial use, I think this statement should be taken as a matter of long term potential rather than immediate application. It is certainly difficult for us to identify any immediate practical applications which could be pursued as a commercial venture, even assuming that publication had not already occurred. I would add that the general field of genetic engineering is a particularly difficult area from the patent point of view and it is not immediately obvious what patentable features are at present disclosed in the Nature paper.

In summary, therefore, unless further work indicates a diagnostic application or industrial end product which we can protect, despite the disclosure in the Nature paper, we would not suggest taking any further action ourselves.

Kind regards,

Yours sincerely,

Eric.

E.J. Tridgell
Biosciences Group

26/7/76 EX A2 50 mls George Kohler
" A3 " Basel Institute
" A5 " of Immunology
Sp1/HK " 487 Grenzacher
Sp2/HK " St
Basel, Switzerland

7/9/76 X63Ag8 30 mls H. Koprowski
Wistar Institute
36th St at Spruce
Philadelphia Pa. [illegible]

9/9/76 Sp6/HL 20 mls G. Klaus
Sp0/GL " Mill Hill.
Sp6/HLGK "

5/10/76 IF1 30 mls G. Kohler
(Paul Knoll)
Basel

5/10/76 X63Ag8 30 ml Dr D. Zagury
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de Microscopie Electronique
105 Boulevard
Raspail
75006 Paris.
Dr D. Zagury
G. Kohler.

11-10-76 X63Ag8 30 mls
20-10-76 " "

Dr. Barbara Osborne
X63Ag8 Genetics Dept
Stanford Medical School
Stanford, Calif 94305
USA

11-11-76 X63Ag8 20 mls "
289/16 "

7-12-76 X63Ag8 30 mls N. Cowan
Princeton University
Dept. Biochem. sciences
Frick. chem. Laboratory
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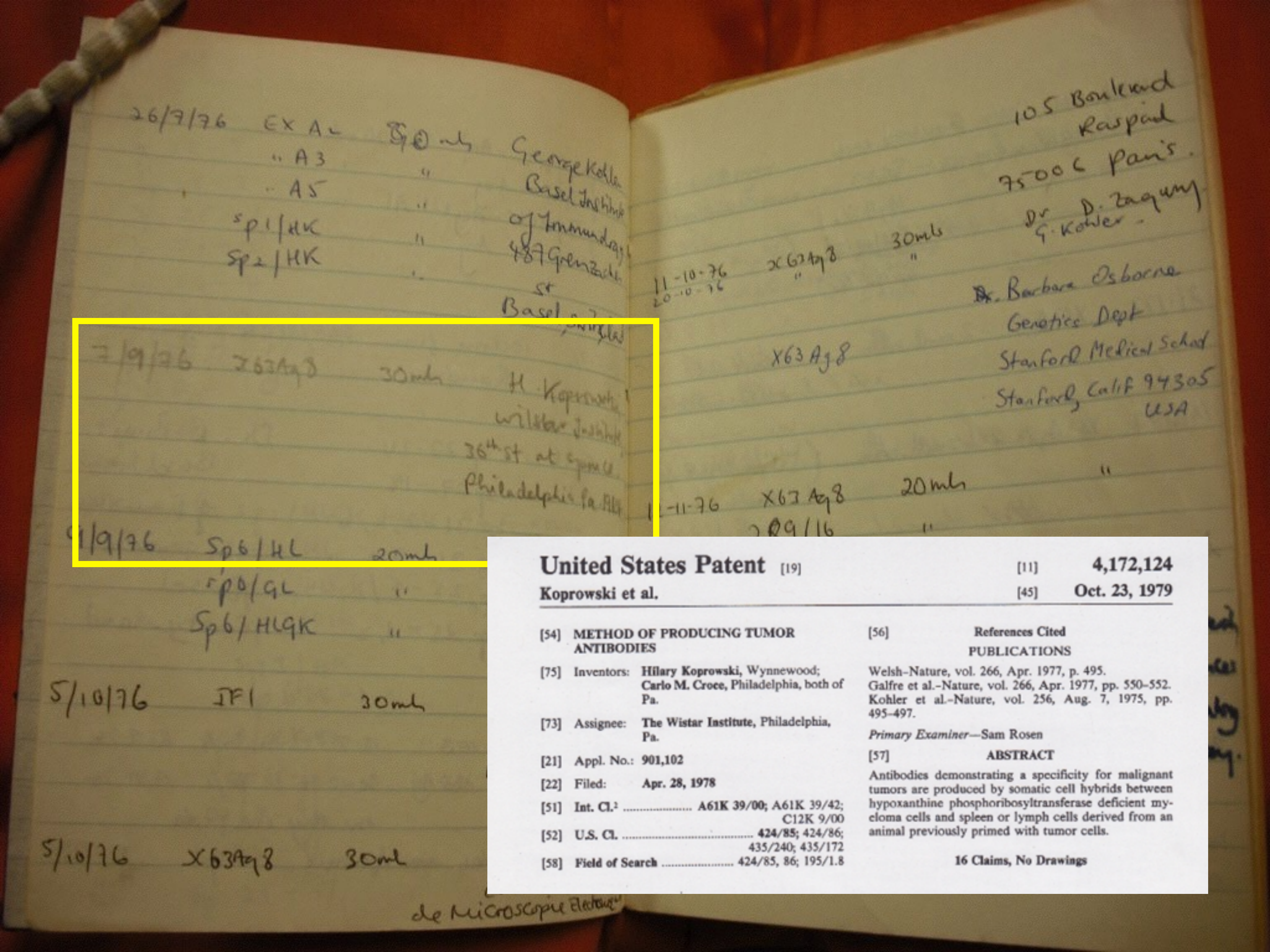
USA. 08540.



United States Patent [19] | [11] **4,172,124**

Koprowski et al. | [45] **Oct. 23, 1979**

[54] **METHOD OF PRODUCING TUMOR ANTIBODIES**

[75] Inventors: **Hilary Koprowski,** Wynnewood; **Carlo M. Croce,** Philadelphia, both of Pa.

[73] Assignee: **The Wistar Institute,** Philadelphia, Pa.

[21] Appl. No.: **901,102**

[22] Filed: **Apr. 28, 1978**

[51] Int. Cl.^{2} **A61K 39/00;** A61K 39/42; C12K 9/00

[52] U.S. Cl. **424/85;** 424/86; 435/240; 435/172

[58] **Field of Search** 424/85, 86; 195/1.8

[56] **References Cited**

PUBLICATIONS

Welsh–Nature, vol. 266, Apr. 1977, p. 495.
Galfre et al.–Nature, vol. 266, Apr. 1977, pp. 550–552.
Kohler et al.–Nature, vol. 256, Aug. 7, 1975, pp. 495–497.

Primary Examiner—Sam Rosen

[57] **ABSTRACT**

Antibodies demonstrating a specificity for malignant tumors are produced by somatic cell hybrids between hypoxanthine phosphoribosyltransferase deficient myeloma cells and spleen or lymph cells derived from an animal previously primed with tumor cells.

16 Claims, No Drawings

U$ 100 bilhões foram movimentados em 2017 pelo mercado global de anticorpos monoclonais

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What's Trending in Monoclonal Antibodies (Market by Structure [Chimeric, Humanized], by Target [EGFR, TNF, HER2, CD20,PD-1, Other] and by Disease [Autoimmune, Oncology, Neurological, Other])

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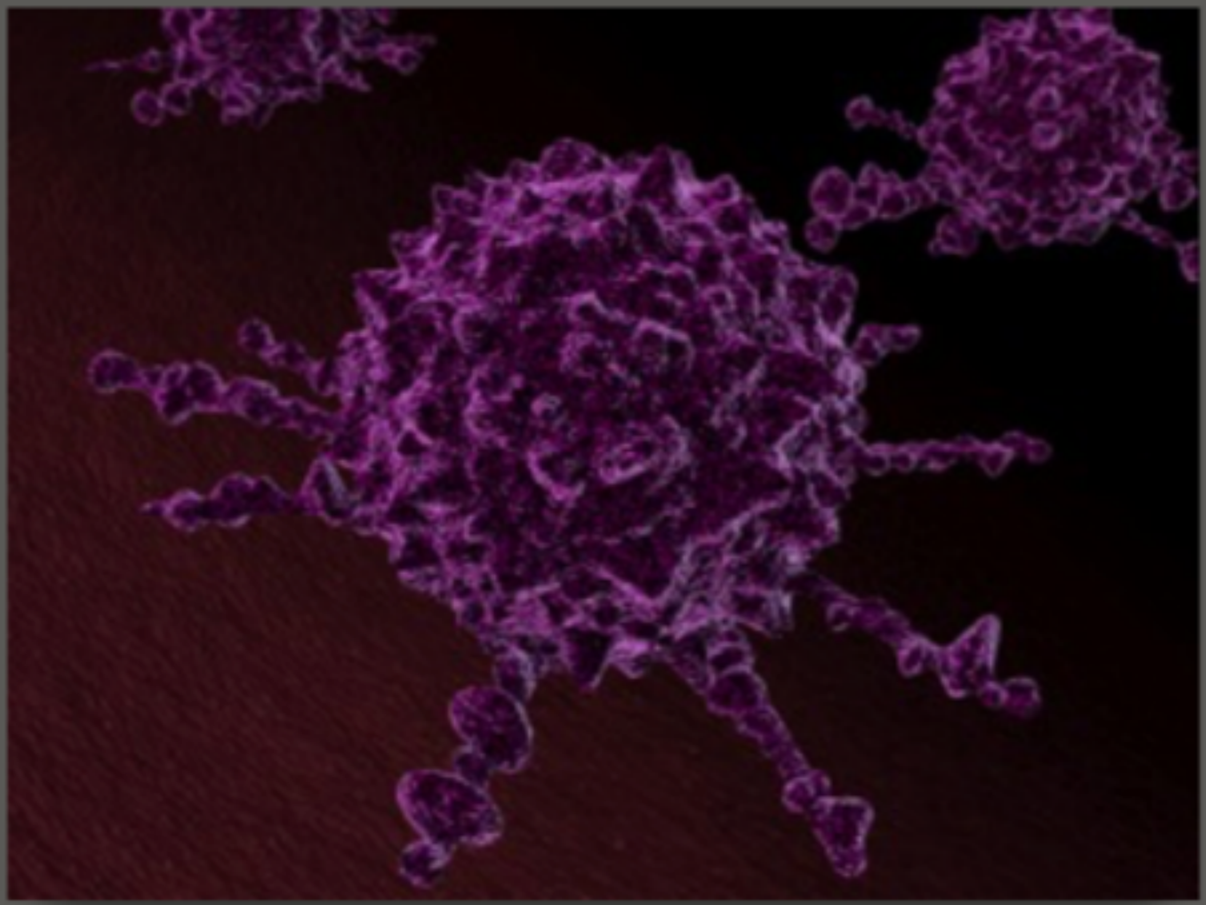
1977

NOBEL PRIZE: ROSALYN YALOW

"… for the development of radioimmunoassays of peptide hormones"



1982

PERSONALIZED CANCER THERAPY USING MONOCLONAL ANTIBODIES

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1984

NOBEL PRIZE: NIELS K. JERNE, CÉSAR MILSTEIN, GEORGES J.F. KÖHLER

"…for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"