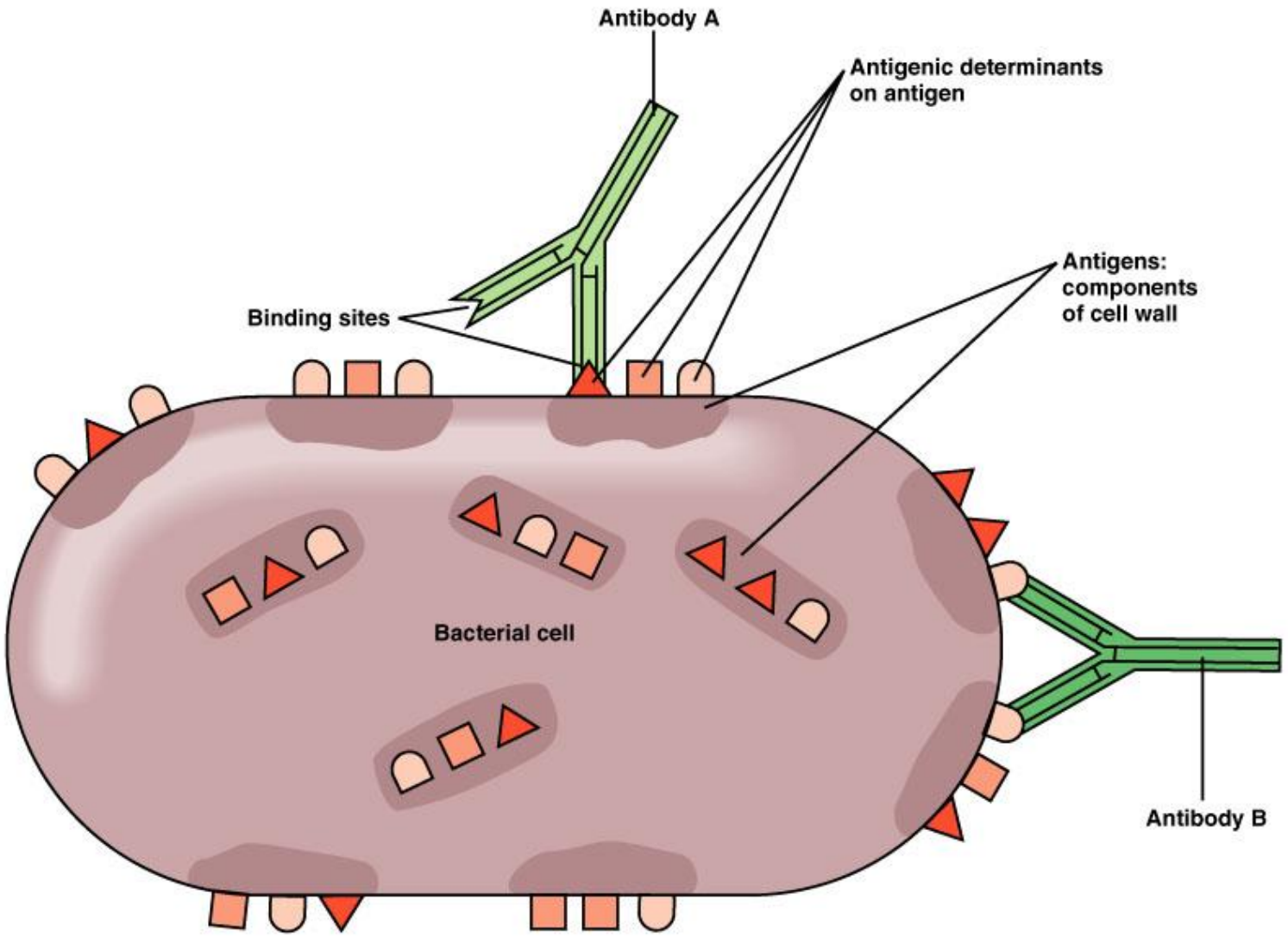
Imunoglobulins – structure and function

Production of immunoglobulins

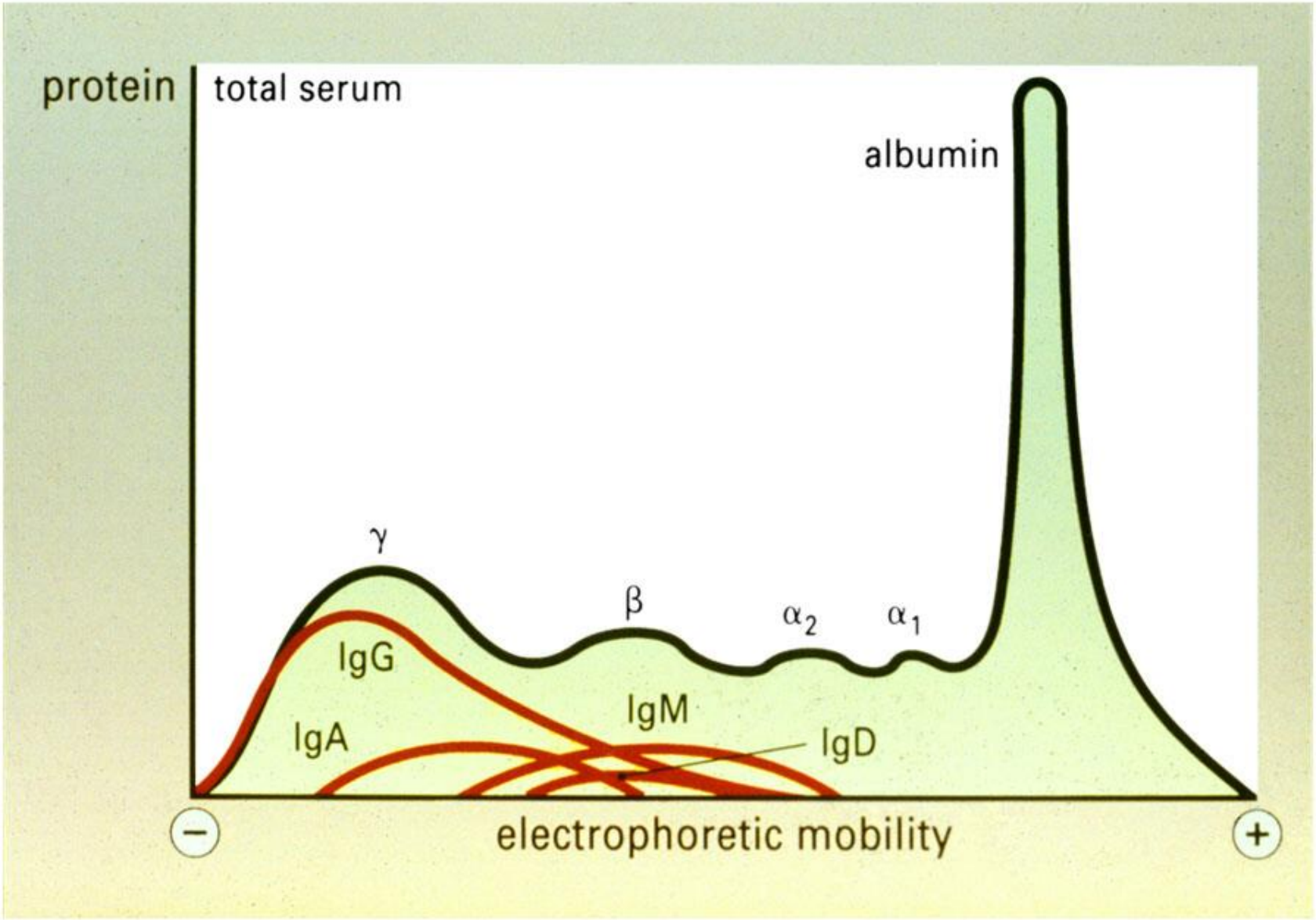
Genetic determination of immunoglobulin production

Clonal selection theory

Antigen and epitope



Distribution of the major human immunoglobulins



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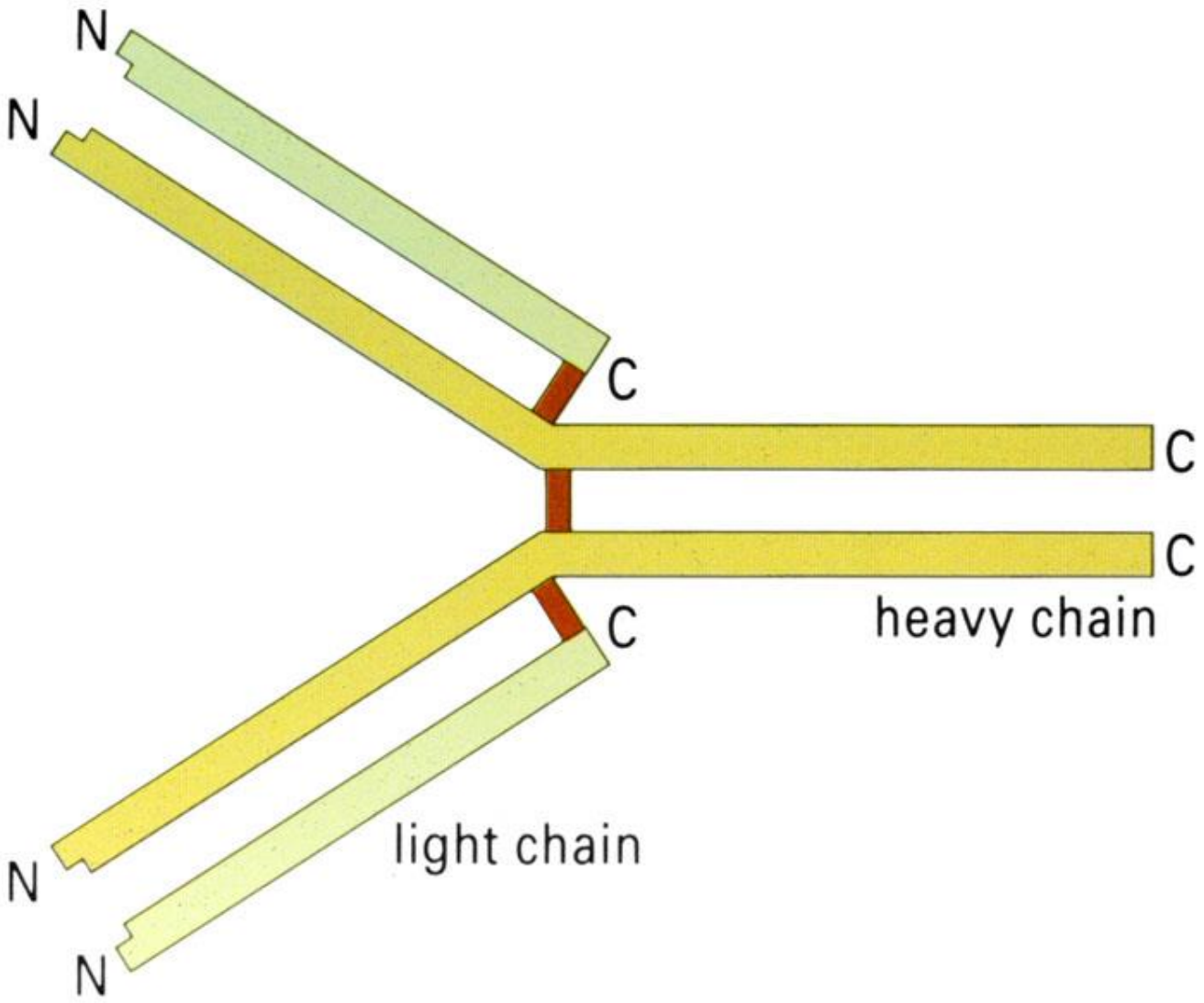
The basic chain structure of immunoglobulins



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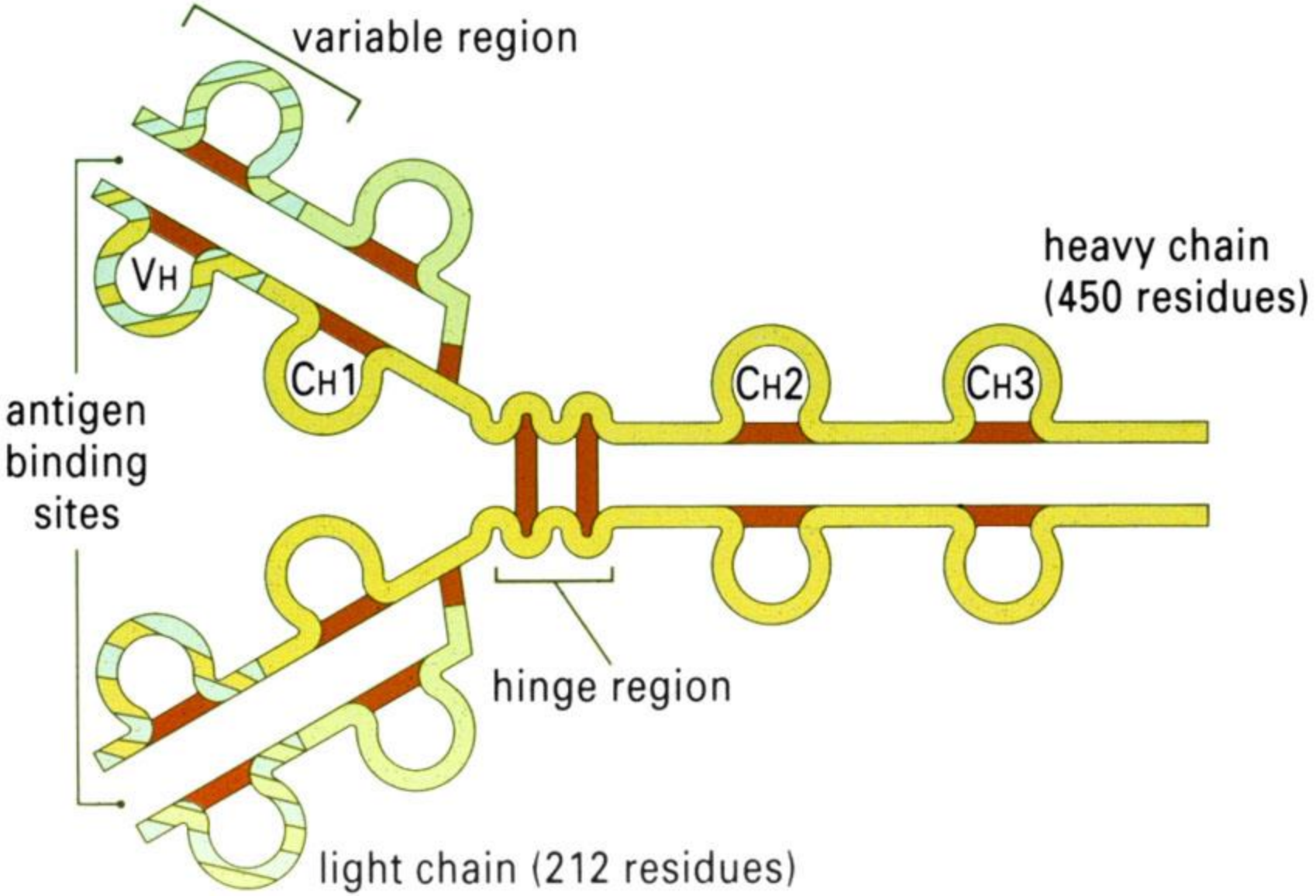
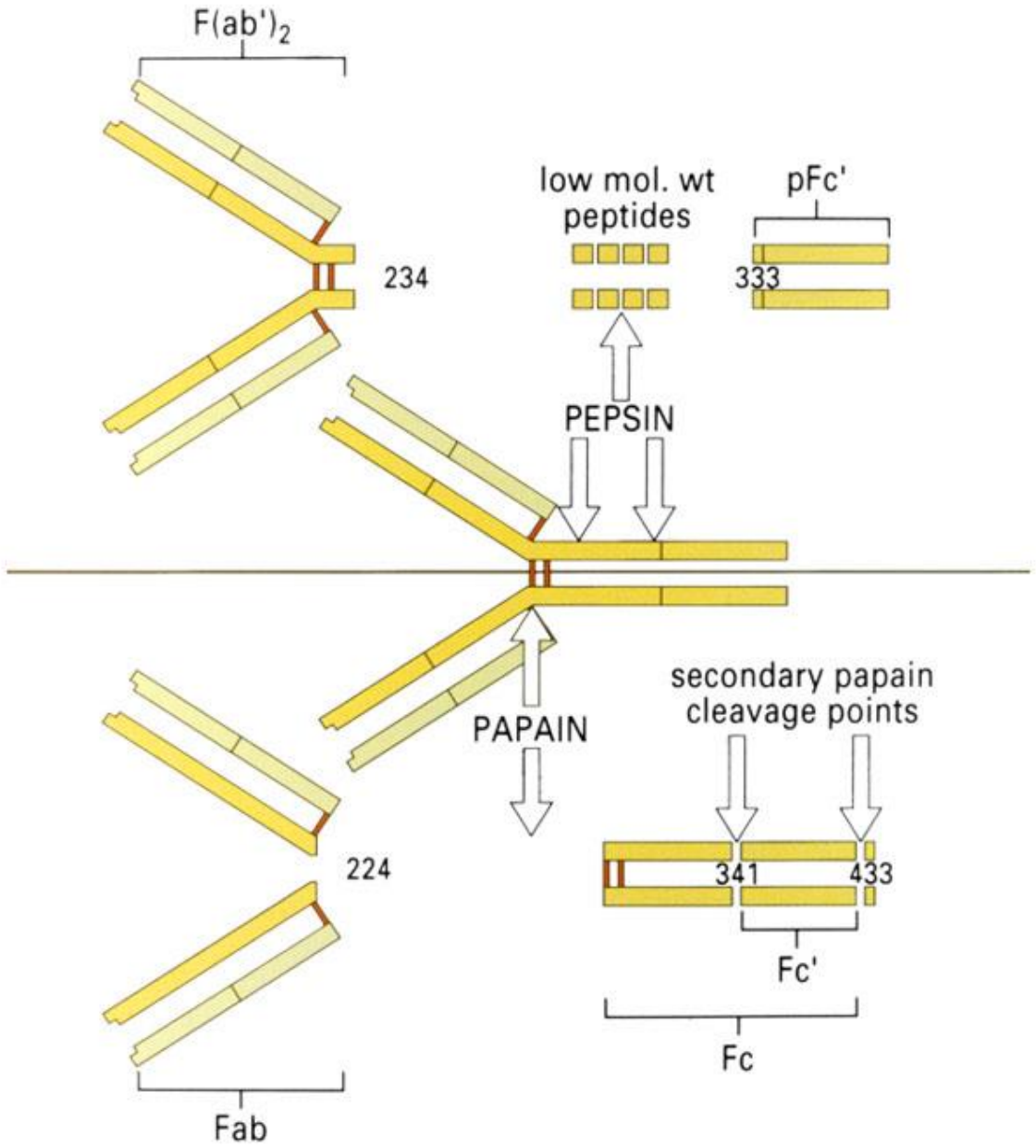
The basic structure of IgG1



Enzymic cleavage of human IgG1



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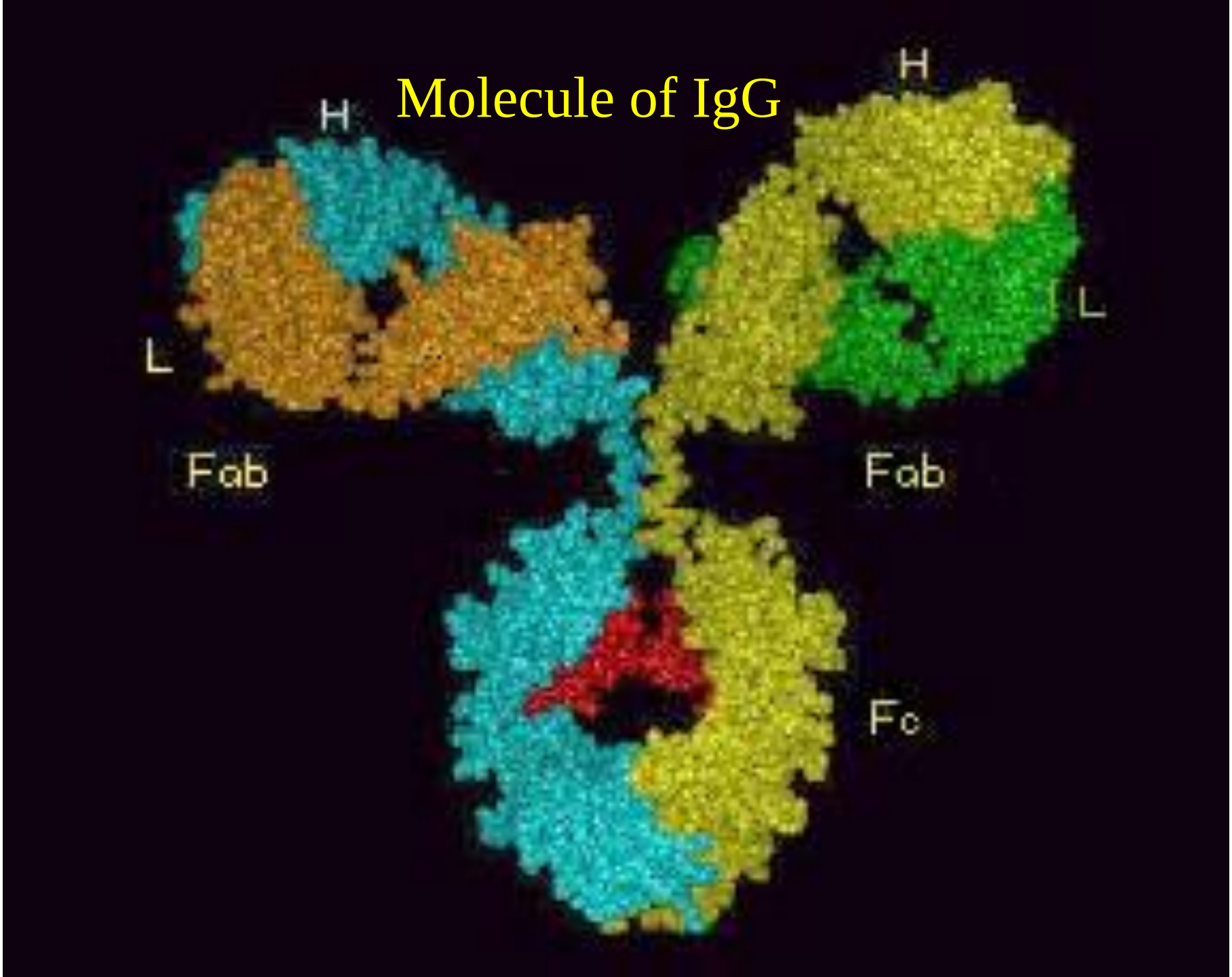
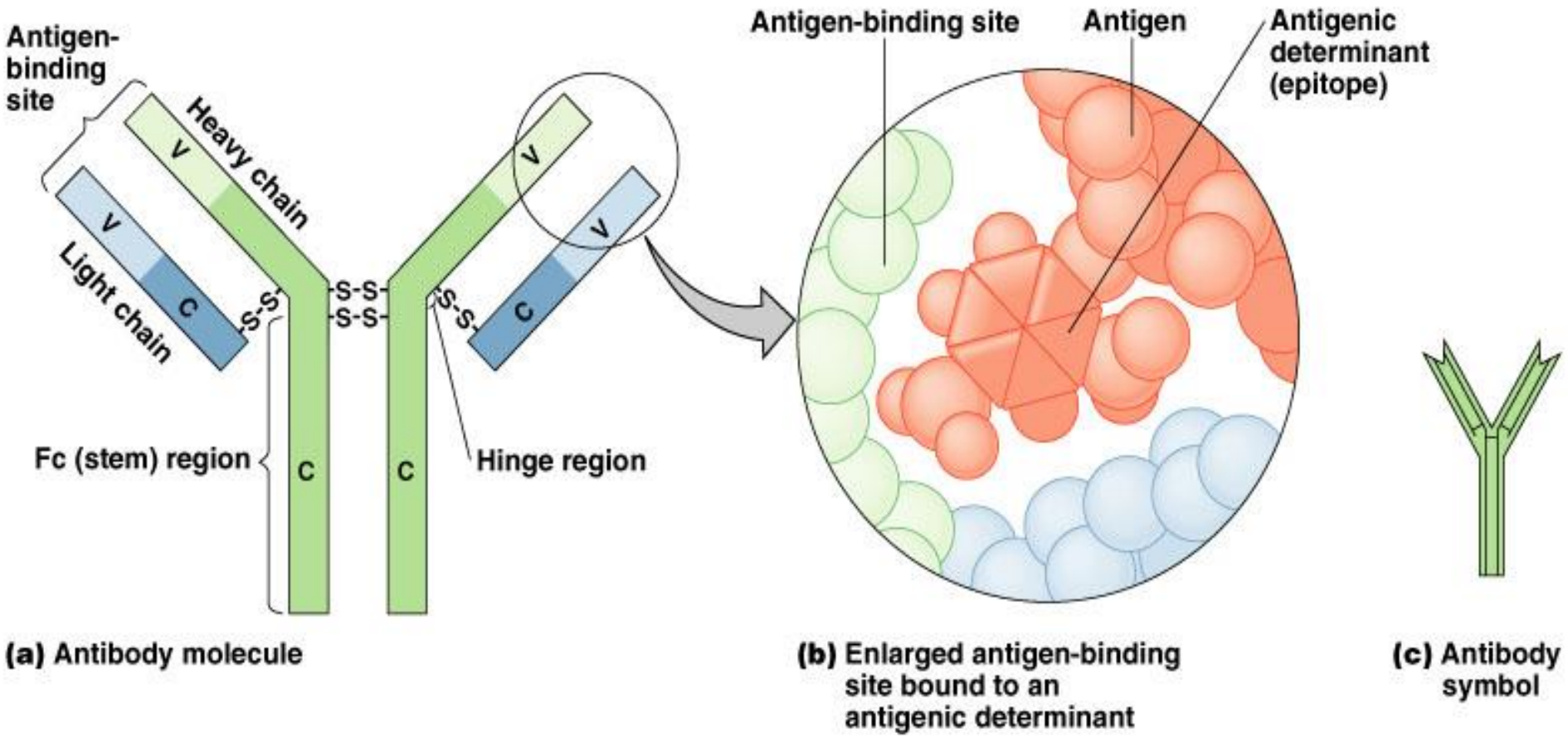
Molecule of IgG

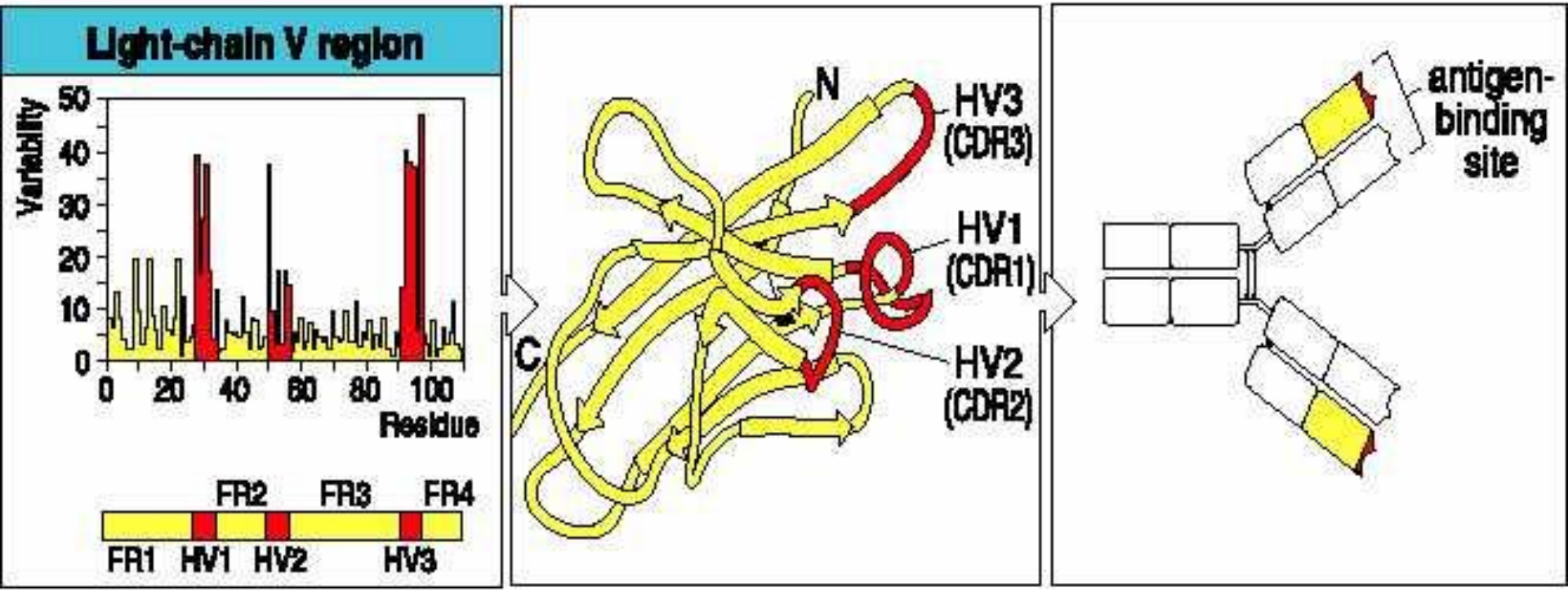


Hypervaribale region of immunoglobulin molecule binds epitope of the antigen

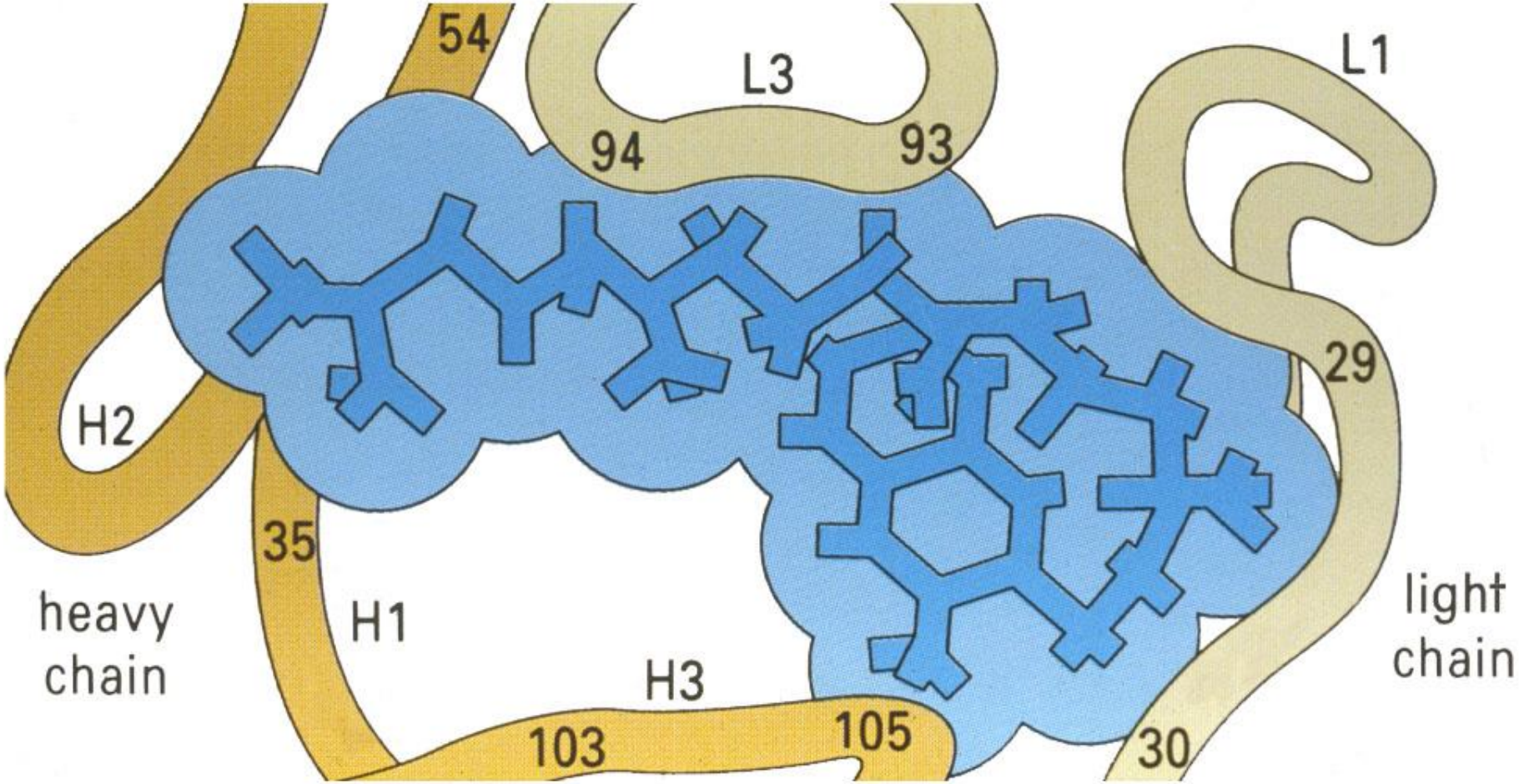


Variable region of immunoglobulin molecule

Figure 2.7



The antibody combining site



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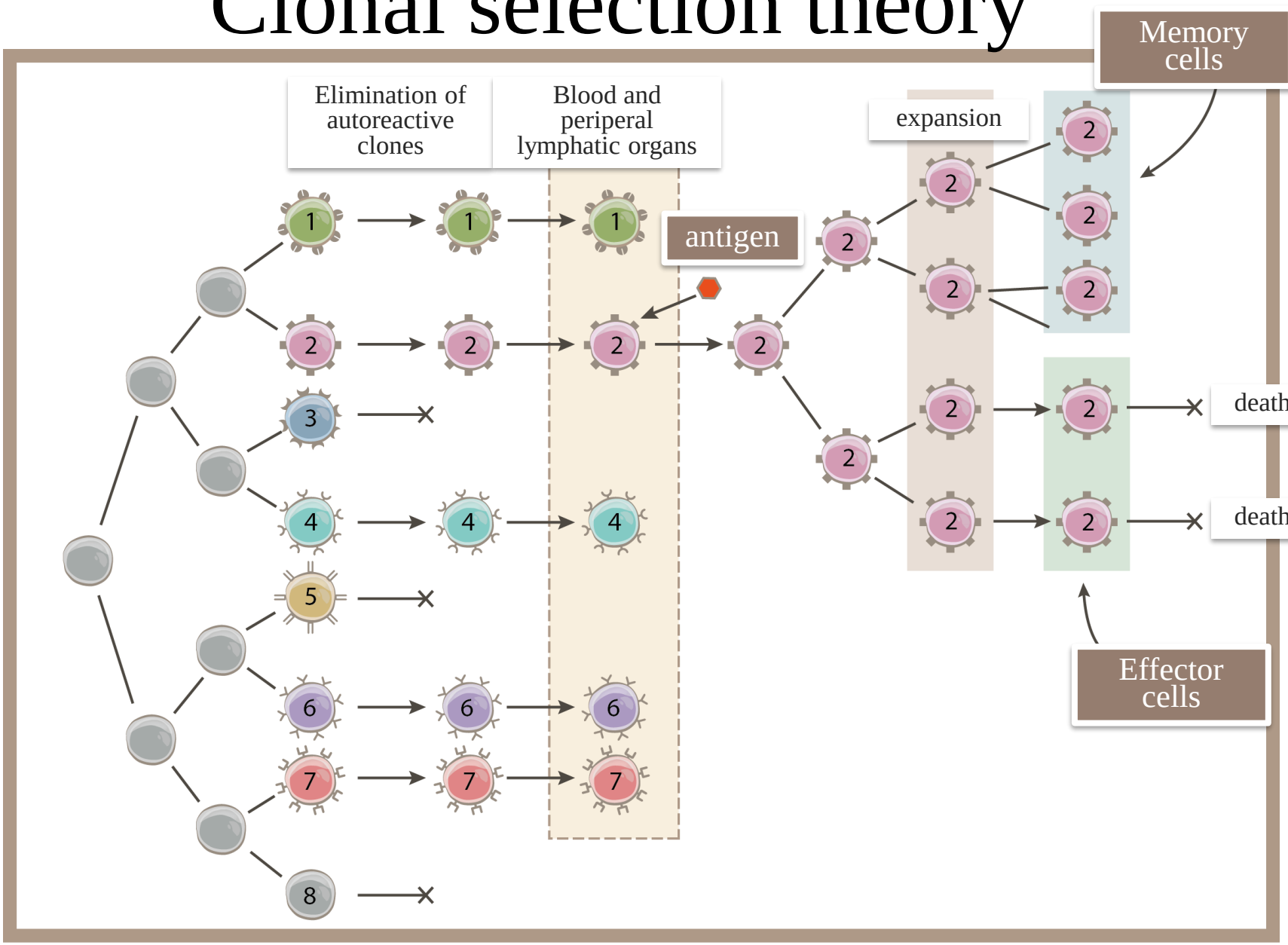
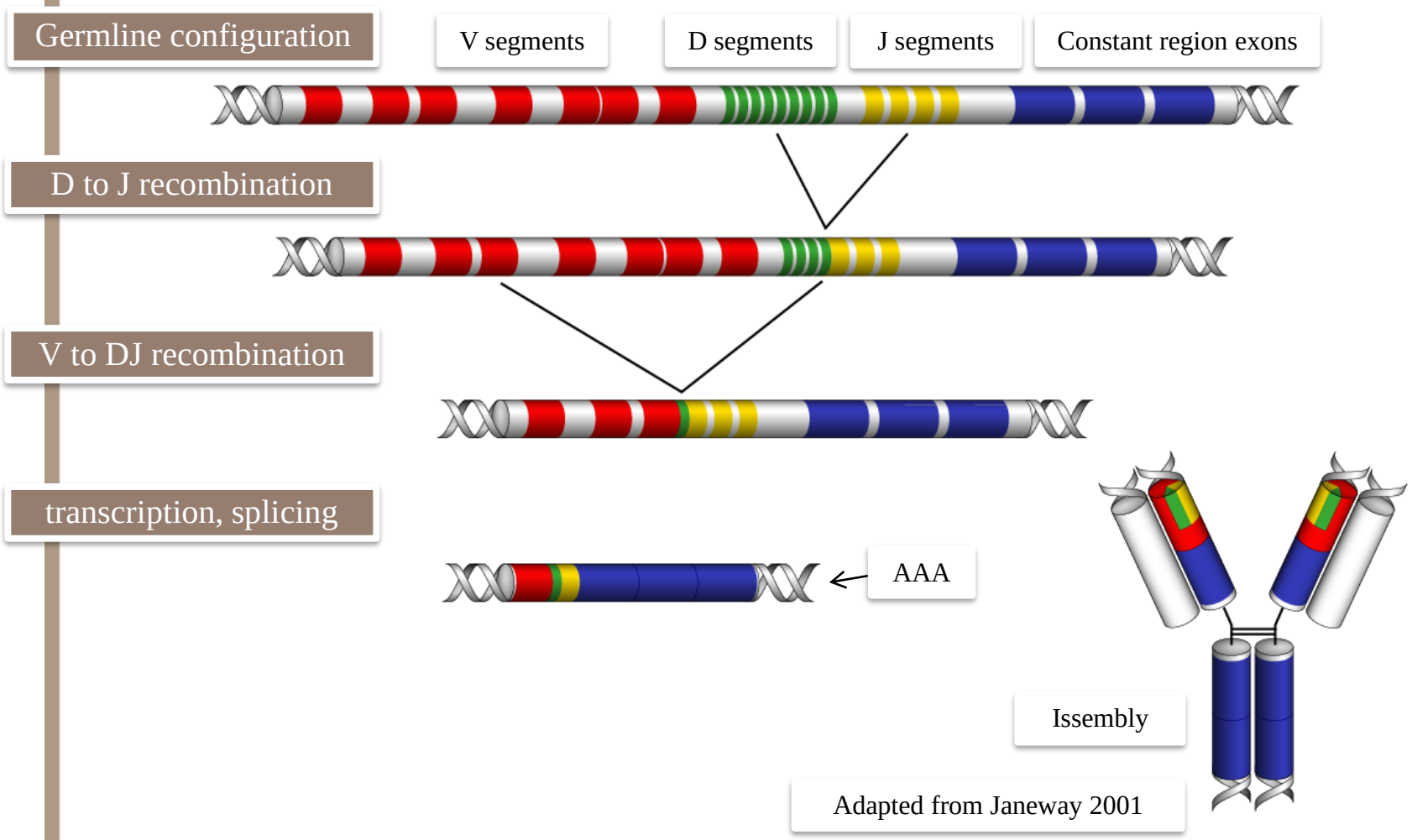
Clonal selection theory
F.M. Burnet, 1957

- During (mainly fetal) development immunocompetent cells of the immune system develop. Each sell is characterized by its own antigen specific receptor. Each cell reacts only with one concrete specific antigen.
- After exposure to autoantigen during fetal life autoreactive clones are eliminated („forbidden clones“).
- If a concrete cell recognizes its specific antigen, it is stimulated, proliferates and forms a clone = clonal selection.
- After repeated divisions the cell becomes a terminally differentiated cell, that does not proliferate and after some time dies.
- The cells of the clone that do not differentiate into the terminal stage become a memory cells which will quickly react after the second exposure to the antigen.

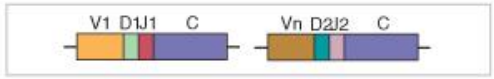
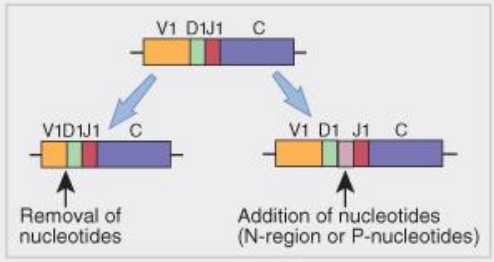
Clonal selection theory



VDJ Recombination



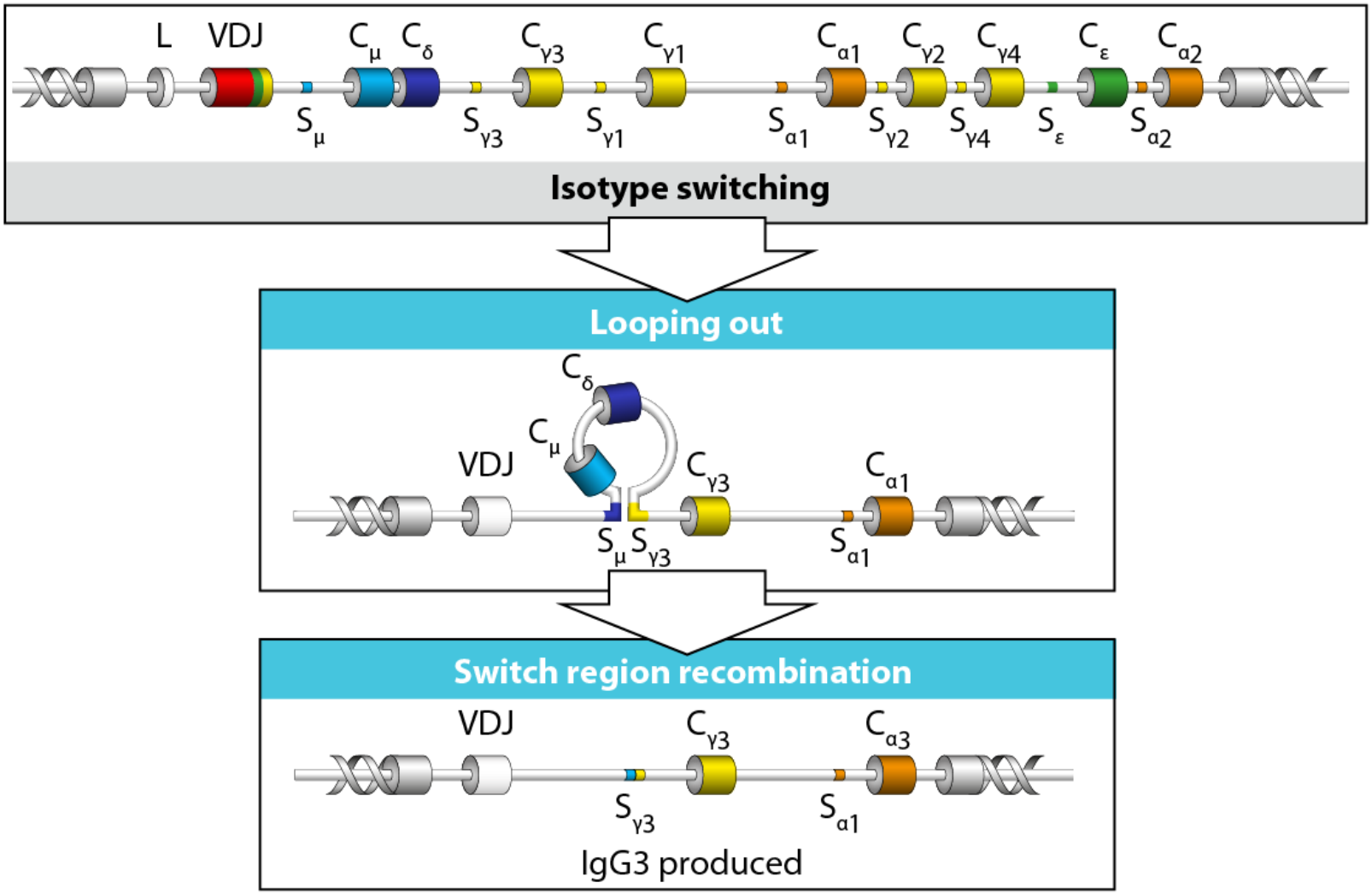
VDJ genes for BCR, and TCR

	Immunoglobulin		T cell receptor	
	Heavy chain	κ	α	β
Number of V gene segments	45	35	45	50
Number of diversity (D) gene segments	23	0	0	2
Number of joining (J) gene segments	6	5	~50	12
Mechanism				
Combinatorial diversity:				
Number of possible V-(D)-J combinations	Ig: ~10^6		TCR: ~3×10^6	
Junctional diversity:				
Total potential repertoire with junctional diversity	Ig: ~10^{11}		TCR: ~10^{16}	

Somatic hypermutations

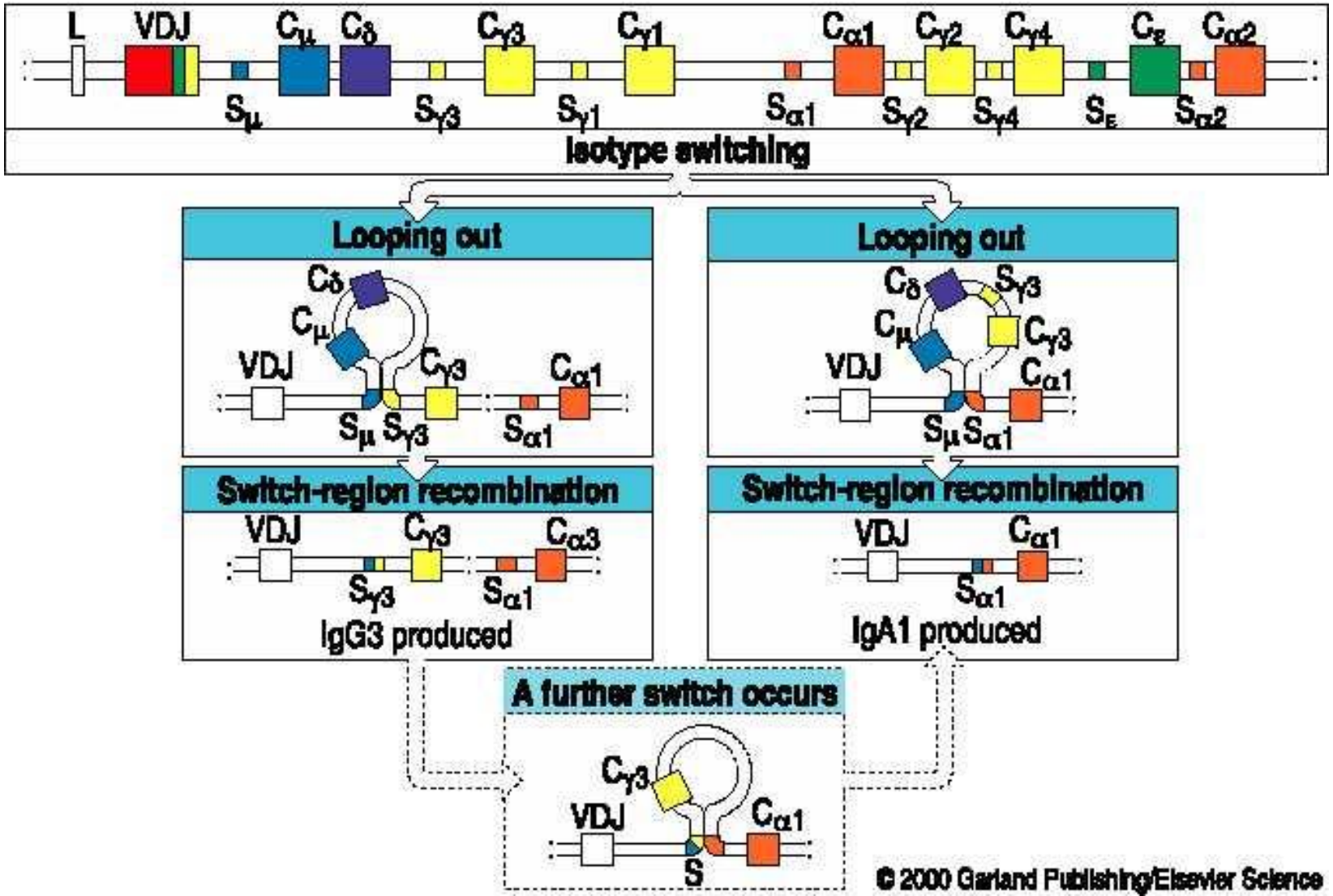
- The process occurs in activated B-lymphocytes, takes place in germinal centers of secondary lymphoid organs.
- Key enzyme is AID (activation-induced deaminase).
- Mutation frequency is approx. 10^6 times higher than in other parts of human genome.
- Antigen presentation by lymphoid dendritic cells to B-cells leads to selection of clones with higher affinity – the process is called affinity maturation.

Isotype switching

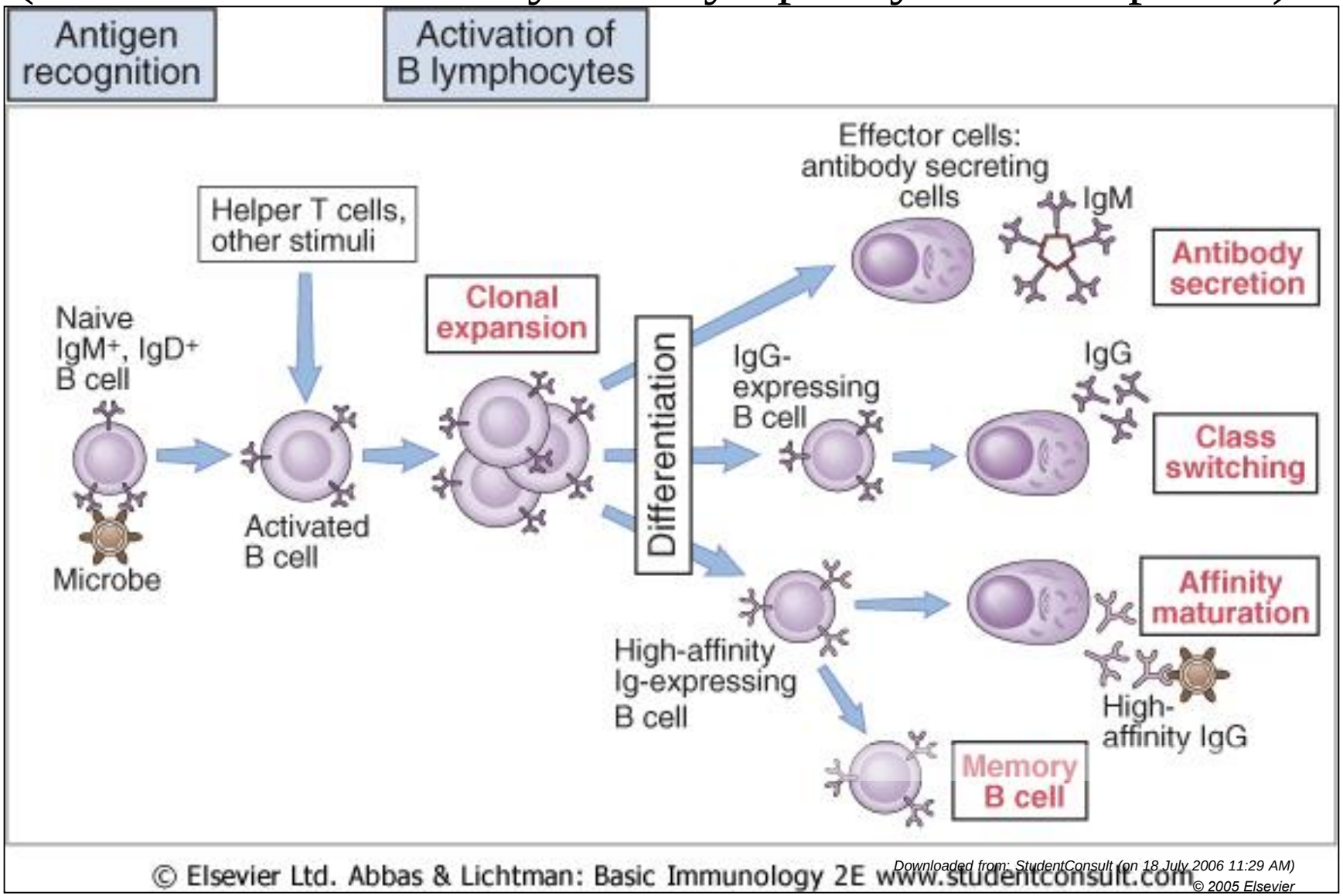


Isotype switching

Figure 2.26



Activation and differentiation of **B**-lymphocytes (clonal selection theory in B-lymphocyte development)



Primary phase of the antibody response

- Naive or opsonised antigen captured by follicular dendritic cells.
- Primary stimulation of B-cells in lymphoid folicles.
- The antigen also stimulates T cells (after adequate presentation) in T-cell zones. T-cells migrate toward the lymphoid folicles.
- Newly formed plasma cells produce mainly IgM(mainly in bone marrow).

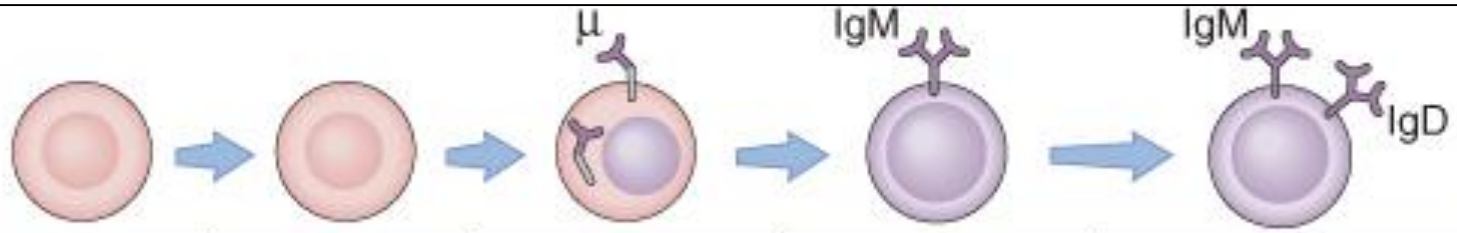
Secondary phase of the antibody response

- Occurs in newly formed germinal centers of lymphoid folicles
- Th lympocytes stimulate B-lymphocytes to somatic hypermutations and isotype switching.
- This leads to selection of B- cells producing high-affinity antibodies (affinity maturation).
- Majority of B-cells producing low-affinty antibodies die.

Development of B-cells in the bone marrow

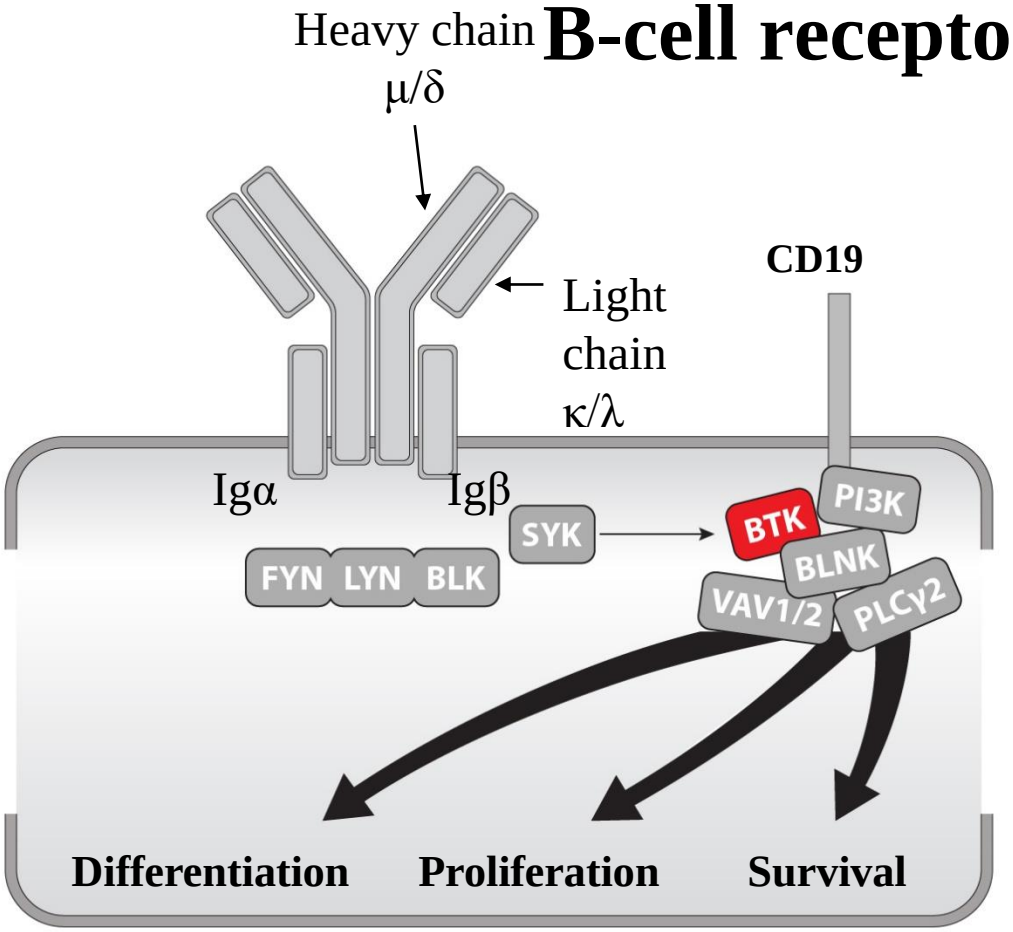
- **Stem cells**: no B-cell surface markers, no rearrangement of Ig genes
- **Pro-B lymphocyte** – rearrangement of heavy chain , expression of several B-cell surface markers (e.g. CD19).
- **Pre-B-lymphocytes** VDJ has of heavy chain has been completed, μ chain can be detected in cytoplasm. Pre-B receptor – composed of μ chain and surrogate chains V-preB and λ5 is expressed on the surface of the cell. Signal transduction though this receptor is essential for B- cell development.
- **Imature B-cell** – light chain rearrangement (V-J) completed B-cell receptor is composed of monomeric IgM
- **Mature B-lymphocyte has** IgM and IgD B-cell receptors

Development of B-cells in the bone marrow

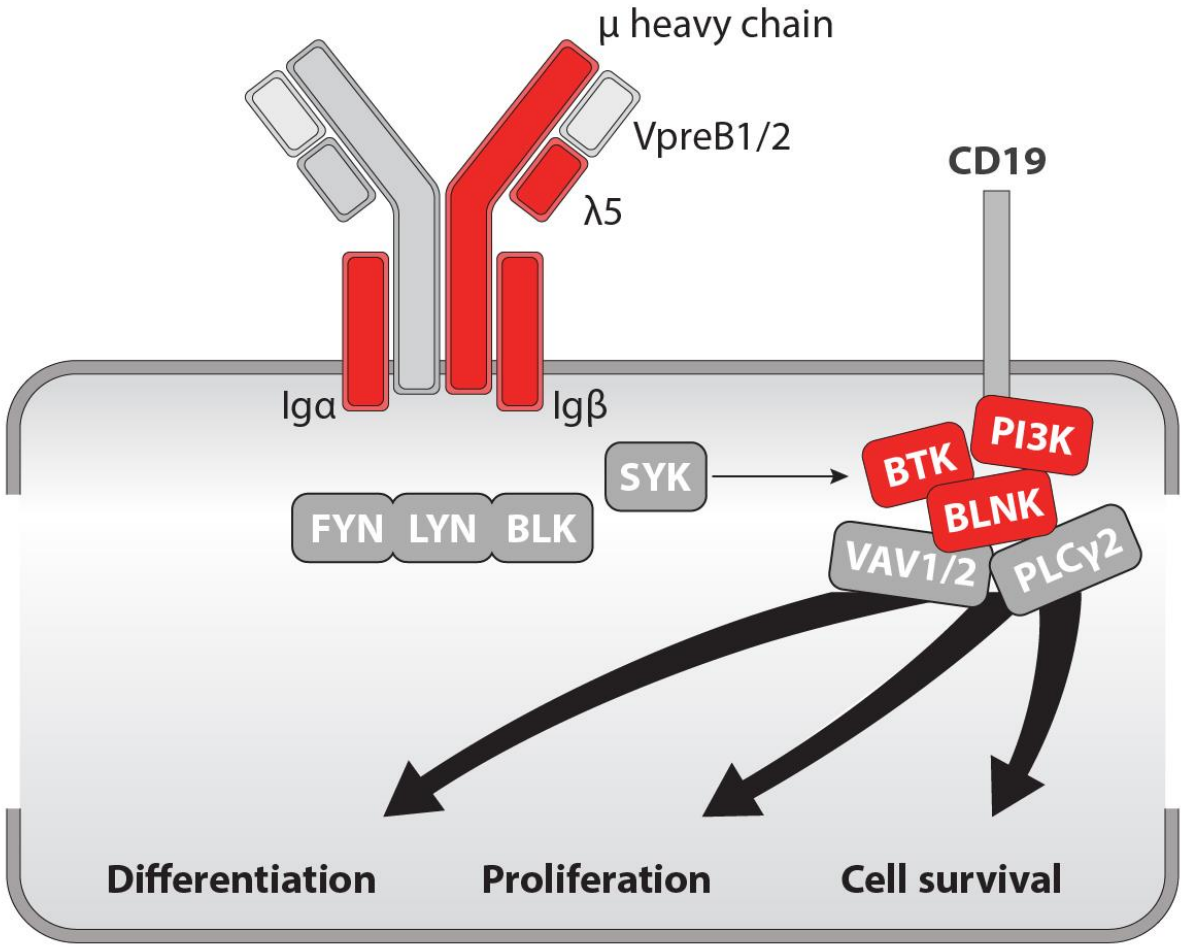


	Stem cell	Pro-B	Pre-B	Immature B	Mature B
Ig DNA, RNA	Germline DNA	Germline DNA	Recombined H chain gene (VDJ); μ mRNA	Recombined H chain gene, κ or λ genes; μ and κ or λ mRNA	Alternative splicing of primary transcript to form C_μ and C_δ mRNA
Ig expression	None	None	Cytoplasmic μ and pre-B receptor-associated μ	Membrane IgM (μ+κ or λ light chain)	Membrane IgM and IgD

B-cell receptor



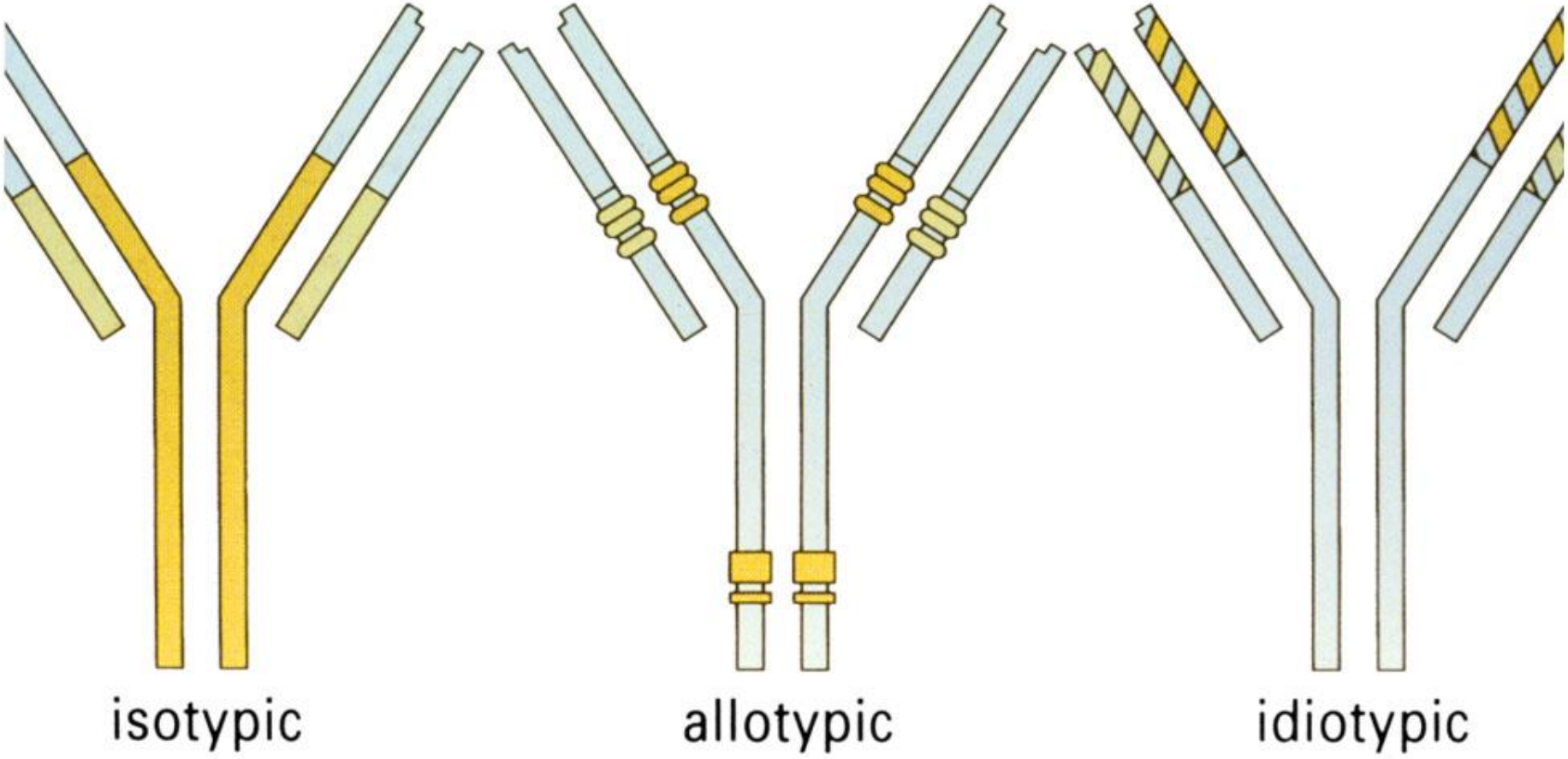
Pre B-cell receptor



Bruton´s tyrosine kinase (BTK)

- BTK binds fosfatidylinoisitoltriphosphate (3,4,5)-(PIP3).
- Activates phospholipase C, leading to hydrolysis of phapsphatidylinositol (PIP_2) into inositoltriphophate (IP3) and diacyglycerol(DAG).
- This is key process in activation, differentian and development of B-cells.
- Mutations of BTK lead to X-linked (Bruton´s) agammaglobulinemia.
- BTK blockers (e.g. ibrutimib) are used for the treatment of B- cell malignancies.

Antibody variants



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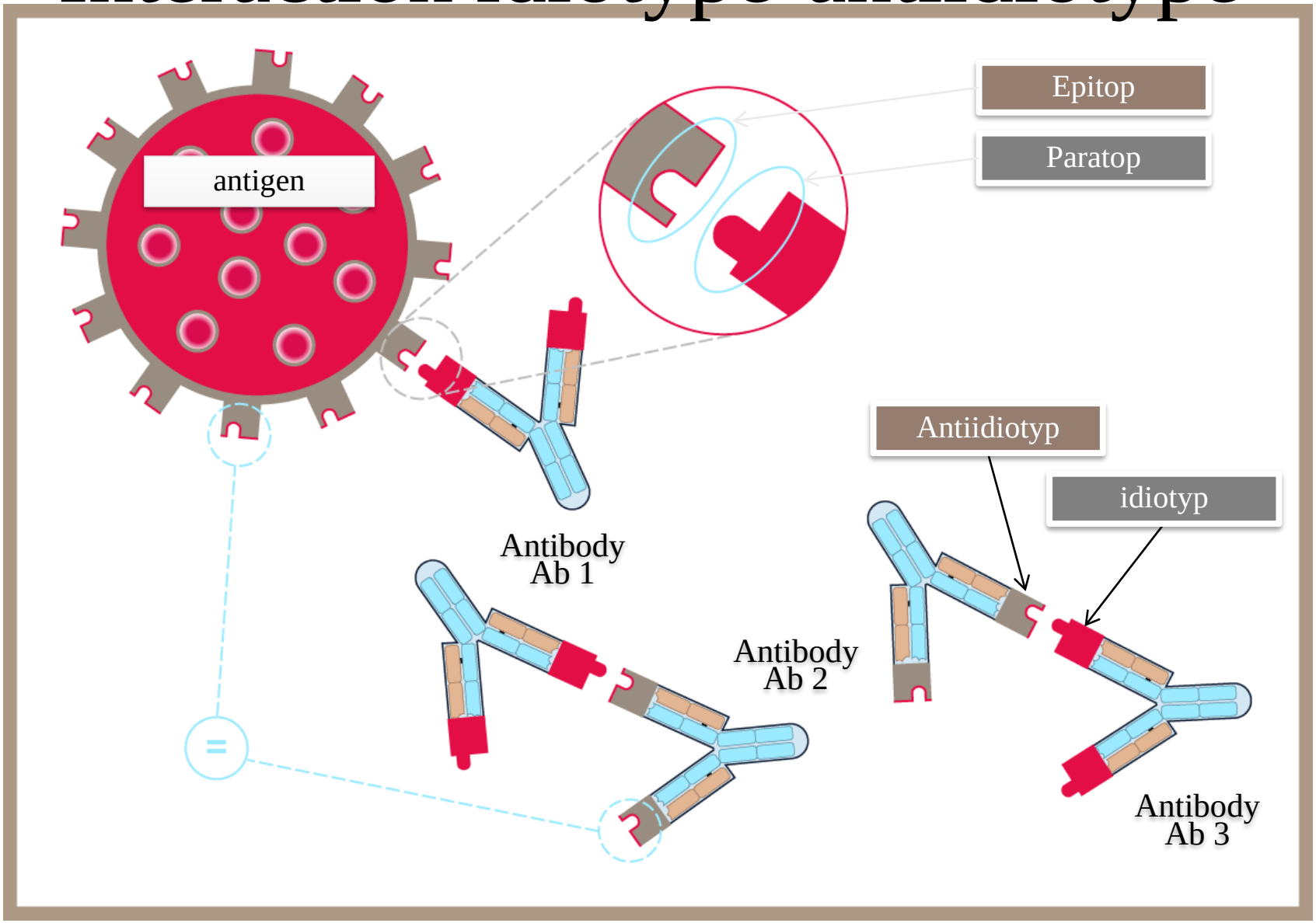
Isotype

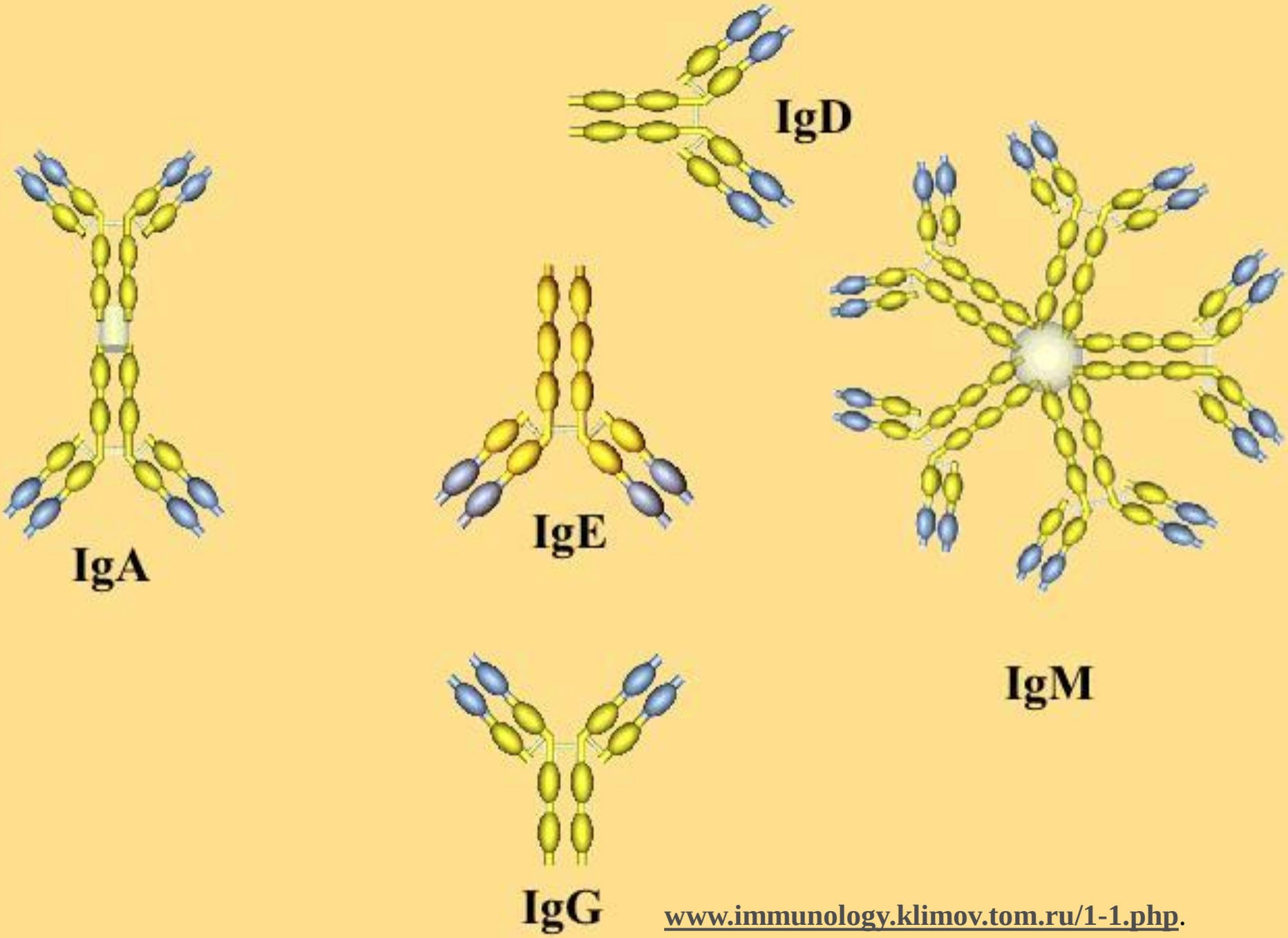
- The class or subclass of an immunoglobulin.
- Antigenic determinats are on constant part of immunoglobulin molecule.

Idiotype

- An antigenic determinant on the variable region of a specific antibody.

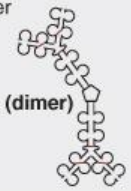
Interaction idiotype-antiidiotype



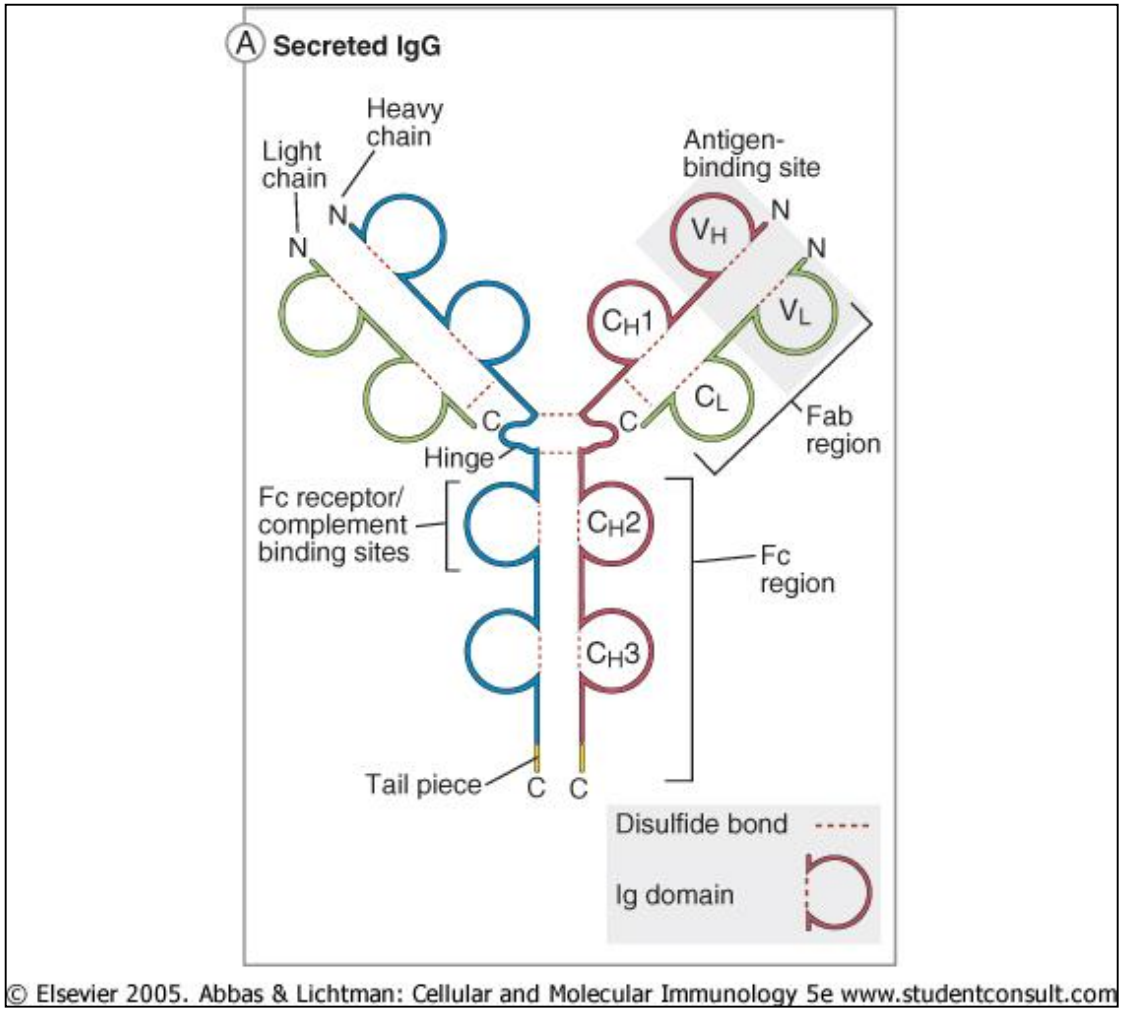


www.immunology.klimov.tom.ru/1-1.php.

Characteristics of immunoglobulin classes

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

IgG


A Secreted IgG
Heavy chain
Light chain
N
N
Antigen-binding site
V_H
N
N
V_L
C_H1
C_L
C
C
Hinge
Fab region
Fc receptor/ complement binding sites
C_H2
Fc region
C_H3
Tail piece
C C
Disulfide bond
Ig domain
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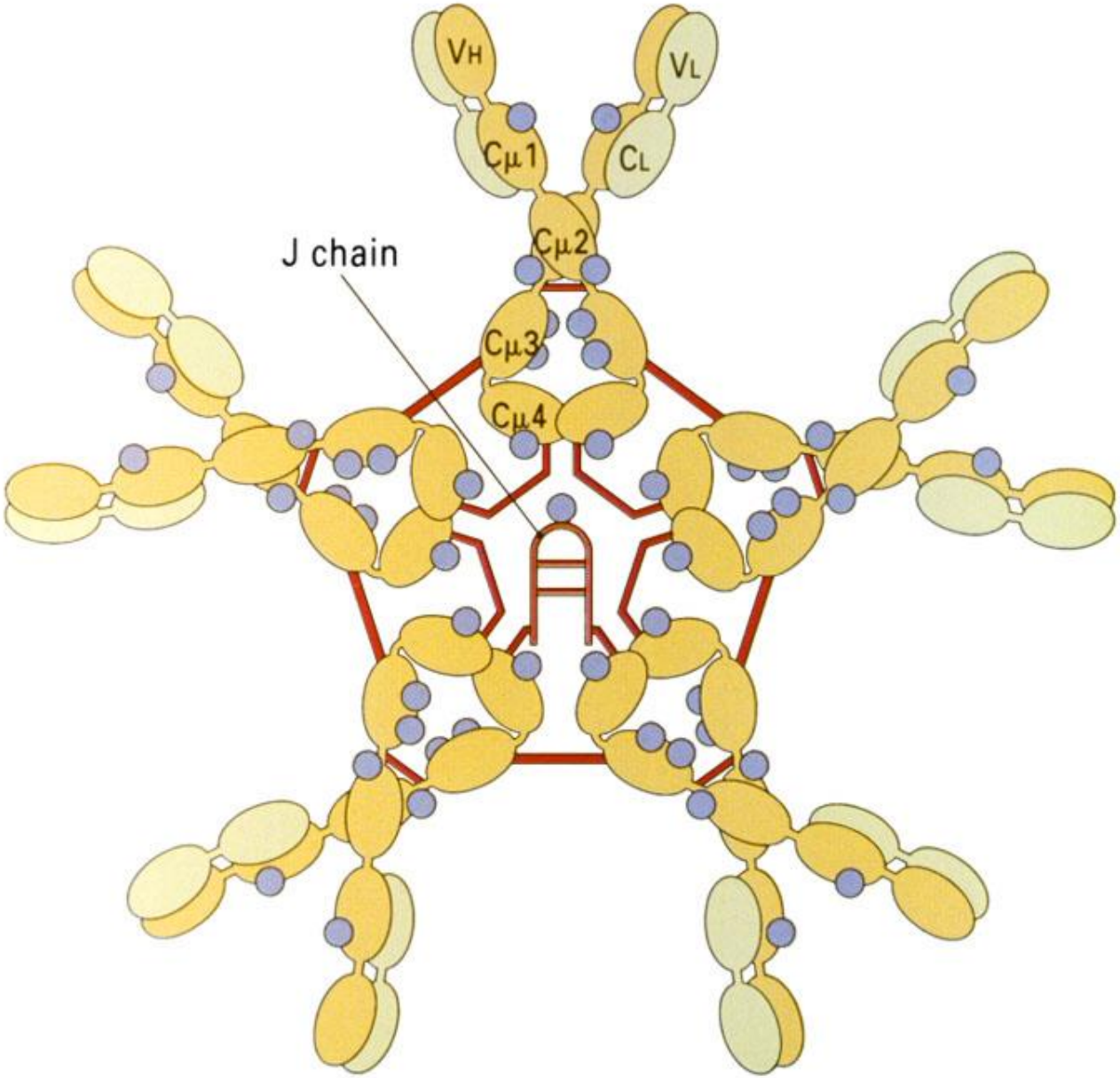
Structure of human IgM



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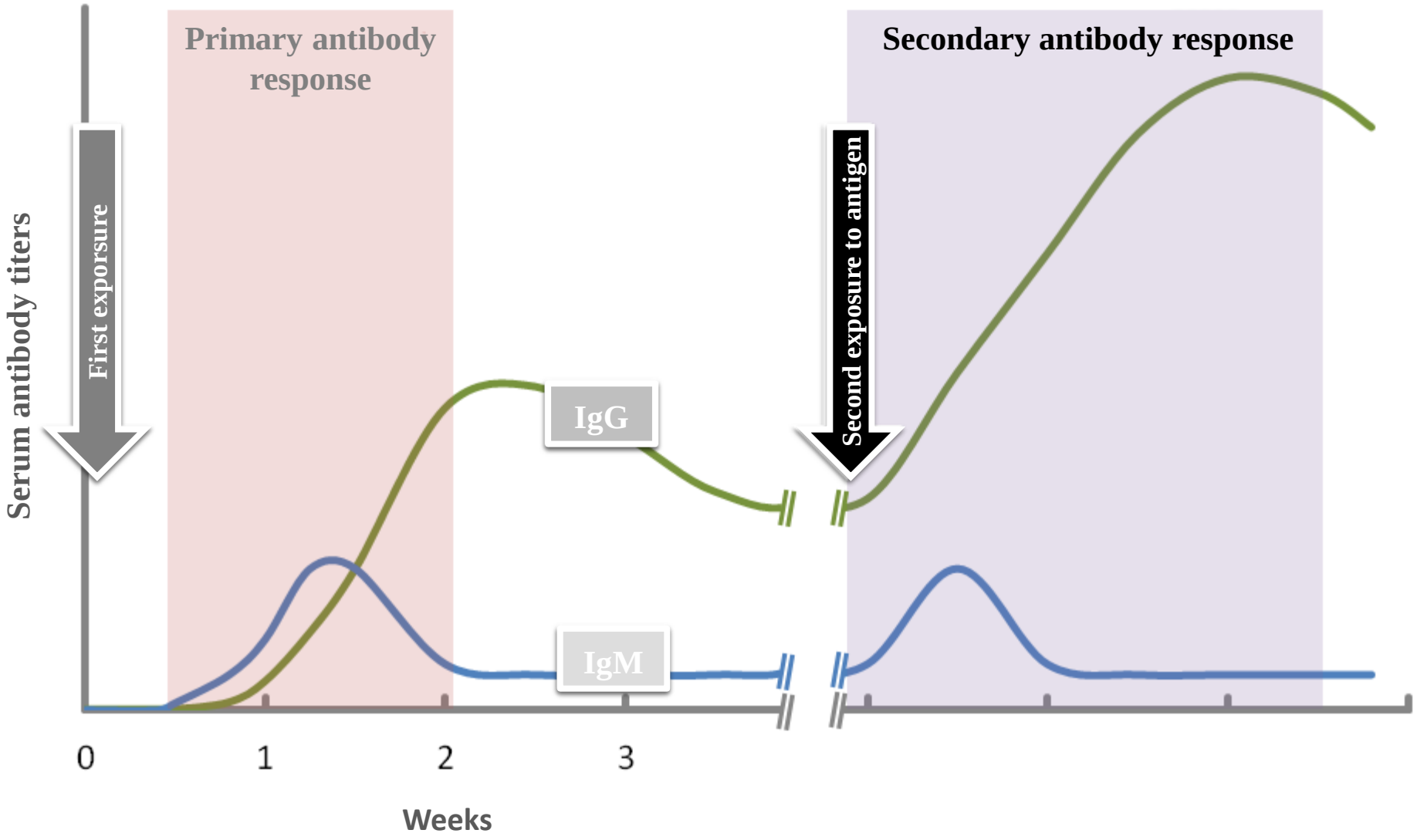
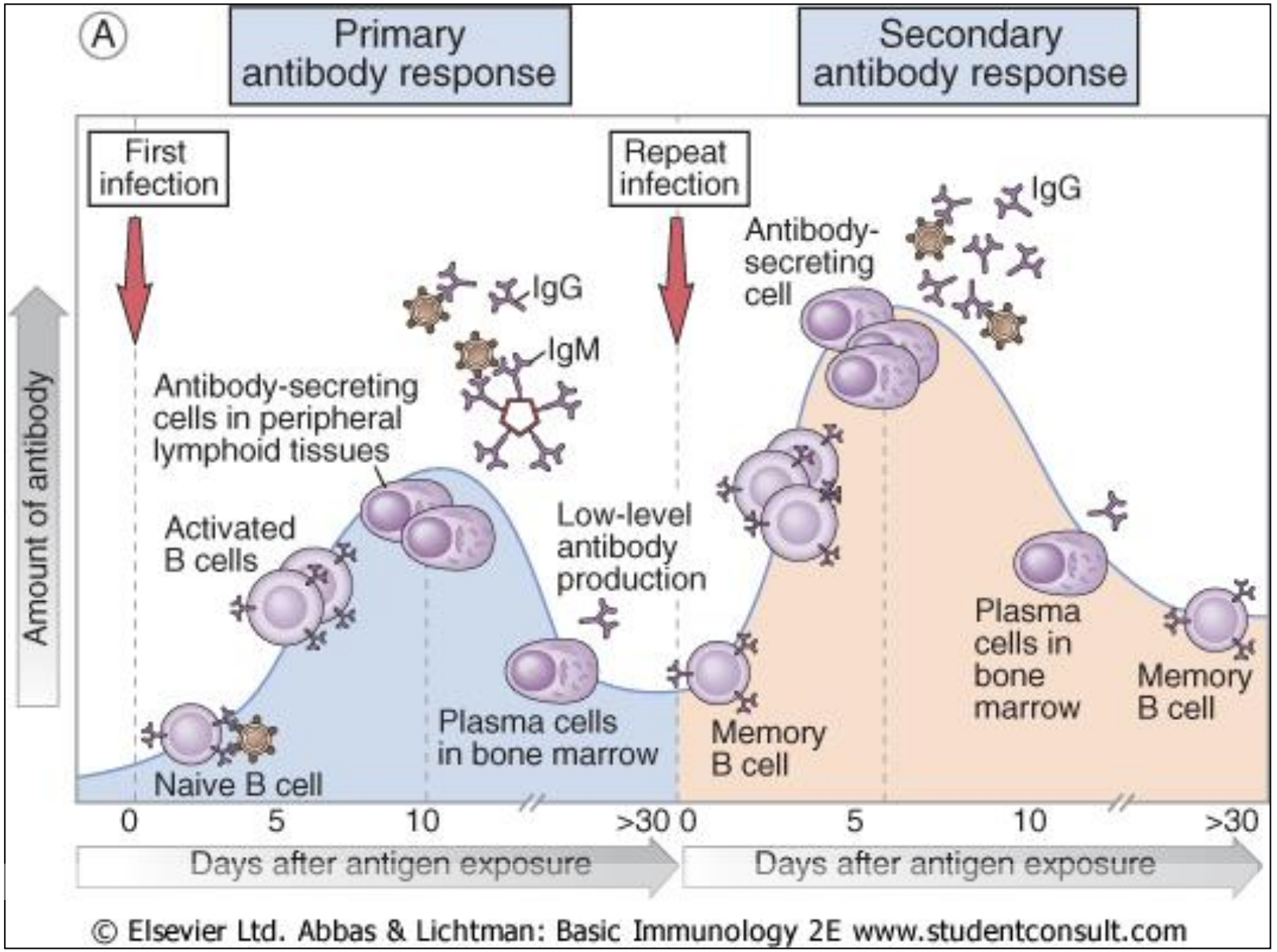
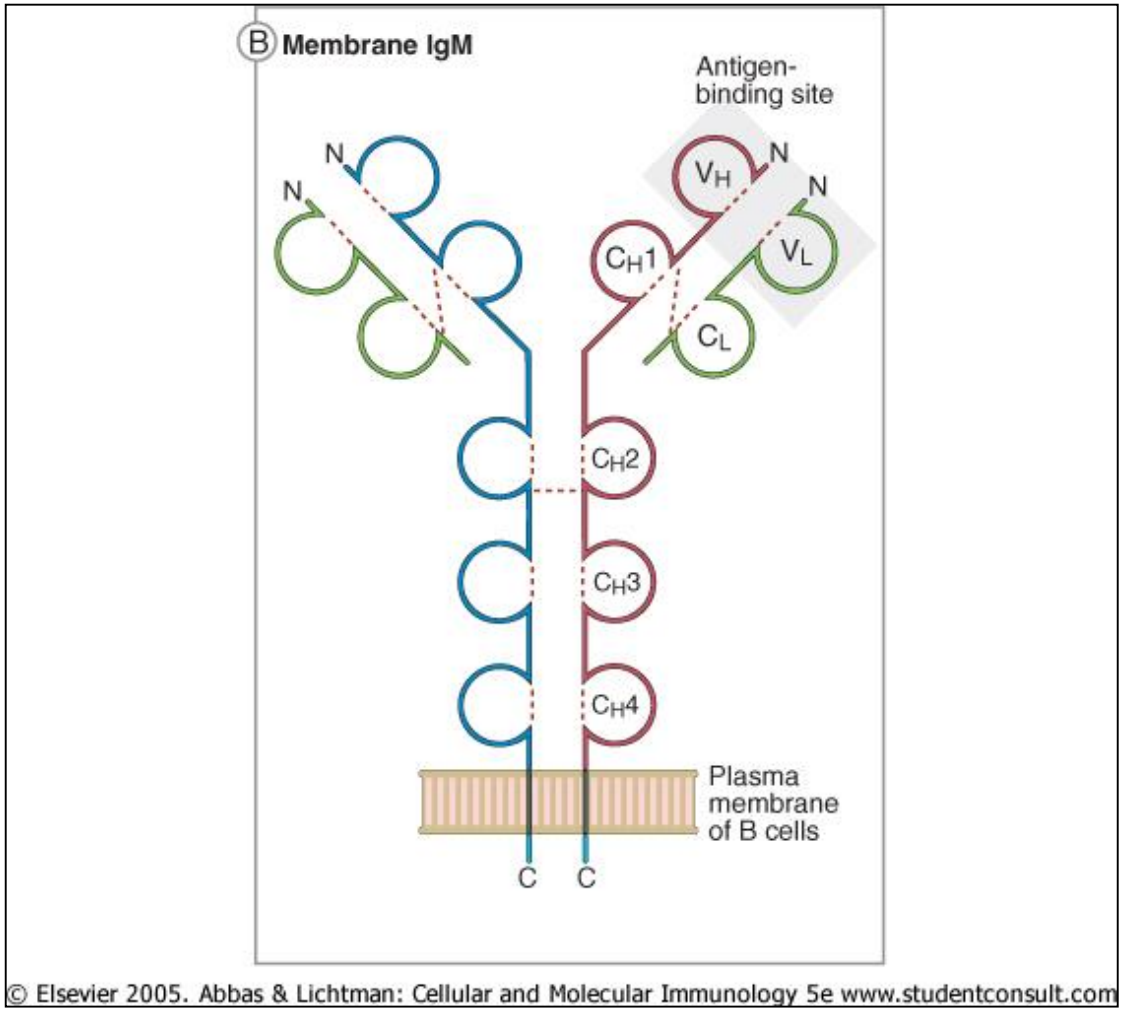
Antibody response after primary and secondary antigen exposure

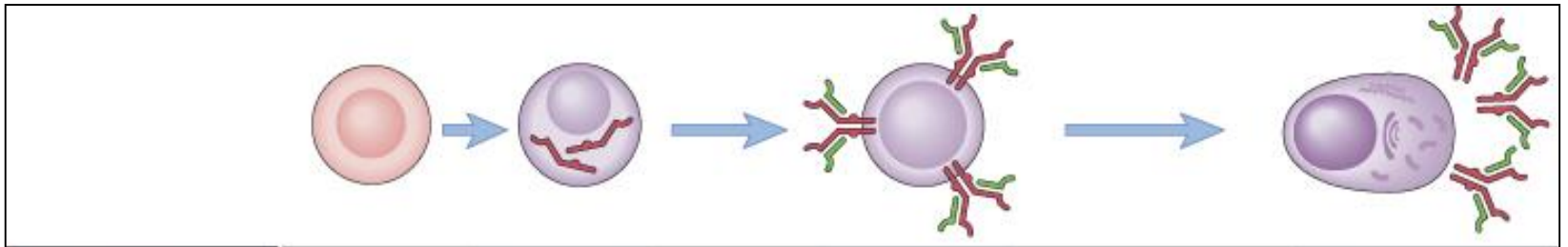




IgM on B-cell membrane

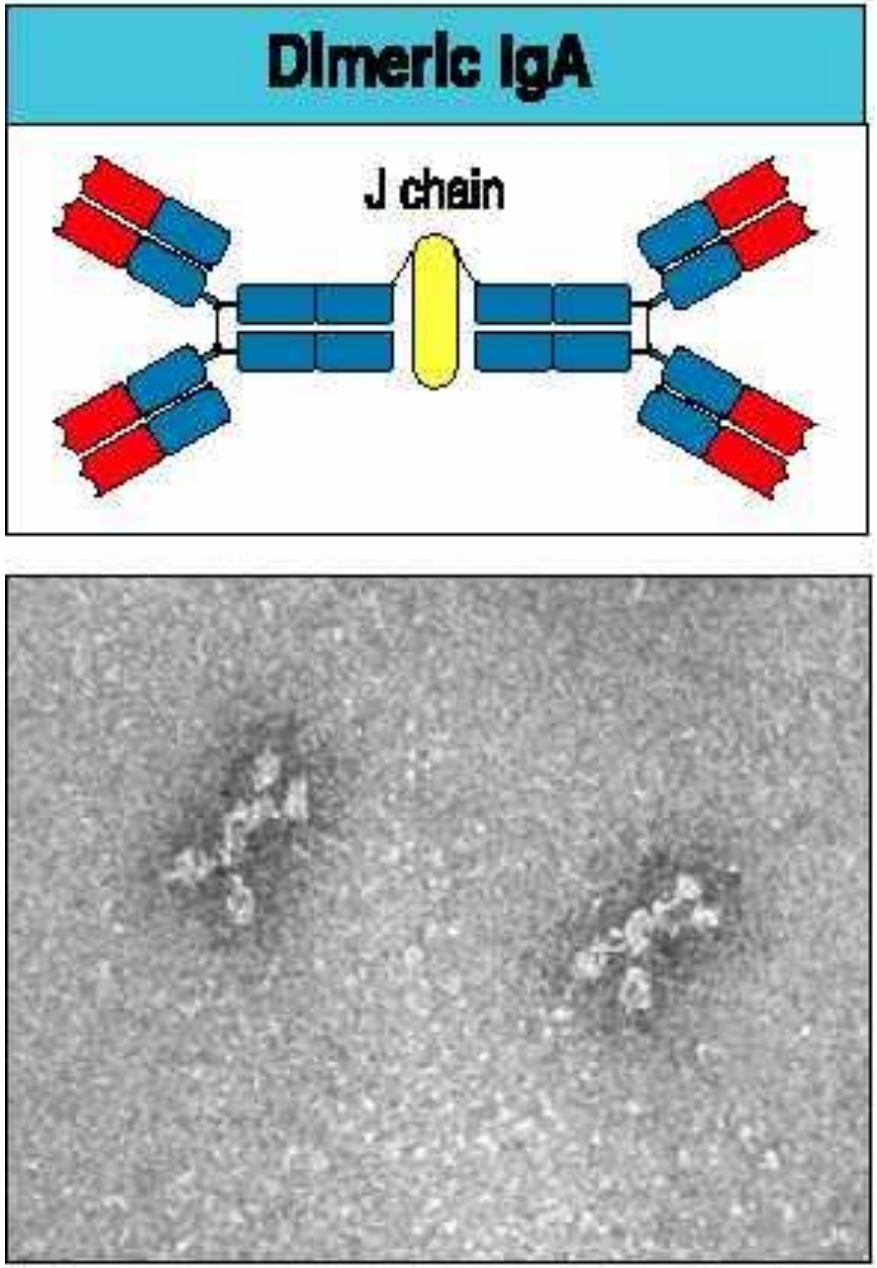


Expression of surface immunoglobulins on B-cells

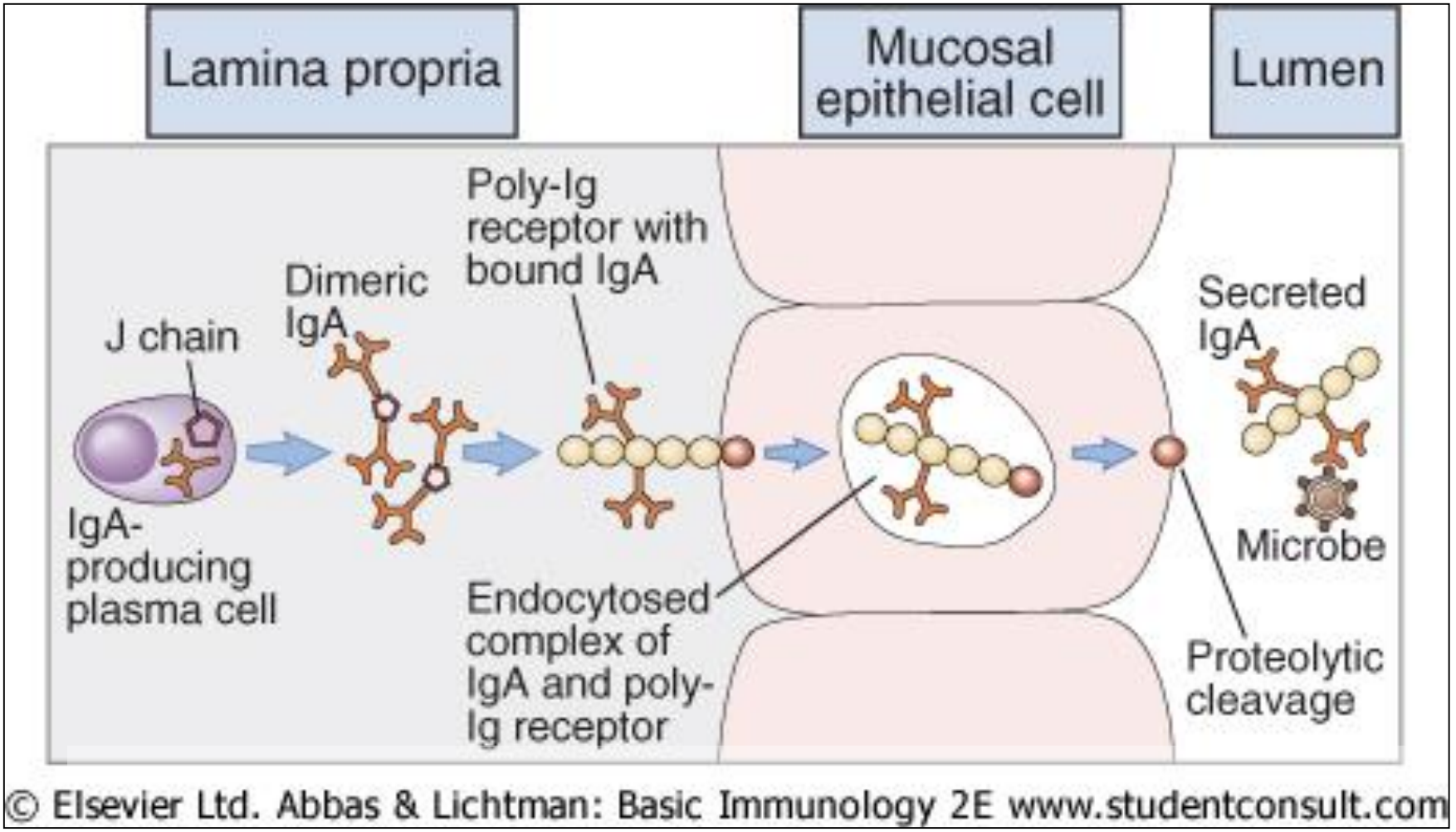


Stage of maturation	Stem cell	Pre-B cell	Immature B cell	Mature B cell	Activated B cell	Antibody-secreting cell
Pattern of immunoglobulin production	None	Cytoplasmic μ heavy chain	Membrane IgM	Membrane IgM, IgD	Low-rate Ig secretion; heavy chain isotype switching; affinity maturation	High-rate Ig secretion; reduced membrane Ig

Figure 2.29

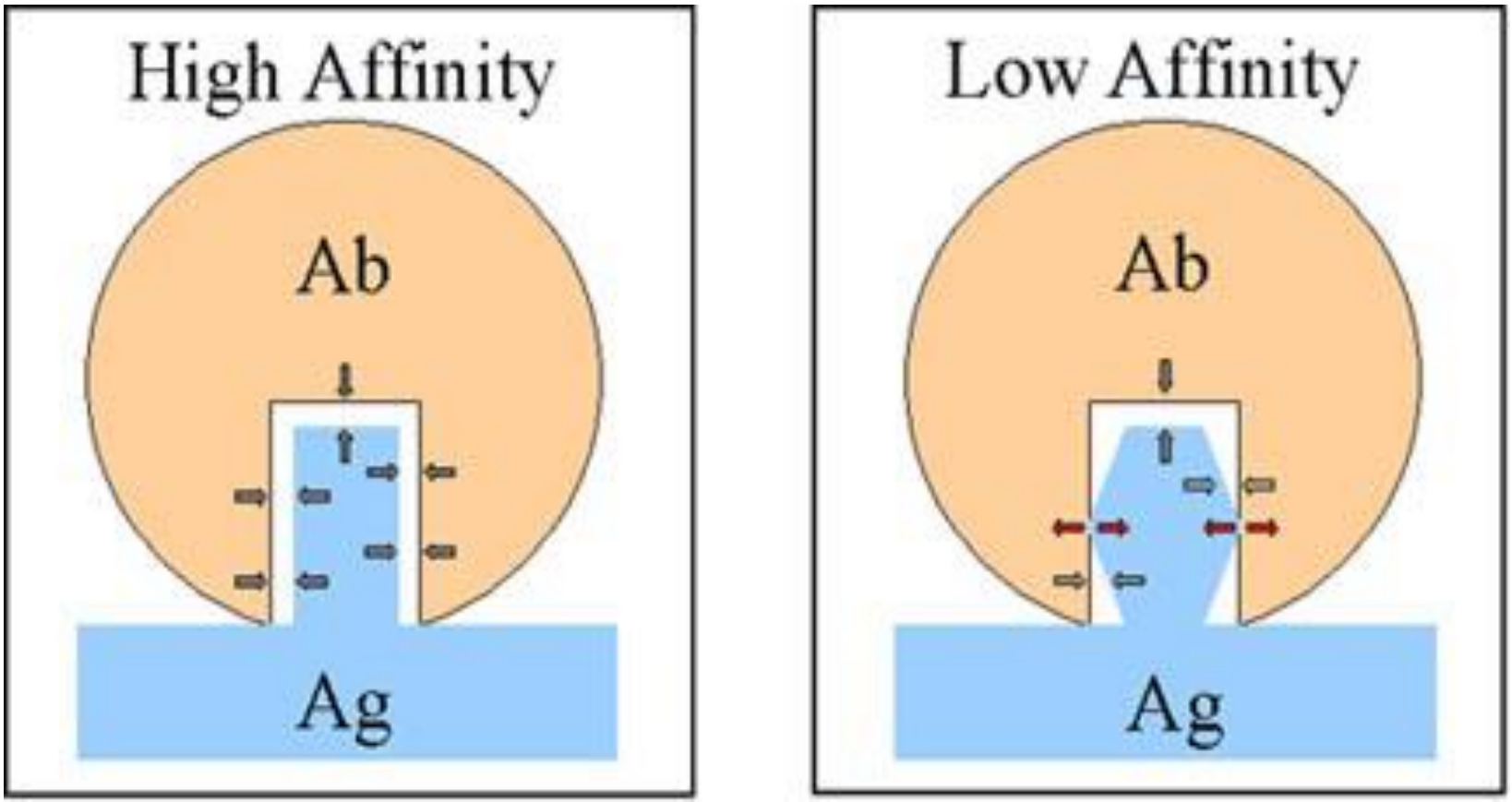


Formation of Secretory IgA



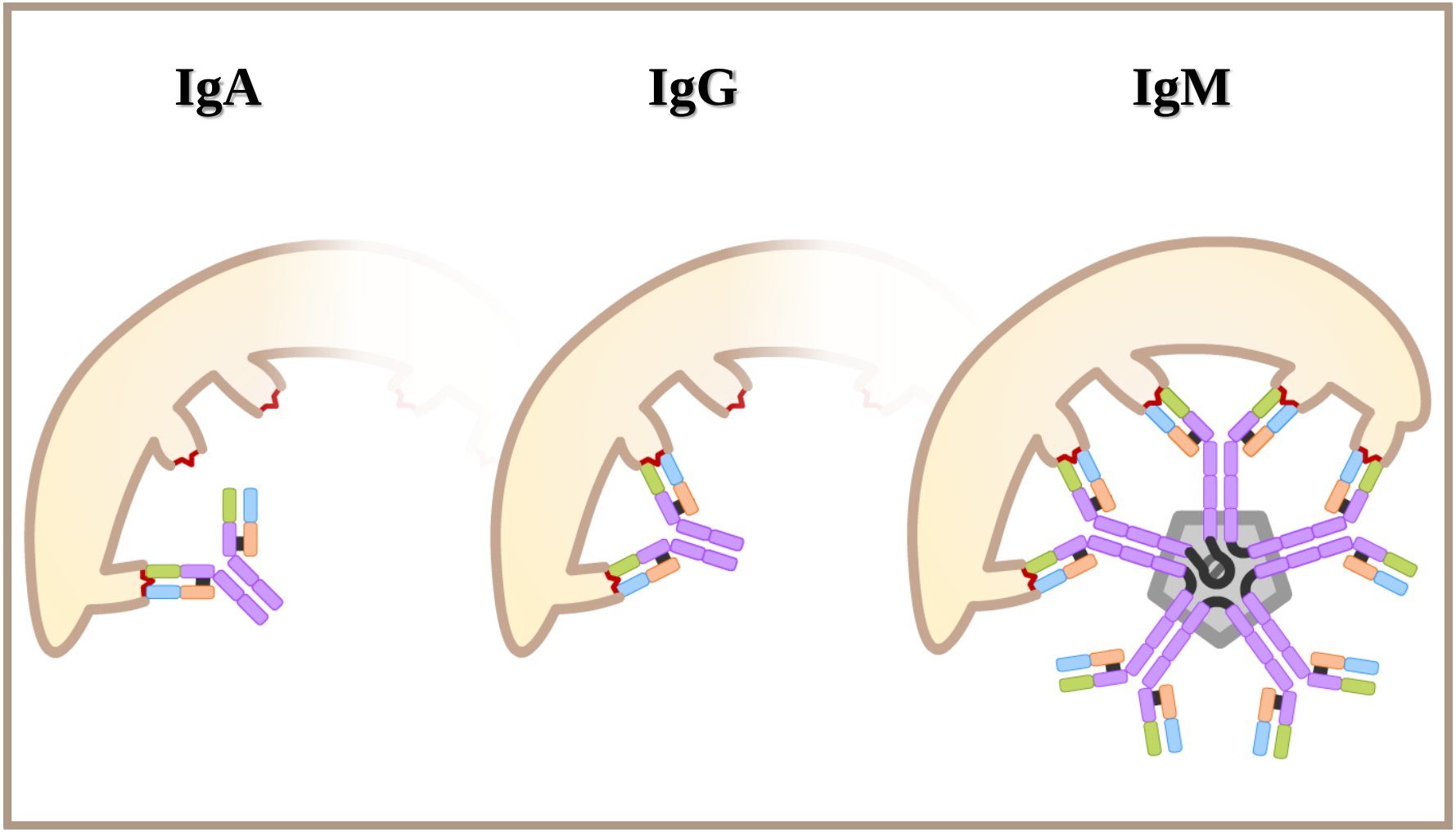
- **Affinity:** The strength of the binding between a single site of an antibody (one variable region) and an epitope.
- **Avidity:** The overall strength of interaction between and antibody and antigen. The avidity depends on affinity and the valency of interactions.

Antibody affinity



http://pathmicro.med.sc.edu/mayer/rx-2.jpg

Affinity and avidity



Biological functions of immunoglobulin molecules

- Activation of complement system (IgG, IgM)
- Opsonization (particularly IgG)
- Neutralization of antigens (IgG, IgA, IgM)
- Adherence interference (IgA, IgG)
- Antibody dependent cellular cytotoxicity (ADCC)
- Agglutation, precipitation (IgG, IgM)
- Mast cells degranulation (IgE)
- Transport through placenta (IgG)
- Imunoregulation (mainly IgG)

Ⓑ Antibody isotype	Isotype specific effector functions
IgG	Neutralization of microbes and toxins Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cellular cytotoxicity mediated by NK cells Neonatal immunity: transfer of maternal antibody across placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement
IgA	Mucosal immunity: secretion of IgA into lumens of gastrointestinal and respiratory tracts, neutralization of microbes and toxins
IgE	Antibody-dependent cellular cytotoxicity mediated by eosinophils Mast cell degranulation (immediate hypersensitivity reactions)

Antibody dependent cellular cytotoxicity (ADCC)