เอกสารประกอบการสอนวิชา Infection and Immunity (01419461)

เรื่อง immunoglobulin genes

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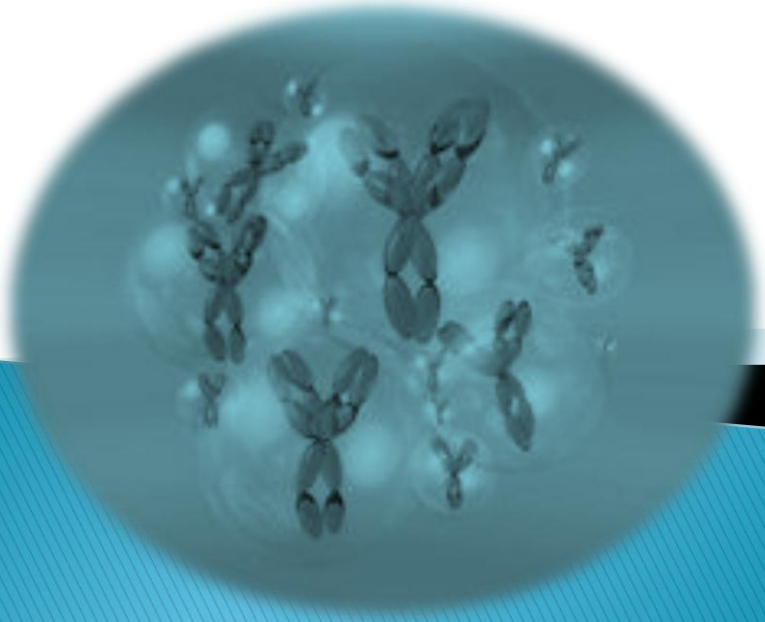
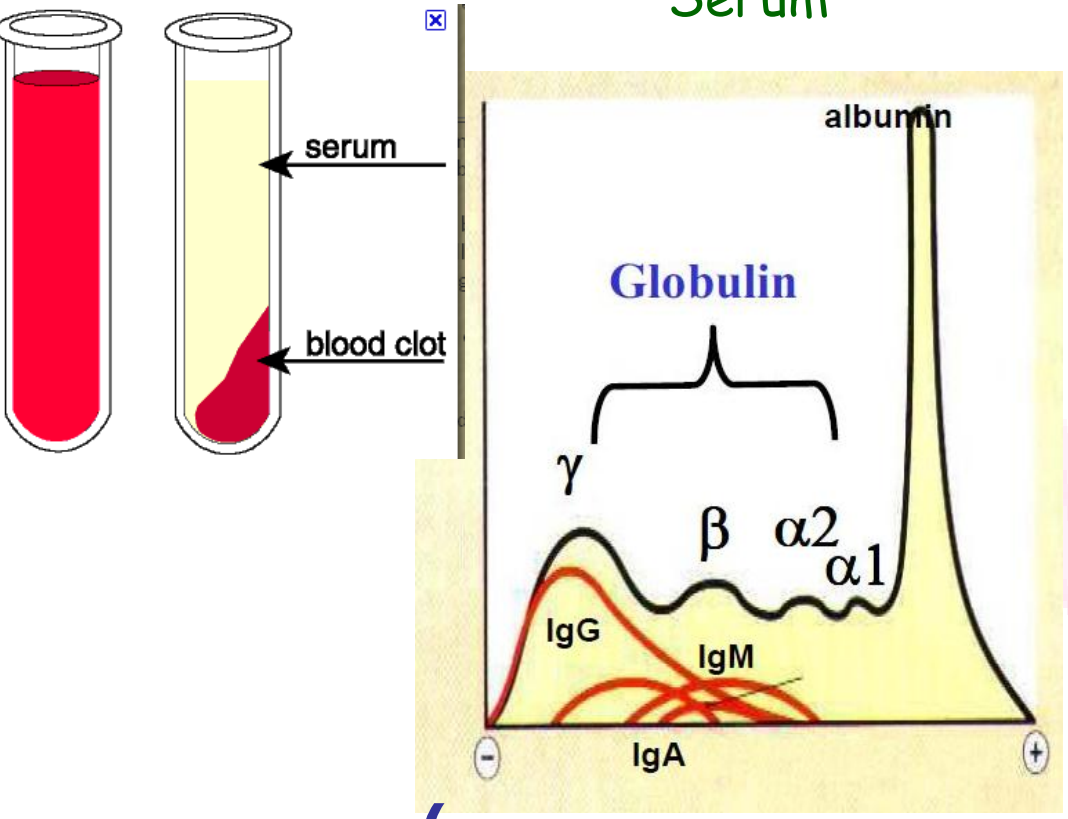
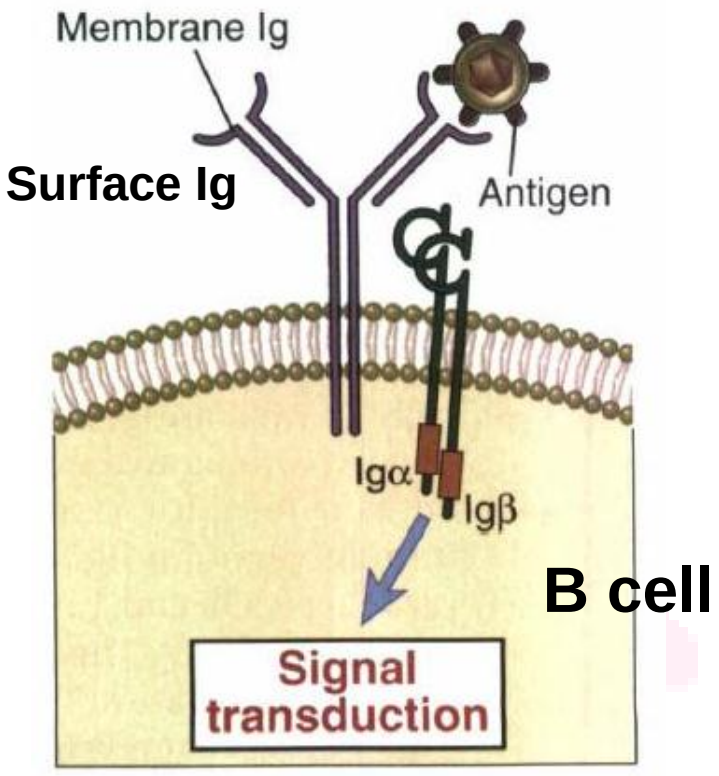


What are Immunoglobulins (Ig) ?

- They are glycoproteins that are found in blood or other bodily fluids.
- There are 2 forms of Ig: secreted and membrane-bound forms.

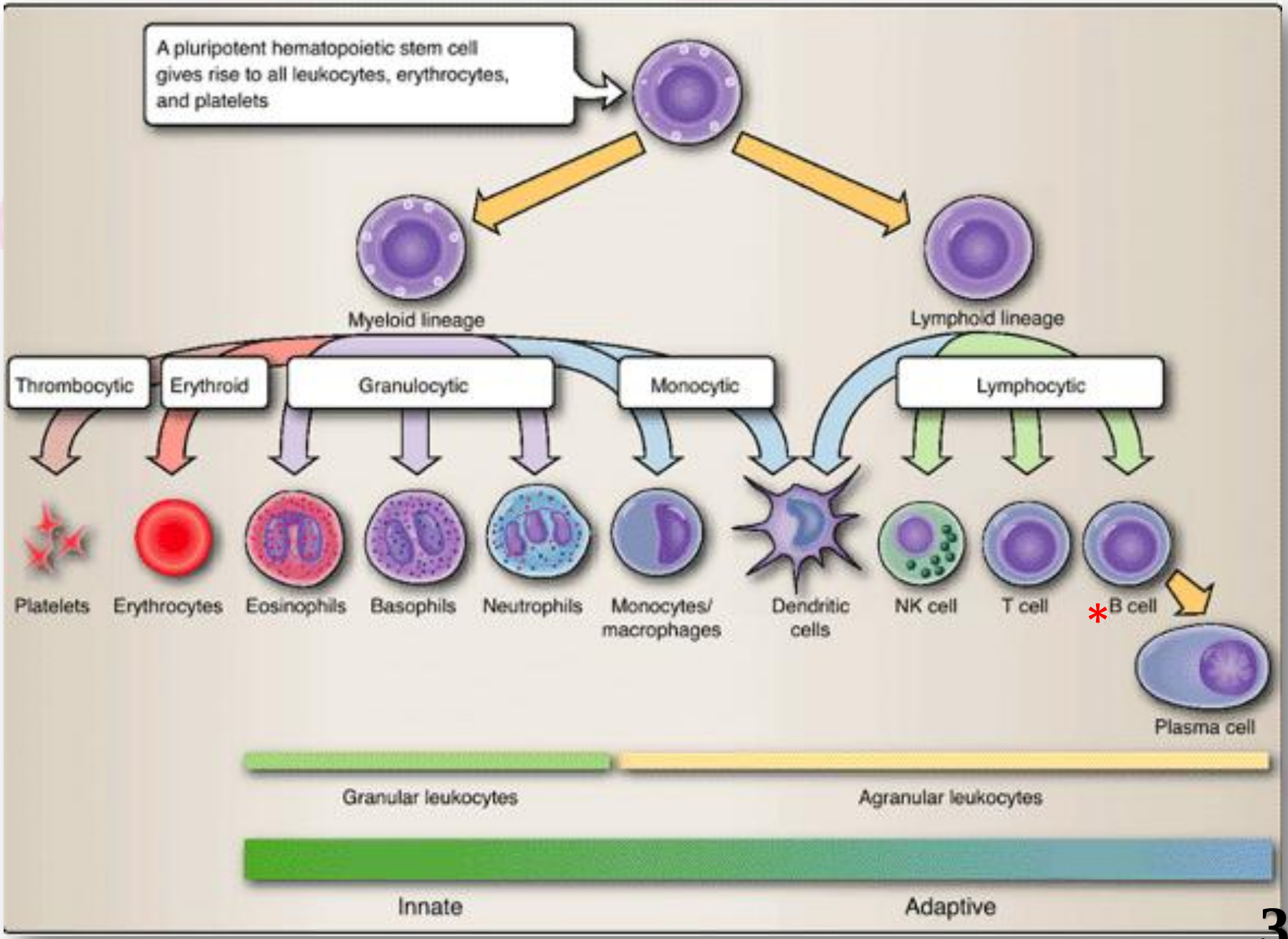


(A. Tiselius and E. A.Kabat, in 1939)



(Abbus AK; 6th ed, p138)

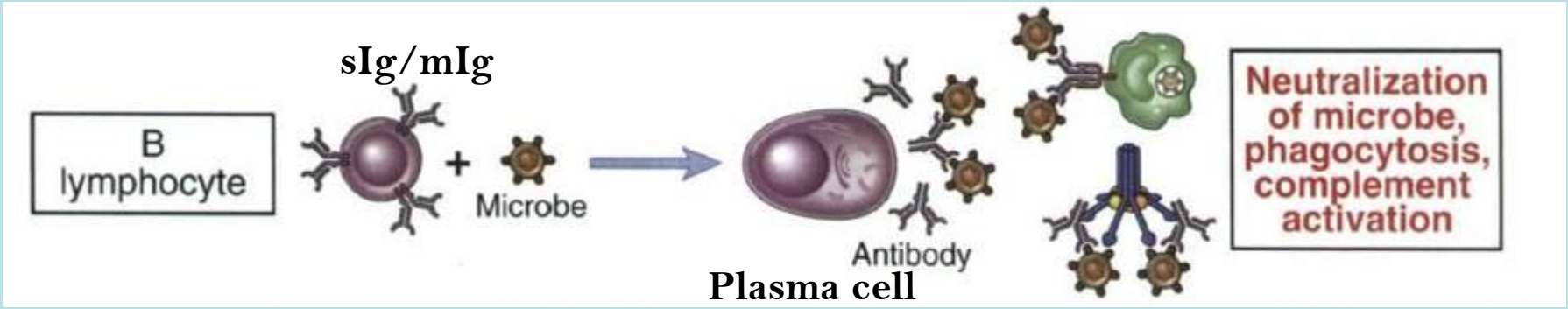
⇨ Ig are synthesized by B lymphocytes



What are Immunoglobulins (Ig) ?

- Ig are synthesized by B lymphocytes.
- Its functions are …

1. Surface/membrane Ig 2. Secreted Ig



(Abbus AK et al., Cellular and Molecular Immunology 6th Edition;2007;p12)

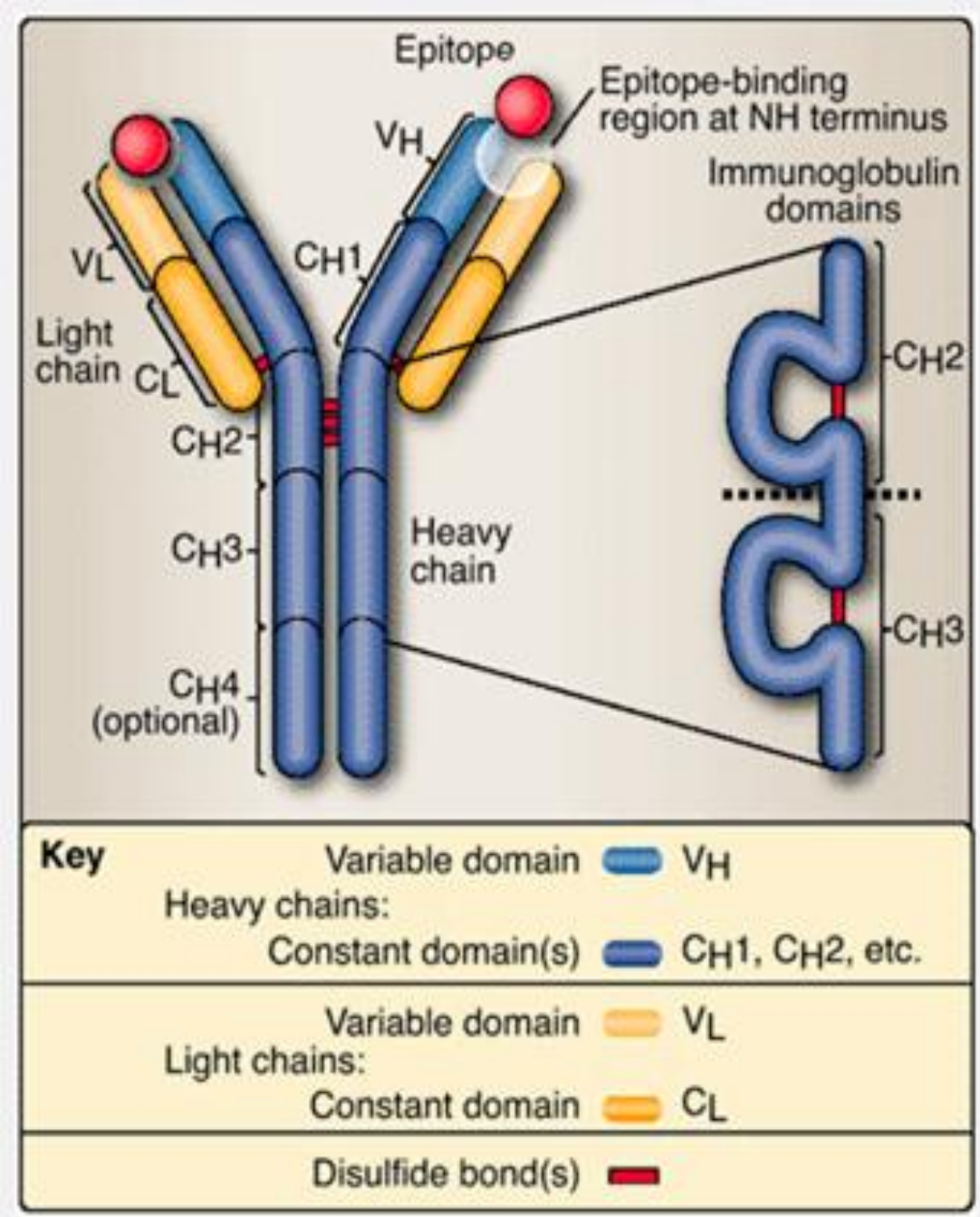
Basic structure of Ig

ประกอบด้วย polypeptide 4 สาย

- Light chain 2 สาย
- Heavy chain 2 สาย

NH2-variable region (V)

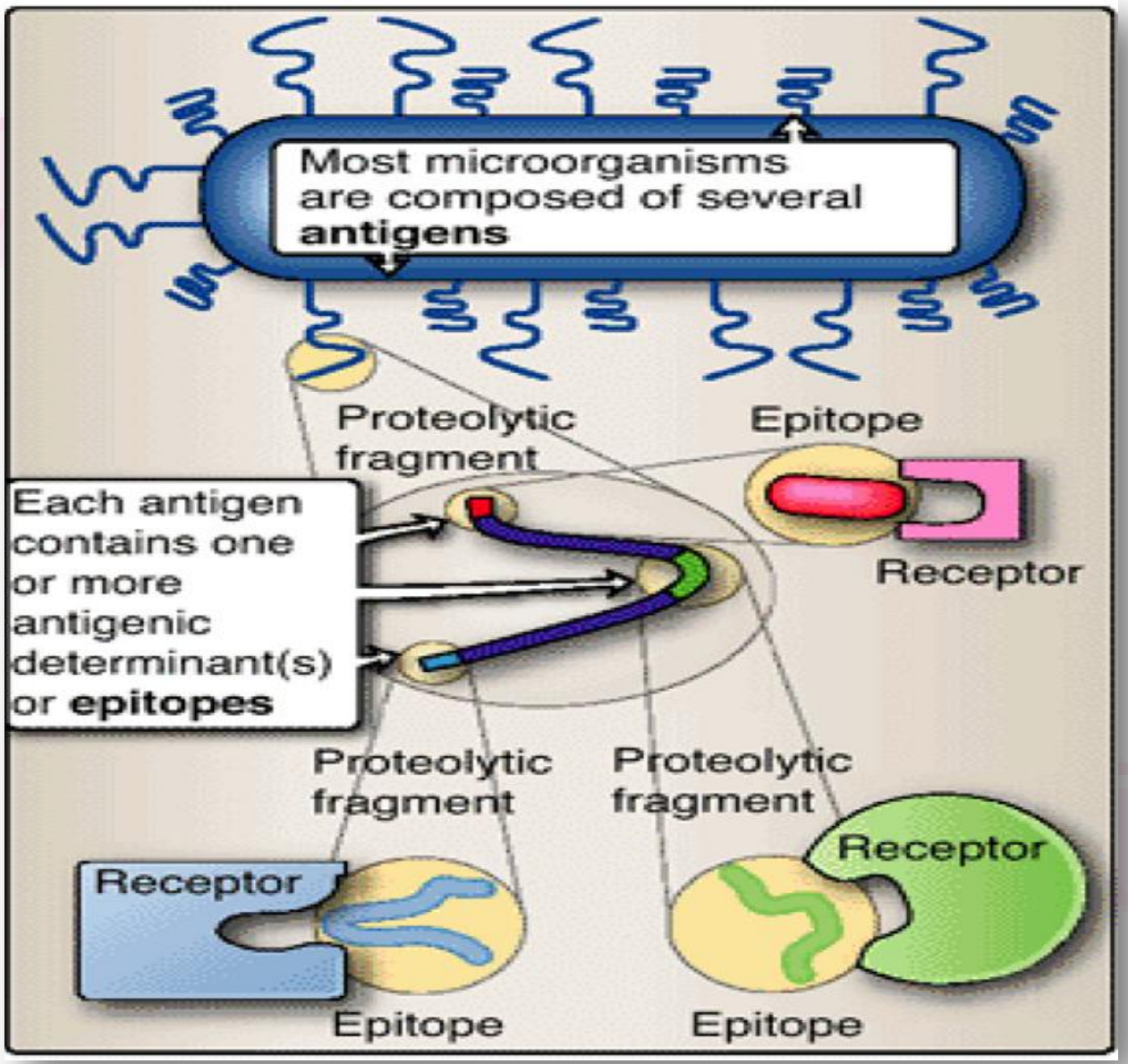
COOH-constant region (C)



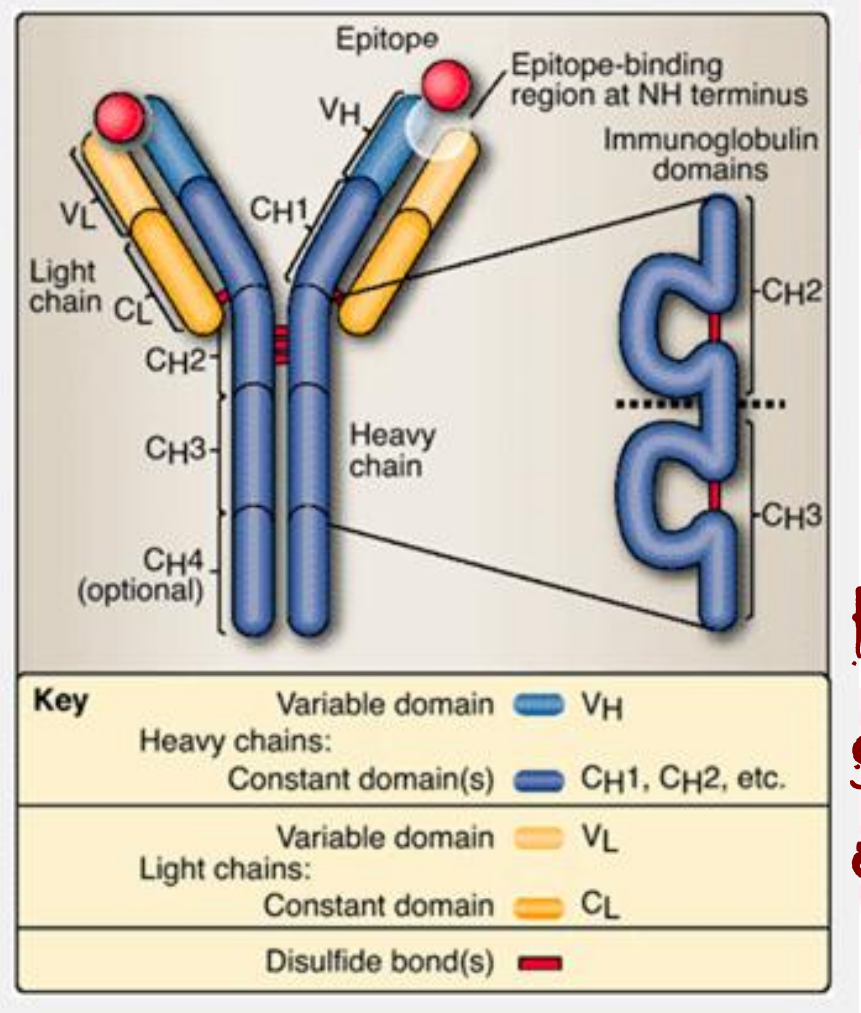
Epitopes (Antigenic or immunogenic determinants)

- ตำแหน่งย่อยบนโมเลกุลของแอนติเจนที่กระตุ้น immune response

8-22 aa



Basic structure of Ig



- B cell epitopes > 10^{19}
- 1 gene → 1 transcript → 1 protein

  Ig > 10^{19} genes
- Human genome : 20,000-25,000 genes

How can the immune system generate enough different Ig with different antigen specificities??

(Figure from Doan T et al., Lippincott's Illustrated Reviews: Immunology 1st Edition;2007;p57)

Hypotheses

1. Germ-line theory

: The genome contributed by the germ cells, egg and sperm, contains a large repertoire of immunoglobulin genes.

2. Somatic mutation theory

: The genome contains a relatively small number of immunoglobulin genes, from which a large number of antibody specificities are generated in the somatic cells by mutation or recombination.

3. Two-gene model

: in 1965 proposed by Dreyer & Bennett

(Kuby J. Immunology 5th ed; p107-108)

Two-gene model

In 1965, *Dreyer and Bennett* proposed that two or more genes could control the production of one polypeptide chain.

{**opposed the one gene, one polypeptide theory**}

- A single C region gene encoded in the GERMLINE and separate from the V region genes

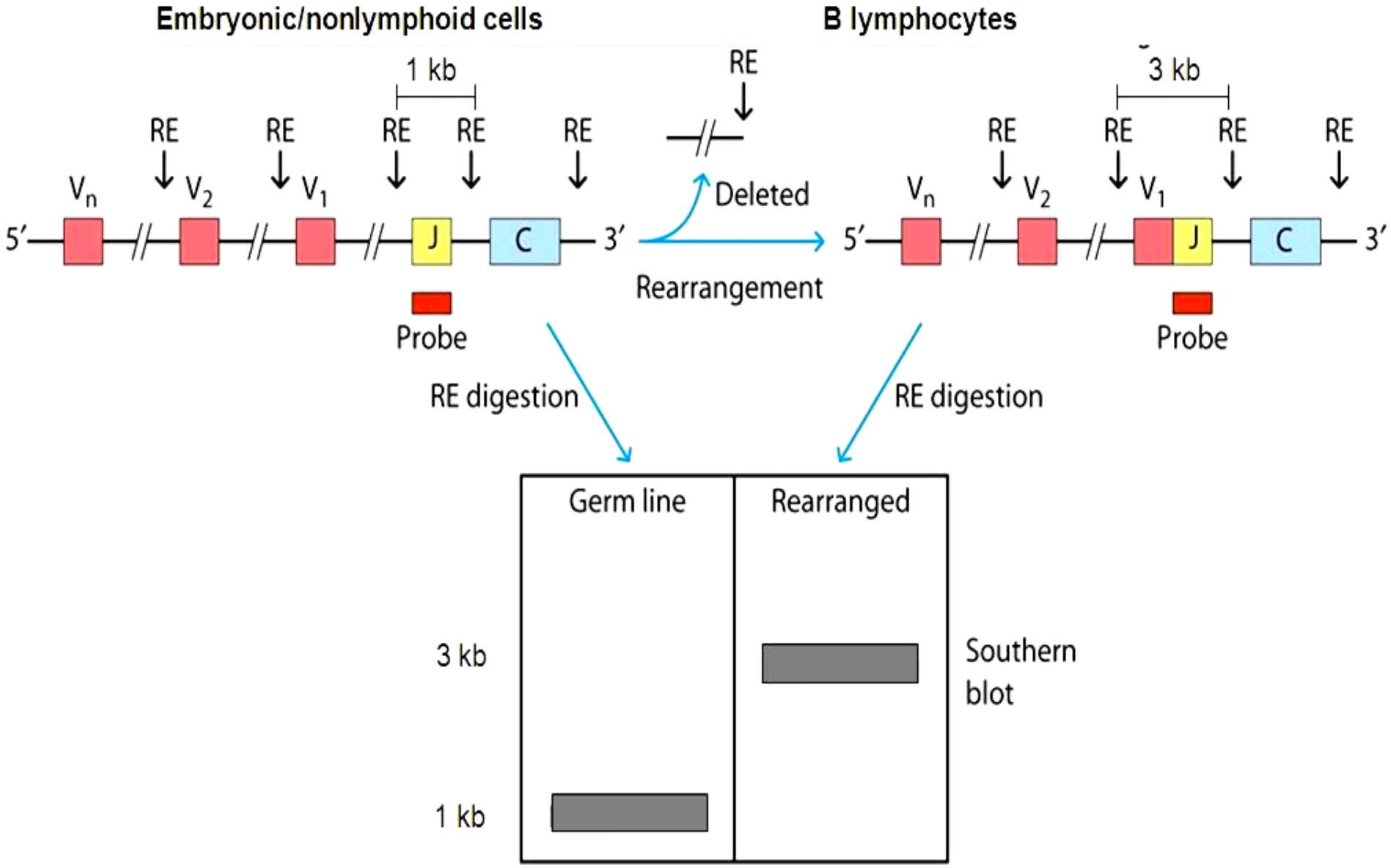
- Multiple choices of V region genes available

- A mechanism to rearrange V and C genes in the genome so that they can fuse to form a complete Immunoglobulin gene

(Dryer, W.J., and Bennett, J., Proc. Natl. Acad. Sci. USA 54, 864-869; 1965; Nandini Shetty; Immunology Introductory Textbook 2nd Ed; 2005; p33)

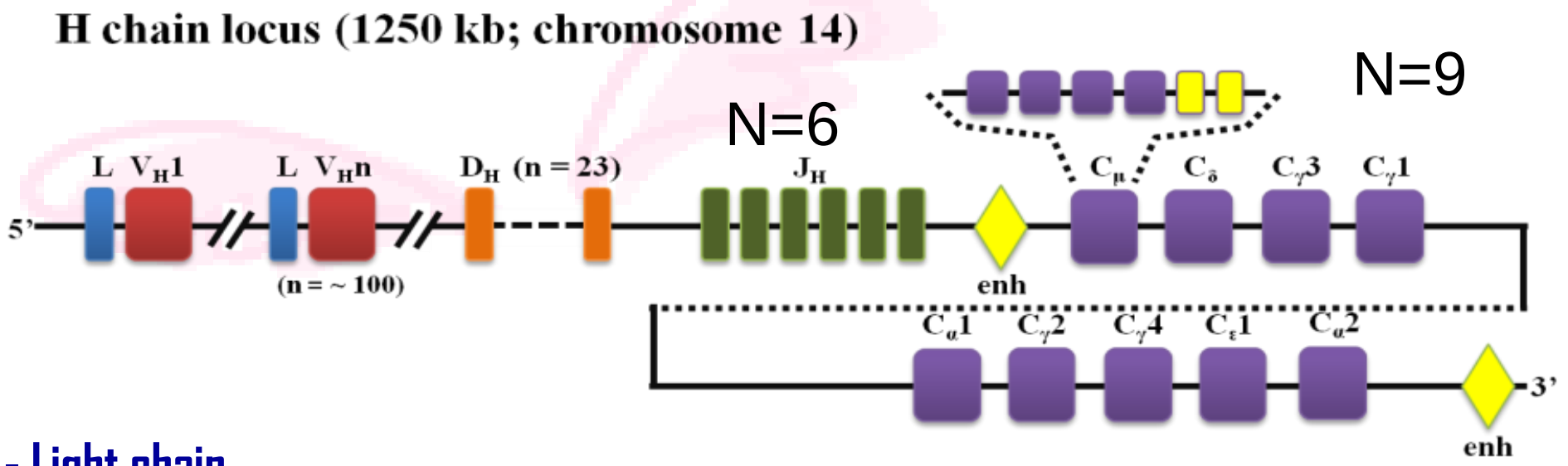
Proof of the Dreyer - Bennett hypothesis by Susumu Tonegawa in 1976

(In 1987, Tonegawa was awarded the Nobel prize)

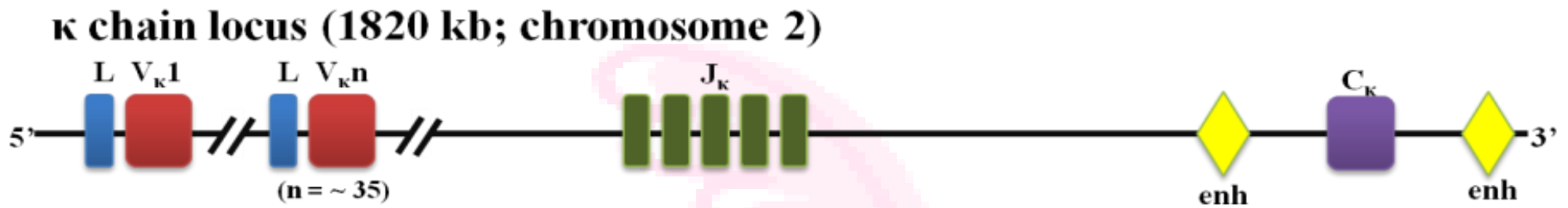


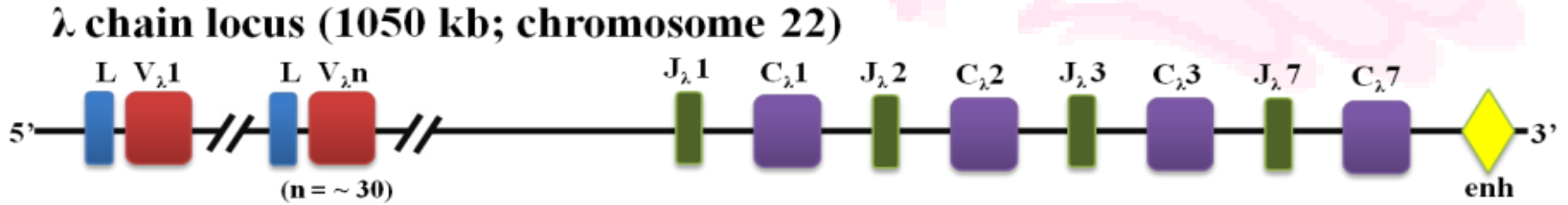
Germline organization of human Ig genes

- Heavy chain

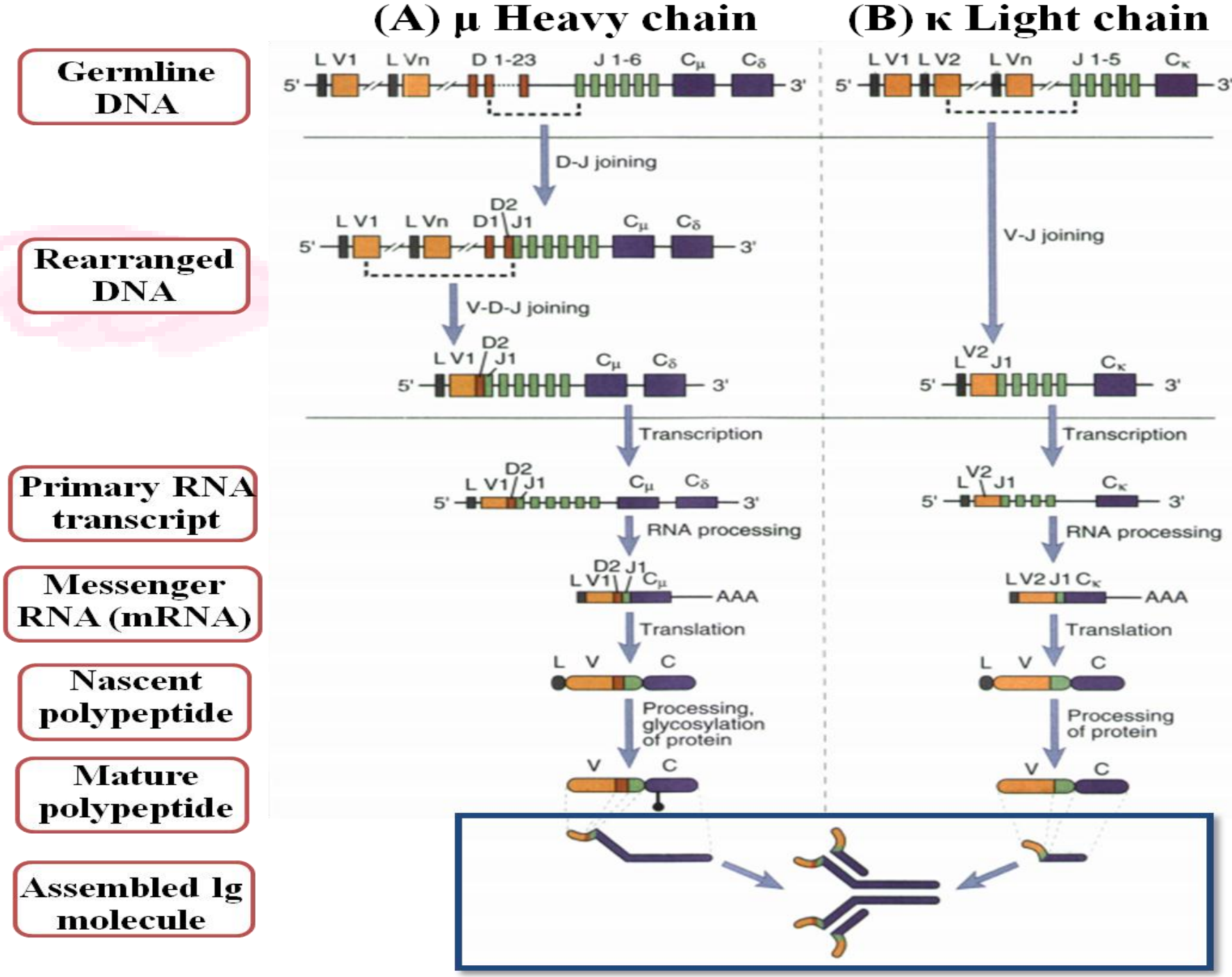


- Light chain



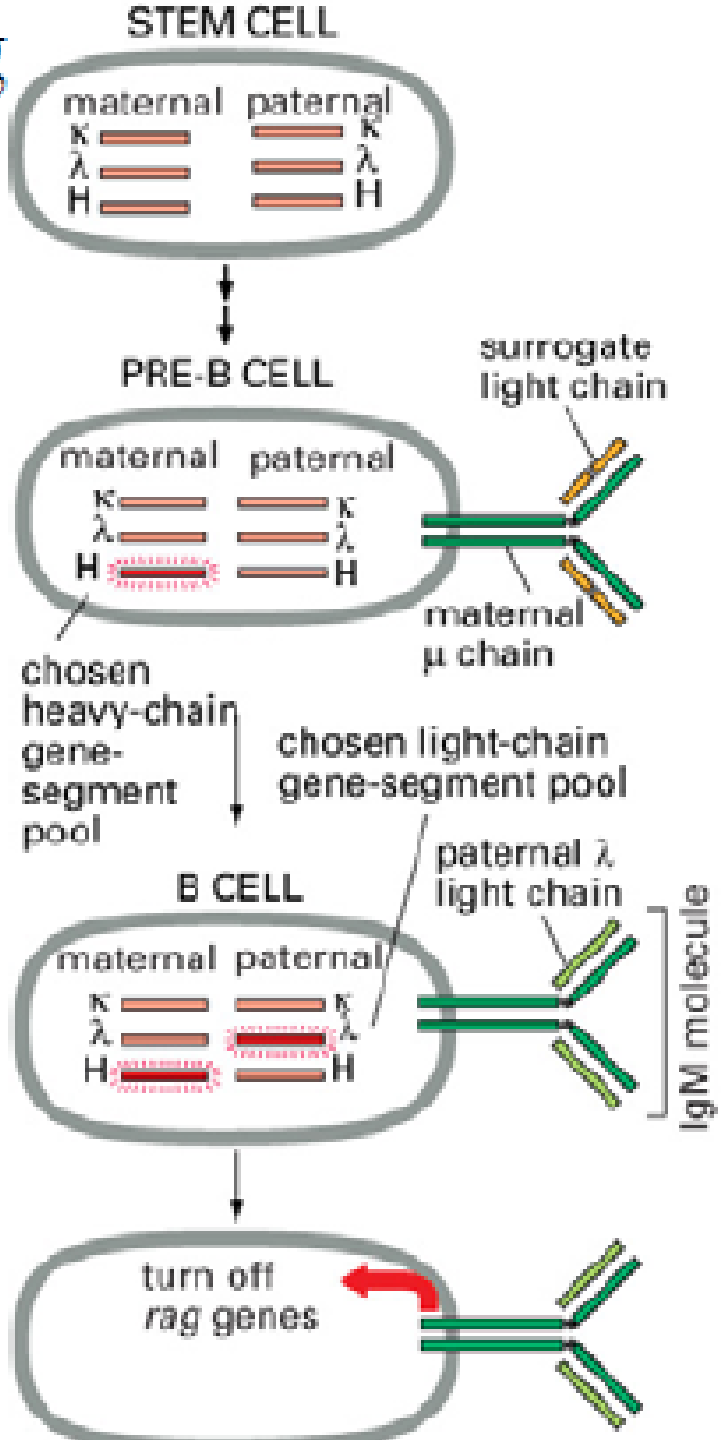


Ig heavy and light chain gene recombination & expression



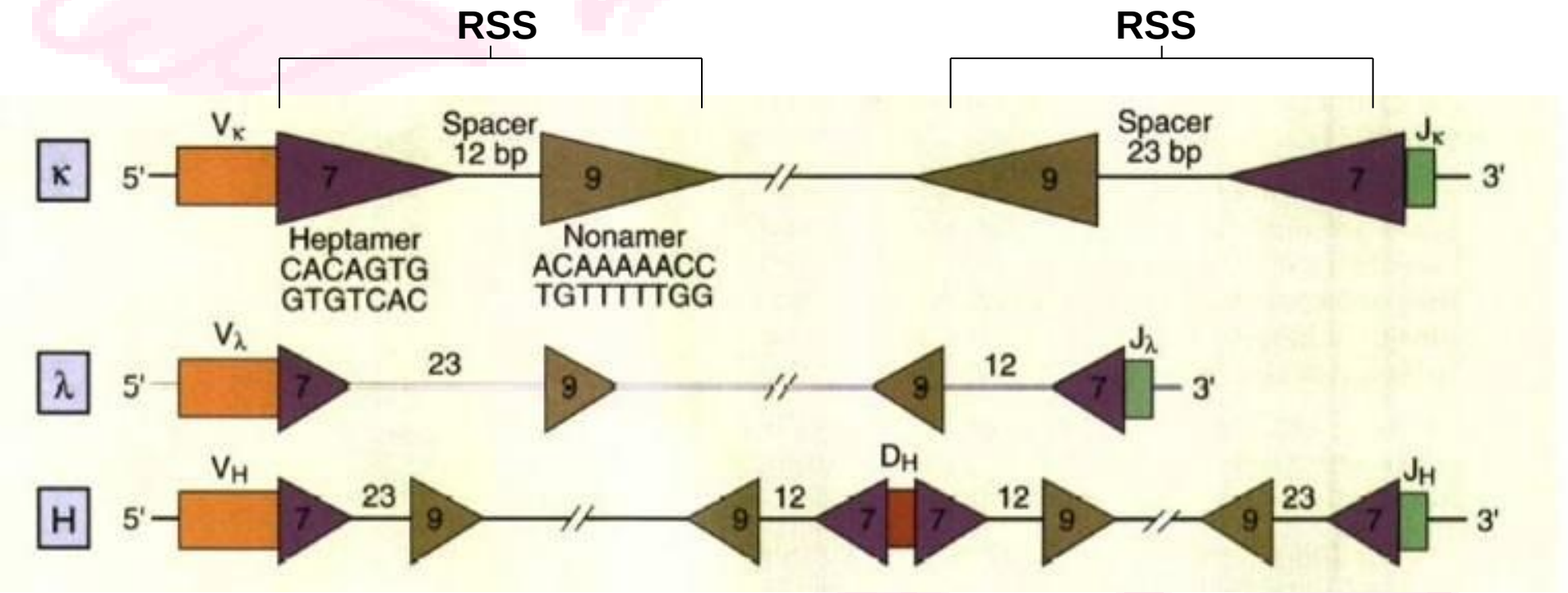
Allelic exclusion ensuring specificity

- Each B cell clone produces only antibody against one antigen. The dimmeric antibody doesn't carry two different antigen recognition sites on two different monomers
  - Ensuring cross-linking of antigens for aggregation and elimination
  - Ensuring no "co-stimulation" of non-specific antigen binding due to the stimulation of the specific antigen binding on the other monomer
- However, there are two sets of chromosomes in each B cells
  - Will use only one each of the light chain and heavy chain genes



Mechanisms of V (D) J recombination

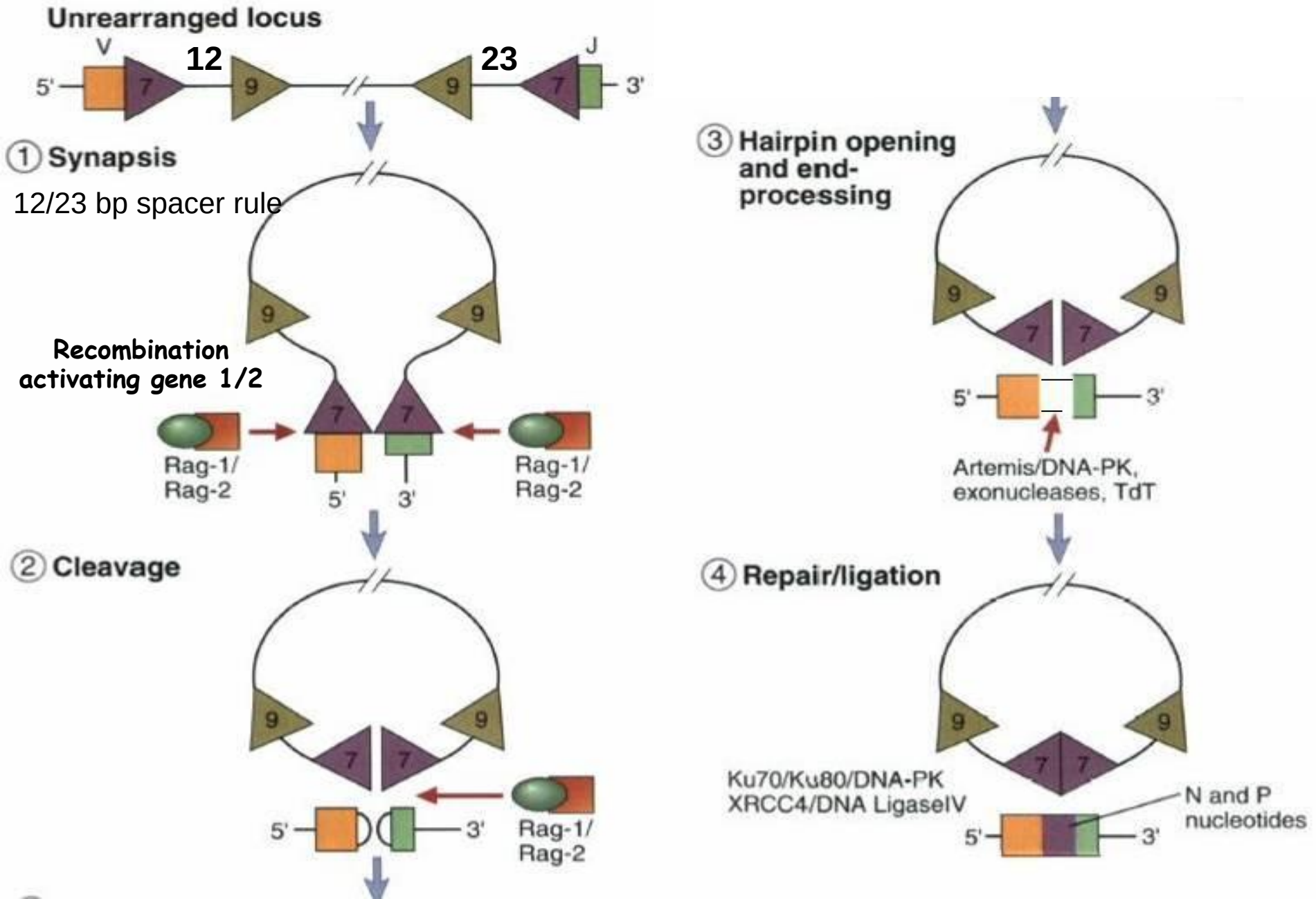
Orientation of V (D) J gene segments and recombination signal sequences (RSS)



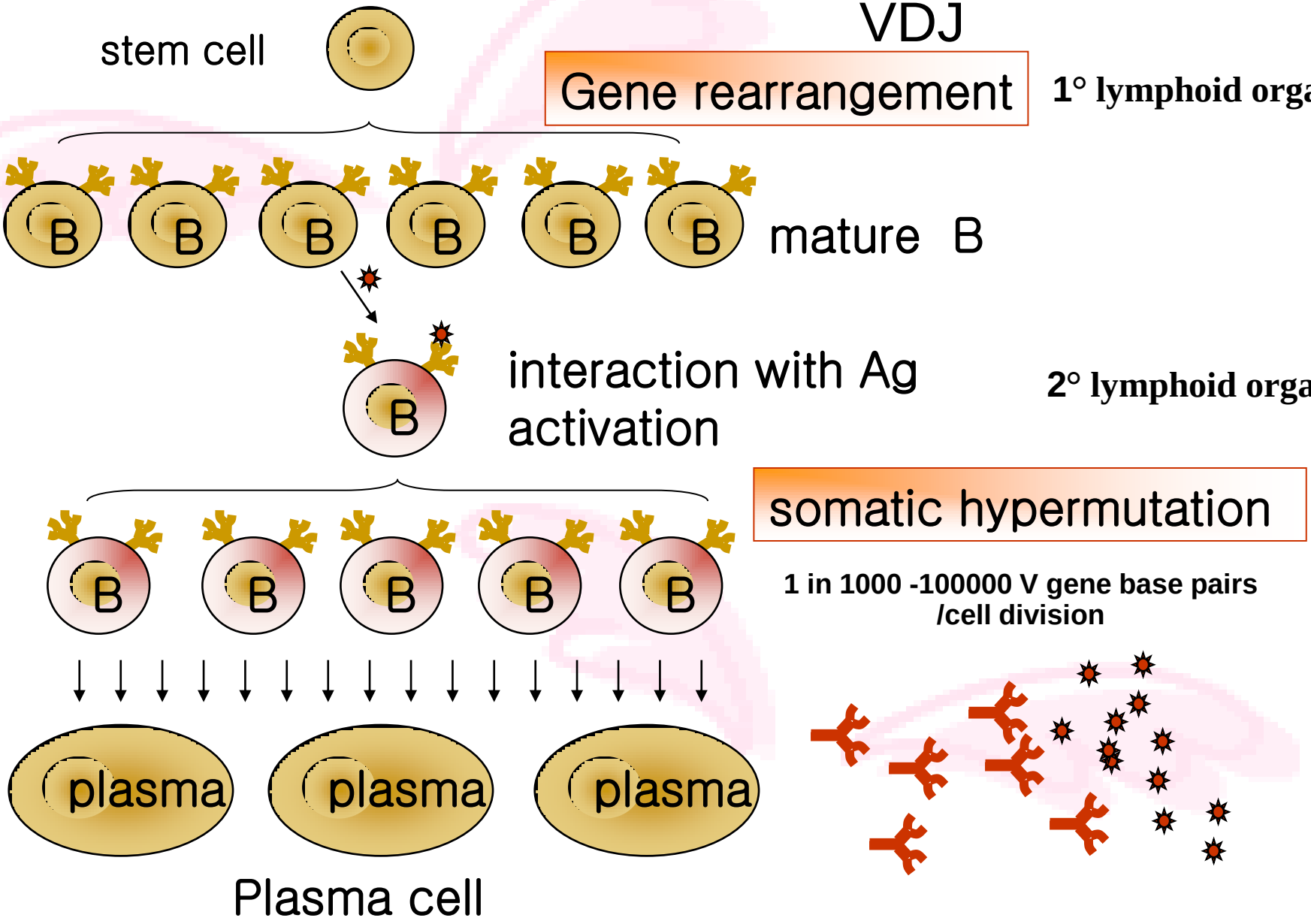
(Abbus AK et al., Cellular and Molecular Immunology 6th Edition;2007;p163)

Process of V (D) J recombination

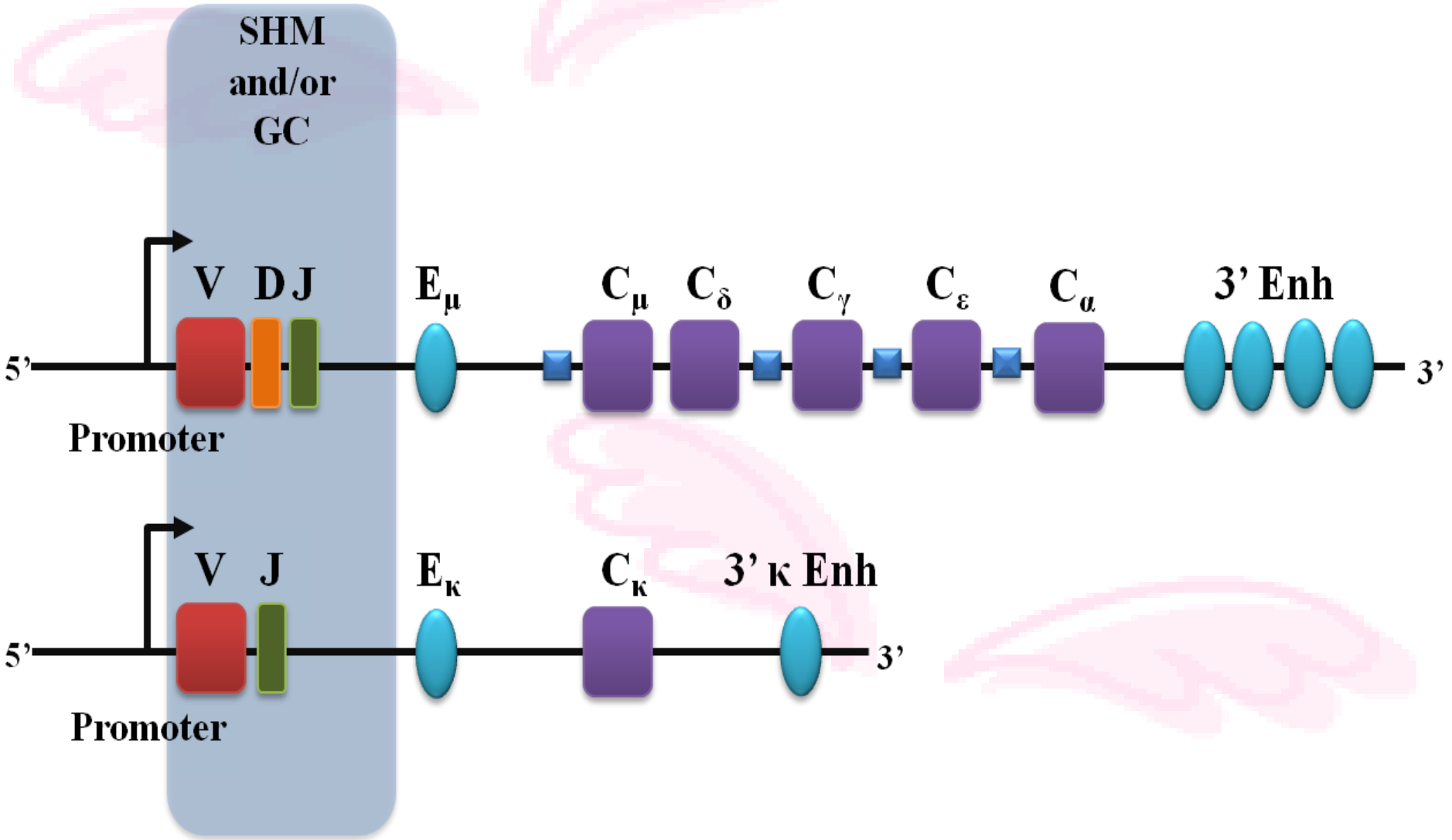
(Abbus AK; 6th ed, p164)



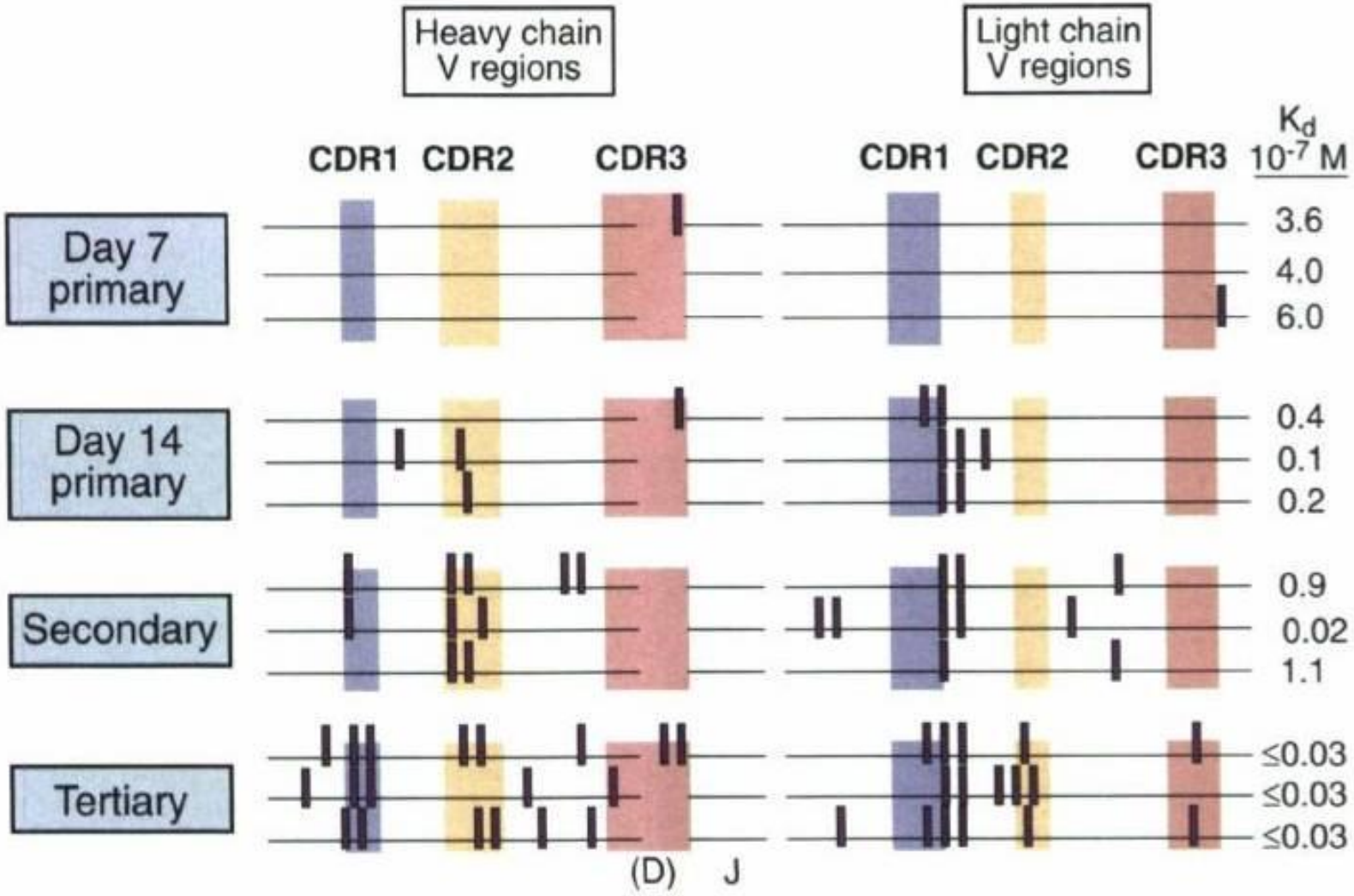
Somatic hypermutation



บริเวณการเกิด somatic hypermutation ในยีนของ Ig heavy-chain และ light-chain



Evidence for somatic mutation in variable regions of Ig genes

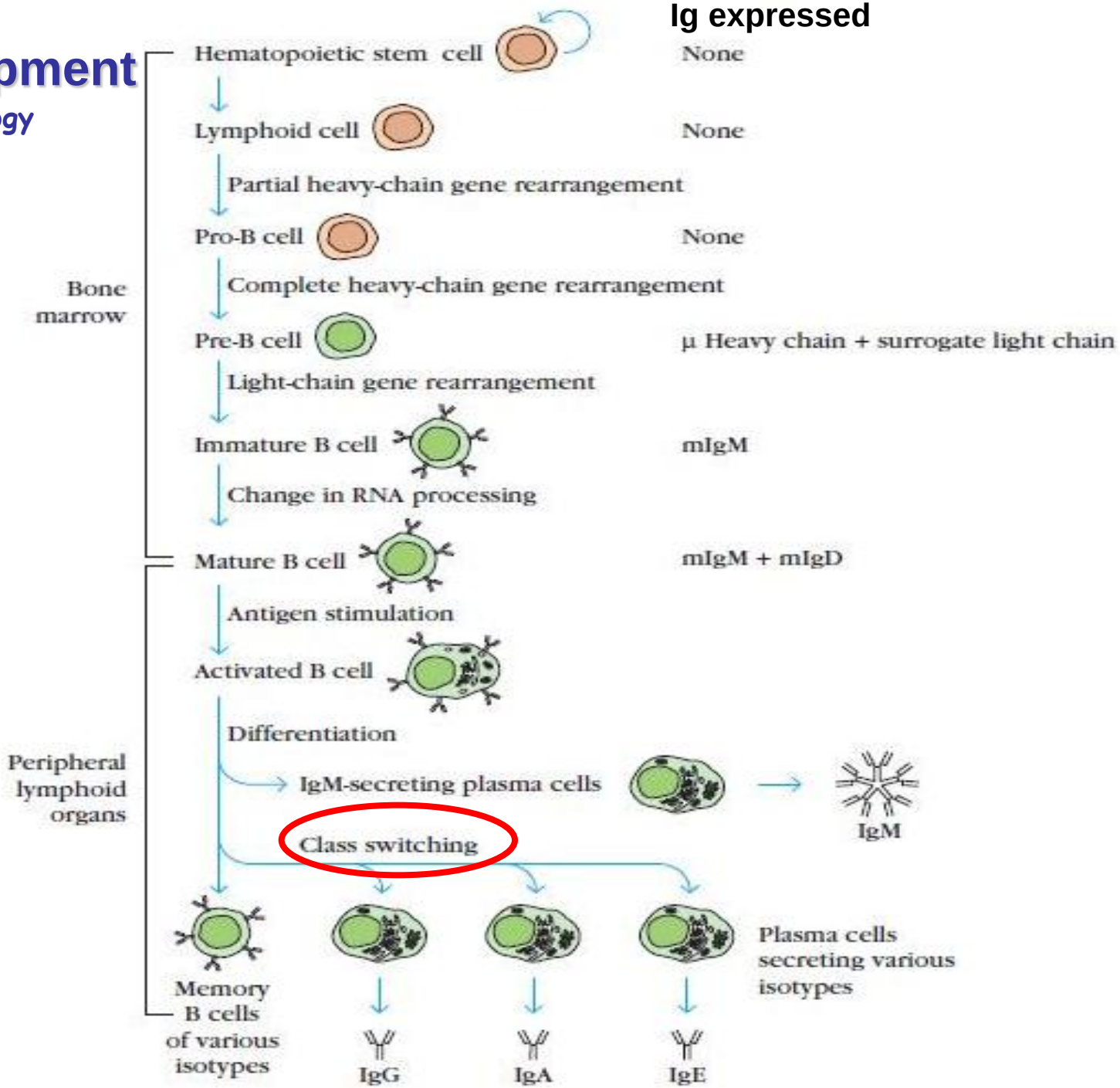


Total potential repertoire $>10^{12}$

(Abbus AK et al., Cellular and Molecular Immunology 6th Edition;2007; p234)

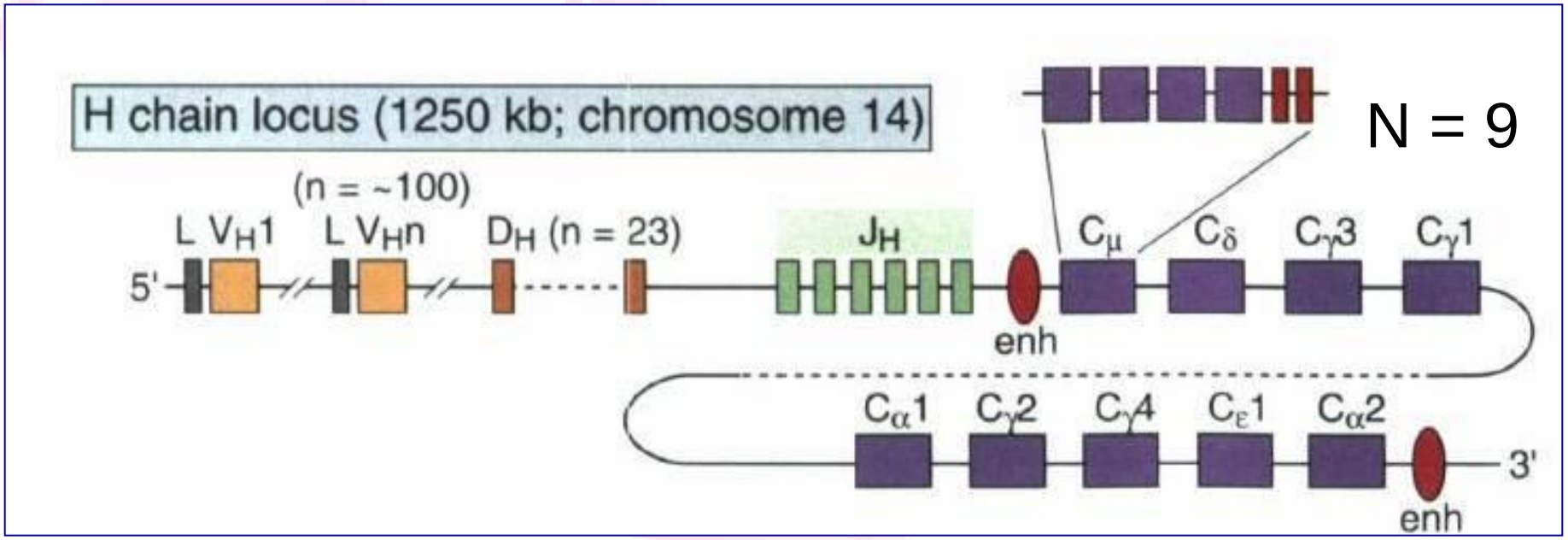
B-cell development

(Kuby J. Immunology 5th ed; p106)

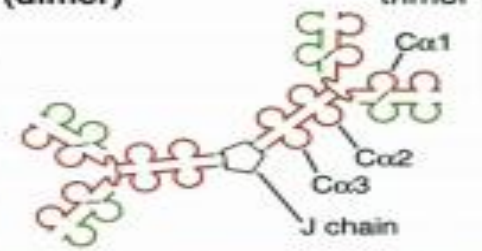
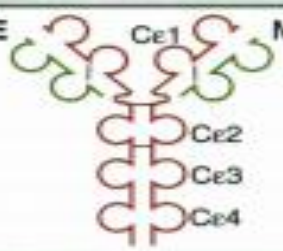
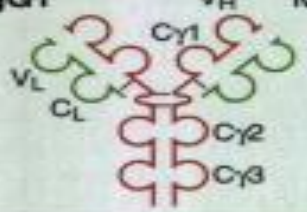
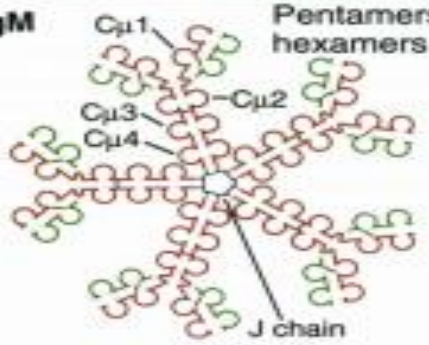


Germline organization of human Ig genes

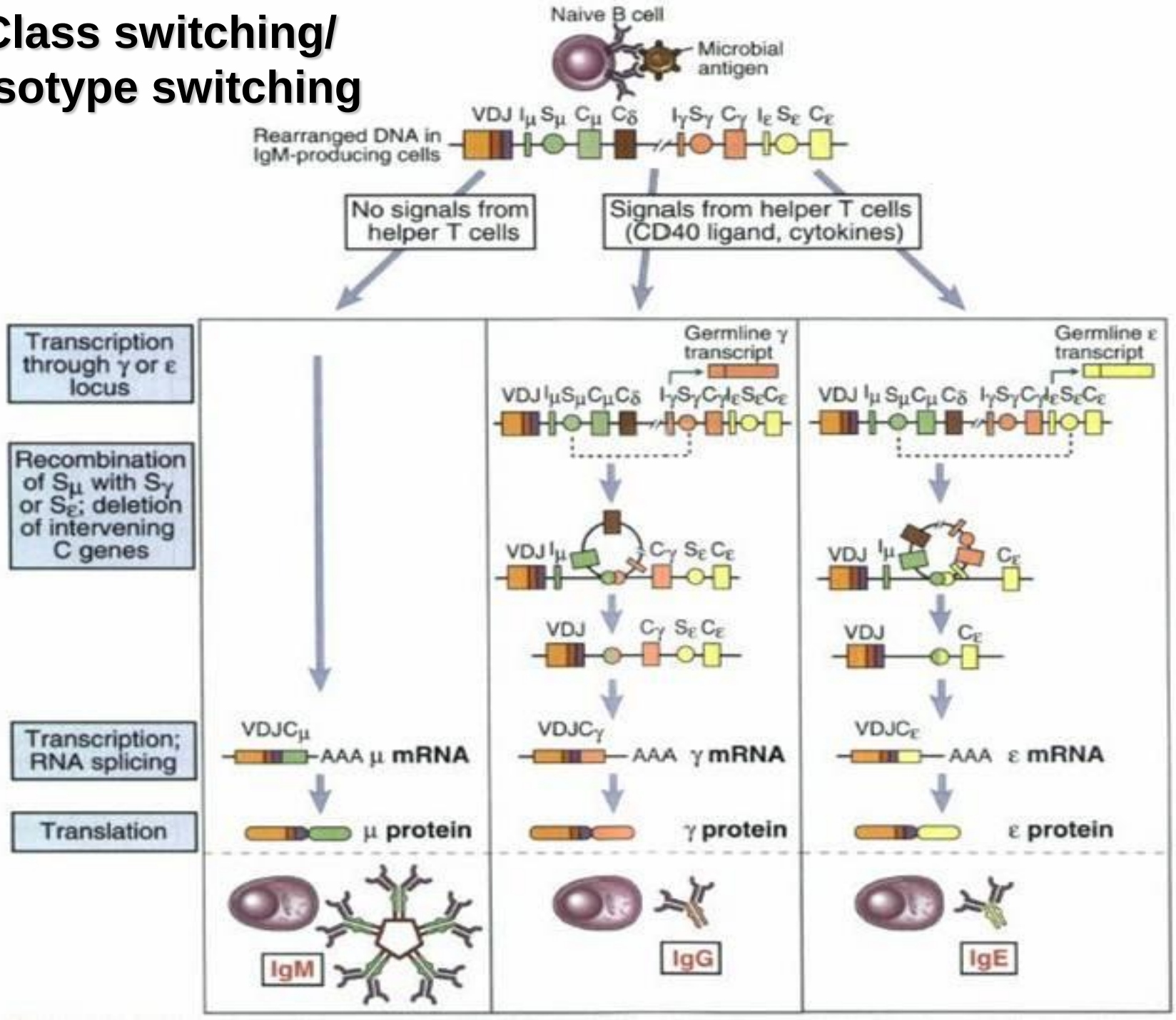
Heavy chain



(Abbus AK et al., Cellular and Molecular Immunology 6th Edition;2007;p158)

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	**IgA (dimer)** Monomer, dimer, trimer 	Mucosal immunity
IgD	None	δ	Trace	3	None	Naive B cell antigen receptor
IgE	None	ε	0.05	2	**IgE** Monomer 	Defense against helminthic parasites, immediate hypersensitivity
IgG	IgG1-4	γ(1,2,3 or 4)	13.5	23	**IgG1** Monomer 	Opsonization, complement activation, antibody-dependent cell-mediated cytotoxicity, neonatal immunity, feedback inhibition of B cells
IgM	None	μ	1.5	5	**IgM** Pentamers, hexamers 	Naive B cell antigen receptor, complement activation

Class switching/ Isotype switching



สรุปปัจจัยที่ทำให้เกิดความหลากหลายของแอนติบอดี

1. Multiple germ-line gene segments

	Heavy chain	κ-light chain	λ-light chain
	Estimated number of segments		
V	100	35	30
D	23	0	0
J	6	5	4

2. Combinational V-(D)-J joining

100 x 23 x 6 = 13800 **35 x 5 = 175** **30 x 4 = 120**

[175 + 120 = 295 light chains]

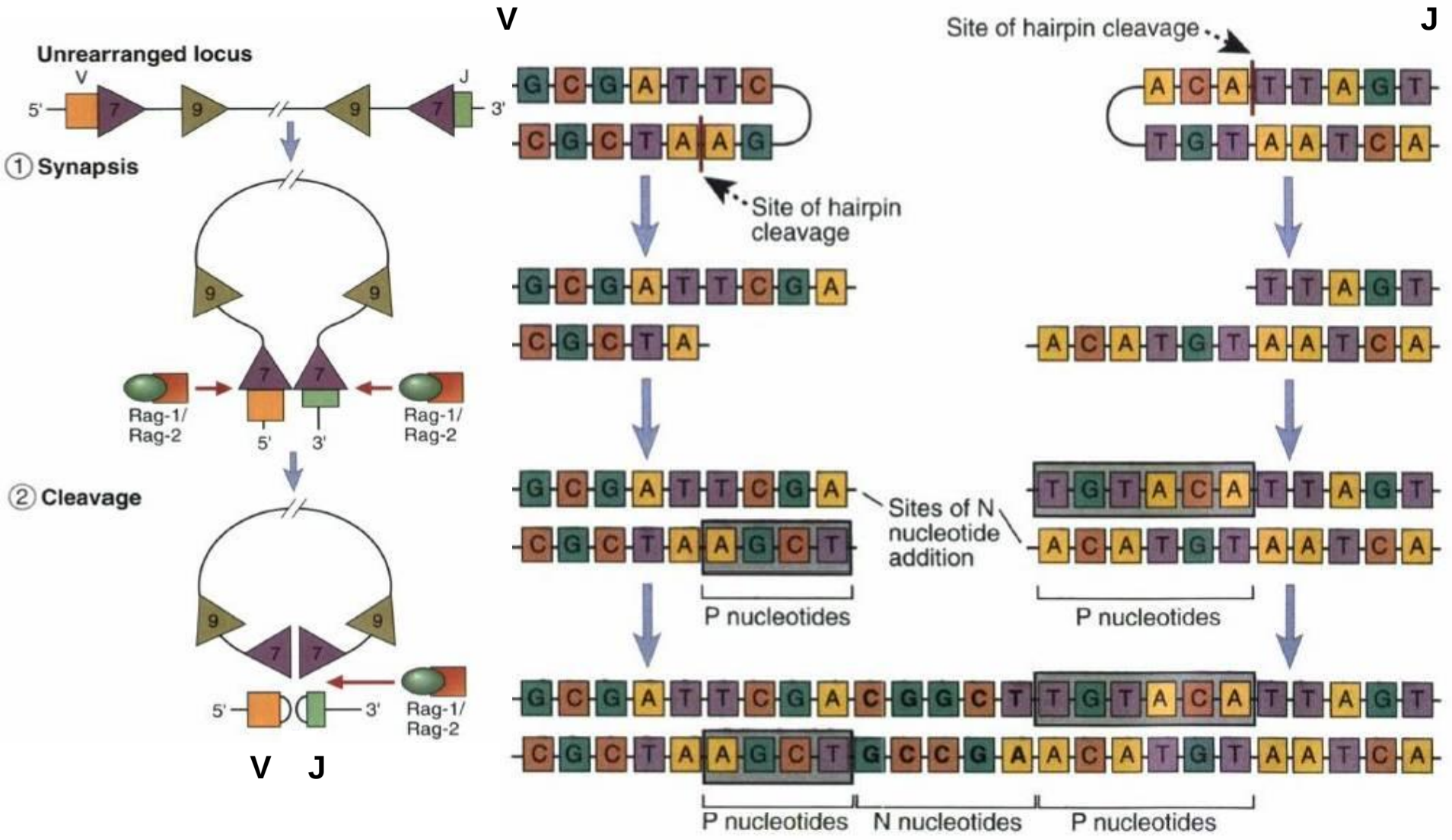
3. Combinational association of heavy and light chains

$13800 \times 295 = 4.07 \times 10^6$

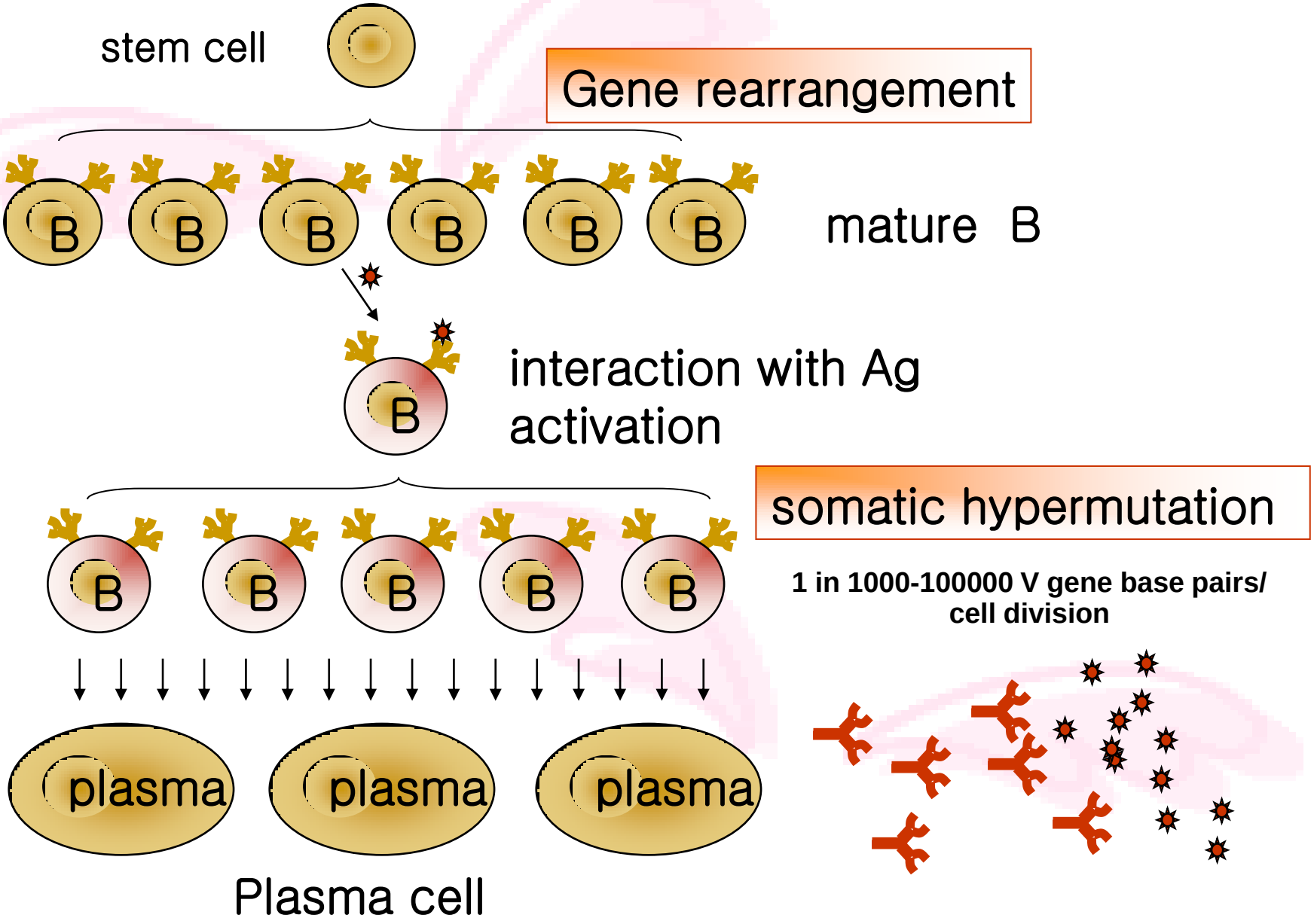
Generation of Antibody Diversity

(Abbus AK; 6th ed, p164)

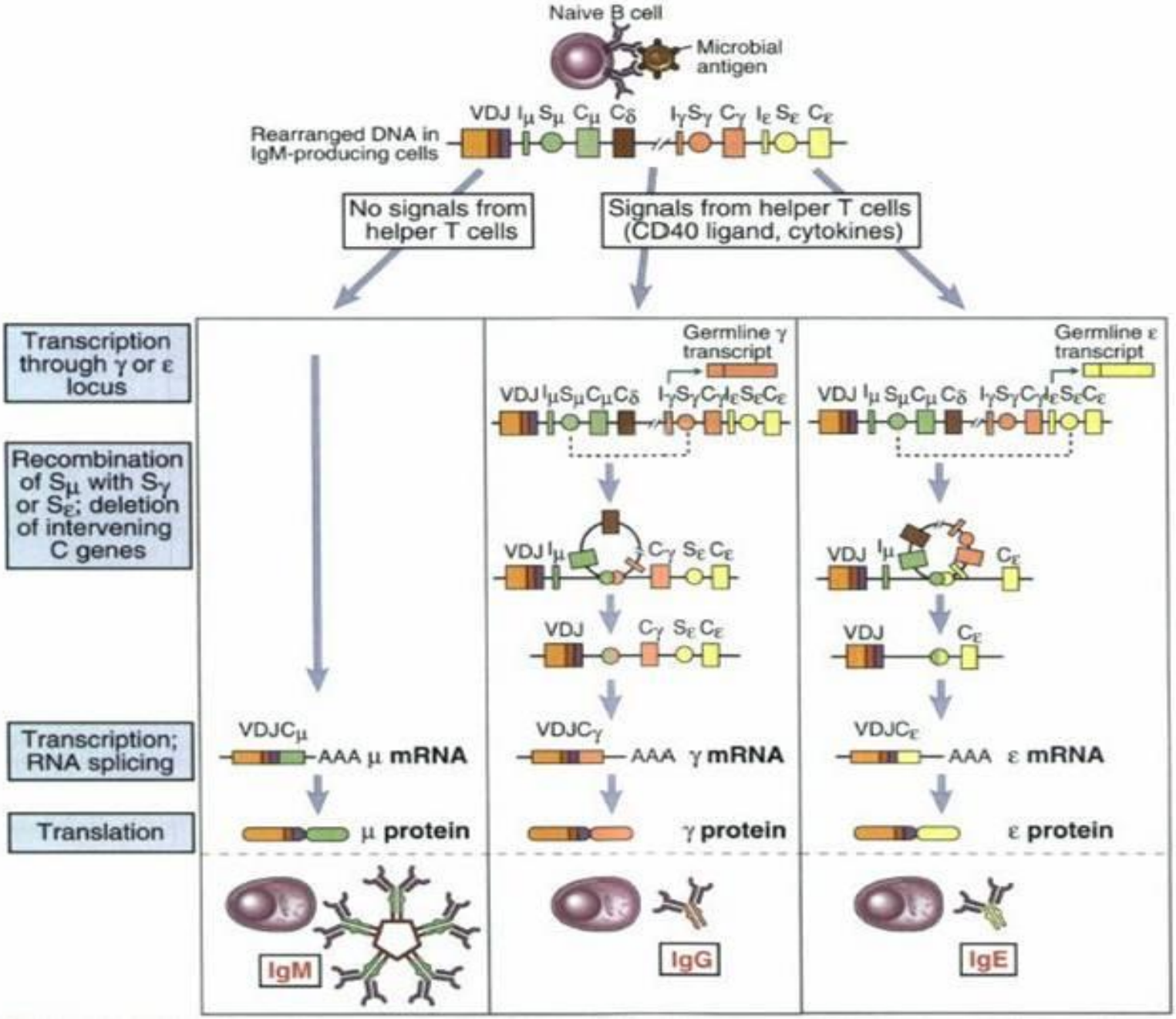
4. Junctional diversity



5. Somatic hypermutation

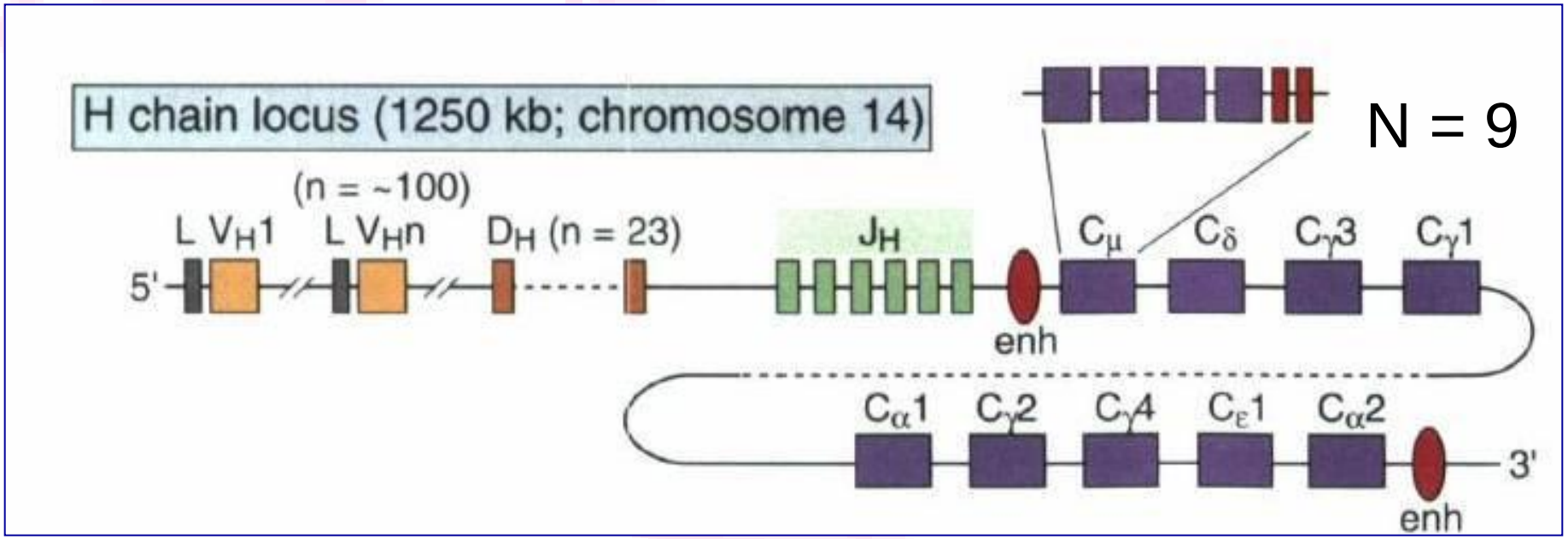


6. Class switch recombination (CSR)



C region is also important!!

Heavy chain



(Abbus AK et al., Cellular and Molecular Immunology 6th Edition;2007;p158)