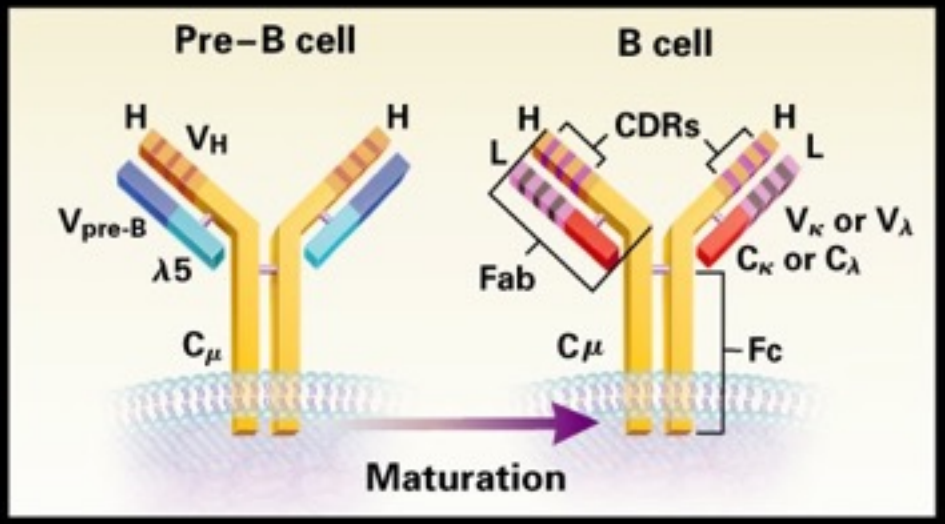
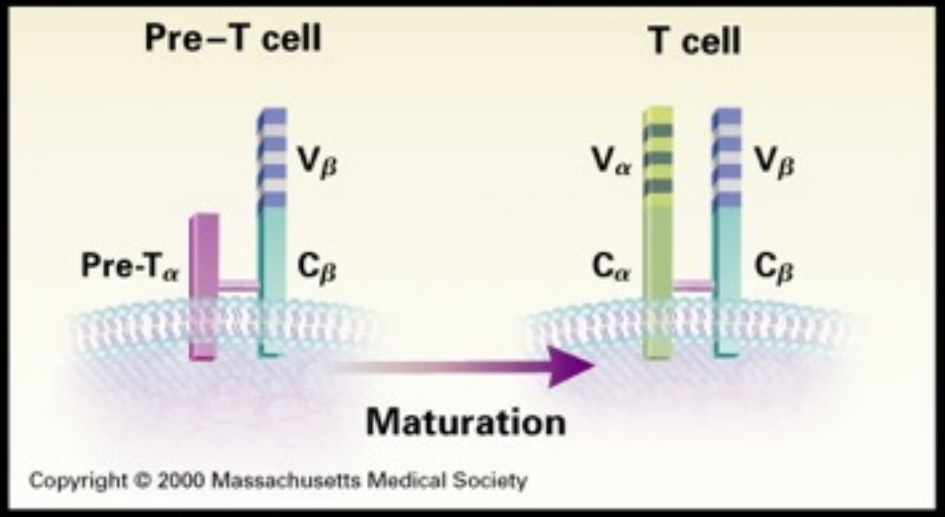
Geração de Receptores de Antígenos de Linfócitos T e B

Structure of Immature and Mature B-Cell and T-Cell Antigen Receptors





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Delves PJ, Roitt IM.
The Immune System (Part1).
N Engl J Med 2000;343:37-49.

The New England Journal of Medicine

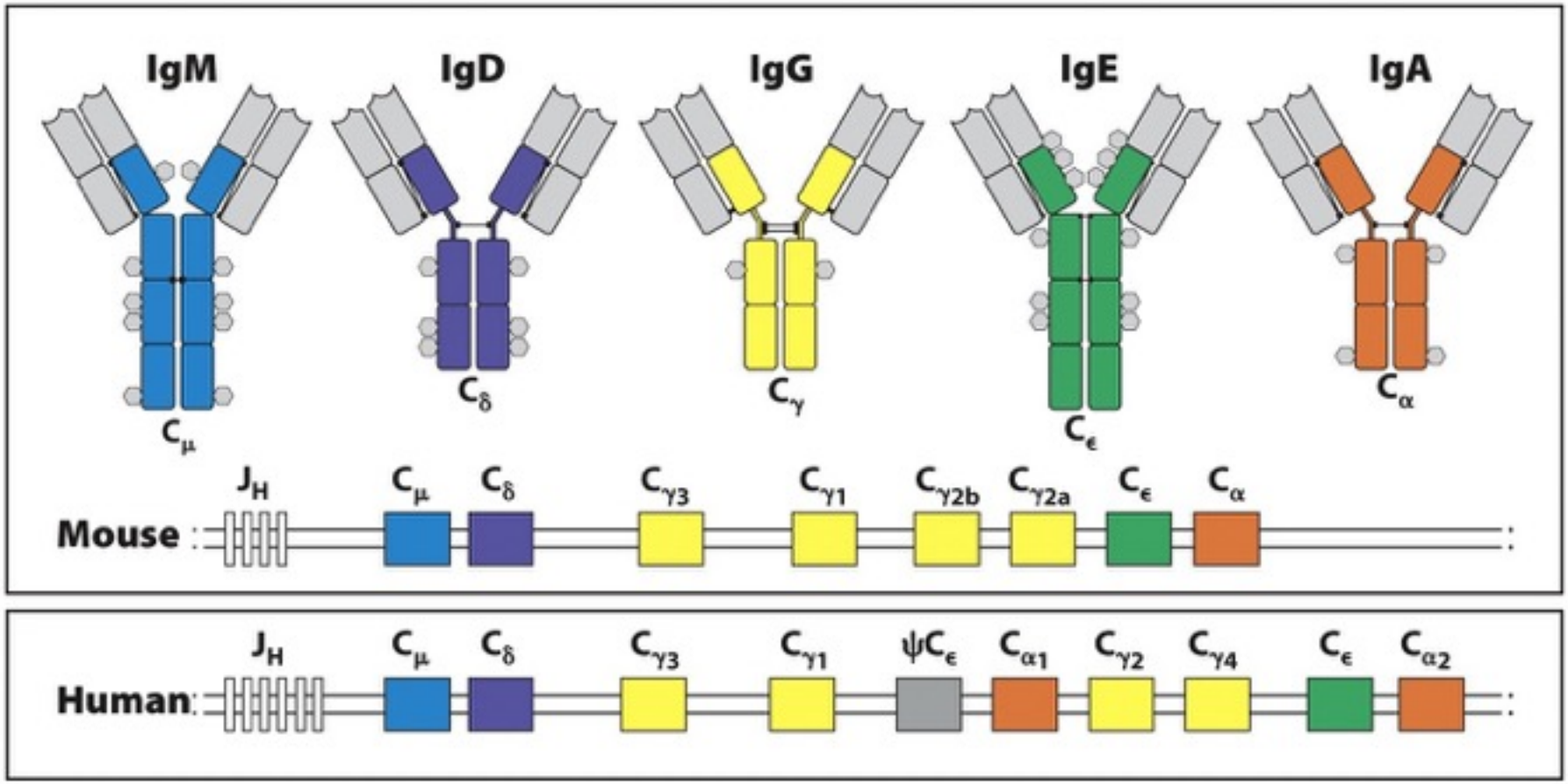

Figure 5.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

	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)

Mecanismos geradores de diversidade nos receptores BCR e TCR:

* recombinação V(D)J —> T e B
    * diversidade funcional
    * adição aleatória de bases

* hipermutação somática (maturação de afinidade) —> somente B
* troca de classe ou isotipo —> somente B
* conversão fênica —> somente B

Mecanismos geradores de diversidade nos receptores BCR e TCR:

* recombinação V(D)J —> T e B
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* troca de classe ou isotipo —> somente B
* conversão fênica —> somente B


ENTER

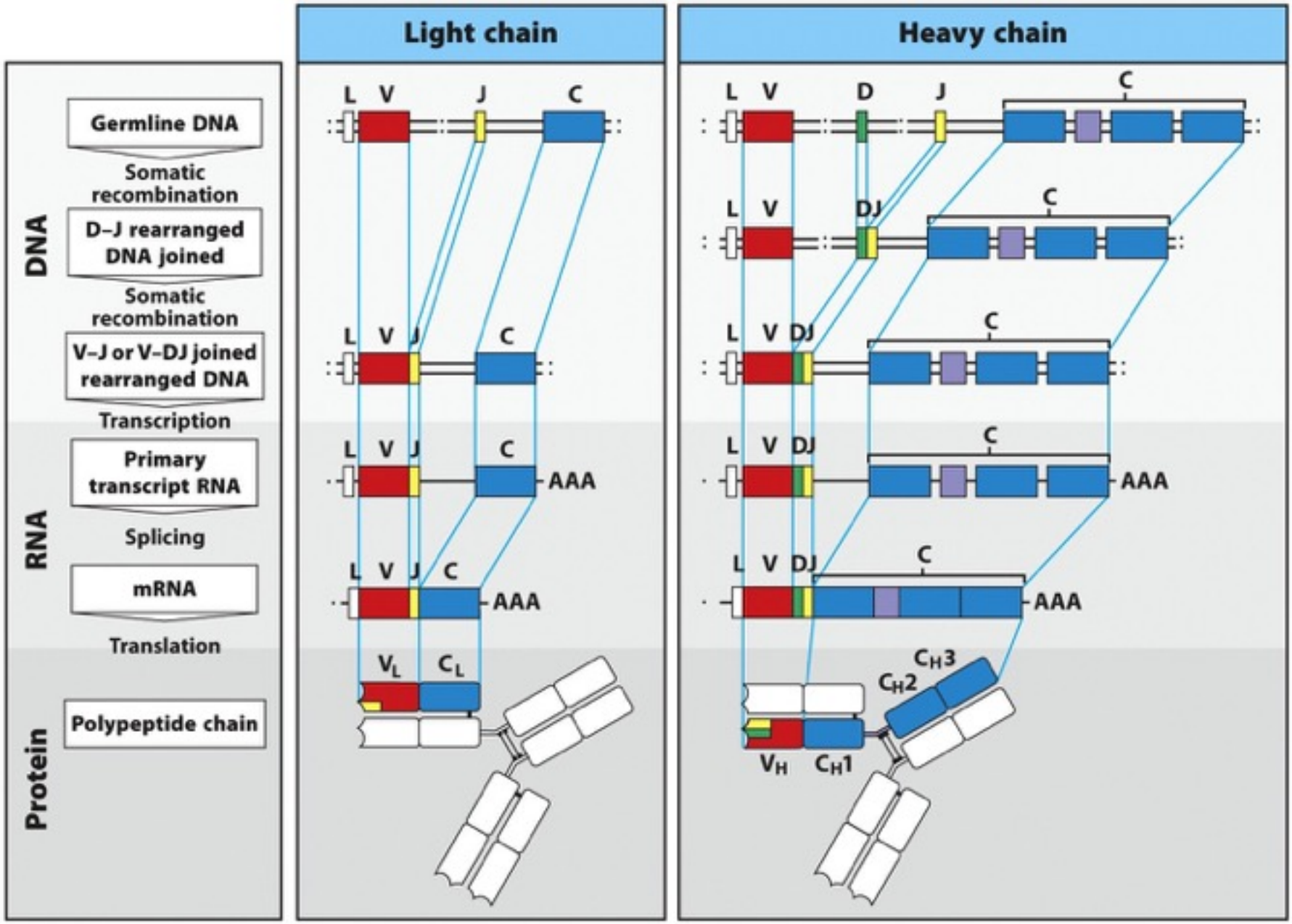


Figure 5.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Immunology wars: A billion antibodies
Nature Videos

https://youtu.be/Na-Zc-xWCLE

Number of functional gene segments in human immunoglobulin loci

Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	34–38	29–33	38–46
Diversity (D)	0	0	23
Joining (J)	5	4–5	6
Constant (C)	1	4–5	9

Figure 5.2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

BCR

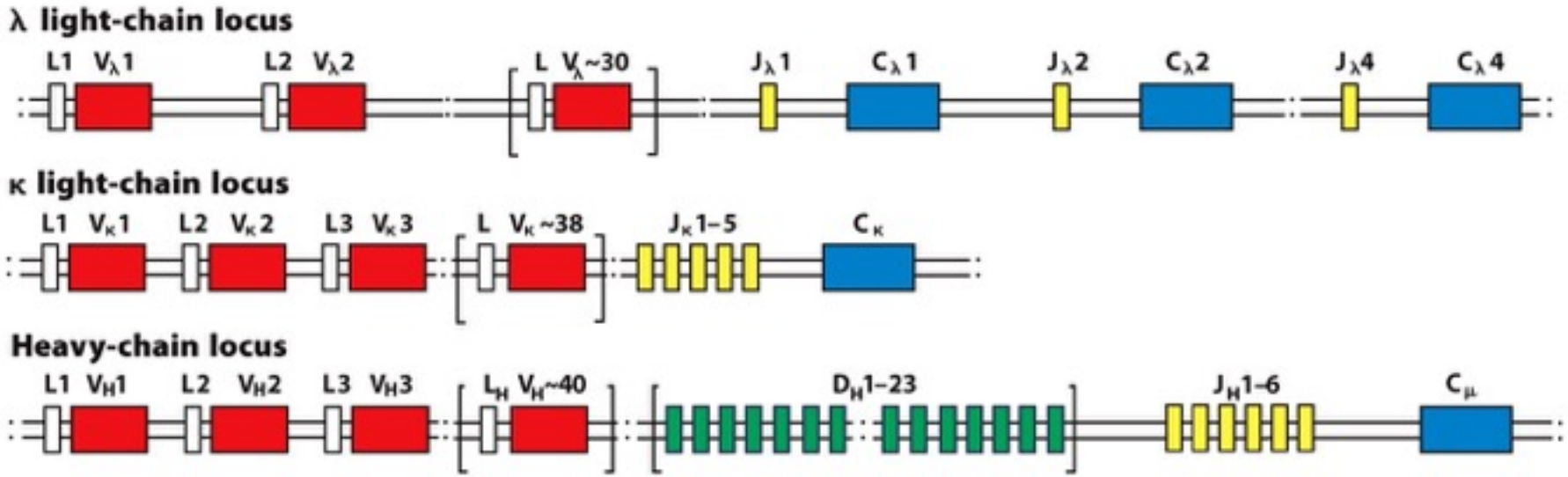


Figure 5.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

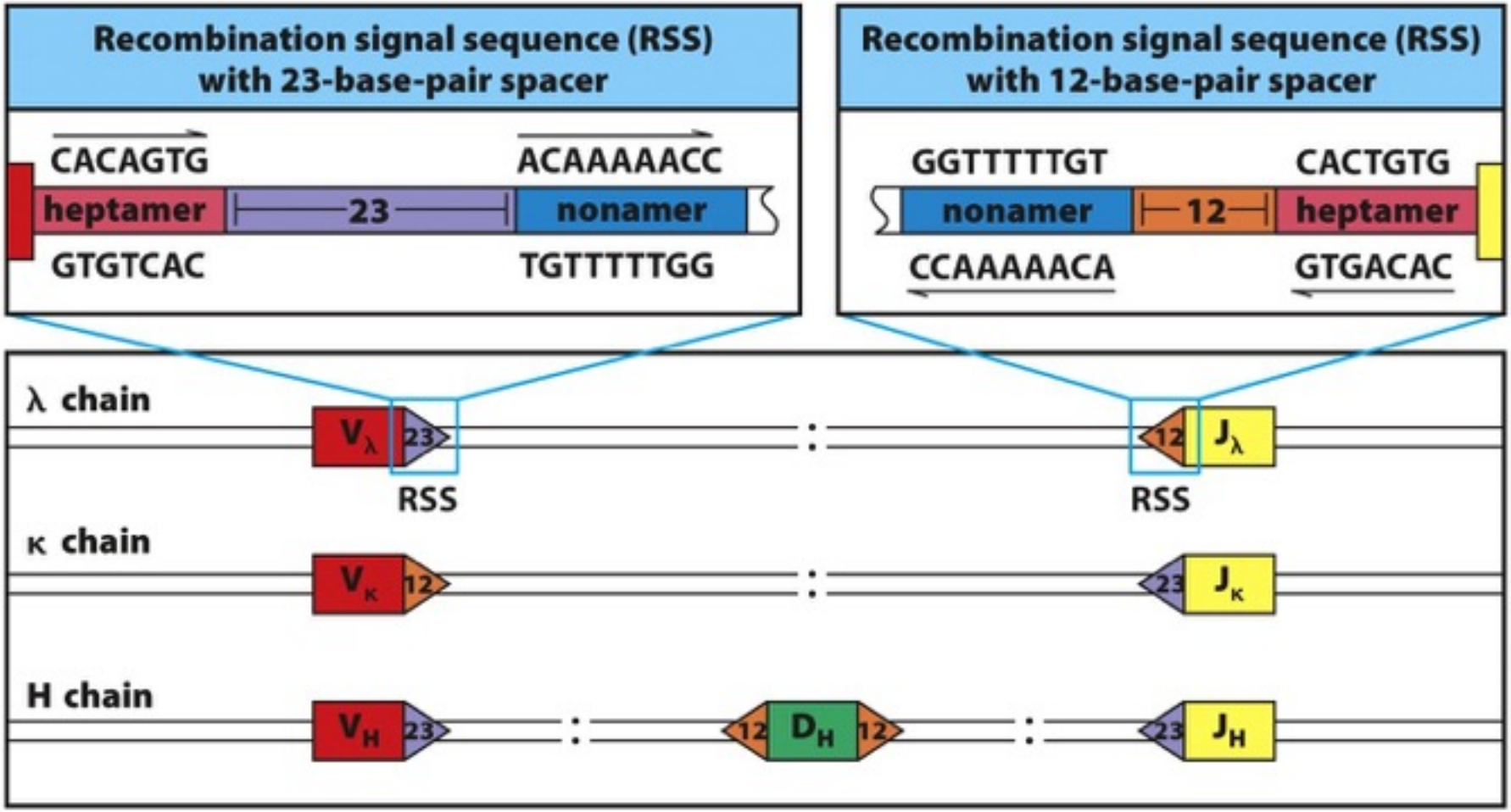


Figure 5.4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

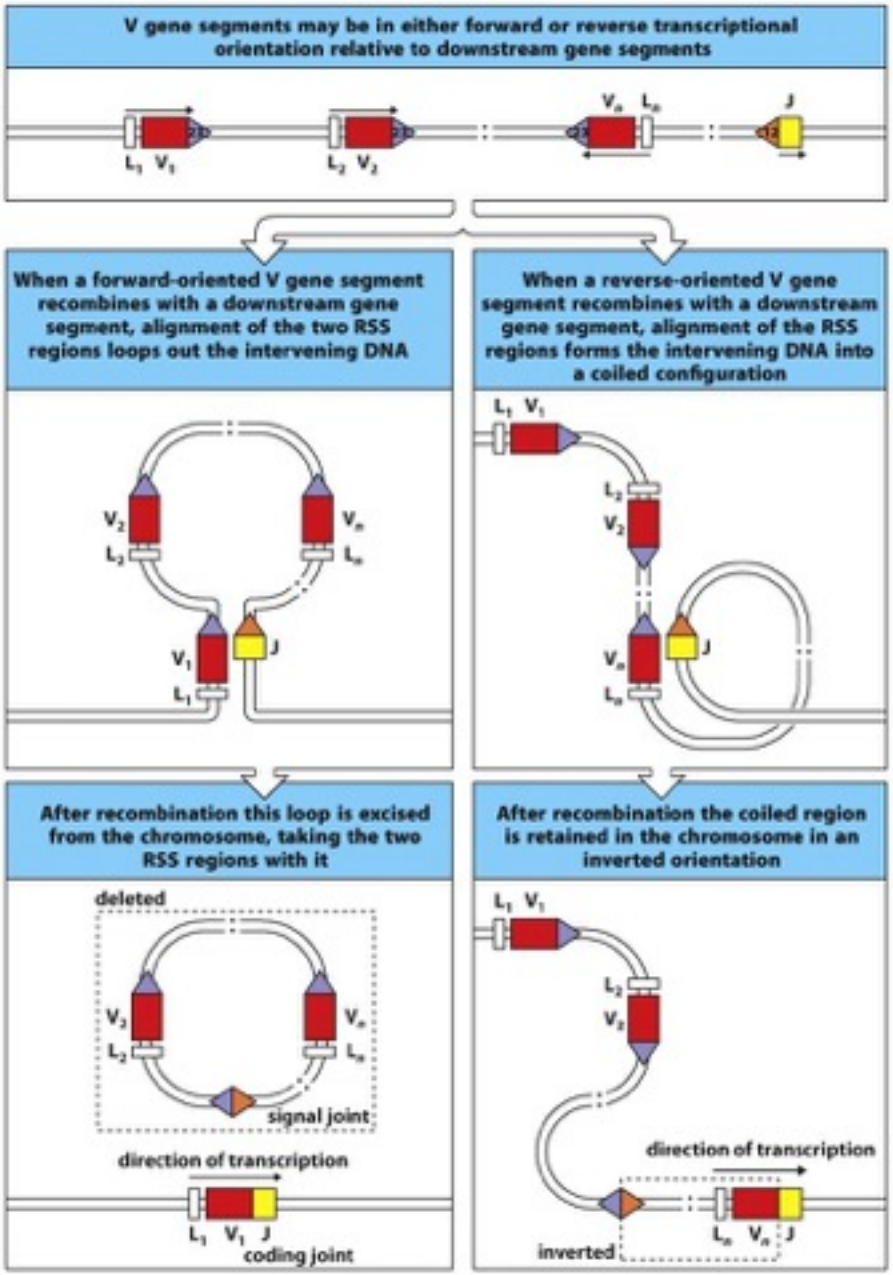


Figure 5.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

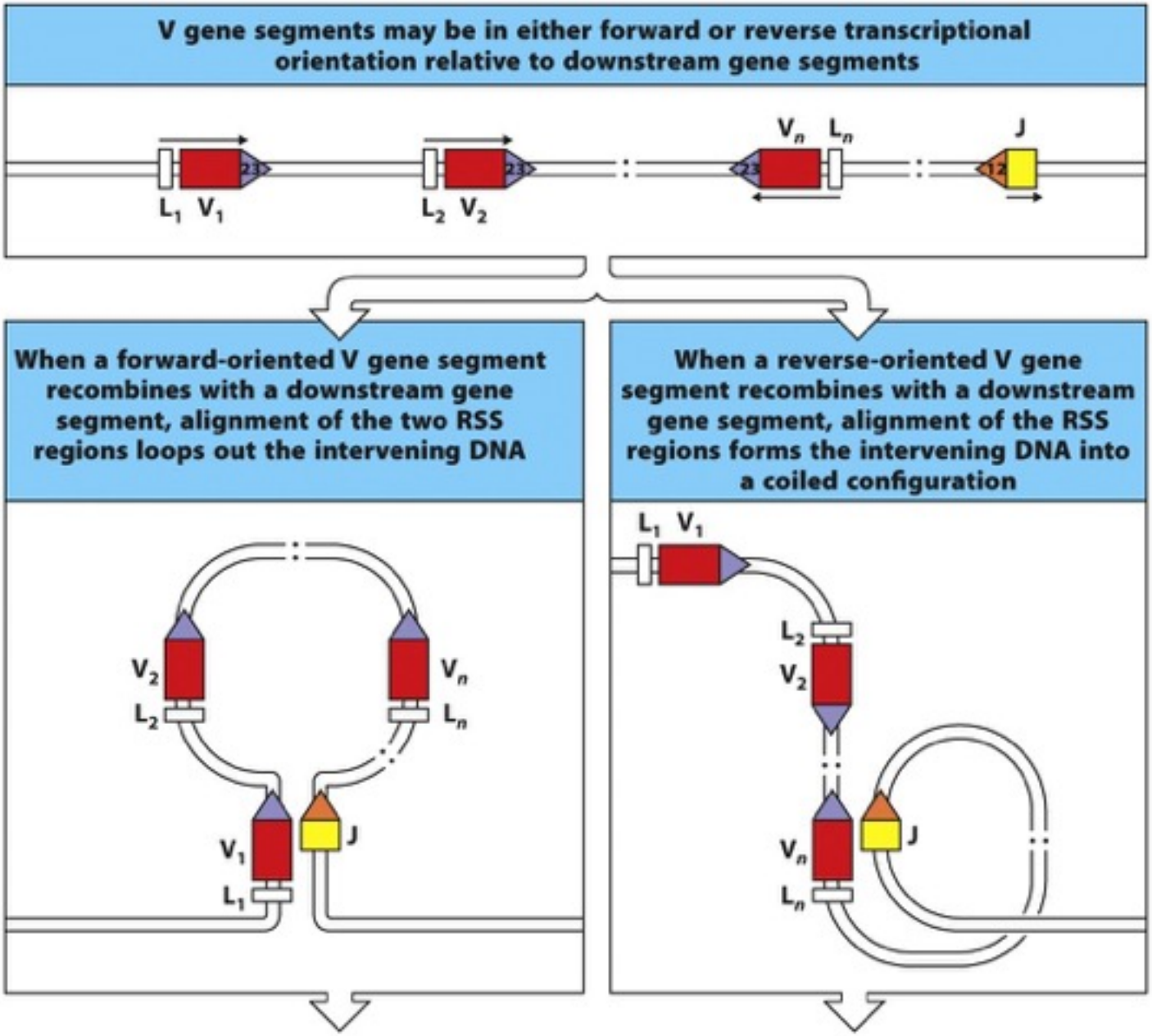


Figure 5.5 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

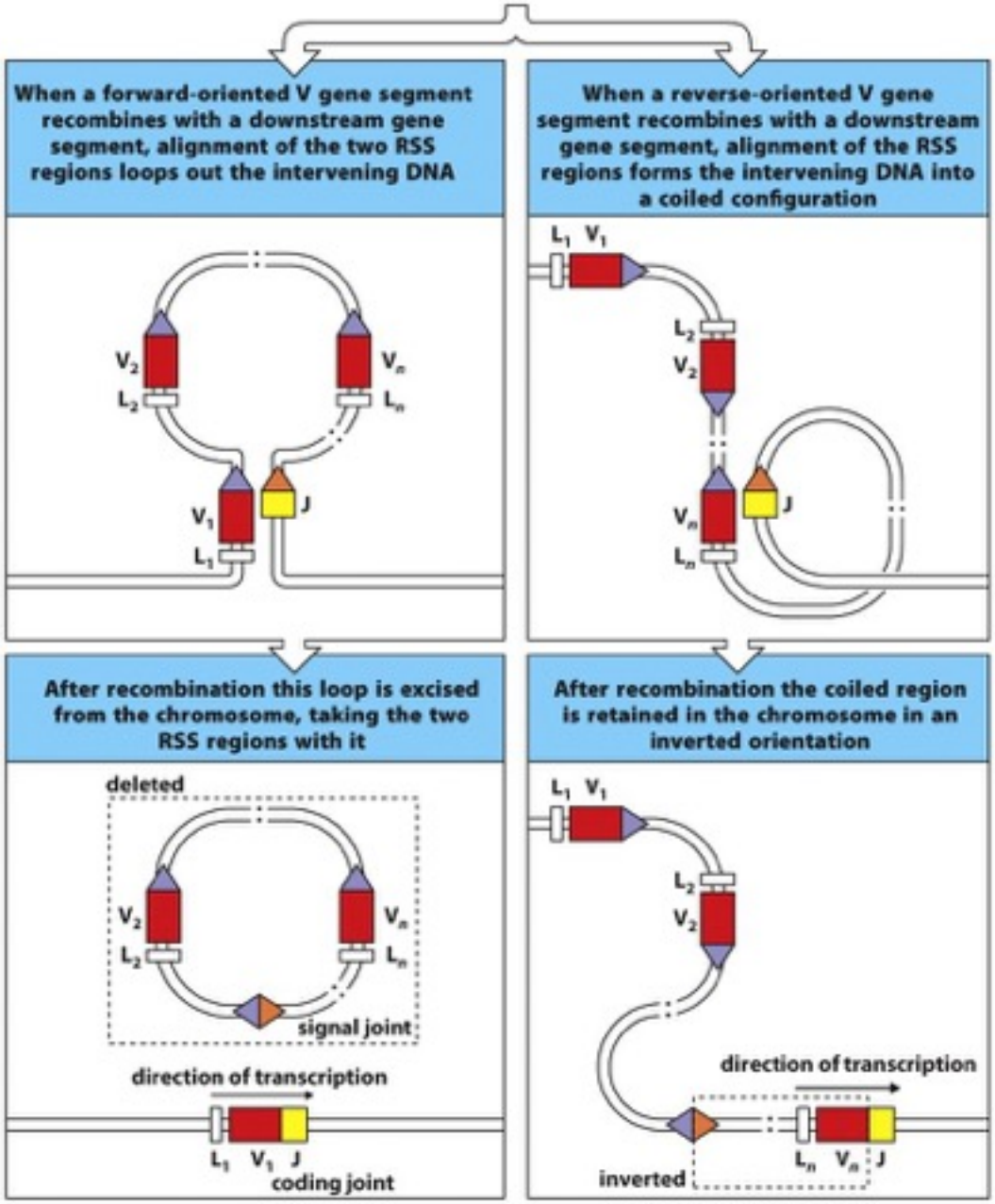


Figure 5.5 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

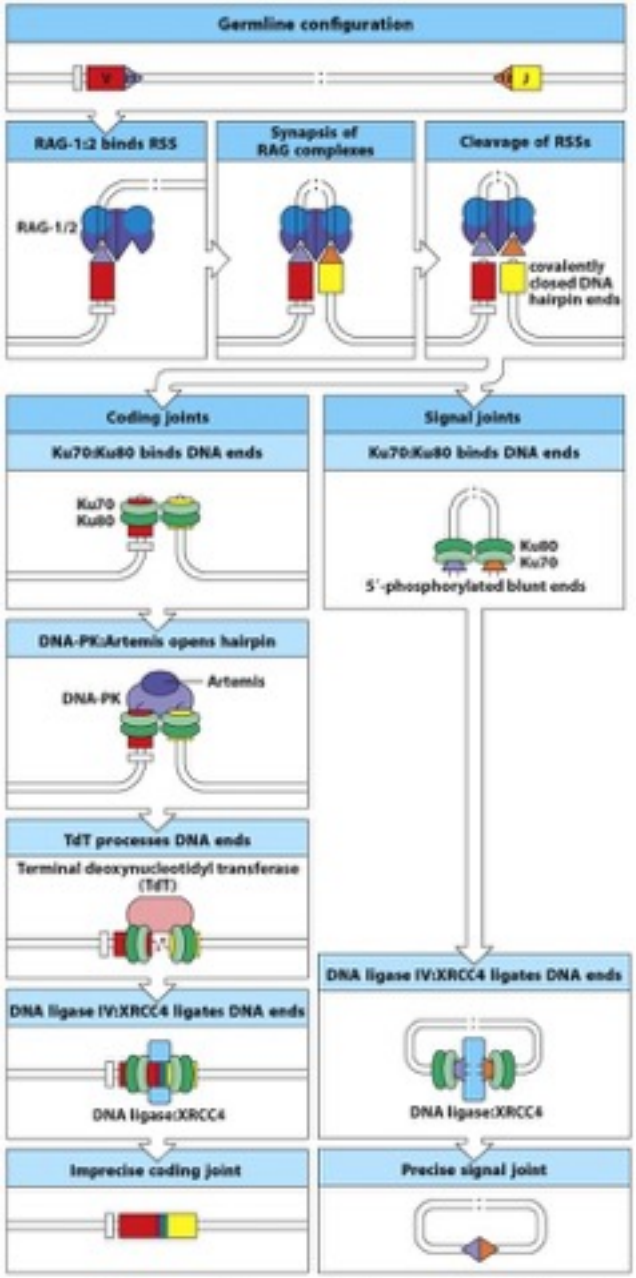


Figure 5.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

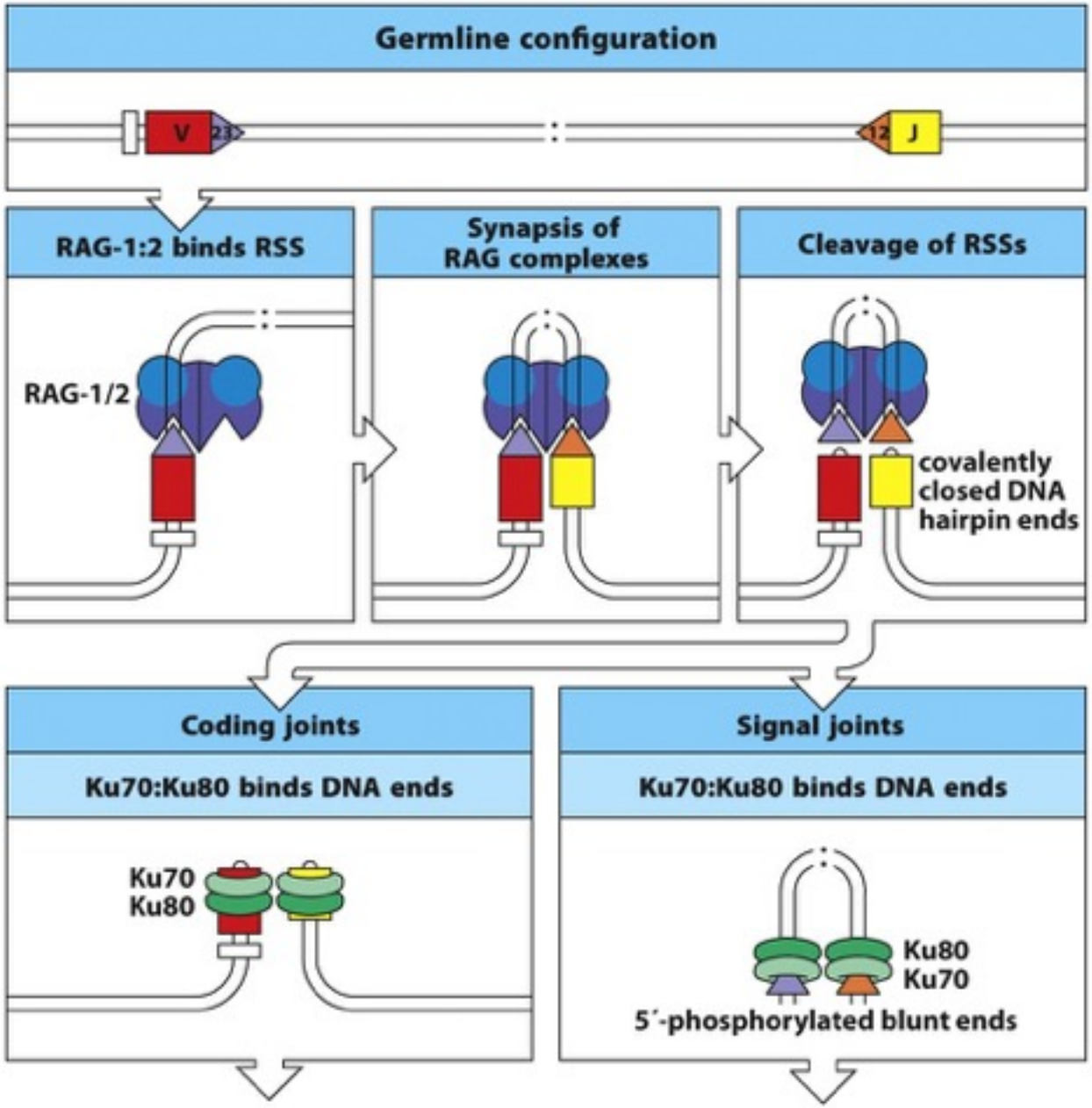


Figure 5.6 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

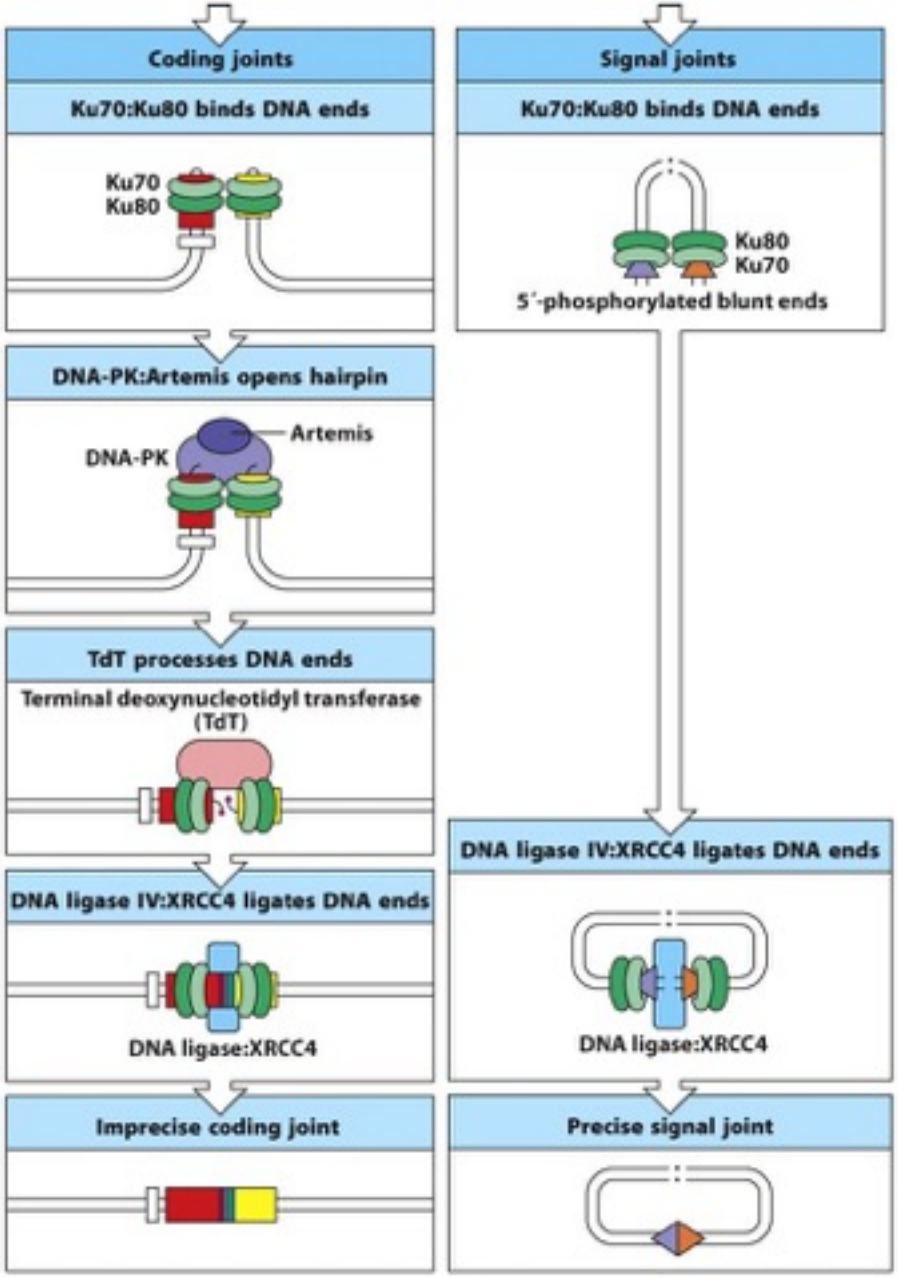


Figure 5.6 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

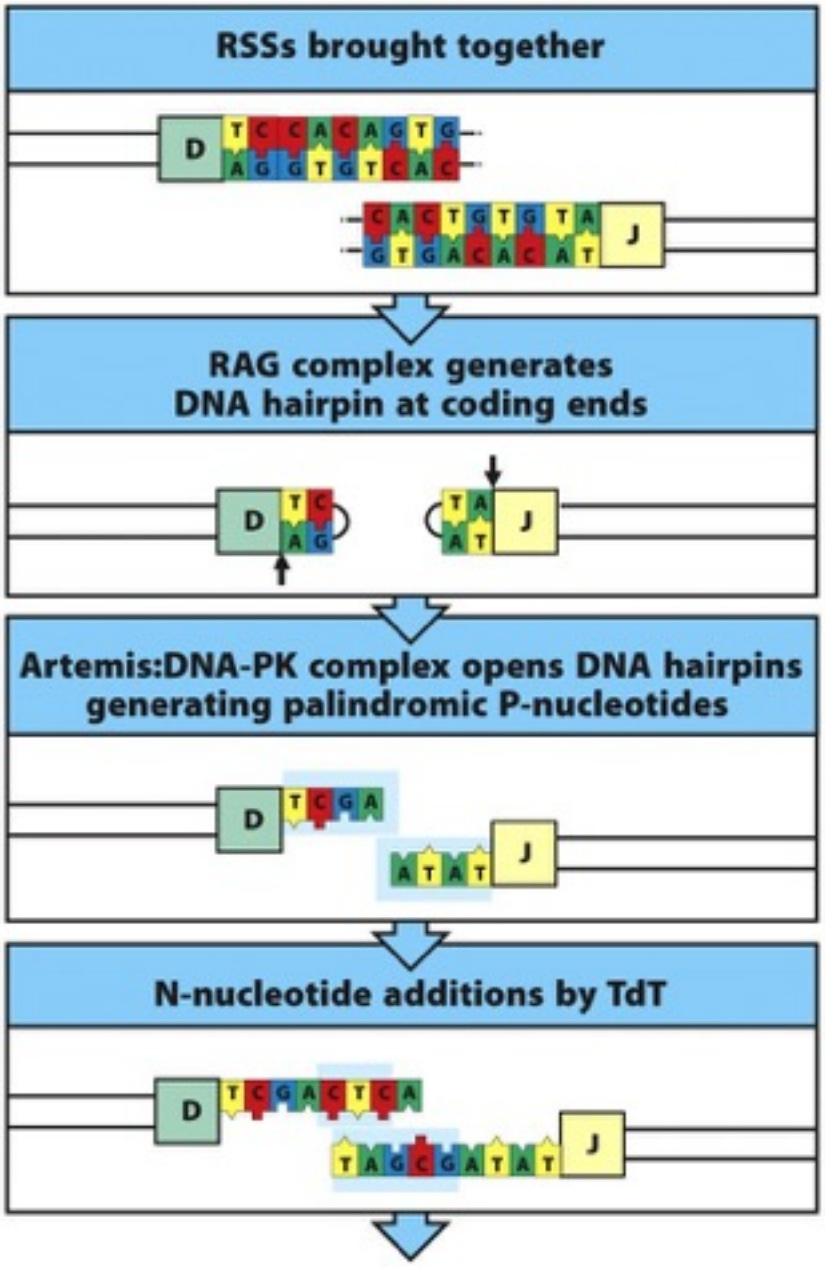


Figure 5.7 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

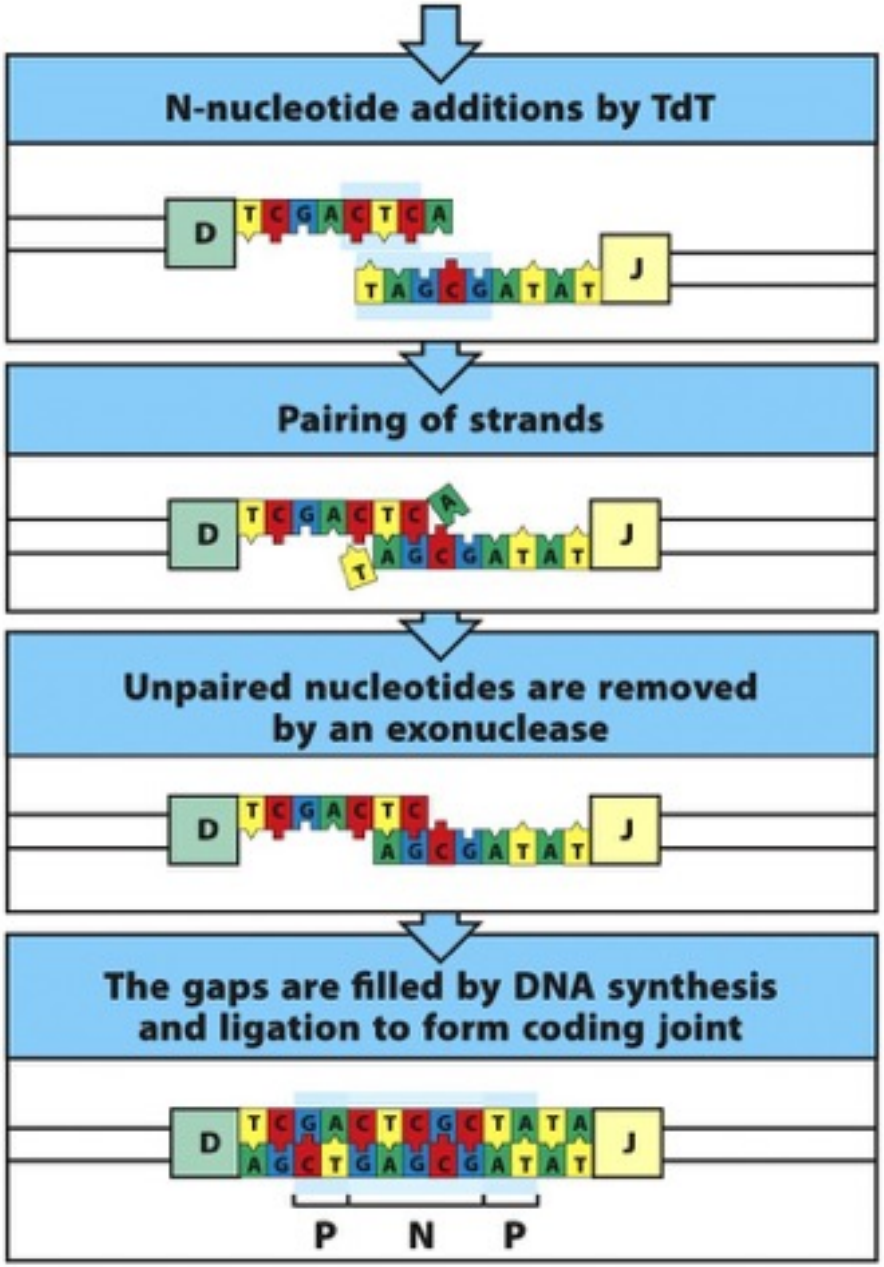


Figure 5.7 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

TCR

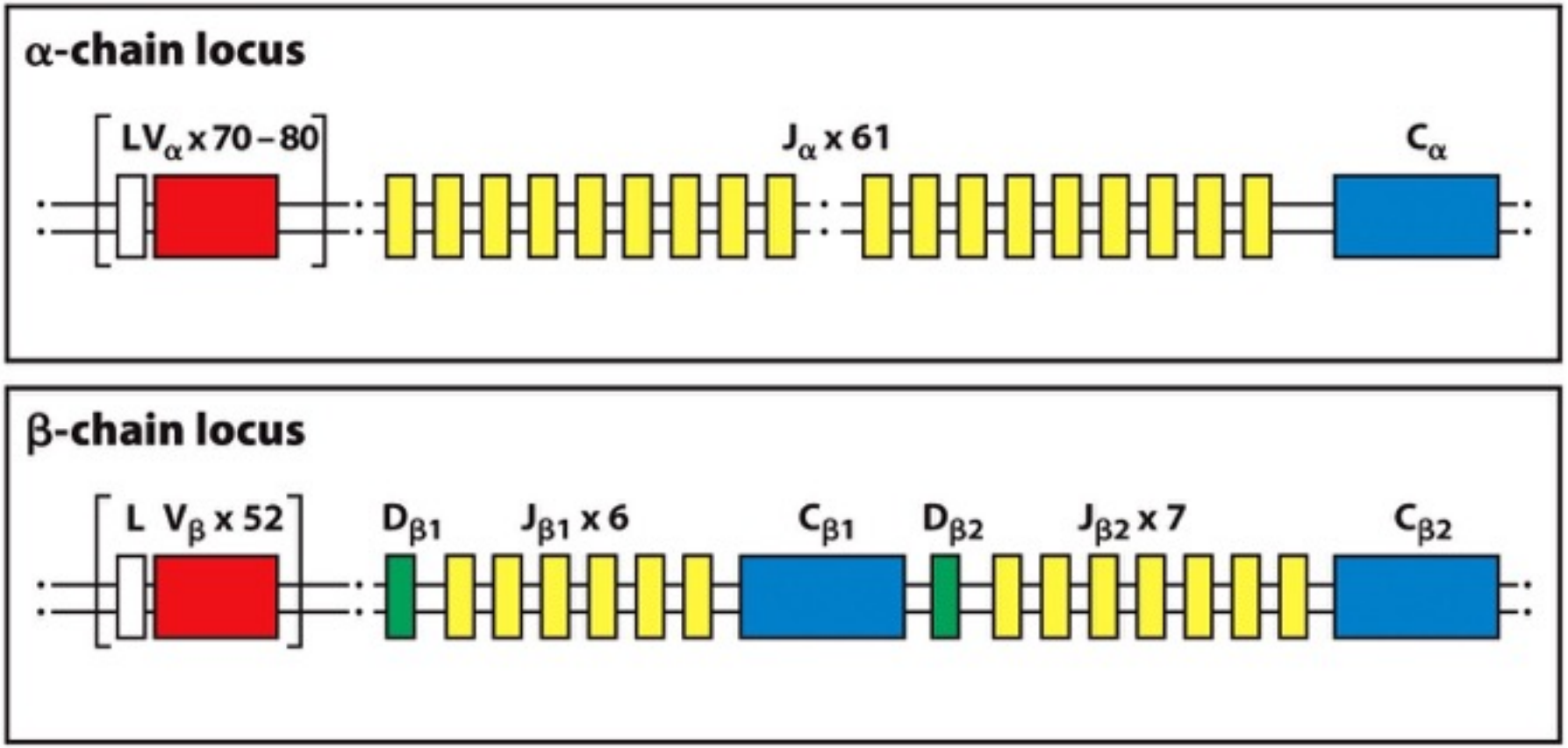


Figure 5.8 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

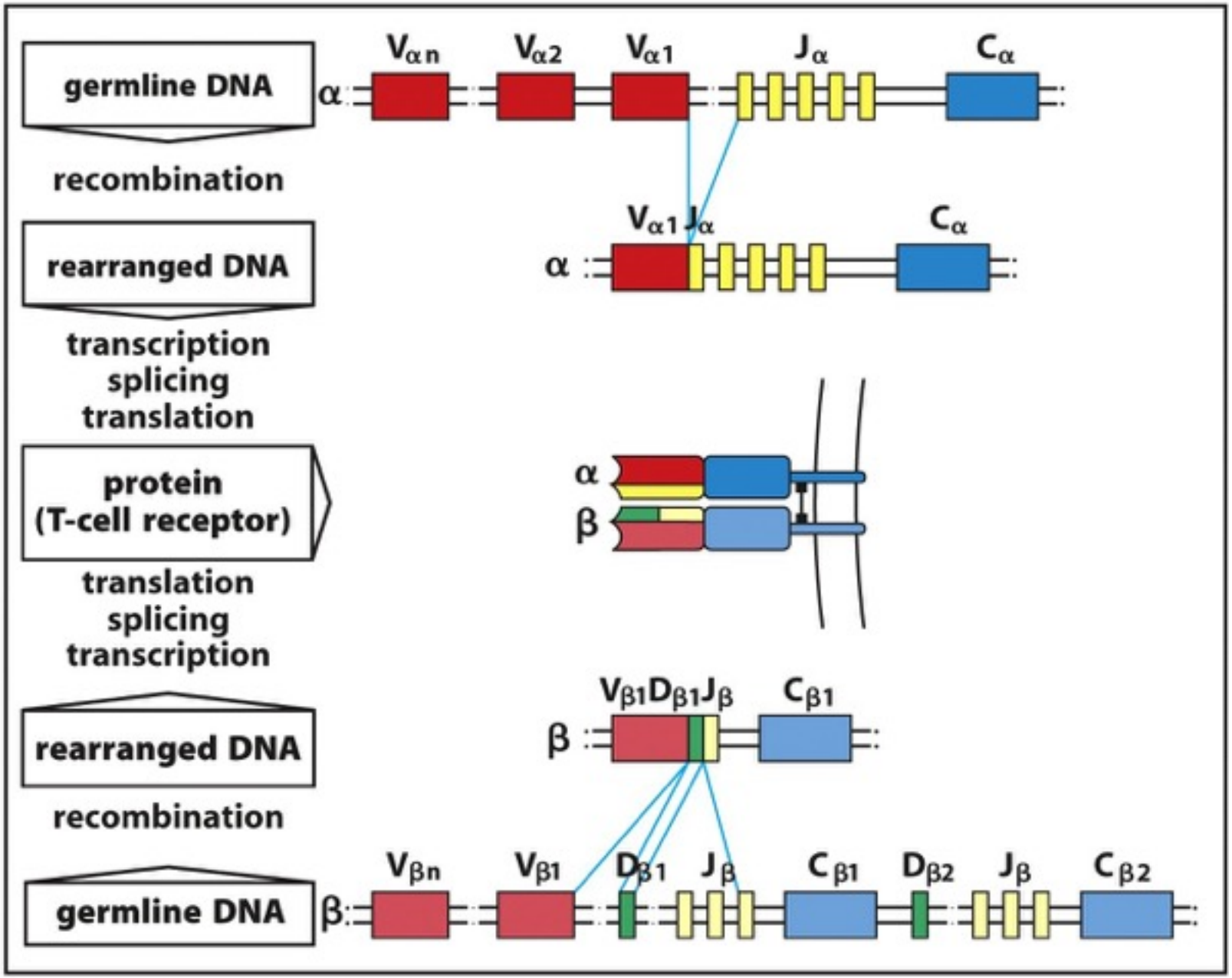


Figure 5.9 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

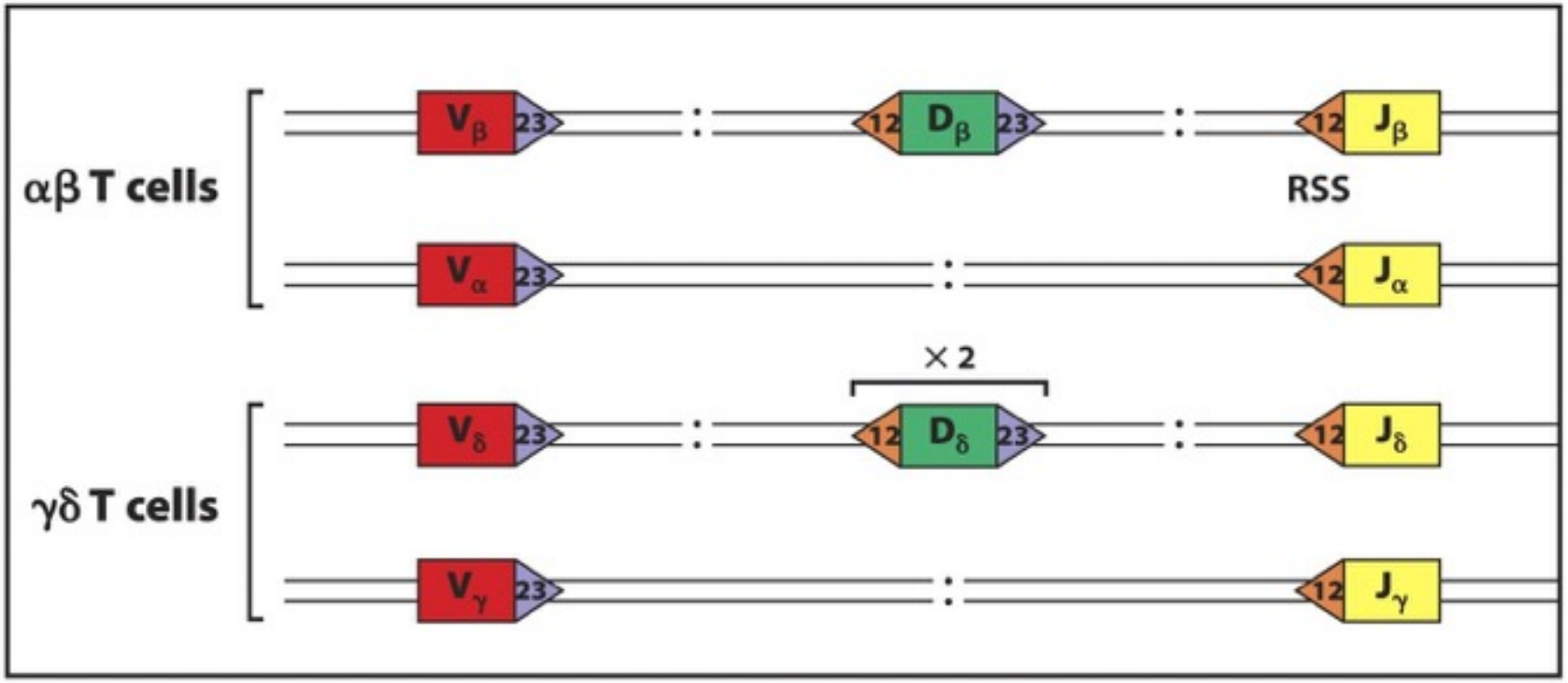
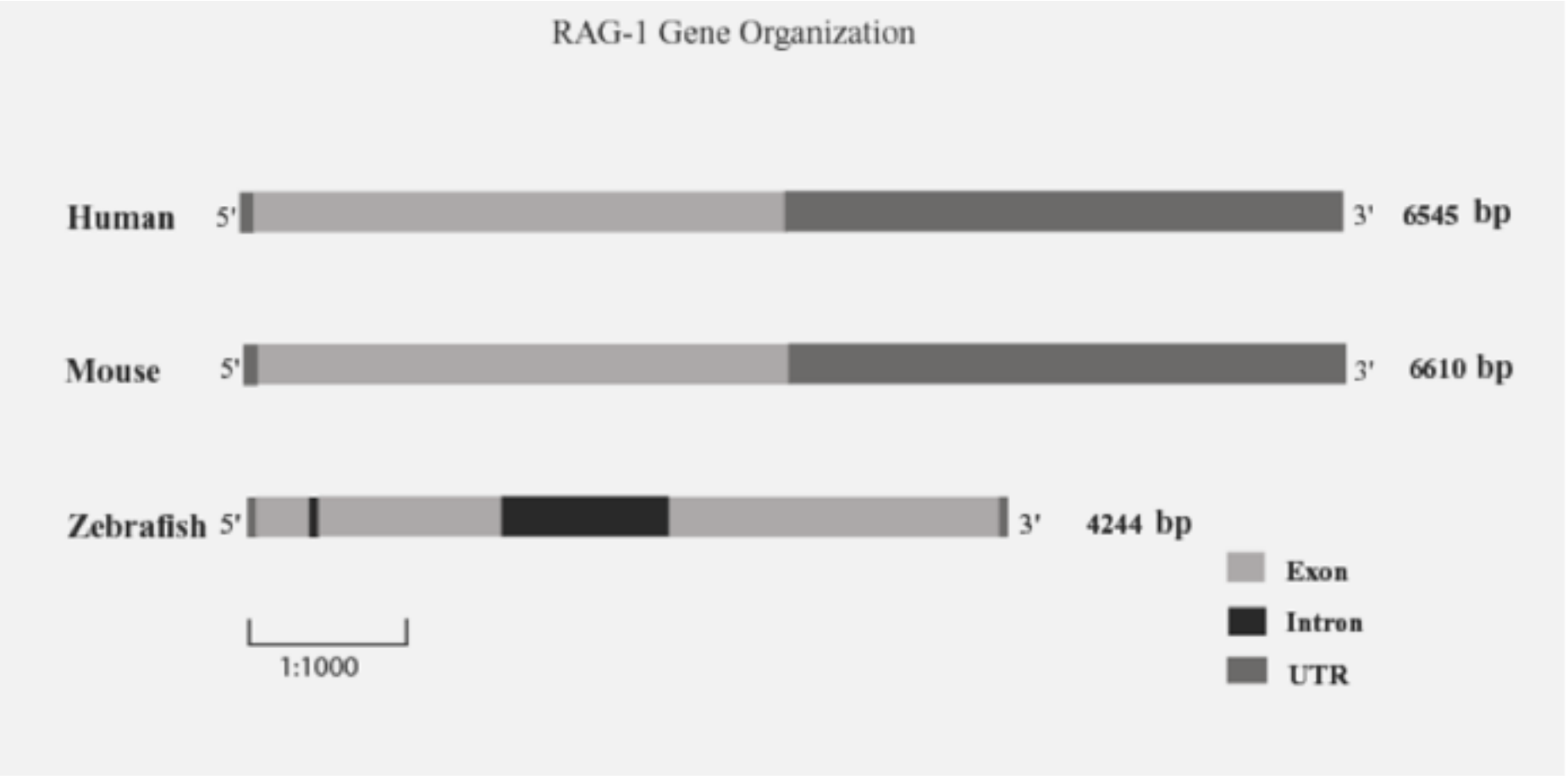


Figure 5.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Element	Immunoglobulin		α:β T-cell receptors	
	H	κ+λ	β	α
Variable segments (V)	~40	~70	52	~70
Diversity segments (D)	23	0	2	0
D segments read in three frames	rarely	–	often	–
Joining segments (J)	6	5(κ) 4(λ)	13	61
Joints with N- and P-nucleotides	2	50% of joints	2	1
Number of V gene pairs	1.9×10^6		5.8×10^6	
Junctional diversity	$\sim 3 \times 10^7$		$\sim 2 \times 10^{11}$	
Total diversity	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

Figure 5.11 Janeway's Immunobiology, 8ed. (© Garland Science 2012)



Camargo & Nahum, 2005

splicing alternativo gera a forma secretada da IgM

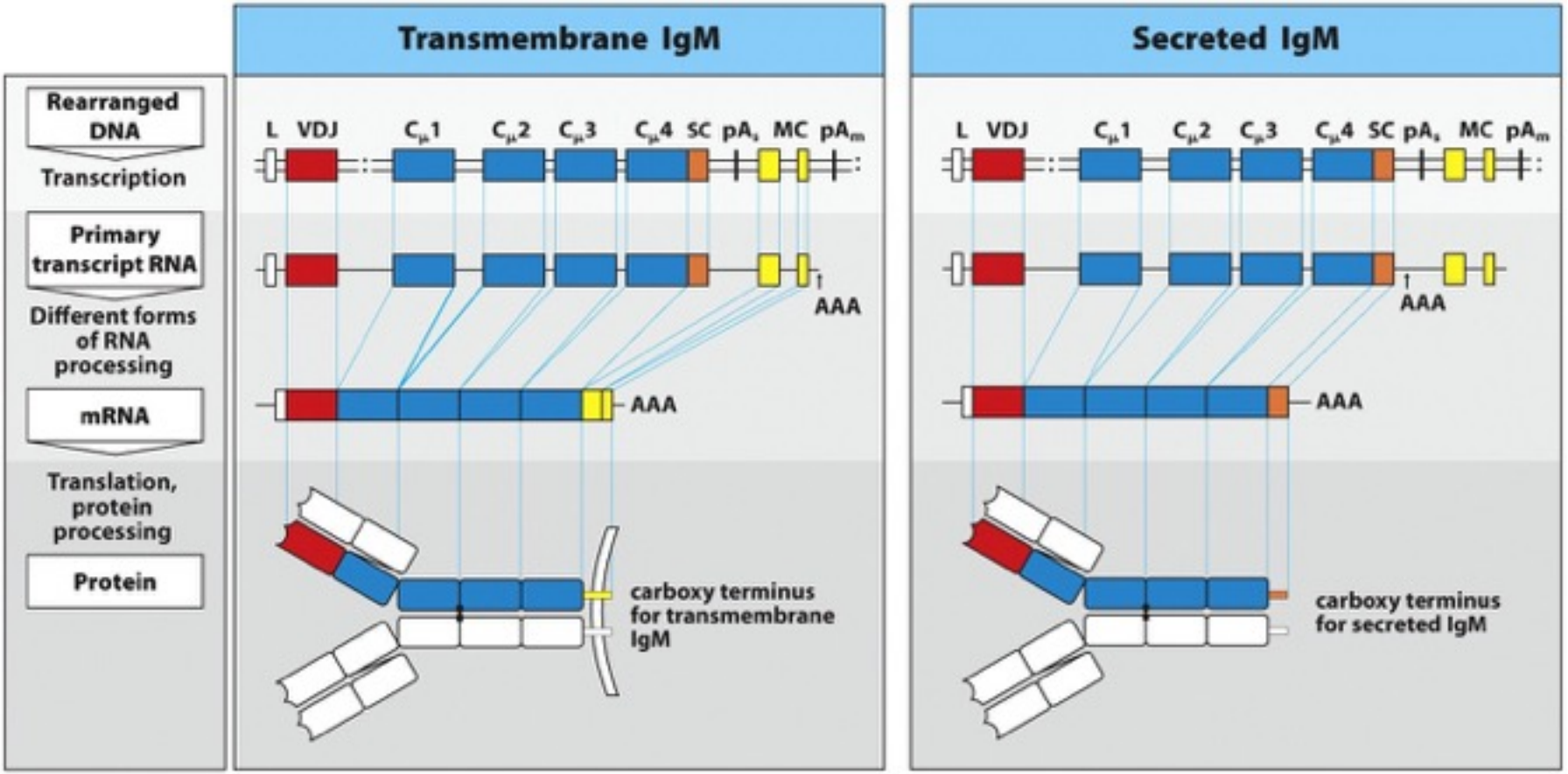


Figure 5.18 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

splicing alternativo gera a IgD (também transmembrana)

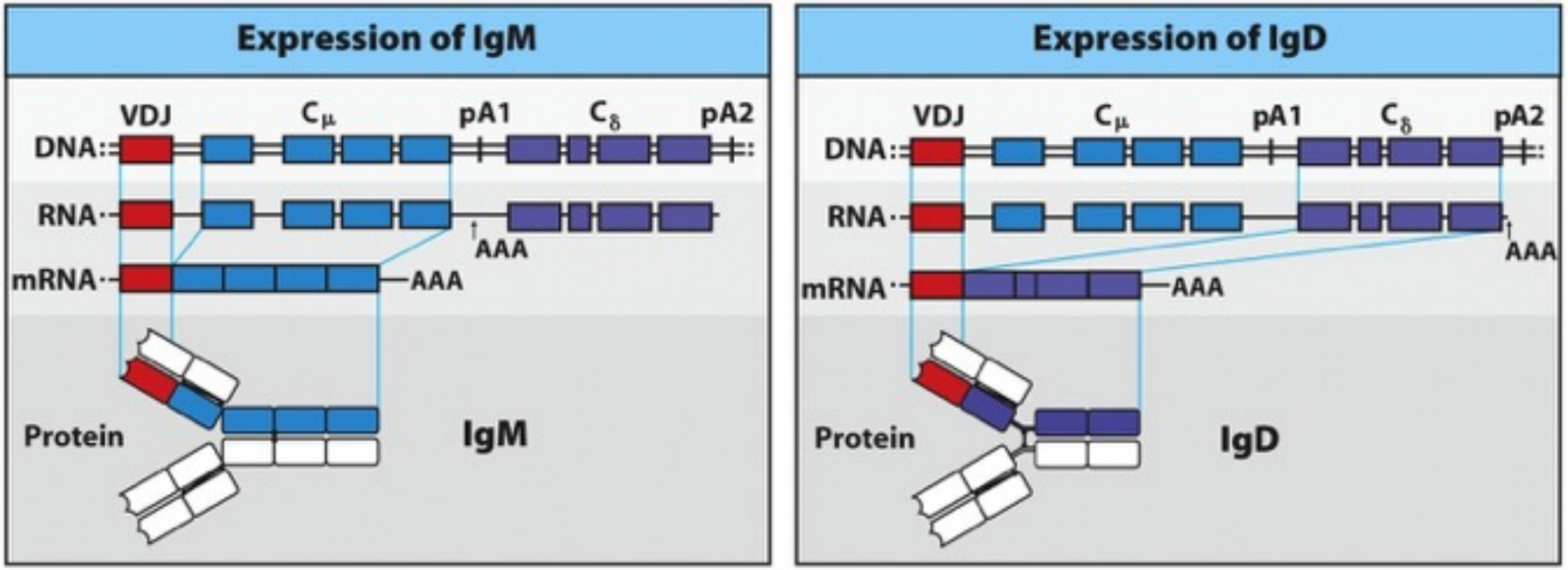


Figure 5.17 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

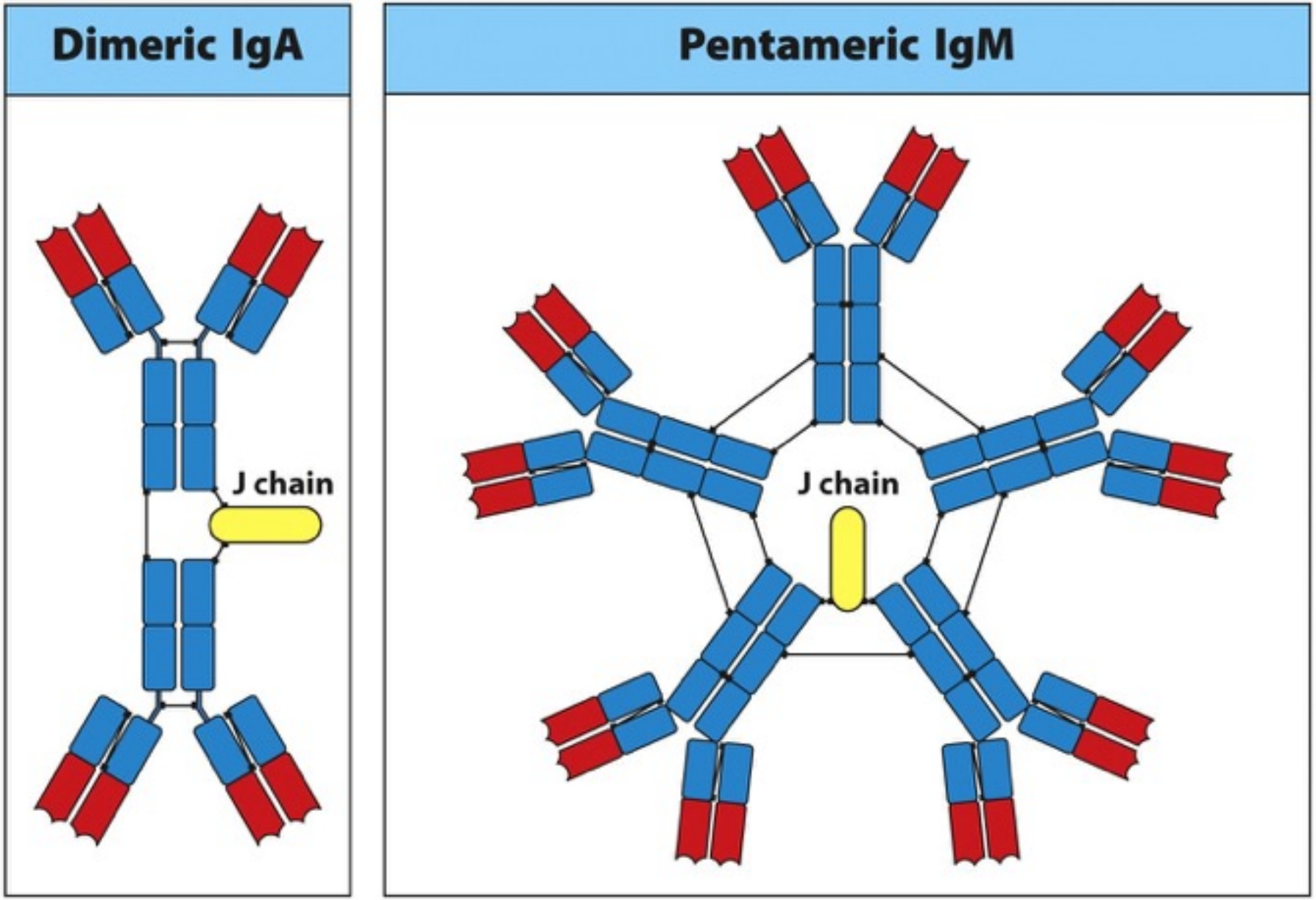


Figure 5.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

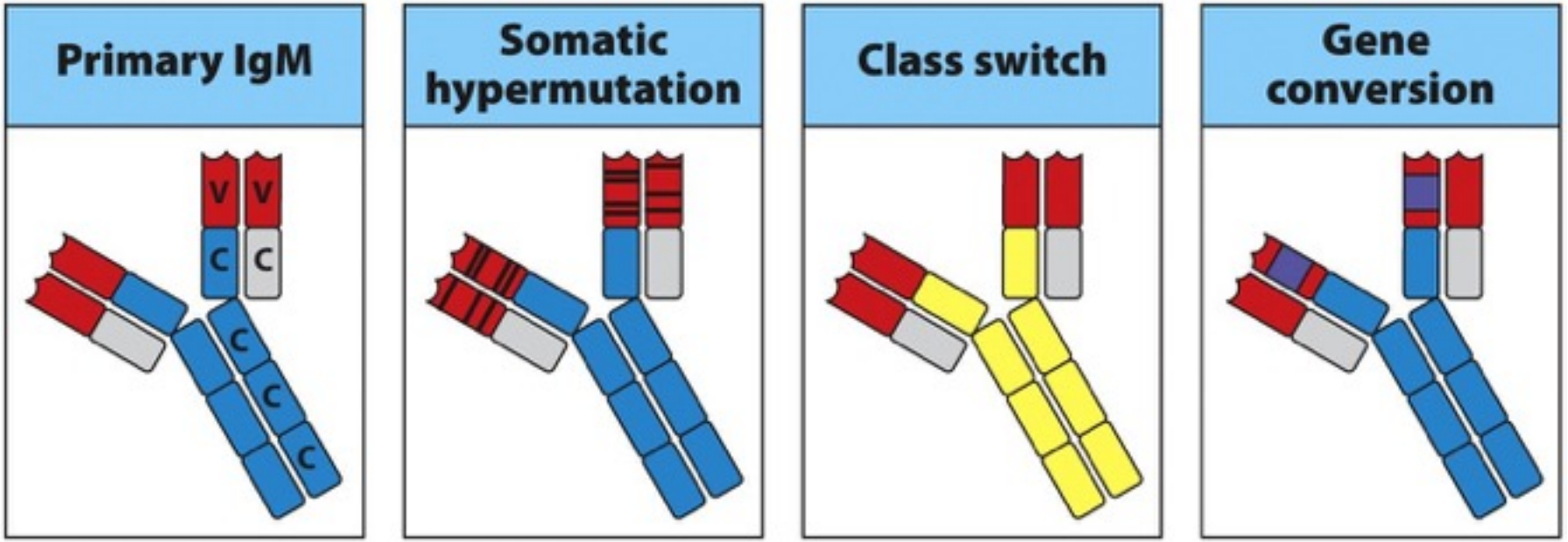


Figure 5.20 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Mecanismos geradores de diversidade nos receptores BCR e TCR:

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    * adição aleatória de bases

* hipermutação somática (maturação de afinidade) —> somente B
* troca de classe ou isotipo —> somente B
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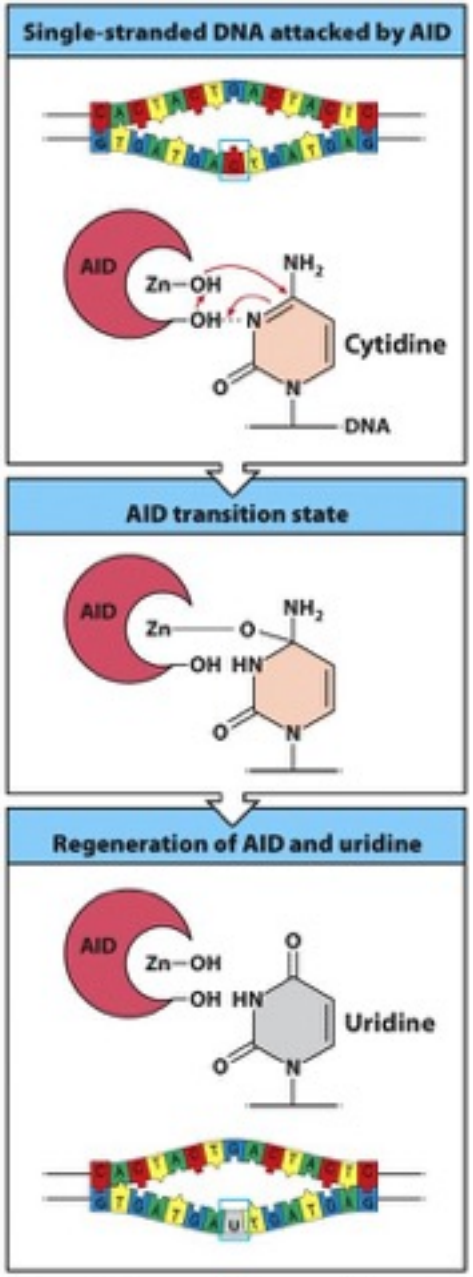


Figure 5.21 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

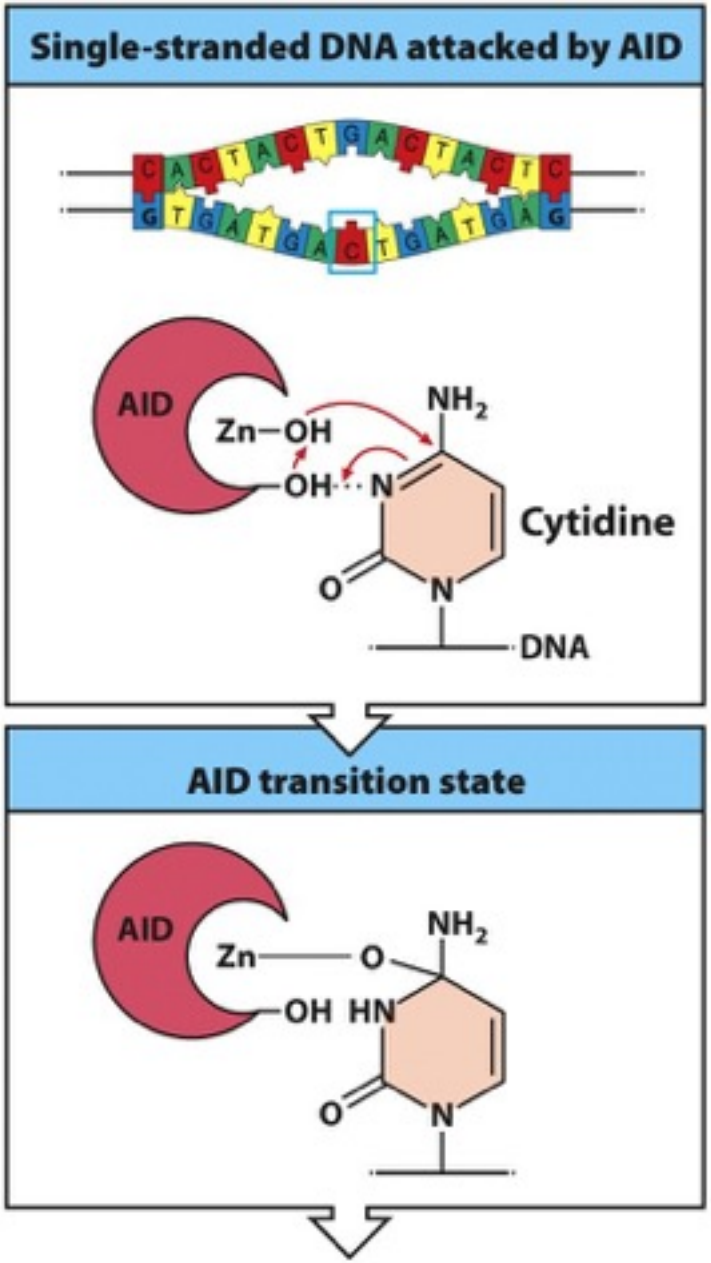


Figure 5.21 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

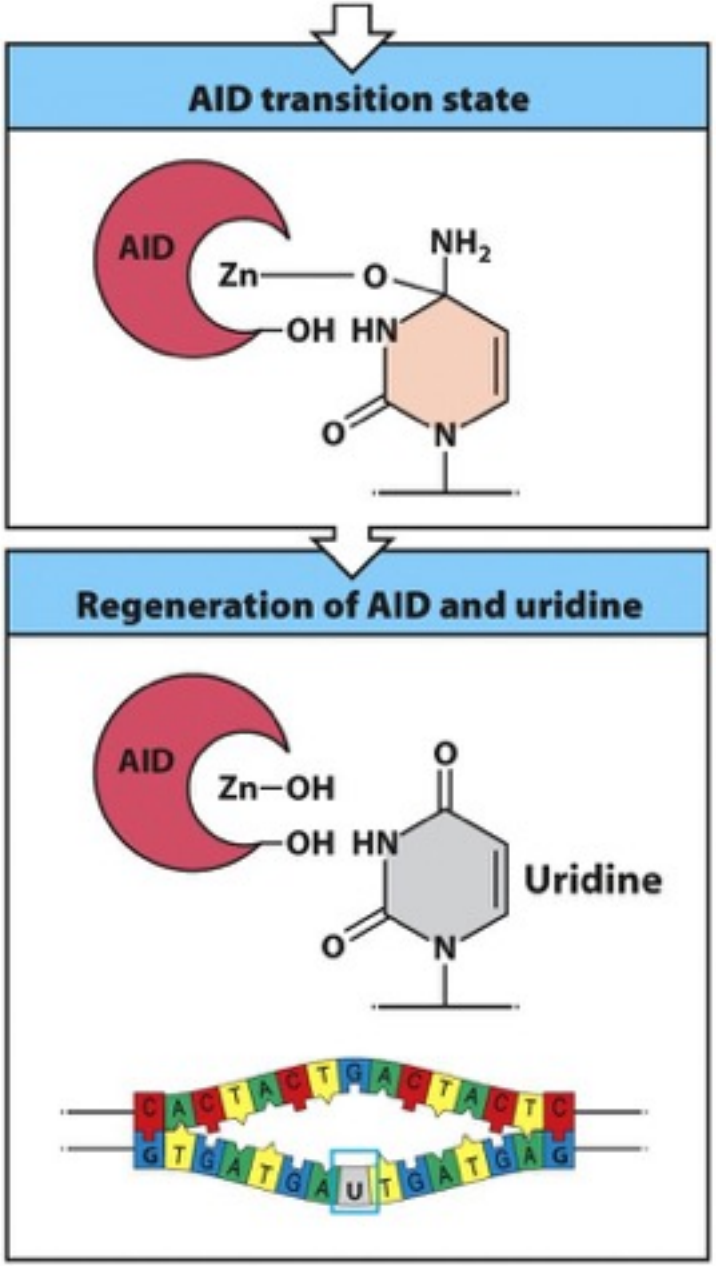


Figure 5.21 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

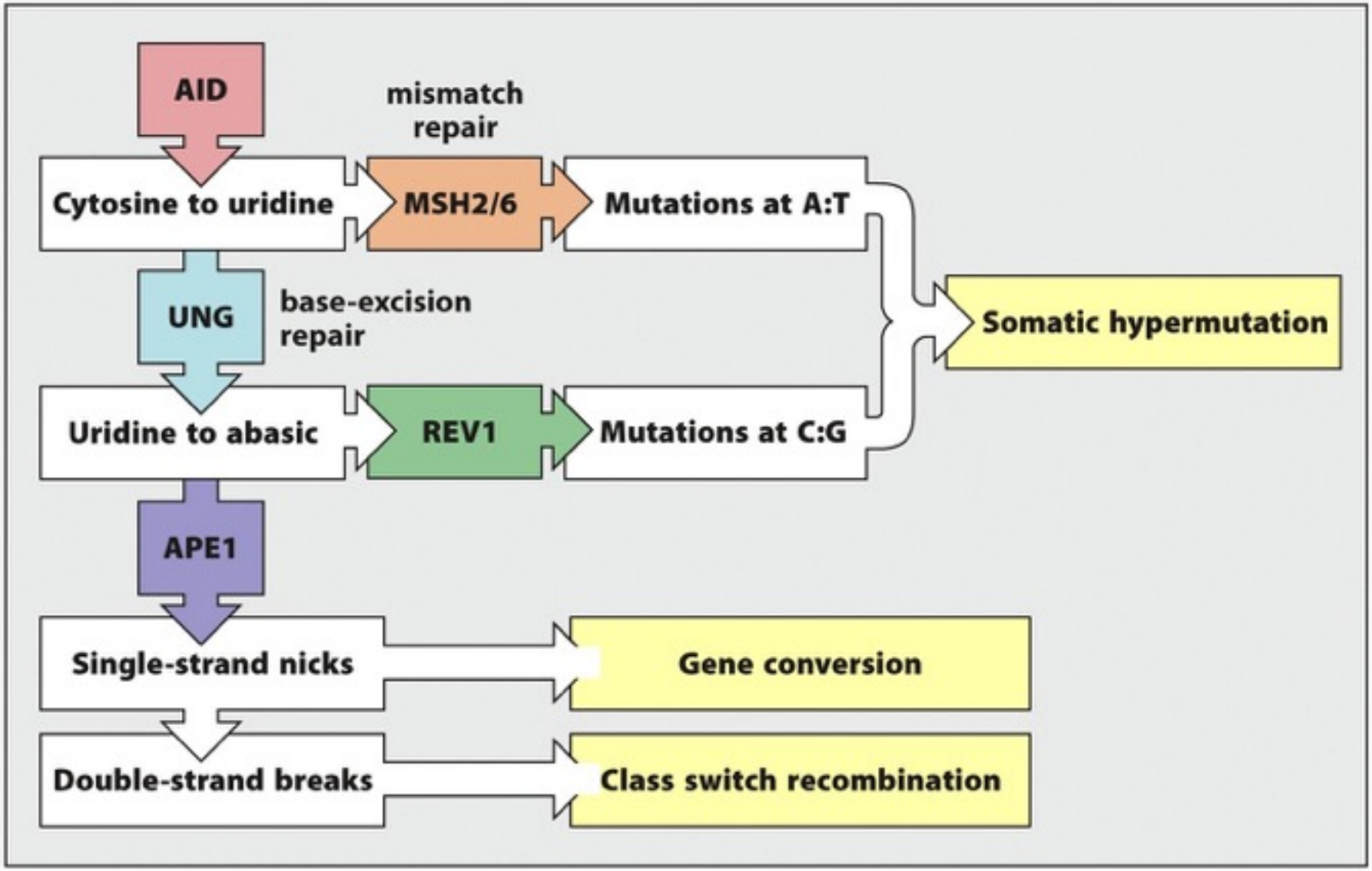


Figure 5.22 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

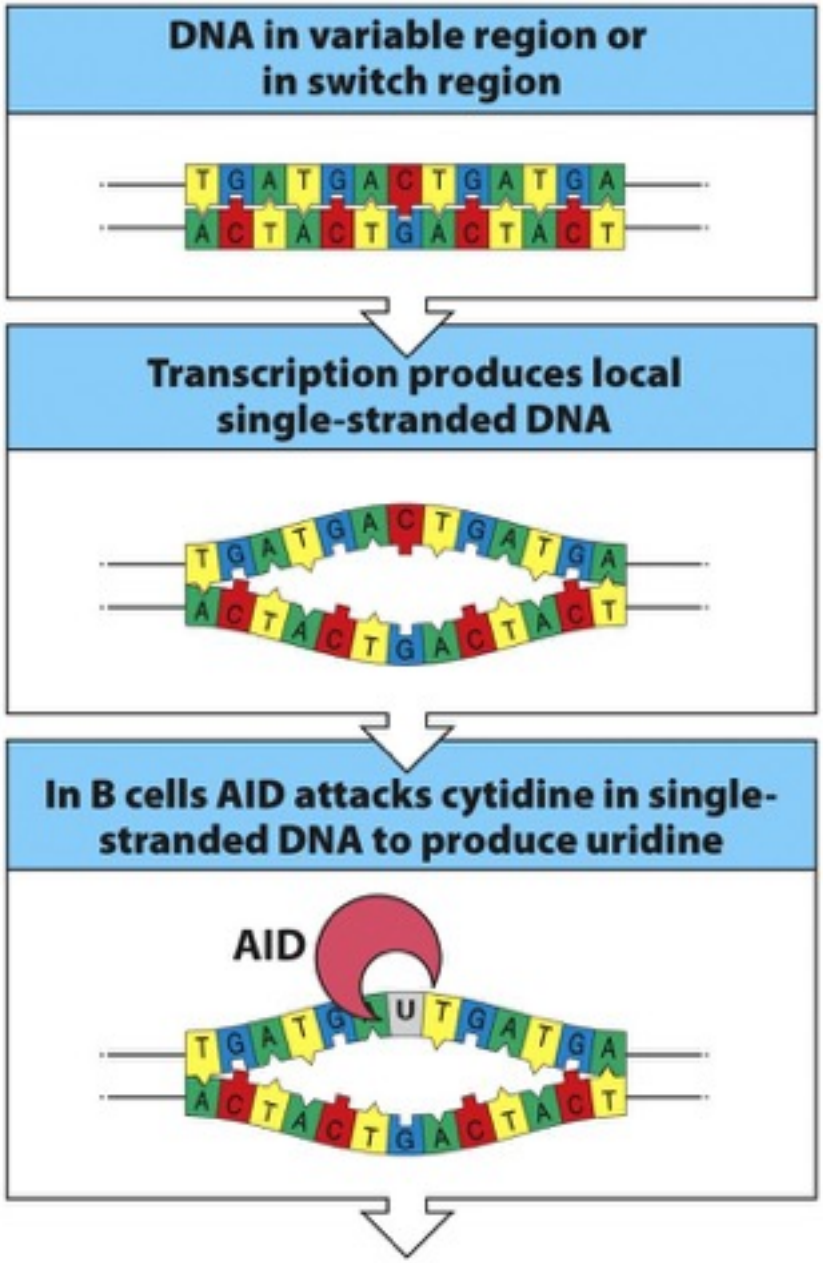


Figure 5.23 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Hipermutação Somática ou Maturação de Afinidade

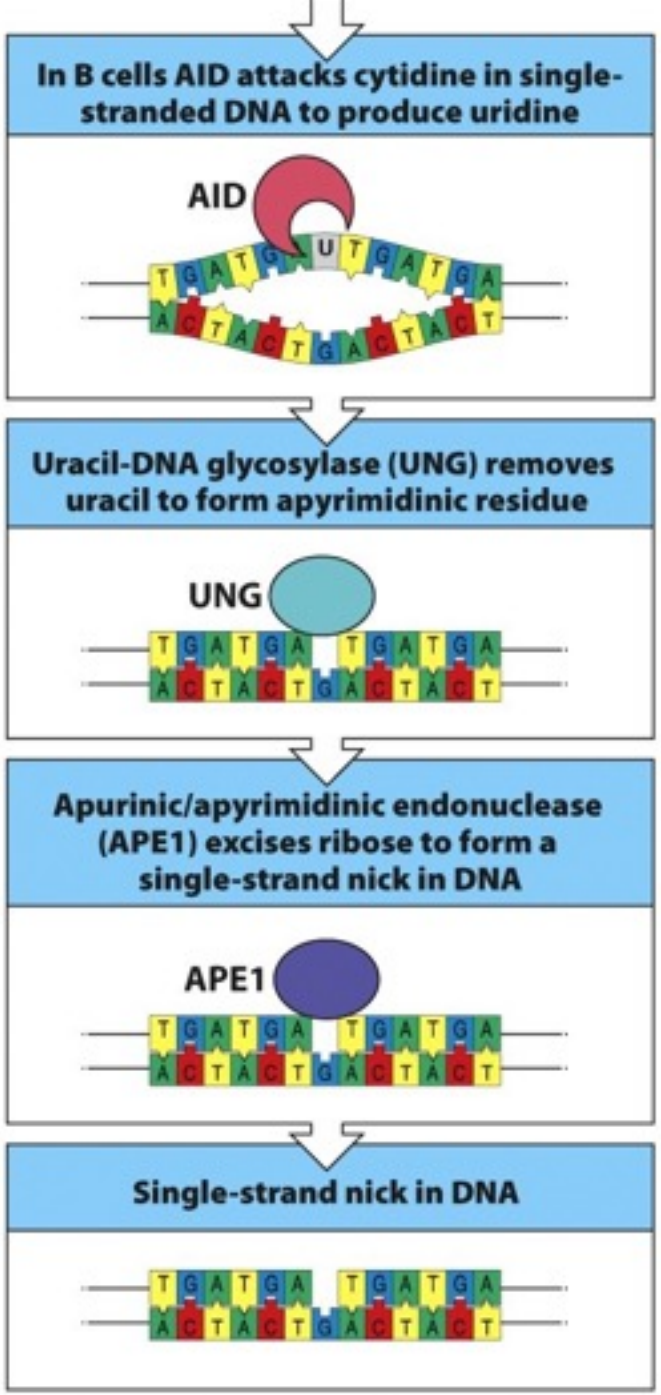


Figure 5.23 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Hipermutação Somática ou Maturação de Afinidade

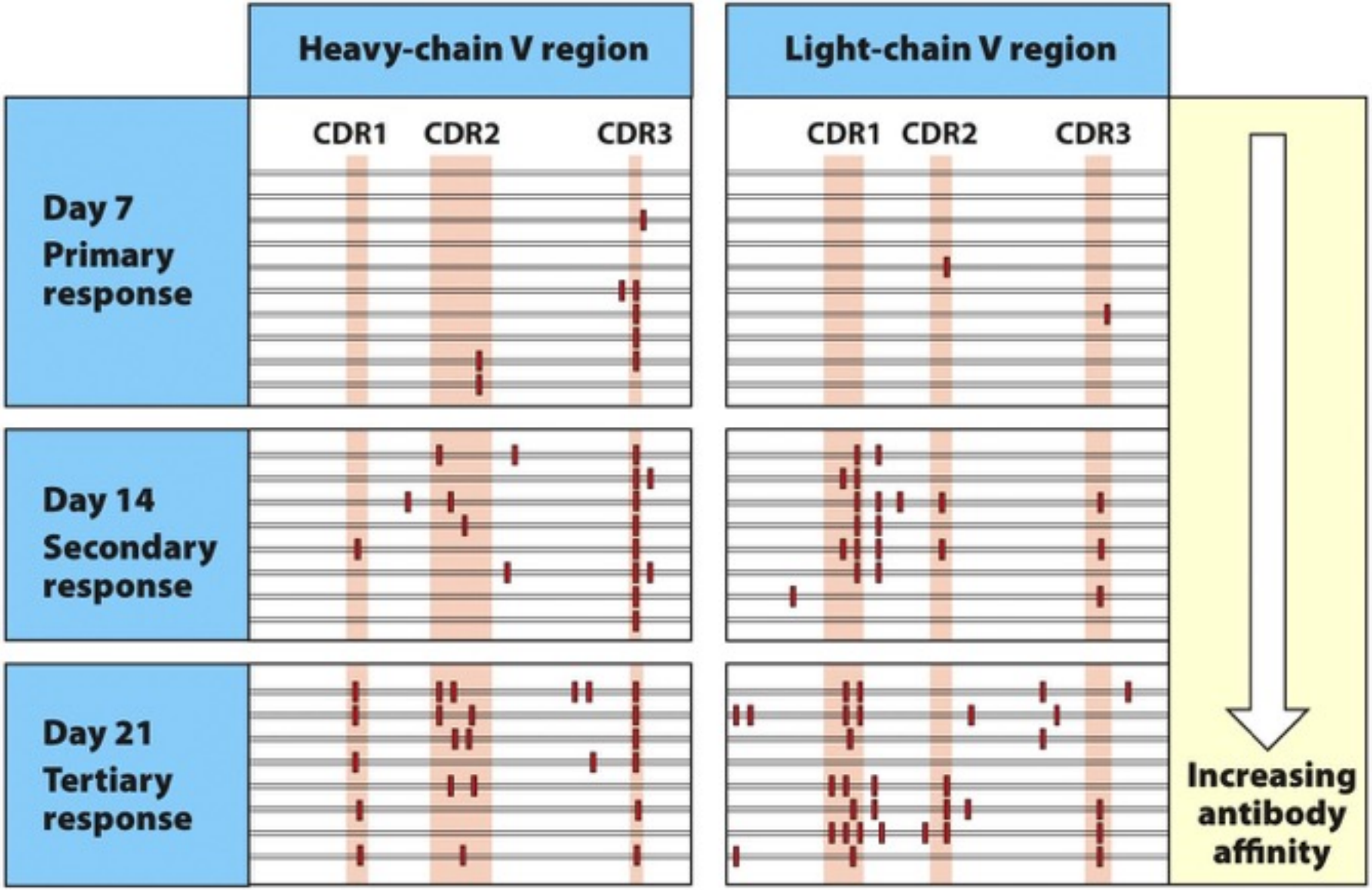


Figure 5.24 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Mecanismos geradores de diversidade nos receptores BCR e TCR:

* recombinação V(D)J —> T e B
    * diversidade funcional
    * adição aleatória de bases

* hipermutação somática (maturação de afinidade) —> somente B
* troca de classe ou isotipo —> somente B
* conversão fênica —> somente B

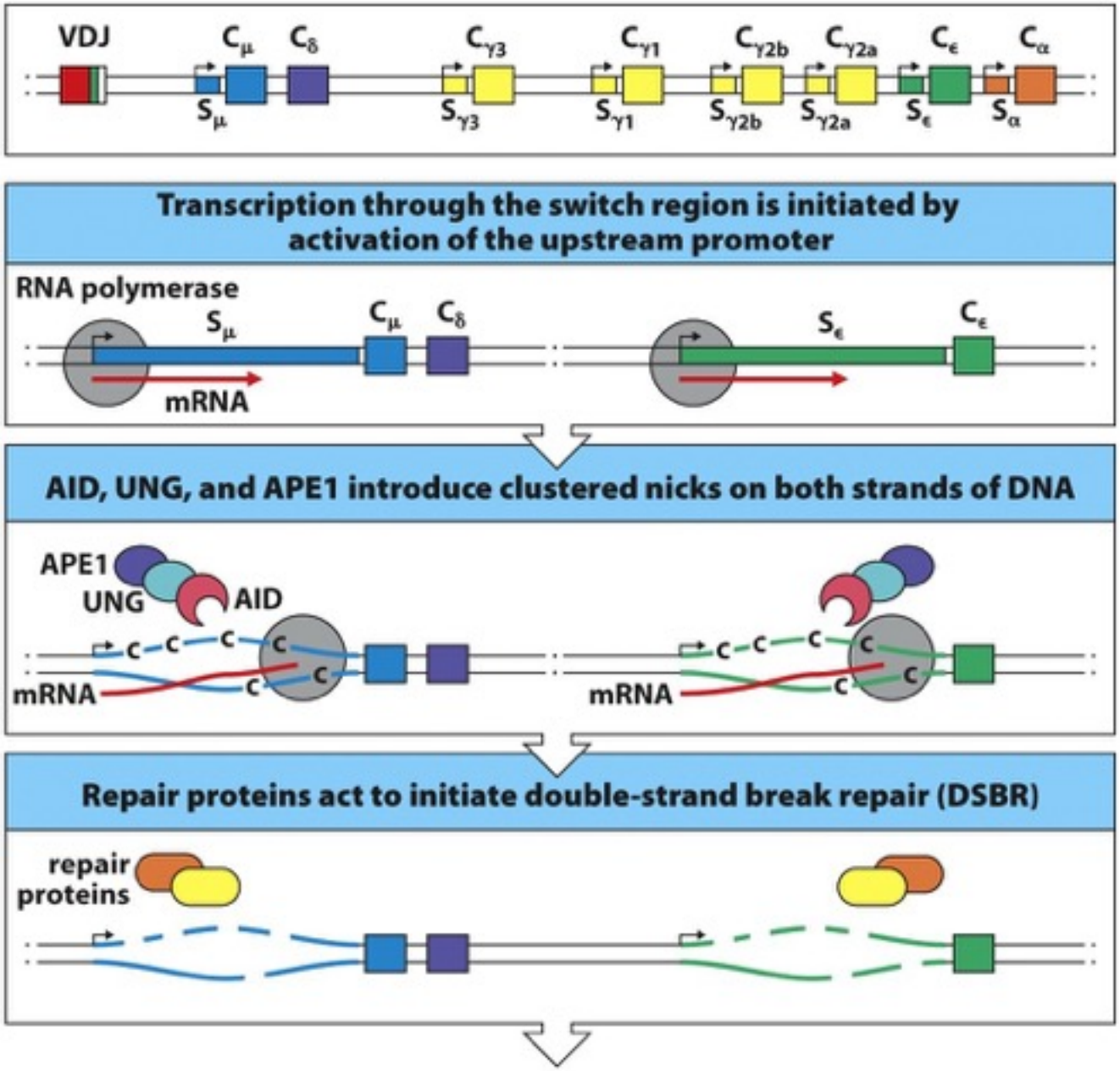


Figure 5.25 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Troca de Classe ou Troca de Isotipo

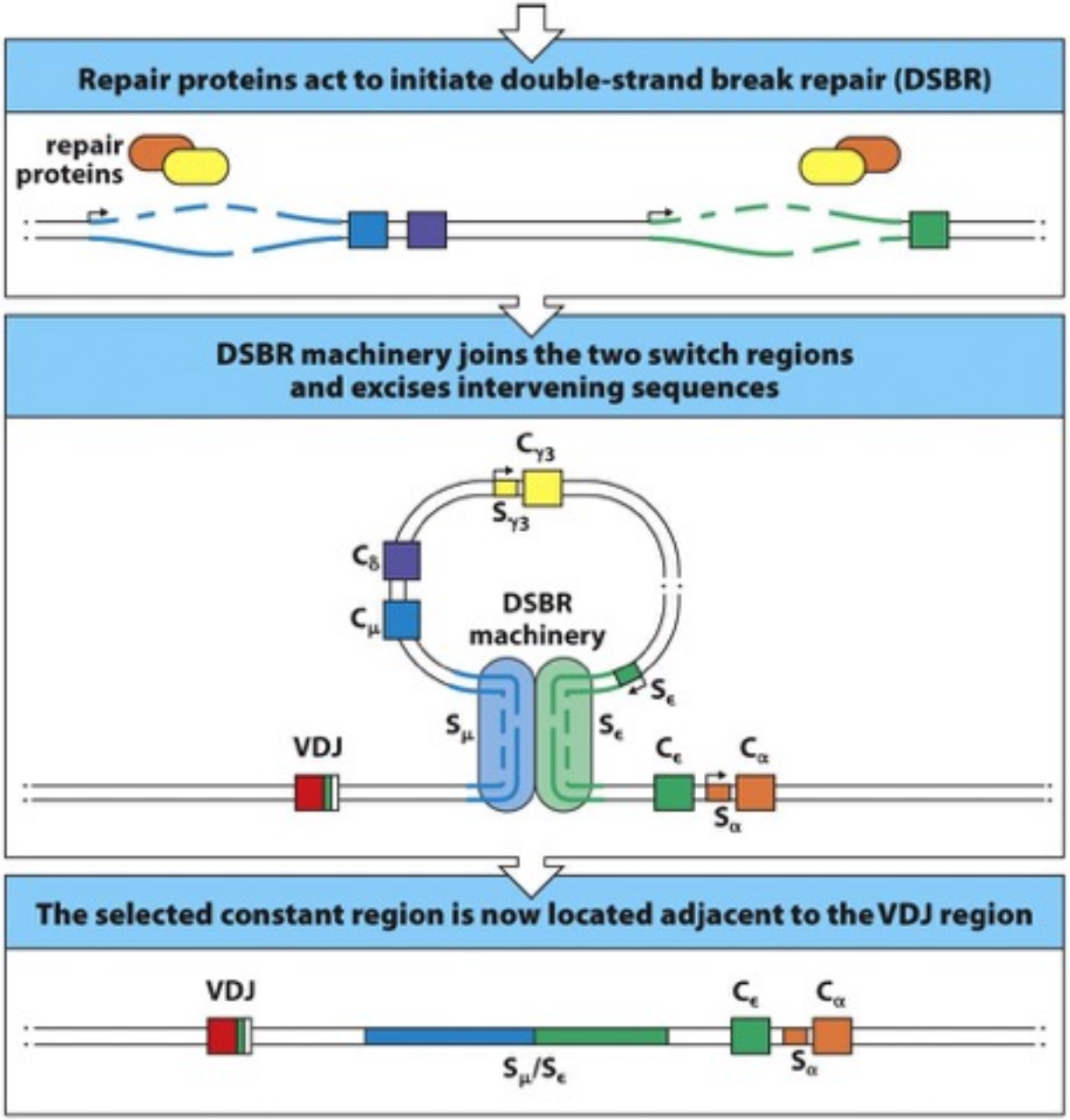


Figure 5.25 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Troca de Classe ou Troca de Isotipo

Mecanismos geradores de diversidade nos receptores BCR e TCR:

* recombinação V(D)J —> T e B
    * diversidade funcional
    * adição aleatória de bases

* hipermutação somática (maturação de afinidade) —> somente B
* troca de classe ou isotipo —> somente B
* conversão gênica —> somente B

Conversão Gênica

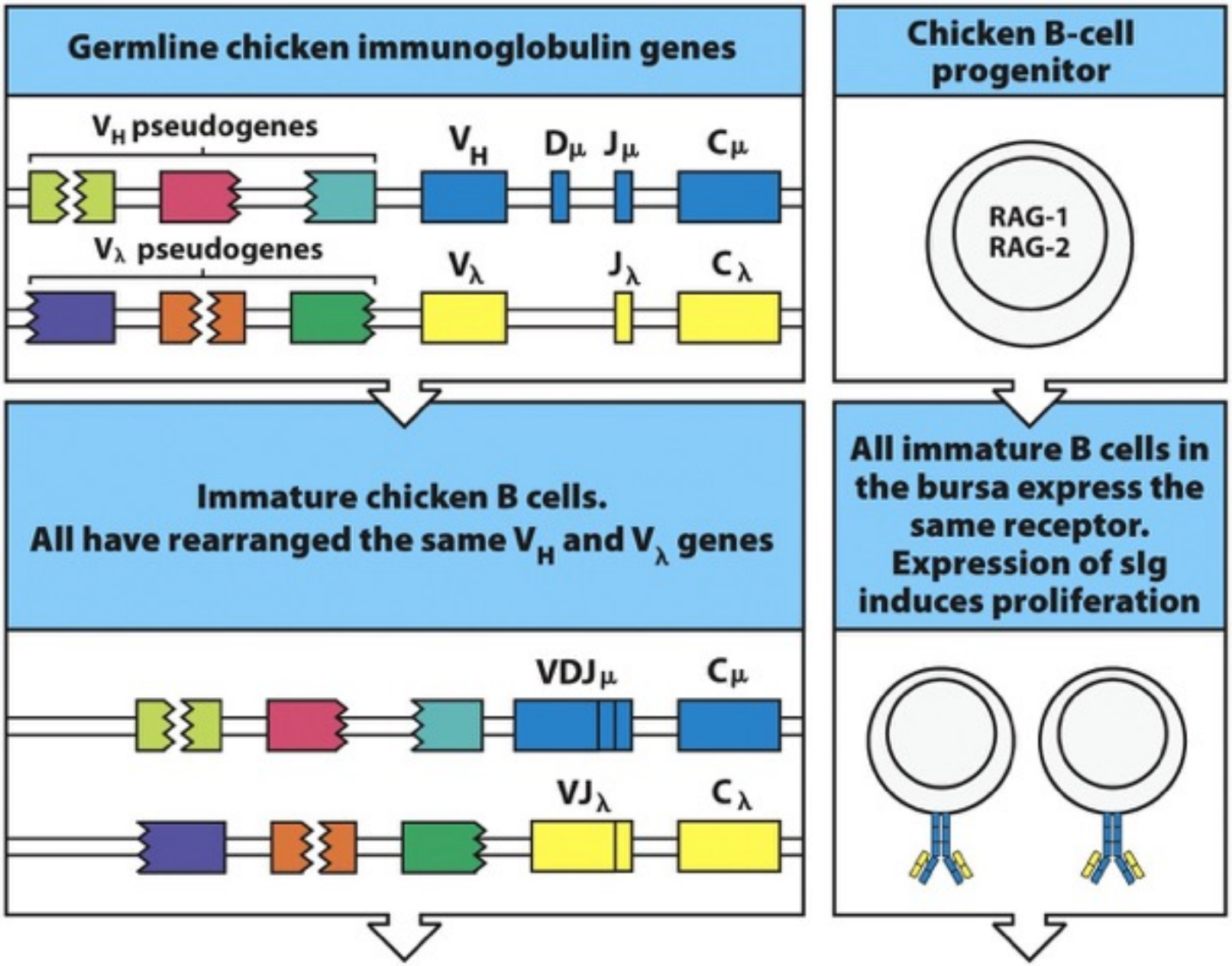


Figure 5.30 part 1 of 3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Conversão Gênica

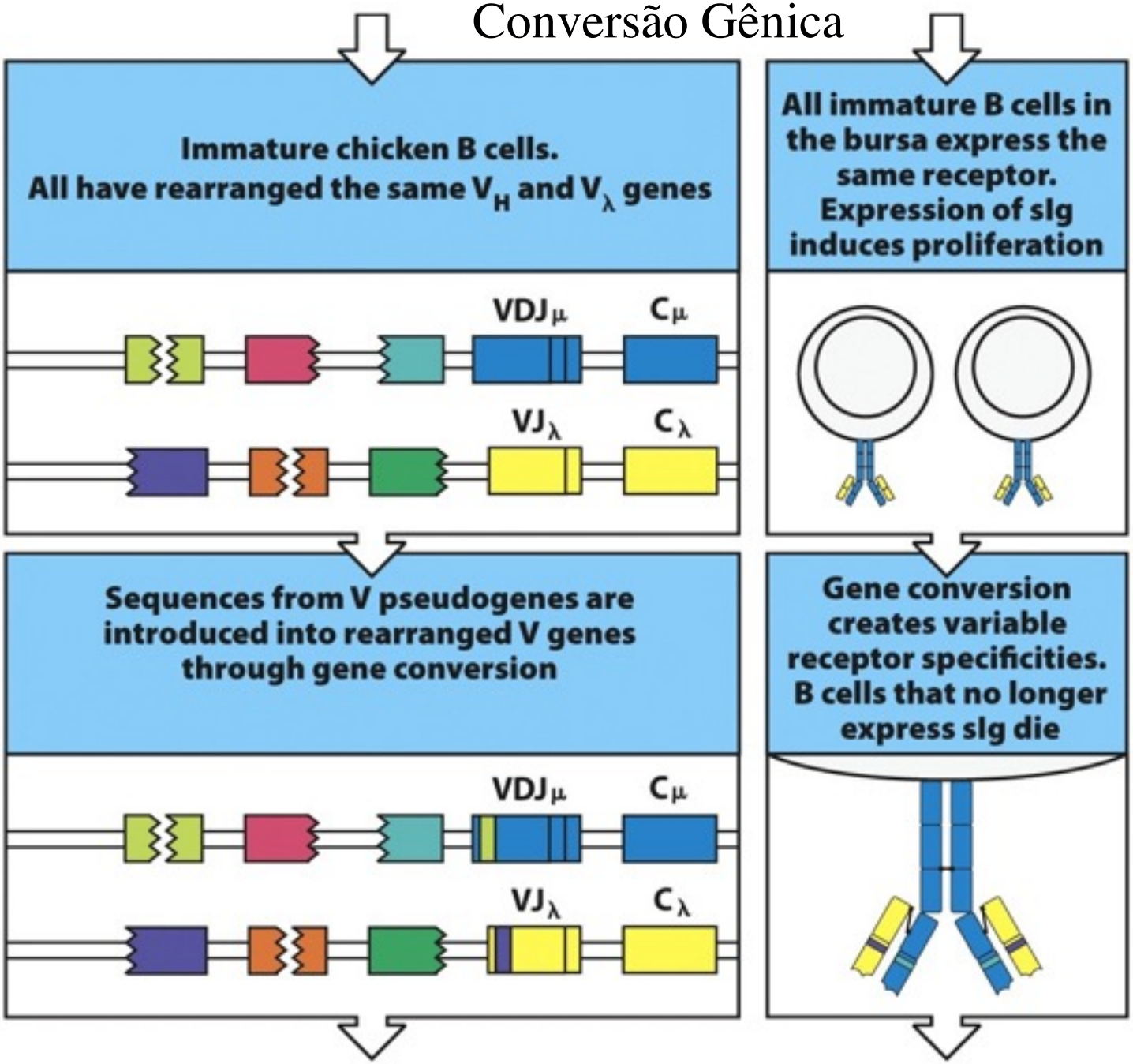


Figure 5.30 part 2 of 3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Conversão Gênica

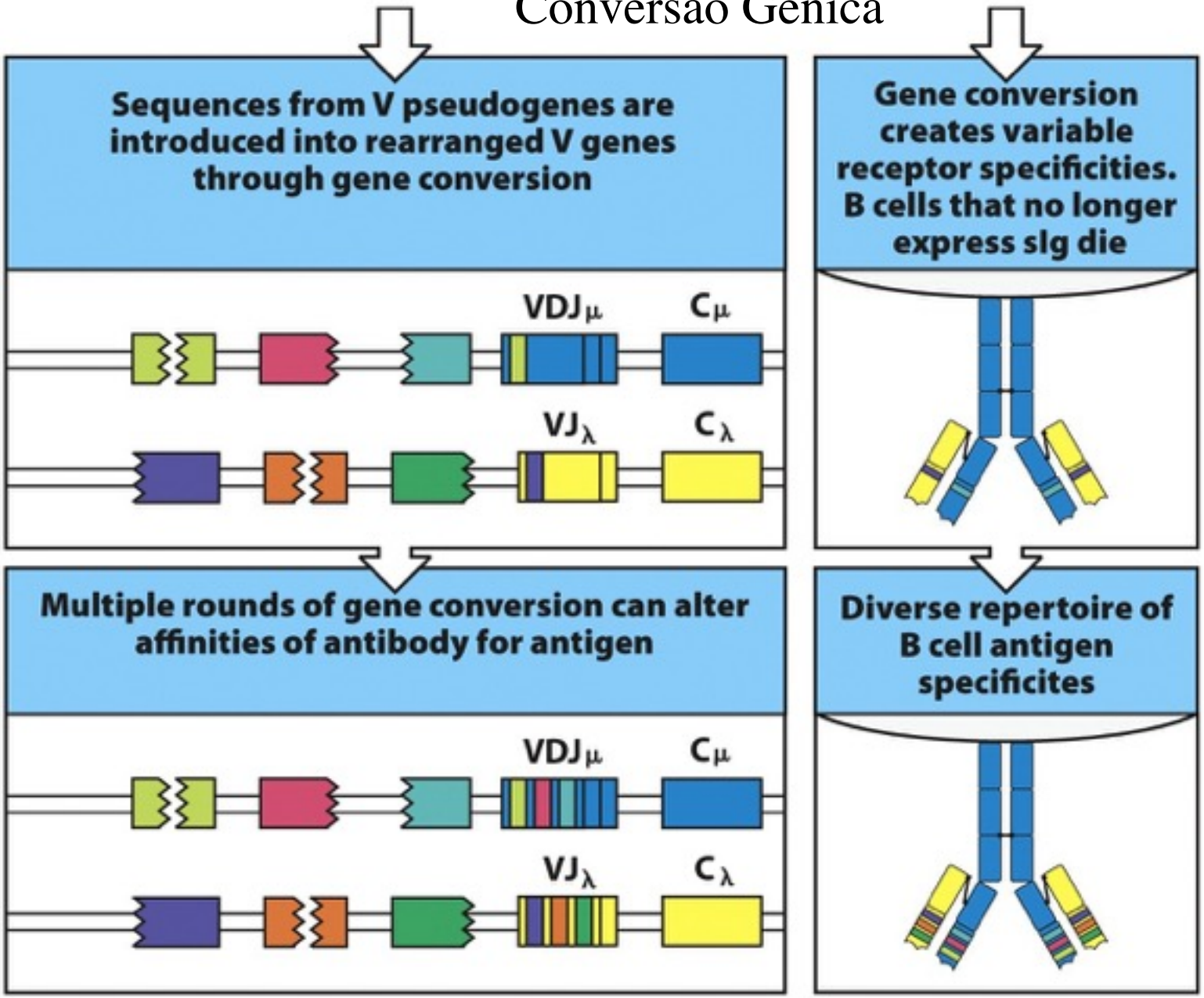
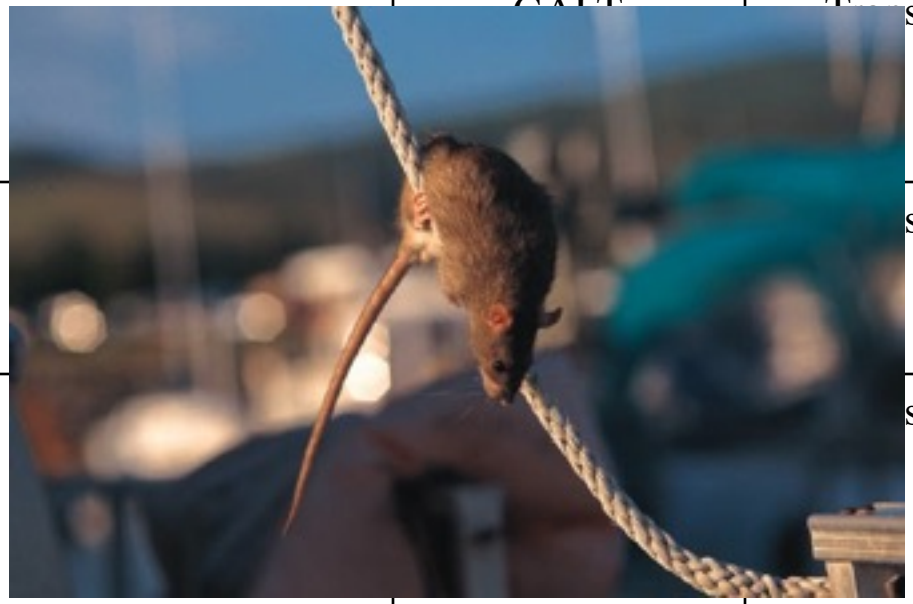


Figure 5.30 part 3 of 3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Espécie	Orgão da diversificação	Configuração	Mecanismo	Rearranjo na idade adulta?
	Fígado fetal, MO	Translocon, famílias VH	Rearranjo	Sim
	GALT	Translocon	Rearranjo e conversão gênica (VH)	Não
		slo		
		slo		
	Pronefro	Transloco cluster famílias		
	Orgão de Leydig	Clust		



Espécie	Orgão da diversificação	Configuração	Mecanismo	Rearranjo na idade adulta?
	Fígado fetal, MO	Translocon, famílias VH	Rearranjo	Sim
	GALT	Translocon	Rearranjo e conversão gênica (VH)	Não
		Translocon	Rearranjo e mutação (VL)	Não
		Translocon	Rearranjo e conversão gênica (VH e VL)	Não
		anslocon (H), cluster (L), famílias VH	Rearranjo	Sim
		Cluster	Rearranjo	Sim

Eastern cottontail rabbit
(Sylvilagus floridanus)

Espécie	Orgão da diversificação	Configuração	Mecanismo	Rearranjo na idade adulta?
	Fígado fetal, MO	Translocon, famílias VH	Rearranjo	Sim
	GALT	Translocon	Rearranjo e conversão gênica (VH)	Não
	Placas de Peyer	Translocon	Rearranjo e mutação (VL)	Não
			njo e o gênica VL)	Não
			anjo	Sim
			anjo	Sim

Espécie	Orgã diversi	Translocon	smo	Rearranjo na idade adulta?
	Fígado f		njo	Sim
	GA		jo e gênica)	Não
	Placas d		jo e (VL)	Não
	Bursa de Fabricius	Translocon	Rearranjo e conversão gênica (VH e VL)	Não
	Pronefro	Translocon (H), cluster (L), famílias VH	Rearranjo	Sim
	Orgão de Leydig	Cluster	Rearranjo	Sim

Espécie	Orgão da diversificação	Configuração	Mecanismo	Rearranjo na idade adulta?
			Rearranjo	Sim
			Rearranjo e onversão gênica (VH)	Não
			Rearranjo e mutação (VL)	Não
			Rearranjo e onversão gênica (VH e VL)	Não
	Pronefro	Translocon (H), cluster (L), famílias VH	Rearranjo	Sim
	Orgão de Leydig	Cluster	Rearranjo	Sim

organização de segmentos em translocon x cluster (peixes ósseos e cartilaginosos)

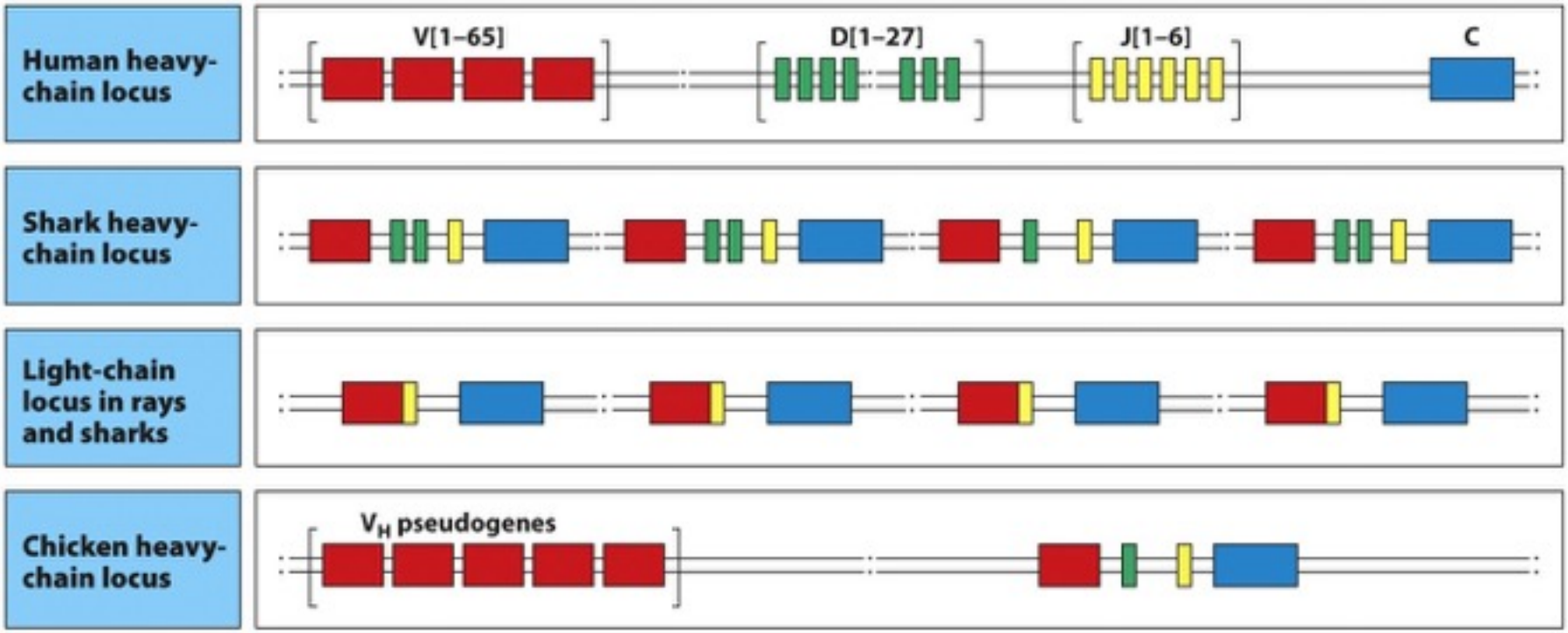
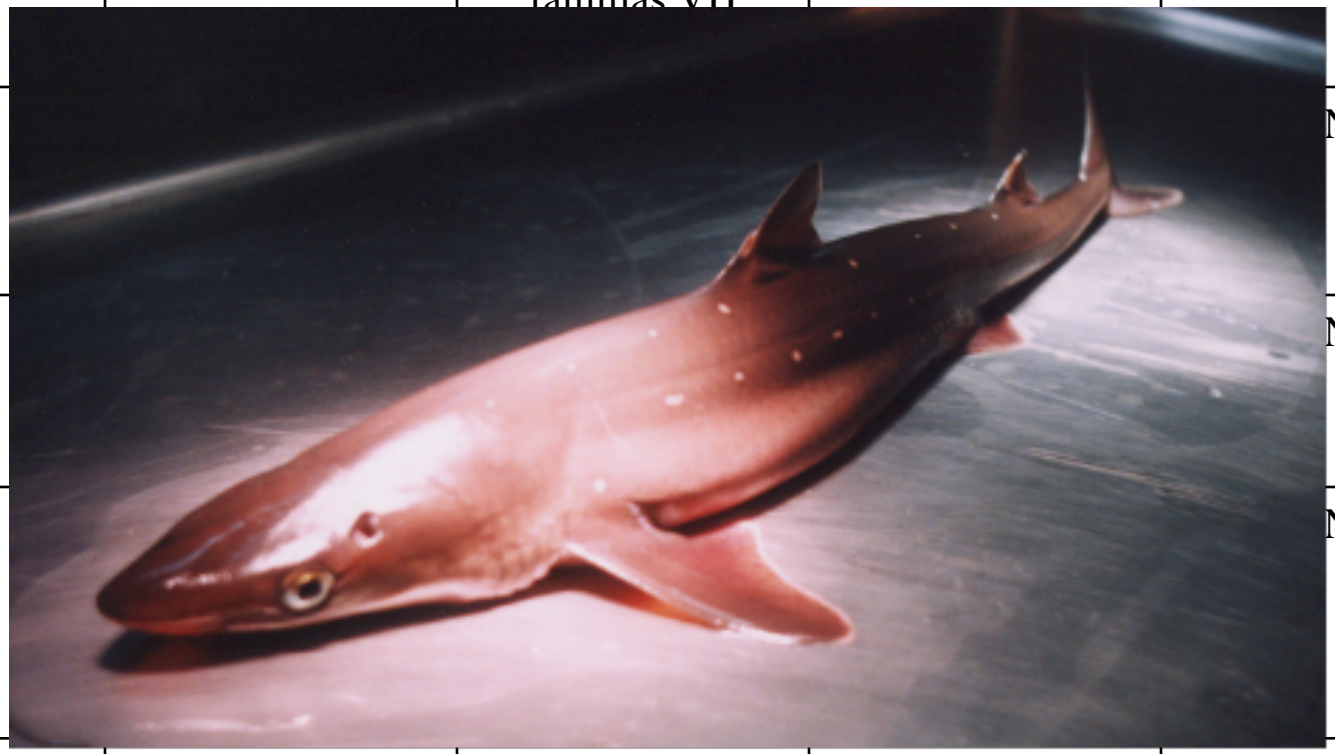
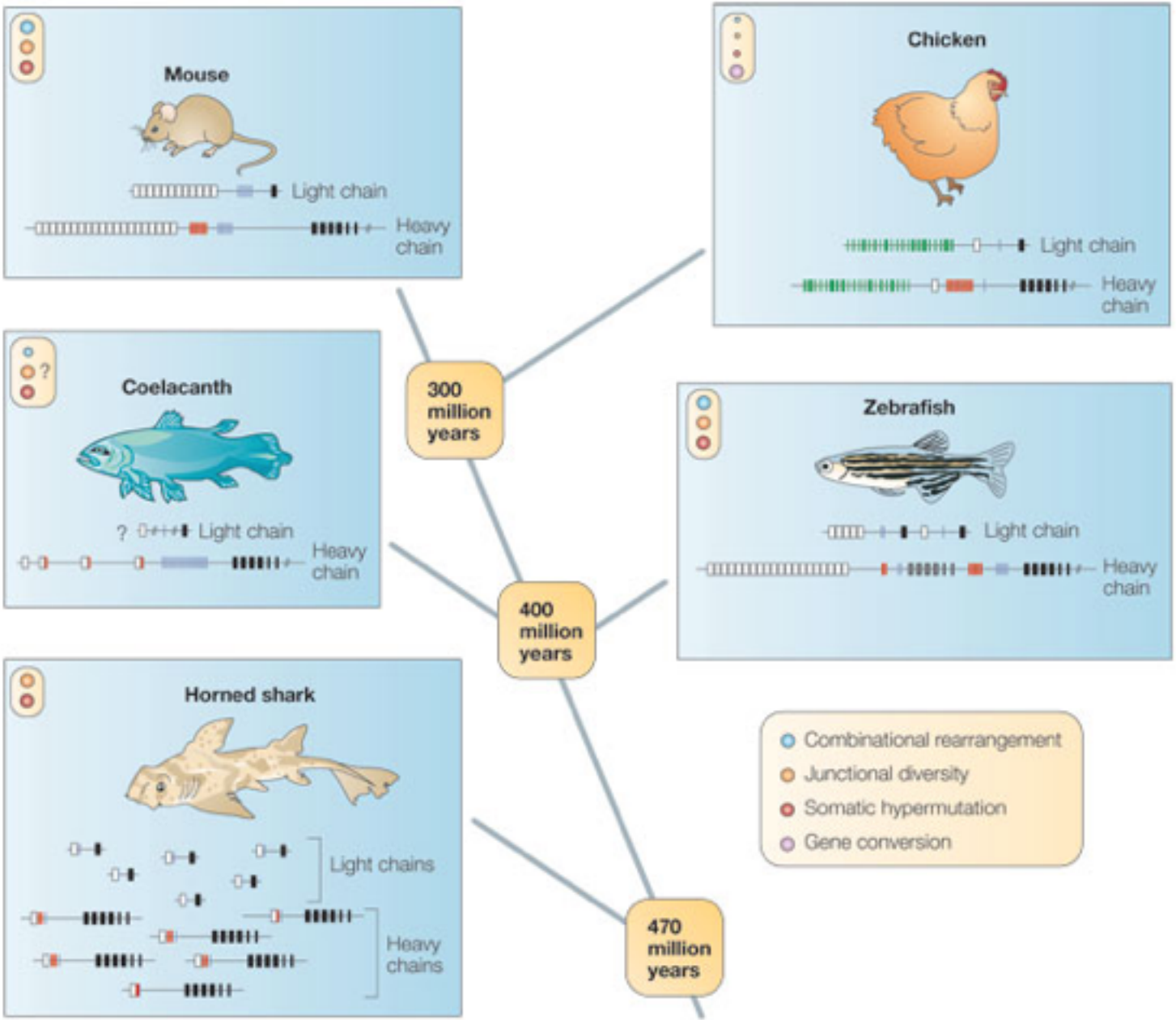


Figure 5.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Espécie	Orgão da diversificação	Configuração	Mecanismo	Rearranjo na idade adulta?
	Fígado fetal, MO	Translocon, famílias VH	Rearranjo	Sim
				Não
				Não
				Não
	Pronefro	Translocon (H), cluster (L), famílias VH	Rearranjo	Sim
	Orgão de Leydig	Cluster	Rearranjo	Sim





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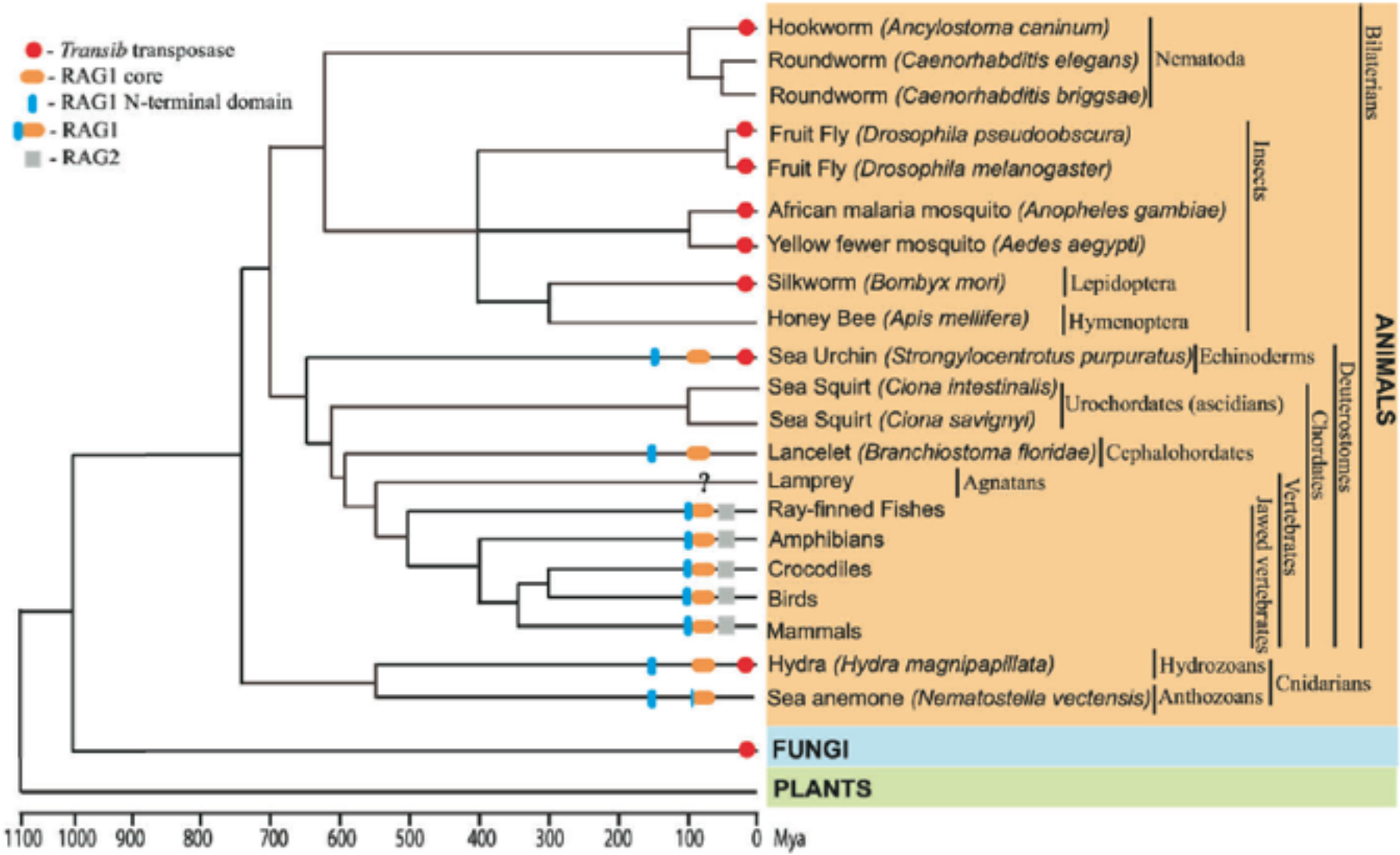
variable

diversity

joining

pseudogene

exon



Kapitonov & Jurka, PLoS Biology, 2005

Event	Process	Nature of change	Process occurs in:	
			B cells	T cells
V-region assembly	Somatic recombination of DNA	Irreversible	Yes	Yes
Junctional diversity	Imprecise joining, N-sequence insertion in DNA	Irreversible	Yes	Yes
Transcriptional activation	Activation of promoter by proximity to the enhancer	Irreversible but regulated	Yes	Yes
Switch recombination	Somatic recombination of DNA	Irreversible	Yes	No
Somatic hypermutation	DNA point mutation	Irreversible	Yes	No
IgM, IgD expression on surface	Differential splicing of RNA	Reversible, regulated	Yes	No
Membrane vs secreted form	Differential splicing of RNA	Reversible, regulated	Yes	No

Figure 5.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

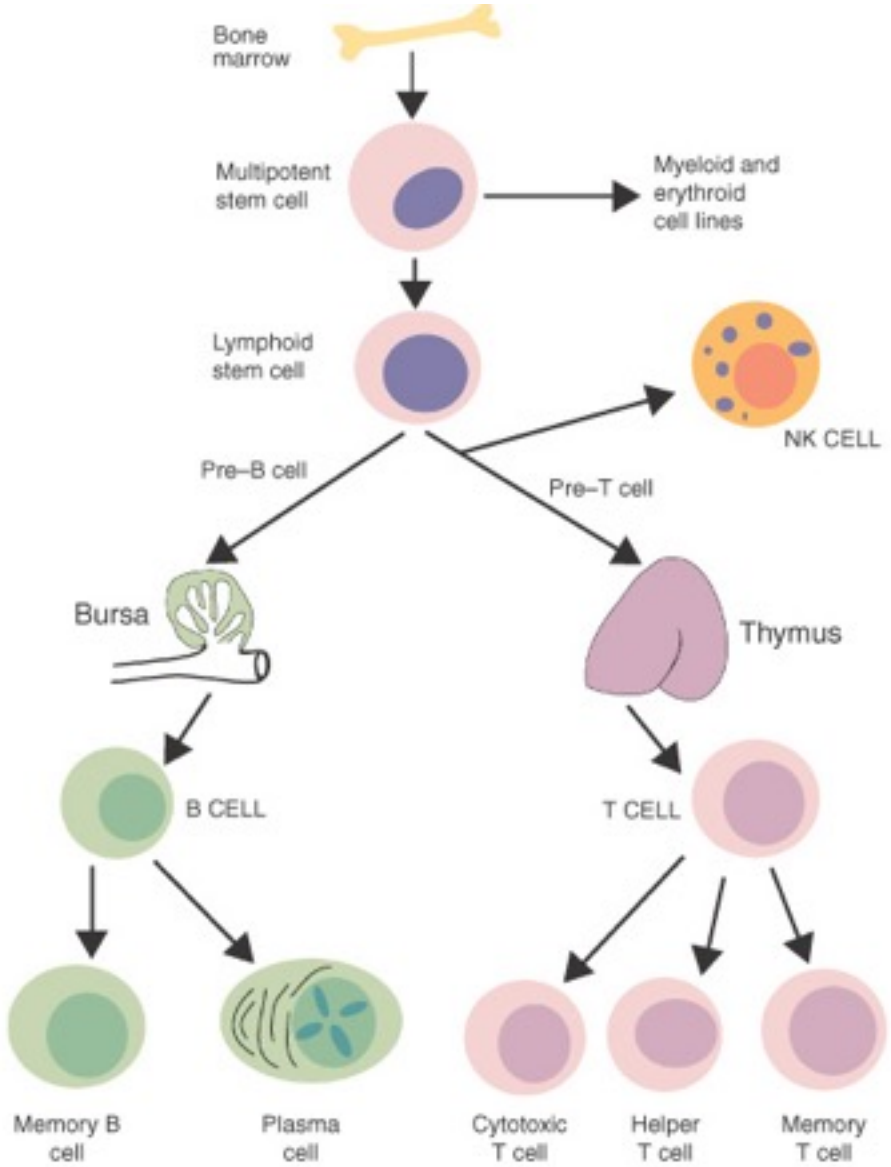


FIGURE 11-6 Development of T and B lymphocytes. Both arise from bone marrow precursors. B cells develop in the bursa, Peyer's patches, or bone marrow. T cells develop in the thymus. Natural killer *(NK)* cells are a third population of lymphocytes that are distinct from T cells and B cells.

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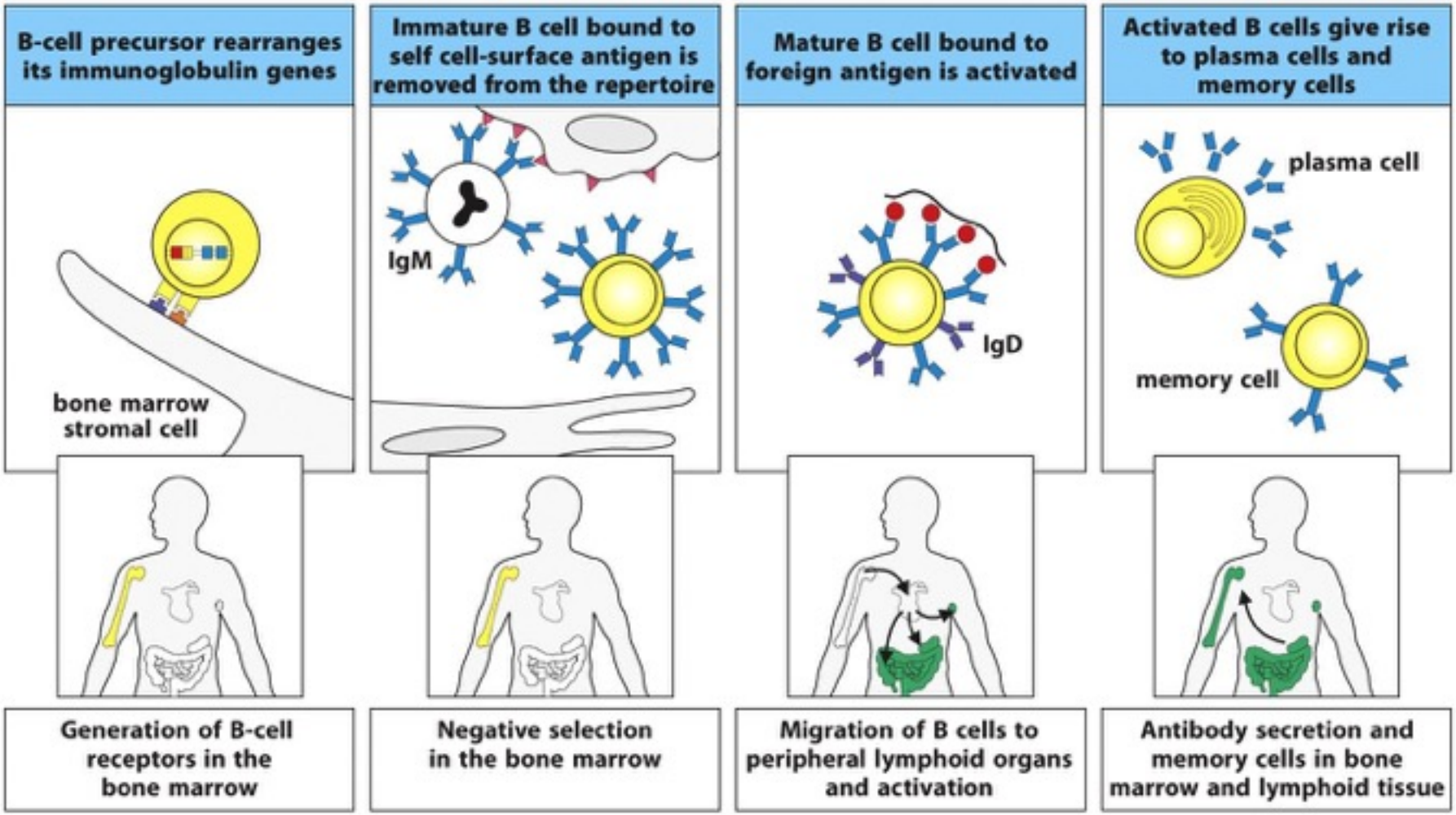


Figure 8.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

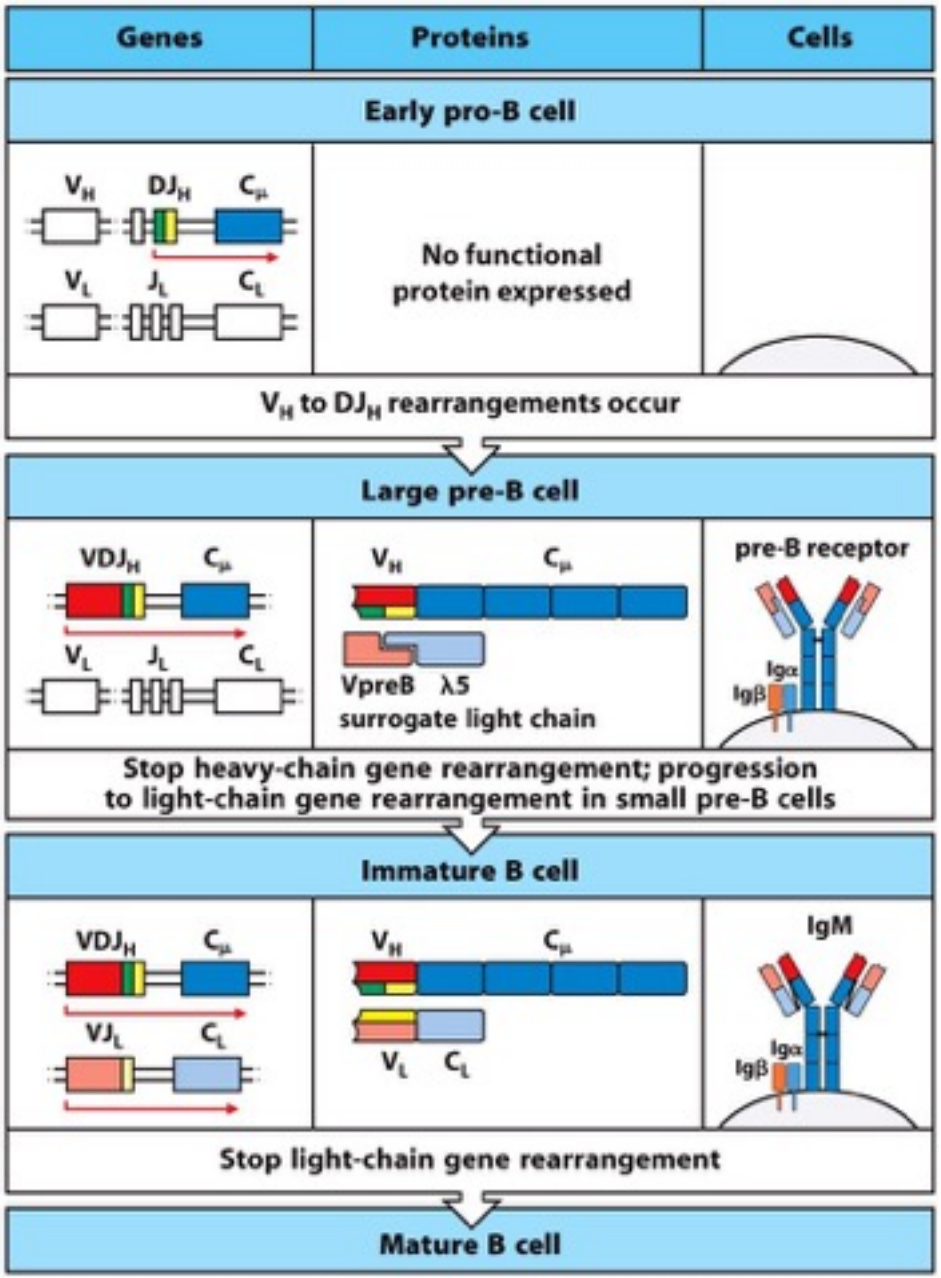


Figure 8.6 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

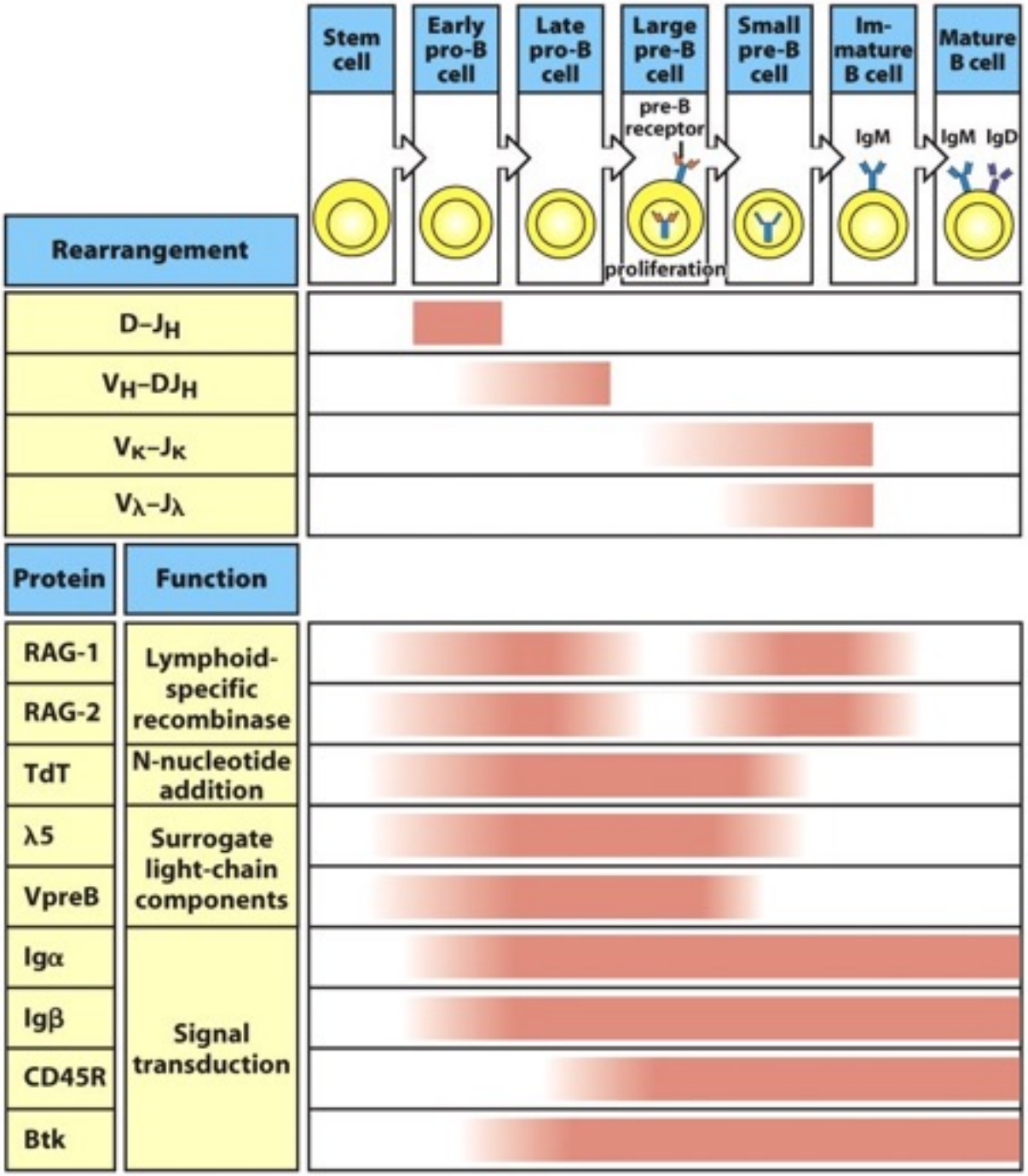


Figure 8.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

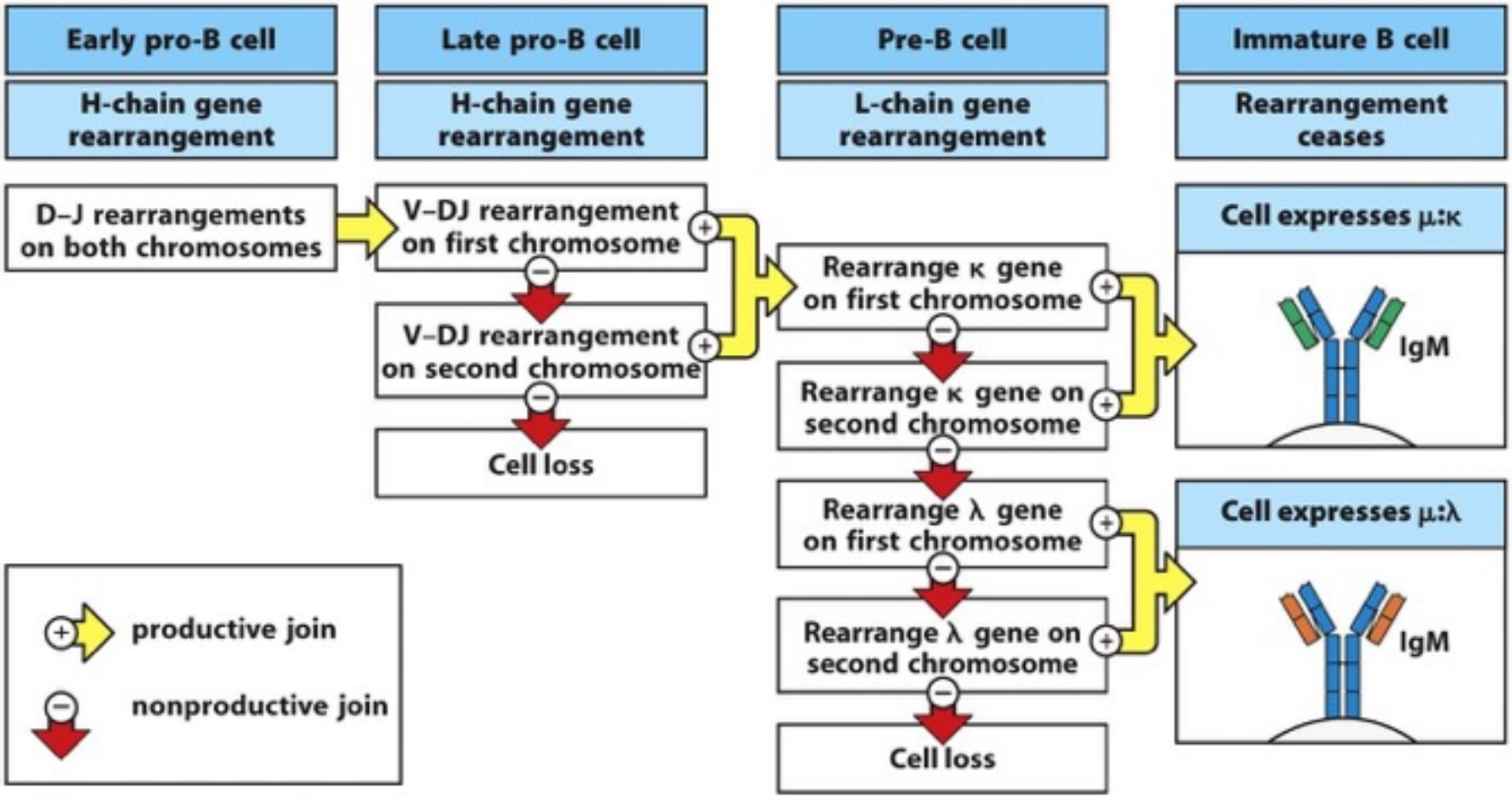


Figure 8.11 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

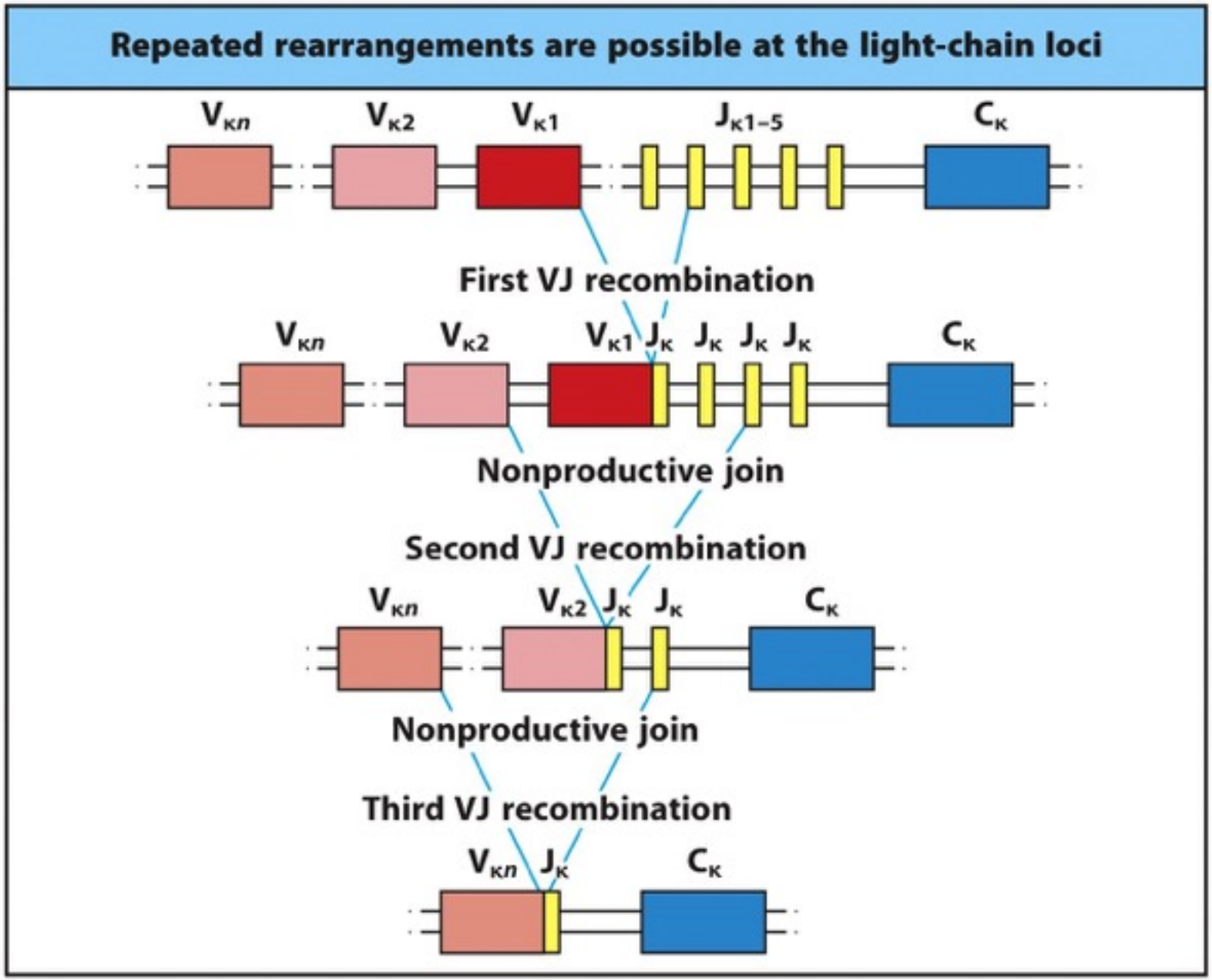


Figure 8.9 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

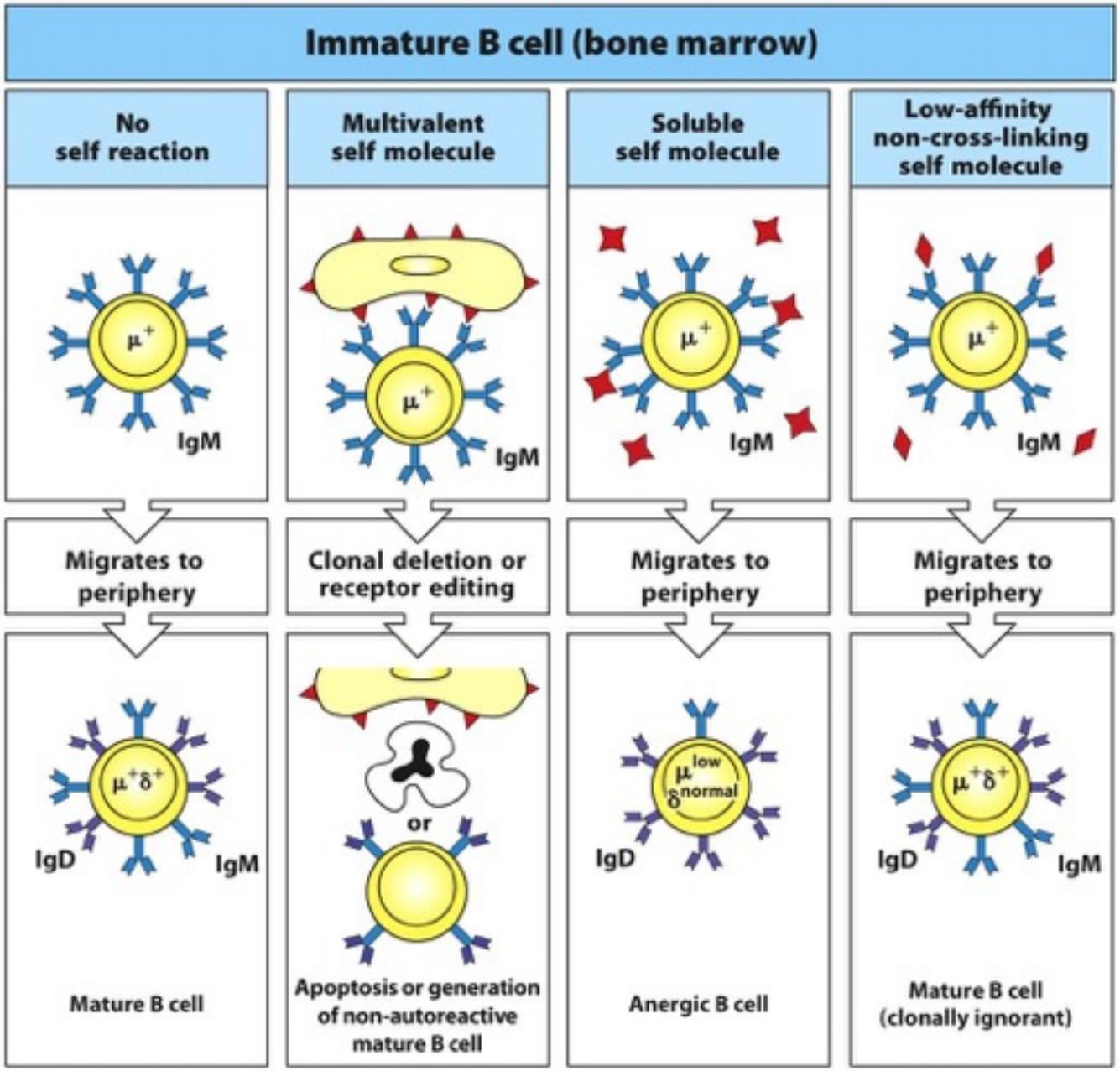


Figure 8.12 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

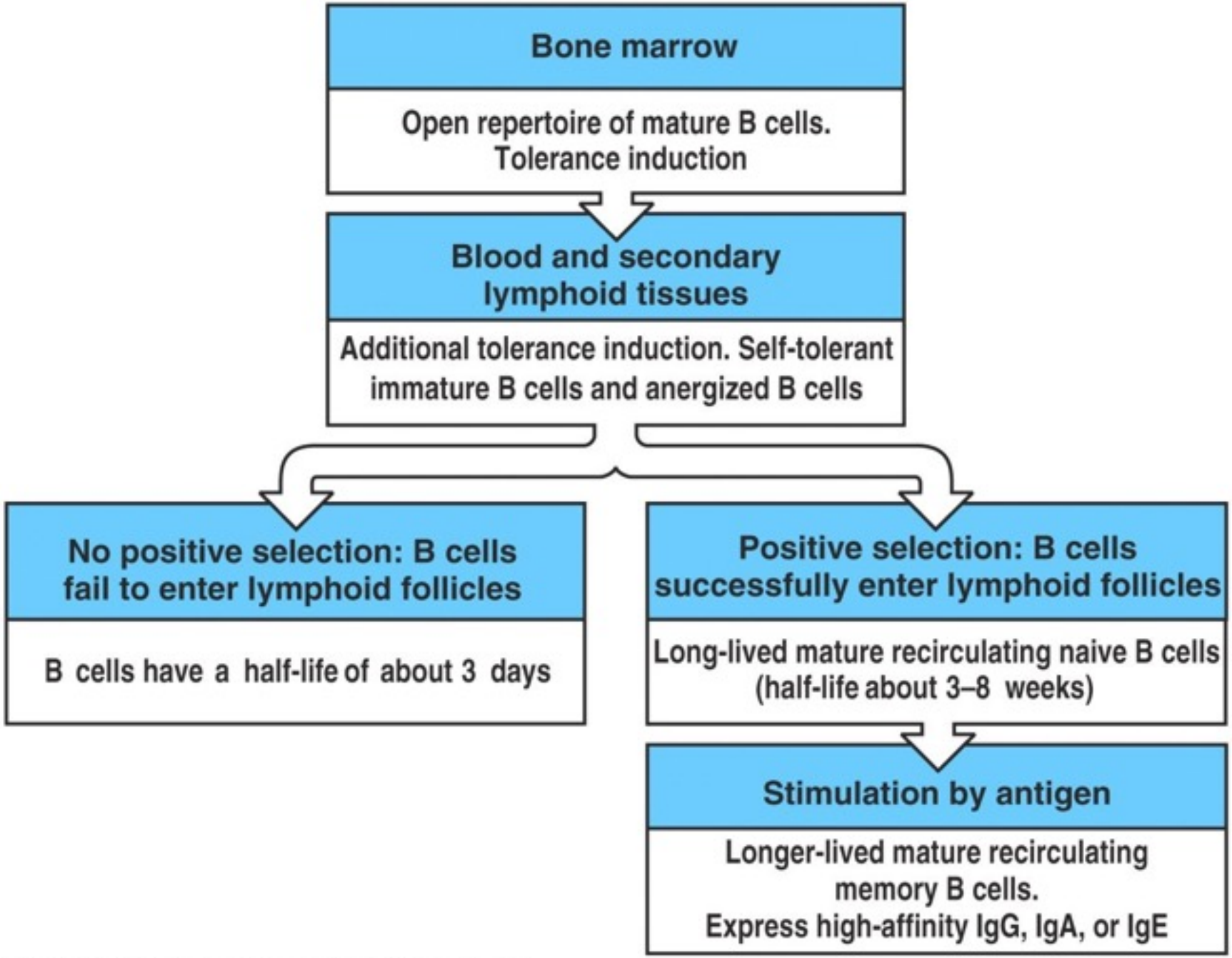


Figure 7-40 Immunobiology, 6/e. (© Garland Science 2005)

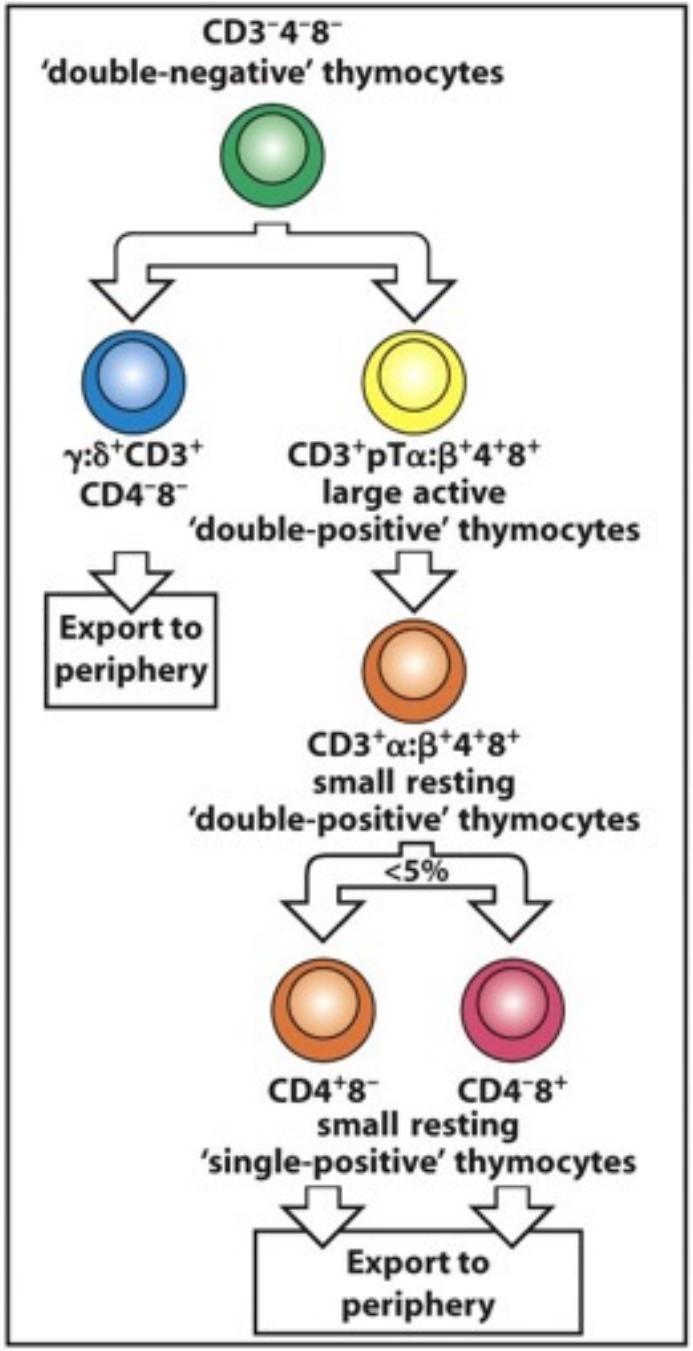


Figure 8.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

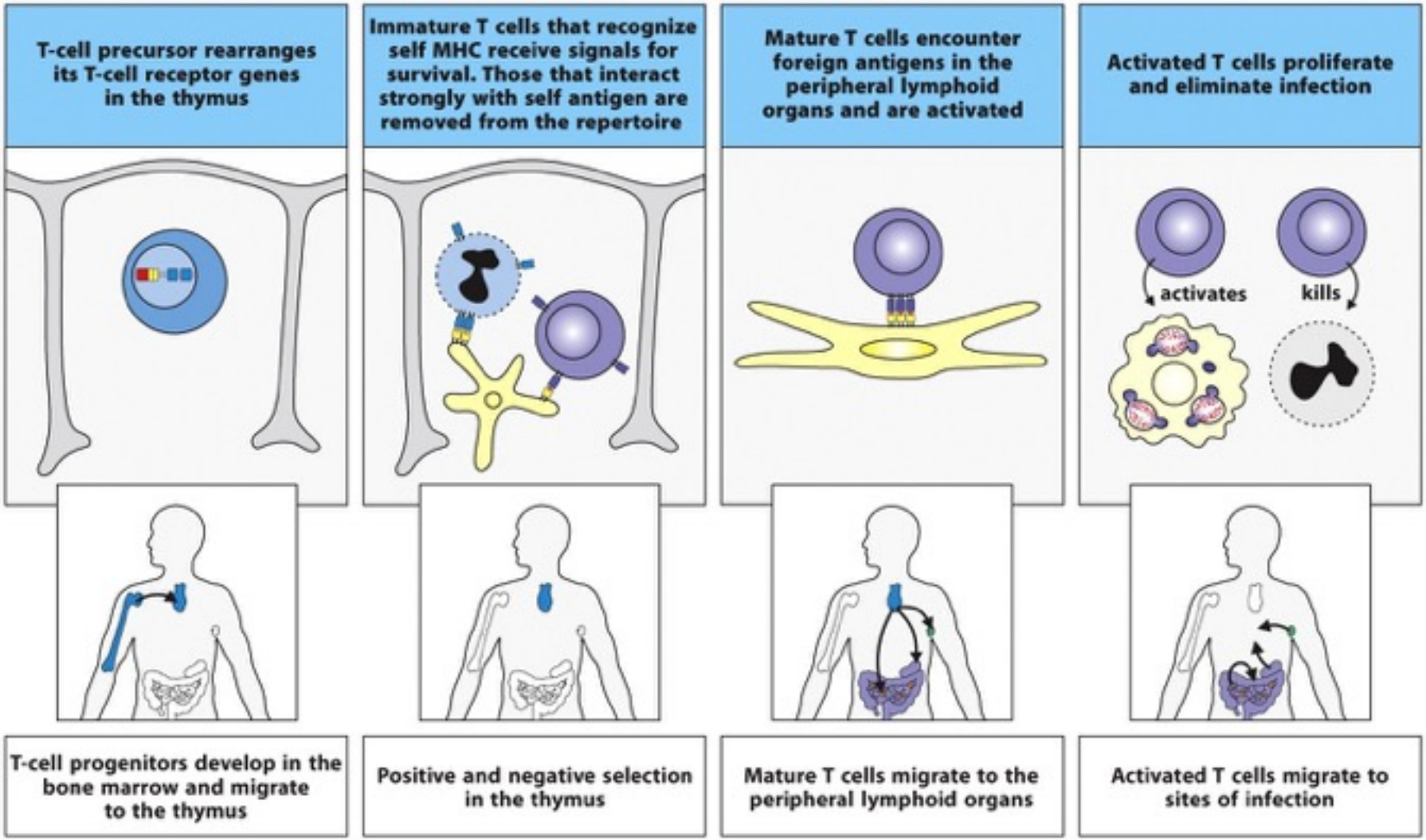
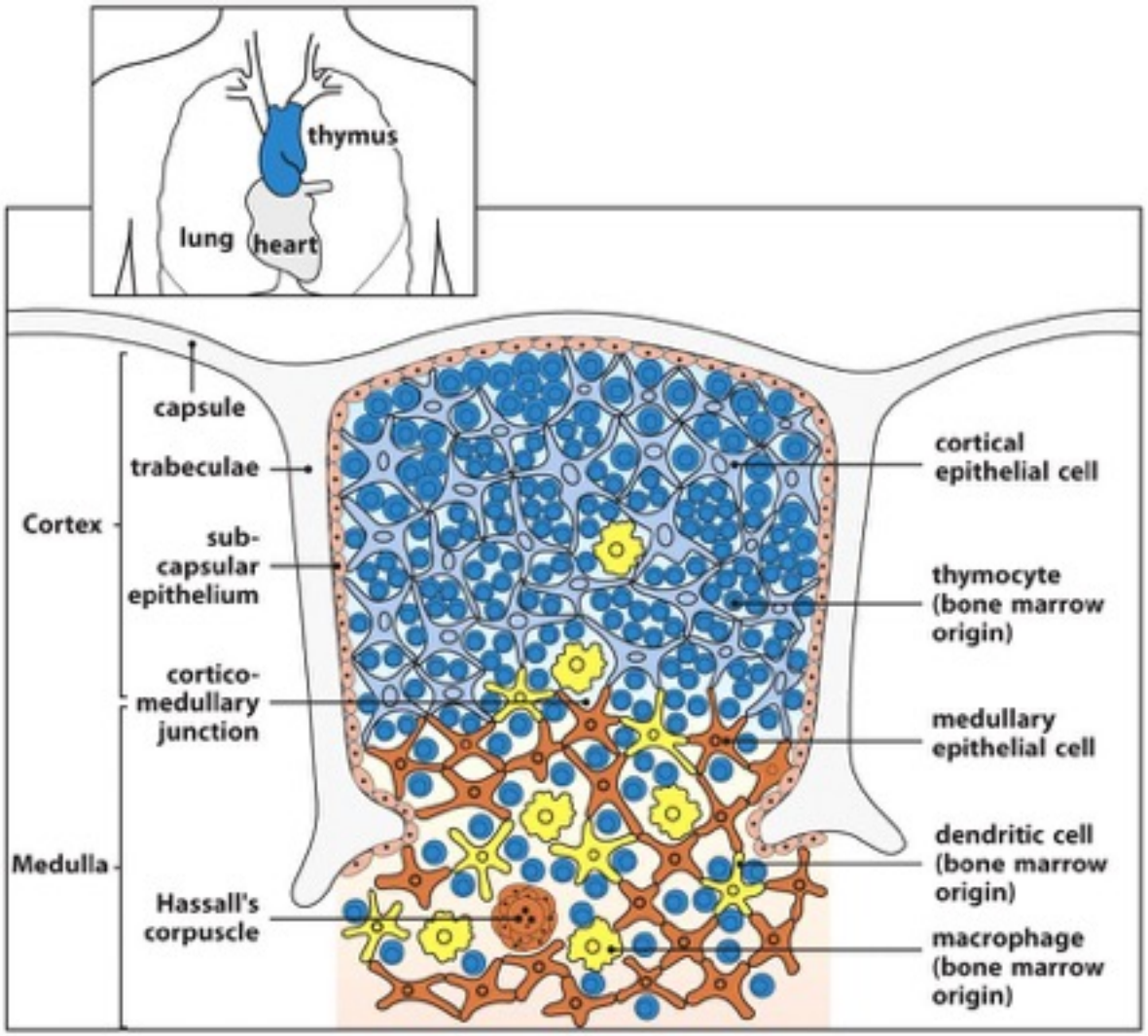


Figure 8.14 Janeway's Immunobiology, 8ed. (© Garland Science 2012)



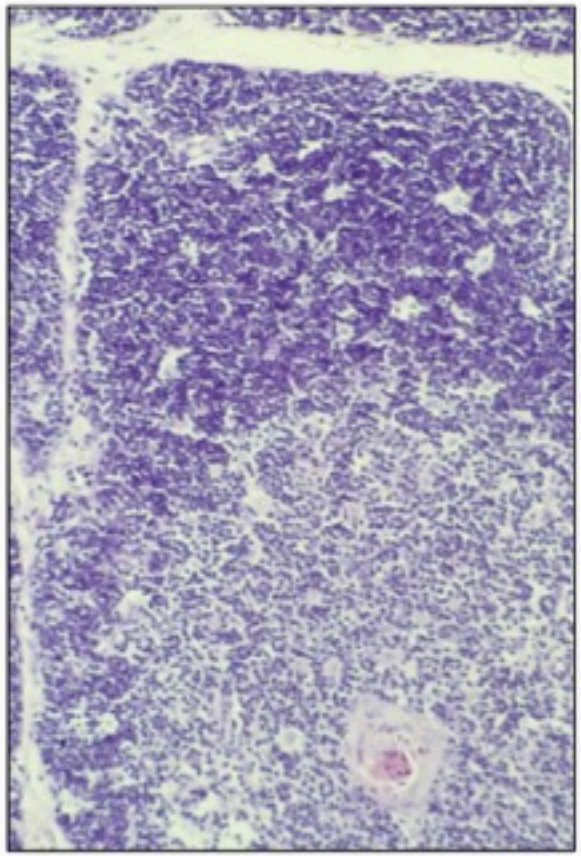
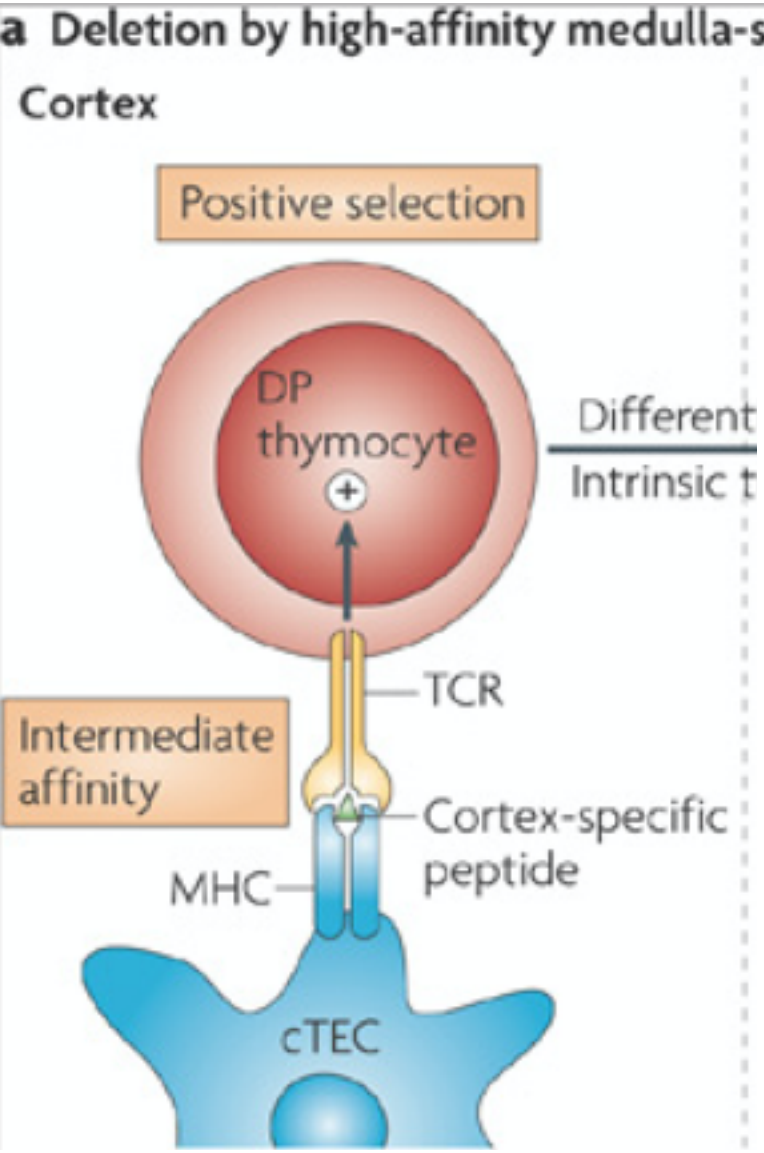
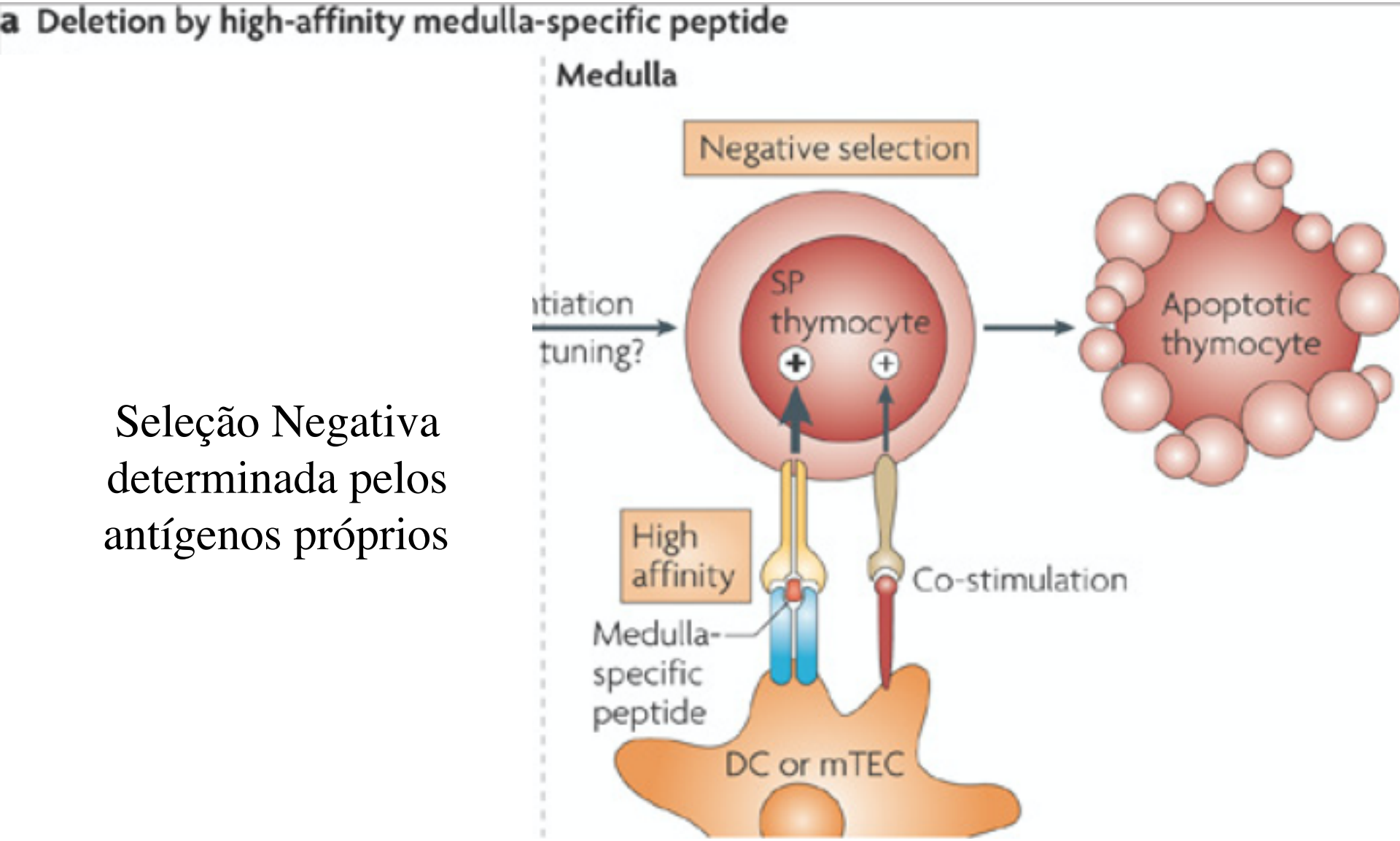


Figure 8.15 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

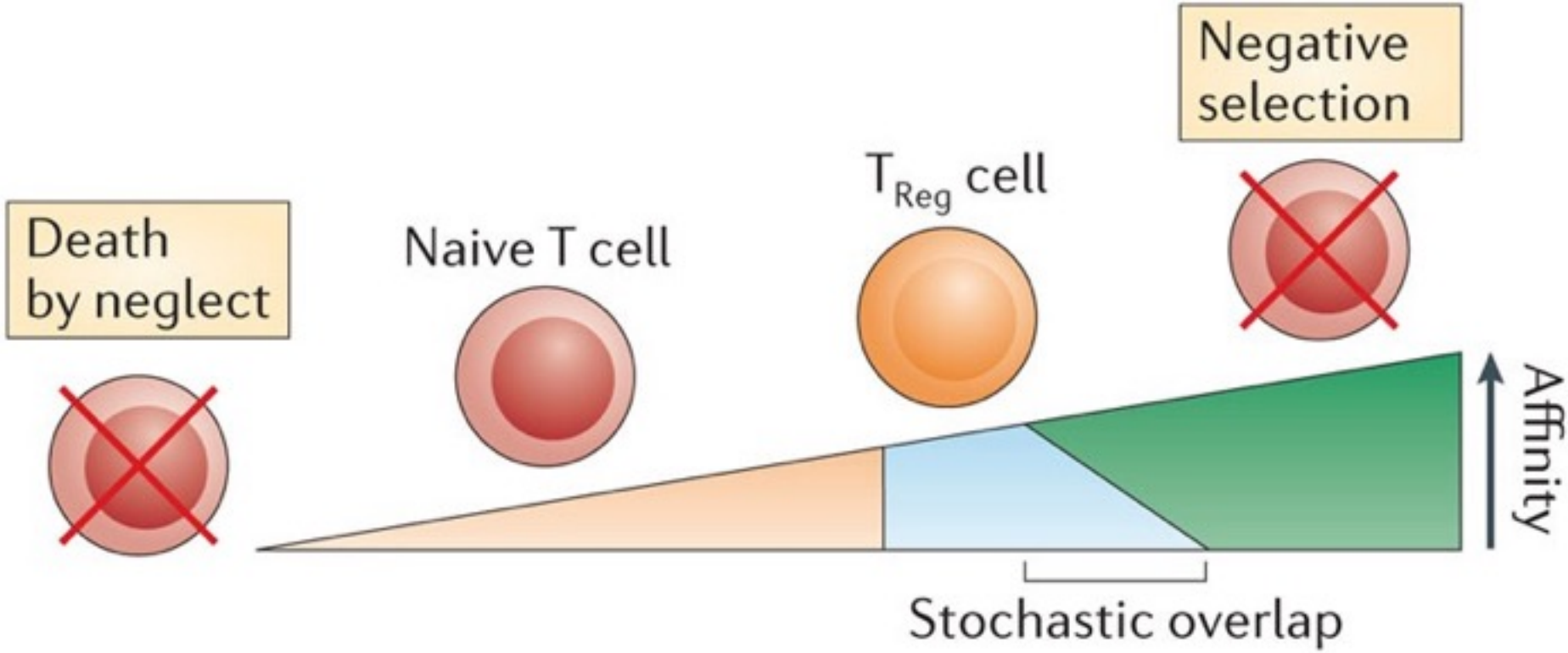


Seleção Positiva determinada pelo MHC próprio

Seleção Negativa determinada pelos antígenos próprios



Quatro destinos para linfócitos T



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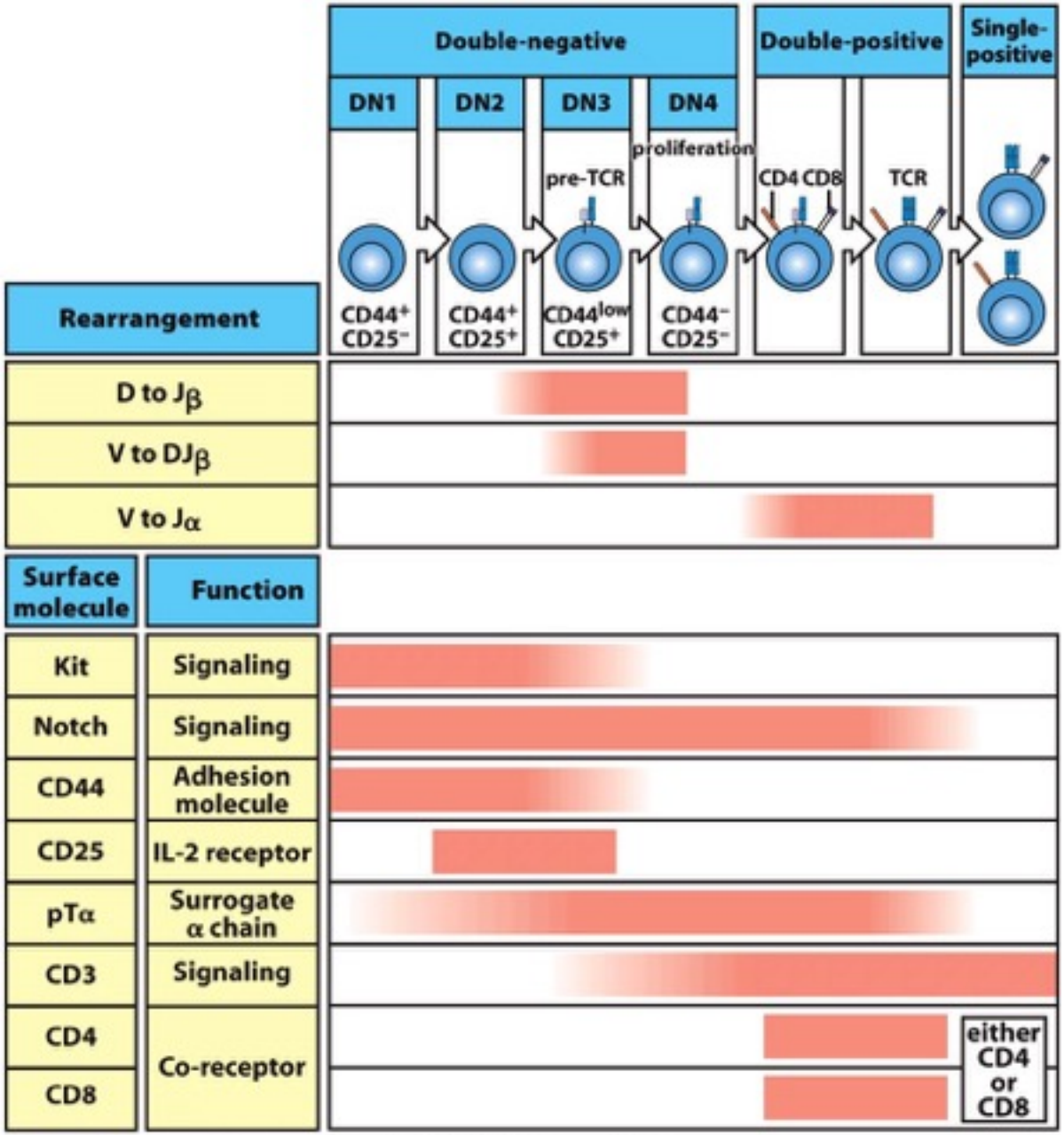

Figure 8.20 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

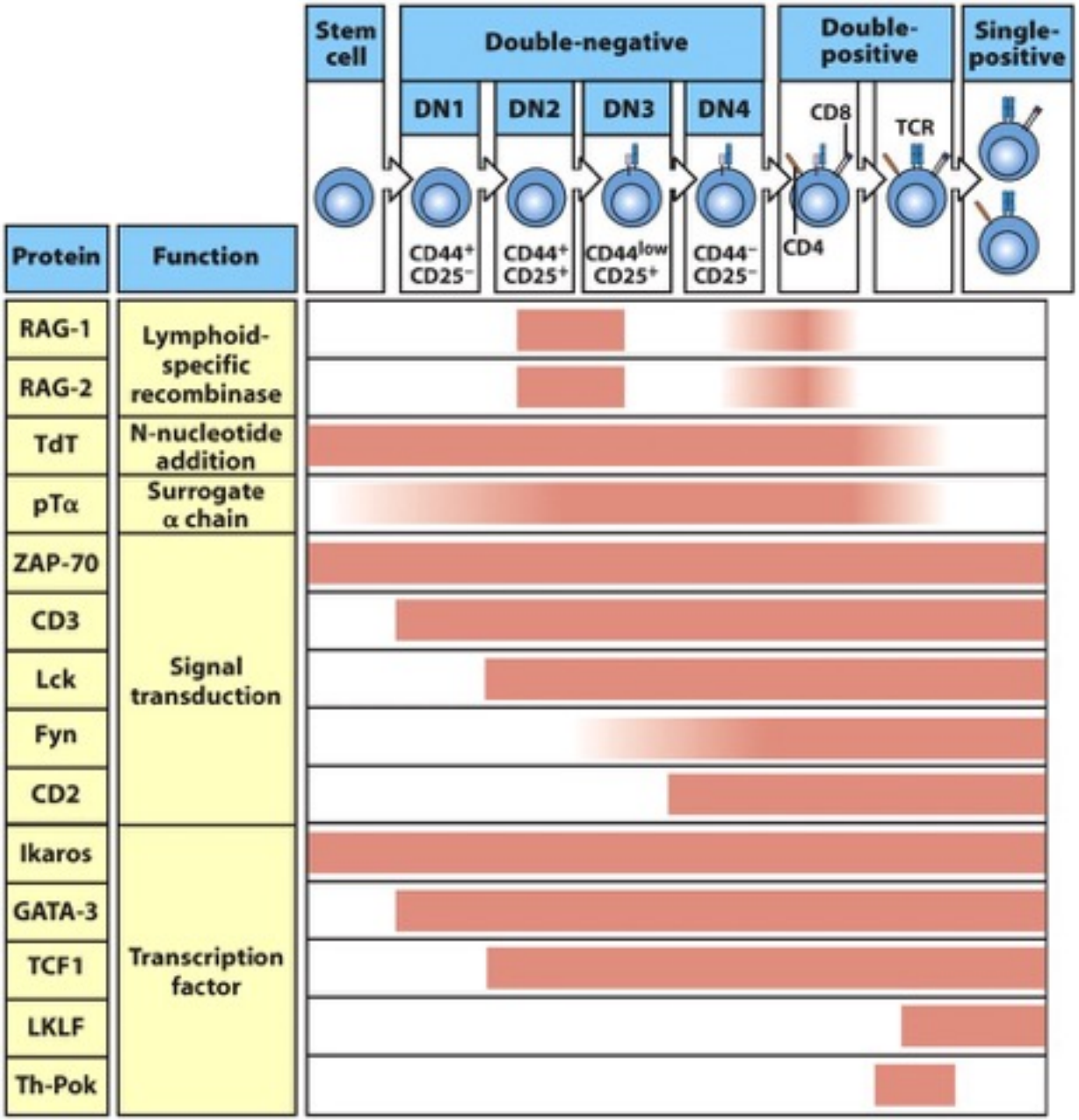

Figure 8.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

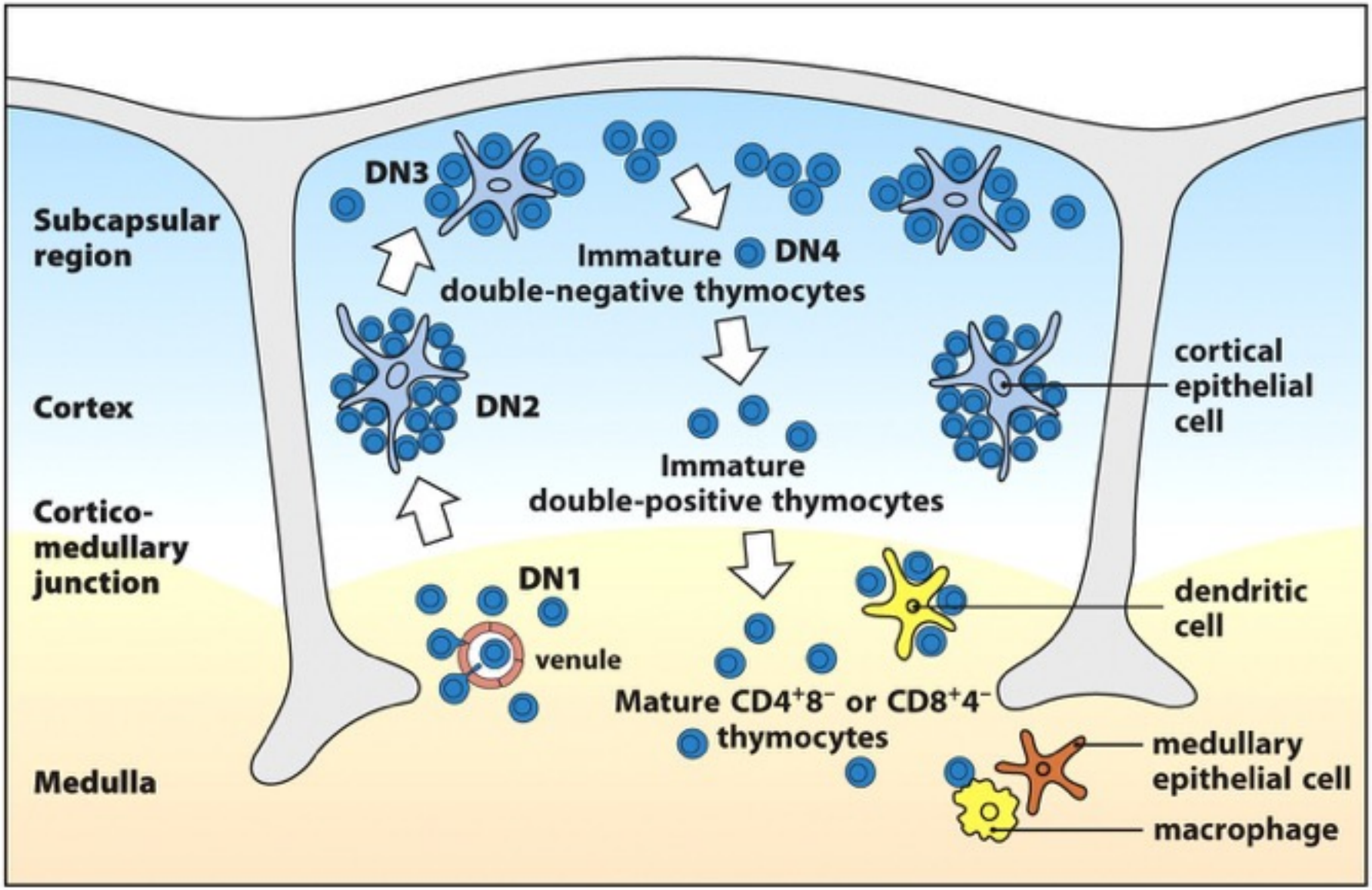

Figure 8.21 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

E o TCR gamma-delta?

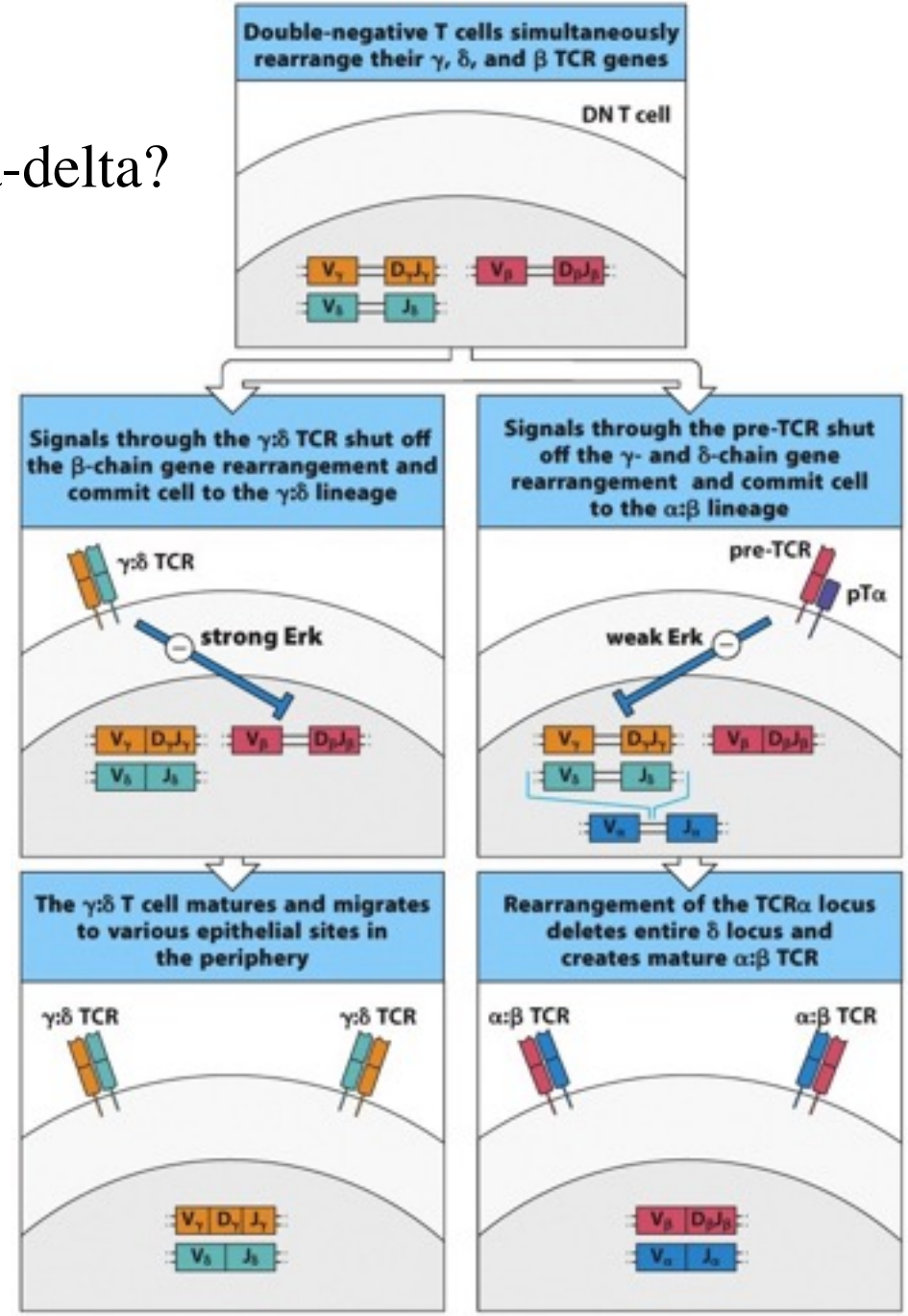

Figure 8.22 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

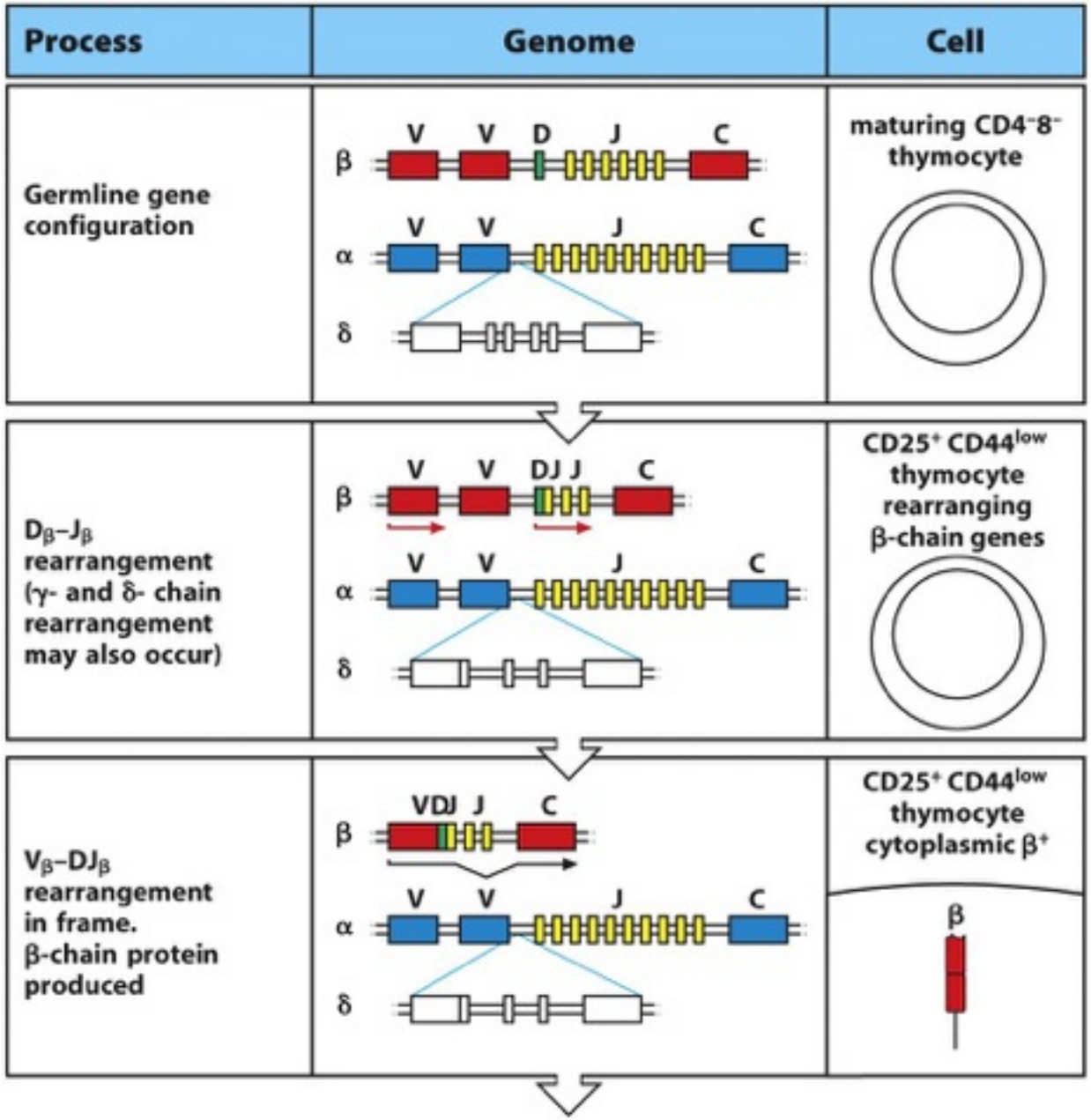

Figure 8.25 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

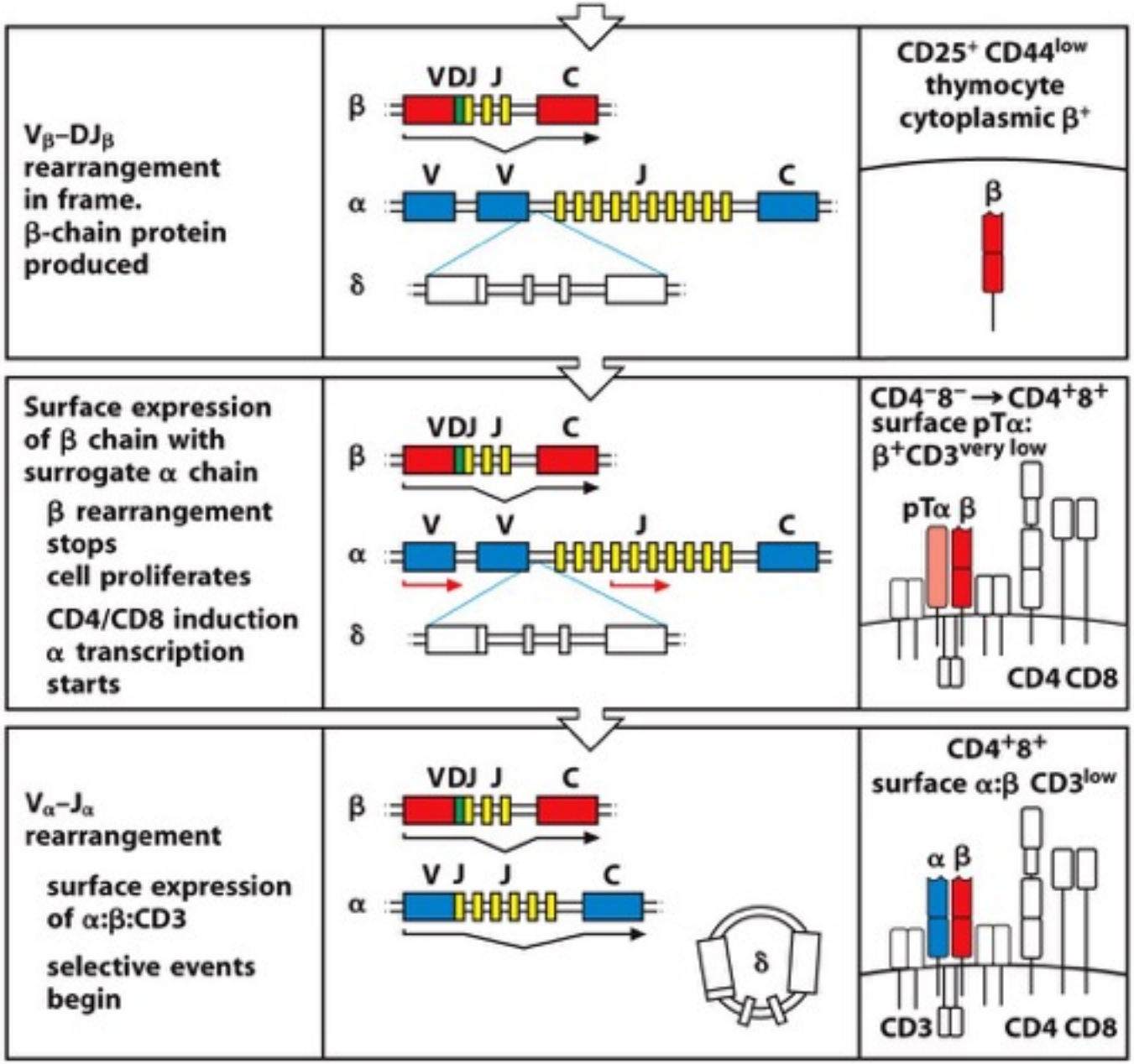

Figure 8.25 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

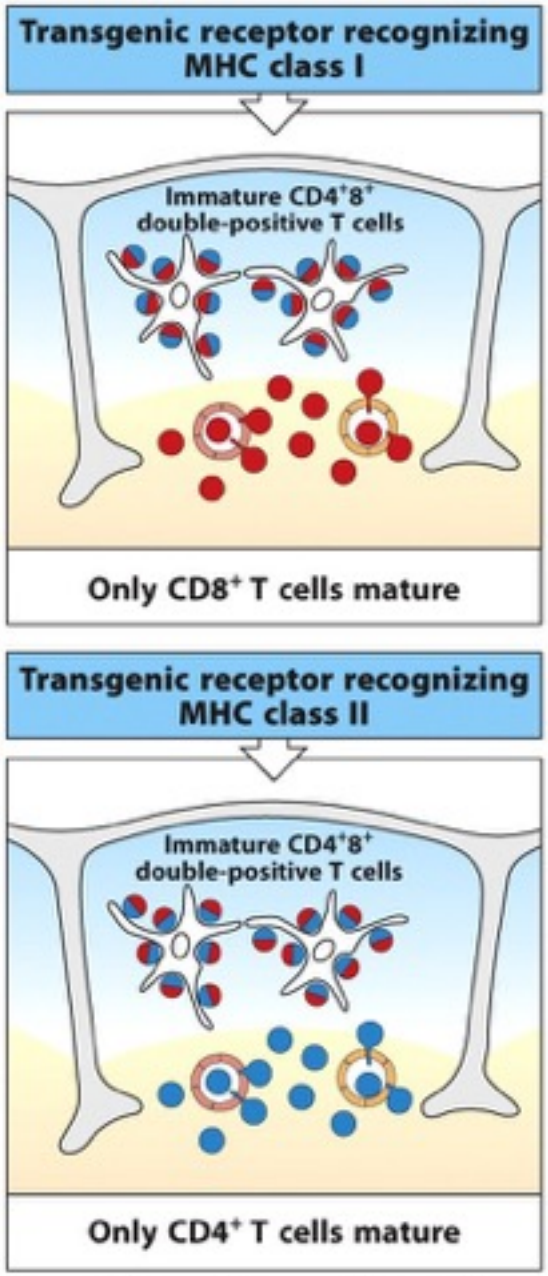

Figure 8.30 Janeway's Immunobiology, 8ed. (© Garland Science 2012)