

Sélection positive et négative des répertoires lymphocytaires

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Université Pierre et Marie Curie

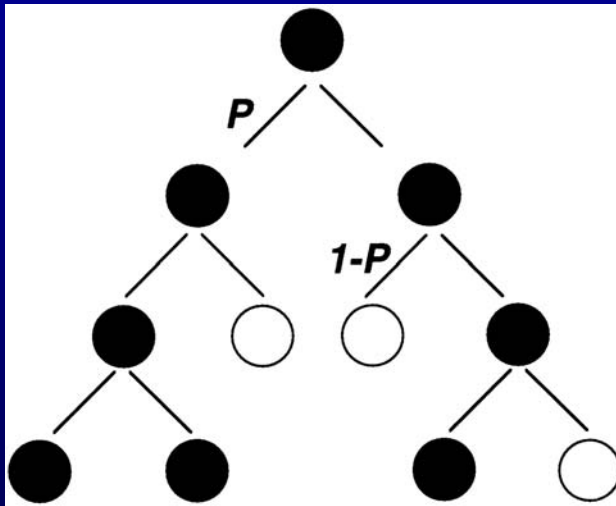
IF2009 IF-VIb
février 2009

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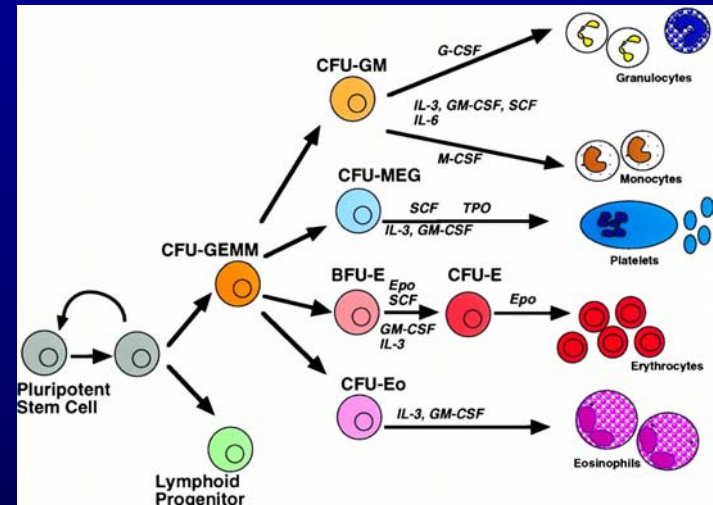
- 1. Introduction**
2. Notion de répertoires
3. Sélection des répertoires B
4. Sélection des répertoires T
5. Conclusion

Modèles de différenciation & sélection

Modèle stochastique



Modèle instructif ou inductif



Modèles mixtes
(asymétrique, permissif, flou, cinétique...)

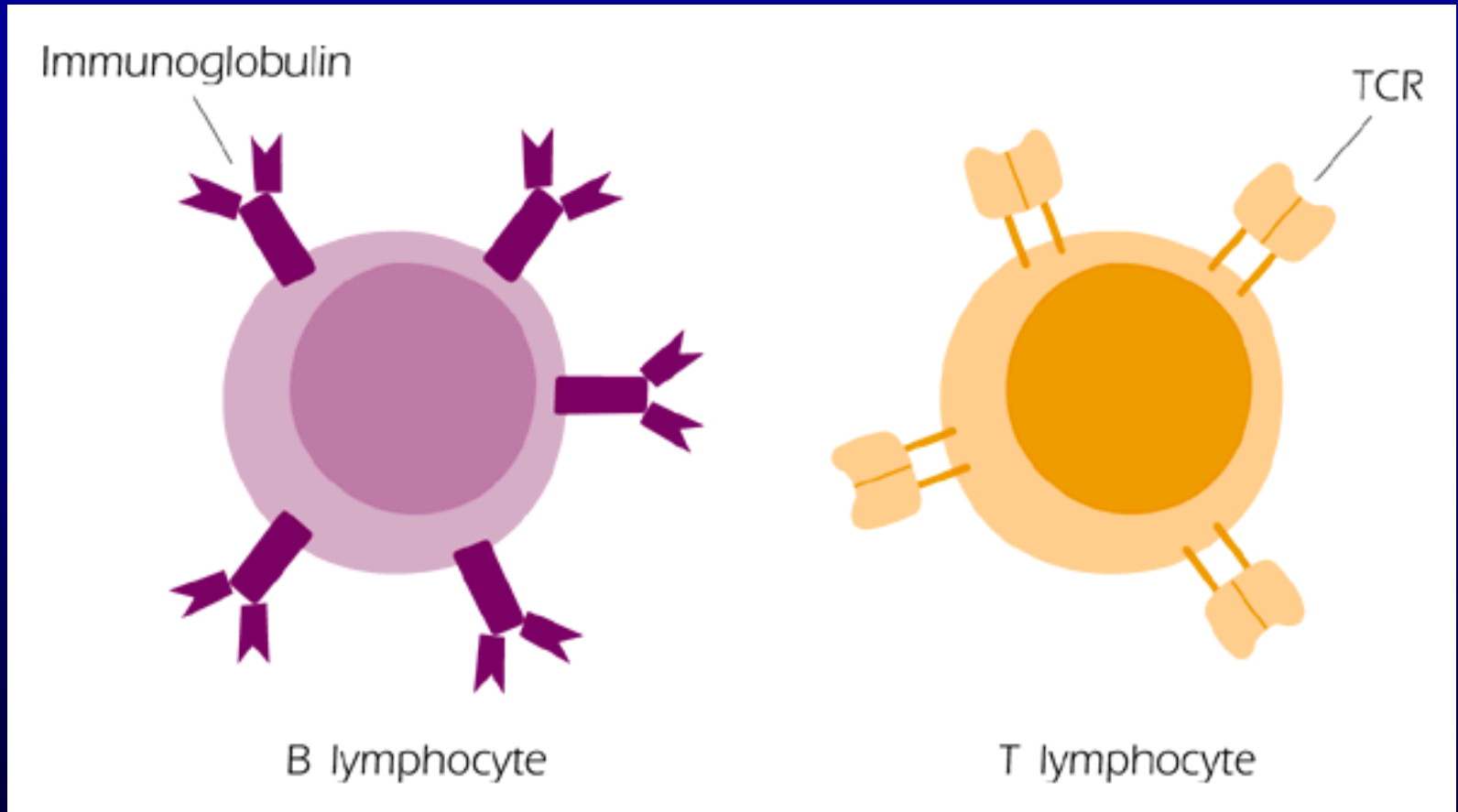
Engagement vs. Sélection

→ Par quel mécanisme les précurseurs s'engagent-ils dans un lignage donné?

→ L'engagement est-il le fruit du hasard?
Est-il contrôlé par un mécanisme de sélection?

→ Au contraire, existe-t-il un signal (contact cellulaire, cytokine...) qui détermine l'engagement?

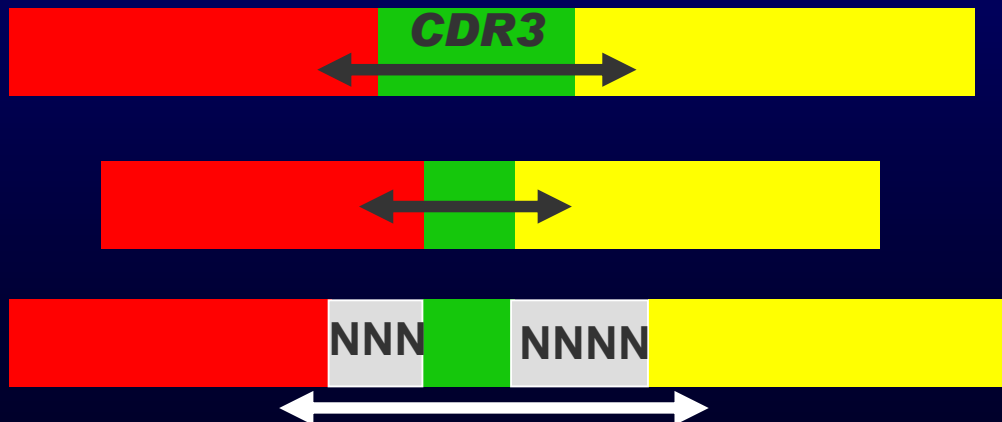
Les lymphocytes B et T



→ caractérisés par leur récepteur spécifique d'antigène

Diversité des chaînes Ig et TCR

- La diversité des chaînes d'Ig et de TCR est le produit de :
 - Combinatoire des segments V(D)J
 - Appariement IgH/L, TCR α / β or TCR γ / δ
 - Ajout/élimination aléatoire de nucléotides à la jonction des segments géniques (CDR3)



Estimation de la diversité (2)

TABLE 9-3 Sources of possible diversity in mouse immunoglobulin and TCR genes

Mechanism of diversity	IMMUNOGLOBULINS		$\alpha\beta$ T-CELL RECEPTOR		$\gamma\delta$ T-CELL RECEPTOR	
	H Chain	κ Chain	α Chain	β Chain	γ Chain	δ Chain
ESTIMATED NUMBER OF FUNCTIONAL GENE SEGMENTS*						
V	101	85	79	21	7	6
D	13	0	0	2	0	2
J	4	4	38	11	3	2
POSSIBLE NUMBER OF COMBINATIONS†						
Combinatorial V-J	$101 \times 13 \times 4$	85×4	79×38	$21 \times 2 \times 11$	7×3	$6 \times 2 \times 2$
and V-D-J joining	5.3×10^3	3.4×10^2	3.0×10^3	4.6×10^2	21	24
Alternative joining of D gene segments	-	-	-	+	-	+
				(some)		(often)
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition‡	+	$\sim 10^{12}$	+	$\sim 10^{15}$	+	$\sim 10^{18}$
P-region nucleotide addition	+	+	+	+	+	+
Somatic mutation	+	+	-	-	-	-
Combinatorial association of chains		+		+		+

*Immunoglobulin data from Table 5-2; TCR data from Baum et al., 2004, *Nucleic Acids Research* **32**:D51.

†A plus sign (+) indicates mechanism makes a significant contribution to diversity but to an unknown extent.

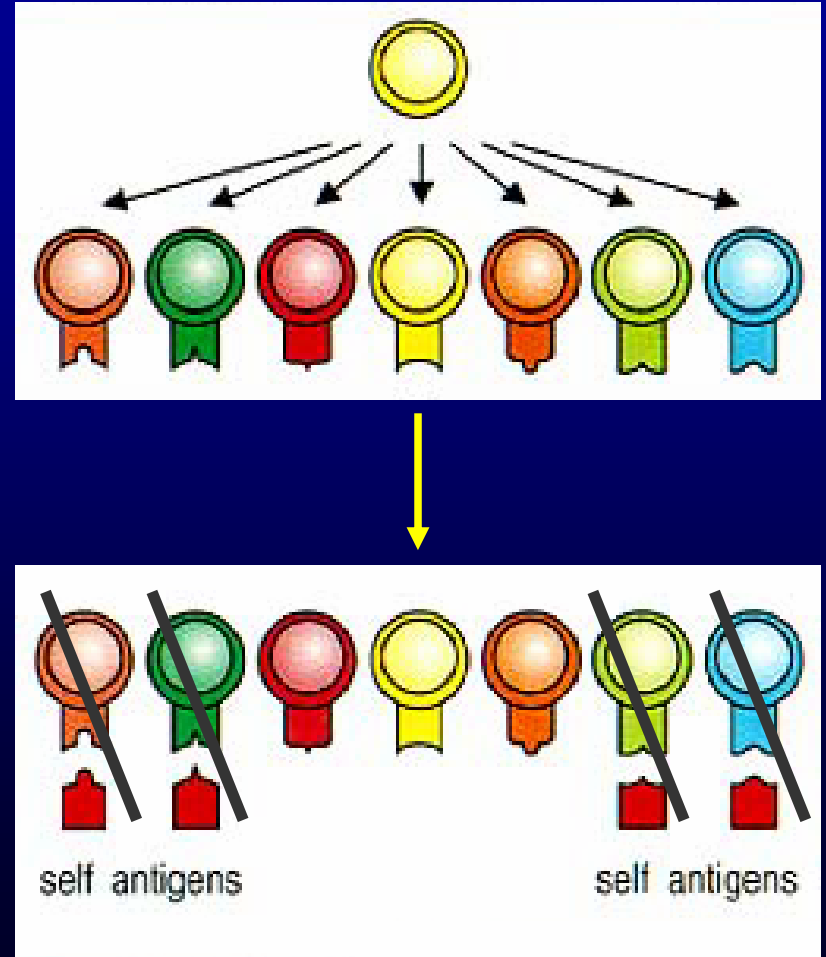
A minus sign (-) indicates mechanism does not operate.

‡See Figure 9-8d for theoretical number of combinations generated by N-region addition.

Théorie de la sélection clonale (1)

Burnet (1899–1985)

- Chaque lymphocyte exprime un type unique de récepteur spécifique d'antigène
- Les lymphocytes exprimant un récepteur dirigé contre un antigène du soi sont éliminés lors de la différenciation

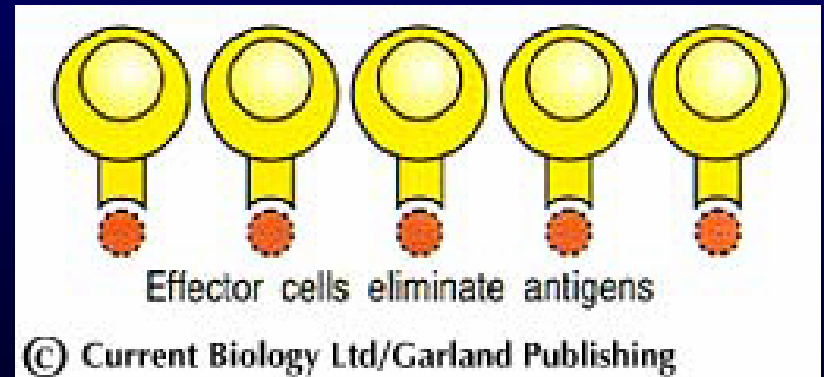


Théorie de la sélection clonale (2)

- La liaison avec une bonne affinité d'une molécule étrangère et d'un récepteur entraîne l'activation du lymphocyte



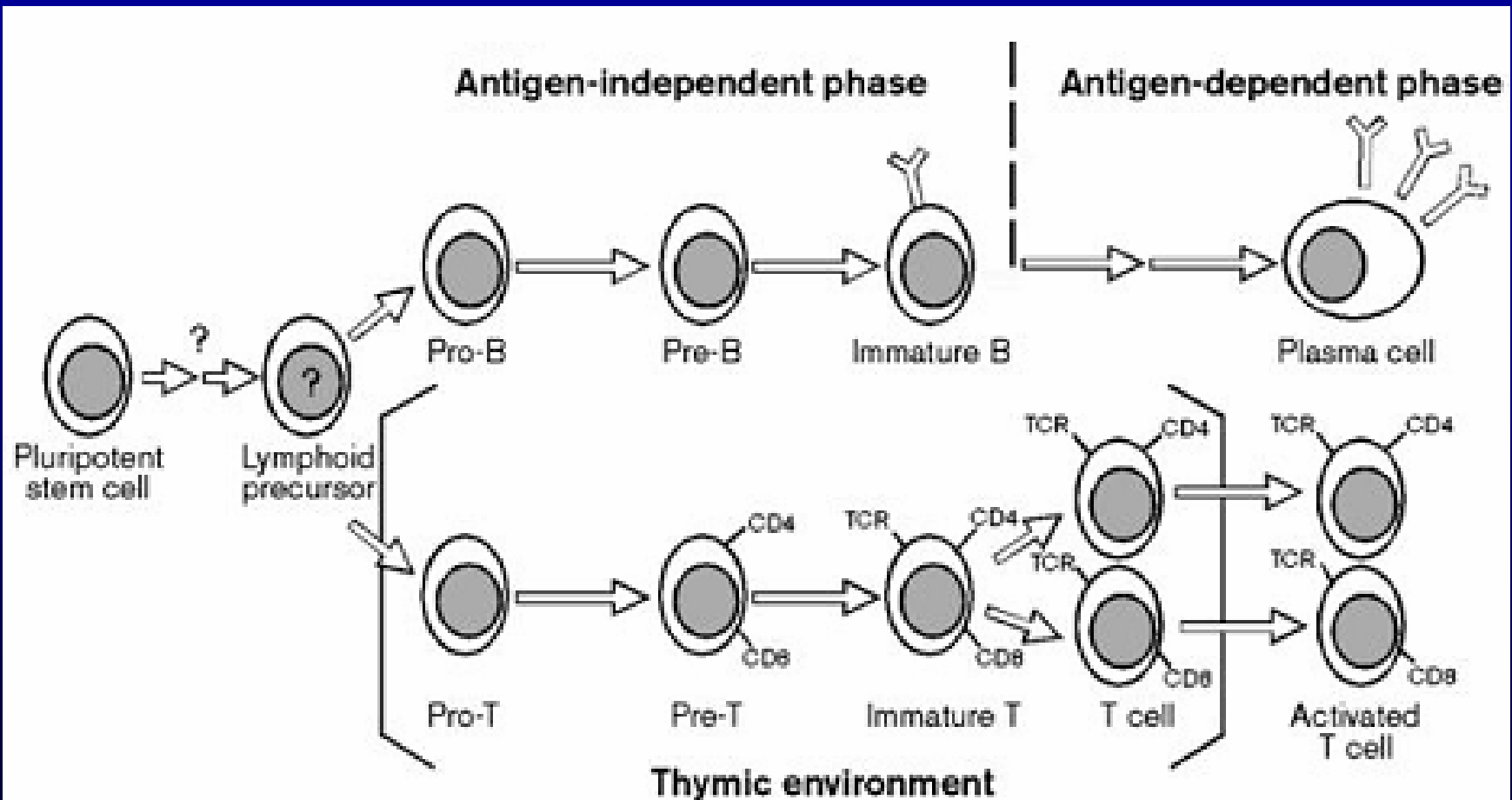
- Les cellules effectrices différenciées à partir d'un lymphocyte activé donné expriment des récepteurs de même spécificité



Sélection positive et négative des répertoires lymphocytaires

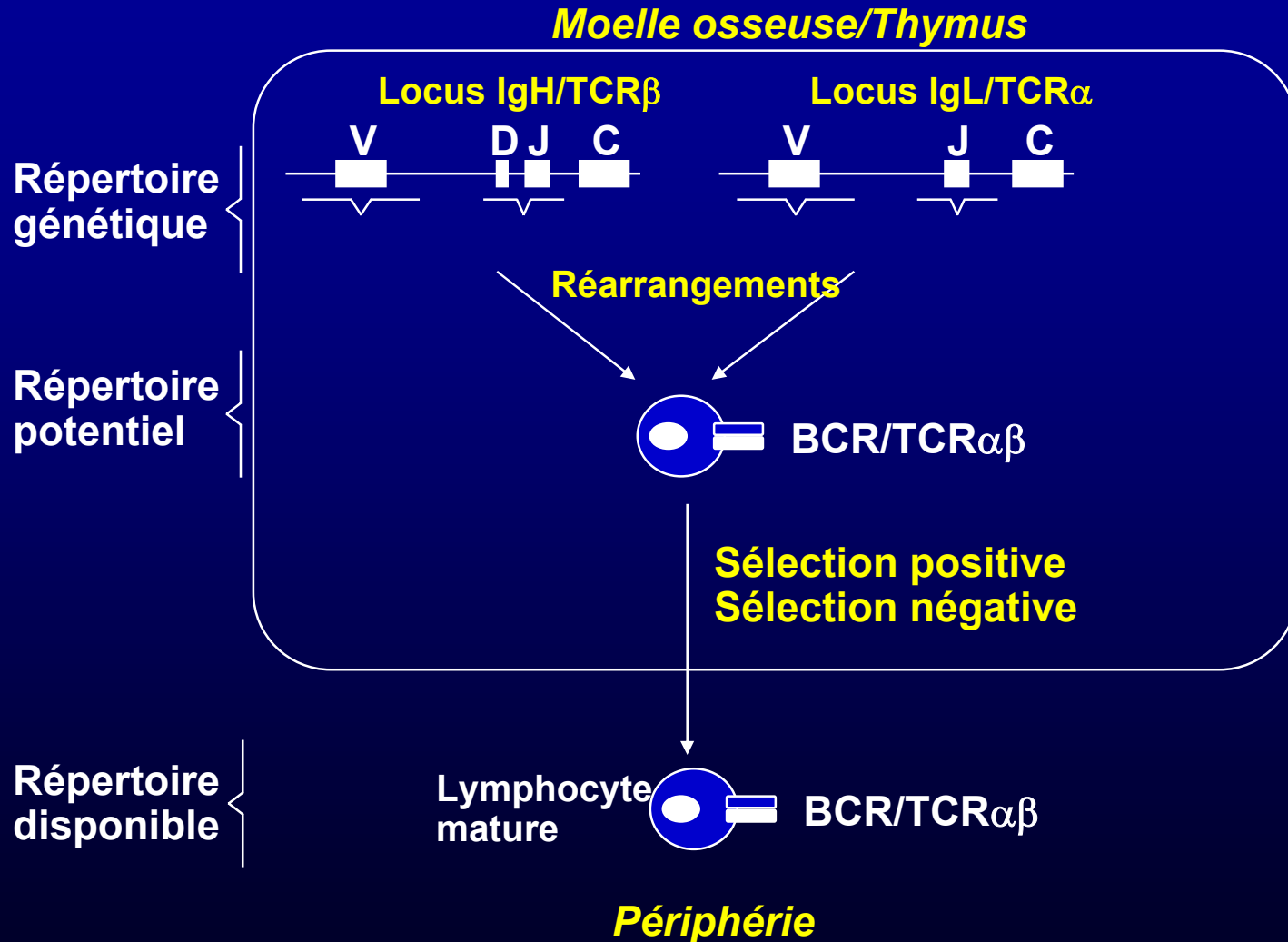
1. Introduction
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Parallèle différenciations B et T

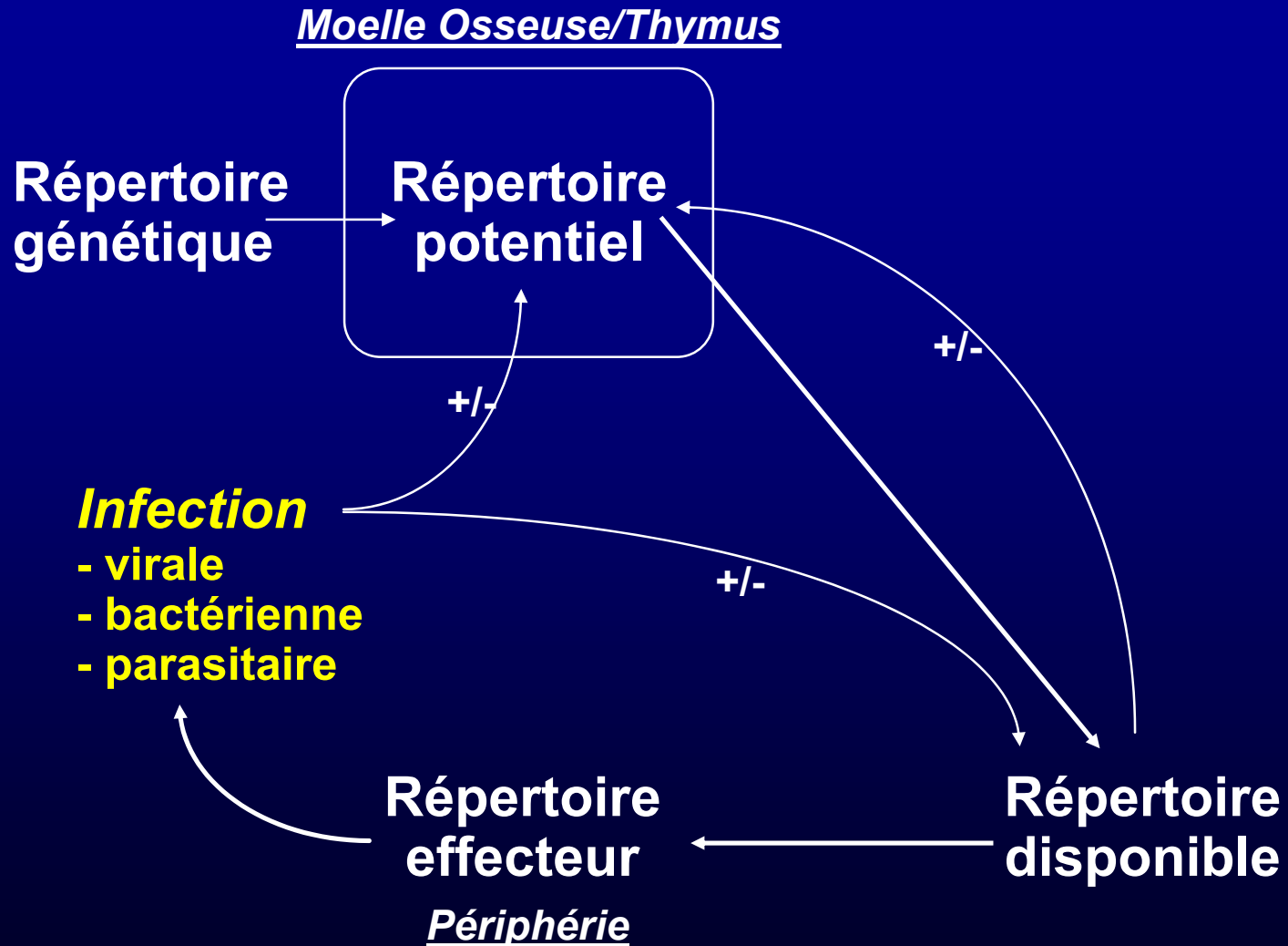


© 1998 Current Opinion in Immunology

Notions de répertoires (1)



Notions de répertoires (2)



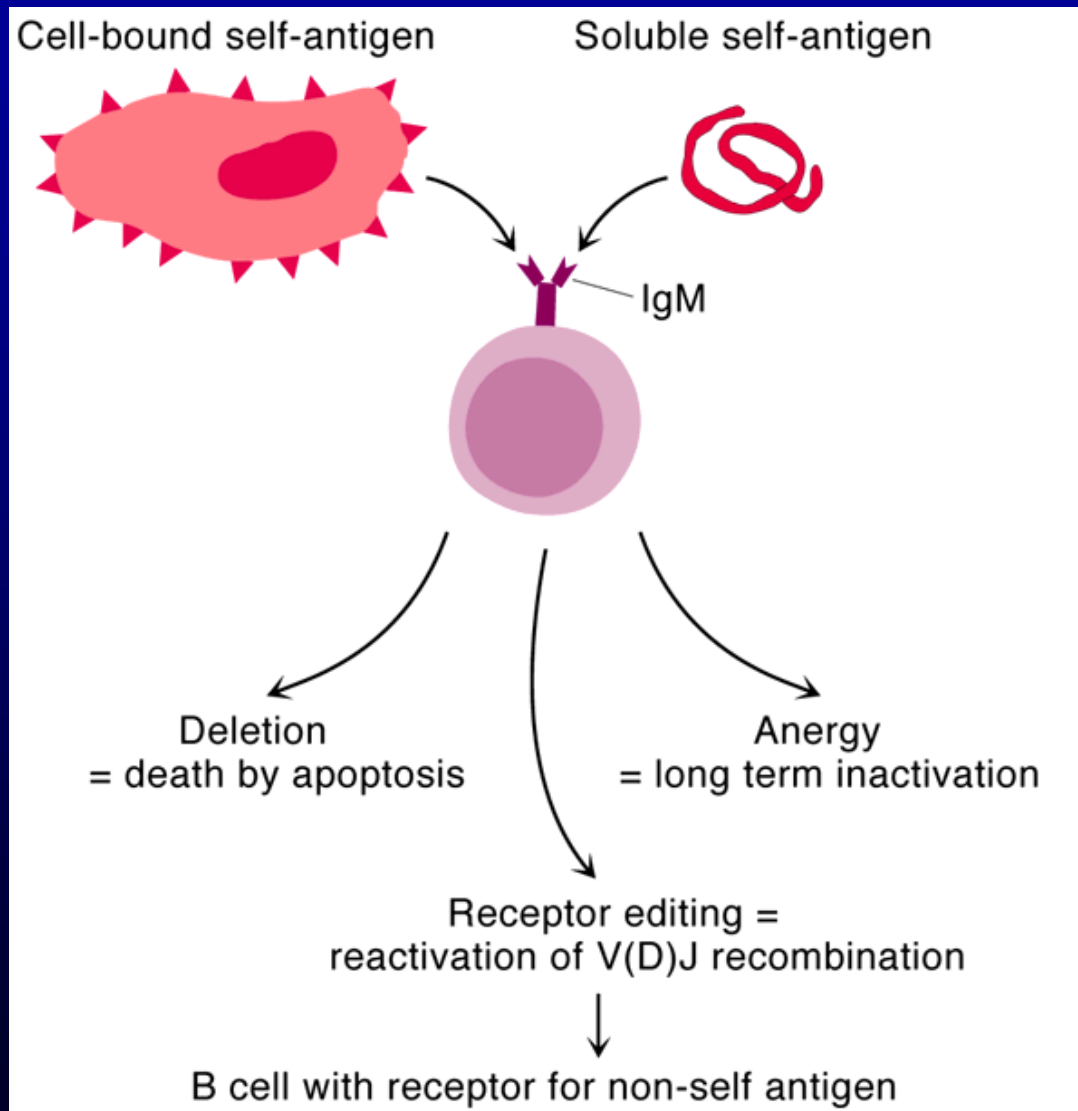
Notions de répertoires (3)

- La diversité des récepteurs spécifiques de l'antigène du **répertoire disponible** de **lymphocytes matures périphériques** conditionne la capacité à répondre aux ***antigènes du non-soi***.
- Cette **diversité disponible** est en fait façonnée, notamment pendant la différenciation lymphocytaire, par les ***antigènes du soi***.

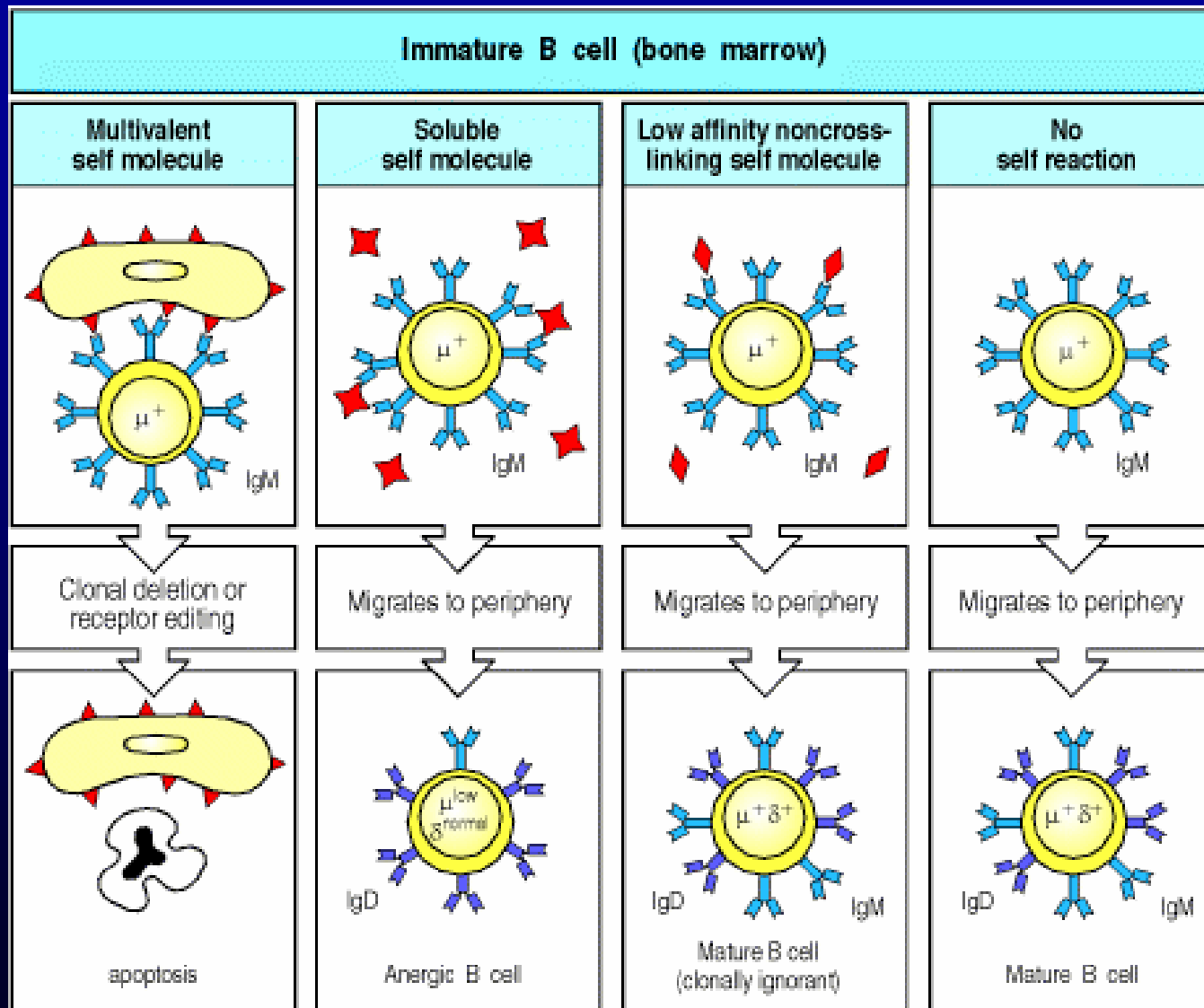
Sélection positive et négative des répertoires lymphocytaires

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Sélection des lymphocytes B (1)



Sélection des lymphocytes B (2)



Délétion clonale (1)

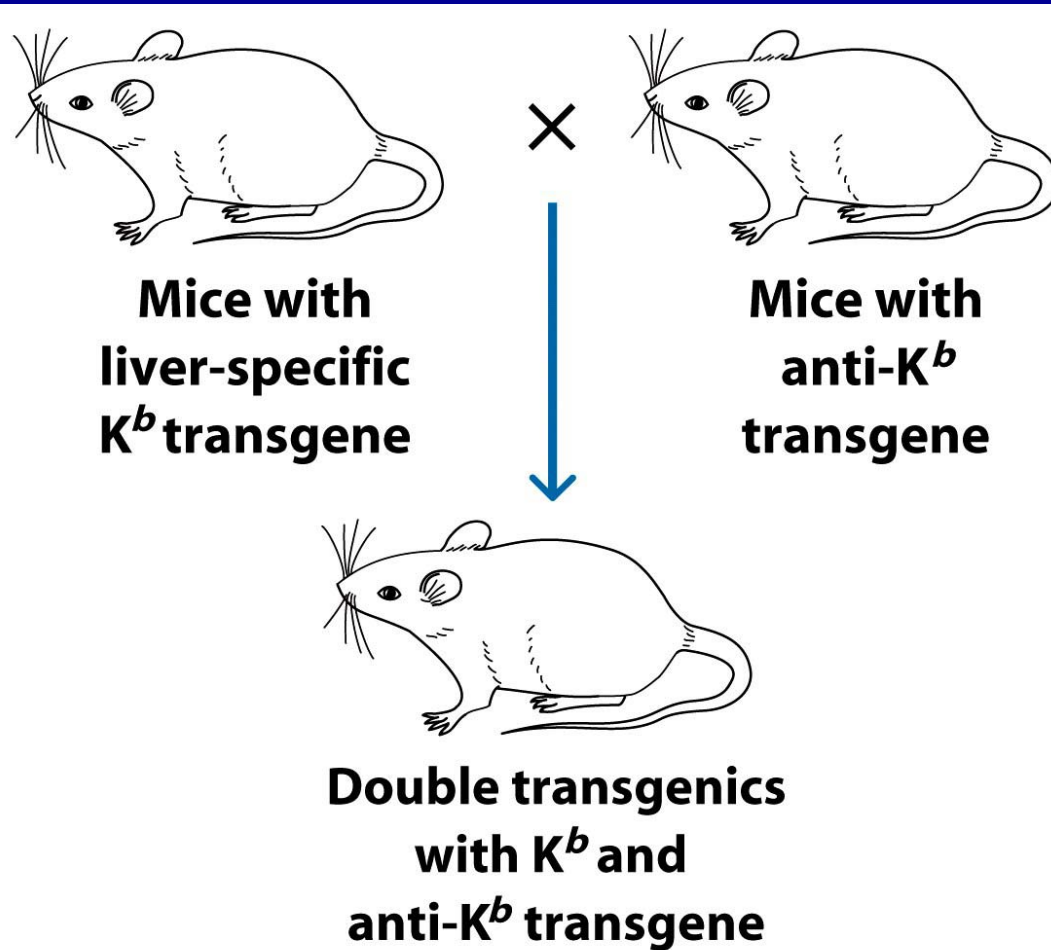


Figure 11-15a
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Délétion clonale (2)

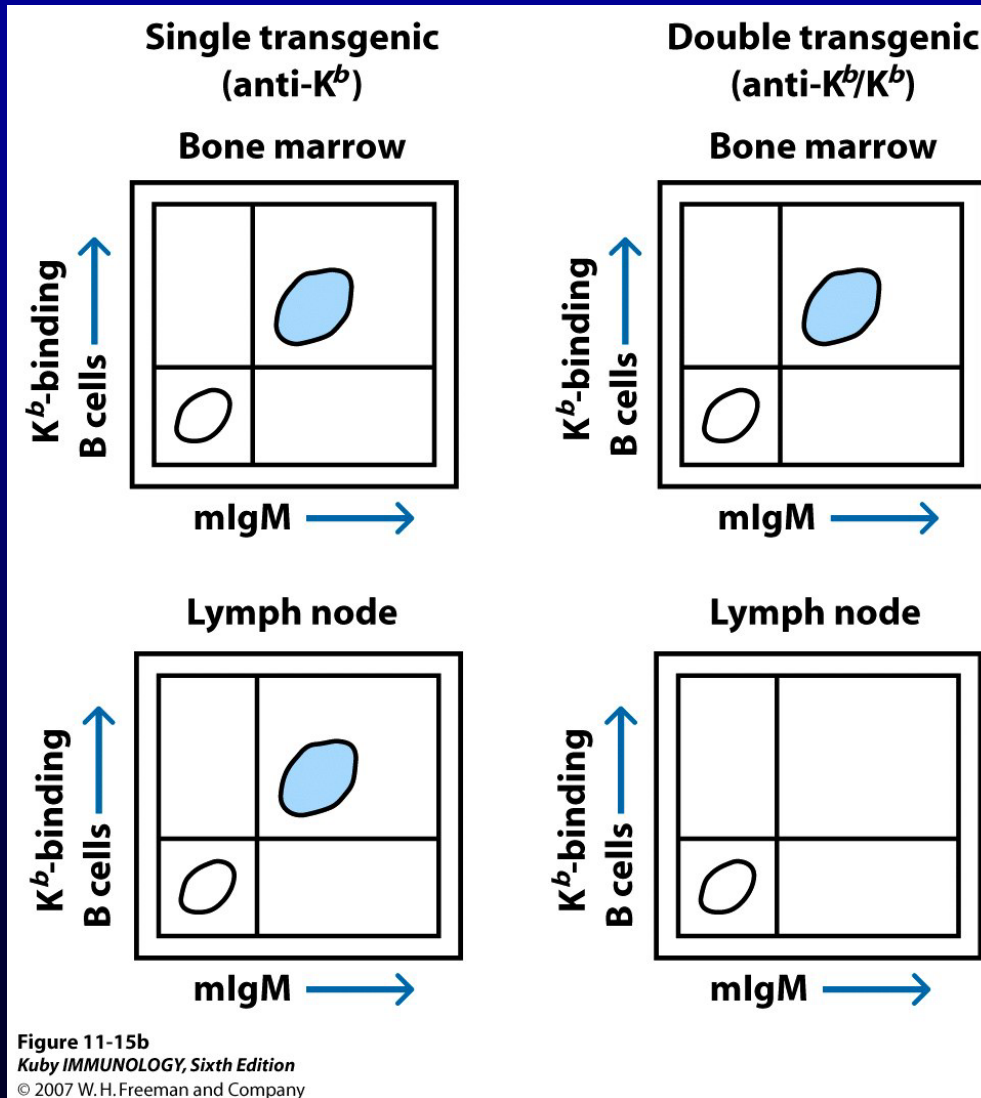


Figure 11-15b
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Anergie (1)

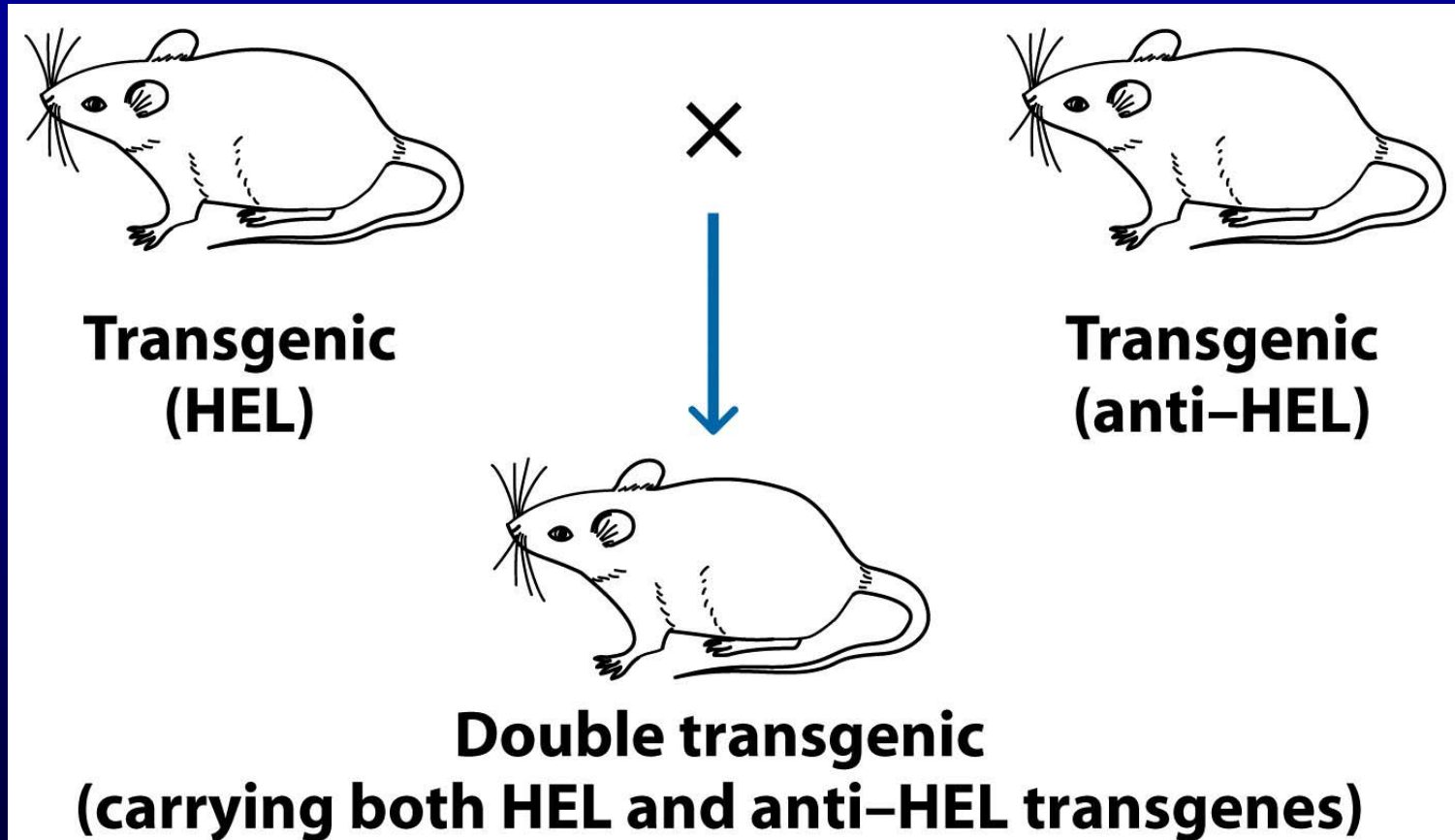


Figure 11-14a
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Anergie (2)

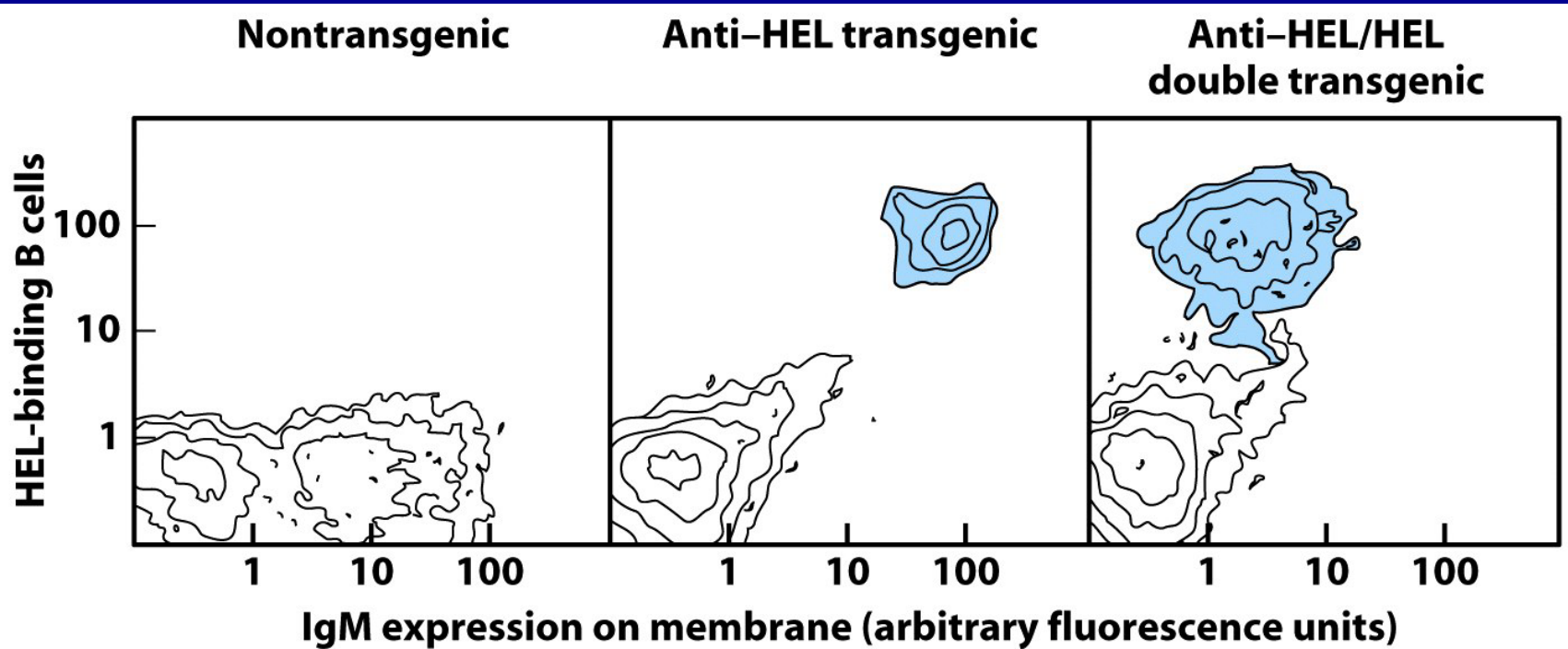
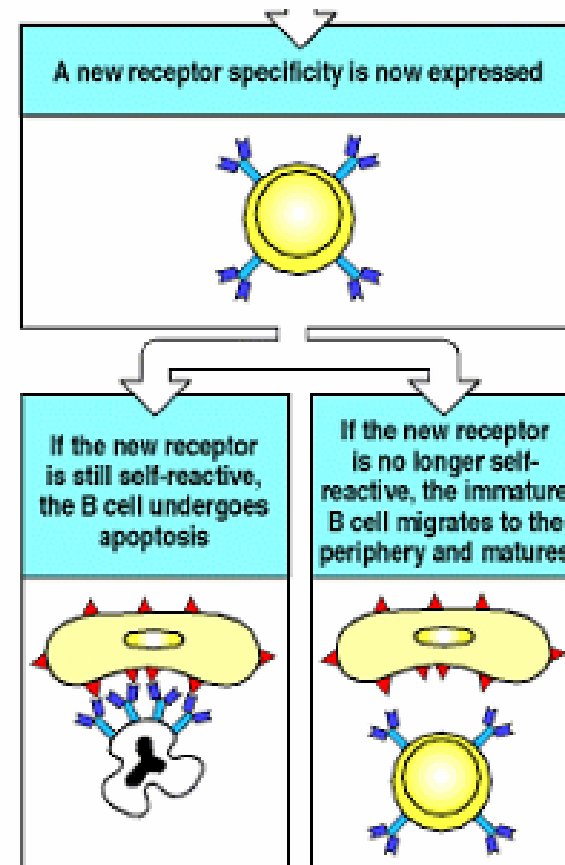
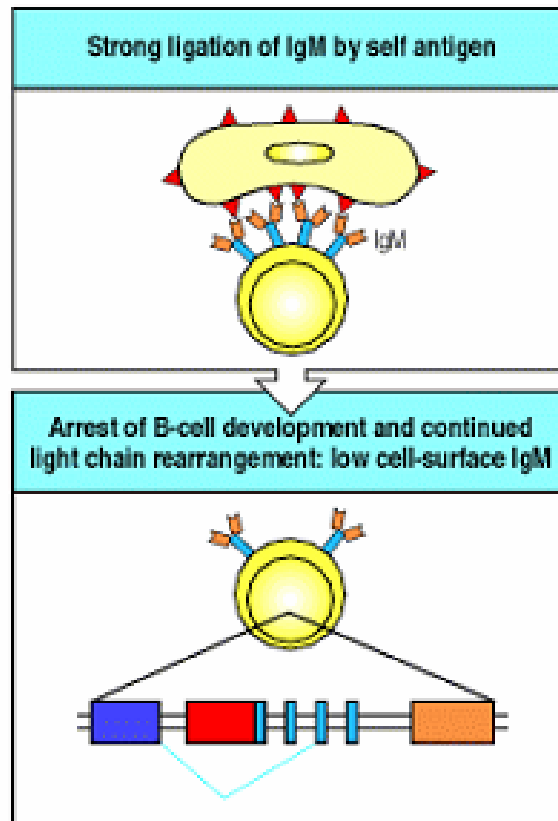


Figure 11-14b
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Sélection des lymphocytes B (3)



Édition du BCR (1)

H-2^{d/k} transgenics

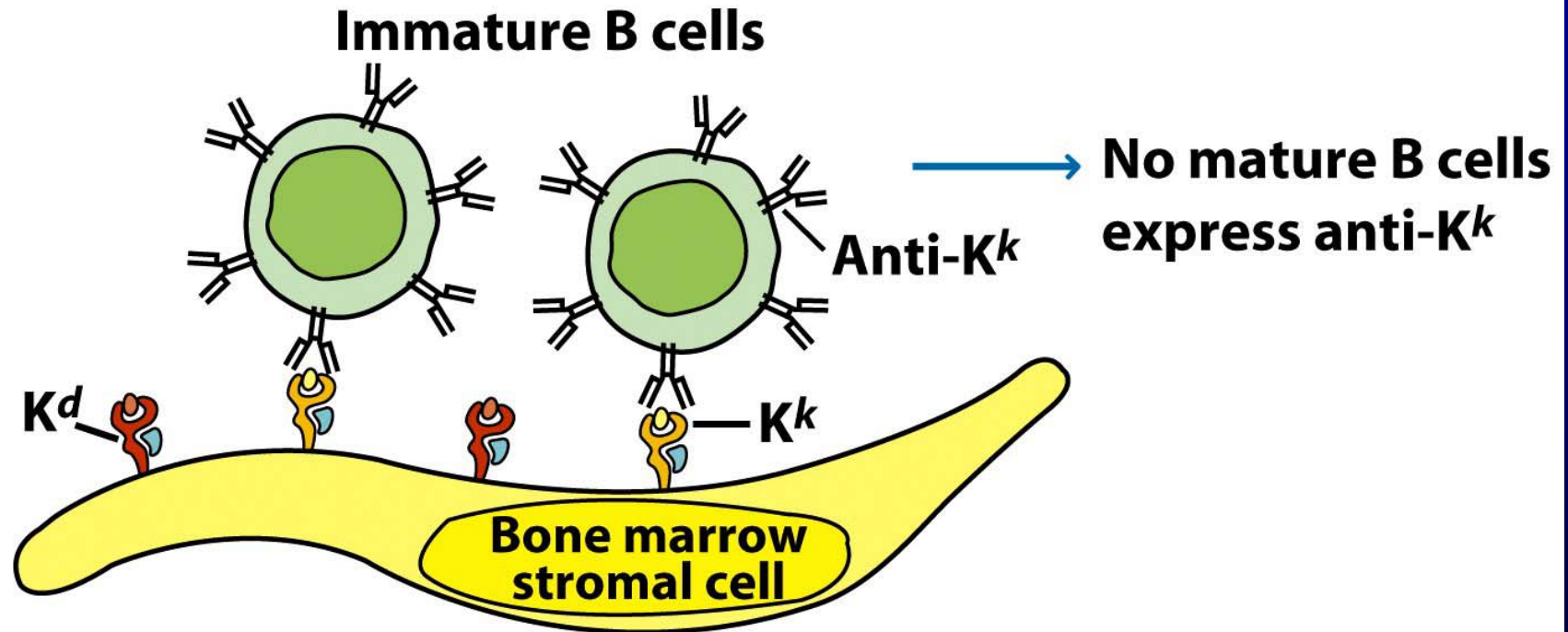


Figure 11-6a
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Édition du BCR (2)

H-2^d transgenics

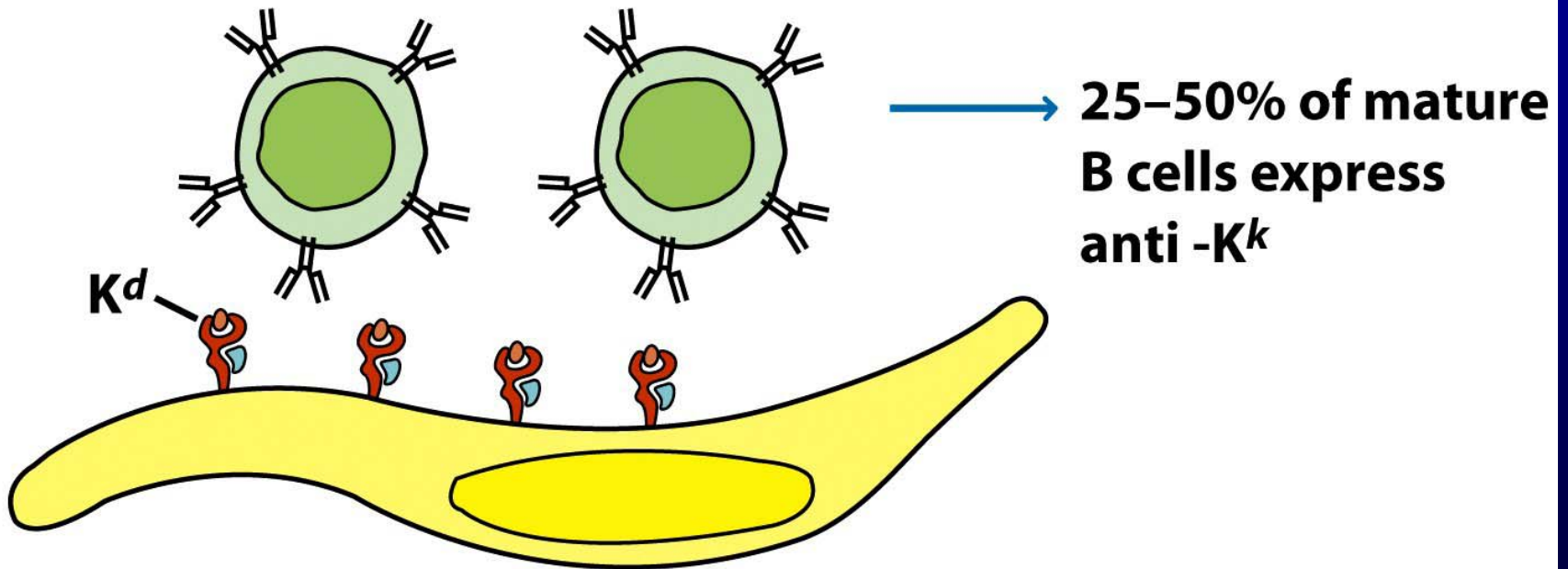


Figure 11-6b
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Édition du BCR (3)

TABLE 11-1

Expression of transgene encoding IgM antibody to H-2^k class I MHC molecules

Experimental animal	Number of animals tested	EXPRESSION OF TRANSGENE	
		As membrane Ab	As secreted Ab (µg/ml)
Nontransgenics	13	(-)	<0.3
H-2 ^d transgenics	7	(+)	93.0
H-2 ^{d/k} transgenics	6	(-)	<0.3
SOURCE: Adapted from D. A. Nemazee and K. Burki, 1989, <i>Nature</i> 337 :562.			

Table 11-1

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Édition du BCR (4)

H-2^{d/k} transgenics

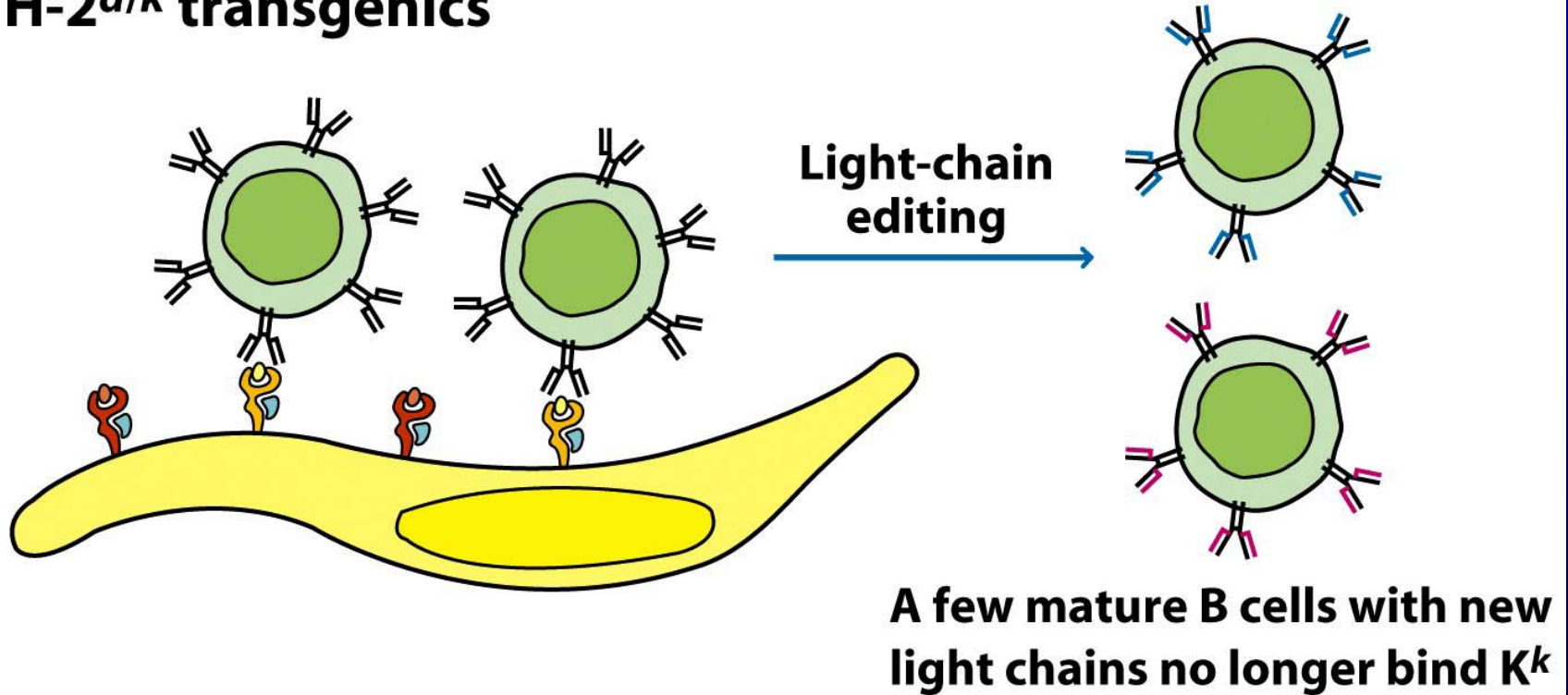
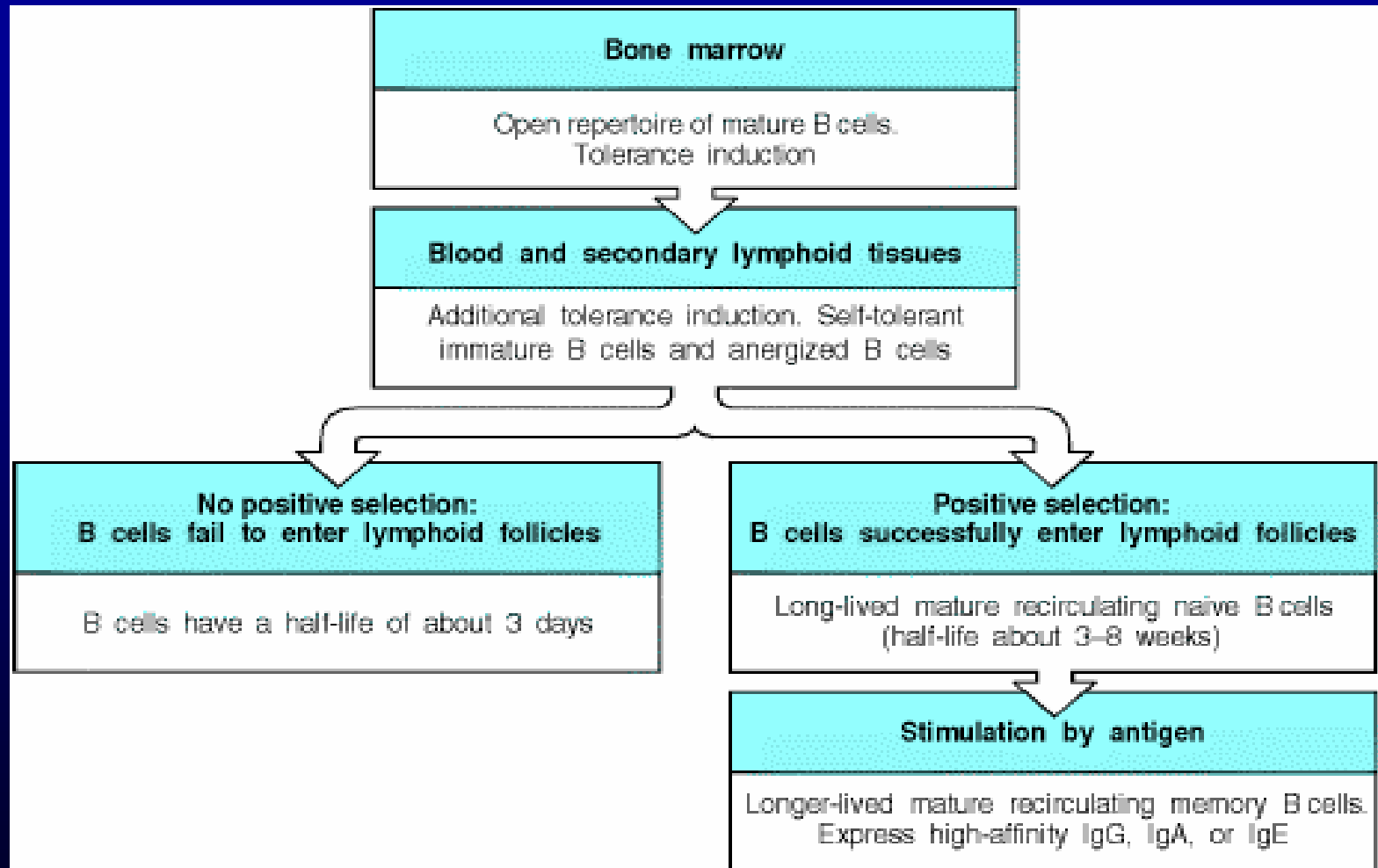
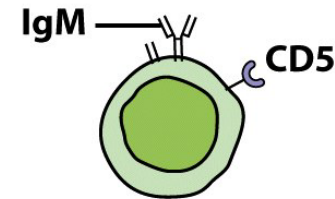
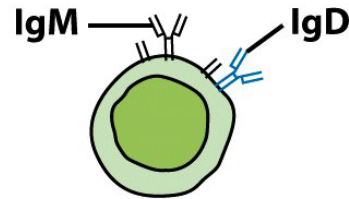


Figure 11-6c
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Sélection des lymphocytes B (4)



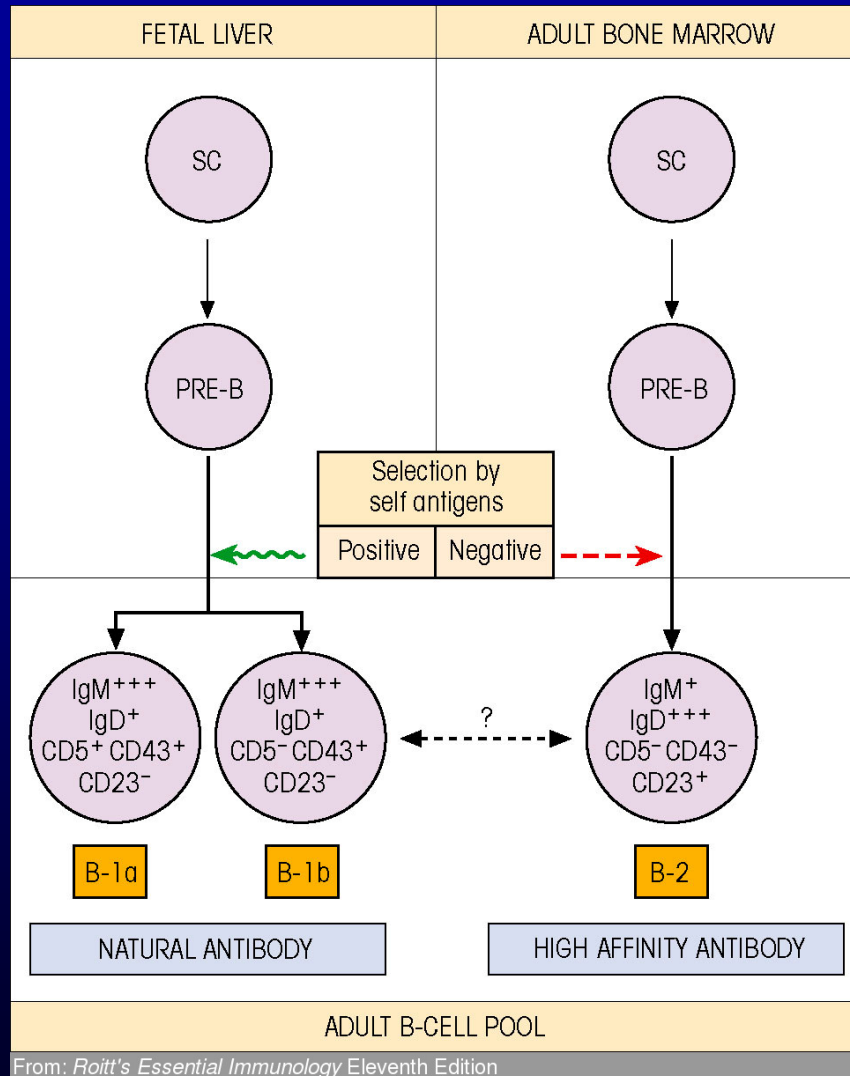
Sélection des lymphocytes B (5)



Attribute	Conventional B cells (B-2 B cells)	B-1 B cells
Major sites	Secondary lymphoid organs	Peritoneal and pleural cavities
Source of new B cells	From precursors in bone marrow	Self-renewing (division of existing B-1 cells)
V-region diversity	Highly diverse	Restricted diversity
Somatic hypermutation	Yes	No
Requirements for T-cell help	Yes	No
Isotypes produced	High levels of IgG	High levels of IgM
Response to carbohydrate antigens	Possibly	Definitely
Response to protein antigens	Definitely	Possibly
Memory	Yes	Very little or none
Surface IgD on mature B cells	Present on naive B cells	Little or none

Figure 11-5
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Sélection des lymphocytes B (6)



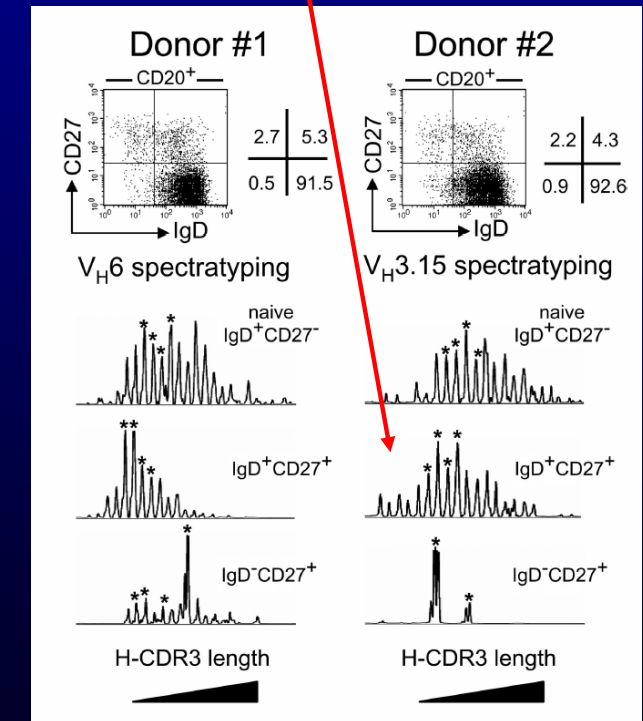
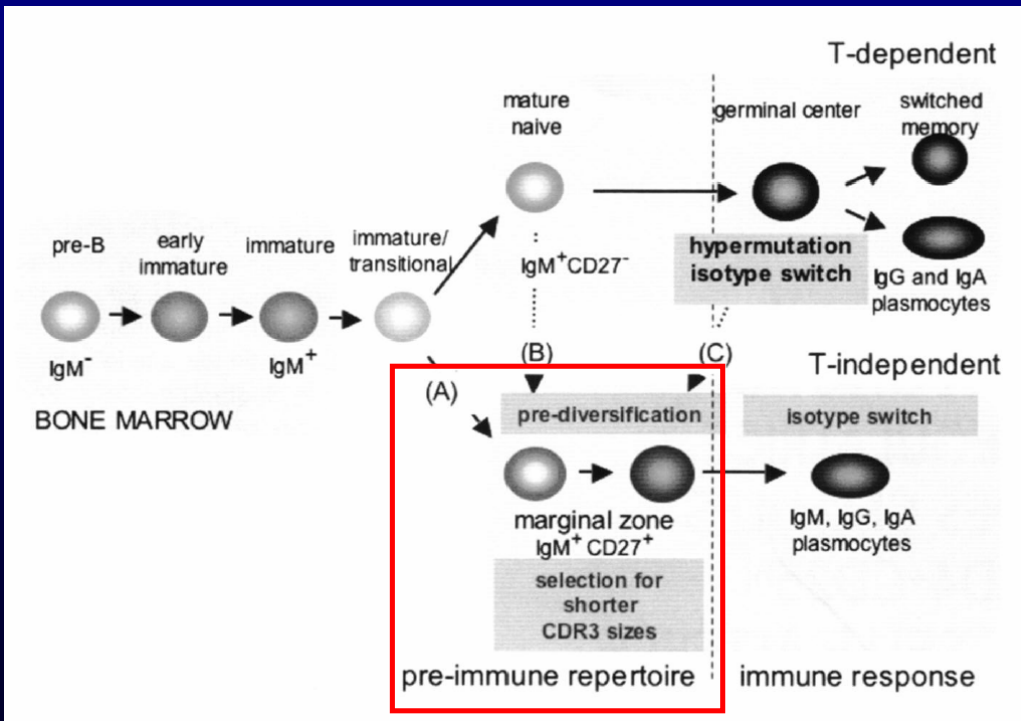
Hypermutations en absence d'antigène

Table IV. Somatic mutations in J_H4-J_H5 introns flanking VDJ_H4 rearrangements from splenic and blood B cell subsets

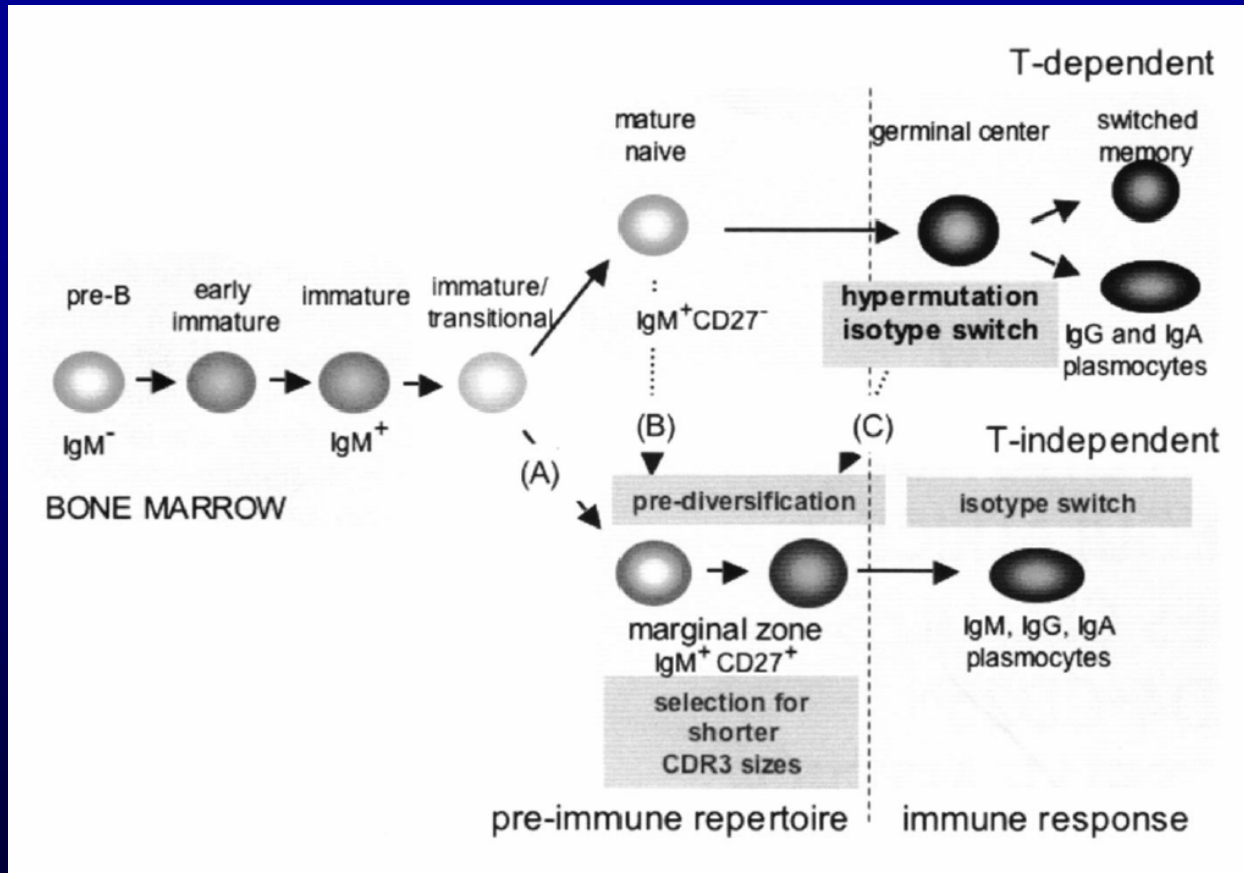
Donors	Age (months)	Tissue	CD20-positive B cell subsets	Number of sequences		Mutations			
				Total	Mutated	Range	Number	Frequency/ total sequences	Frequency/ mutated sequences
D1	11	blood	IgD ⁺ CD27 ⁺	20	15 (75%)	0-17	79	1.16	1.54
			IgD ⁻ CD27 ⁺	20	18 (90%)	0-22	117	1.71	1.90
D2	11	blood	IgD ⁺ CD27 ⁺	18	15 (83%)	0-16	116	1.89	2.27
			IgD ⁻ CD27 ⁺	17	16 (94%)	0-21	127	2.19	2.32

IgM⁺IgD⁺CD27⁺ humaines

- Zone marginale de la rate
- Mutations somatiques
- Diversité CDR3 « normale »



Hypermutations en absence d'antigène



Compétition antigénique

TABLE 11-7

Antigenic competition between sheep and horse RBCs

IMMUNIZING ANTIGEN		HEMOLYTIC PLAQUE ASSAY (DAY 8)	
Ag1 (day 0)	Ag2 (day 3)	Test Ag	PFC / 10 ⁶ * spleen cells
None	HRBC	HRBC	205
SRBC	HRBC	HRBC	13
None	SRBC	SRBC	626
HRBC	SRBC	SRBC	78

*PFC = plaque-forming cells.

Dominance clonale: idiotype T15 (1)

Anticorps inhibiteurs	Nombre de PFC anti-PC/rate
-	120 000
S1 60	115 000
S1 04	117 000
2E8	800
F6	950

-S160, S104, 2E8 et F6 sont quatre anticorps monoclonaux anti-T15, une immunoglobuline IgA, κ anti-phosphorylcholine.

-S160 est dirigé contre un épitope de Ig α ; S104 est spécifique de IgA, κ ; 2E8 et F6 sont des anticorps anti-idiotypiques.

-Les quatre anticorps ont été utilisés pour tenter d'inhiber des plages d'hémolyses locales (PFC) obtenues en mélangeant *in vitro* des cellules de souris BALB/c anti-PC, de la PC couplée à des globules rouges de mouton et du complément.

Dominance clonale: idiotype T15 (2)

TABLE 1
Number of PC-Specific Foci and Percentages of T15⁺ Foci as a Function of Development

Age of donor mice in days ^a	Number of donor mice ^b	Total number of cells analyzed	Number of PC ⁺ foci	Frequency (in 10 ⁶ spleen cells) ^c	Number of T15 ⁺ foci	%T15 ⁺
2	58	2 × 10 ⁸	0	0	0	0
3	52	2 × 10 ⁸	0	0	0	0
4	31	2 × 10 ⁸	1	0.125	0	0
6	17	2 × 10 ⁸	7	0.875	2	28.5
7	13	3 × 10 ⁸	15	1.2	6	40.0
8	7	10 ⁸	7	1.7	4	57.1
9	5	10 ⁸	13	3.2	9	69.2
10	6	1.8 × 10 ⁸	30	4.1	24	80.0
12	4	1.5 × 10 ⁸	28	4.6	25	89.2
21	1	1.2 × 10 ⁸	18	3.7	16	88.8
42-46	1	2 × 10 ⁸	69	8.6	63	91.3

^aThe day of birth was counted as day 1. Thus, an age of 2 indicates 1 day after birth, age of 3 indicates 2 days after birth, etc.

^bSpleen cells from mice born within 12 hr of each other were pooled. Results from experiments performed on different days were pooled for the table.

^cCalculated as per Sigal et al. (1977).

Dominance clonale: idiotype T15 (3)

Injection néonatale de R36A *S. pneumoniae* + challenge R36A à 7 semaines
→ Dosage Ac anti-PC

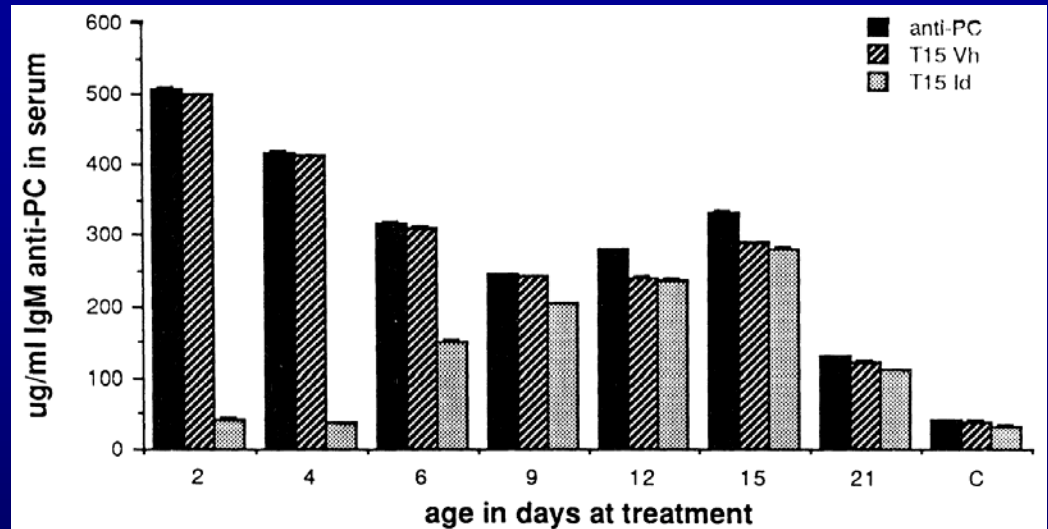


TABLE 3

Treatment of serum donor		Alive/dead postchallenge	
neonatal	adult	3 days	10 days
None	R36A	7/0	5/2
R36A	R36A	0/4 ^a	0/4 ^c
None	None	0/7 ^b	0/7 ^a
No serum		0/7 ^b	0/7 ^a

^aDifferent from none/R36A at $p < 0.01$.

^bDifferent from none/R36A at $p < 0.001$.

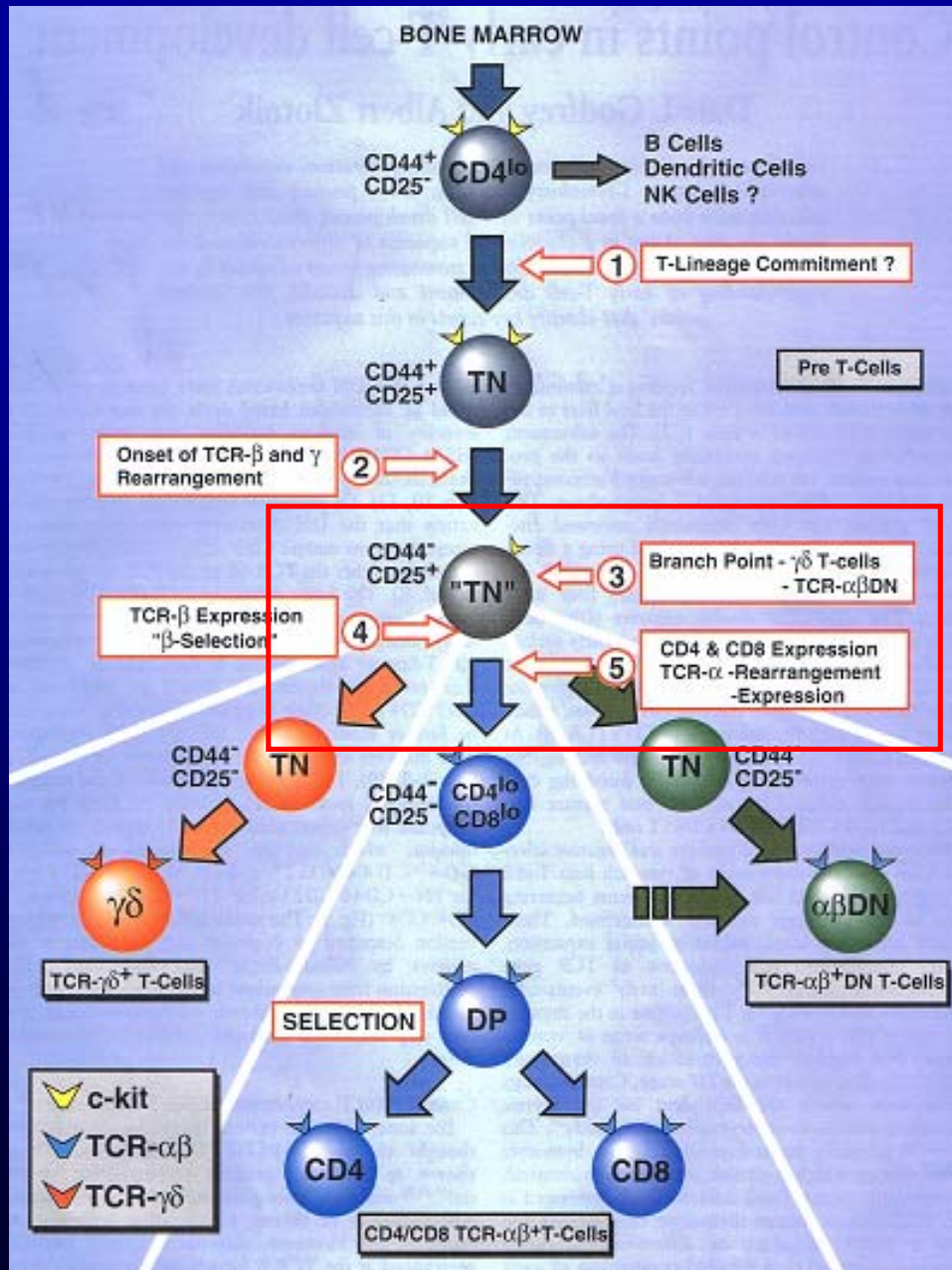
^cDifferent from none/R36A at $p < 0.06$.

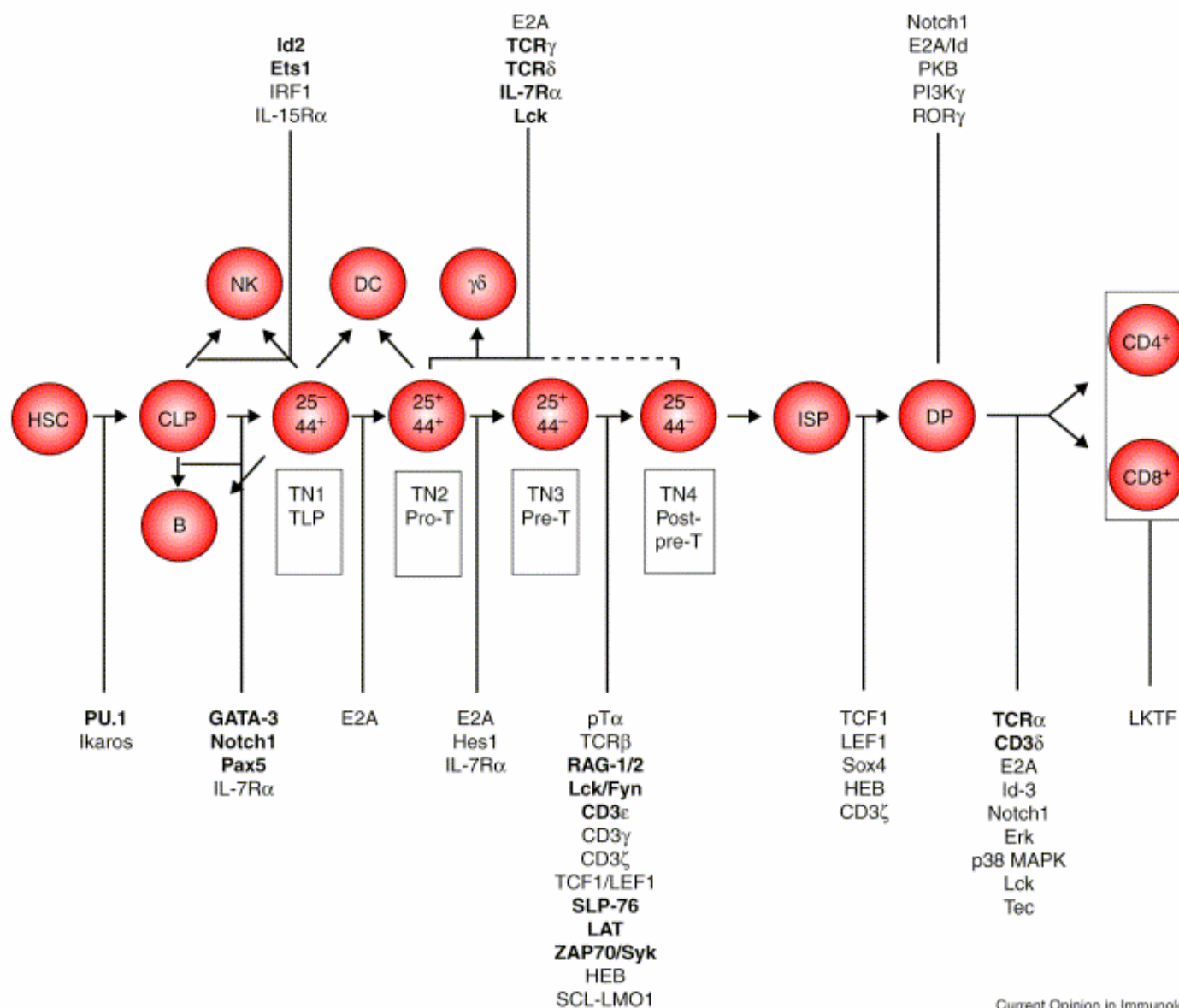
Challenge léthal *S. pneumoniae*
→ Pouvoir protecteur du sérum de souris préalablement exposées?

Vakil, Briles & Kearney (1991) *Dev. Immunol* 1:203.

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Lignées $\alpha\beta$ versus $\gamma\delta$

- Controverse concernant le mécanisme contrôlant le choix vers les lignées T $\alpha\beta$ et $\gamma\delta$
 - Certaines cellules T $\gamma\delta$ expriment TCR β
Certaines cellules T $\alpha\beta$ expriment TCR γ
 - Différent modèles proposés :
 - Réarrangements séquentiels
 - Réarrangements compétitifs
 - Lignées séparées
- } Instructif
- } Aléatoire

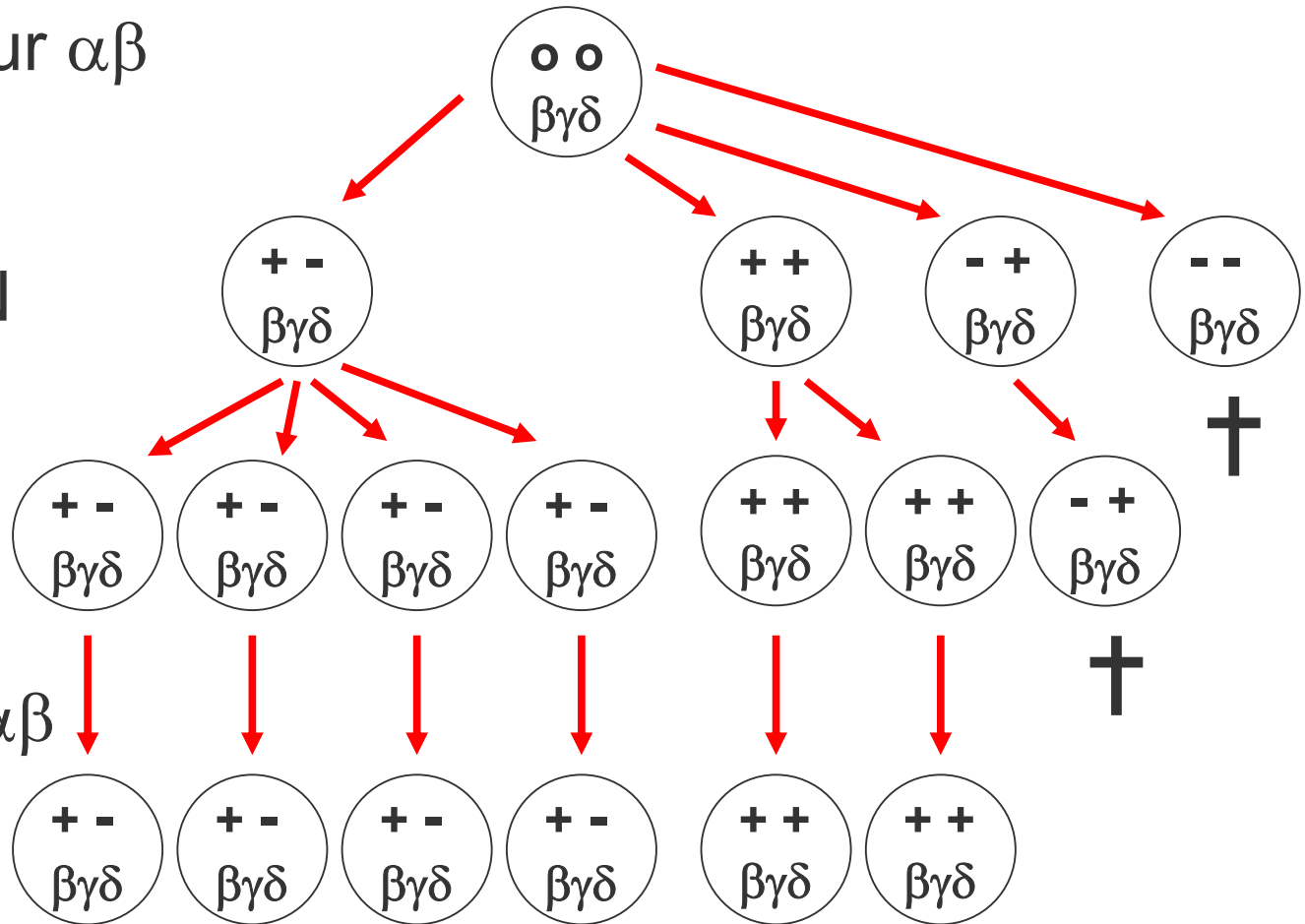
Modèle modifié de lignée séparée (1)

Précurseur $\alpha\beta$

CD25⁺DN

DP

Cellules $\alpha\beta$
matures

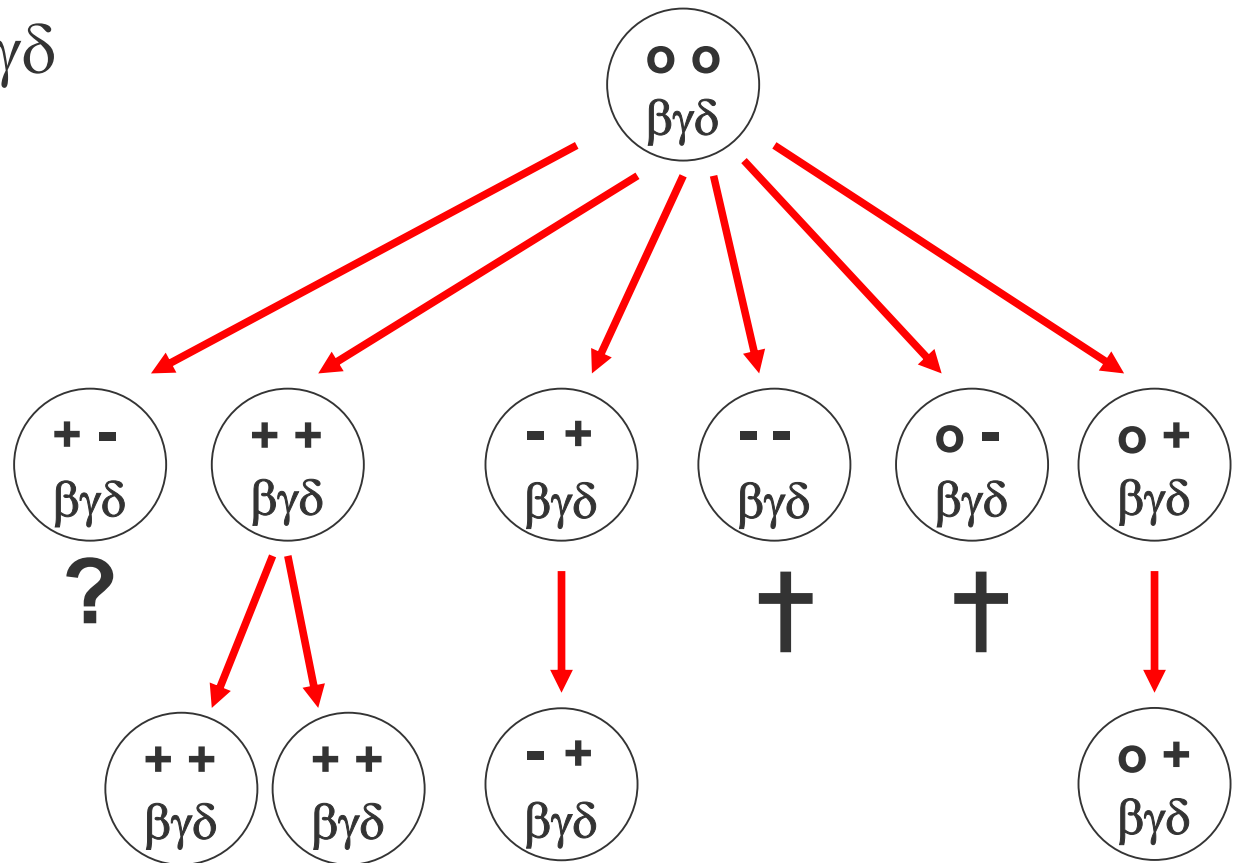


Modèle modifié de lignée séparée (2)

Précurseur $\gamma\delta$

CD25⁺DN

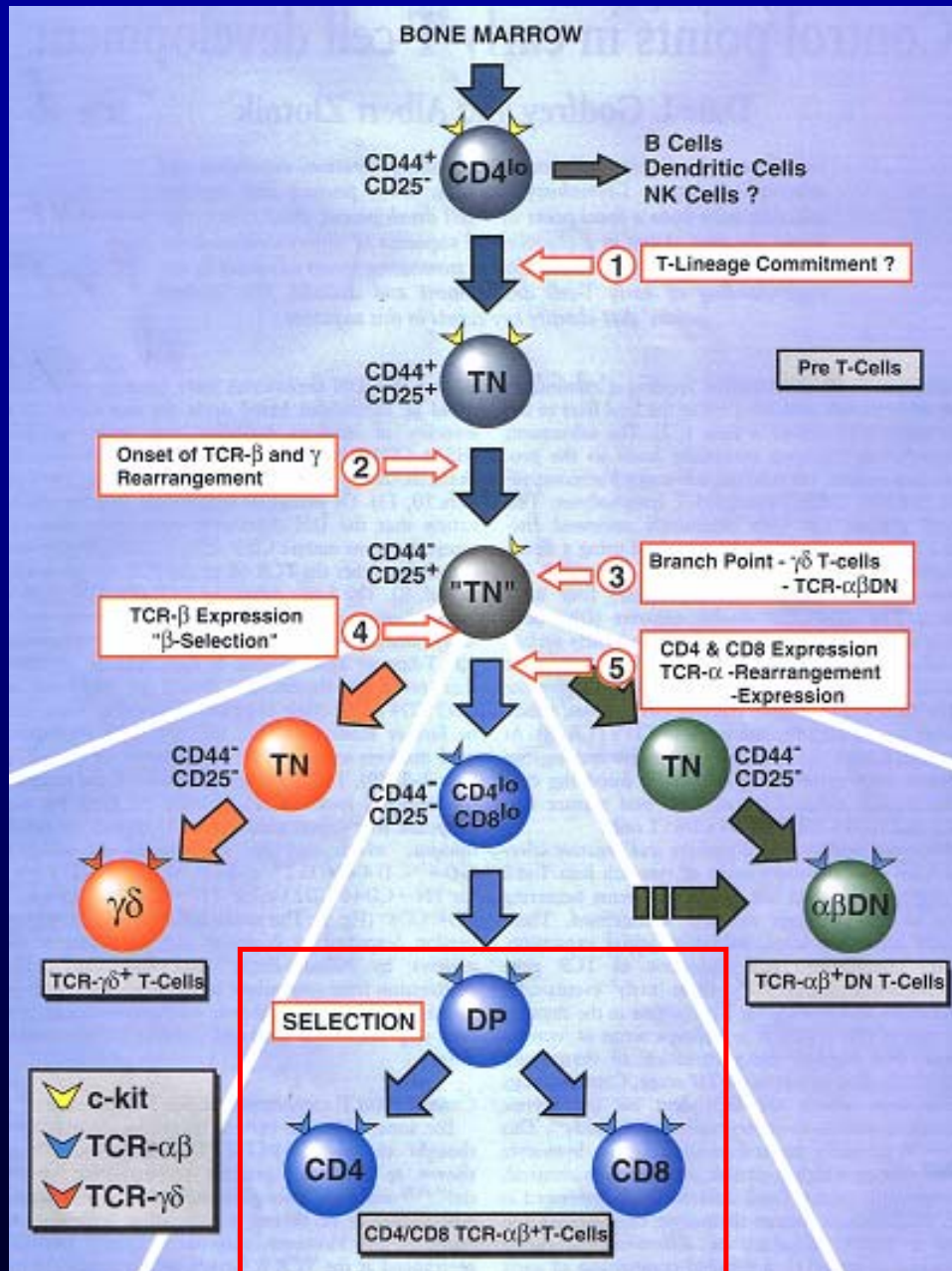
Cellules $\gamma\delta$
matures



Nouveau modèle instructif

T cell receptor–instructed $\alpha\beta$ versus $\gamma\delta$ lineage commitment revealed by single-cell analysis

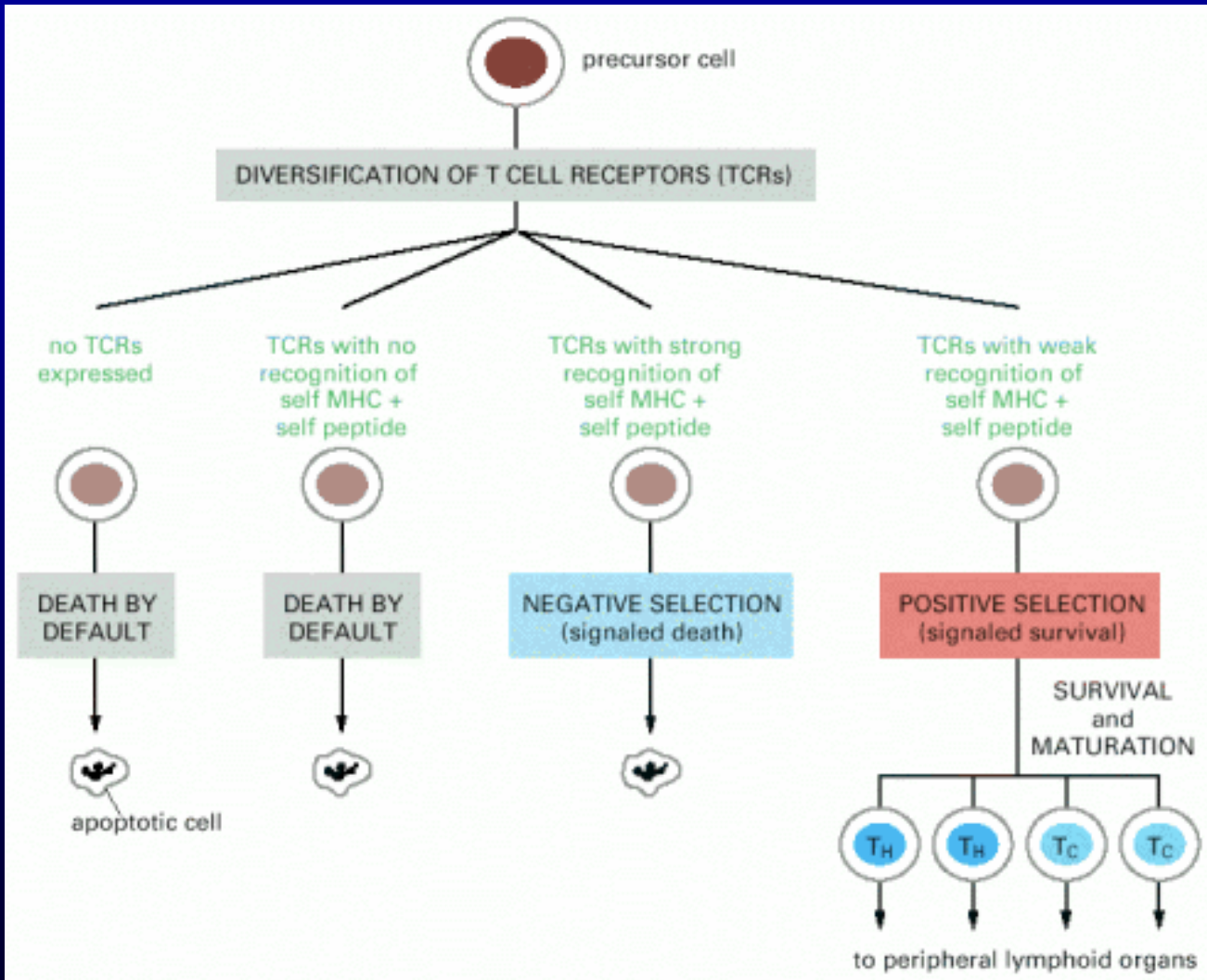
$\alpha\beta$ and $\gamma\delta$ T cell lineages develop in the thymus from a common precursor. It is unclear at which stage of development commitment to these lineages takes place and in which way T cell receptor signaling contributes to the process. Recently, it was demonstrated that strong TCR signals favor $\gamma\delta$ lineage development, whereas weaker TCR signals promote $\alpha\beta$ lineage fate. Two models have been proposed to explain these results. The first model suggests that commitment occurs after TCR expression and TCR signaling directly instructs lymphocytes to adopt one or the other lineage fate. The second model suggests that commitment occurs before TCR expression and that TCR signaling merely confirms the lineage choice. By tracing the fate of single T cell precursors, this study shows that there is no commitment to either the $\alpha\beta$ or $\gamma\delta$ lineage before TCR expression and that modulation of TCR signaling in progeny of a single TCR-expressing cell changes lineage commitment.



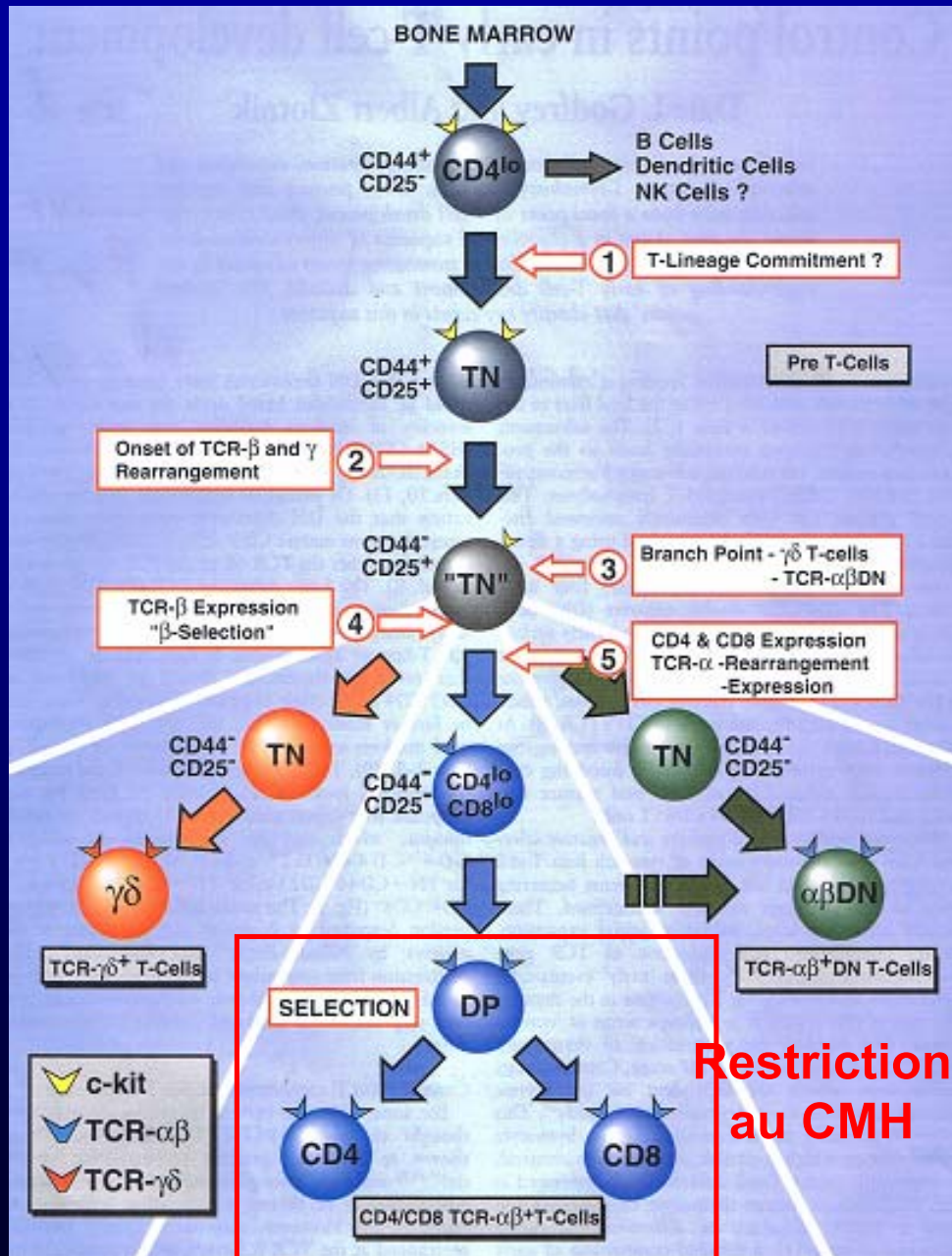
Sélections positive et négative (1)

- **Sélection positive**: le TCR doit avoir une certaine réactivité avec une molécule du CMH du soi
- L'expression du co-récepteur CD4/CD8 suit la restriction pour le CMH
→ **CD4/classe II** et **CD8/classe I**
- **Sélection négative**: les cellules T autoréactives (reconnaissant CMH + peptide du soi) sont éliminées

Sélections positive et négative (2)



→ *Éducation thymique*



Rôle de l'épithélium thymique dans la sélection positive (1)

EXPERIMENT

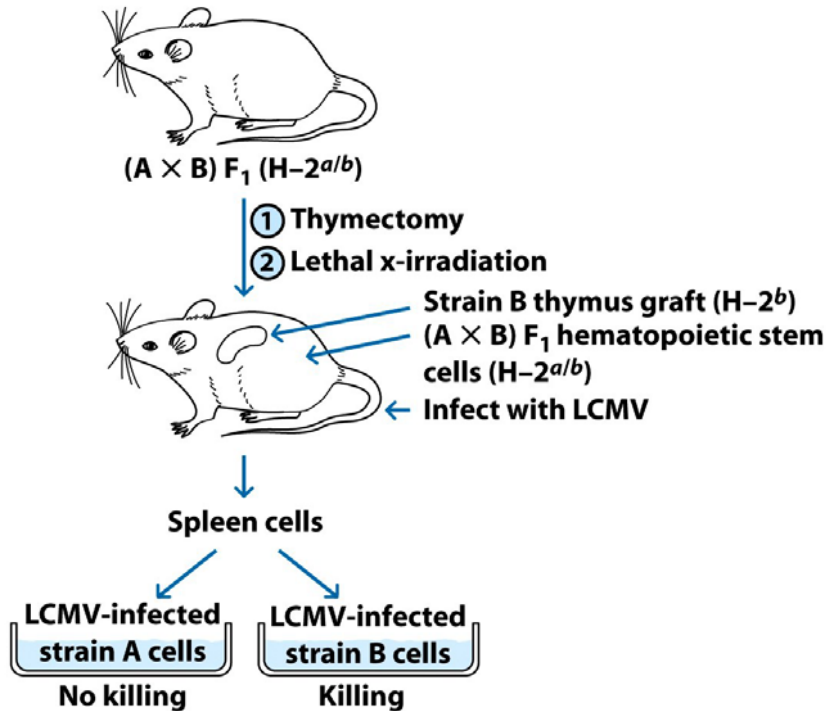


Figure 10-5 part 1
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CONTROL

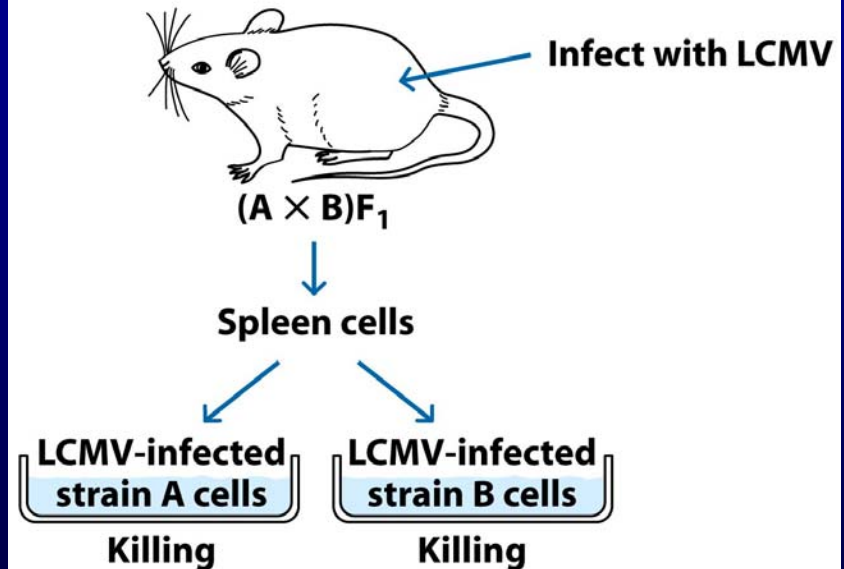
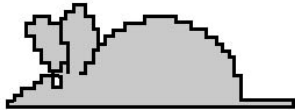
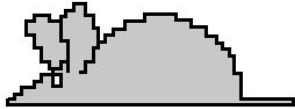
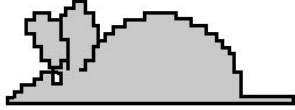
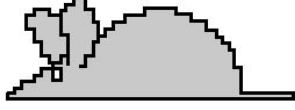


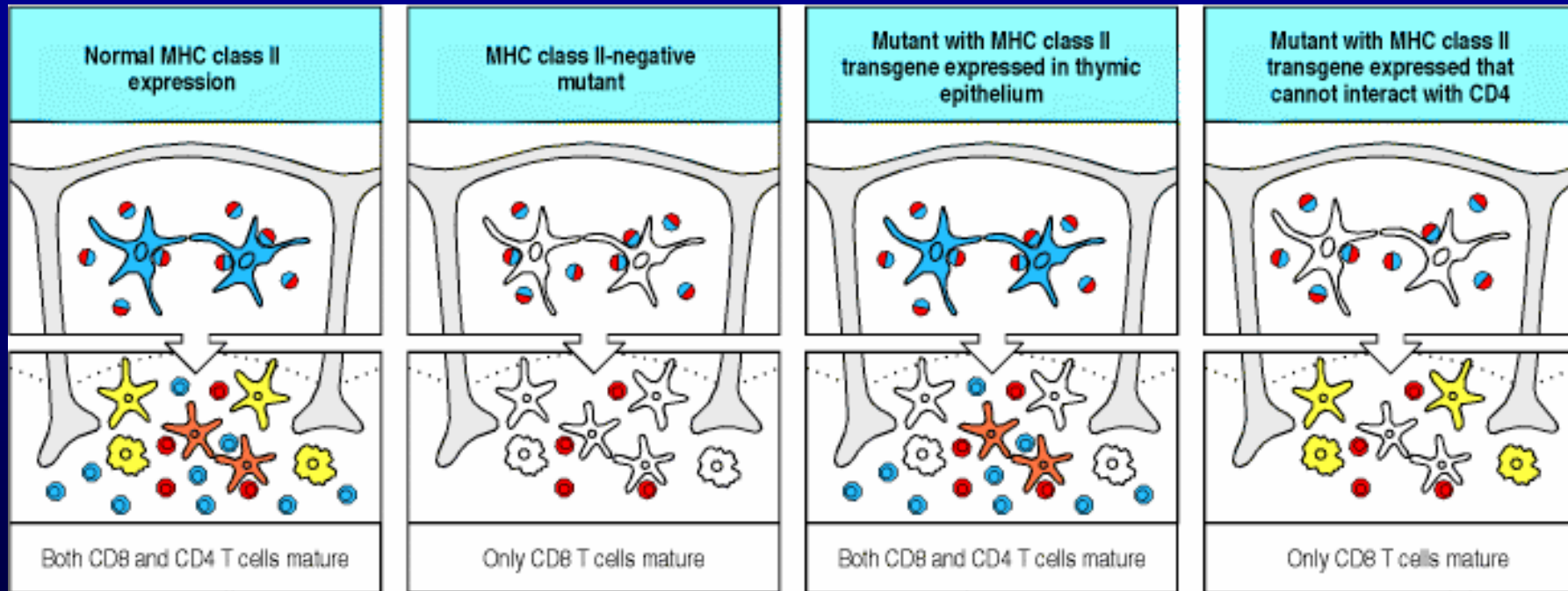
Figure 10-5 part 2
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Rôle de l'épithélium thymique dans la sélection positive (2)

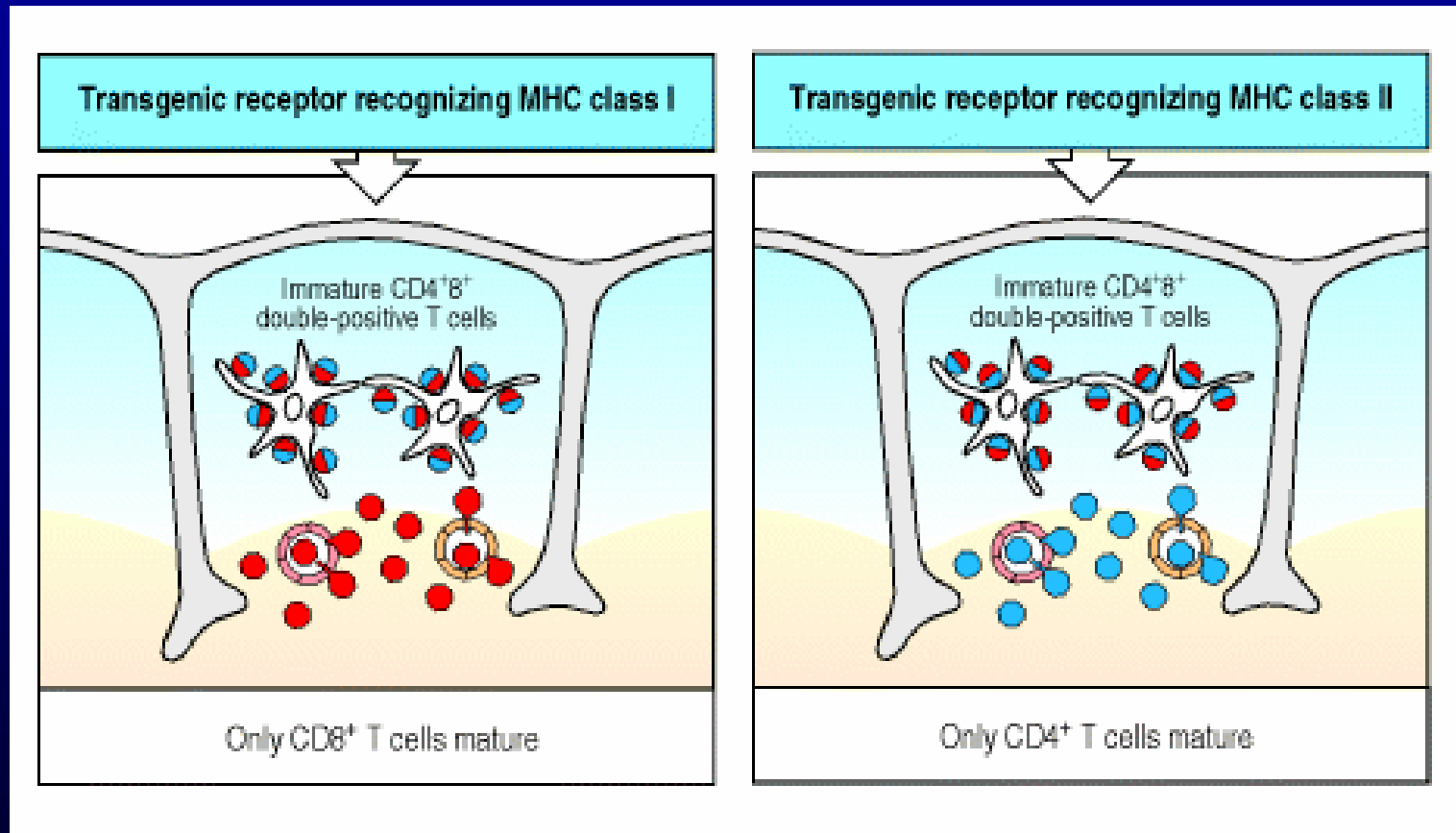
Thymectomize $b \times k$ mice	Graft with thymus of haplotype	Irradiate and reconstitute with $b \times k$ bone marrow	Prime with KLH	Proliferative response of primed T-cells to KLH on antigen-presenting cells of haplotype	
				$H-2^b$	$H-2^k$
	$b \times k$	→	→	+++	+++
	b	→	→	+++	-
	dGuo- treated b	→	→	+++	-
	k	→	→	-	+++
	dGuo- treated k	→	→	-	+++

From: Roitt's Essential Immunology Eleventh Edition

Sélection positive & CMH (1)



Sélection positive & CMH (2)

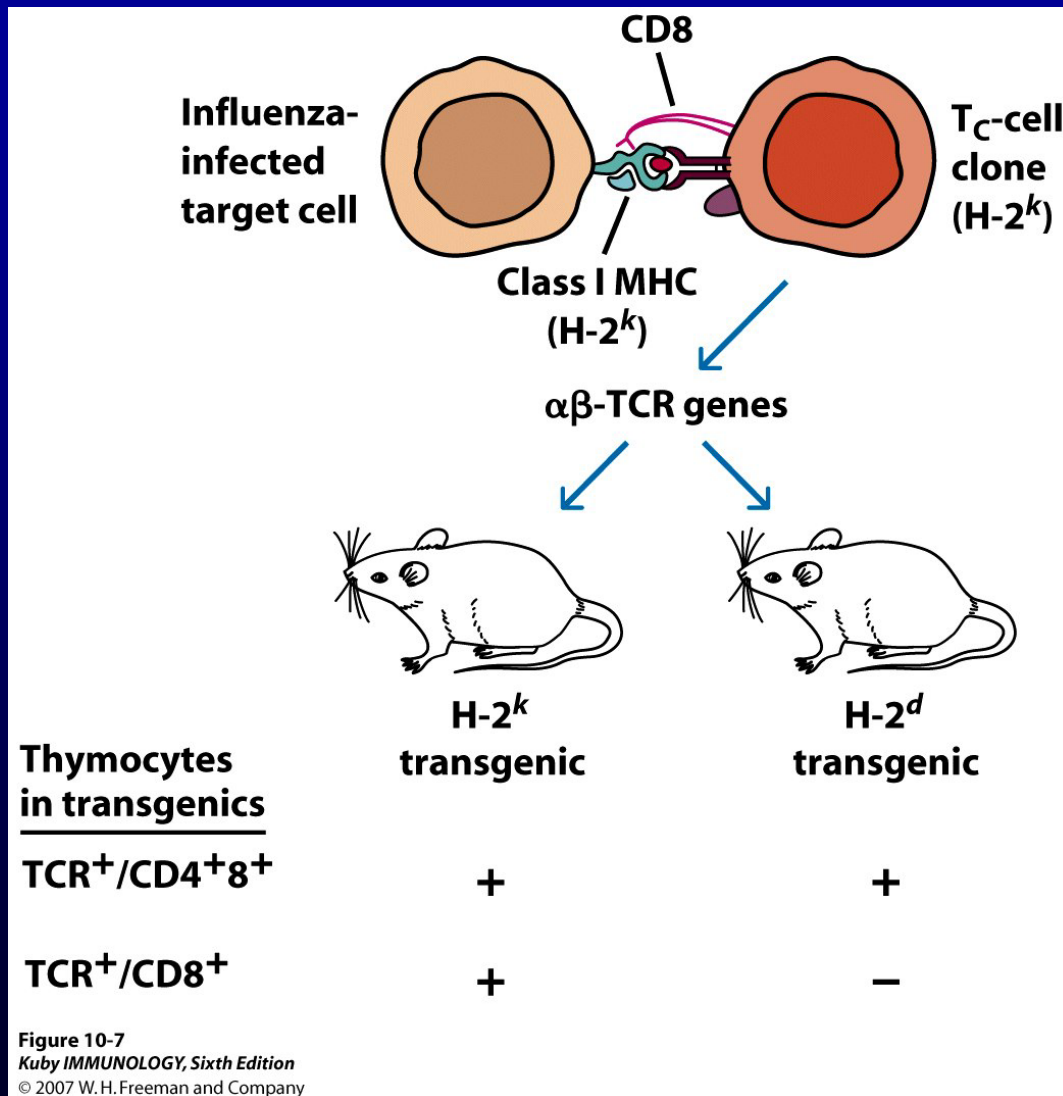


Sélection positive & CMH (3)

TABLE 10-1		Effect of class I or II MHC deficiency on thymocyte populations*	
Cell type	Control mice	KNOCKOUT MICE	
		Class I deficient	Class II deficient
CD4⁻CD8⁻	+	+	+
CD4⁺CD8⁺	+	+	+
CD4⁺	+	+	—
CD8⁺	+	—	+
*Plus sign indicates normal distribution of indicated cell types in thymus. Minus sign indicates absence of cell type.			

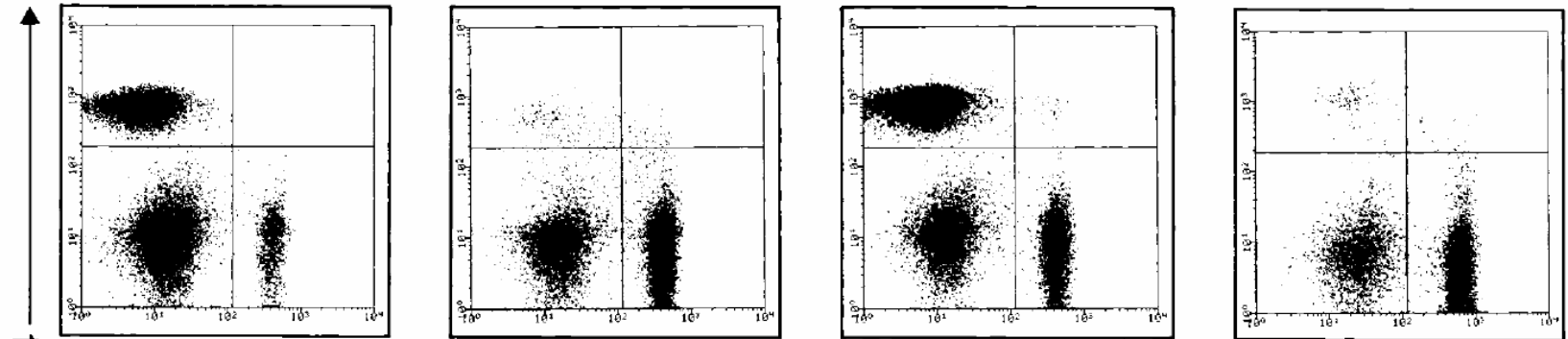
Table 10-1
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Sélection positive & CMH (4)

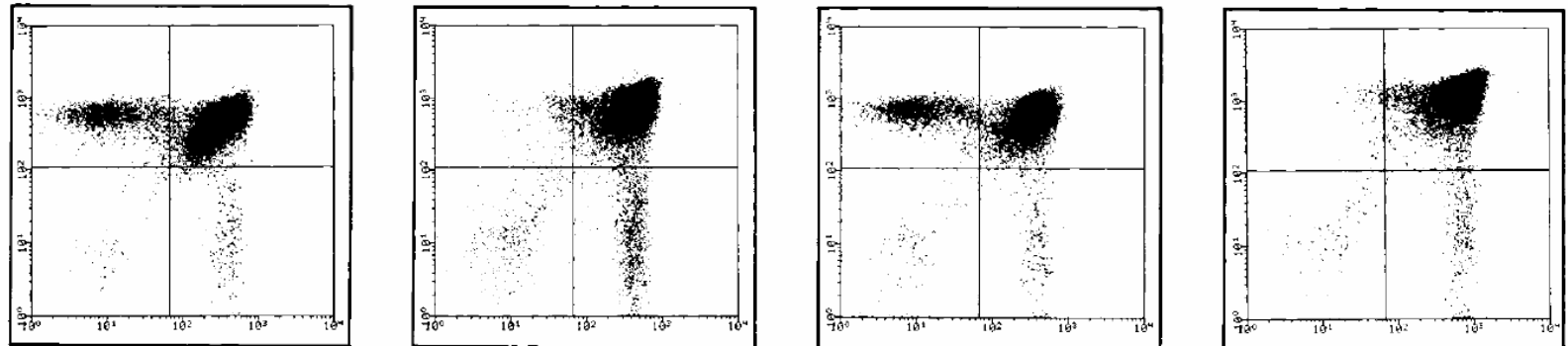


Sélection positive & CMH (4)

LYMPHOCYTES



THYMOCYTES



B6 I-A^{+/+}

B6 I-A^{-/-}

B6-E α^d I-A^{-/-}

B6CD11c-E α^d I-A^{-/-}

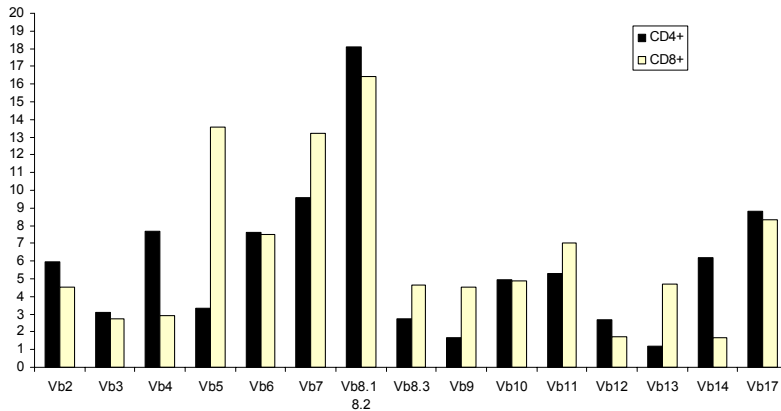
CD8

Fonds C57BL/6 I-E-(I-E α^-), I-A⁺

Sélection positive & CMH (5)

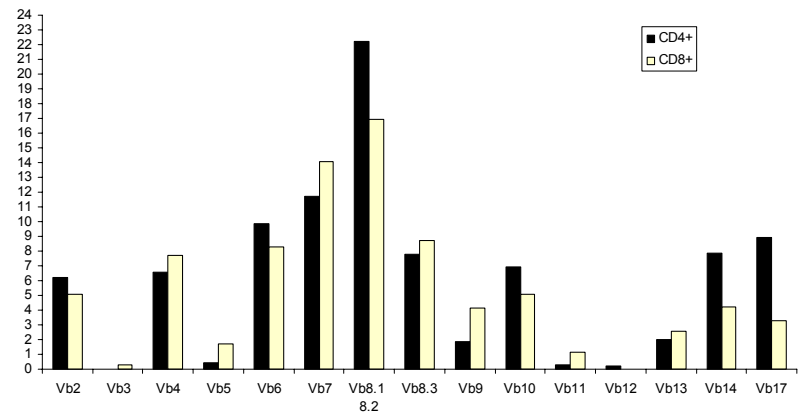
% Vb CD4/CD8 chez C57BL/6

C57BL/6



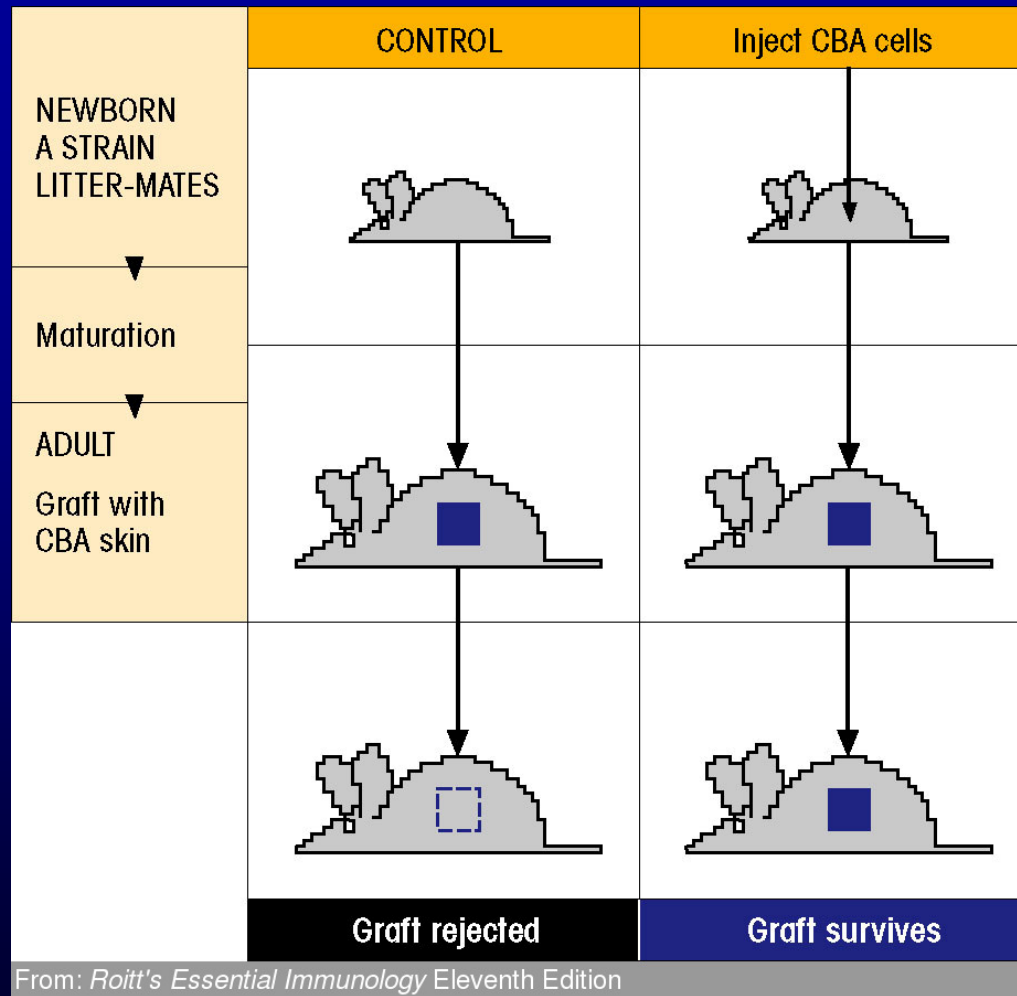
% Vb CD4/CD8 chez BALB/c

BALB/c



C57BL/6 H-2^b
BALB/c H-2^d

Induction de la tolérance



→ Rôle des peptides du soi → Délétion clonal



Délétion clonale et superantigènes (1)

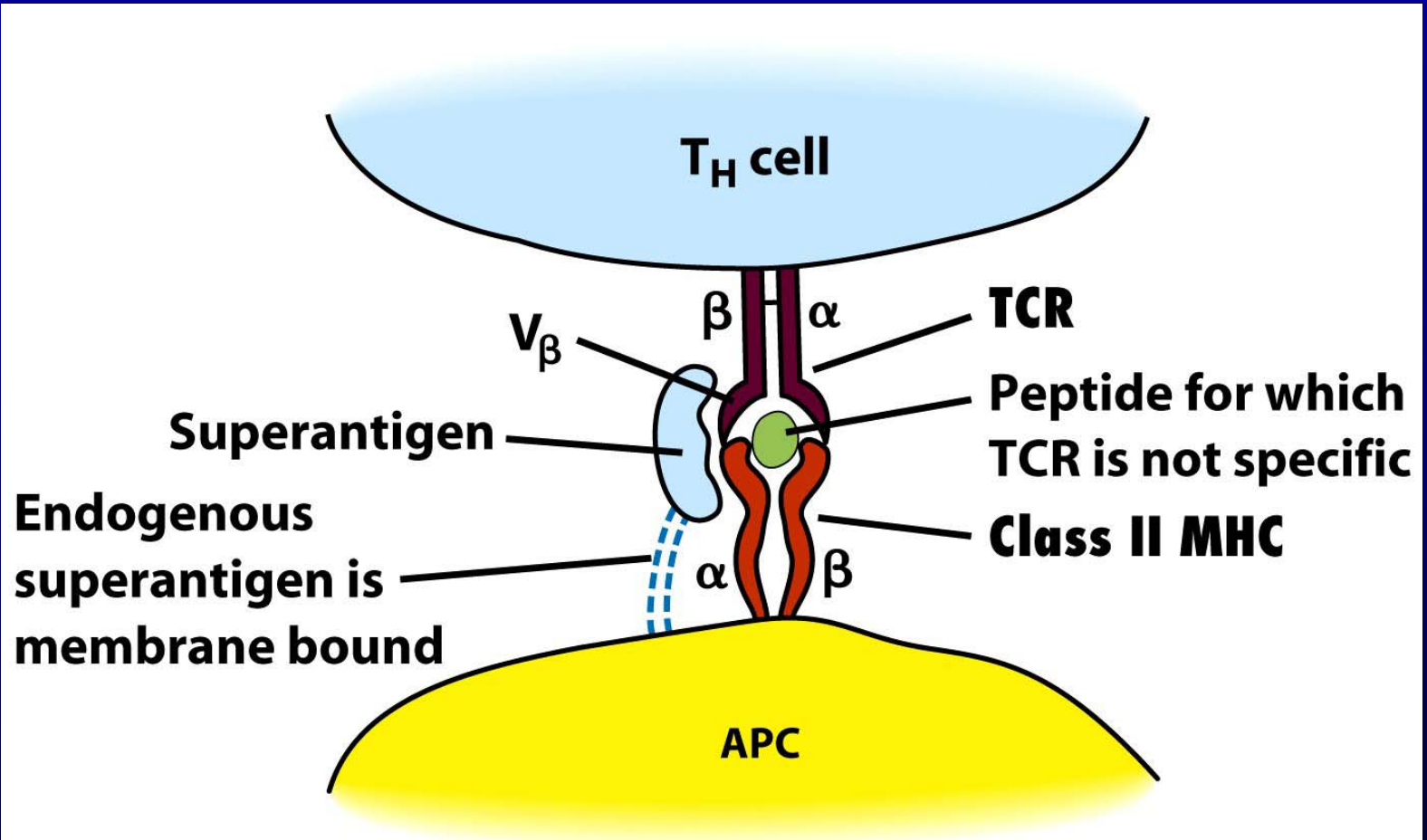


Figure 10-16
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Délétion clonale et superantigènes (2)

TABLE 10-3 Exogenous superantigens and their V_{β} specificity

Superantigen	Disease*	V _β SPECIFICITY	
		Mouse	Human
Staphylococcal enterotoxins			
SEA	Food poisoning	1, 3, 10, 11, 12, 17	nd
SEB	Food poisoning	3, 8.1, 8.2, 8.3	3, 12, 14, 15, 17, 20
SEC1	Food poisoning	7, 8.2, 8.3, 11	12
SEC2	Food poisoning	8.2, 10	12, 13, 14, 15, 17, 20
SEC3	Food poisoning	7, 8.2	5, 12
SED	Food poisoning	3, 7, 8.3, 11, 17	5, 12
SEE	Food poisoning	11, 15, 17	5.1, 6.1–6.3, 8, 18
Toxic shock syndrome toxin (TSST1)	Toxic shock syndrome	15, 16	2
Exfoliative dermatitis toxin (ExFT)	Scalded skin syndrome	10, 11, 15	2
Mycoplasma arthritidis supernatant (MAS)	Arthritis, shock	6, 8.1–8.3	nd
Streptococcal pyrogenic exotoxins (SPE-A, B, C, D)	Rheumatic fever, shock	nd	nd
*Disease results from infection by bacteria that produce the indicated superantigens.			

Table 10-3
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Délétion clonale et superantigènes (3)

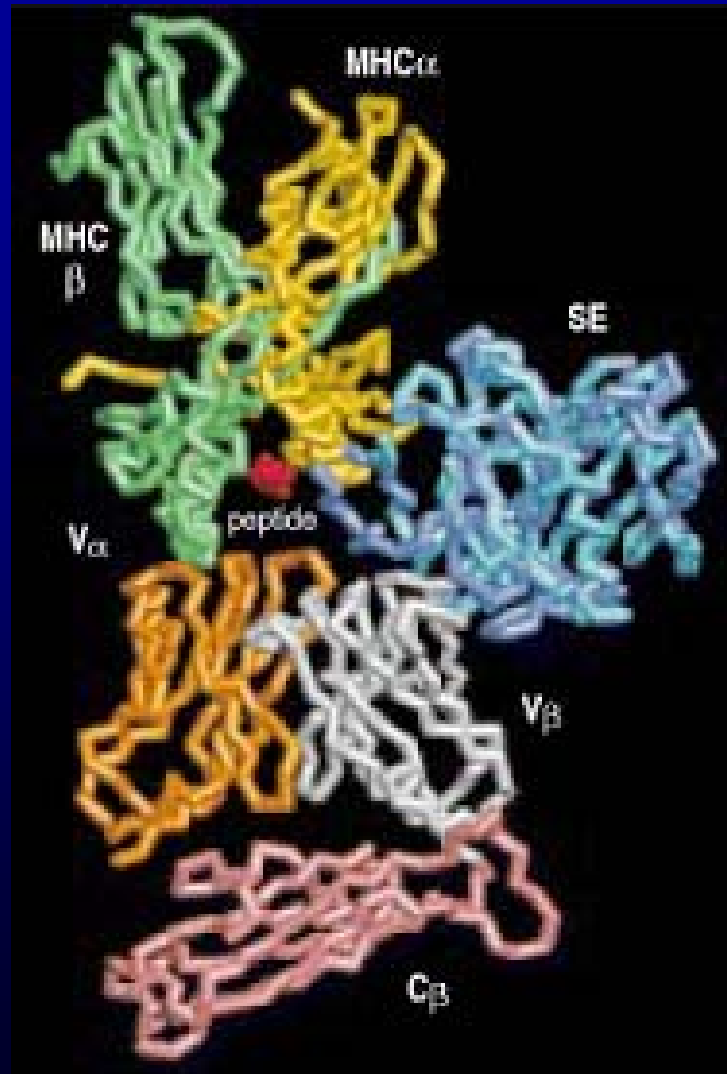
TABLE II
V β Specificity of MMTV Encoded Super-antigens

Mtv	Chromosome	Super-antigen	V β specificity	References
1	7	Mls-2	3	41
2	18		14	44
3	11		3, 17a	89, 92
6	16	Etc-2/Mls-3	3, 5.1, 5.2	35, 40, 41
7	1	Mls-1	6, 7, 8.1, 9	41
8	6	Dvb11-1	5.1, 5.2, 11, 17a	39, 40
9	12	Etc-1/Dvb11-2	5.1, 5.2, 11, 12, 17a	33, 34, 38, 39, 40, 55
11	14	Dvb11-3	11	39
13	4	Mls-2	3	41
?	?		16*	26, 27
?	?		19a*	—†
?	?		20	29
C3H-exo			14, 15	42, 43
BALB/c tumor			2	90

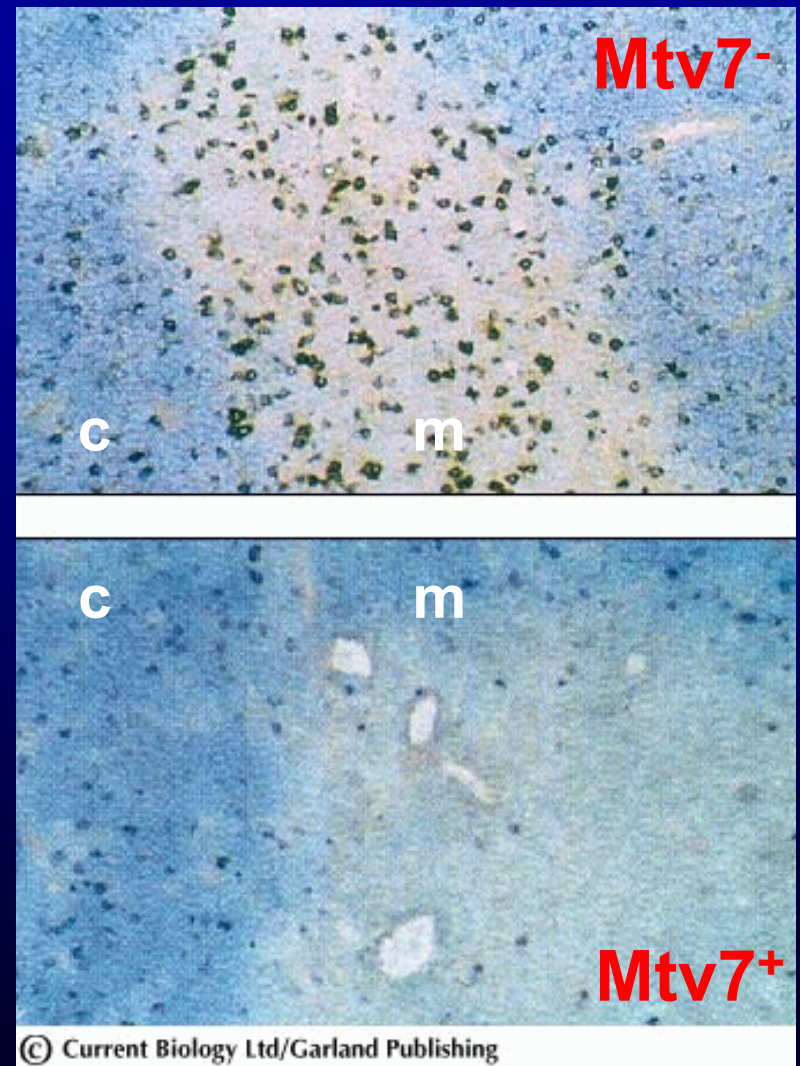
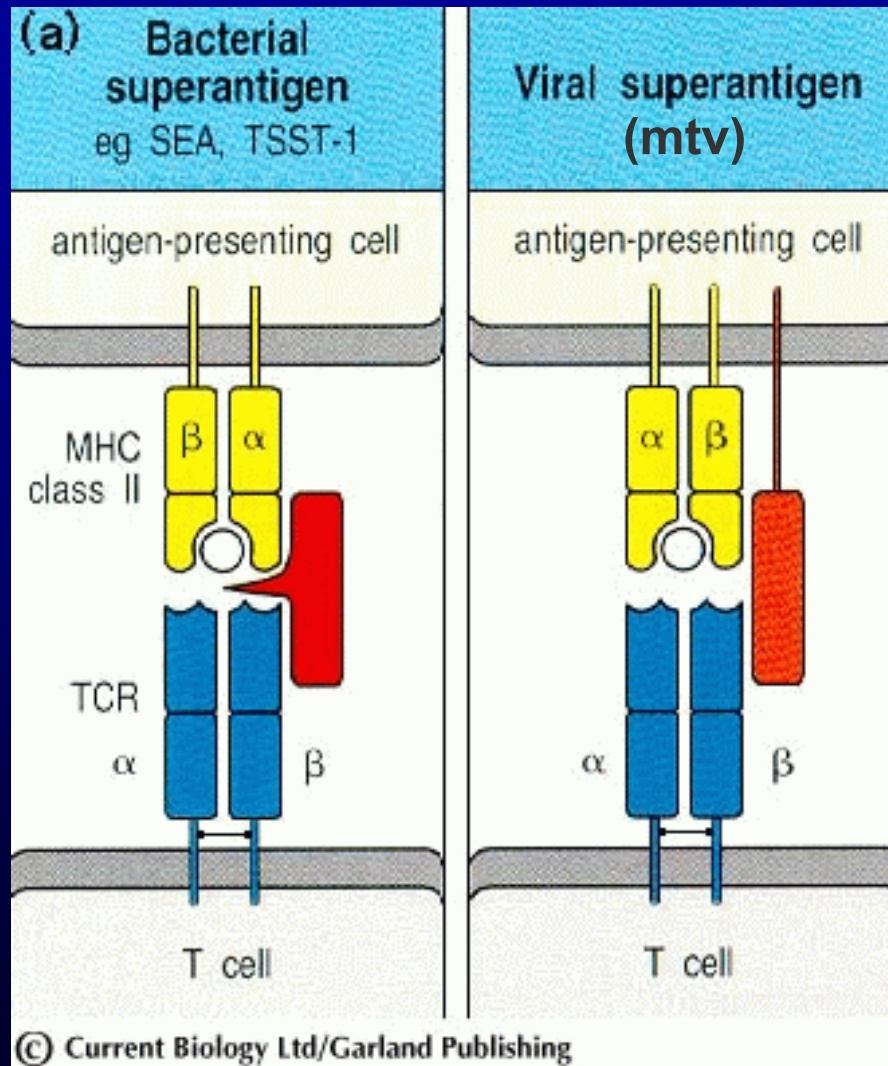
*Super-antigen implicated but not yet demonstrated.

†R. J. Hodes, unpublished.

Délétion clonale et superantigènes (4)



Délétion clonale et superantigènes (5)

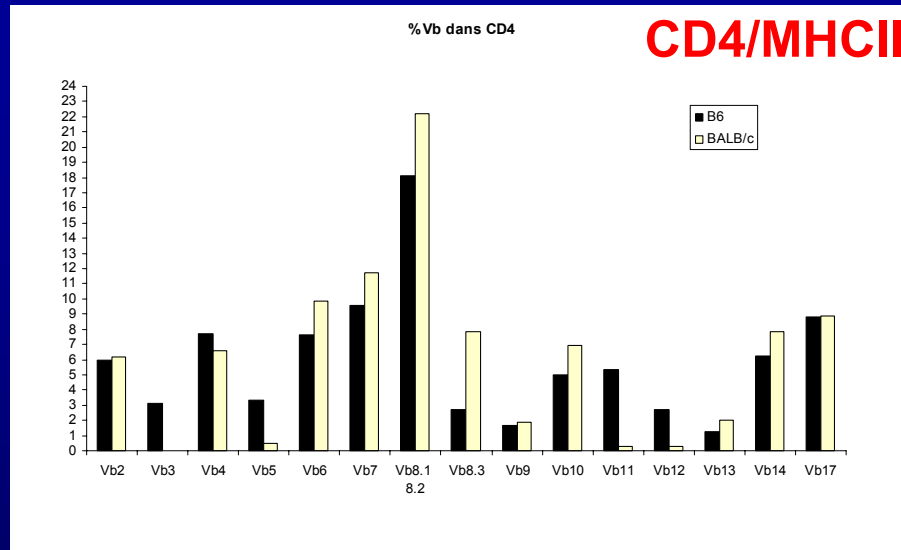


Délétion clonale et superantigènes (6)

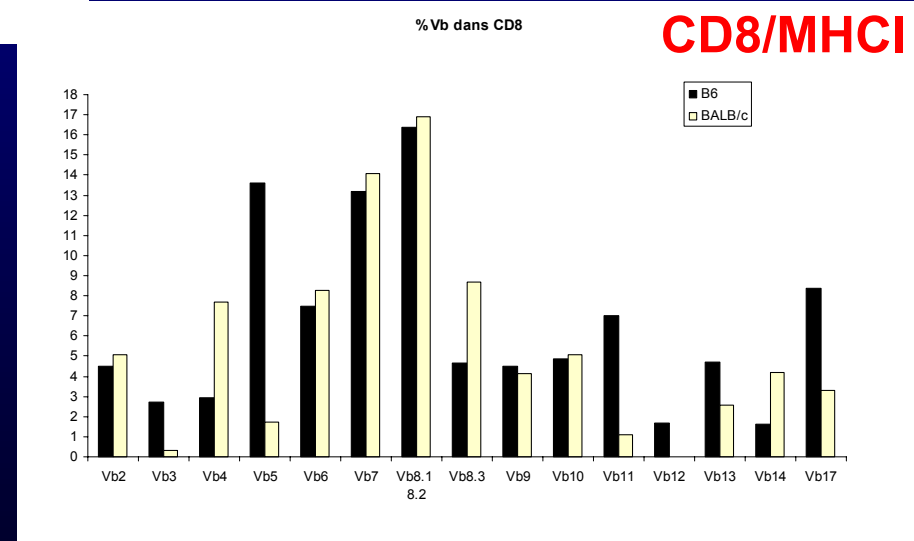
Table 1. Stain distribution of some MTV proviruses. (adapted from Annu. Rev. Cell Biol. 1993.9:101-28)

MTV			1	3	6	7	8	9	11	13	14	17	23	29	30	31†
Chromosome cM from centromere			7 31	11 72	16 31	1 73	6 31	12 40	14 8	4 47	4 10	4 20	6 32	6 20-24	12 2	Y
Vb Specificity (Vβ allele if not b)			3, 17?	3,5 17	3, 5, 17?	6,7, 8.1, 9	5,7 11,12 17?	5, 11,12 17?	11, 12 17	3, 17?	NE	NE	7	16	NE	?
Strains	H2	IE														
A/J	a	k	-	-	+	-	+	-	-	+	-	-	+	-	-	-
AKR/J	k	k	-	-	-	+	+	+	-	-	-	+	+	-	+	+
BALB/cByJ	d	d	-	-	+	-	+	+	-	-	-	-	-	-	-	-
B10.BR	k	k	-	-	-	-	+	+	-	-	-	+	-	-	+	-
C3H/HeJ	k	k	+	-	+	-	+	-	+	-	+	-	-	-	-	-
C57BL/6J	b	-	-	-	-	-	+	+	-	-	-	+	-	-	+	-
C57BR/cdJ(a)	k	k	-	-	-	-	+	+	+	-	-	+	-	+	-	?
C57L/J (a)	b	-	-	-	-	-	+	+	+	-	-	+	-	+	-	?
C58/J	k	k	-	+	-	+	-	-	-	-	-	+	-	-	+	-
CBA/CaJ	k	k	-	-	-	-	+	+	-	-	+	-	-	-	-	-
CBA/J	k	k	-	-	+	+	+	+	-	-	+	+	-	-	-	-

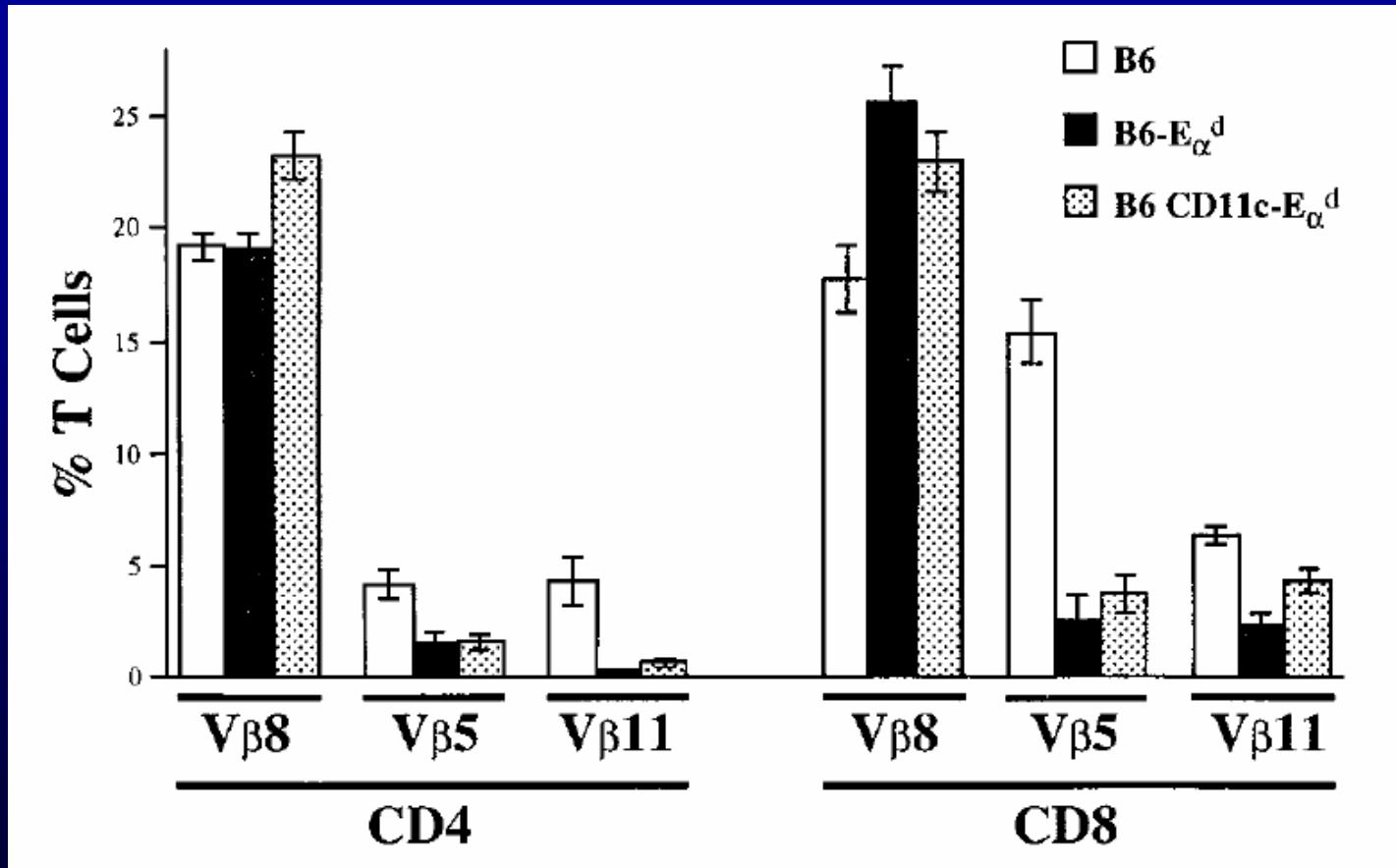
Sélection négative & superantigène (7)



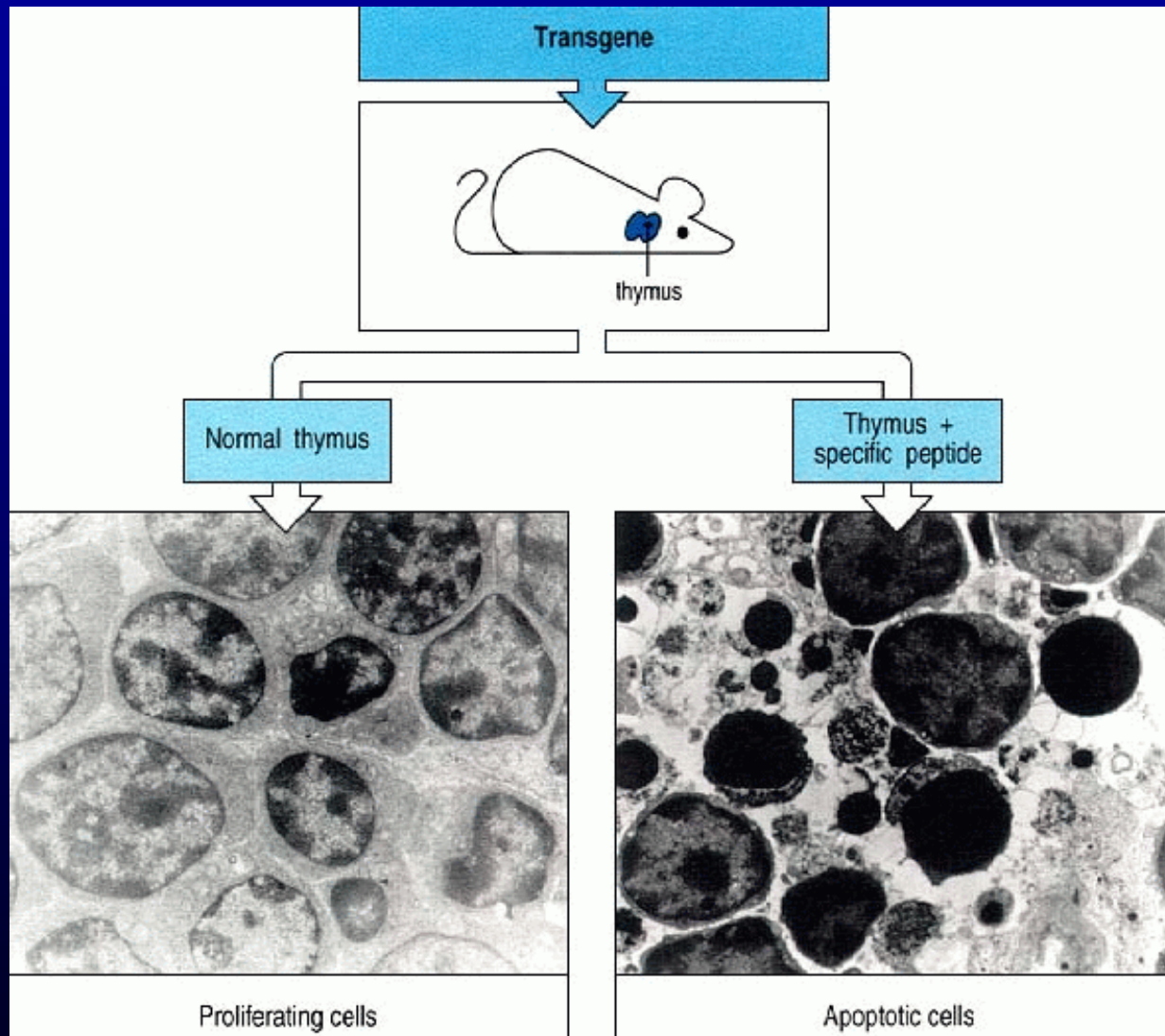
C57BL/6 H-2^b
BALB/c H-2^d

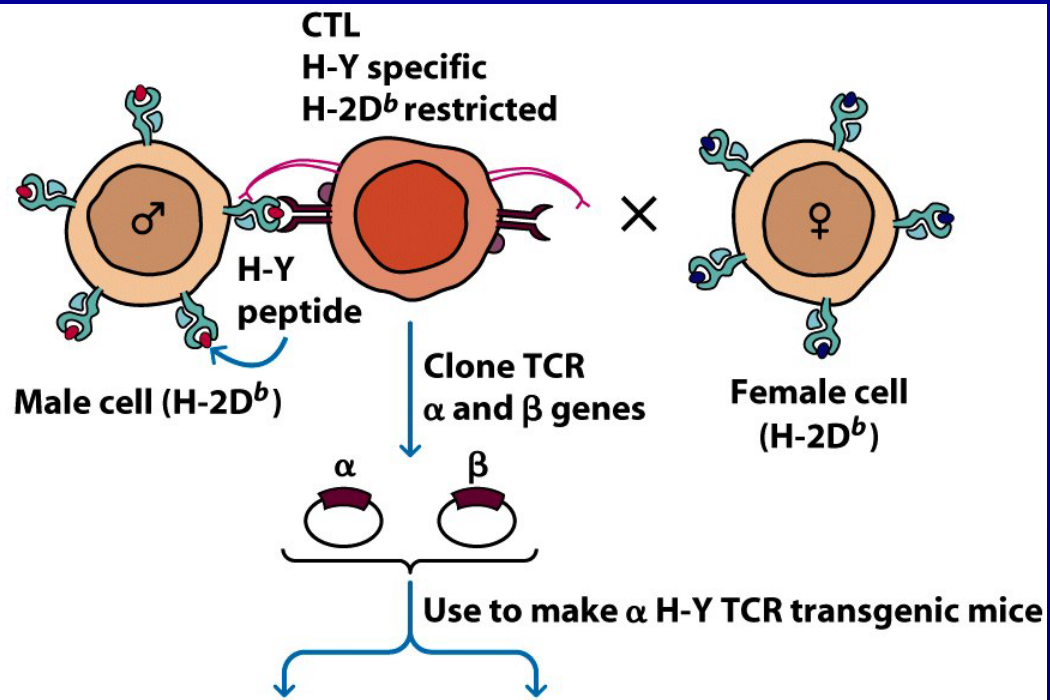


Sélection négative & superantigène (8)



Délétion clonale et TCR transgénique





	Male H-2D ^b	Female H-2D ^b
H-Y expression	+	-
Thymocytes		
CD4 ⁻ 8 ⁻	++	+
CD4 ⁺ 8 ⁺	+	++
CD4 ⁺	+	+
CD8 ⁺	-	++

Figure 10-8
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Sélection et TCR transgénique

Selection in SCID mice transgenic for H-2D^b/H-Y TCR

Phenotype	Positive selection		Negative selection	
	Transgenic females		Transgenic H-2 ^b	
	H-2 ^{b/d}	H-2 ^{d/d}	Males	Females
CD4 ⁻ 8 ⁻ TCR ⁻	+	++	+++	+
CD4 ⁺ 8 ⁺ TCR [±]	++	++	-	+++
CD4 ⁻ 8 ⁺ TCR ⁺⁺	+	-	-	+
CD4 ⁺ 8 ⁻ TCR ⁺⁺	-	-	-	-

Experimental procedure—fetal thymic organ culture (FTOC)



Figure 10-9a
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Development of CD8⁺ CD4⁻ MHC I-restricted cells

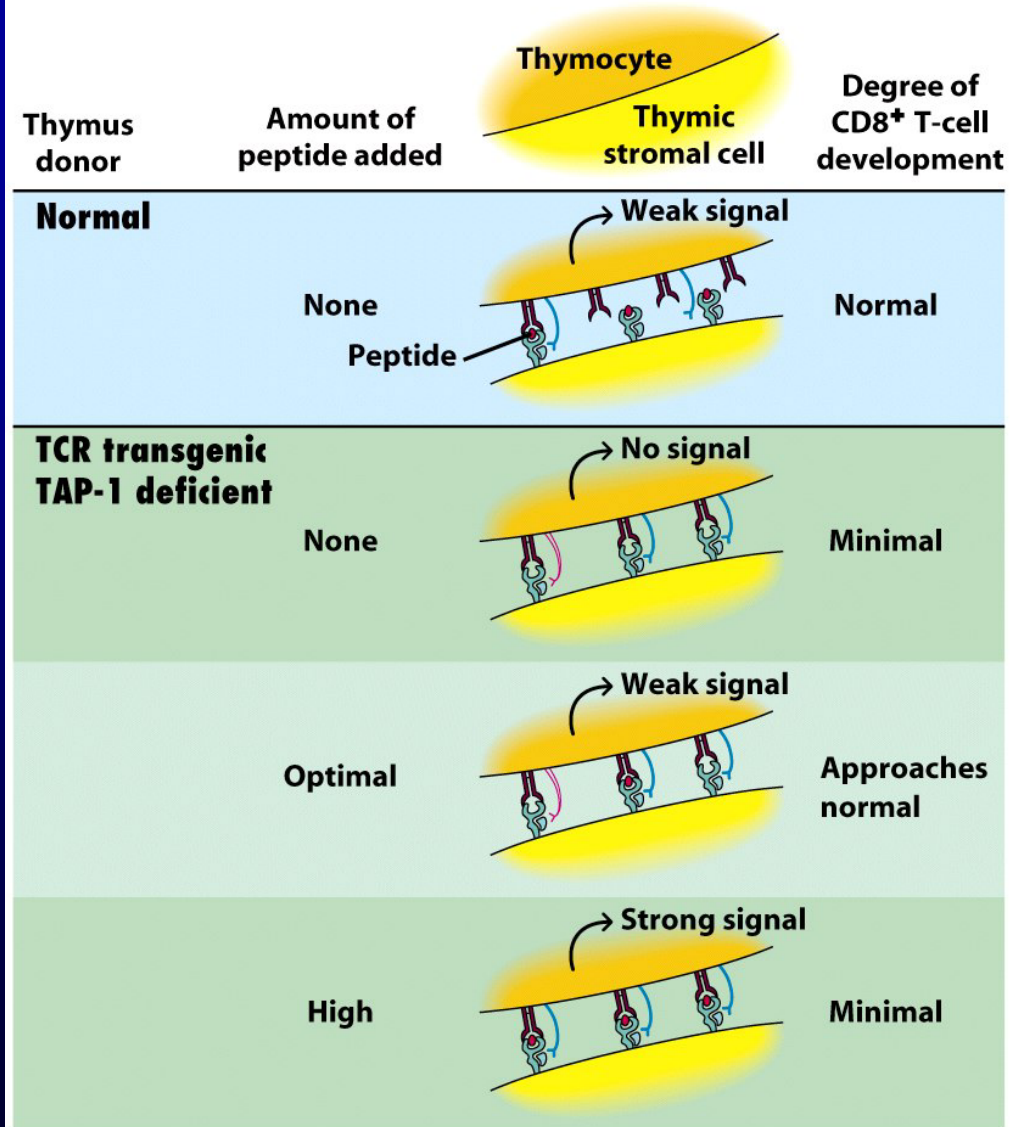
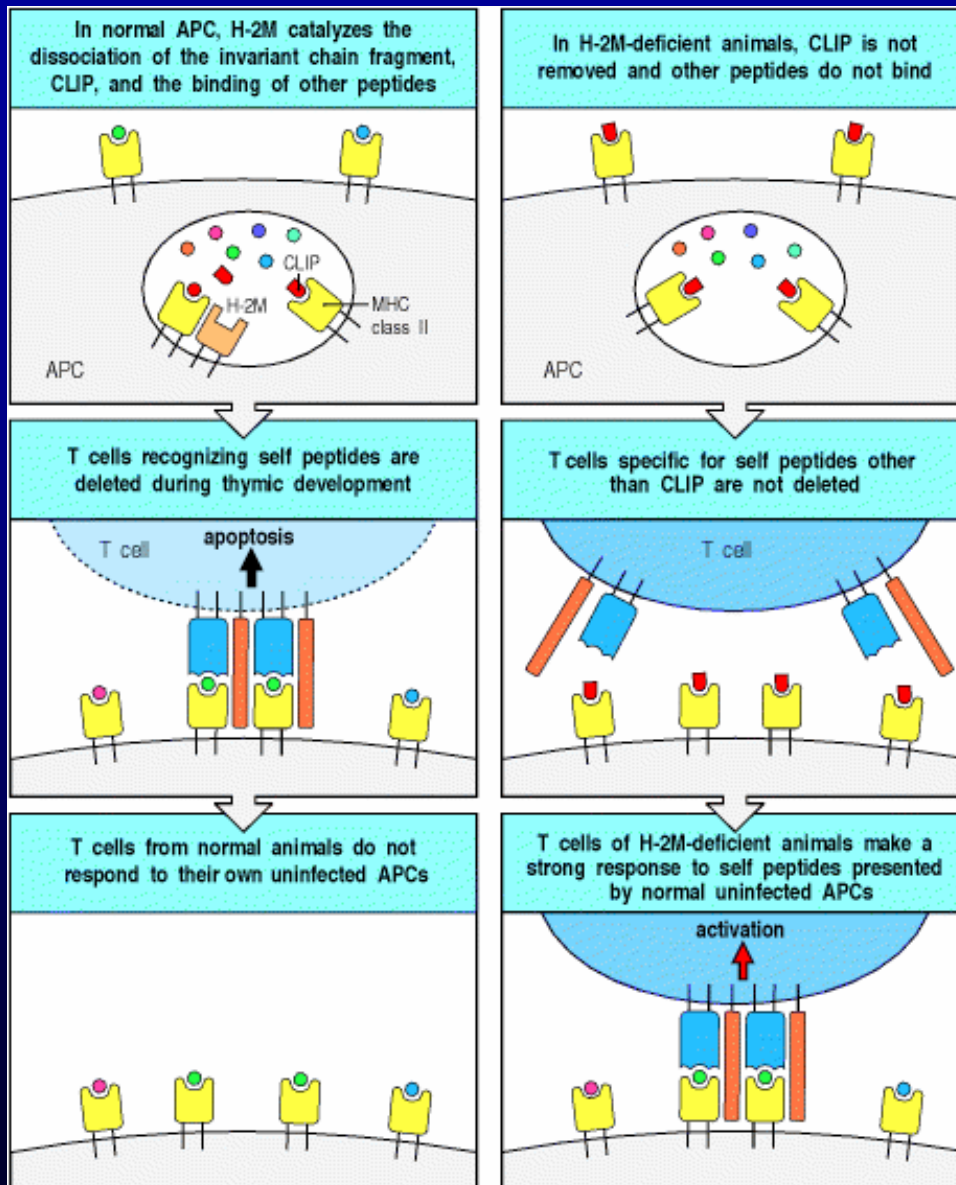


Figure 10-9b
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Peptides agonistes, antagonistes (1)

Peptide ligand altéré (APL)

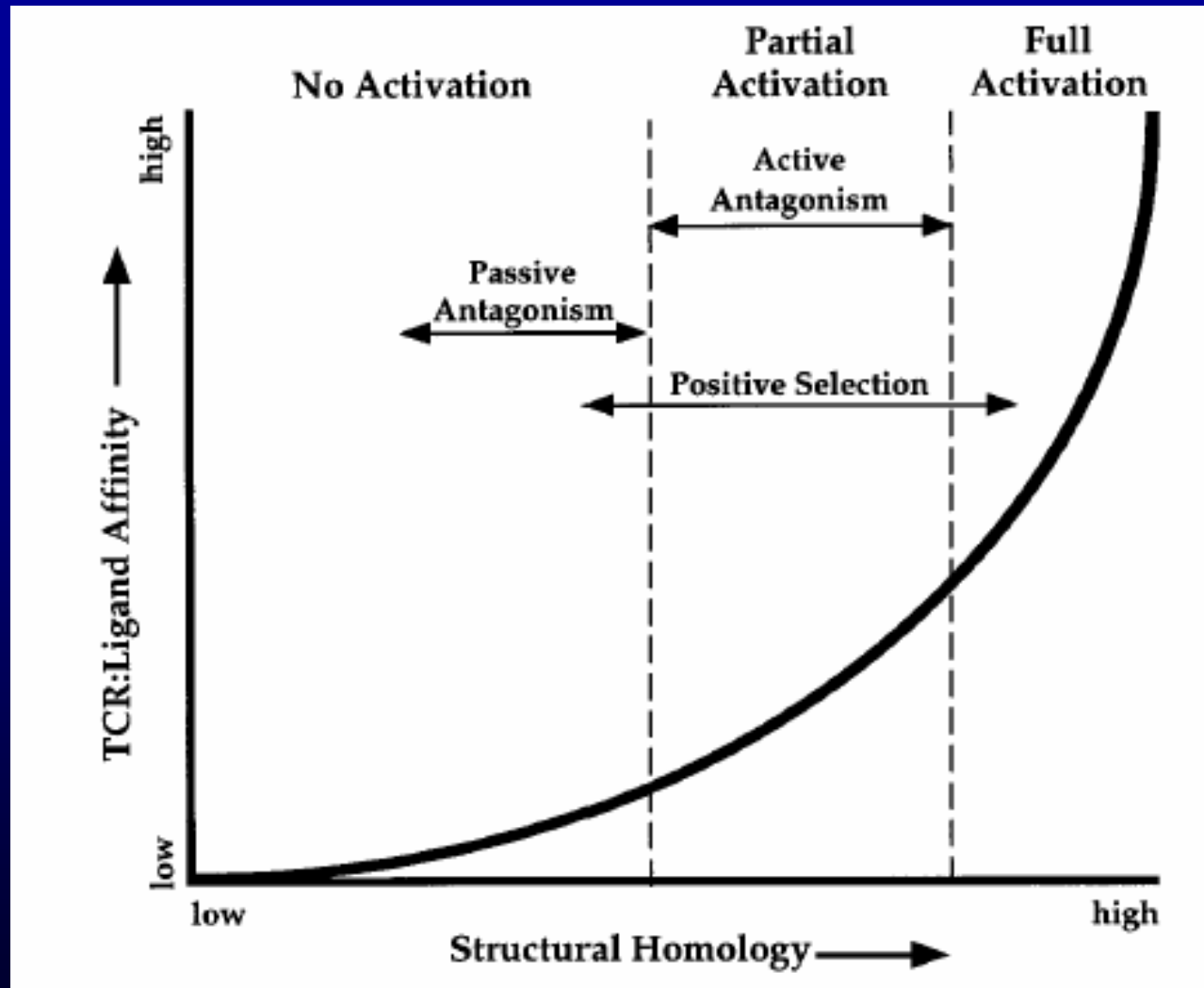
= peptide analogue d'un peptide immunogène

Agoniste → Conserve certaines fonctions d'activation

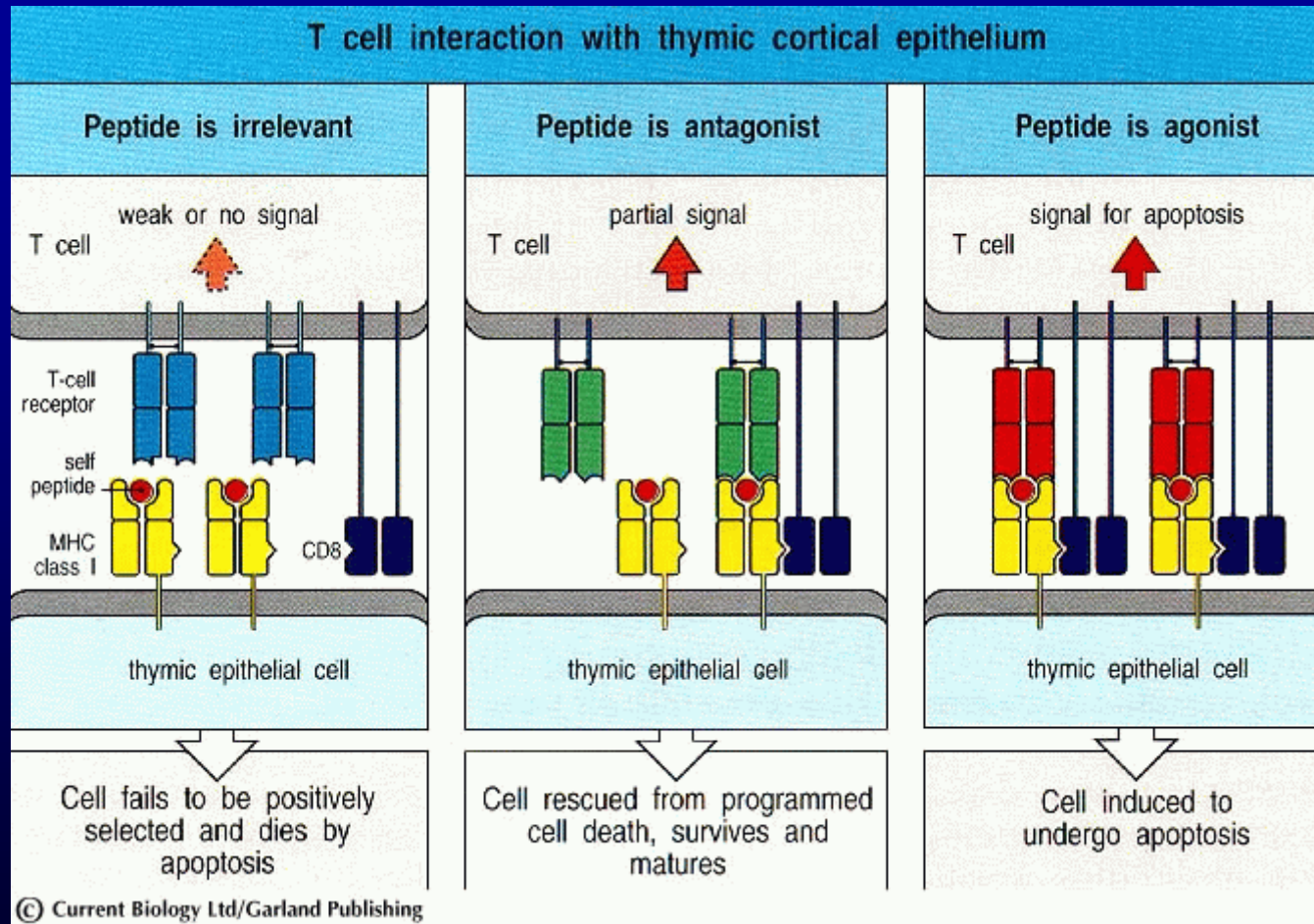
Antagoniste passif → Compétition pour le CMH

Antagoniste actif → induction d'anergie, modification de la cascade d'activation

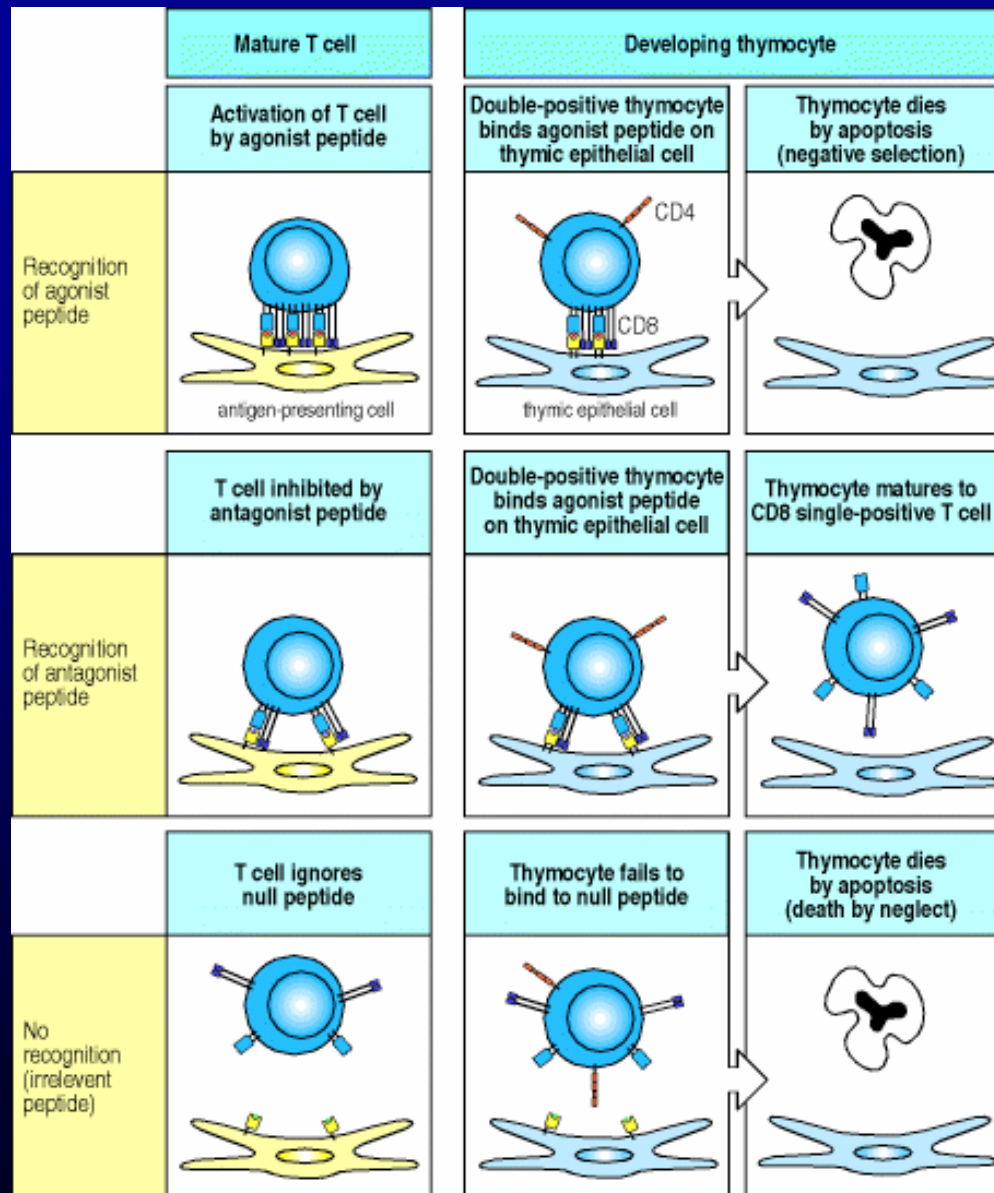
Peptides agonistes, antagonistes (2)

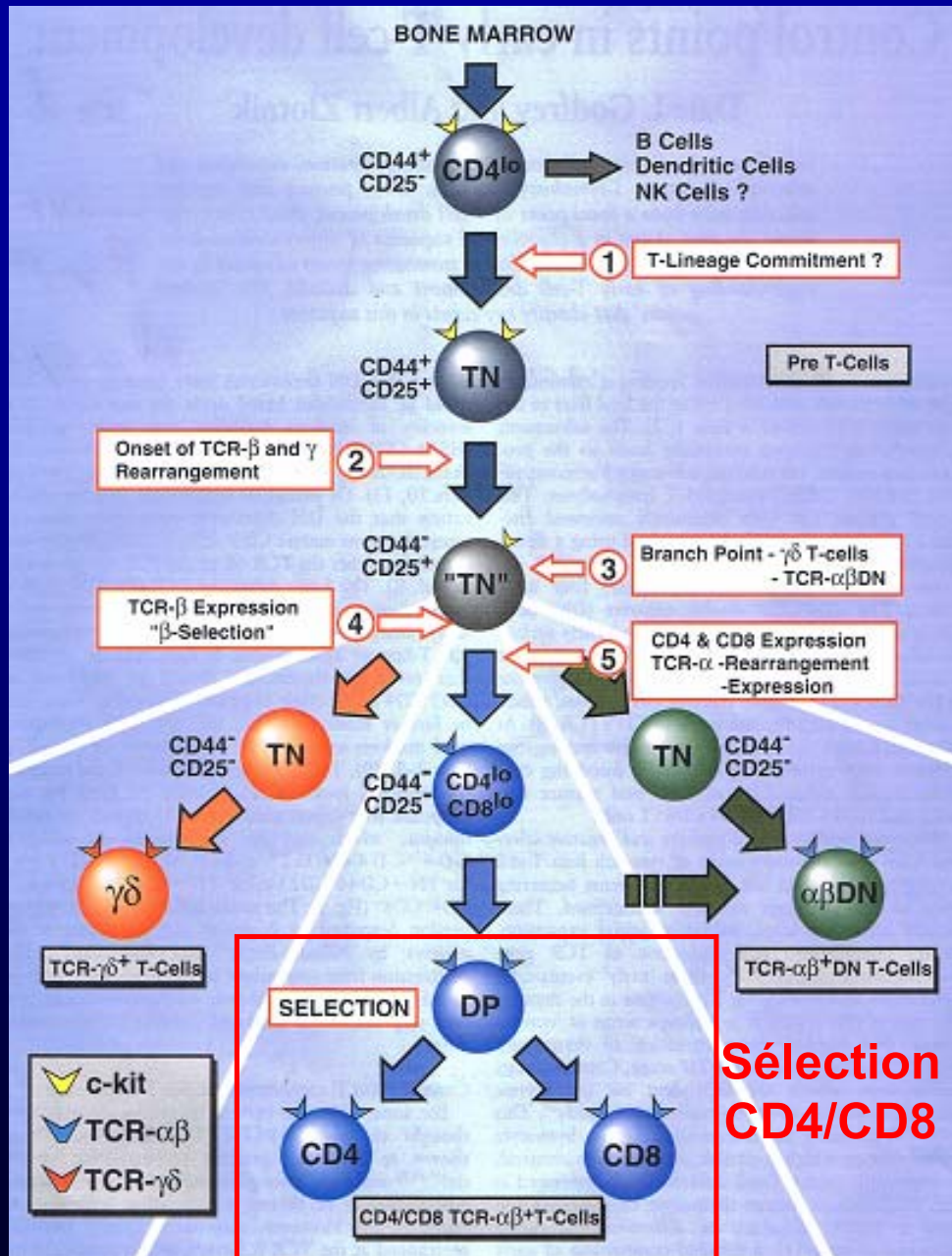


Peptides agonistes, antagonistes (3)

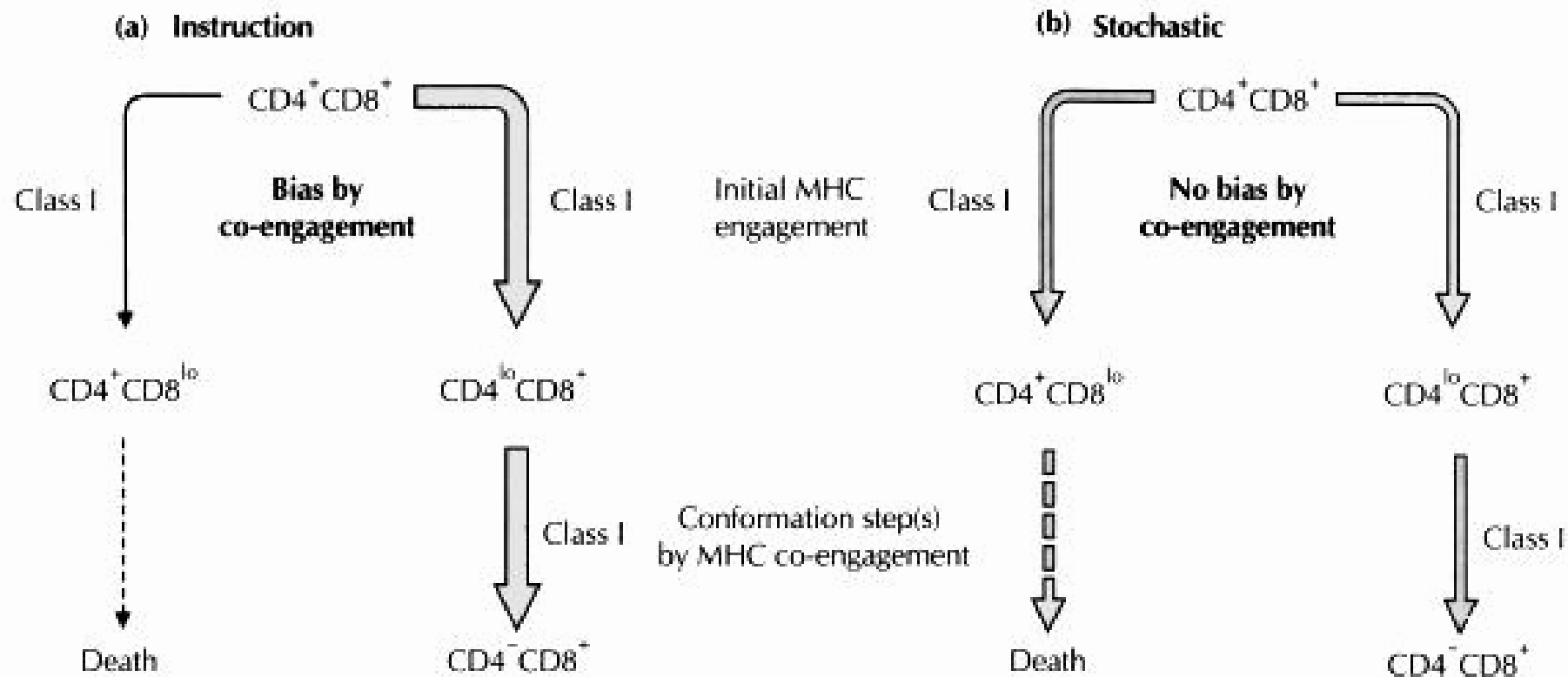


Peptides agonistes, antagonistes (4)





Sélection CD8/CMHI & CD4/CMHII (1)



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Sélection CD8/CMHI & CD4/CMHII (2)

INSTRUCTIVE MODEL

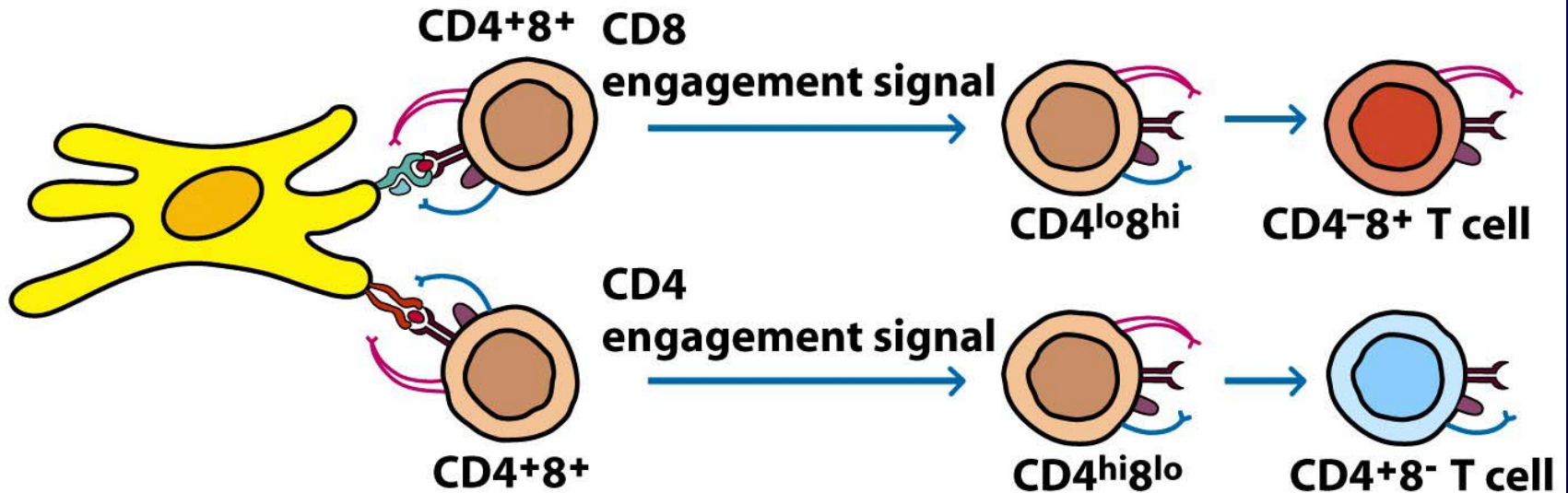


Figure 10-10 part 1
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Sélection CD8/CMHI & CD4/CMHII (3)

STOCHASTIC MODEL

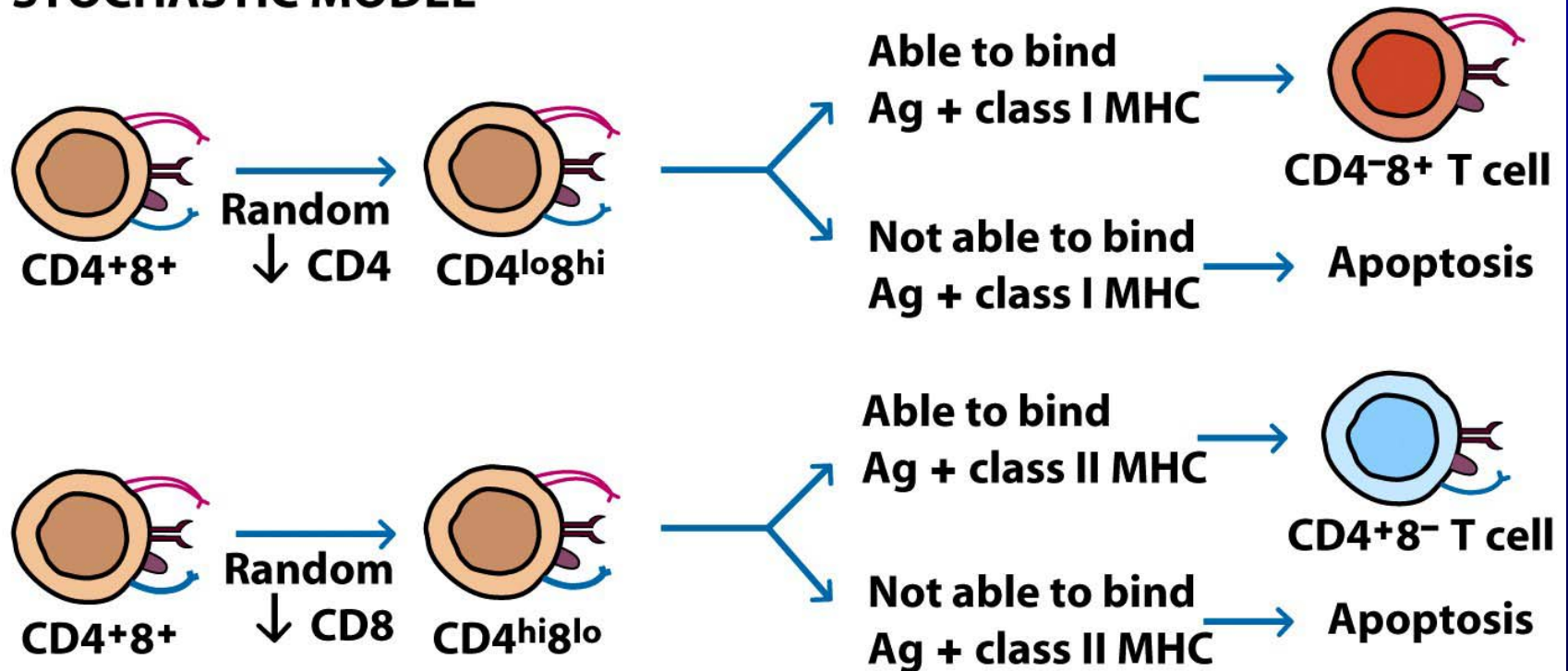
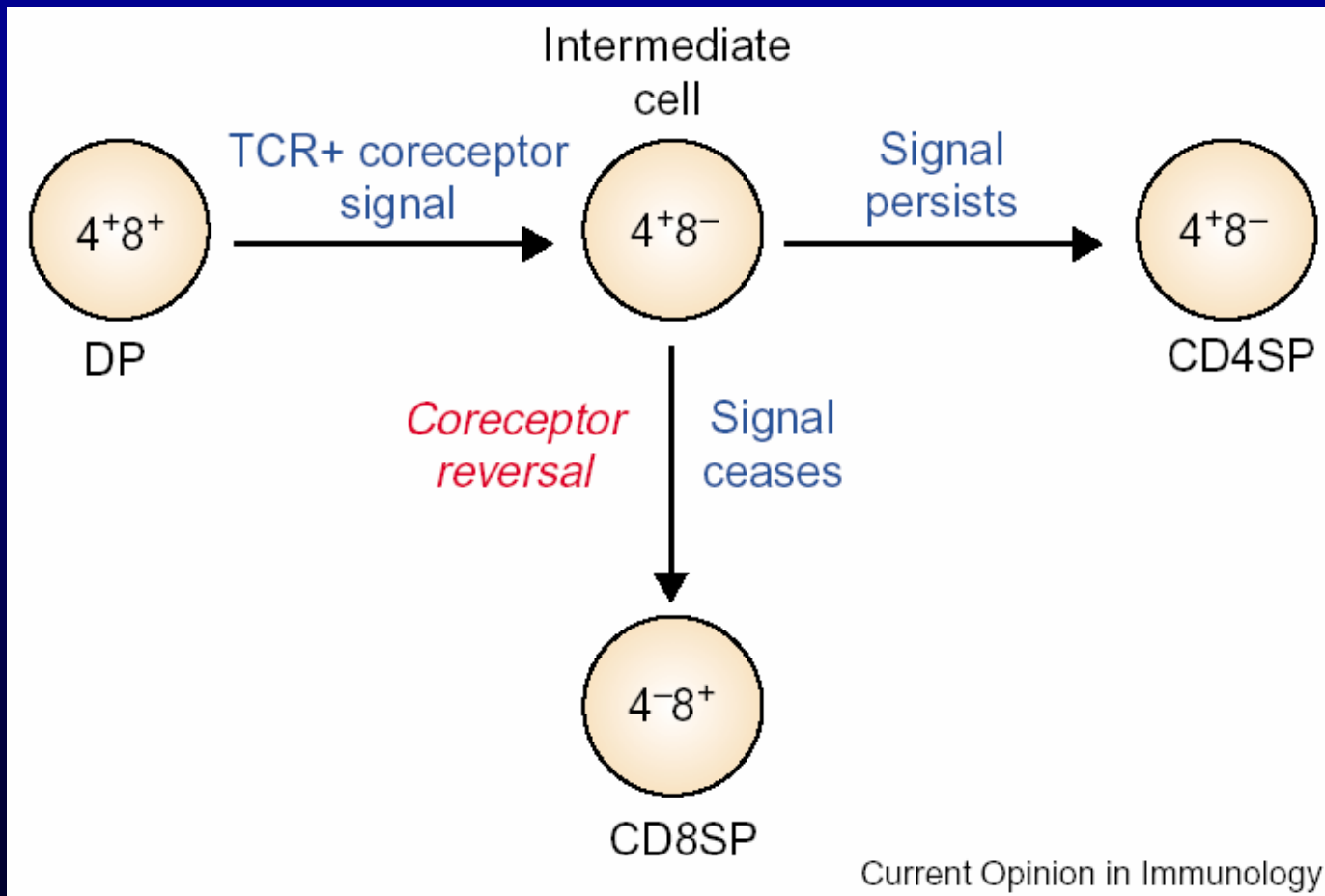


Figure 10-10 part 2
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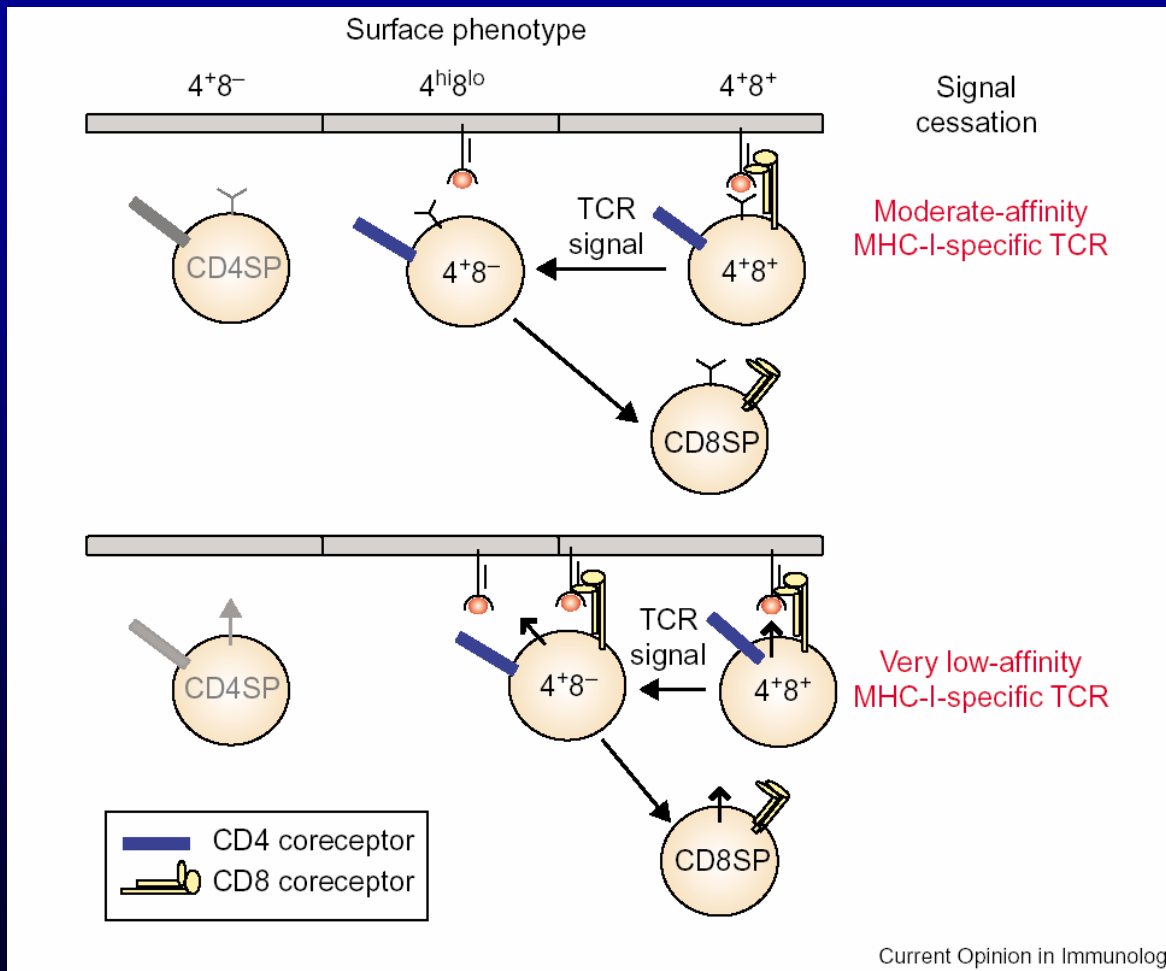
Sélection CD8/CMHI & CD4/CMHII (4)

Modèle cinétique d'engagement CD4/CD8



Sélection CD8/CMHI & CD4/CMHII (5)

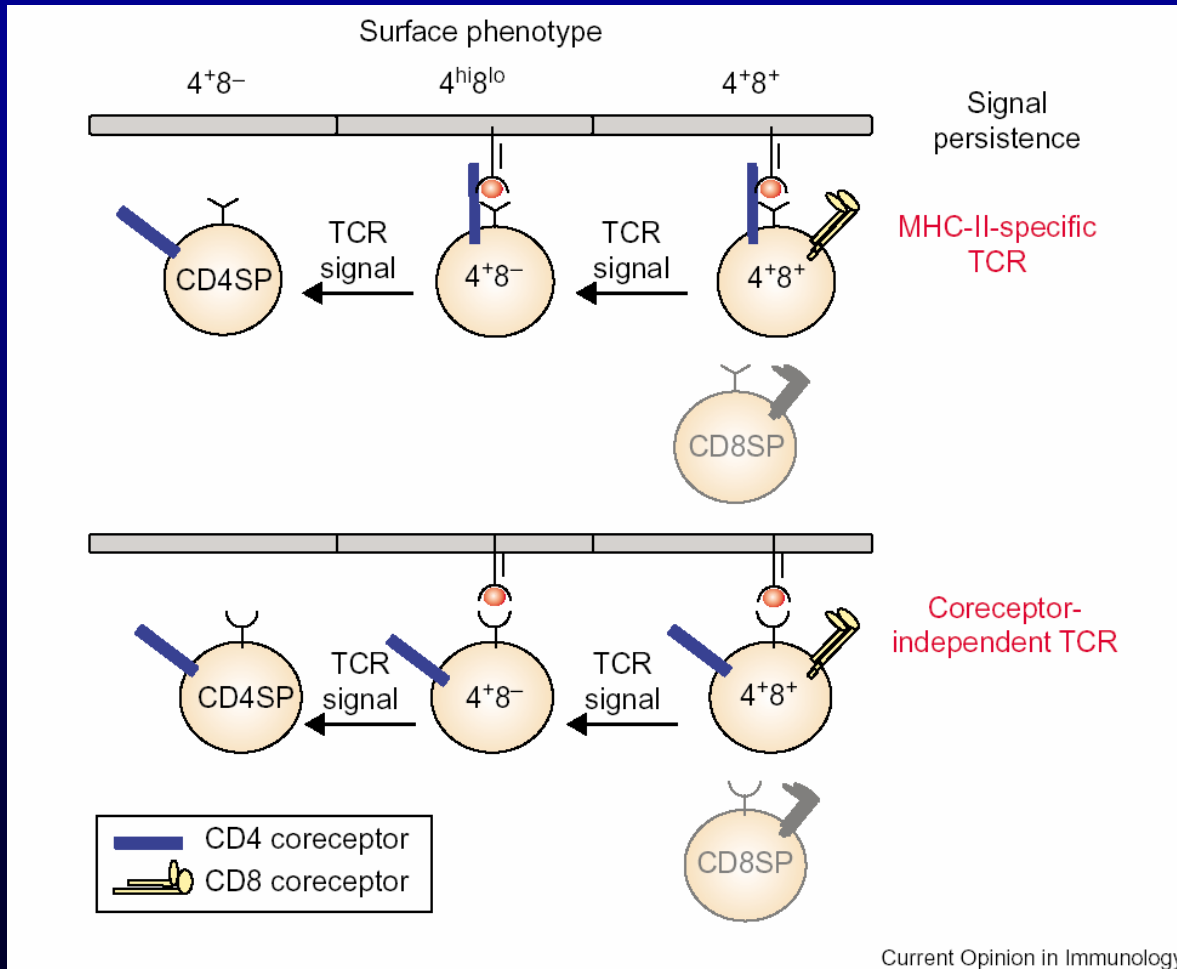
Modèle cinétique d'engagement CD4/CD8



**Un arrêt du signal
promeut la
différenciation en
lymphocyte T CD8SP**

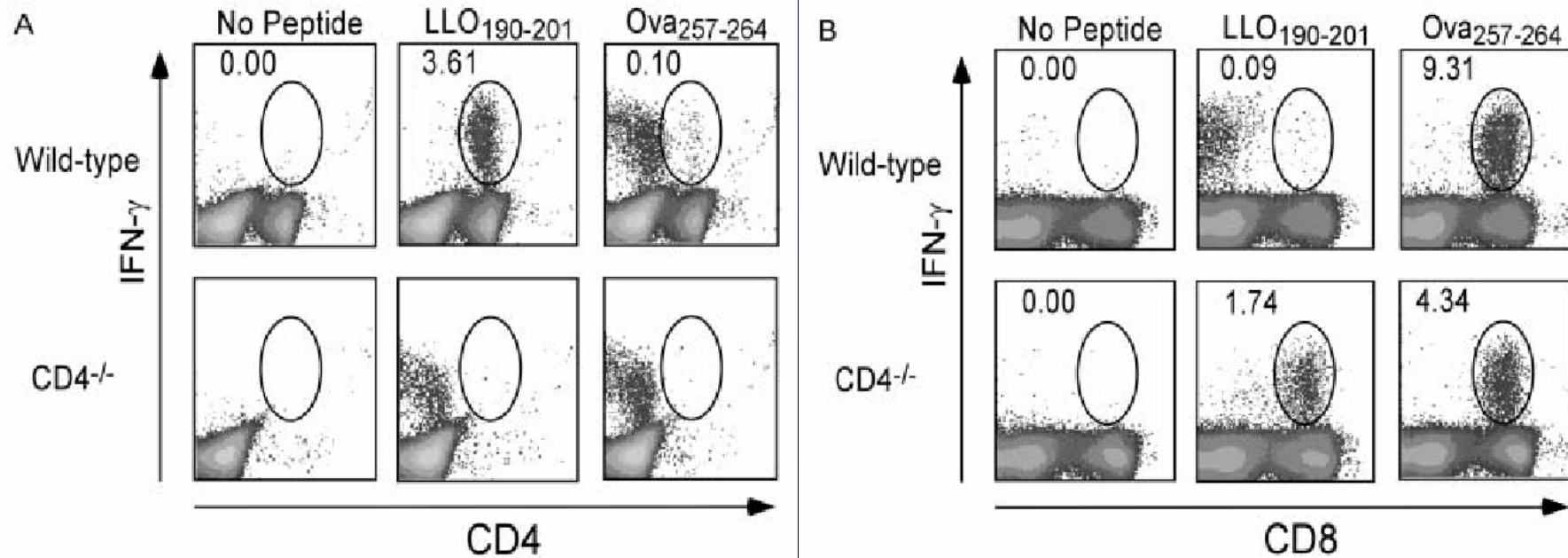
Sélection CD8/CMHI & CD4/CMHII (6)

Modèle cinétique d'engagement CD4/CD8

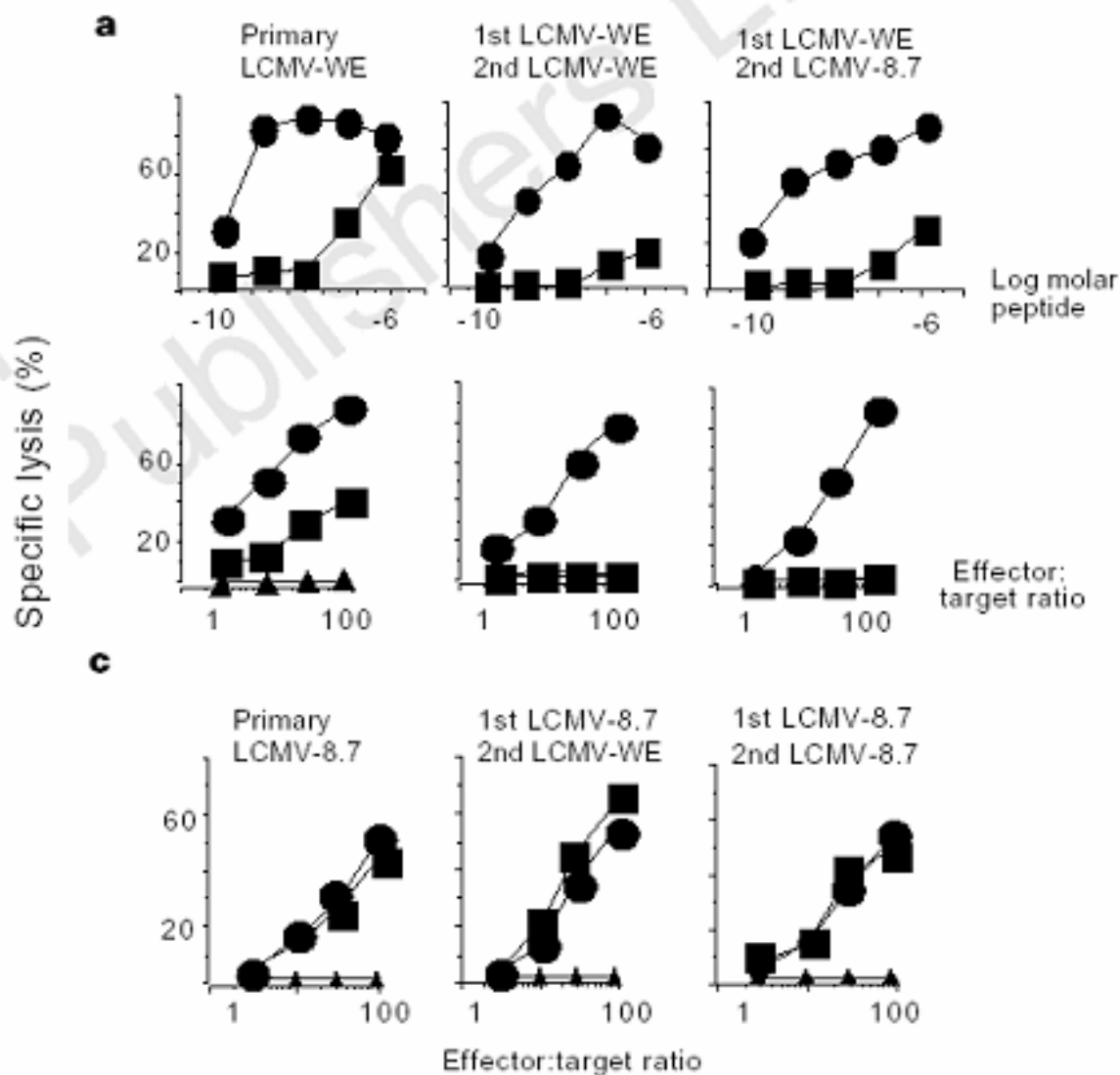


Un signal persistant
promeut la
différenciation en
lymphocyte T CD4SP

Sélection CD8/CMHI & CD4/CMHII (7)



Le « péché originel »



LCMV-WE

→ Sauvage

→ GP33-wt

→ H-2D^b

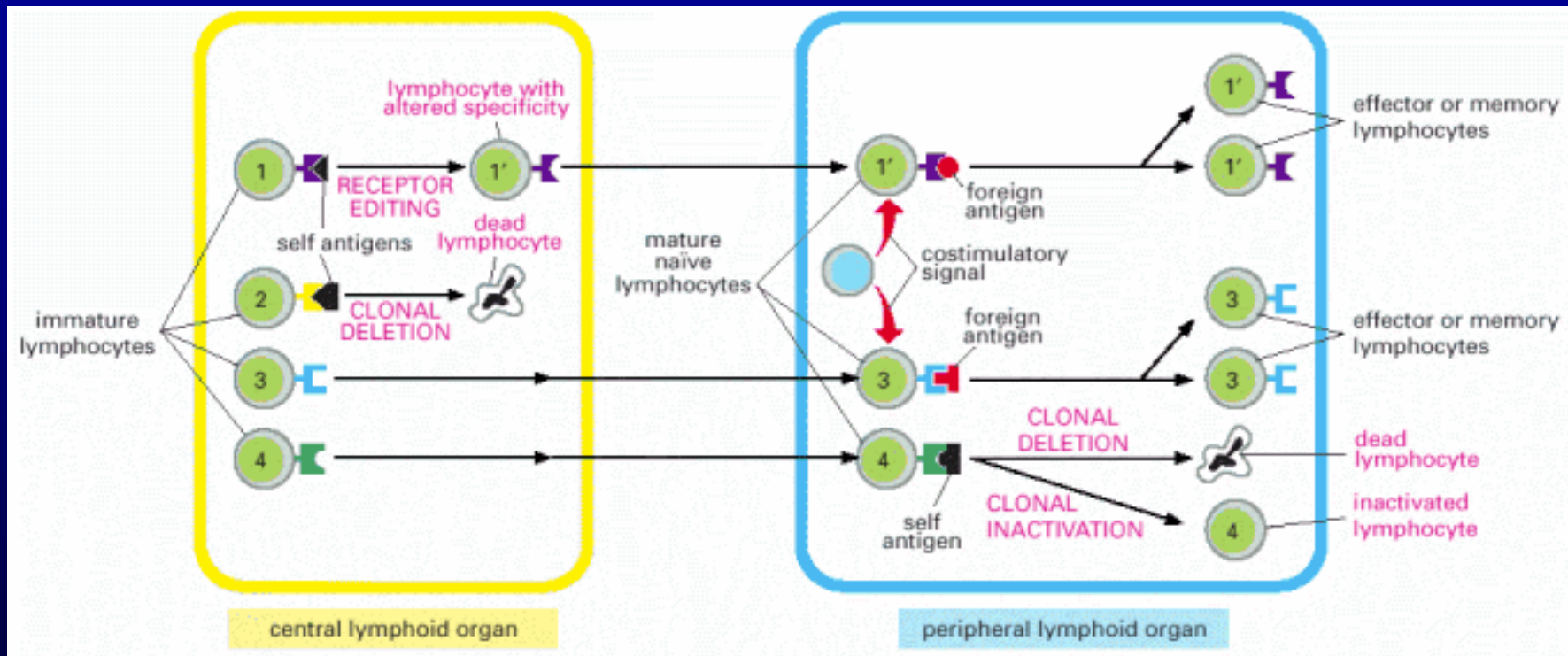
LCMV-8.7

→ Mutant

→ GP33-3L APL

Conclusion

Sélections centrale et périphérique



There is only one immune system! The view from immunopathology. A. M. Silverstein and N. R. Rose. *Semin. Immunol.* 12:173-178, 2000.

- The immune system does not 'decide' that a stimulus is deadly or harmless and respond accordingly.
- The world is not divided between the self and the not-self (foreign). The immune system does not 'know' the difference. Only obedience to the immunological rules defines what is tolerated and what is intolerable.
- SELF IS ONLY THAT COLLECTION OF POTENTIAL IMMUNOGENS THAT CANNOT STIMULATE A RESPONSE (or only a subliminal one) AT THAT TIME AND PLACE! This inability, which we name immunological tolerance [...] is the result of a multitude of central and peripheral down-regulatory mechanisms that have acted according to their own rules.
- Any 'foreign' epitope can become 'self' if administered appropriately, and any 'self' epitope can become 'foreign' and cause autoimmune disease, if tolerance is overcome with an adjuvant, by an intercurrent infection, by molecular mimicry, or by a variety of other means.
- Again, the immune system does not 'choose' immunoprotection or immunopathology in response to a challenge; both will occur in any event, and the fixed rules only determine the relative balance of the two.