

# Tolérance centrale

## Sélection positive et négative des répertoires lymphocytaires

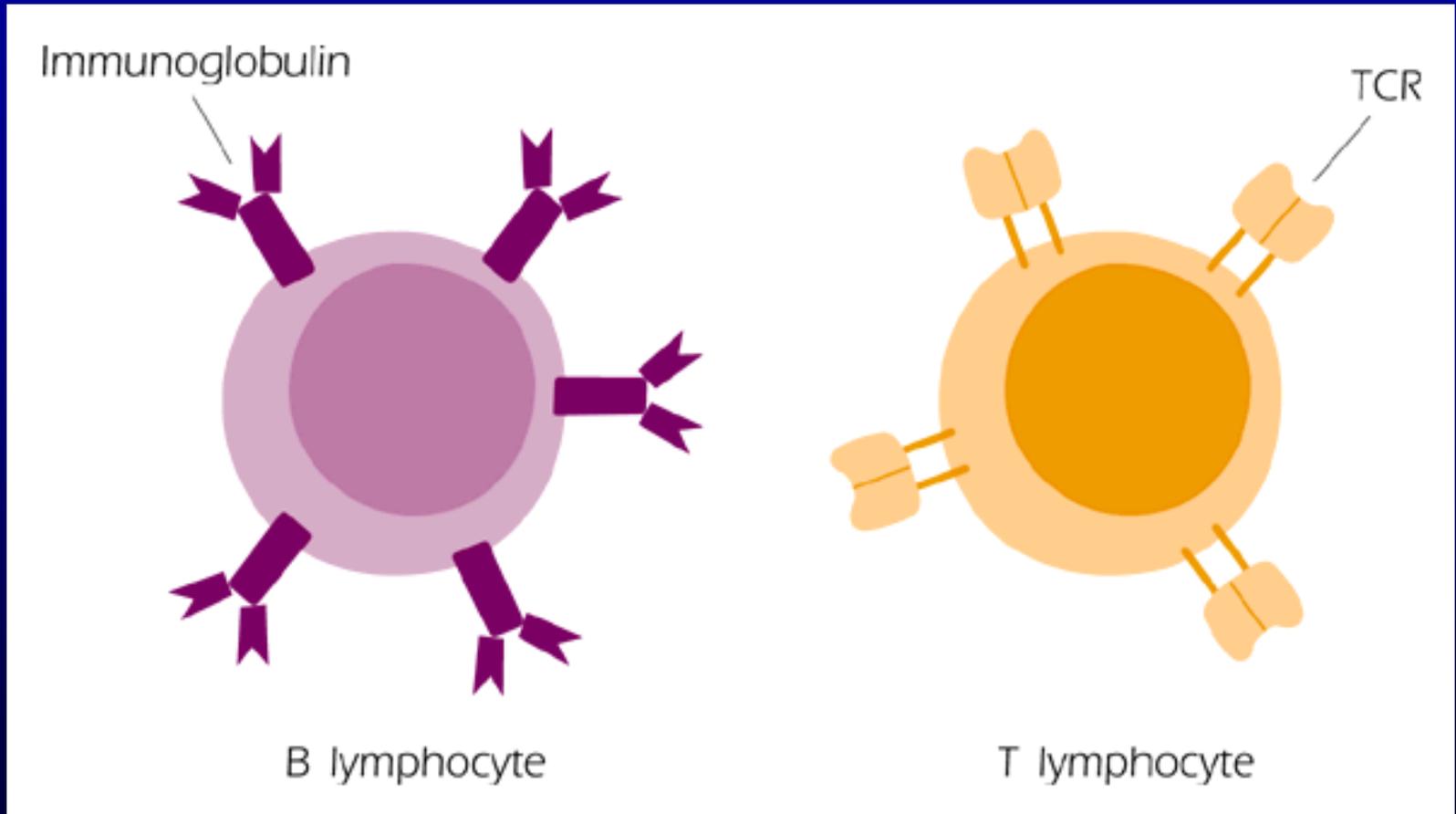
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Université Pierre et Marie Curie

IF-IIIb  
février 2010

# Sélection positive et négative des répertoires lymphocytaires

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

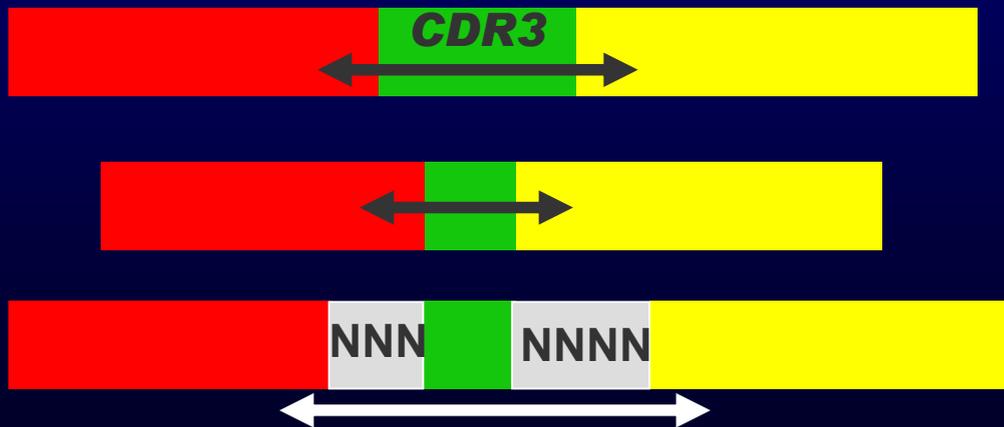
# Les lymphocytes B et T



→ 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 $\alpha$ / $\beta$  or TCR $\gamma$ / $\delta$
  - 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	$\kappa$ Chain	$\alpha$ Chain	$\beta$ Chain	$\gamma$ Chain	$\delta$ 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 and V-D-J joining	$101 \times 13 \times 4$	$85 \times 4$	$79 \times 38$	$21 \times 2 \times 11$	$7 \times 3$	$6 \times 2 \times 2$
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.

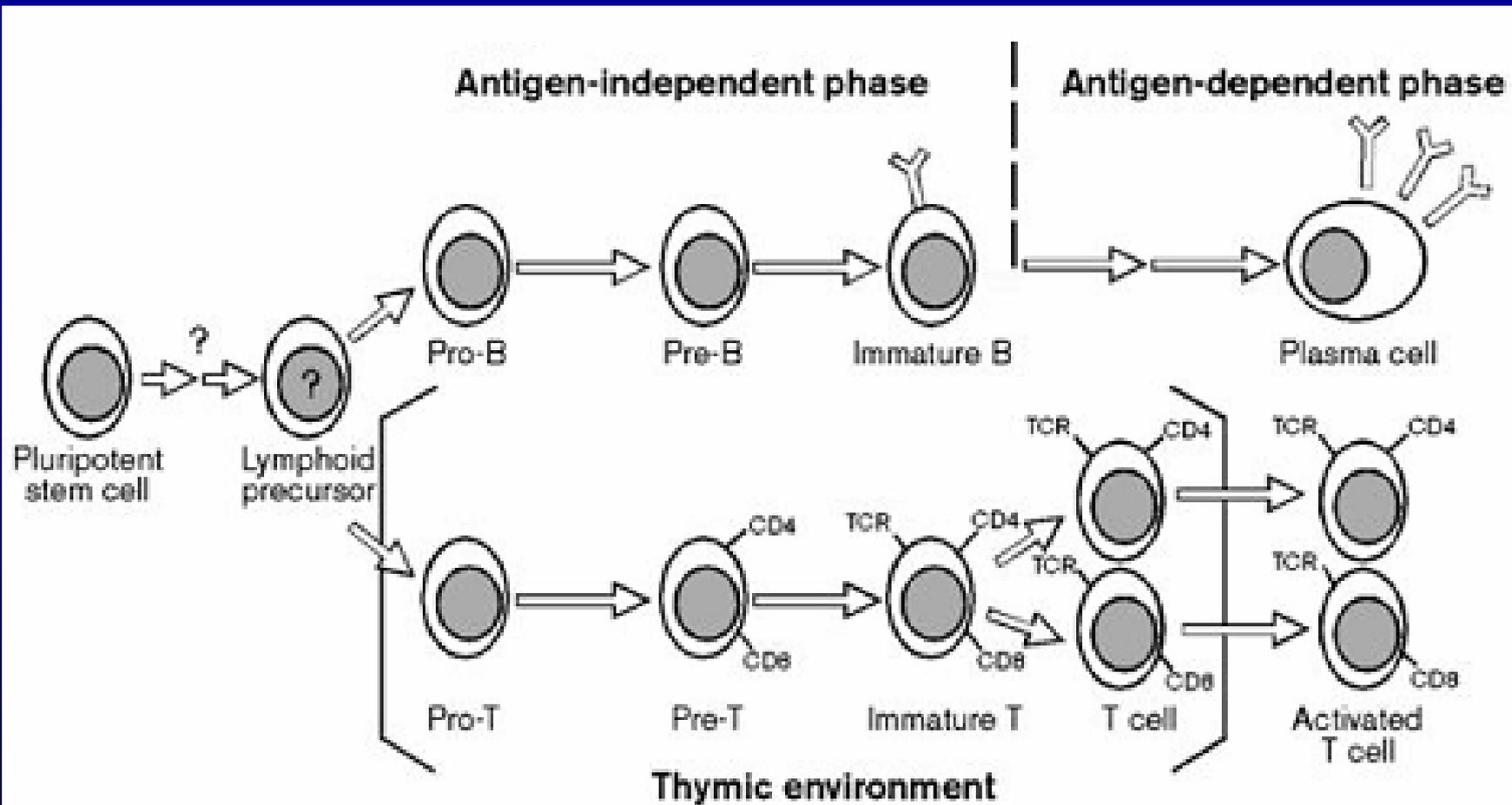
‡See Figure 9-8d for theoretical number of combinations generated by N-region addition.

Table 9-3

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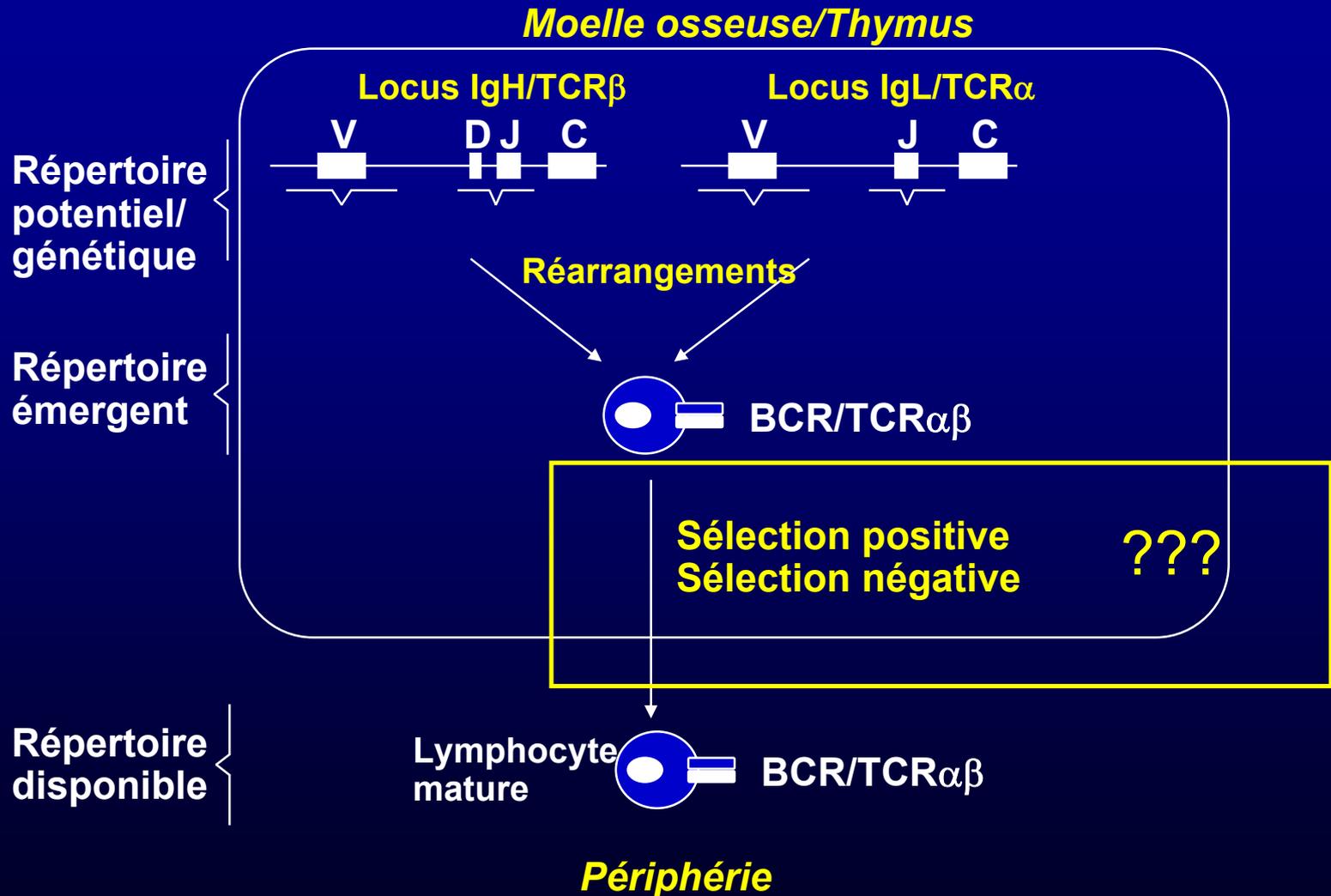
# Parallèle différenciations B et T



© 1998 Current Opinion in Immunology

D'après Fitzsimmons et Hagman (1996) *Curr. Op. Immunol.* 8:166.

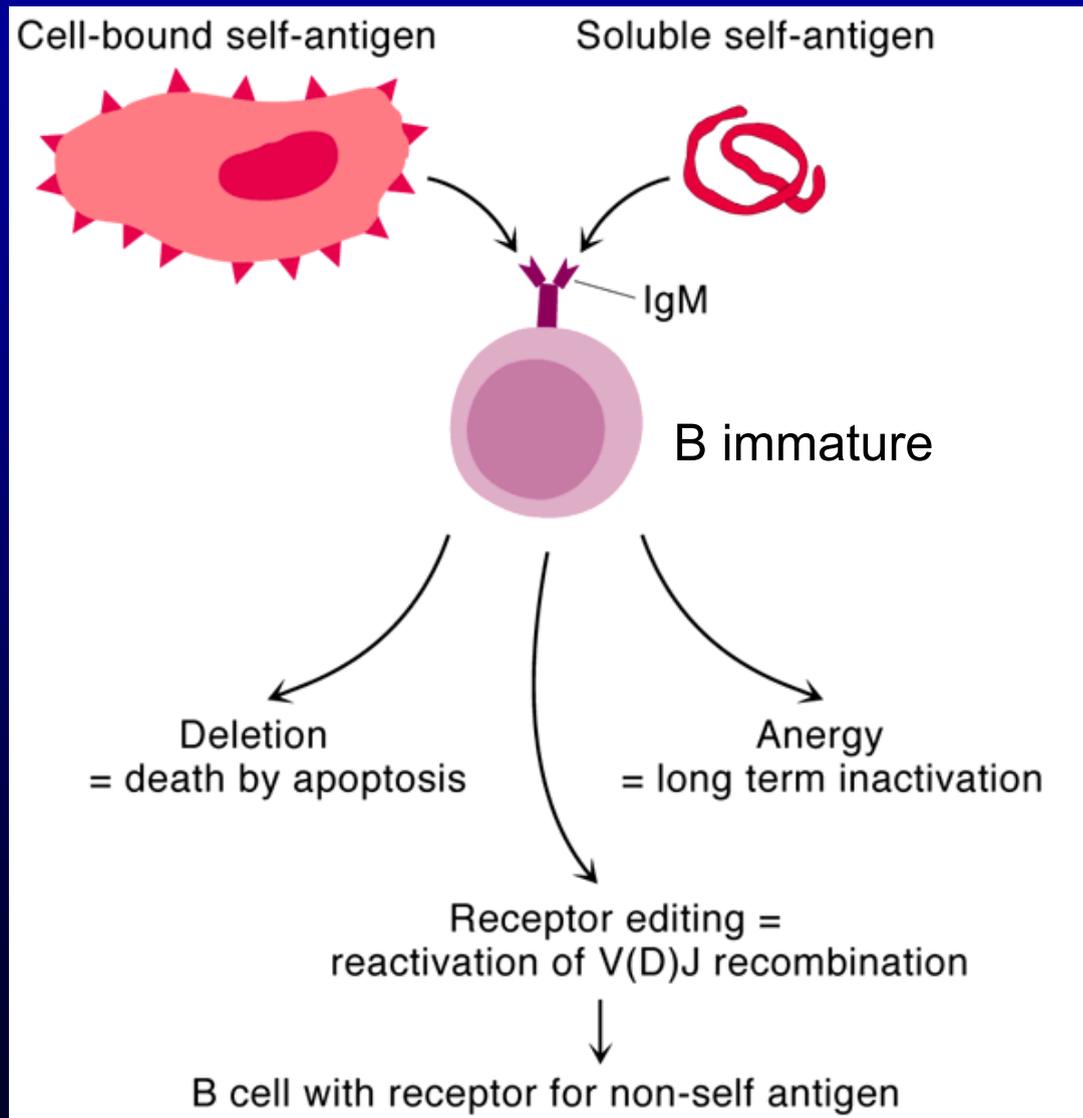
# Mise en place des répertoires



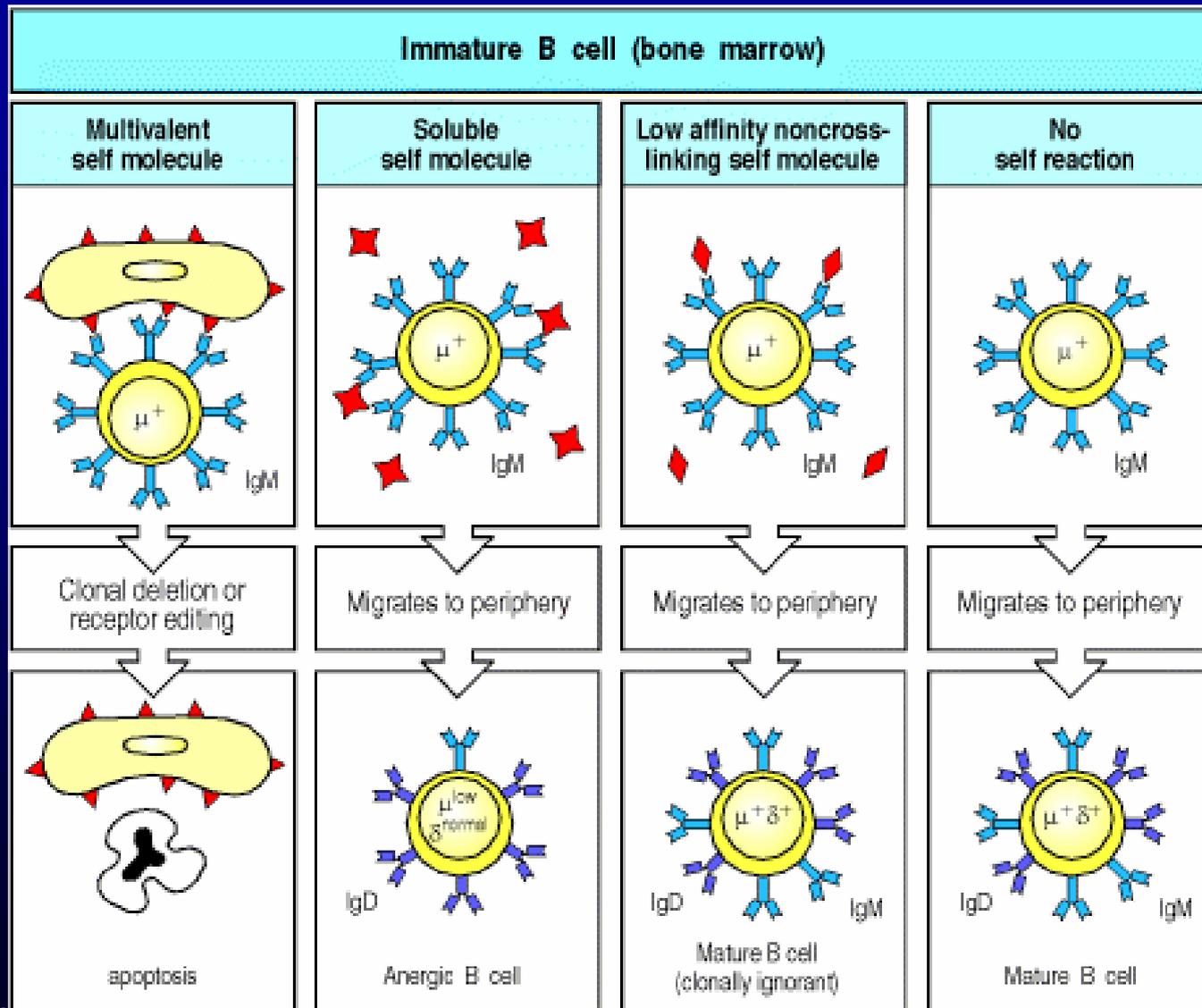
# Sélection positive et négative des répertoires lymphocytaires

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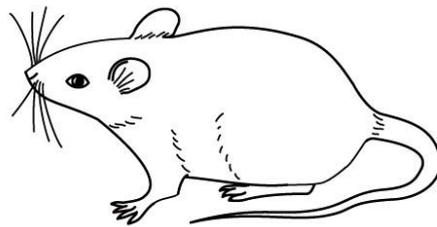
# Sélection des lymphocytes B (1)



# Sélection des lymphocytes B (2)

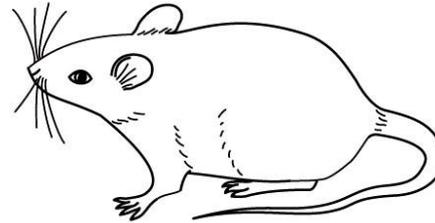


# Délétion clonale (1)

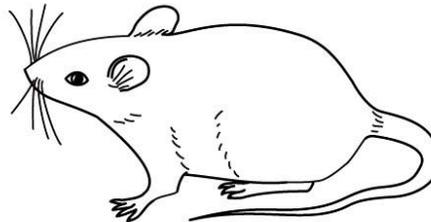


**Mice with  
liver-specific  
 $K^b$  transgene**

×



**Mice with  
anti- $K^b$   
transgene**



**Double transgenics  
with  $K^b$  and  
anti- $K^b$  transgene**

**Figure 11-15a**  
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# Délétion clonale (2)

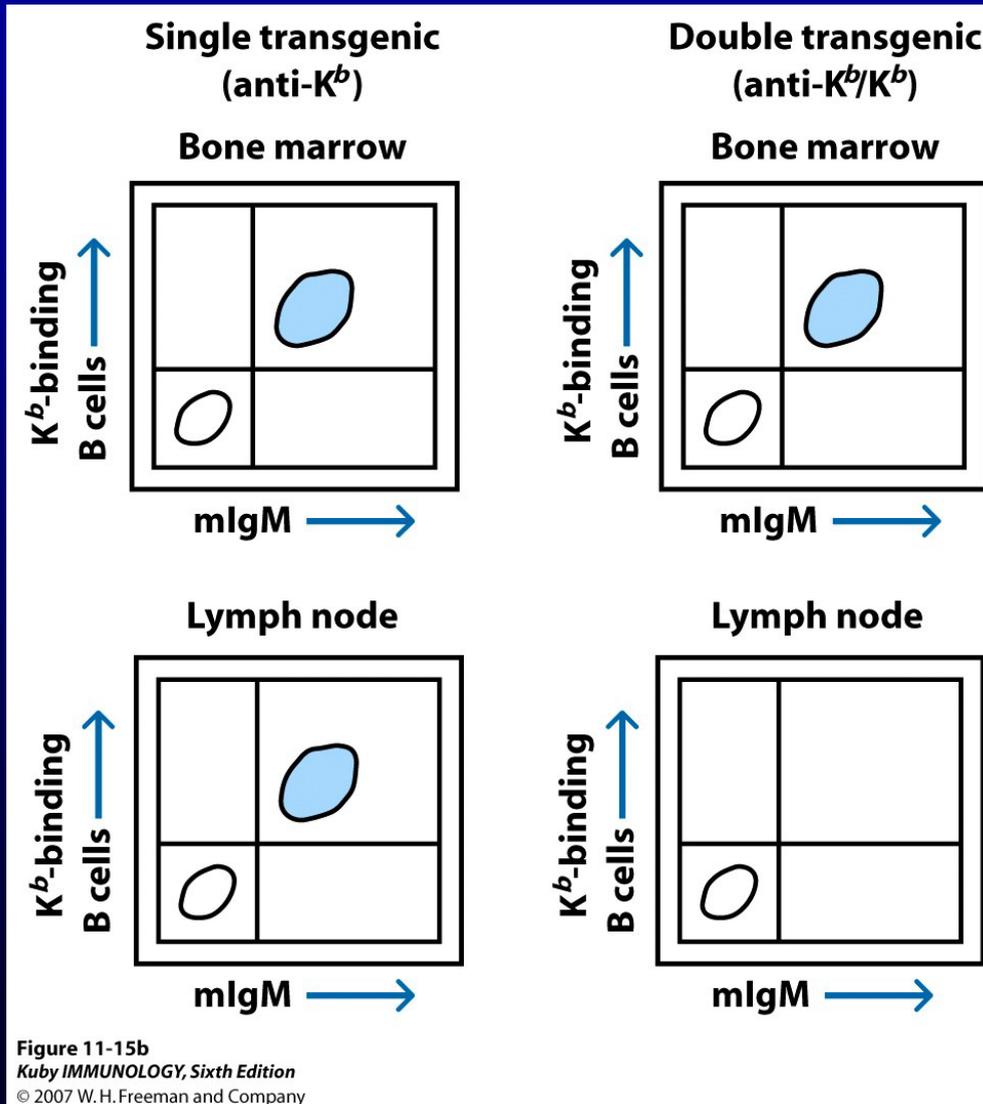


Figure 11-15b  
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# Anergie (1)

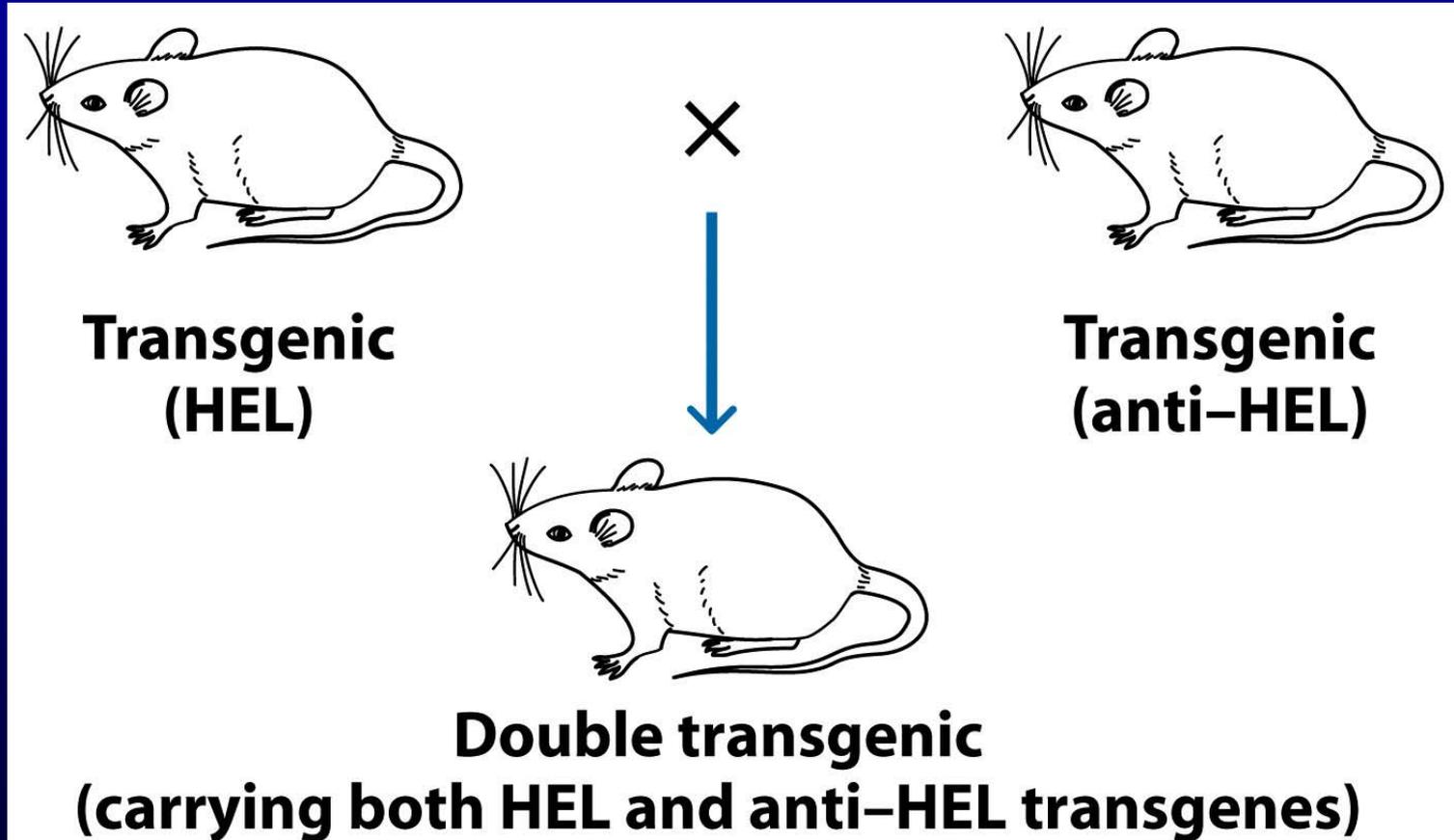


Figure 11-14a  
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# Anergie (2)

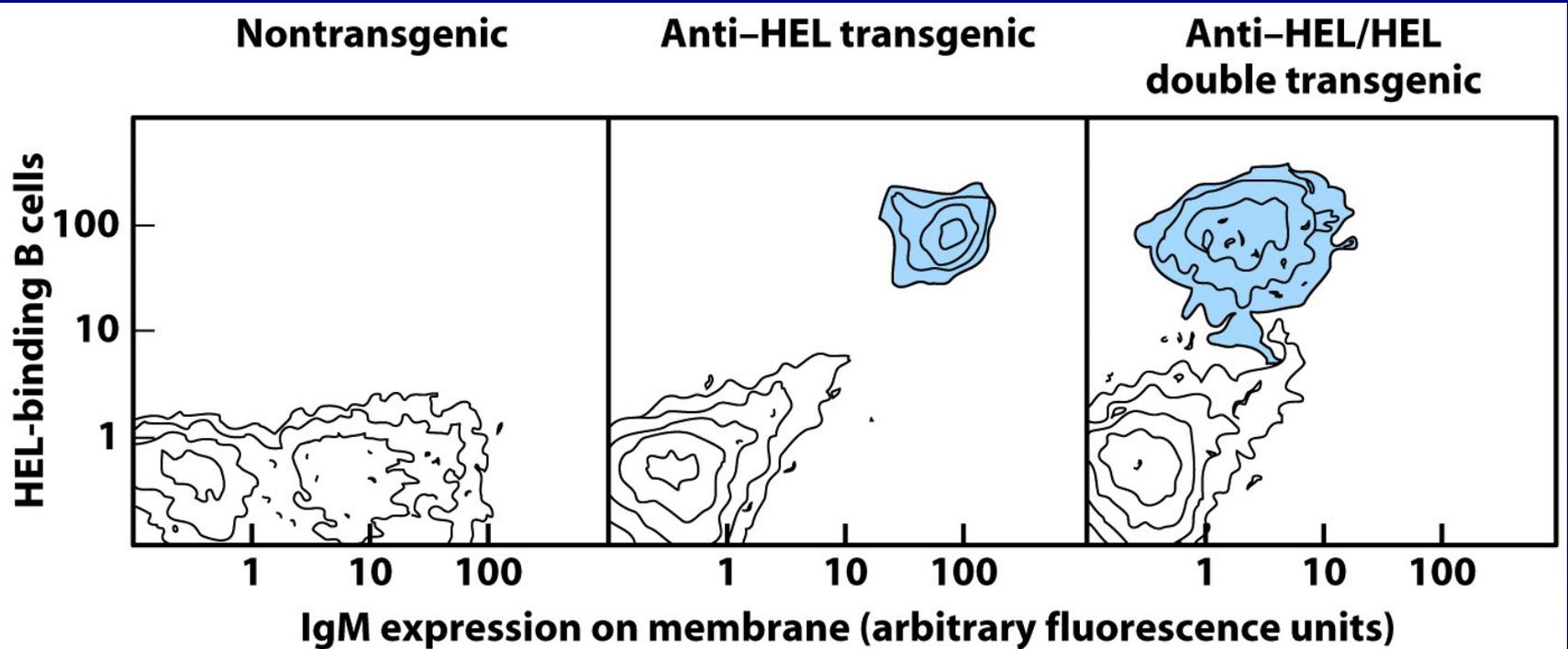
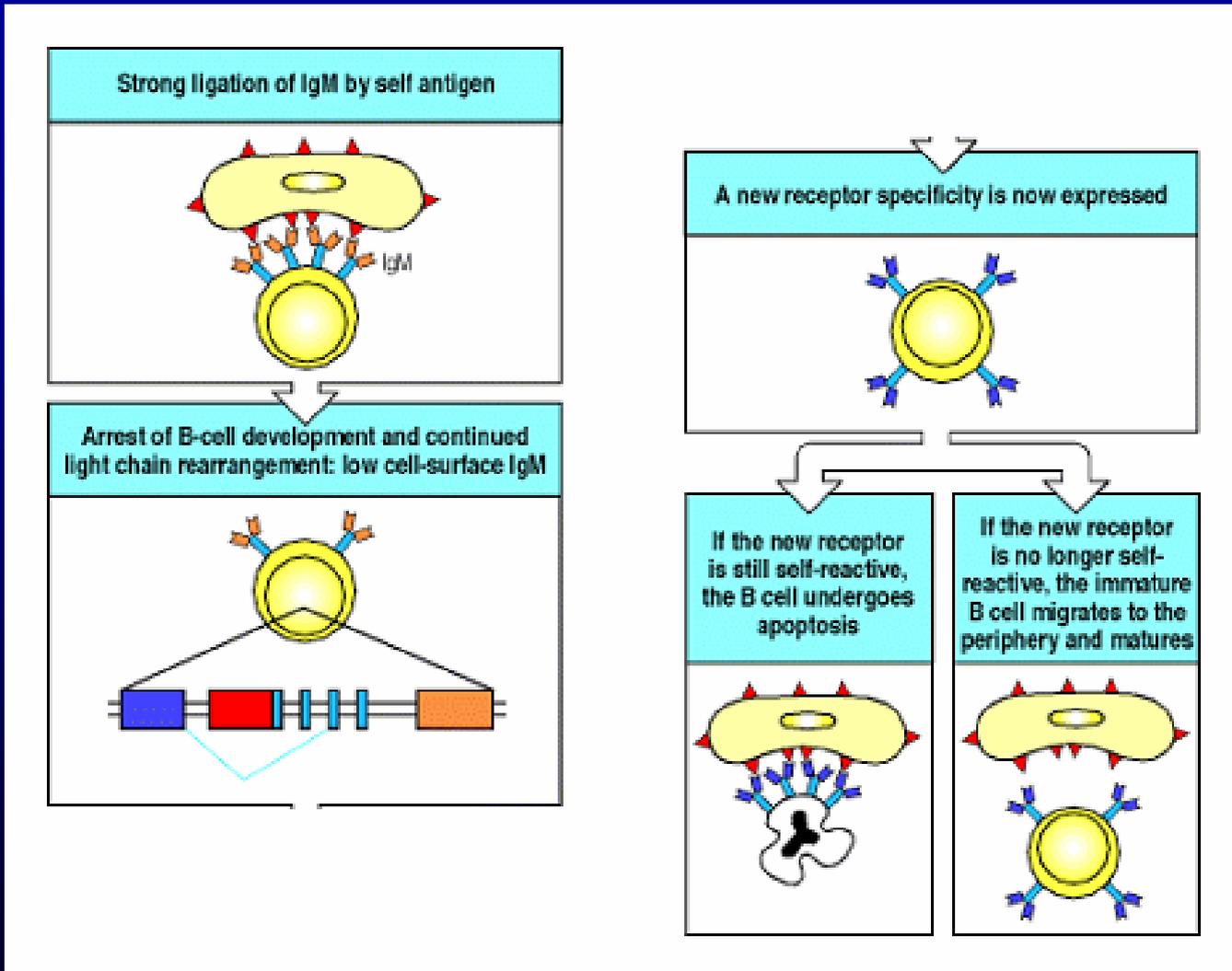


Figure 11-14b  
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# Sélection des lymphocytes B (3)



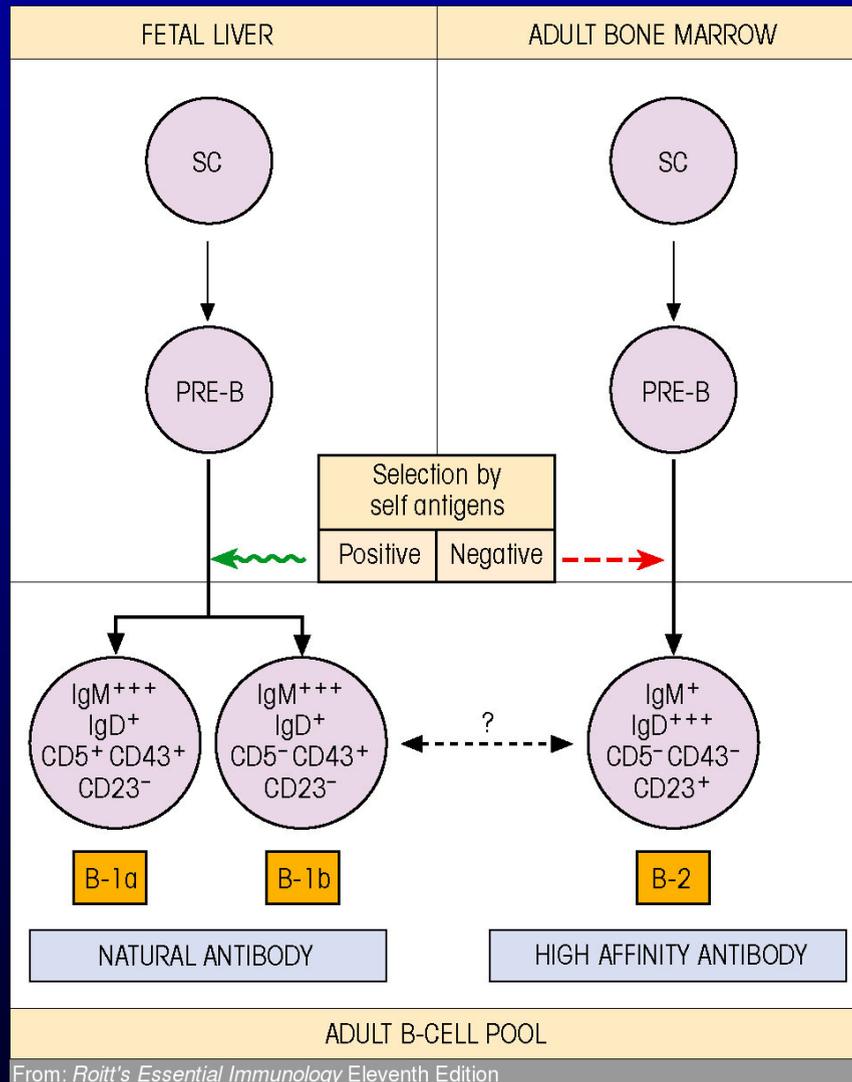
# Sélection des lymphocytes B (4)



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 (5)

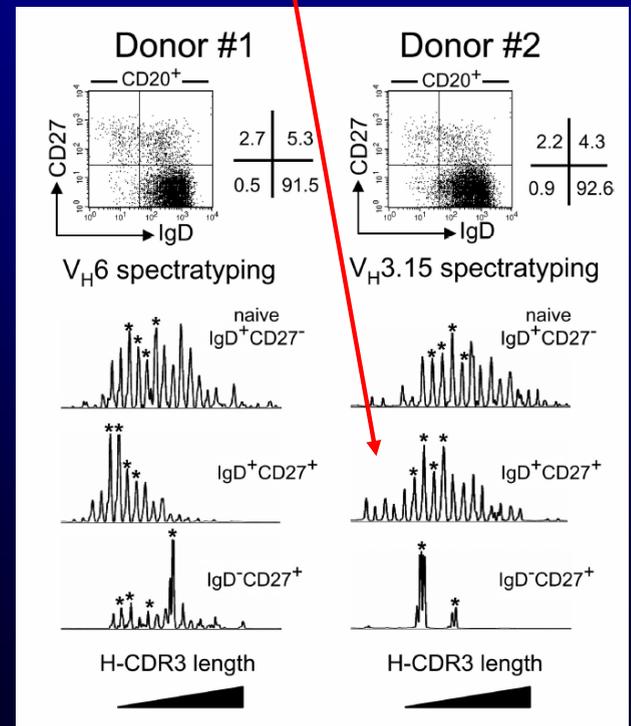
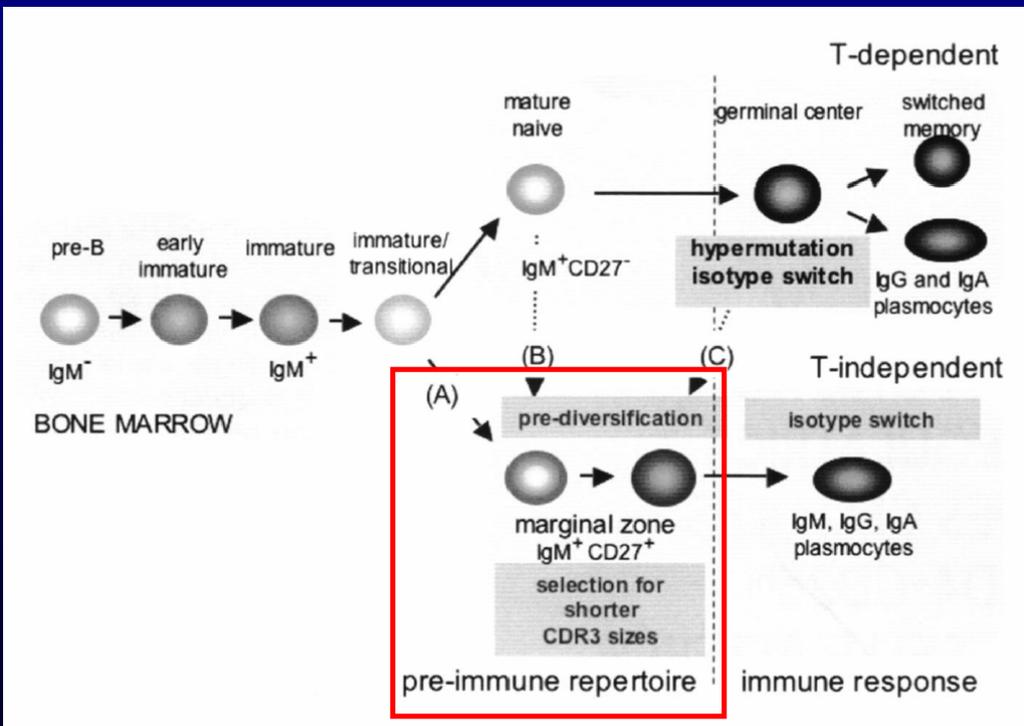


# Hypermutations en absence d'antigène

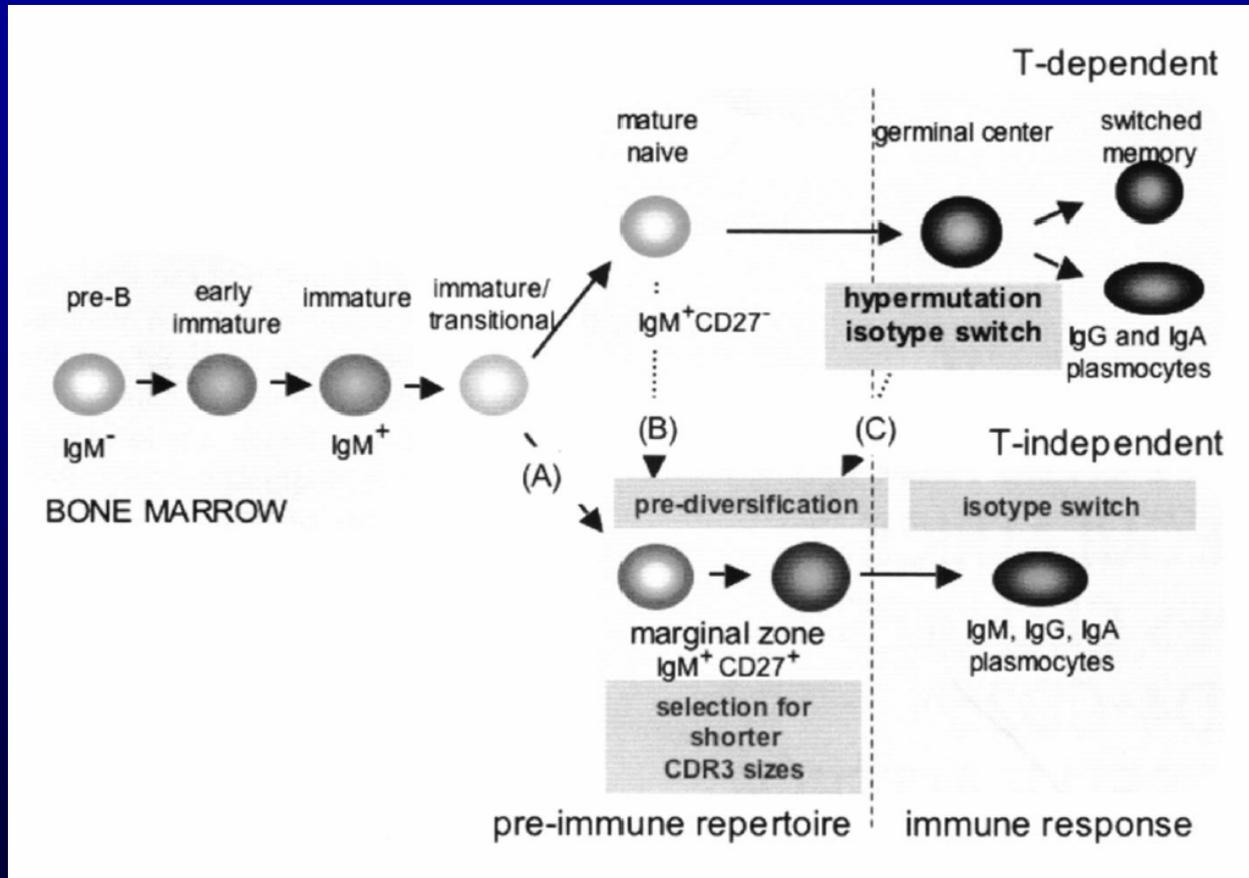
**Table IV.** Somatic mutations in  $J_H4$ - $J_H5$  introns flanking  $VDJ_H4$  rearrangements from splenic and blood B cell subsets

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 <sup>+</sup> CD27 <sup>+</sup>	20	15 (75%)	0-17	79	1.16	1.54
			IgD <sup>-</sup> CD27 <sup>+</sup>	20	18 (90%)	0-22	117	1.71	1.90
D2	11	blood	IgD <sup>+</sup> CD27 <sup>+</sup>	18	15 (83%)	0-16	116	1.89	2.27
			IgD <sup>-</sup> CD27 <sup>+</sup>	17	16 (94%)	0-21	127	2.19	2.32

- IgM<sup>+</sup>IgD<sup>+</sup>CD27<sup>+</sup> 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 <sup>6</sup> * spleen cells
None	HRBC	HRBC	205
SRBC	HRBC	HRBC	13
None	SRBC	SRBC	626
HRBC	SRBC	SRBC	78

\*PFC = plaque-forming cells.

Table 11-7  
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# 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, $\kappa$  anti-phosphorylcholine.

-S160 est dirigé contre un épitope de Ig $\alpha$ ; S104 est spécifique de IgA, $\kappa$ ; 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<sup>+</sup> Foci as a Function of Development

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

<sup>a</sup>The 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.

<sup>b</sup>Spleen cells from mice born within 12 hr of each other were pooled. Results from experiments performed on different days were pooled for the table.

<sup>c</sup>Calculated as per Sigal et al. (1977).

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

# Dominance clonale: idiotype T15 (3)

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

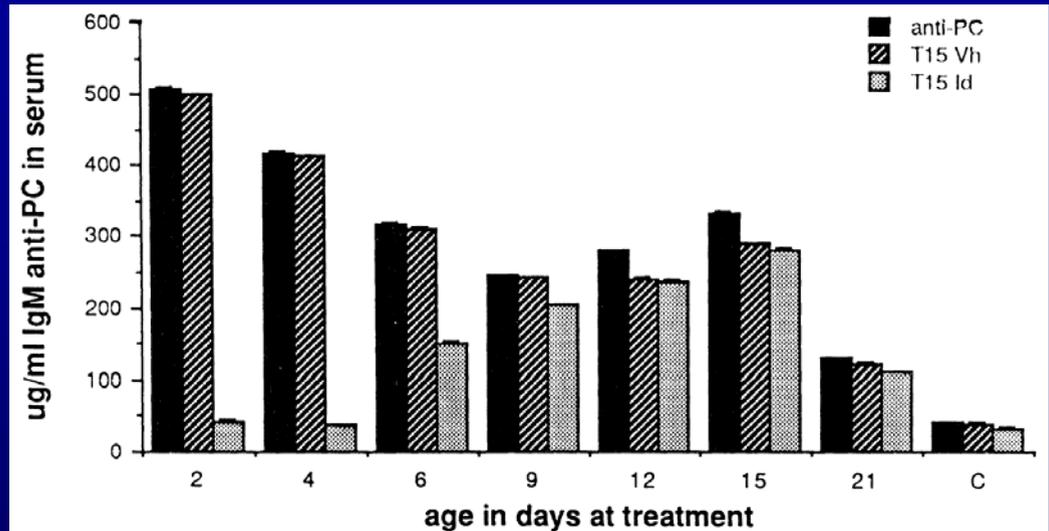


TABLE 3

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

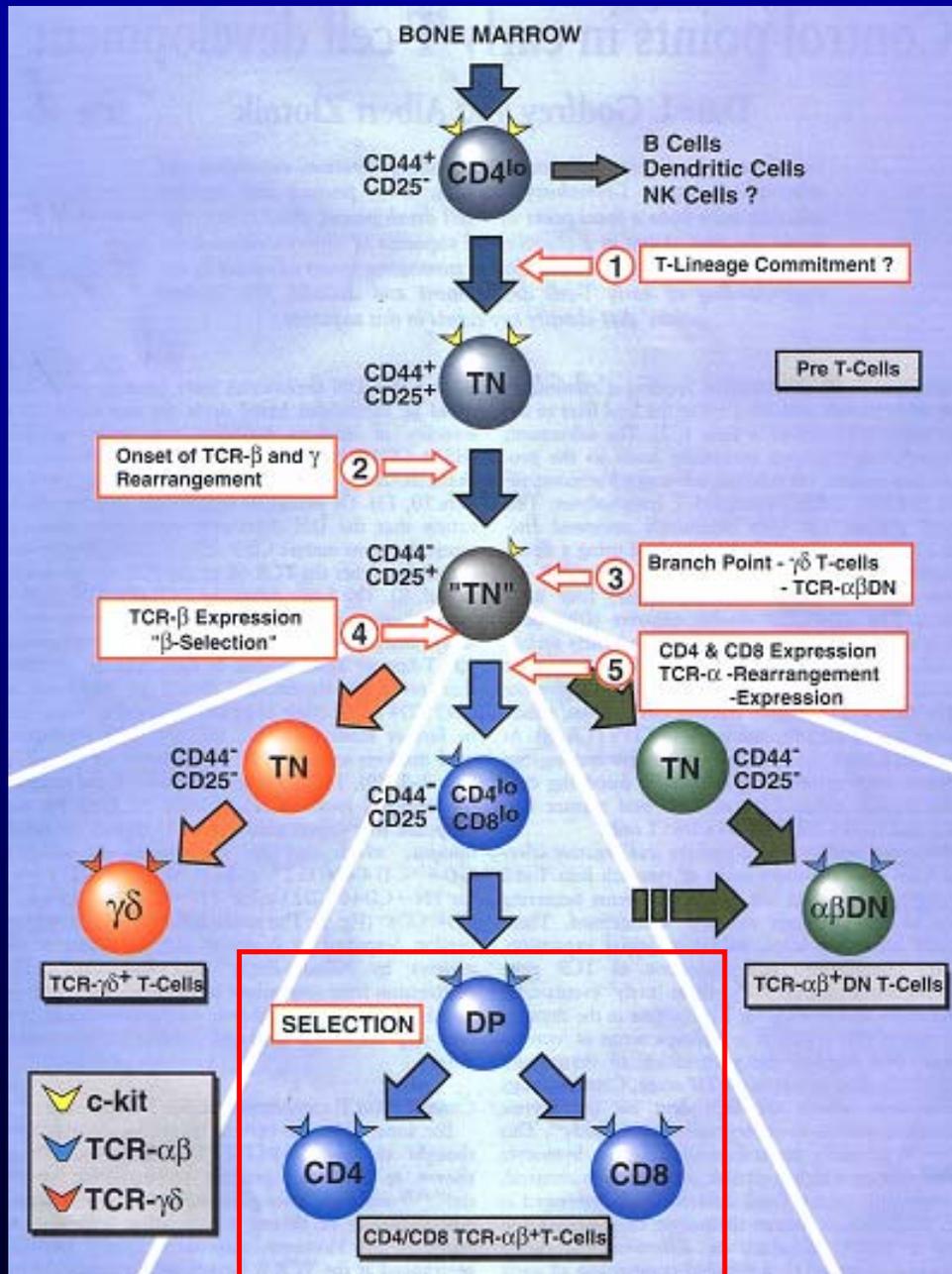
<sup>a</sup>Different from none/R36A at  $p < 0.01$ .  
<sup>b</sup>Different from none/R36A at  $p < 0.001$ .  
<sup>c</sup>Different from none/R36A at  $p < 0.06$ .

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

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

# Sélection positive et négative des répertoires lymphocytaires

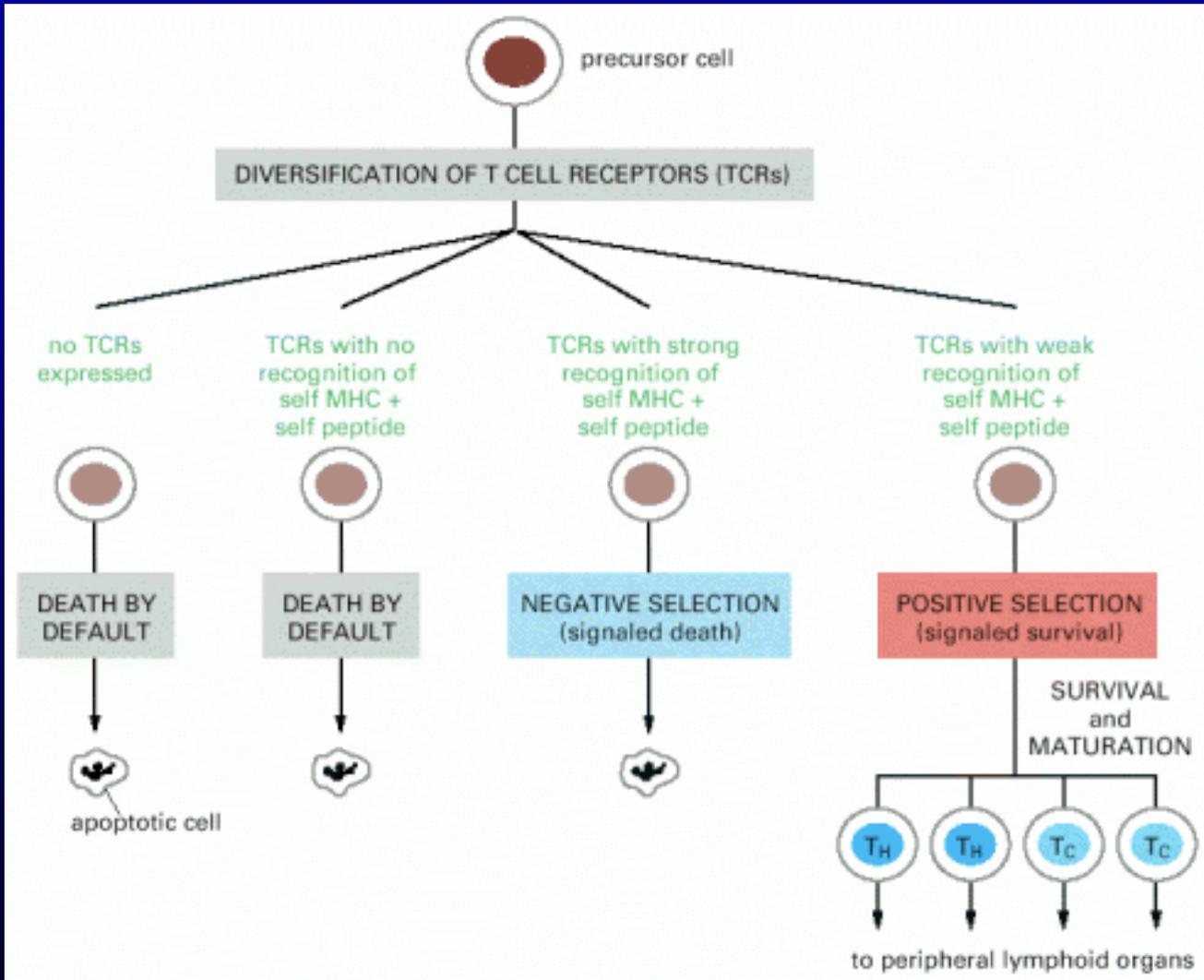
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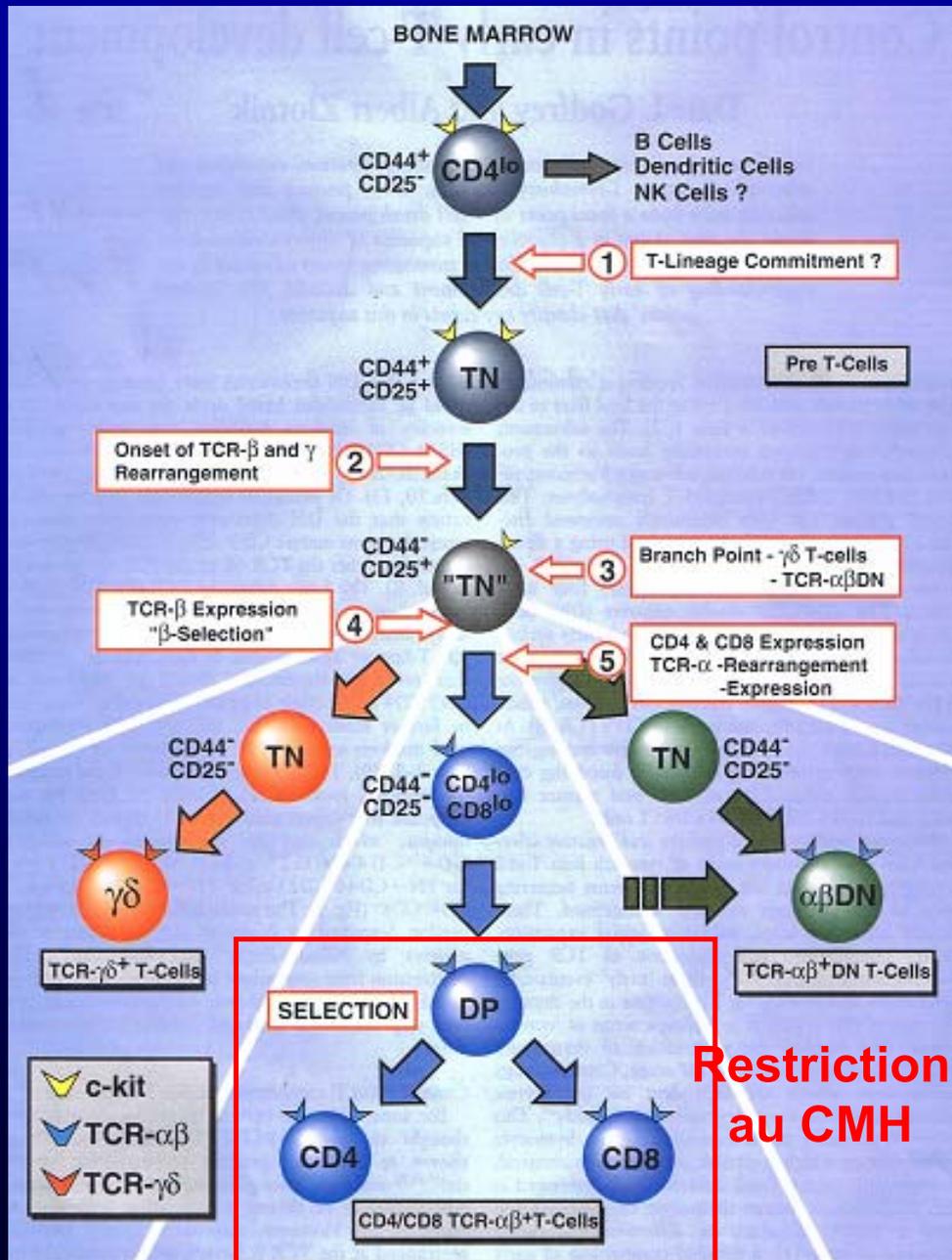
# Sélections positive et négative (1)

- **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

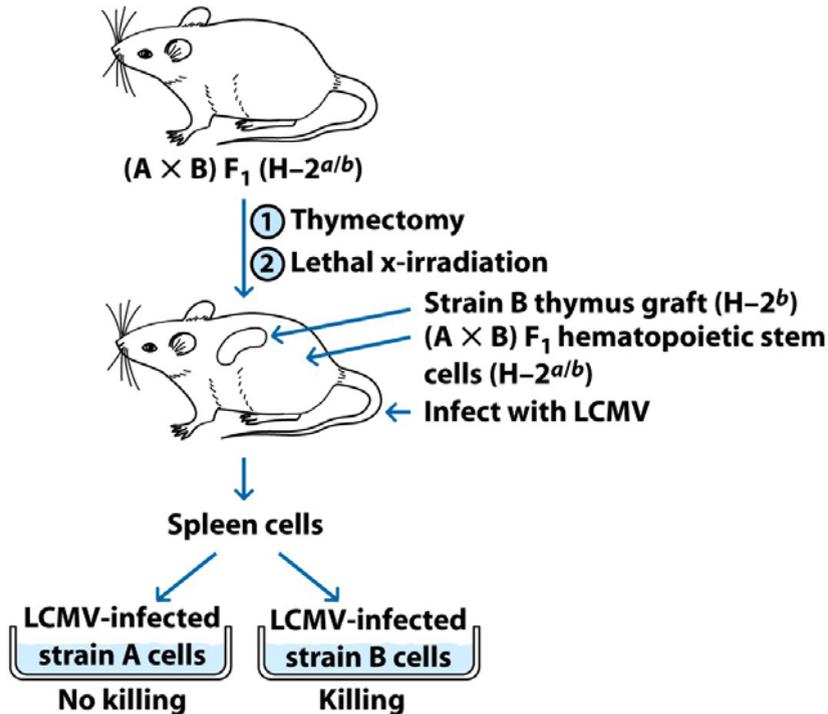


Figure 10-5 part 1  
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## CONTROL

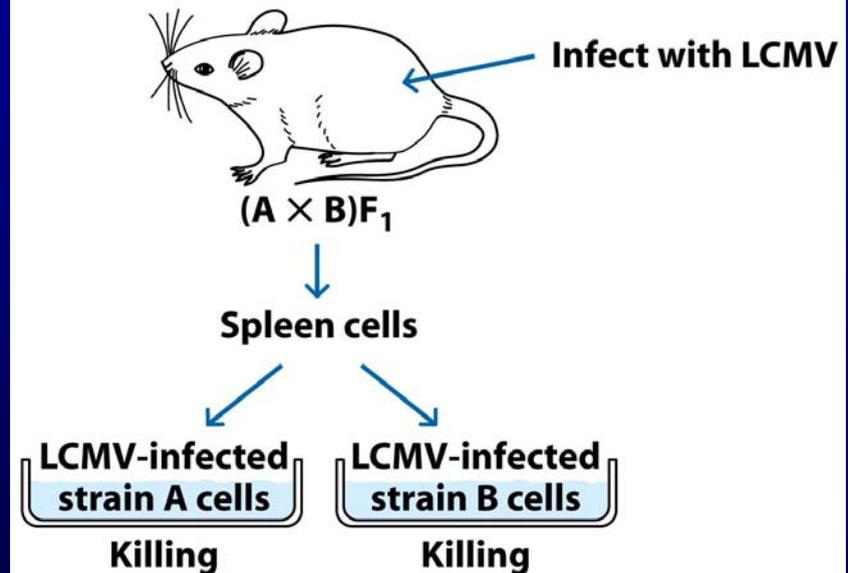
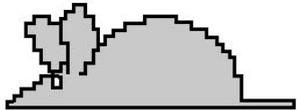
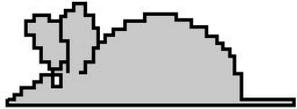
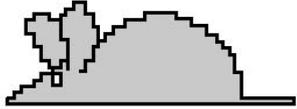
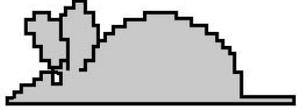
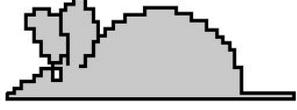


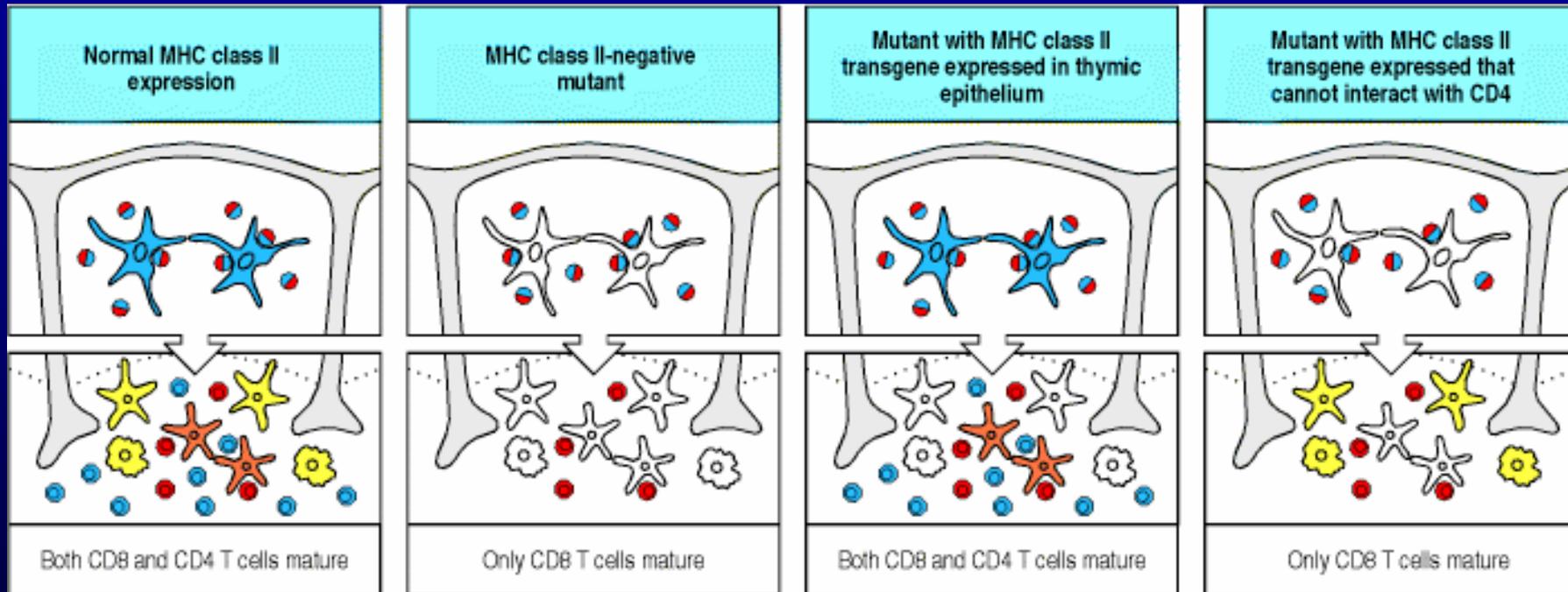
Figure 10-5 part 2  
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# Rôle de l'épithélium thymique dans la sélection positive (2)

Thymectomize <i>b</i> x <i>k</i> mice	Graft with thymus of haplotype	Irradiate and reconstitute with <i>b</i> x <i>k</i> bone marrow	Prime with KLH	Proliferative response of primed T-cells to KLH on antigen-presenting cells of haplotype	
				<i>H-2<sup>b</sup></i>	<i>H-2<sup>k</sup></i>
	<i>b</i> x <i>k</i>	→	→	+++	+++
	<i>b</i>	→	→	+++	-
	dGuo-treated <i>b</i>	→	→	+++	-
	<i>k</i>	→	→	-	+++
	dGuo-treated <i>k</i>	→	→	-	+++

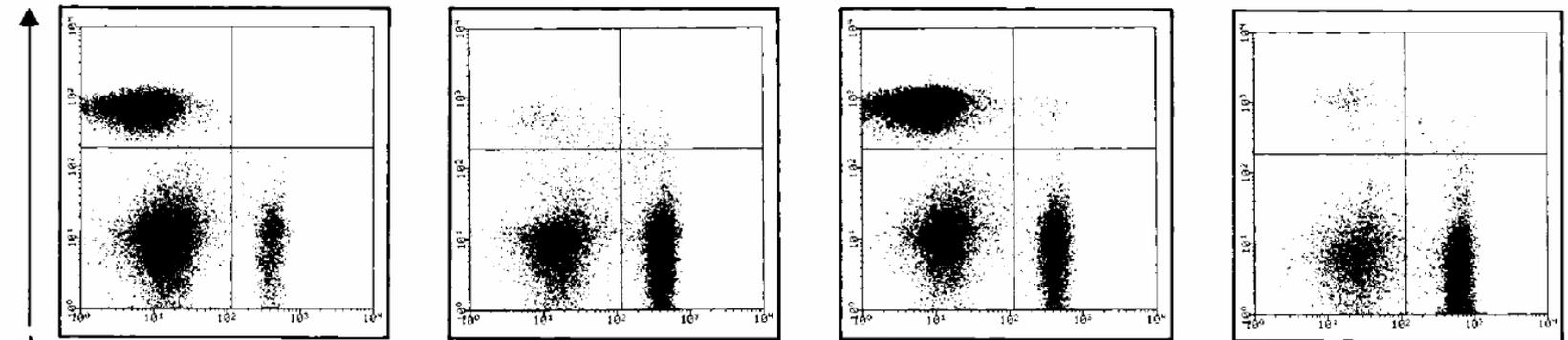
From: Roitt's Essential Immunology Eleventh Edition

# Sélection positive & CMH (1)

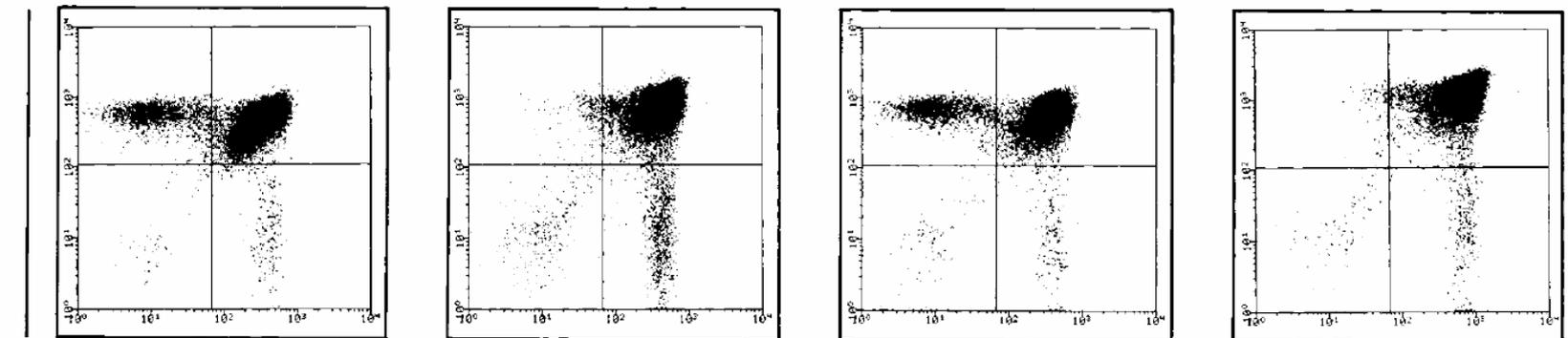


# Sélection positive & CMH (4)

LYMPHOCYTES



THYMOCYTES



B6 I-A<sup>+/+</sup>

B6 I-A<sup>-/-</sup>

B6-E<sub>α</sub><sup>d</sup> I-A<sup>-/-</sup>

B6CD11c-E<sub>α</sub><sup>d</sup> I-A<sup>-/-</sup>

CD8

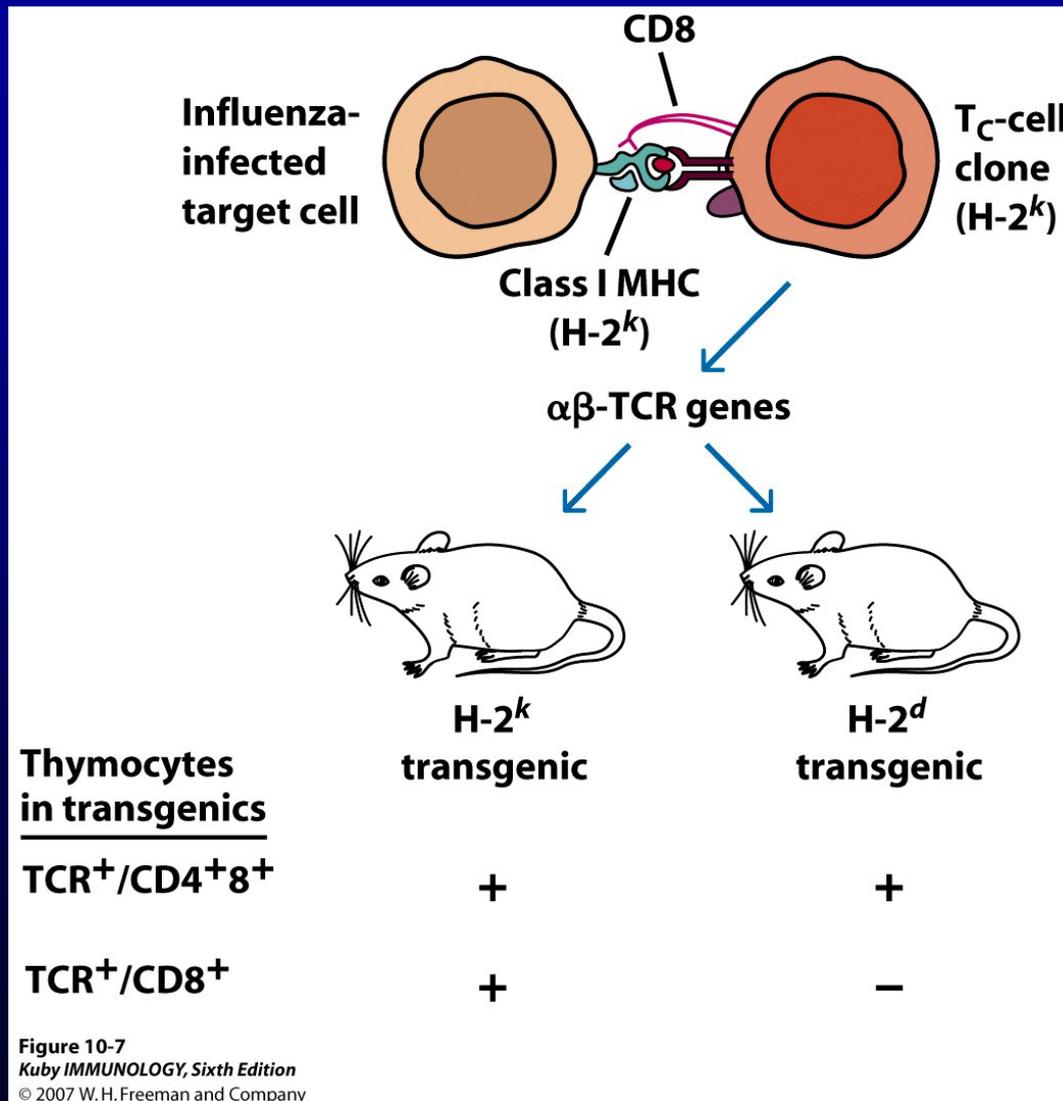
# Sélection positive & CMH (3)

Cell type	Control mice	KNOCKOUT MICE	
		Class I deficient	Class II deficient
CD4 <sup>-</sup> CD8 <sup>-</sup>	+	+	+
CD4 <sup>+</sup> CD8 <sup>+</sup>	+	+	+
CD4 <sup>+</sup>	+	+	-
CD8 <sup>+</sup>	+	-	+

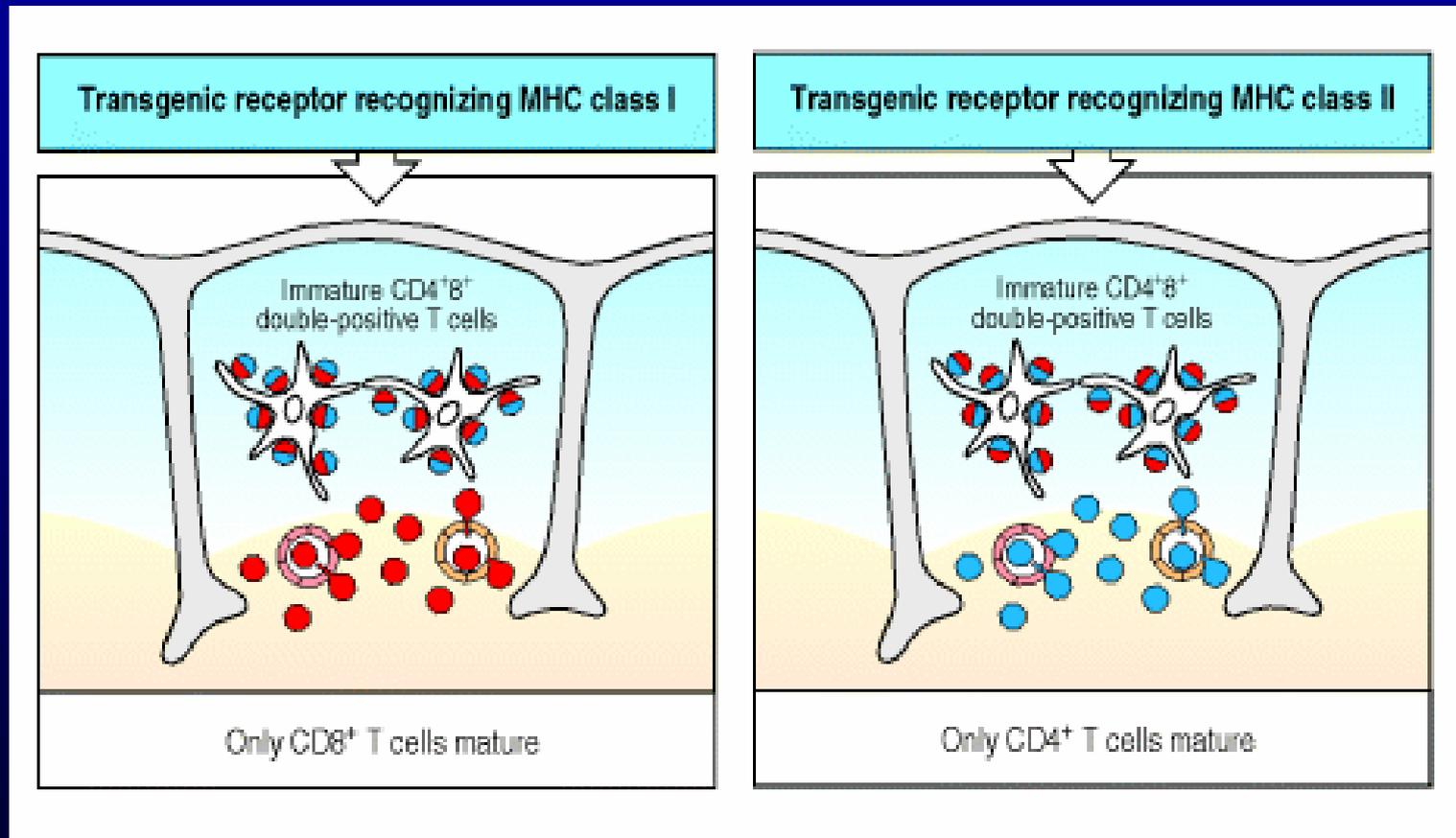
**\*Plus sign indicates normal distribution of indicated cell types in thymus. Minus sign indicates absence of cell type.**

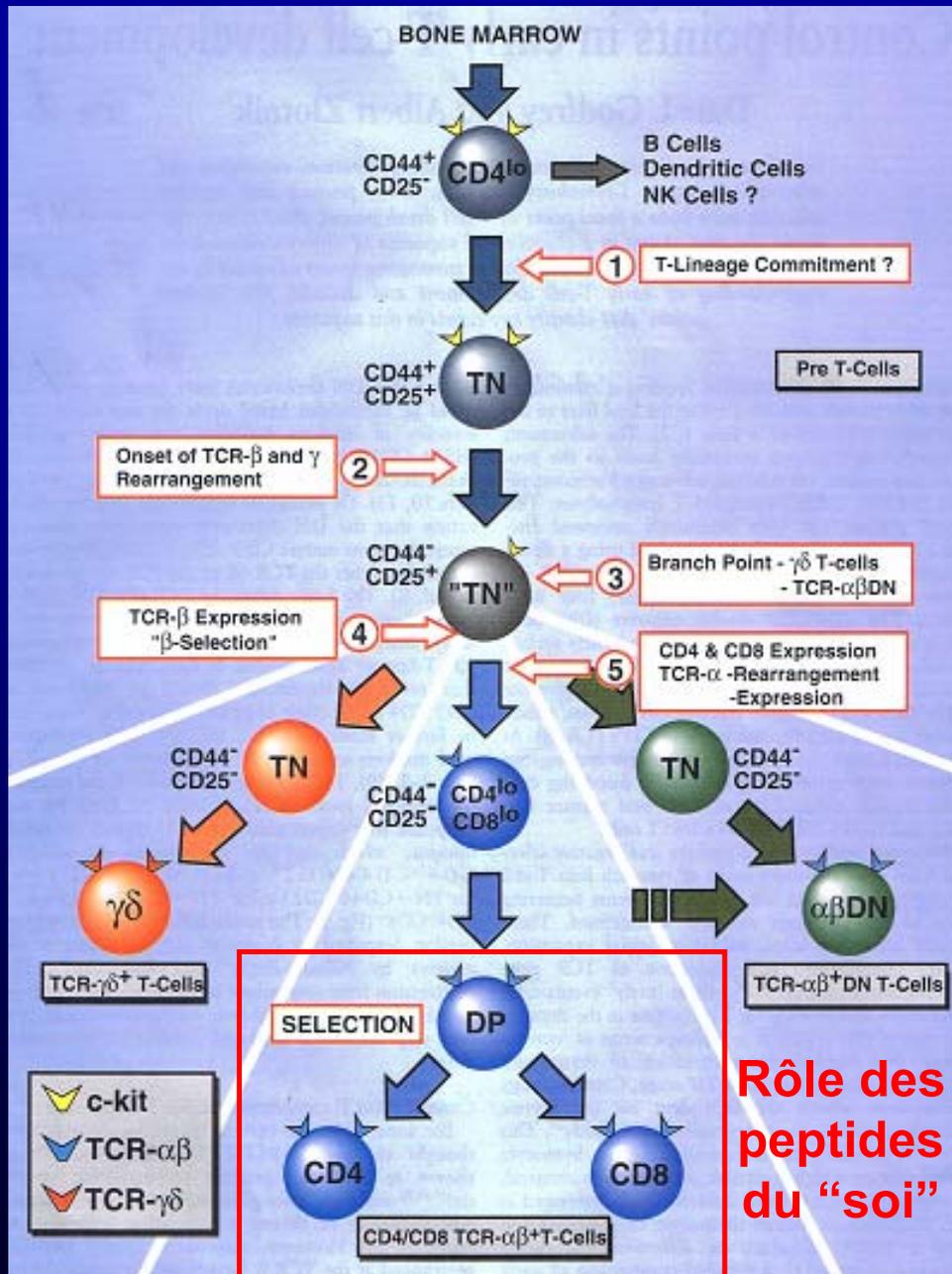
Table 10-1  
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# Sélection positive & CMH (4)

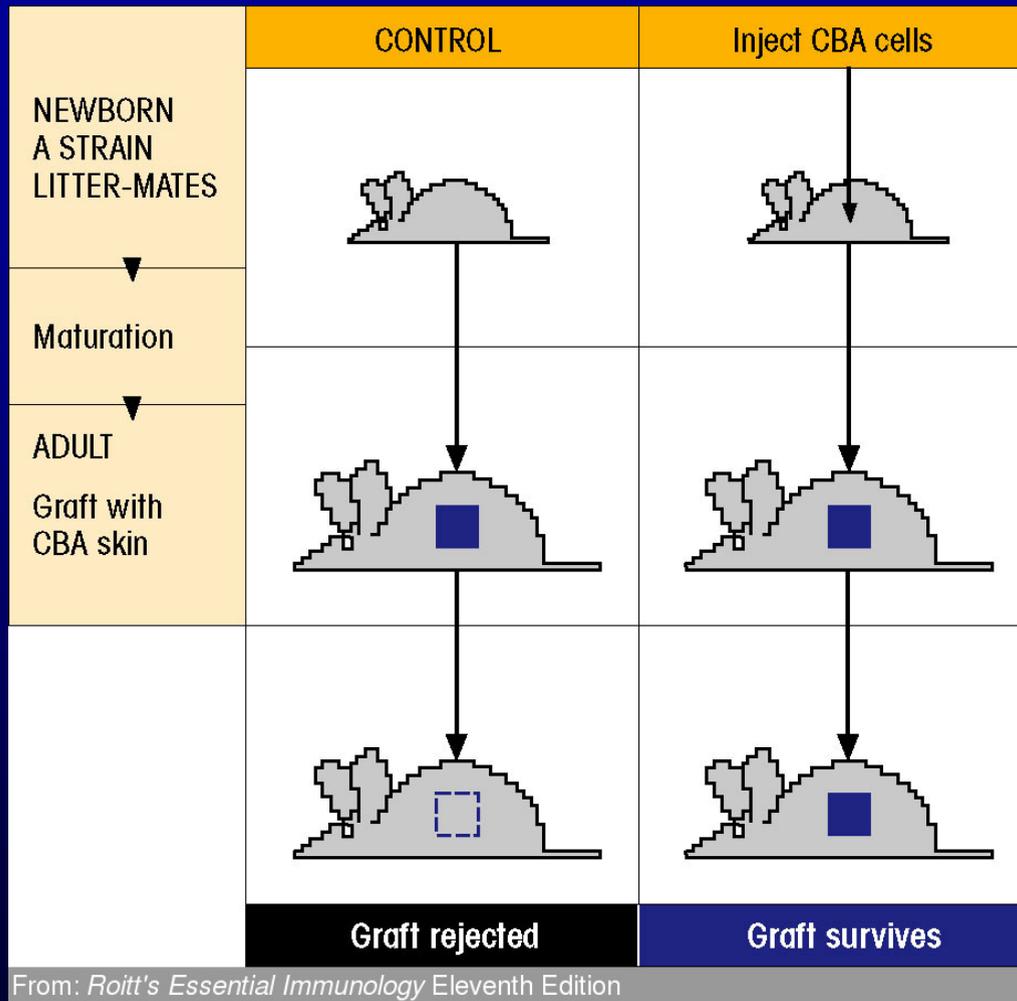


# Sélection positive & CMH (2)

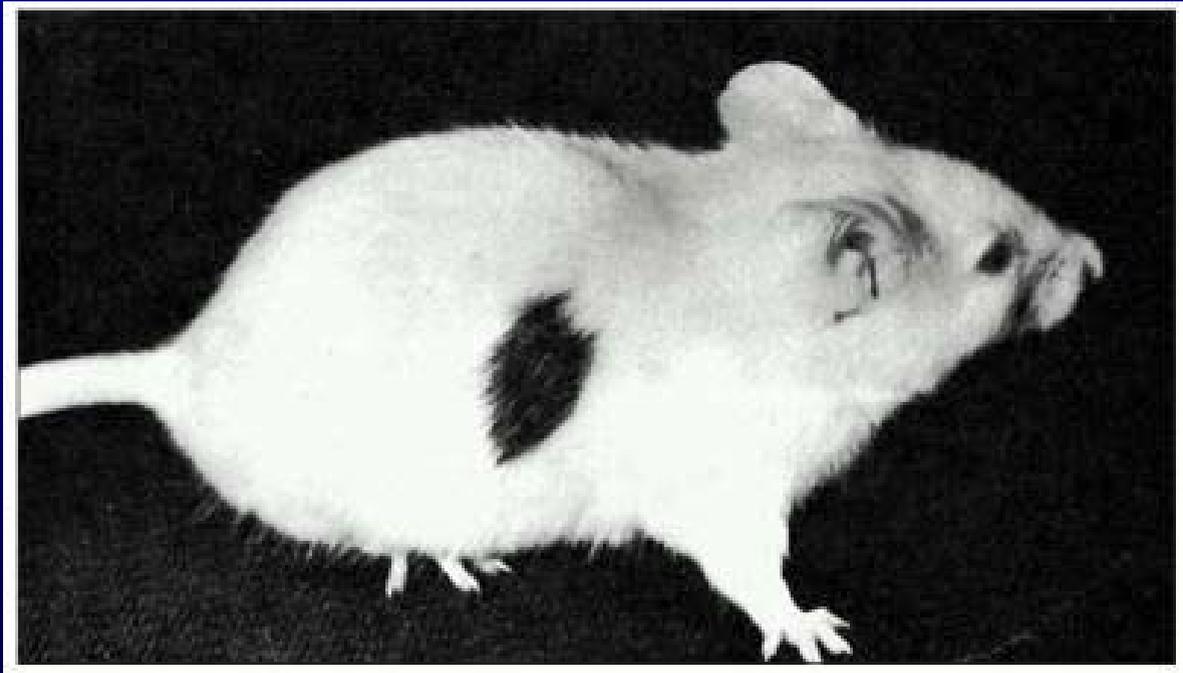




# Induction de la tolérance



→ Rôle des peptides du soi → Délétion clonale



# Délétion clonale et superantigènes (1)

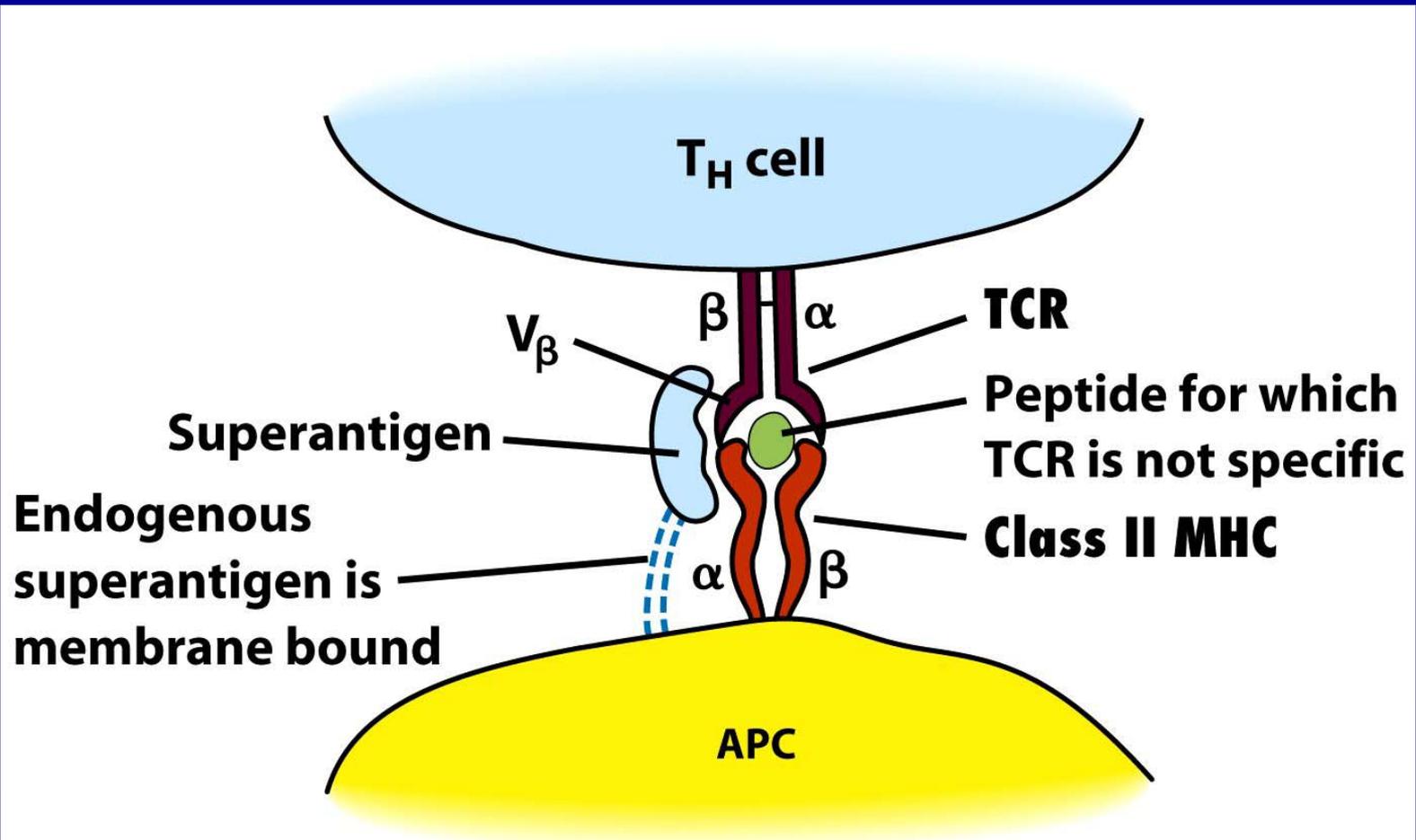


Figure 10-16  
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# Délétion clonale et superantigènes (2)

**TABLE 10-3** Exogenous superantigens and their  $V_{\beta}$  specificity

Superantigen	Disease*	$V_{\beta}$ SPECIFICITY	
		Mouse	Human
<b>Staphylococcal enterotoxins</b>			
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.

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# Délétion clonale et superantigènes (3)

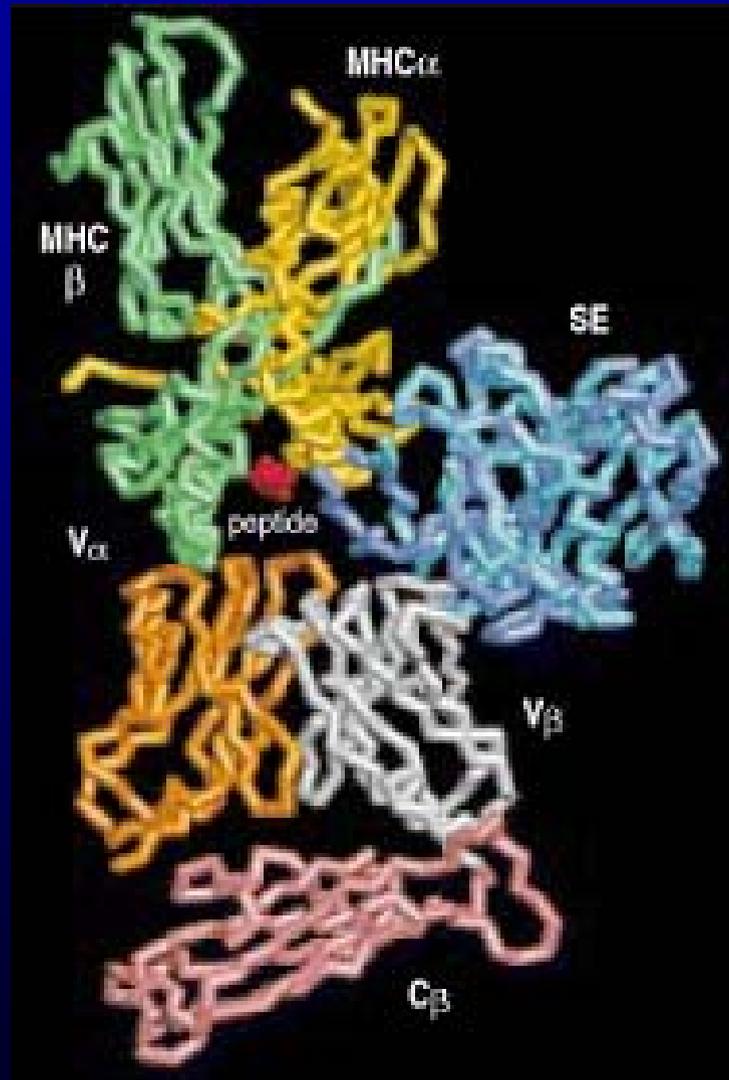
TABLE II  
V $\beta$  Specificity of MMTV Encoded Super-antigens

Mtv	Chromosome	Super-antigen	V $\beta$ 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*	— <sup>†</sup>
?	?		20	29
C3H-exo			14, 15	42, 43
BALB/c tumor			2	90

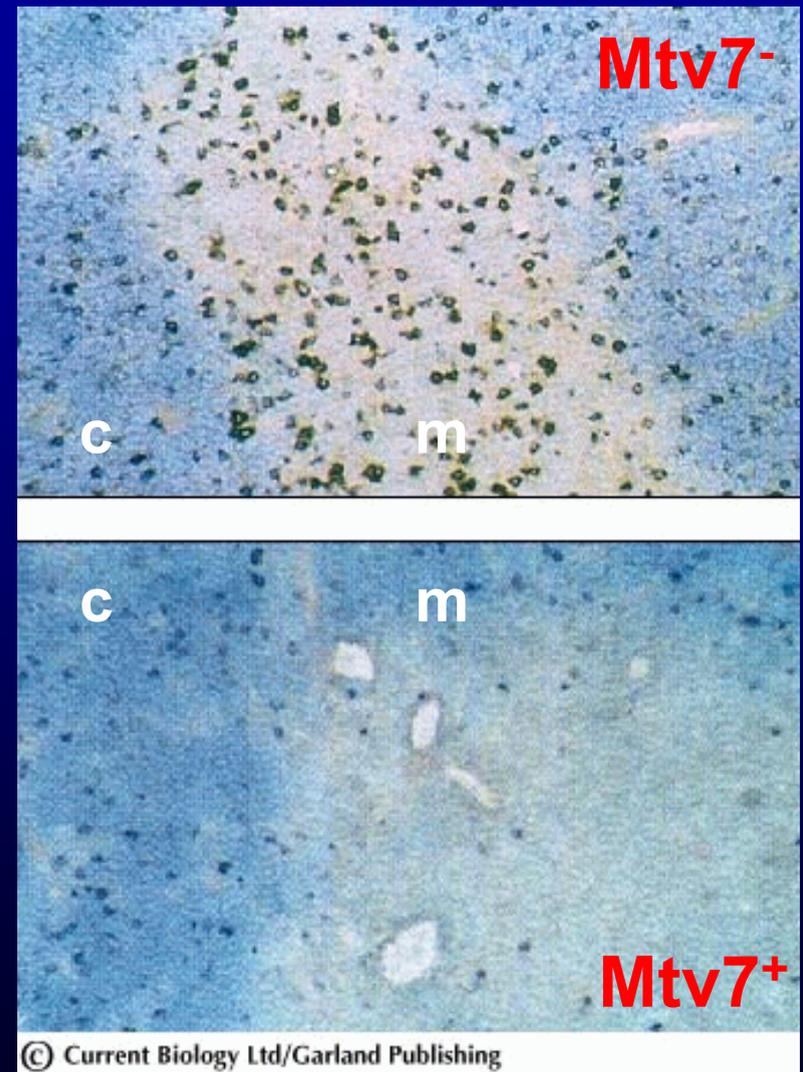
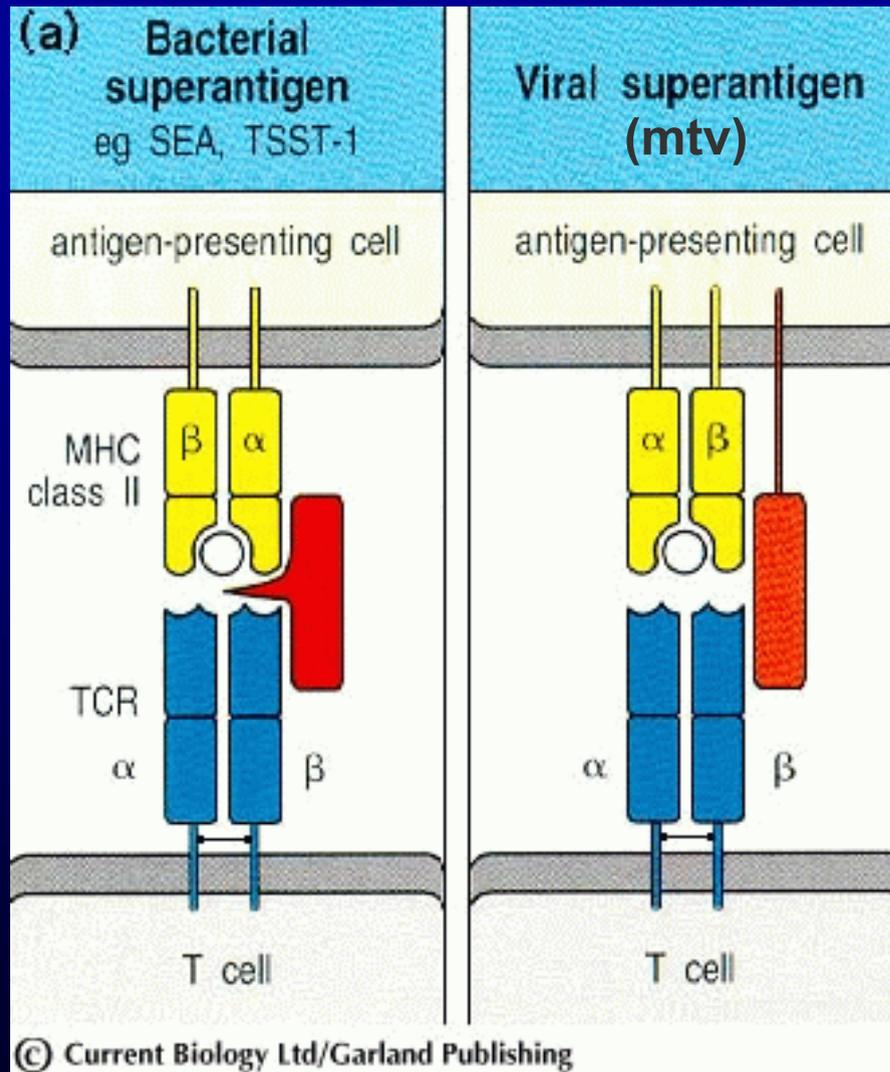
\*Super-antigen implicated but not yet demonstrated.

<sup>†</sup>R. J. Hodes, unpublished.

# Délétion clonale et superantigènes (4)



# Délétion clonale et superantigènes (5)

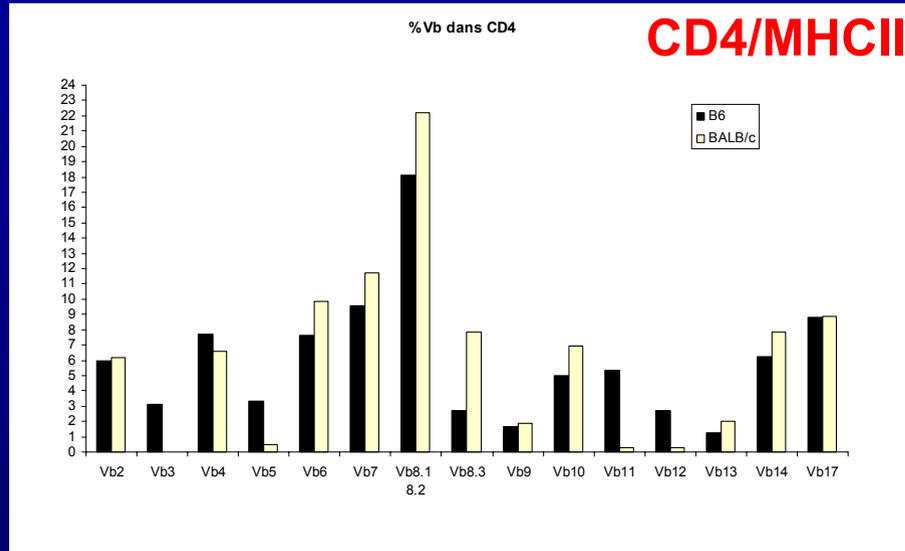


# Délétion clonale et superantigènes (6)

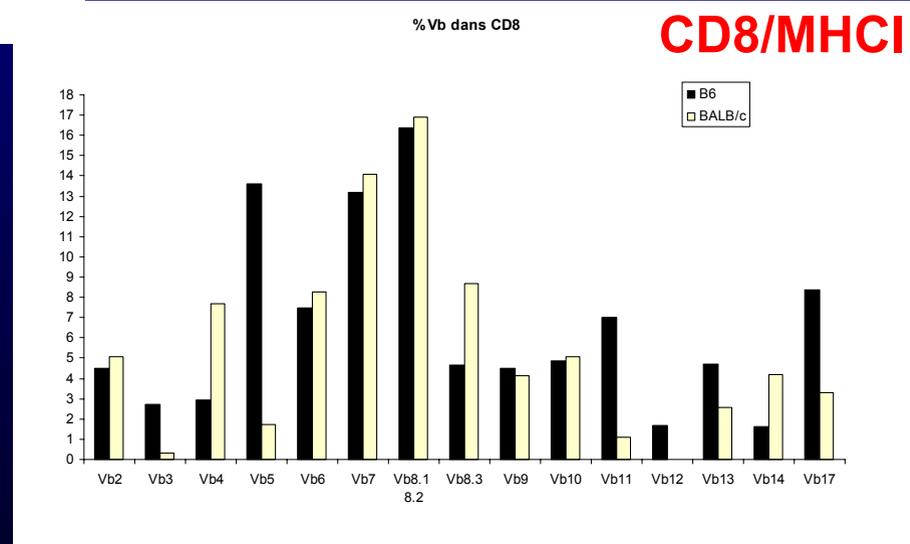
Table 1. Stain distribution of some MTV proviruses. (adapted from *Annu. Rev. Cell Biol.* 1993.9:101-28)

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 (Vb 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	-	-	+	+	+	+	-	-	+	+	-	-	-

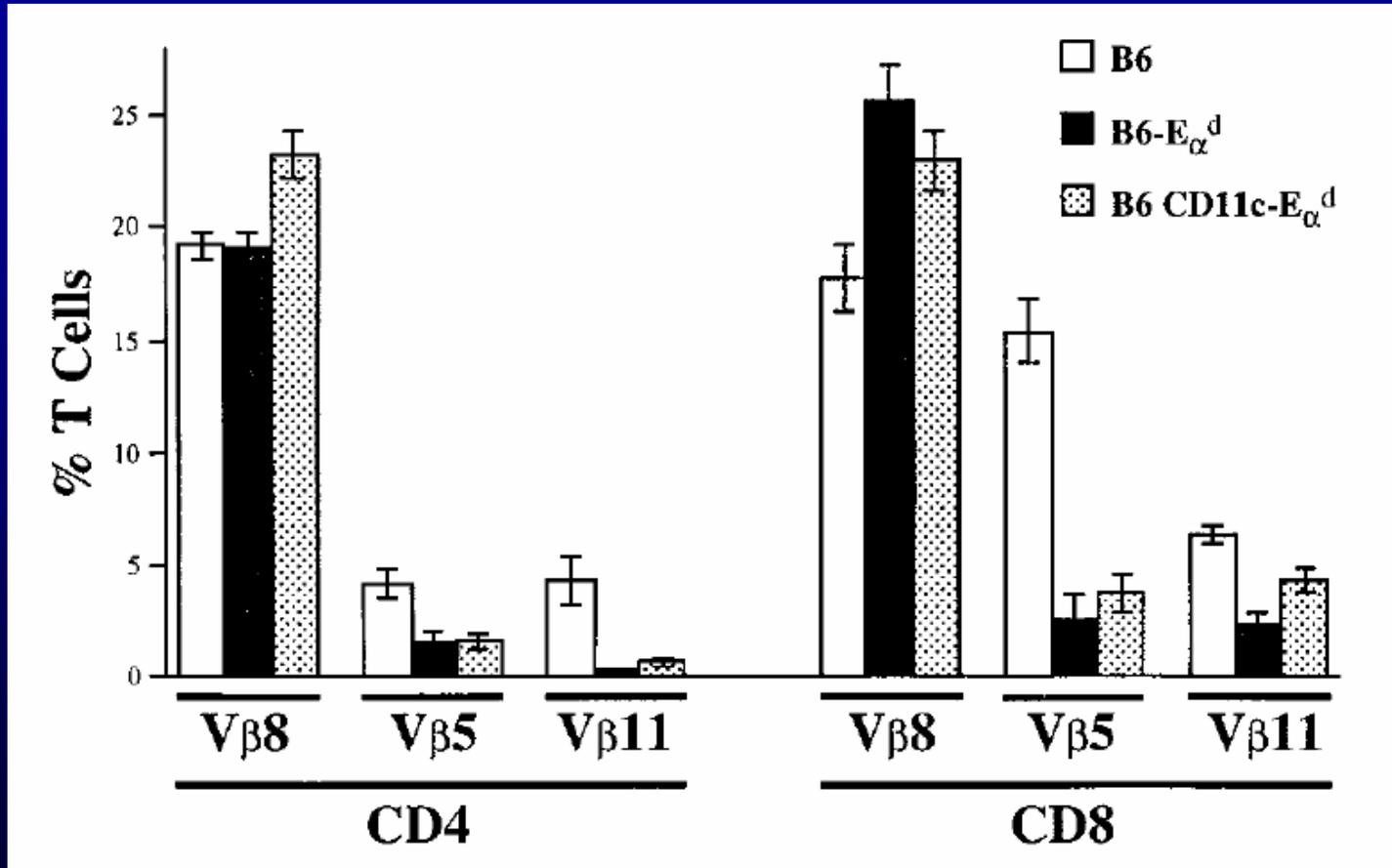
# Sélection négative & superantigène (7)



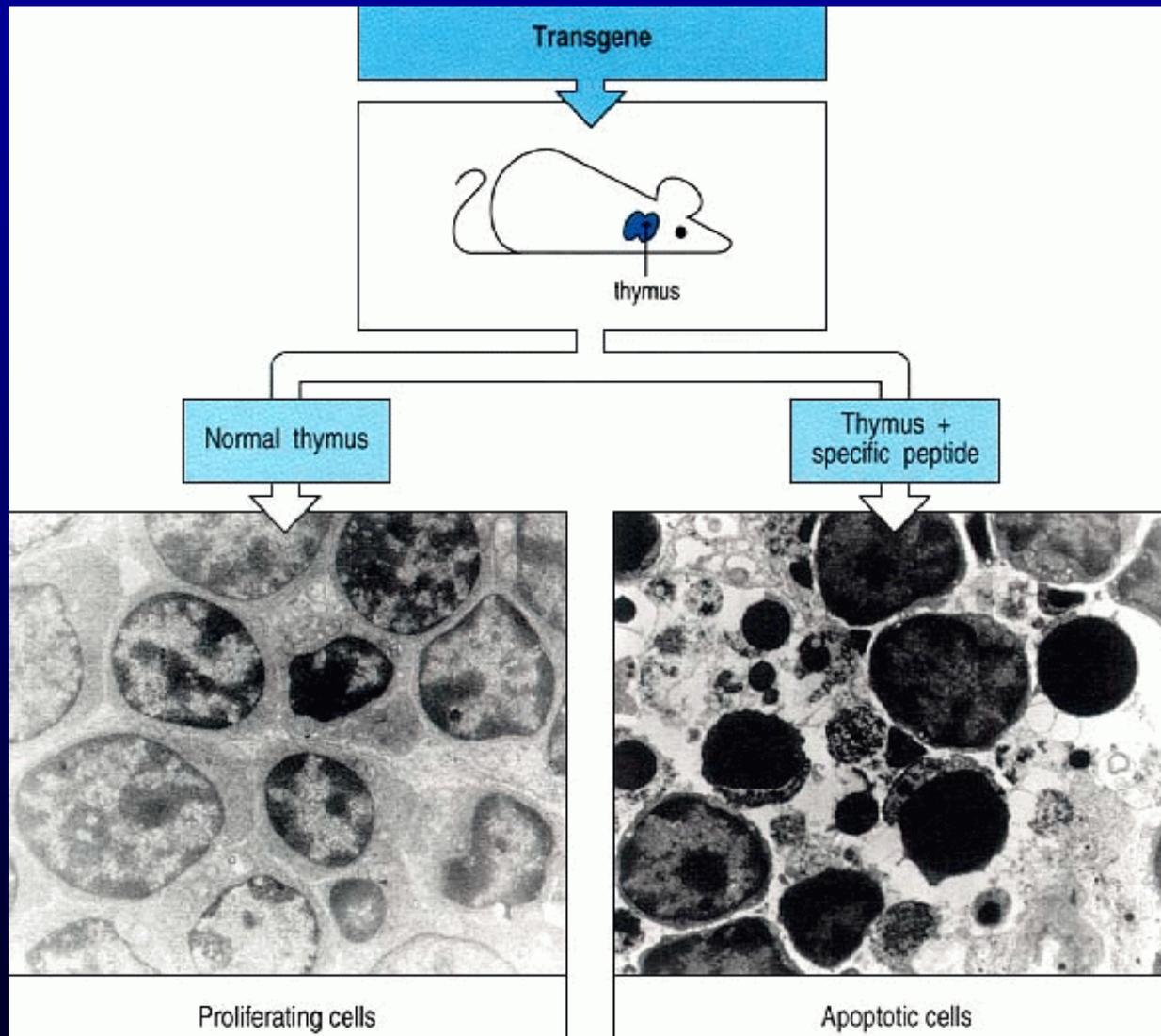
C57BL/6 H-2<sup>b</sup>  
BALB/c H-2<sup>d</sup>

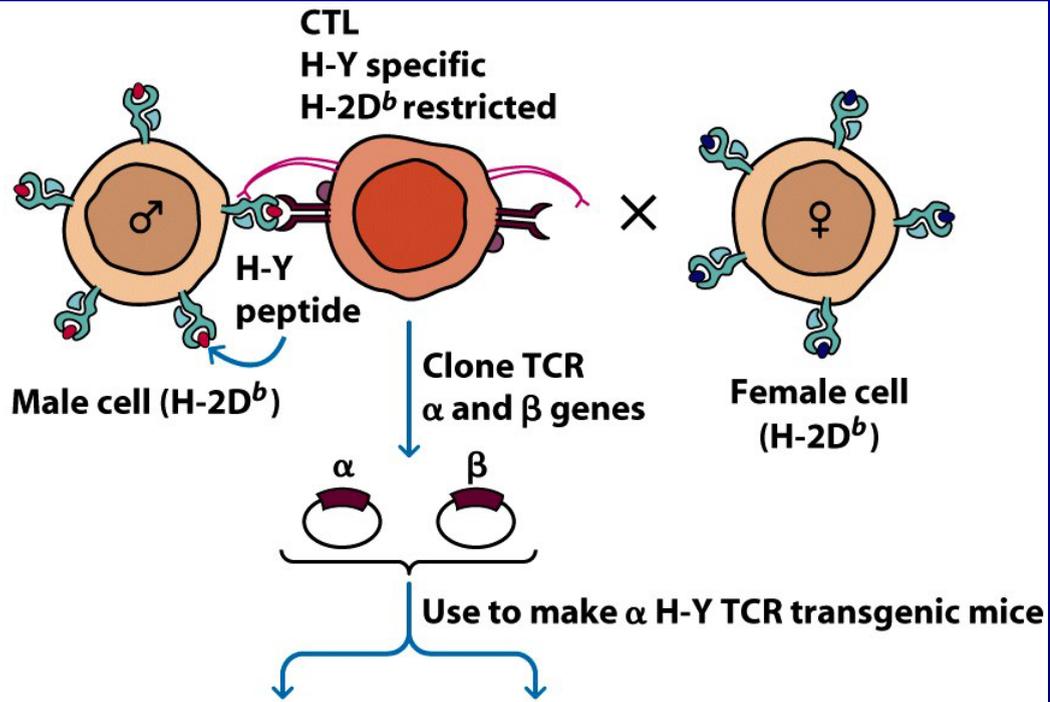


# Sélection négative & superantigène (8)



# Délétion clonale et TCR transgénique





	Male H-2D <sup>b</sup>	Female H-2D <sup>b</sup>
H-Y expression	+	-
<b>Thymocytes</b>		
CD4 <sup>-</sup> 8 <sup>-</sup>	++	+
CD4 <sup>+</sup> 8 <sup>+</sup>	+	++
CD4 <sup>+</sup>	+	+
CD8 <sup>+</sup>	-	++

Figure 10-8  
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# Sélection et TCR transgénique

**Selection in SCID mice transgenic for H-2D<sup>b</sup>/H-Y TCR**

Phenotype	Positive selection		Negative selection	
	Transgenic females		Transgenic H-2 <sup>b</sup>	
	H-2 <sup>b/d</sup>	H-2 <sup>d/d</sup>	Males	Females
CD4 <sup>-</sup> 8 <sup>-</sup> TCR <sup>-</sup>	+	++	+++	+
CD4 <sup>+</sup> 8 <sup>+</sup> TCR <sup>±</sup>	++	++	-	+++
CD4 <sup>-</sup> 8 <sup>+</sup> TCR <sup>++</sup>	+	-	-	+
CD4 <sup>+</sup> 8 <sup>-</sup> TCR <sup>++</sup>	-	-	-	-

## Experimental procedure—fetal thymic organ culture (FTOC)

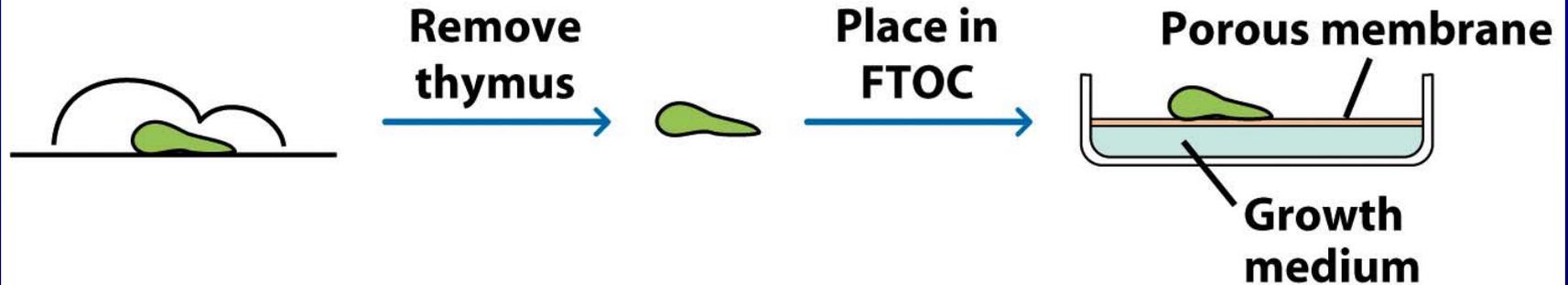


Figure 10-9a  
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# Development of CD8<sup>+</sup> CD4<sup>-</sup> MHC I-restricted cells

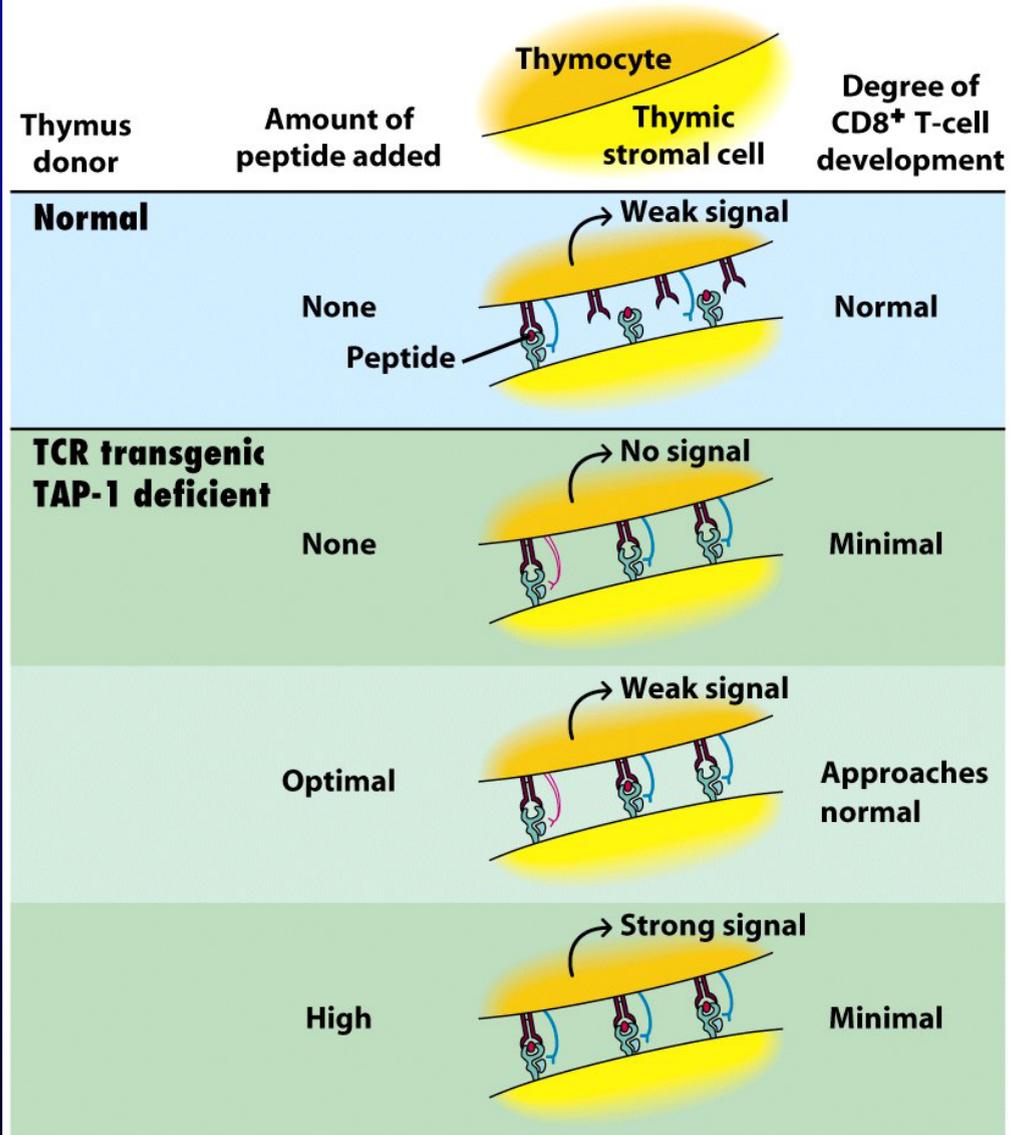
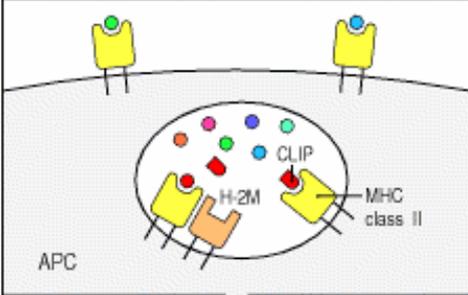
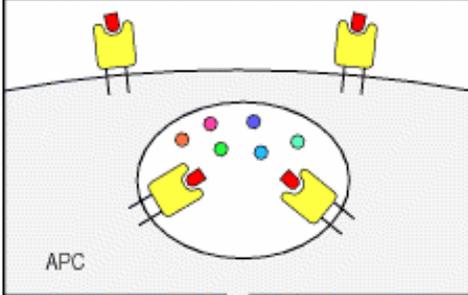


Figure 10-9b  
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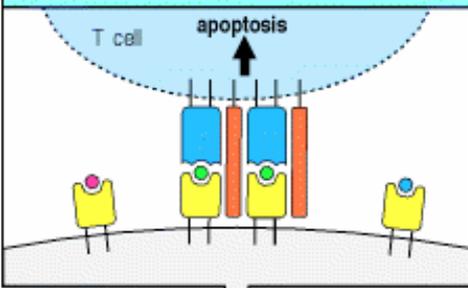
In normal APC, H-2M catalyzes the dissociation of the invariant chain fragment, CLIP, and the binding of other peptides



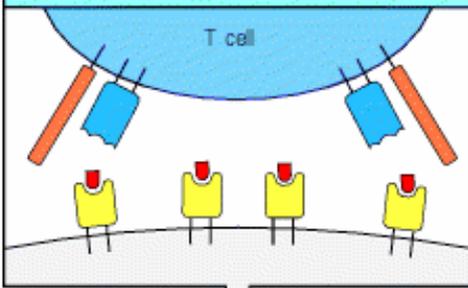
In H-2M-deficient animals, CLIP is not removed and other peptides do not bind



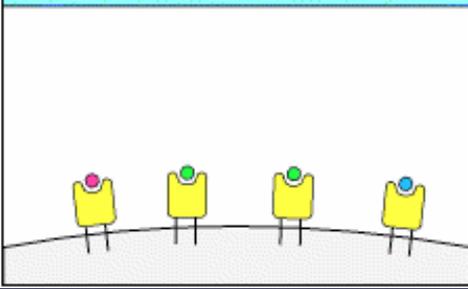
T cells recognizing self peptides are deleted during thymic development



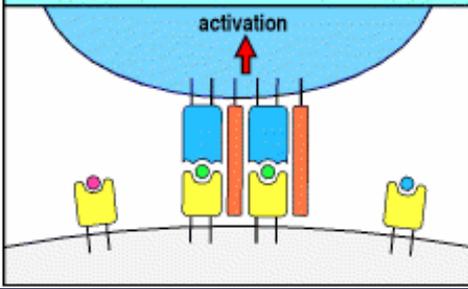
T cells specific for self peptides other than CLIP are not deleted



T cells from normal animals do not respond to their own uninfected APCs



T cells of H-2M-deficient animals make a strong response to self peptides presented by normal uninfected APCs



# Peptides agonistes, antagonistes (1)

Peptide ligand altéré (APL)

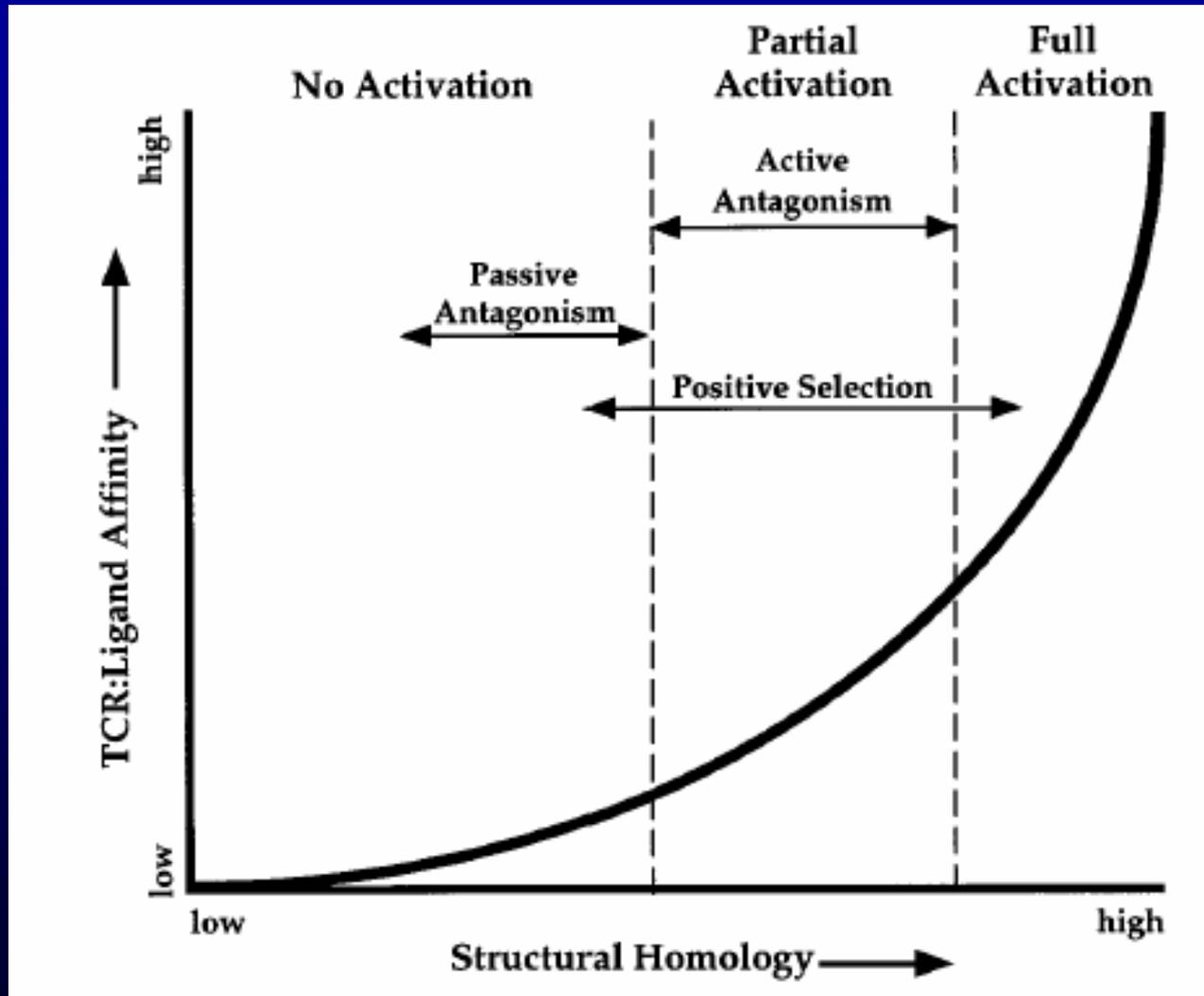
= peptide analogue d'un peptide immunogène

Agoniste → Conserve certaines fonctions d'activation

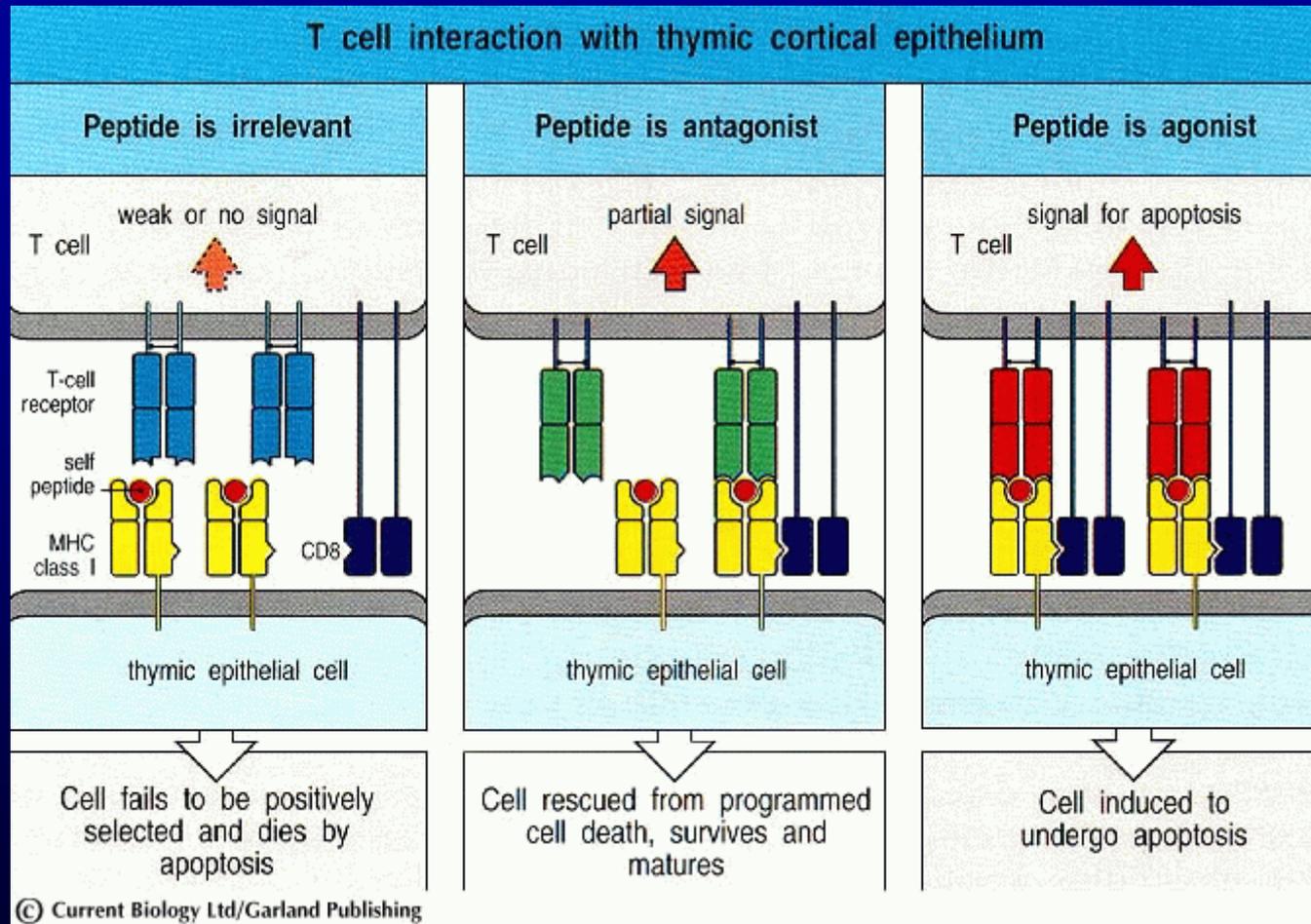
Antagoniste passif → Compétition pour le CMH

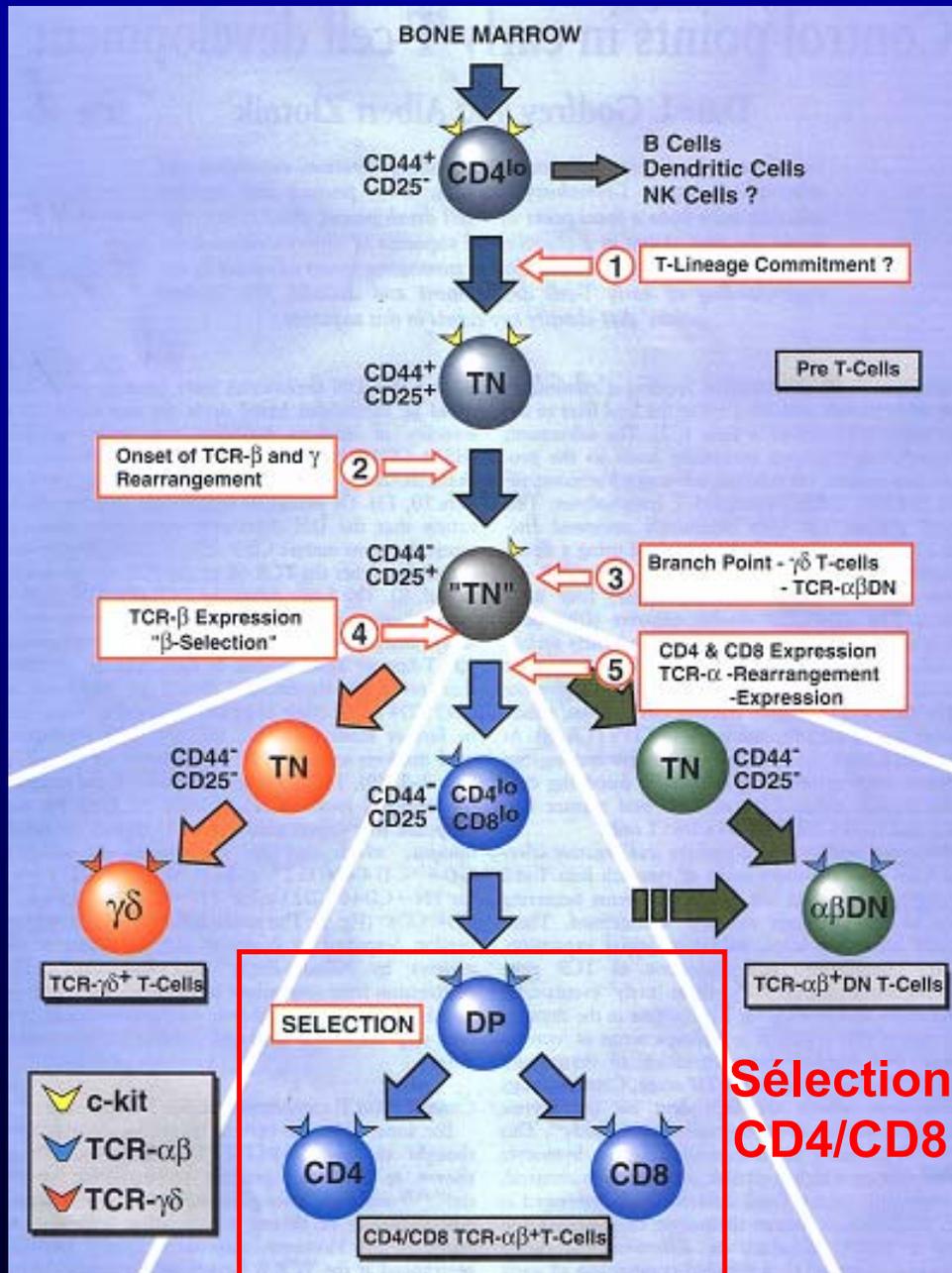
Antagoniste actif → induction d'anergie, modification de la cascade d'activation

# Peptides agonistes, antagonistes (2)



# Peptides agonistes, antagonistes (3)

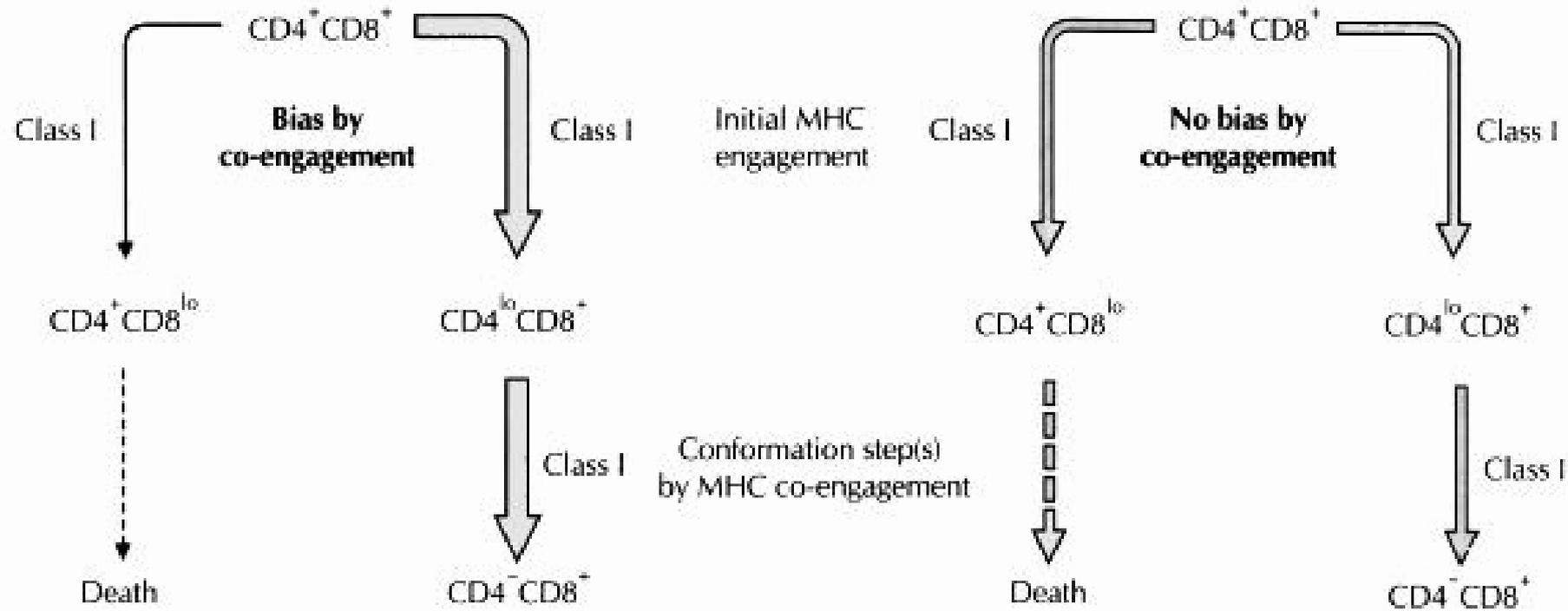




# Sélection CD8/CMHI & CD4/CMHII (1)

(a) Instruction

(b) Stochastic



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# Sélection CD8/CMHI & CD4/CMHII (2)

## INSTRUCTIVE MODEL

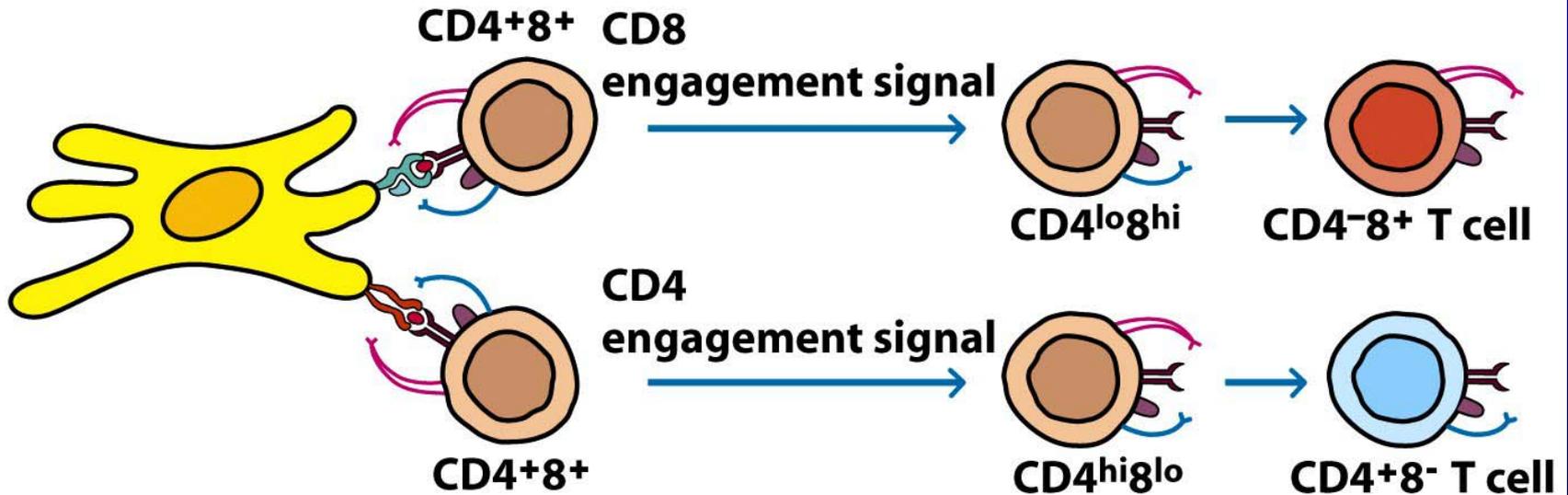


Figure 10-10 part 1  
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# Sélection CD8/CMHI & CD4/CMHII (3)

## STOCHASTIC MODEL

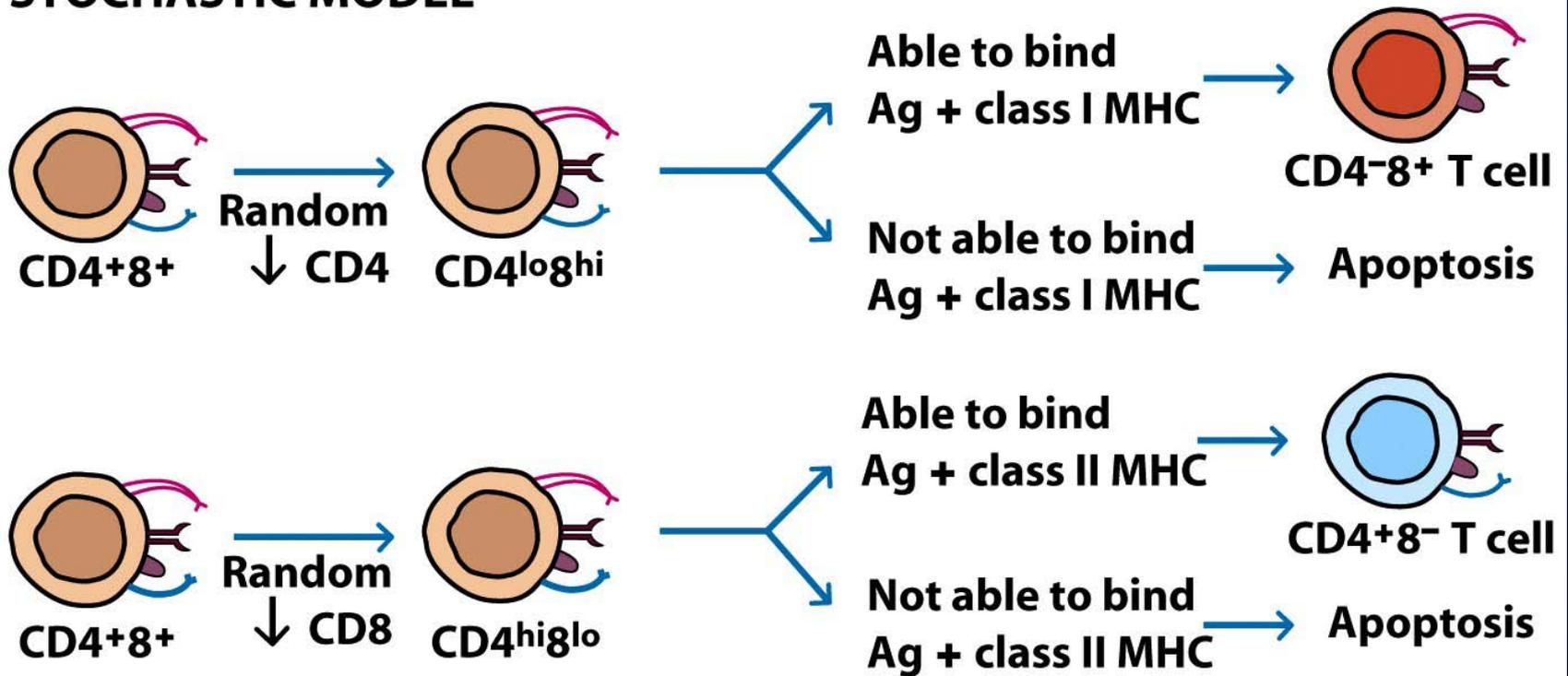
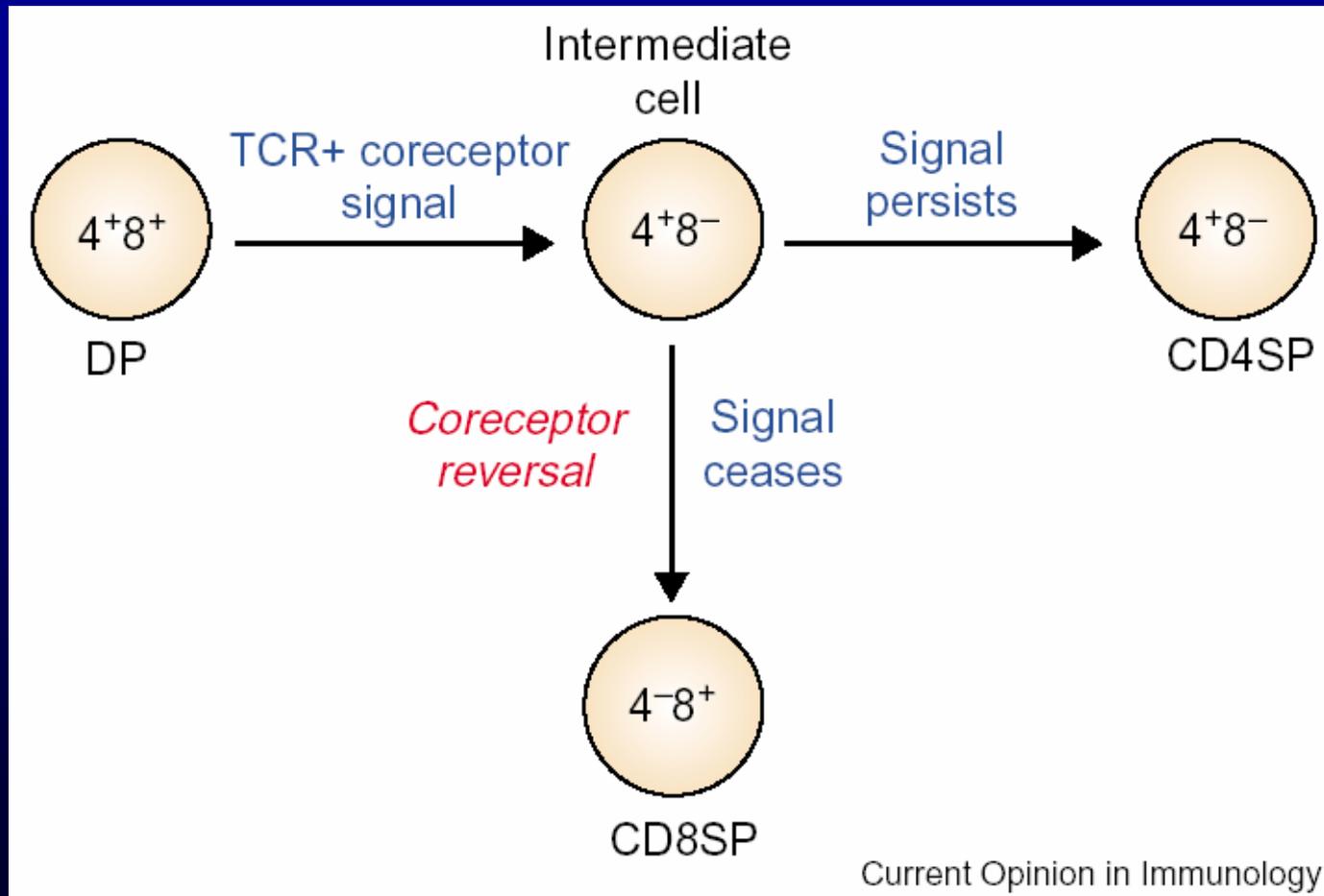


Figure 10-10 part 2  
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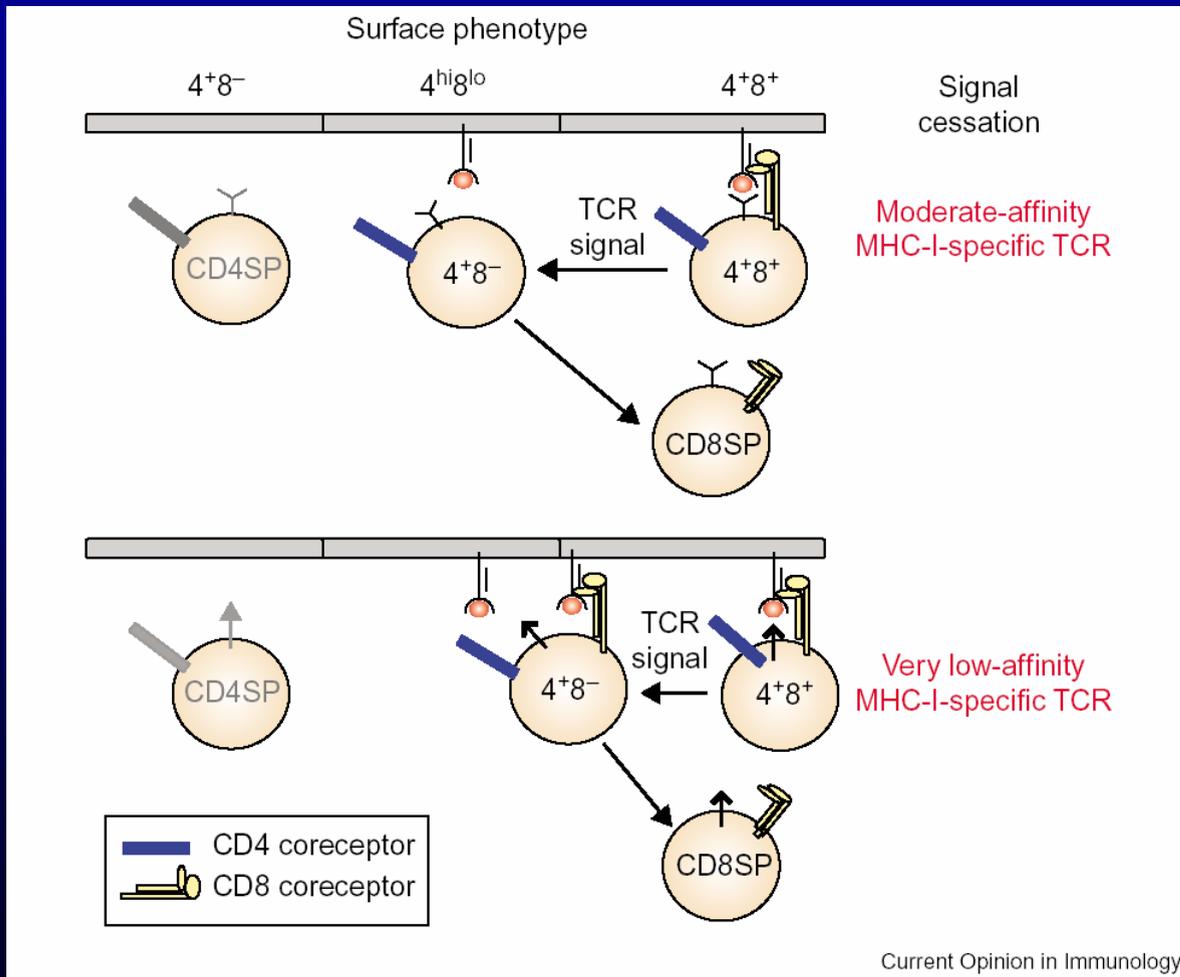
# Sélection CD8/CMHI & CD4/CMHII (4)

Modèle cinétique d'engagement CD4/CD8



# Sélection CD8/CMHI & CD4/CMHII (5)

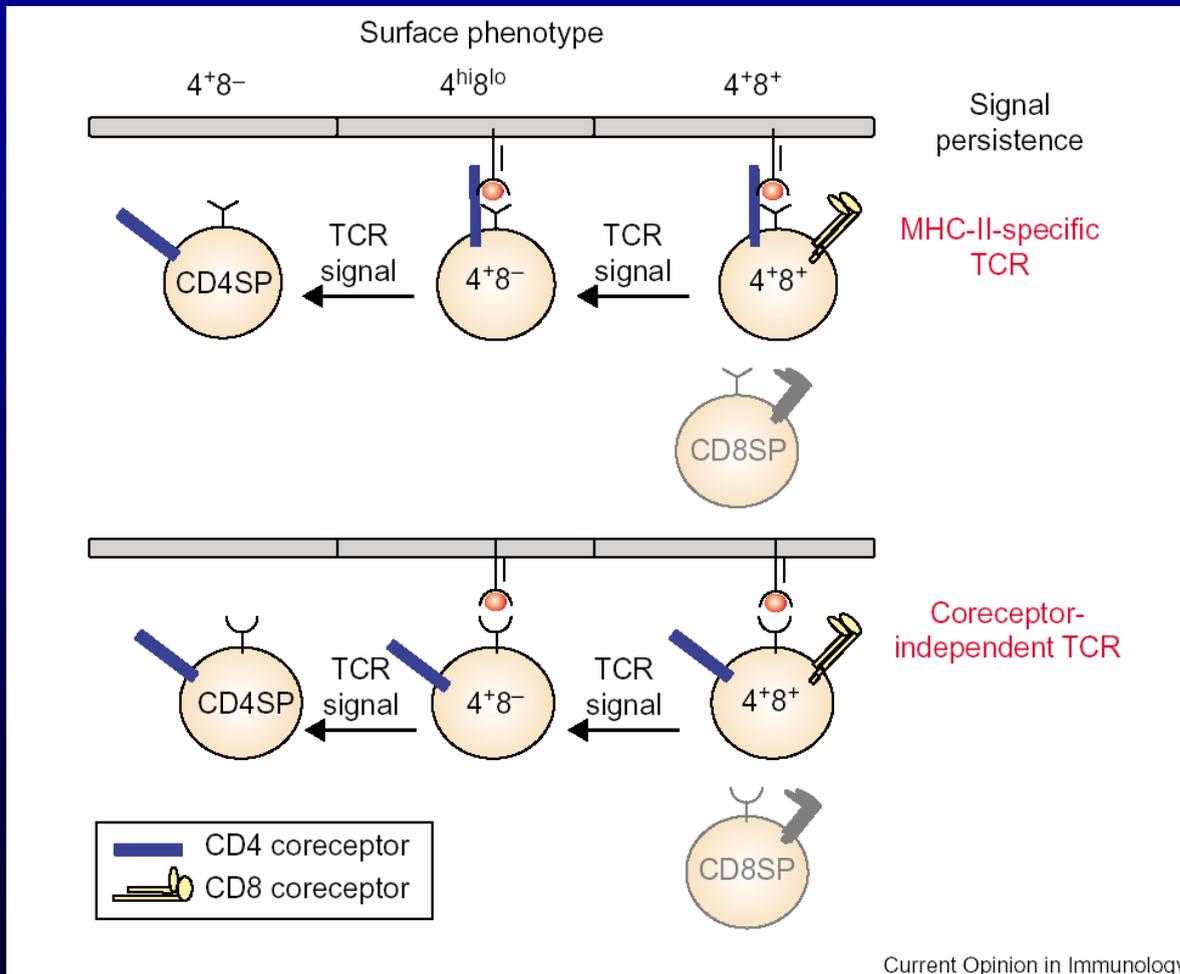
## Modèle cinétique d'engagement CD4/CD8



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

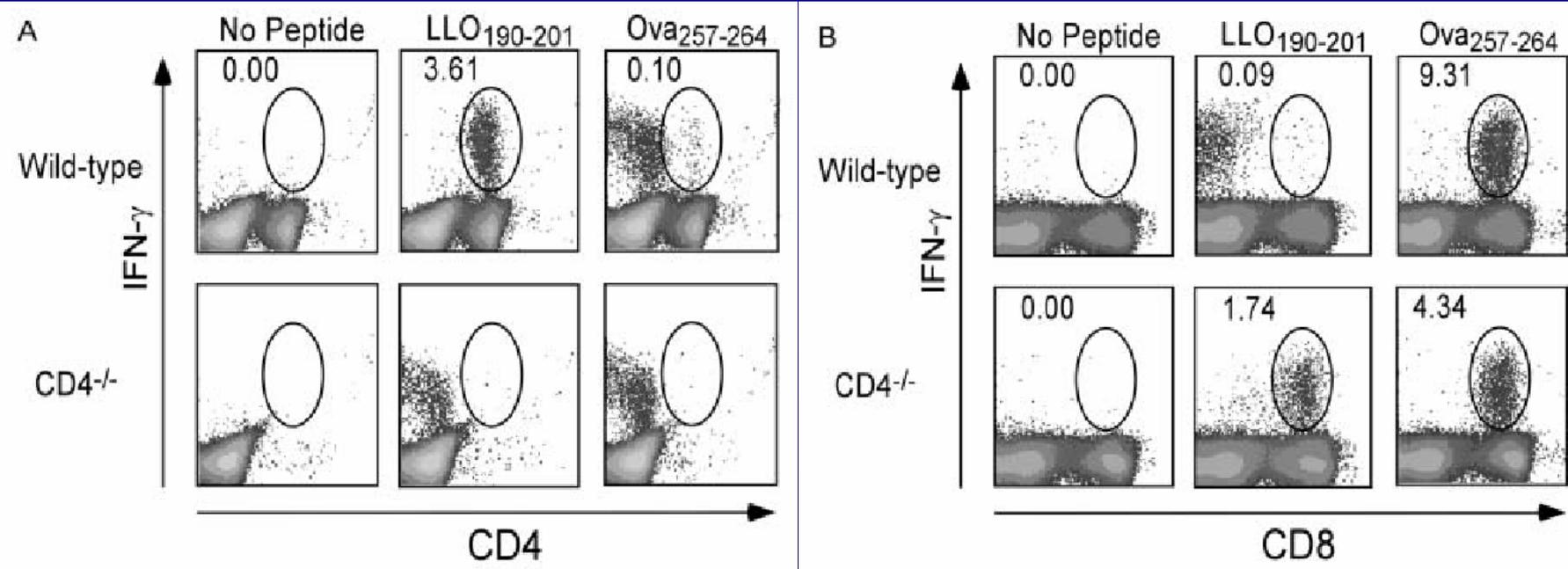
# Sélection CD8/CMHI & CD4/CMHII (6)

## Modèle cinétique d'engagement CD4/CD8



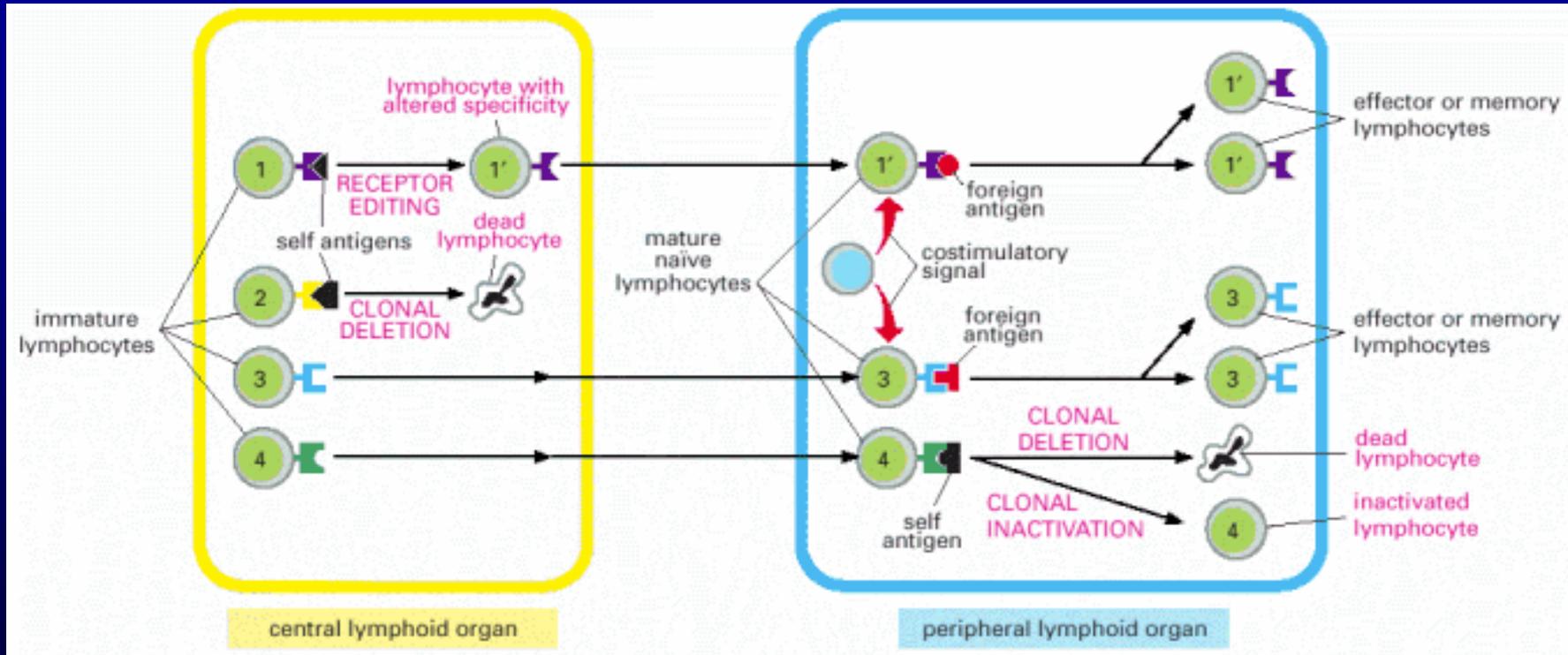
Un signal persistant promeut la différenciation en lymphocyte T CD4SP

# Sélection CD8/CMHI & CD4/CMHII (7)



# Conclusion

# Sélections centrale et périphérique



# 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***.

# 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.