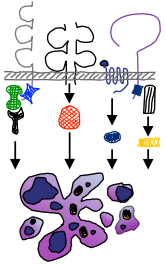


LABORATÓRIO DE BIOLOGIA CELULAR E MOLECULAR
Instituto de Ciências Biomédicas
Universidade de São Paulo

50 ANOS ICB USP

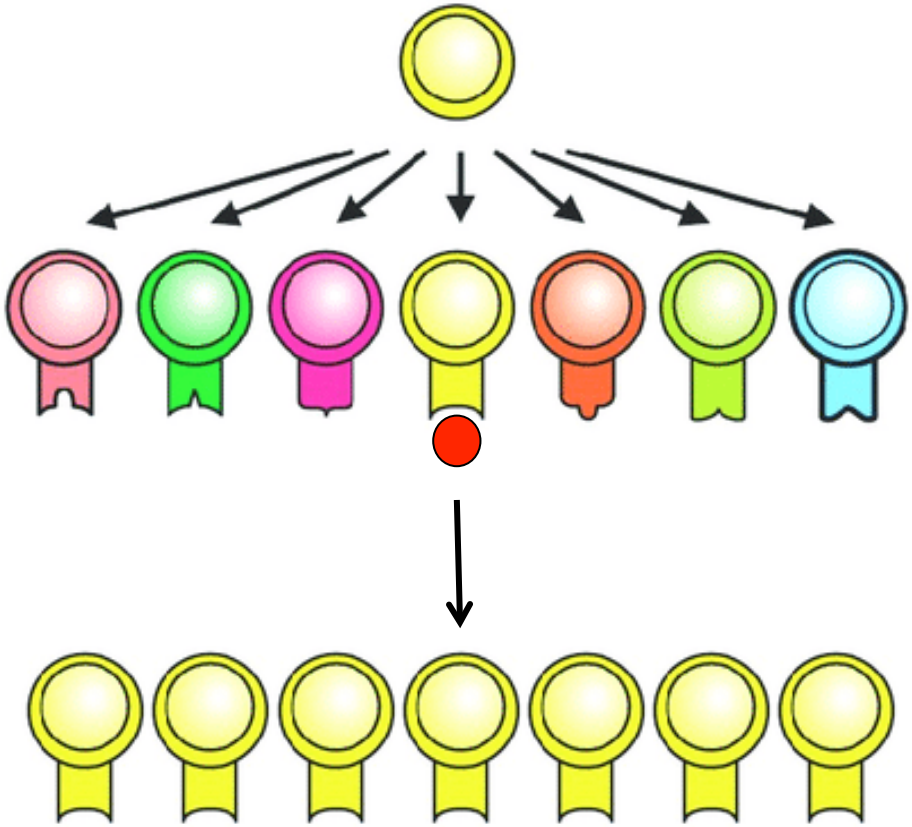
Estrutura do MHC, processamento e apresentação de antígenos

Prof. Dr. Gustavo P. Amarante-Mendes

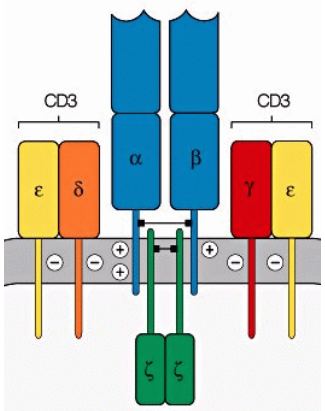
Nutrição 2020

Estratégia de reconhecimento pela Imunidade Adaptativa

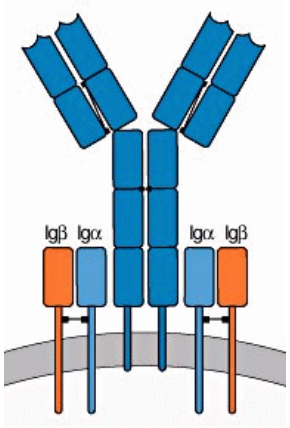
- Altíssima especificidade – reconhece "particularidades"
- Distribuição clonal



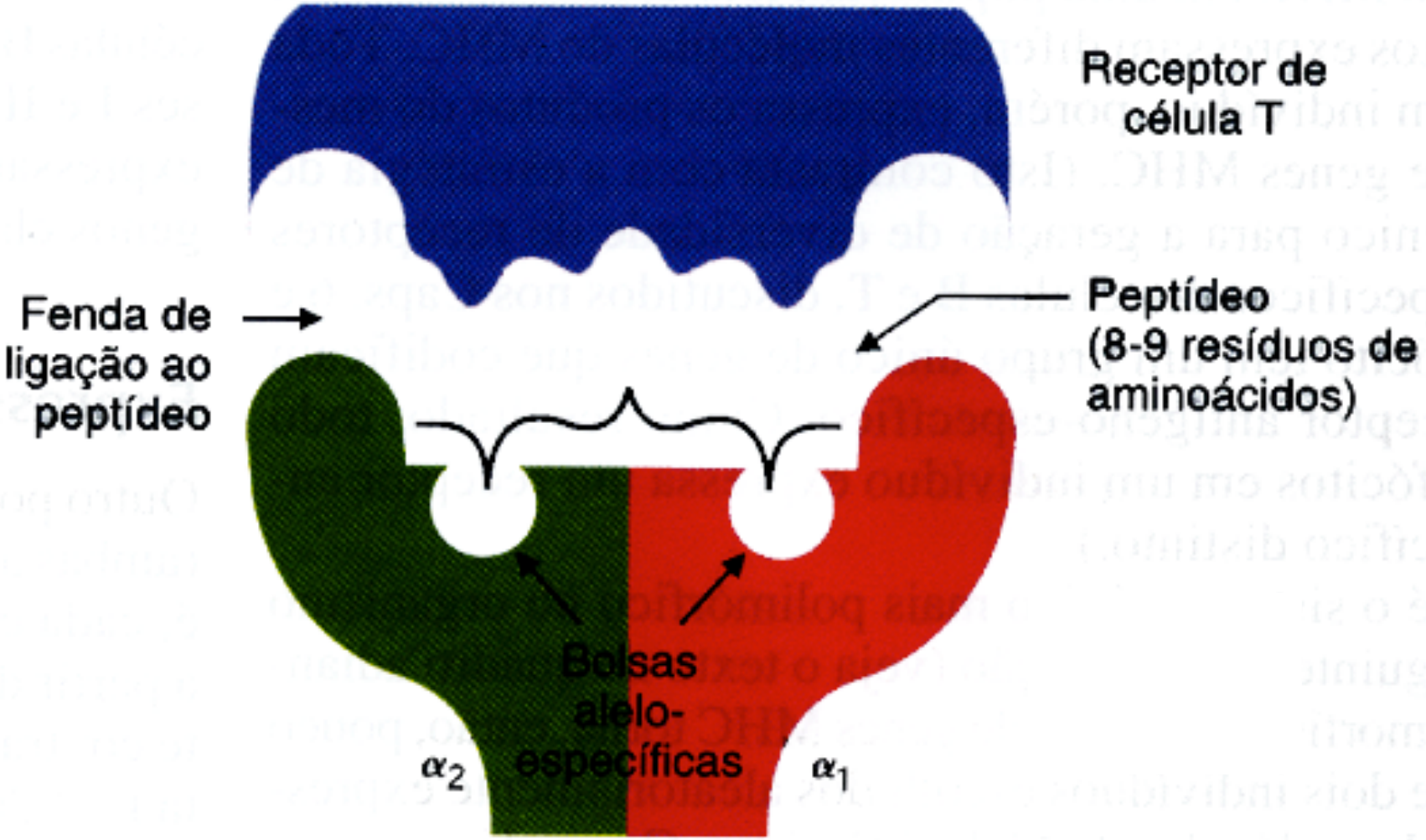
TCR



BCR

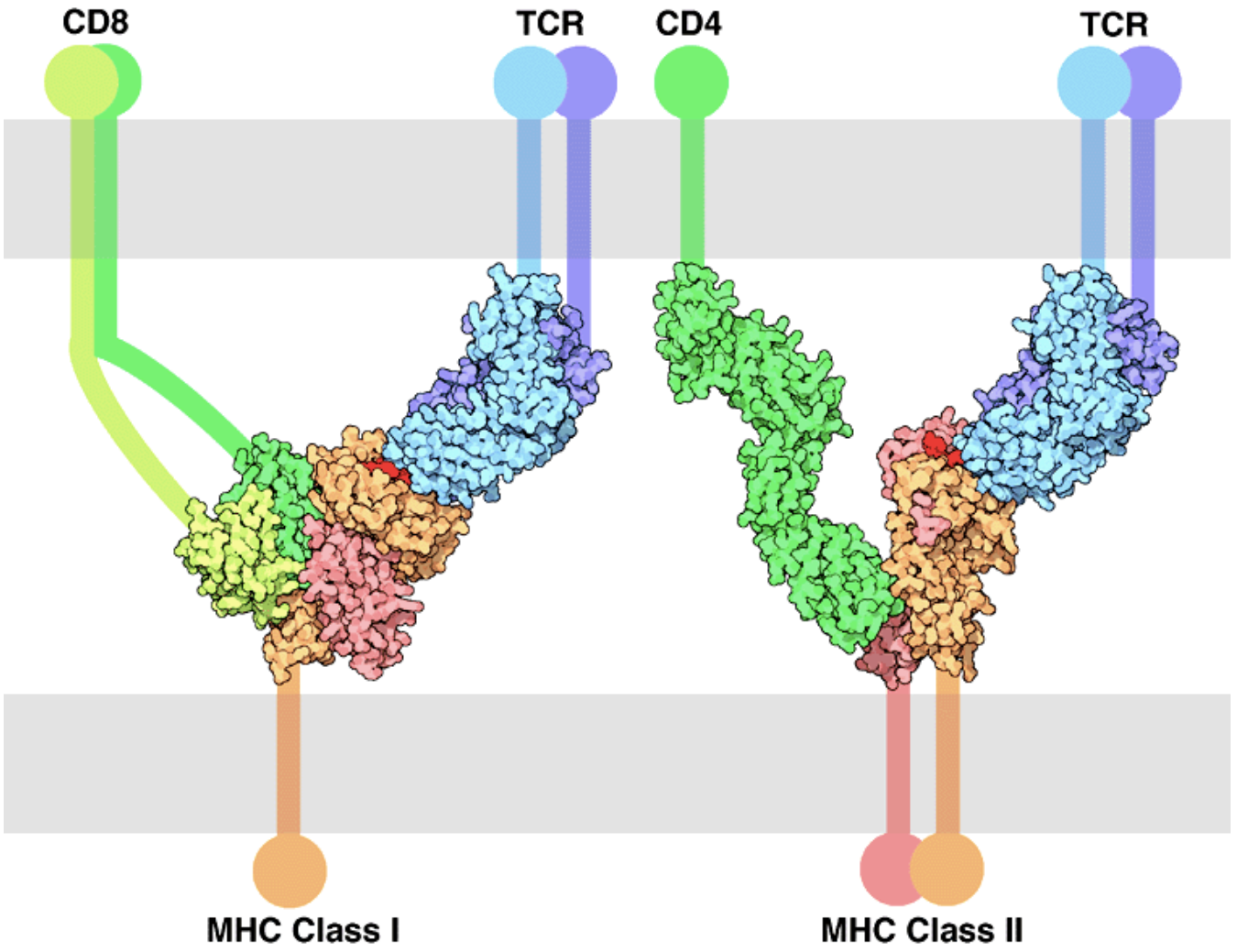


Interação TCR-MHC+peptídeo



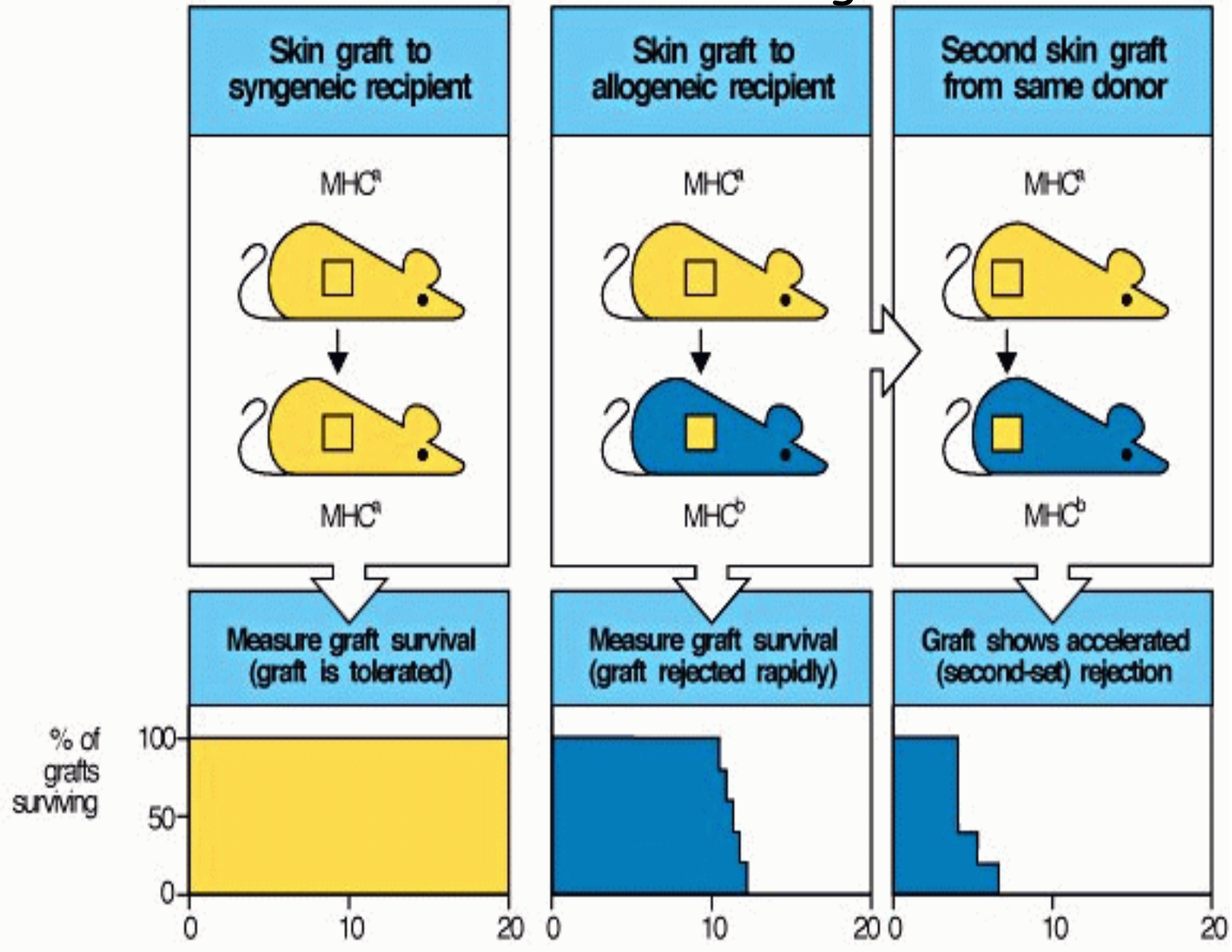
Interação TCR-MHC+peptídeo

Receptores e Co-receptores

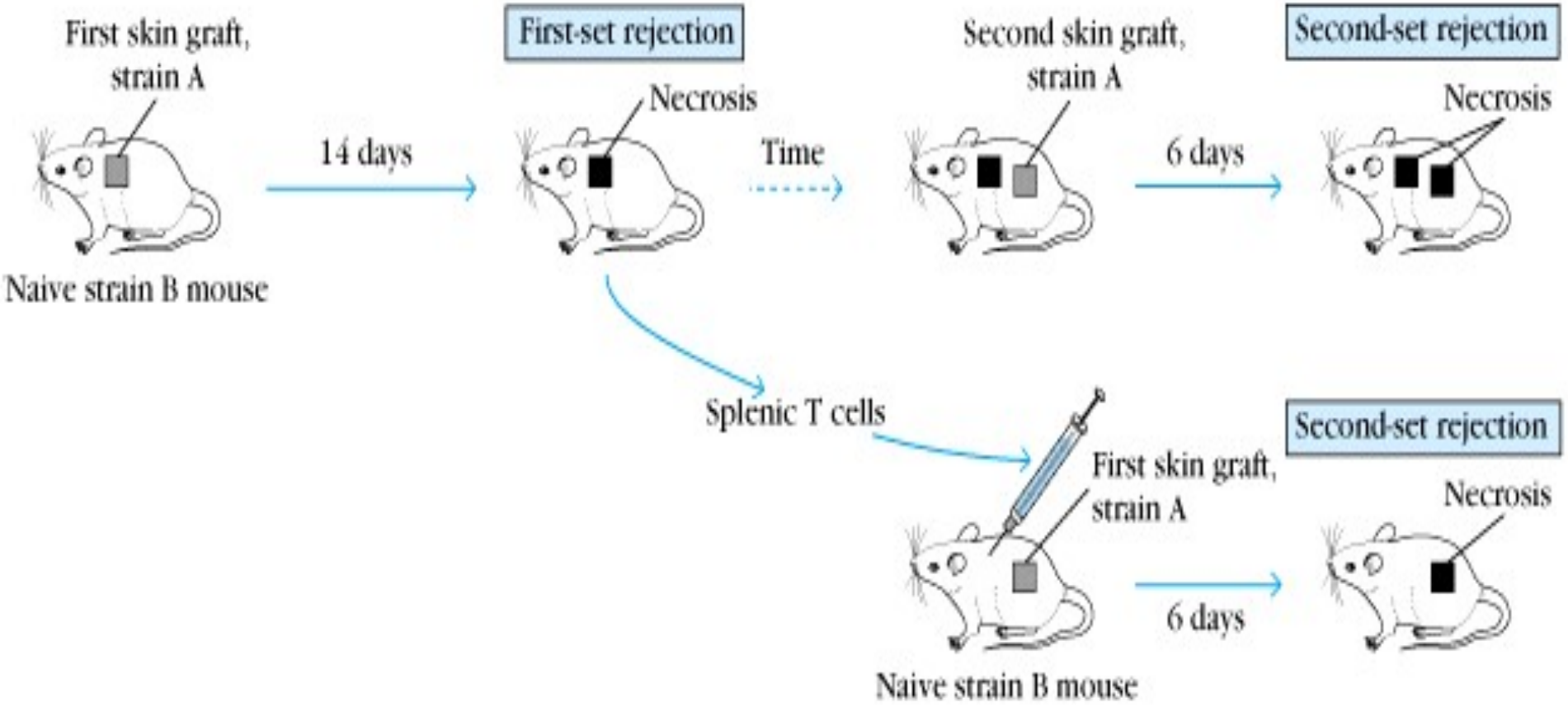


HISTOCOMPATIBILIDADE

Peter Gorer (1930s) and George Snell (1940-50s)



Linfócitos T “transferem” rejeição



Rejeição de transplantes

Resposta Imune Adaptativa

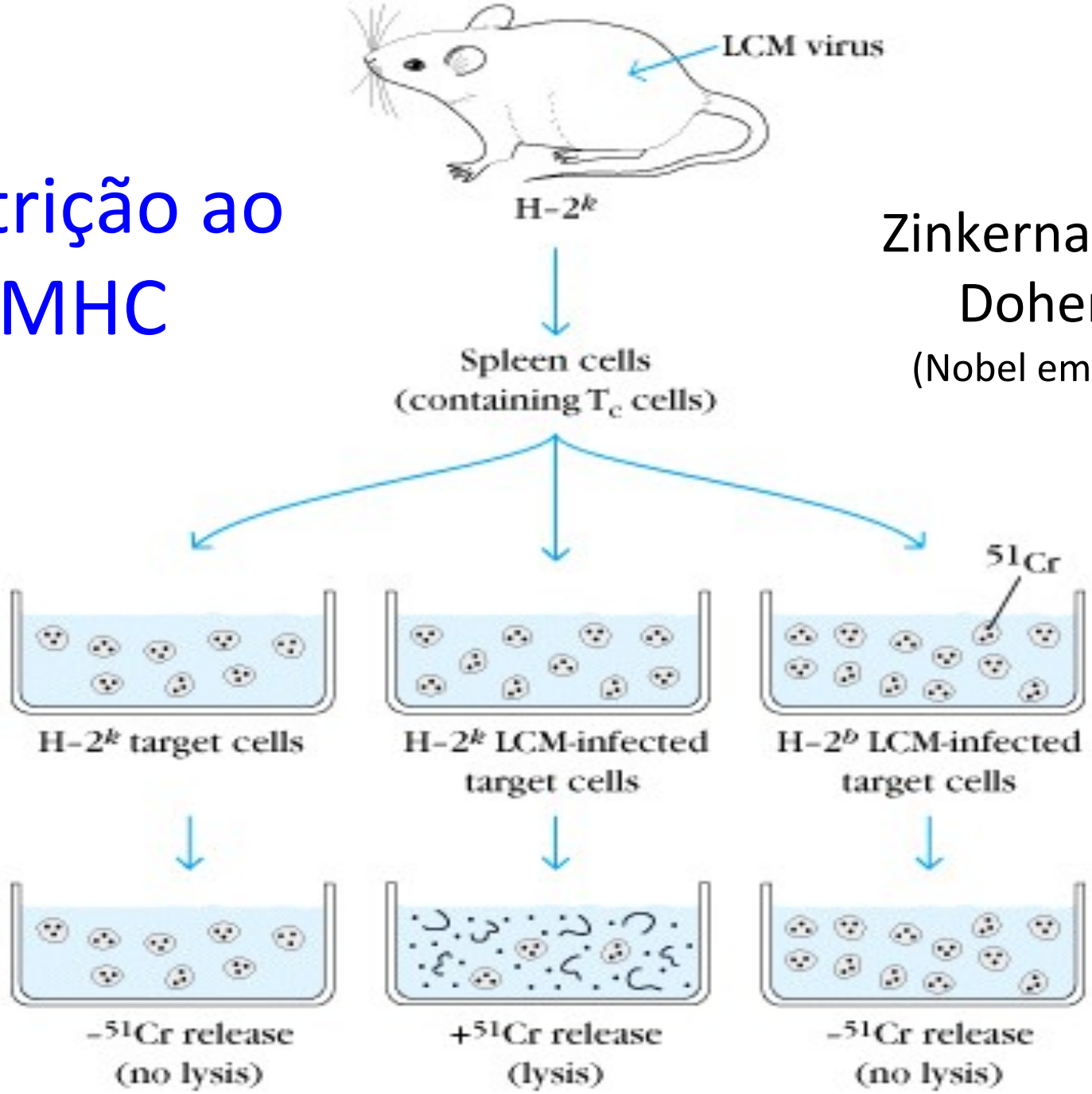
Mediada por linfócitos T

Contra aloantígenos
(sobretudo o MHC)

Restrição ao MHC

Zinkernagel & Doherty

(Nobel em 1996)



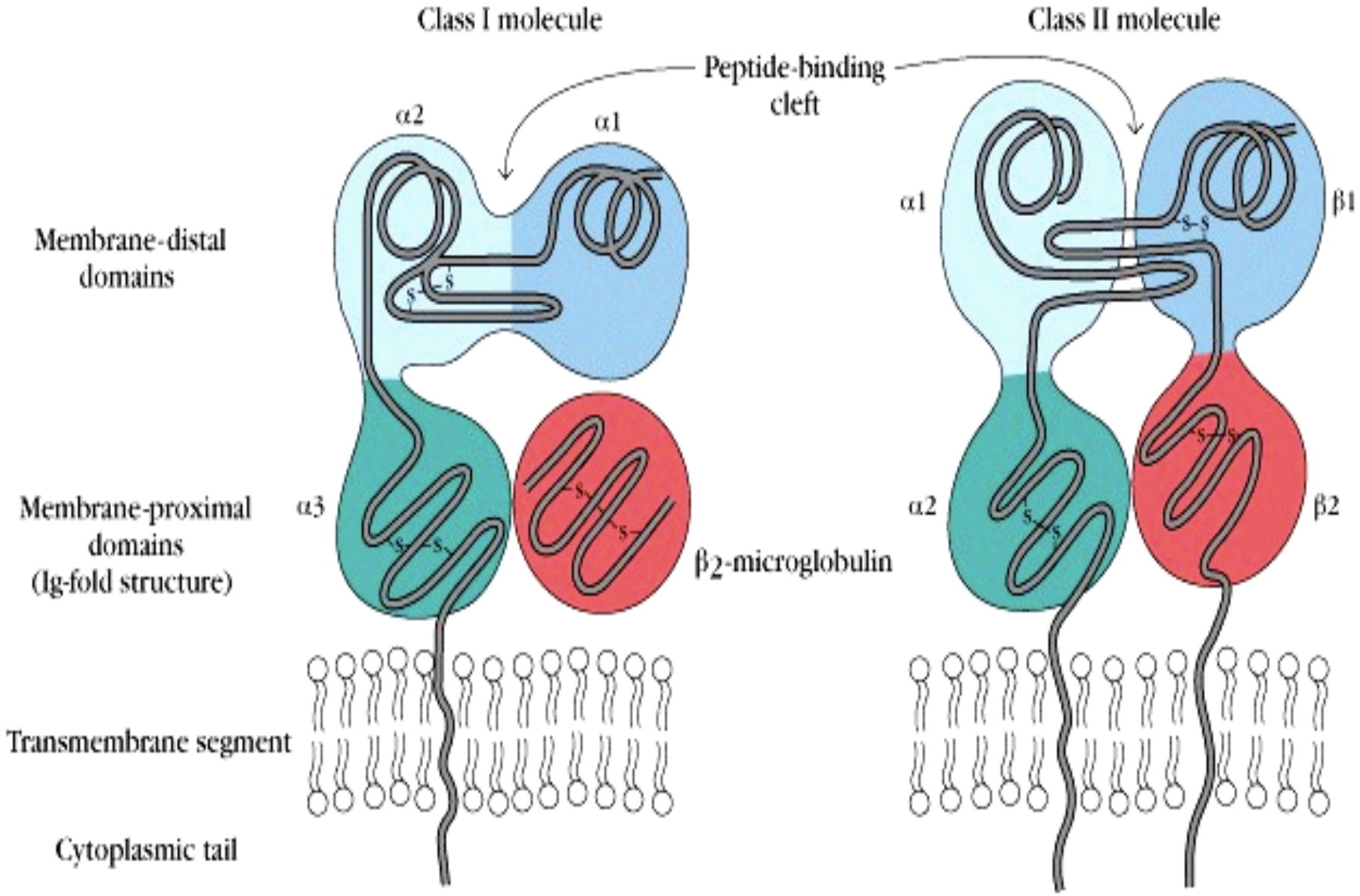
Características das moléculas do MHC

Proteínas Altamente Polimórficas

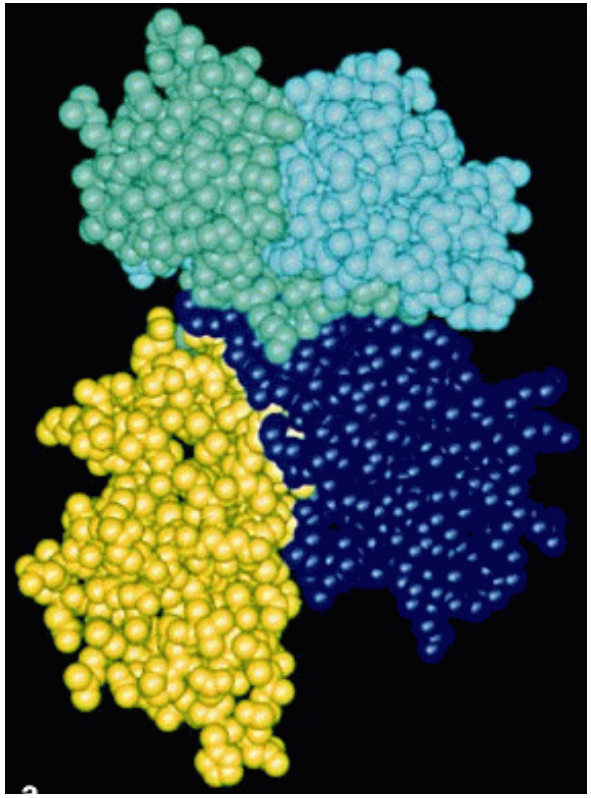
Sistema Poligênico

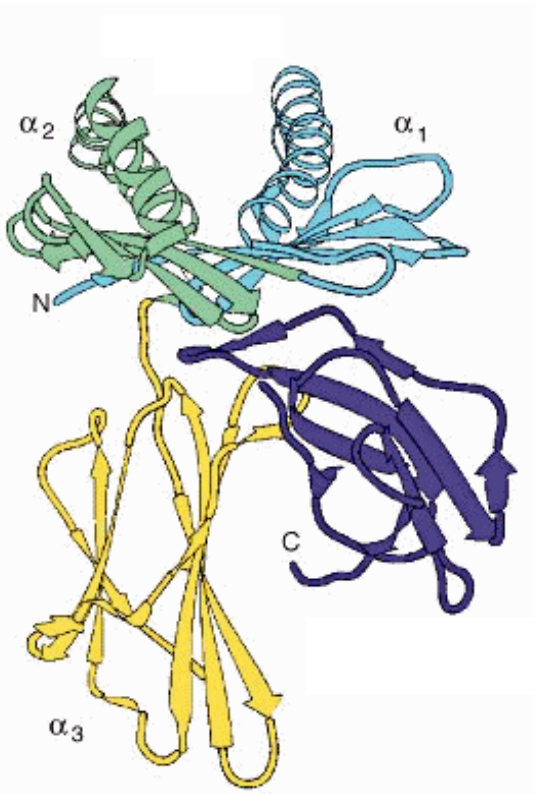
Expressão co-dominante

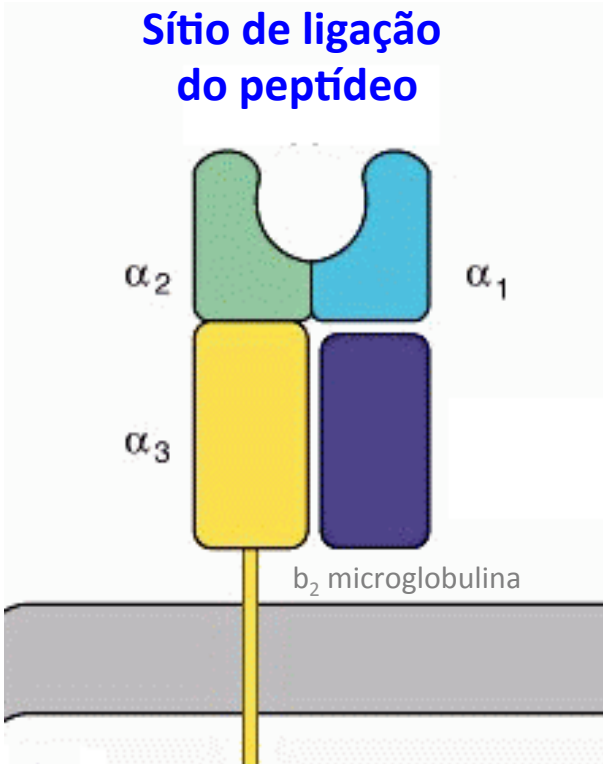
Herdadas em blocos (“HAPLÓTIPOS”)


Class I molecule
Class II molecule
Peptide-binding cleft
α2
α1
α1
β1
Membrane-distal domains
Membrane-proximal domains (Ig-fold structure)
α3
α2
β2
β2-microglobulin
Transmembrane segment
Cytoplasmic tail

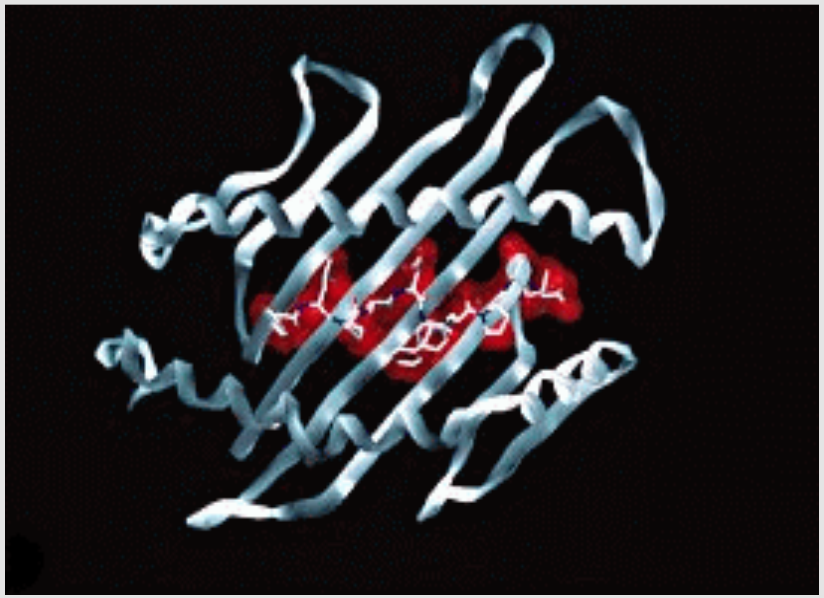
Estrutura da molécula de MHC classe I

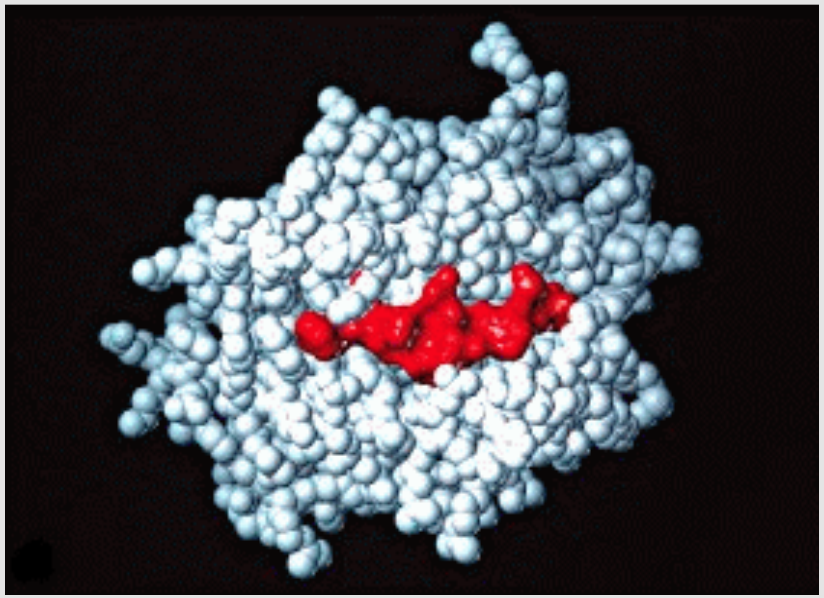


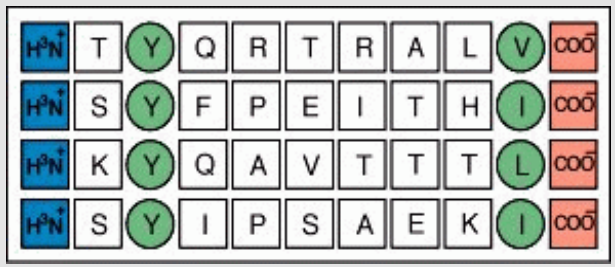




Ligação do peptídeo à molécula de MHC classe I







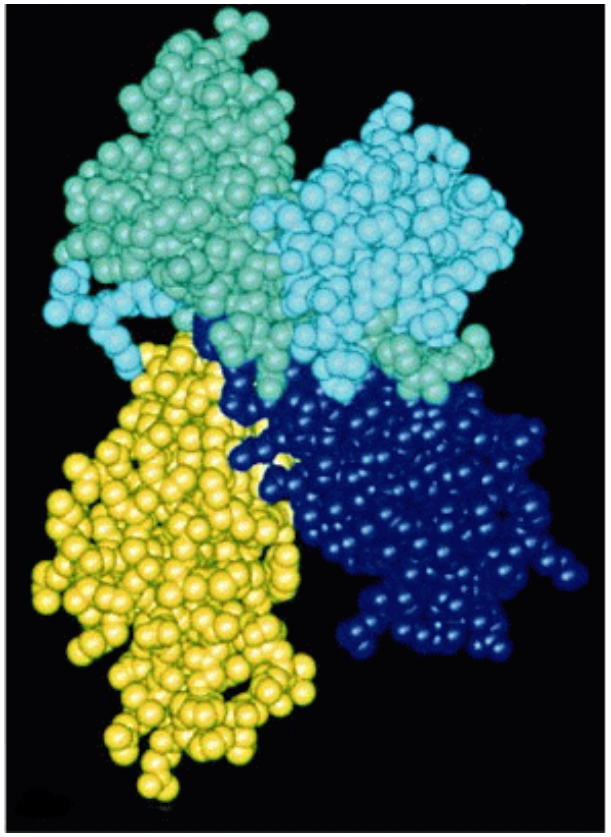
8-10 aa

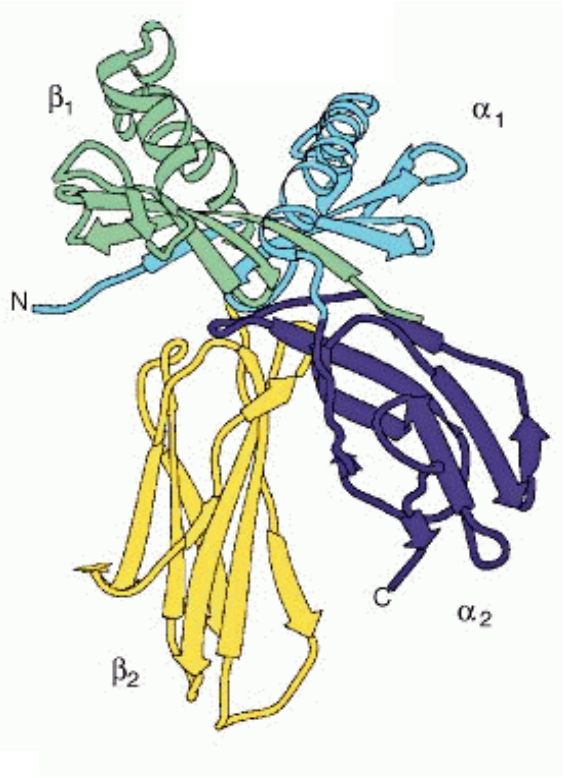
Ligam ~ 2000 peptídeos

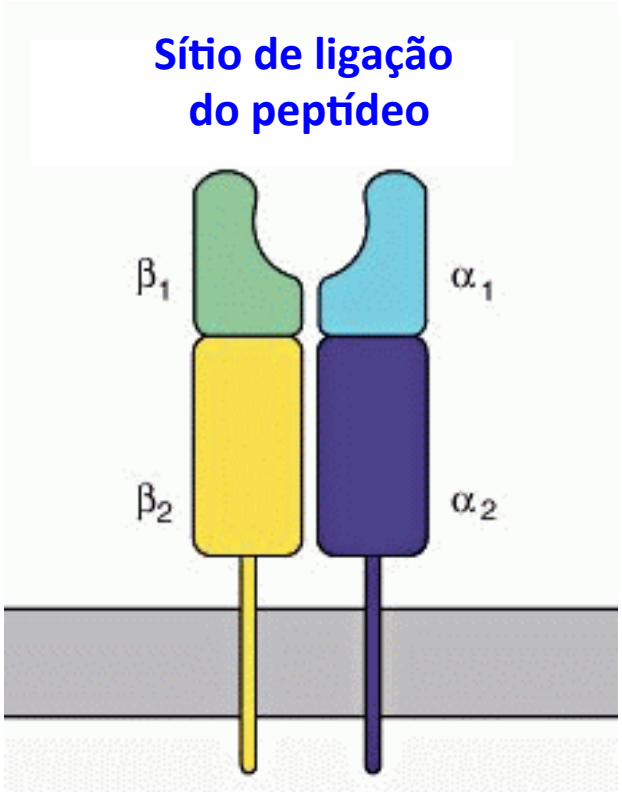
10^5 de cada variante alélica por célula

apresentação ~ 100-4000 cópias

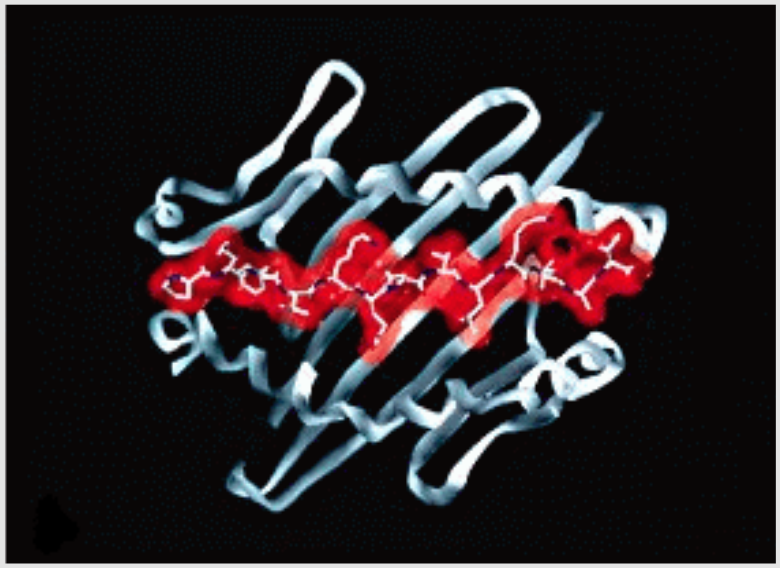
Estrutura da molécula de MHC classe II

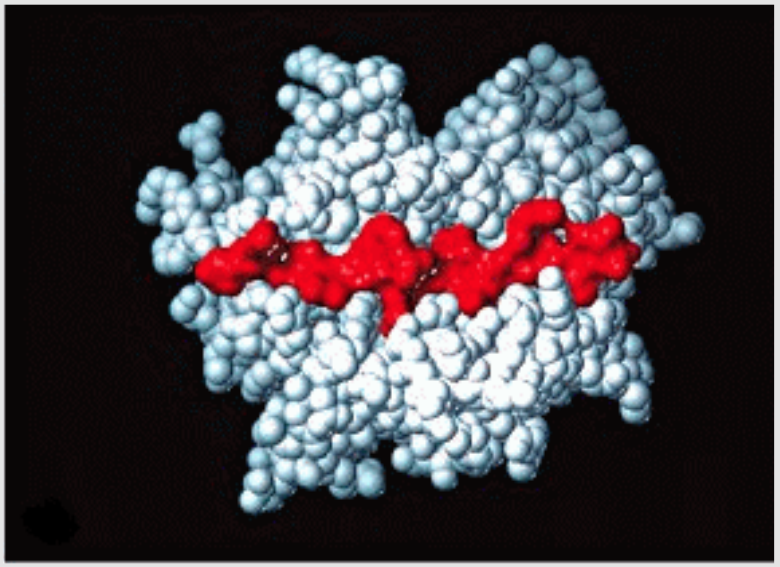


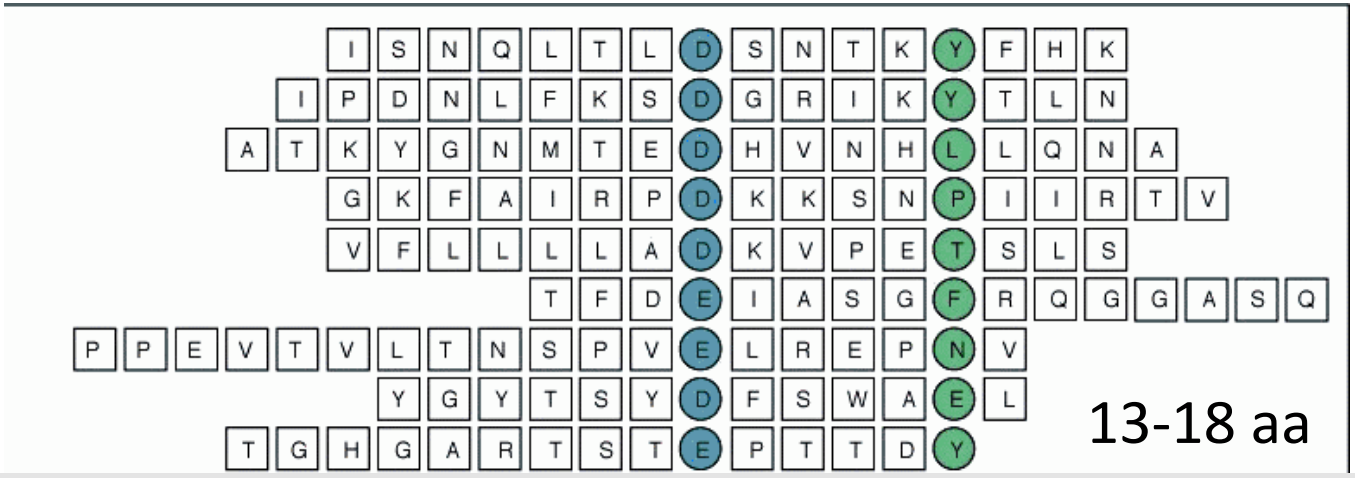




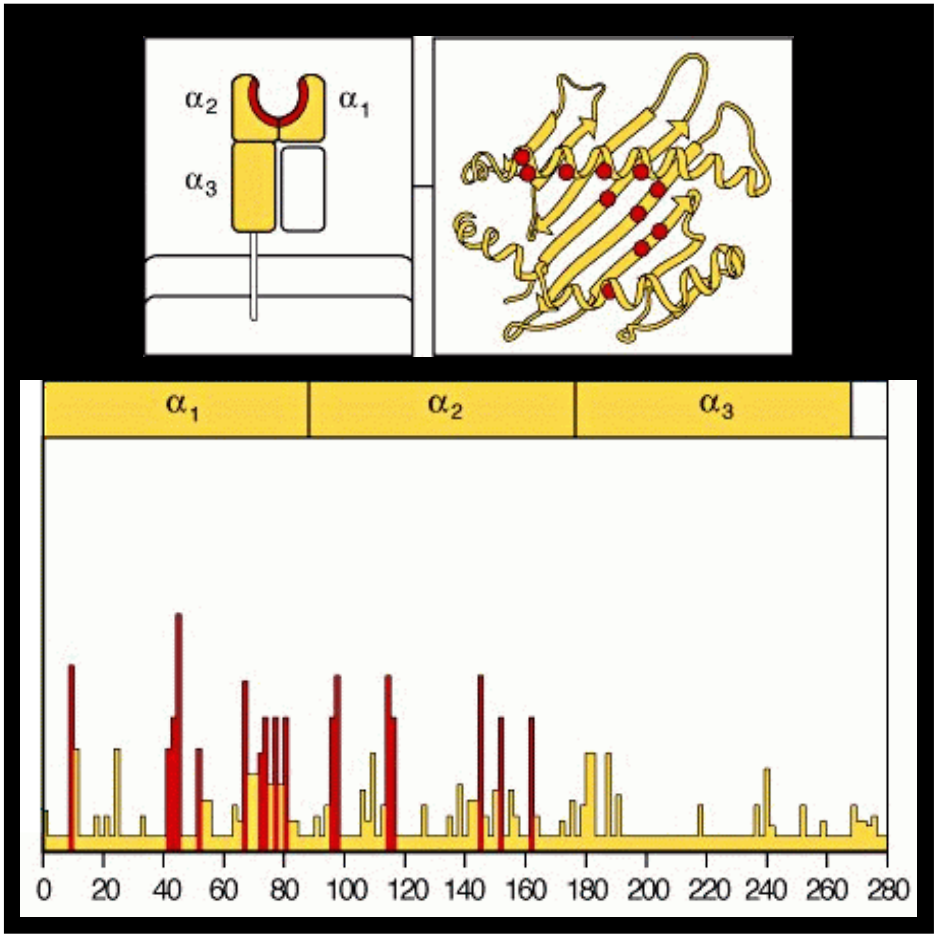
Ligação do peptídeo à molécula de MHC classe II



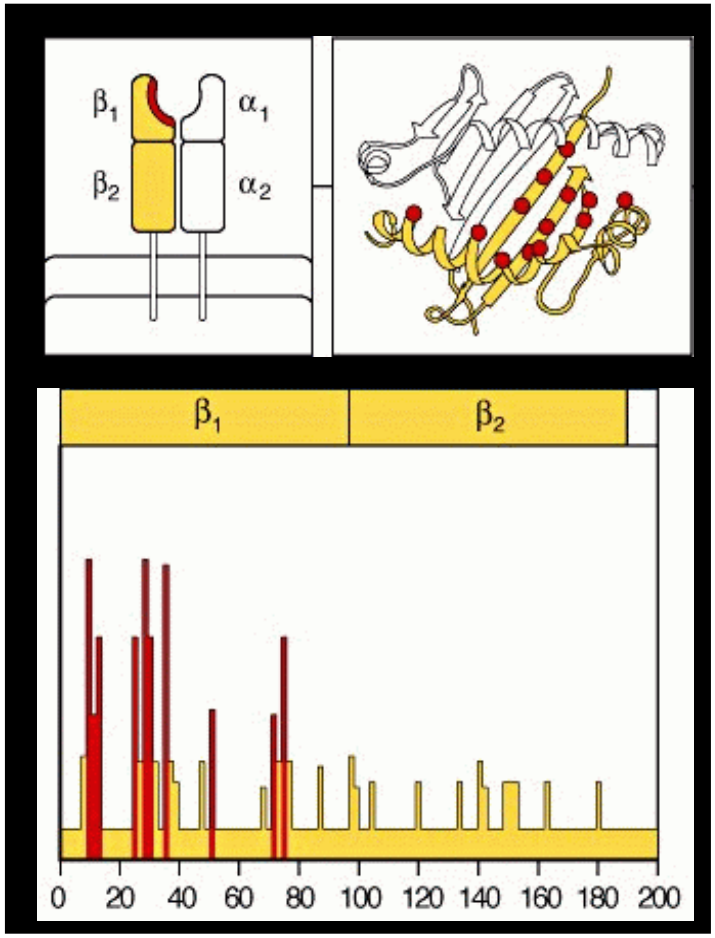




Localização da variação alélica



Molécula de MHC classe I



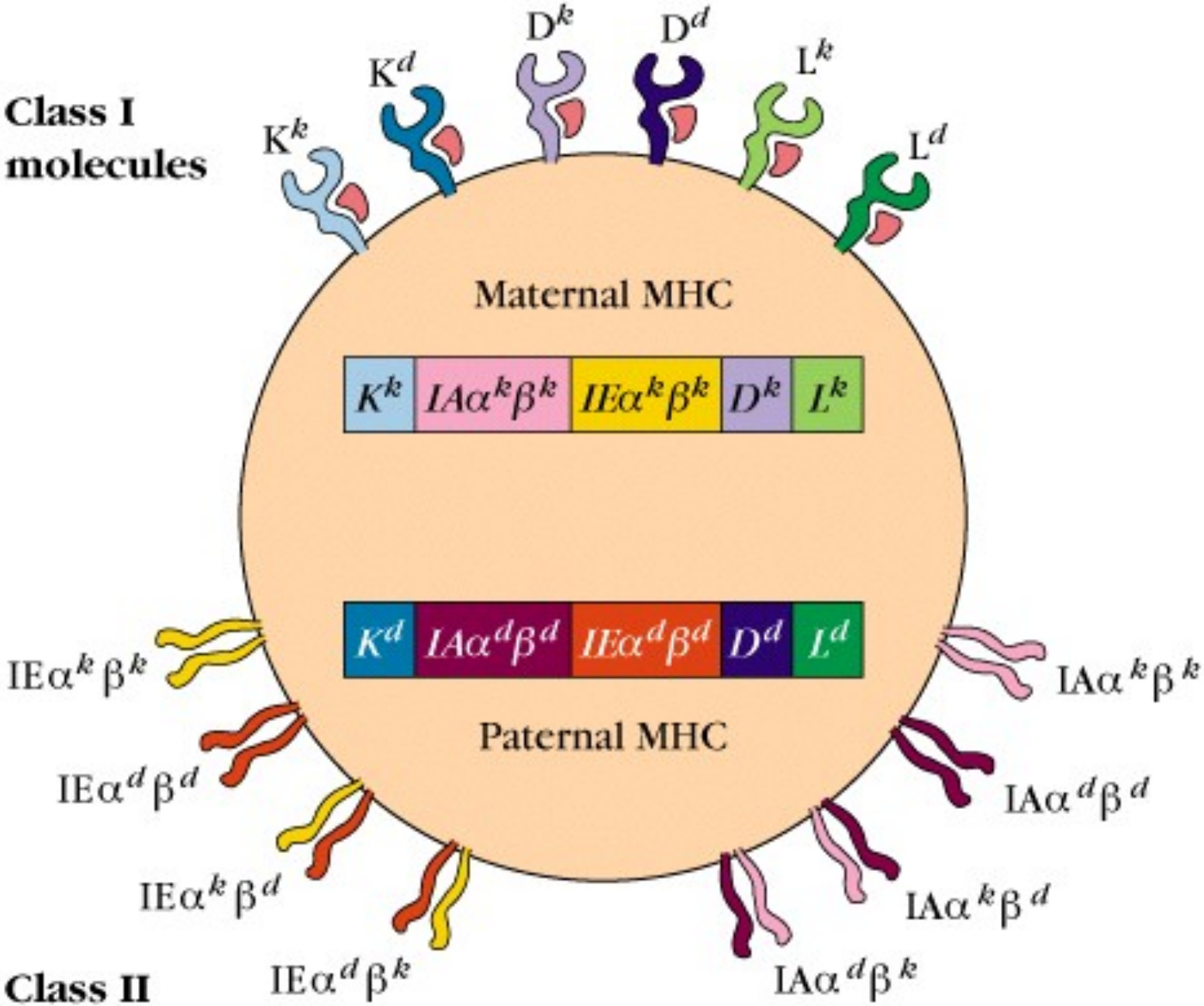
Molécula de MHC classe II

Mouse H-2 complex (Chromosome 17)

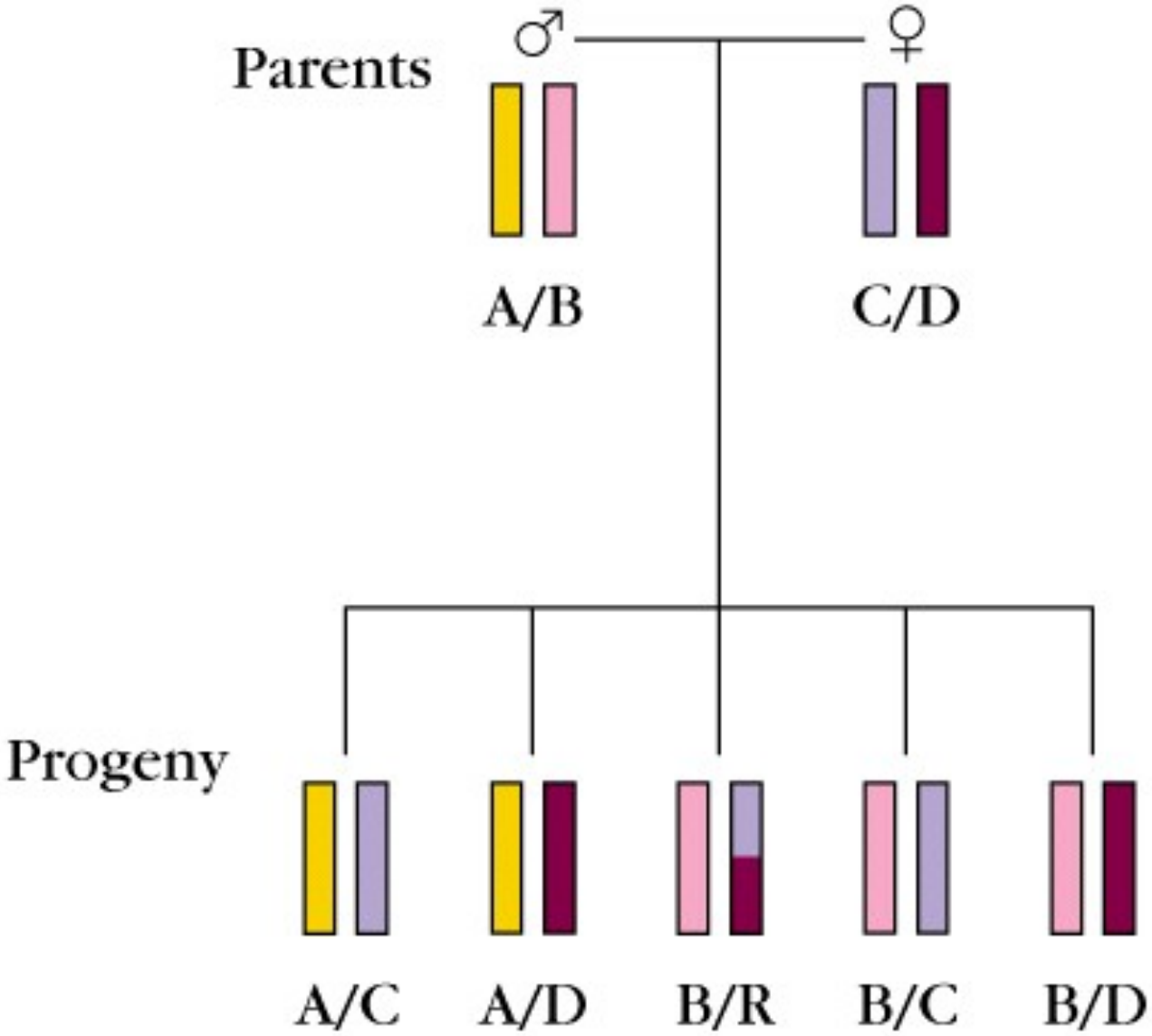
Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H-2D	H-2L

Human HLA complex (Chromosome 6)

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A


Class I molecules
K^k
K^d
D^k
D^d
L^k
L^d
Maternal MHC
K^k $IA\alpha^k\beta^k$ $IE\alpha^k\beta^k$ D^k L^k
K^d $IA\alpha^d\beta^d$ $IE\alpha^d\beta^d$ D^d L^d
Paternal MHC
$IE\alpha^k\beta^k$
$IE\alpha^d\beta^d$
$IE\alpha^k\beta^d$
$IE\alpha^d\beta^k$
$IA\alpha^k\beta^k$
$IA\alpha^d\beta^d$
$IA\alpha^k\beta^d$
$IA\alpha^d\beta^k$
Class II molecules

(c) Inheritance of HLA haplotypes in a typical human family

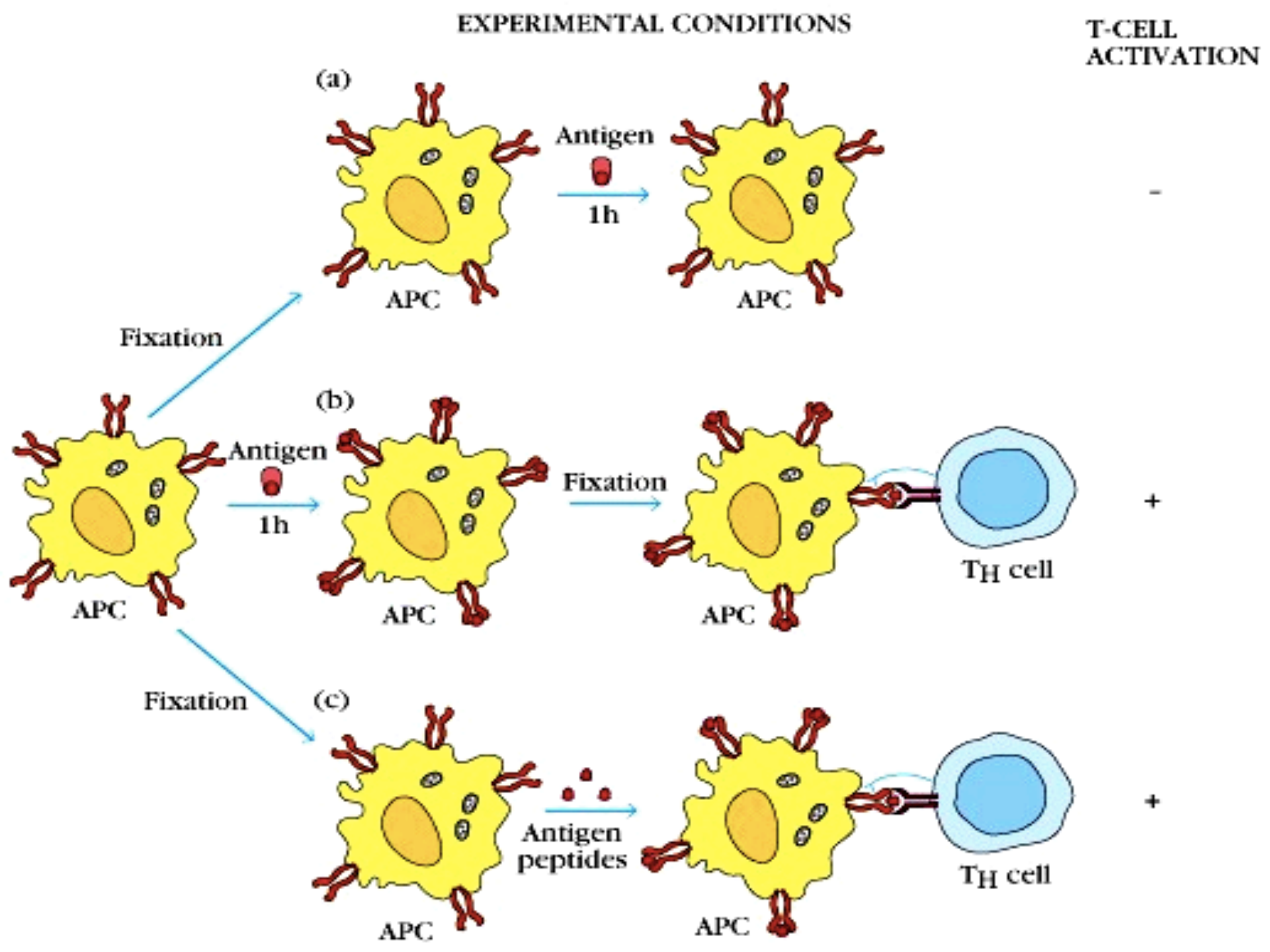


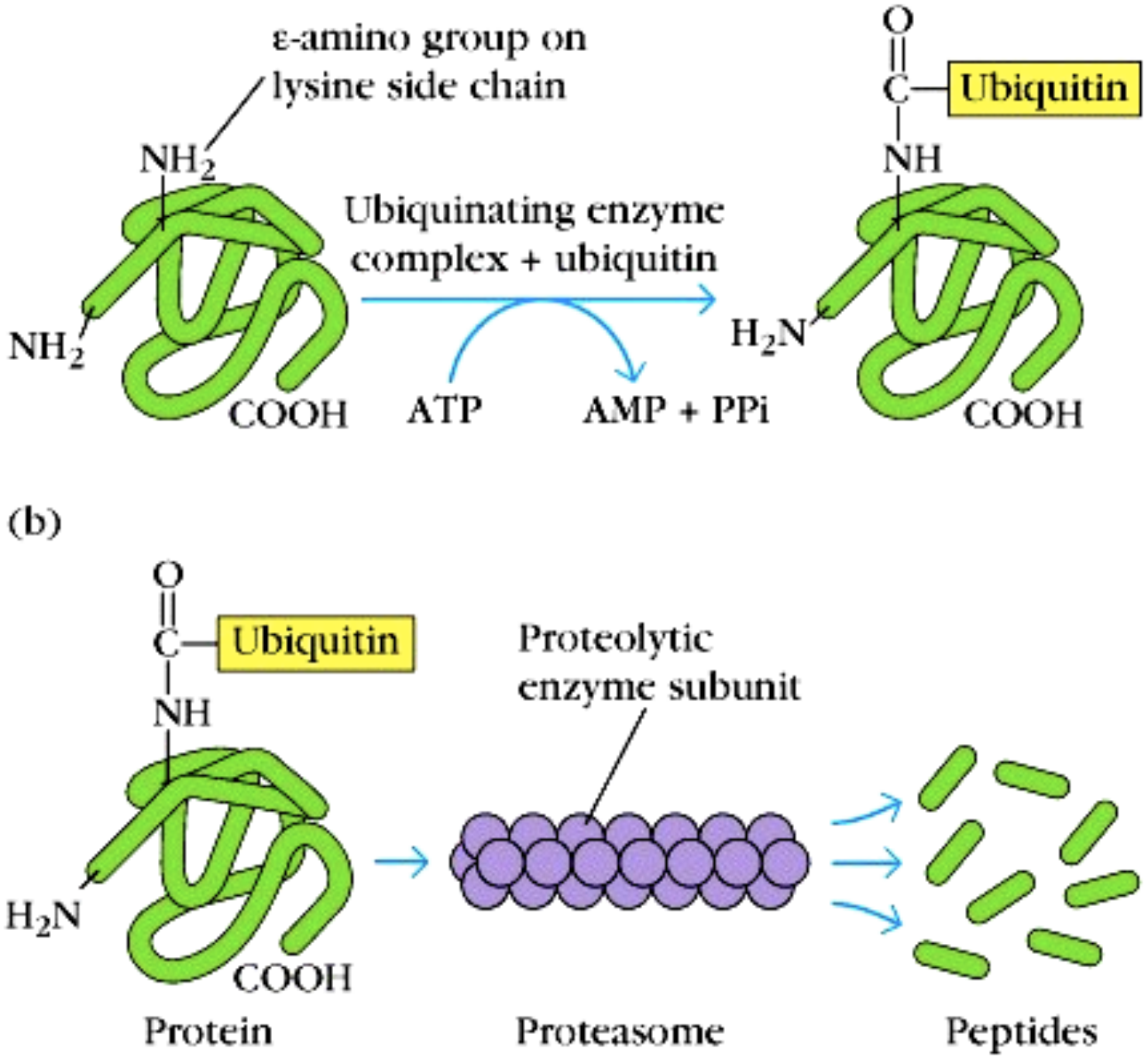
Polimorfismo das moléculas de MHC classe I e classe II

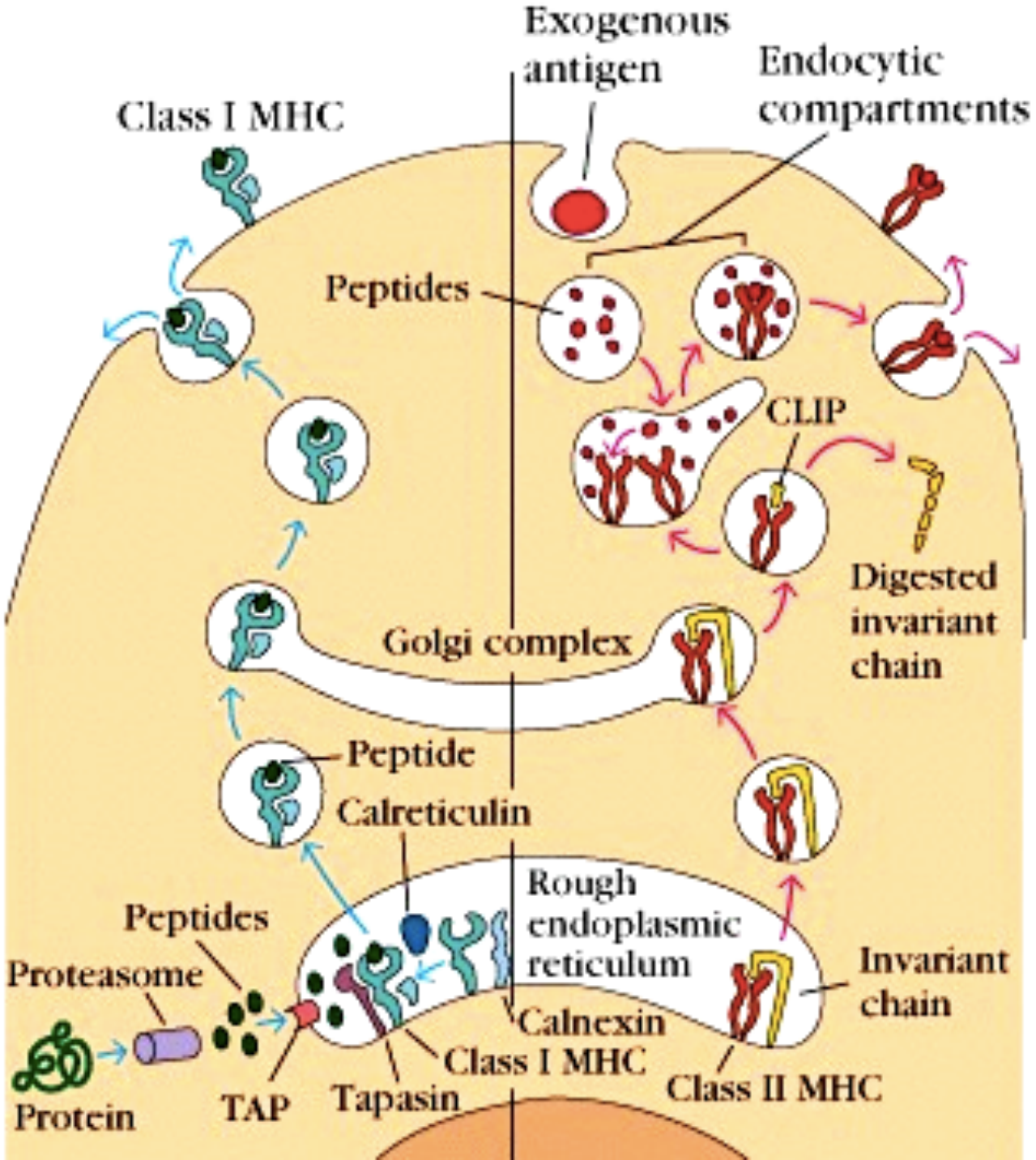
100 (K) x 100 (IAa) x 100 (IAb)

x 100 (IEa) x 100 (IEb) x 100 (D)

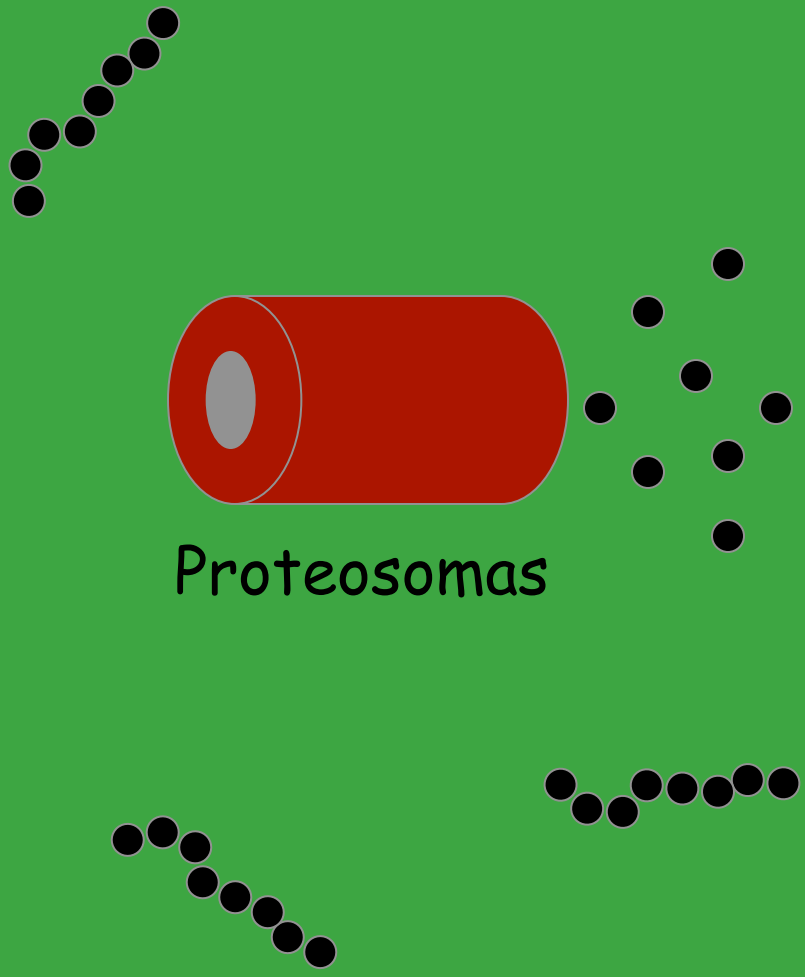
$= 10^{12}!!!!$


EXPERIMENTAL CONDITIONS
T-CELL ACTIVATION
(a)
Antigen
1h
APC
APC
-
Fixation
(b)
Antigen
1h
APC
APC
Fixation
APC
TH cell
+
Fixation
(c)
Antigen peptides
APC
APC
TH cell
+

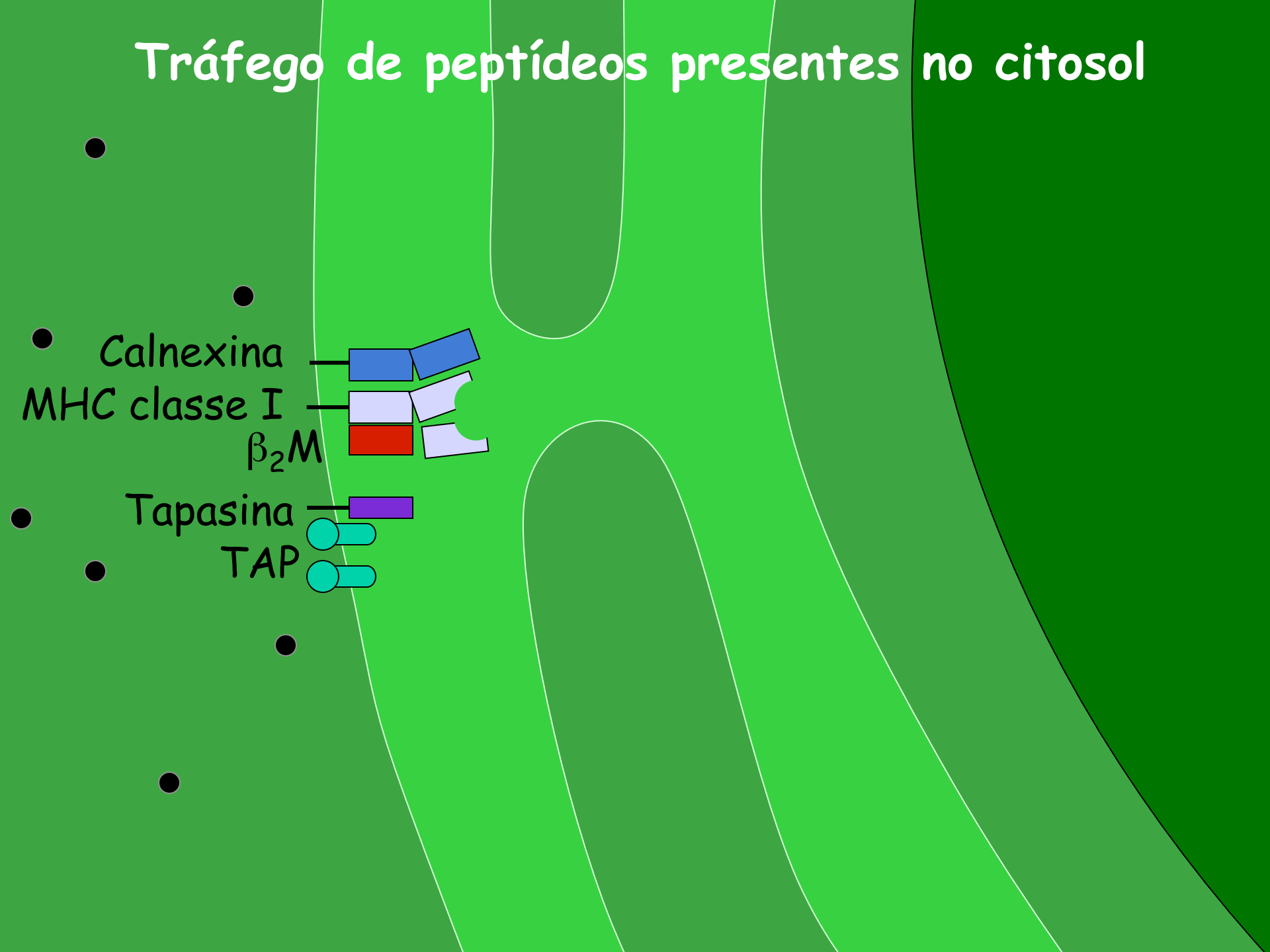

ε-amino group on
lysine side chain
NH2
NH2
COOH
Ubiquinating enzyme
complex + ubiquitin
ATP
AMP + PPi
O
C
Ubiquitin
NH
H2N
COOH
(b)
O
C
Ubiquitin
NH
H2N
COOH
Protein
Proteolytic
enzyme subunit
Proteasome
Peptides


Exogenous antigen
Endocytic compartments
Class I MHC
Peptides
CLIP
Digested invariant chain
Golgi complex
Peptide
Calreticulin
Peptides
Proteasome
Rough endoplasmic reticulum
Invariant chain
Calnexin
Class I MHC
Class II MHC
Protein
TAP
Tapasin

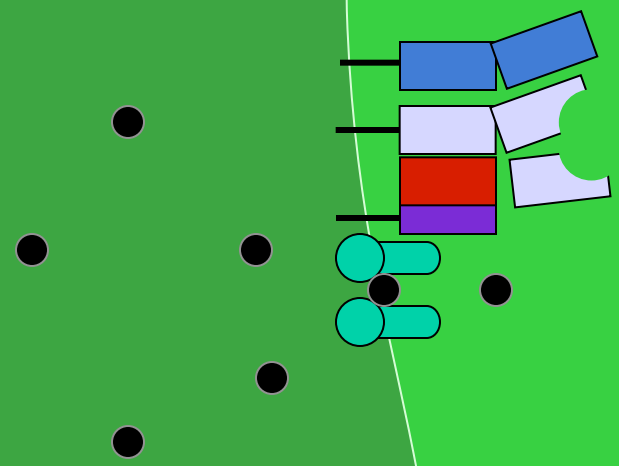
Degradação de substâncias presentes no citosol



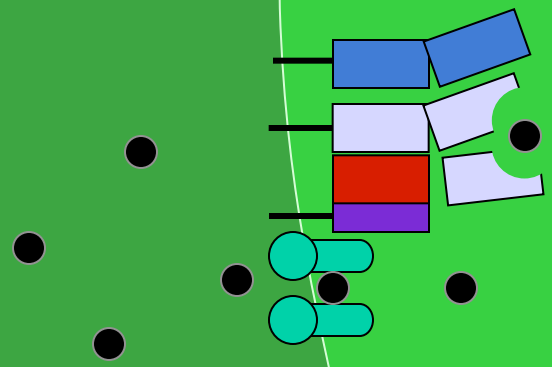
Tráfego de peptídeos presentes no citosol



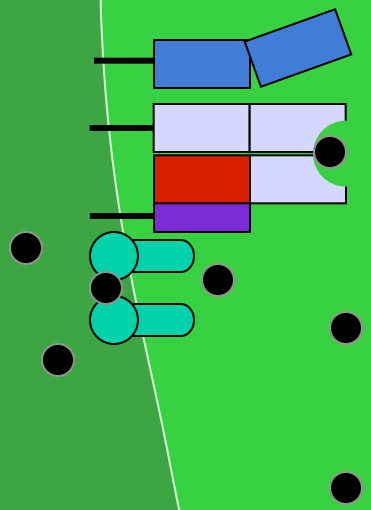
Tráfego de peptídeos presentes no citosol



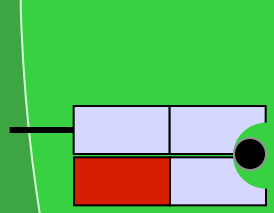
Tráfego de peptídeos presentes no citosol



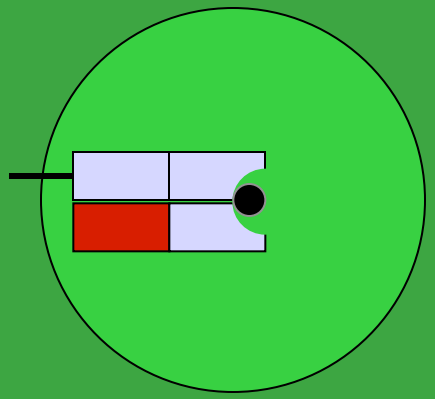
Tráfego de peptídeos presentes no citosol

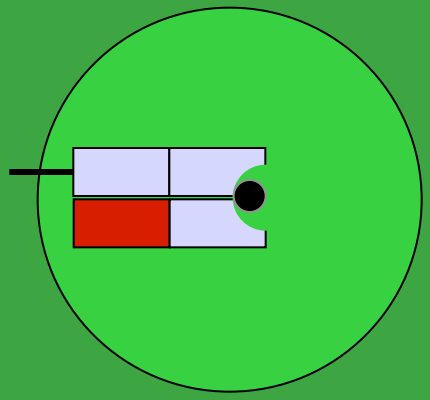


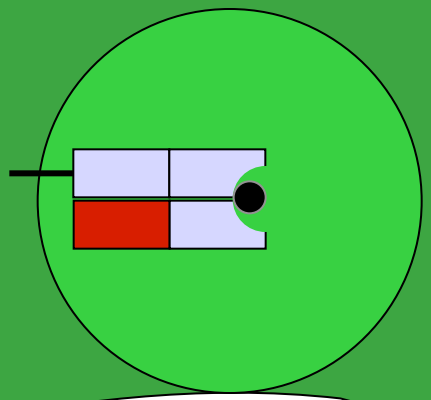
Tráfego de peptídeos presentes no citosol

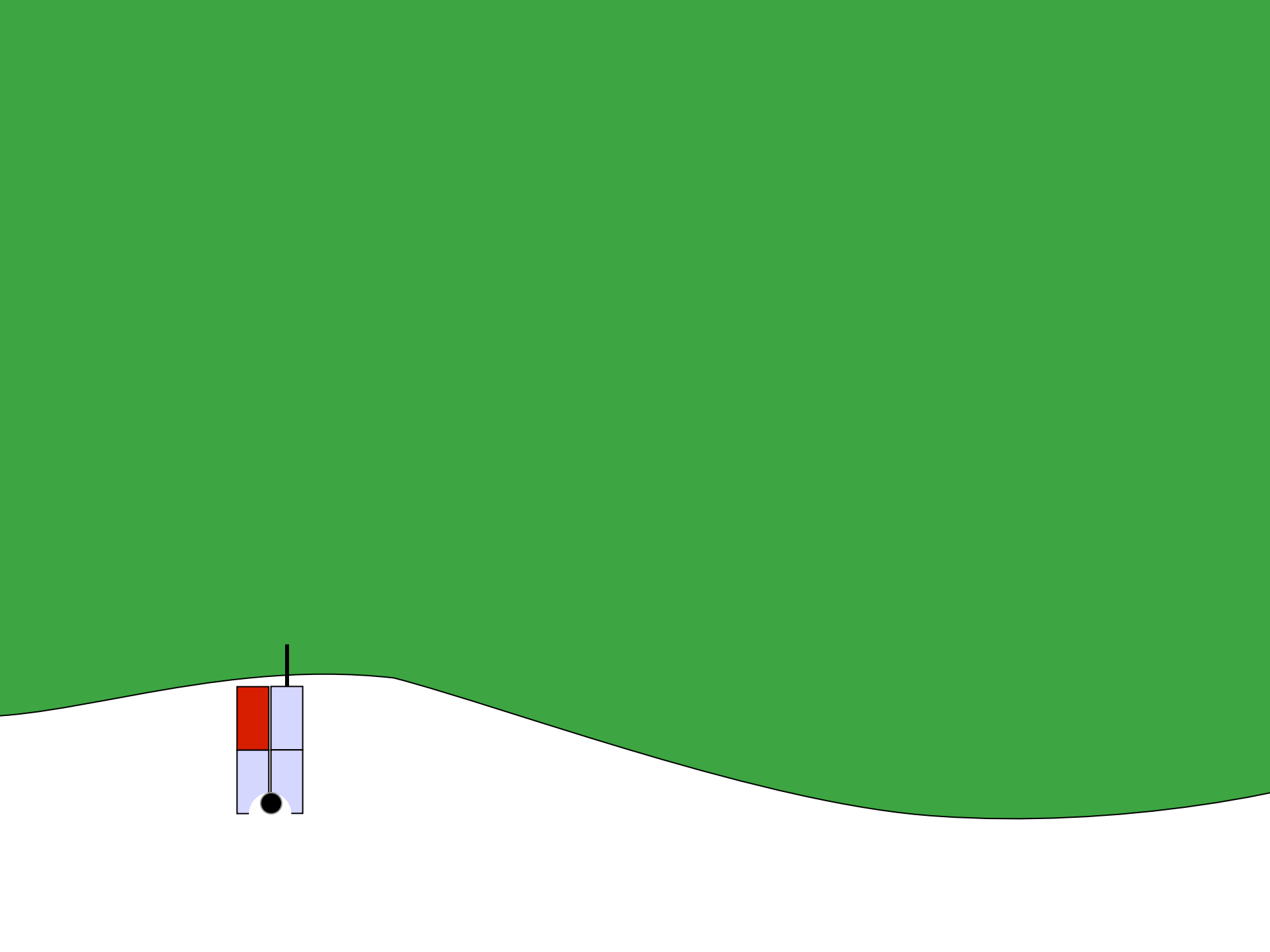


Tráfego de peptídeos presentes no citosol







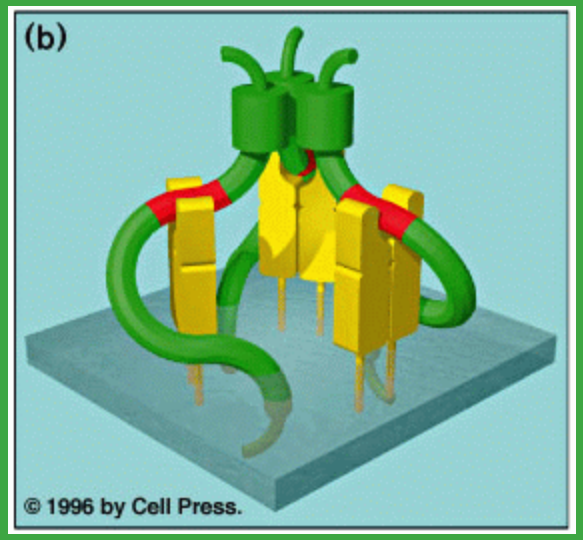


Síntese da molécula de classe II do MHC

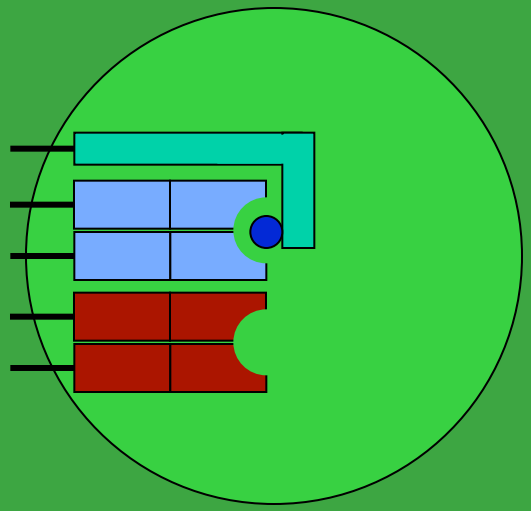
Cadeia invariante

MHC classe II

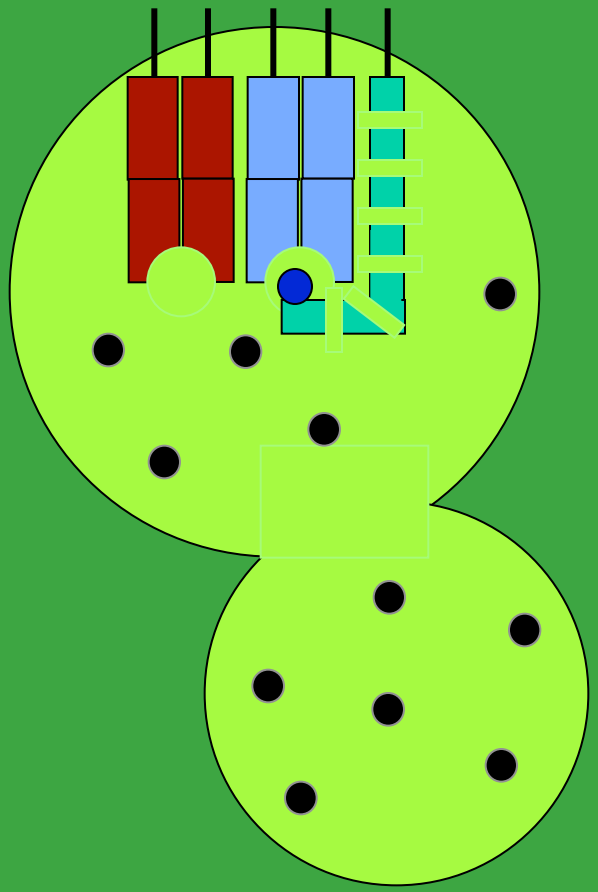
HLA-DM



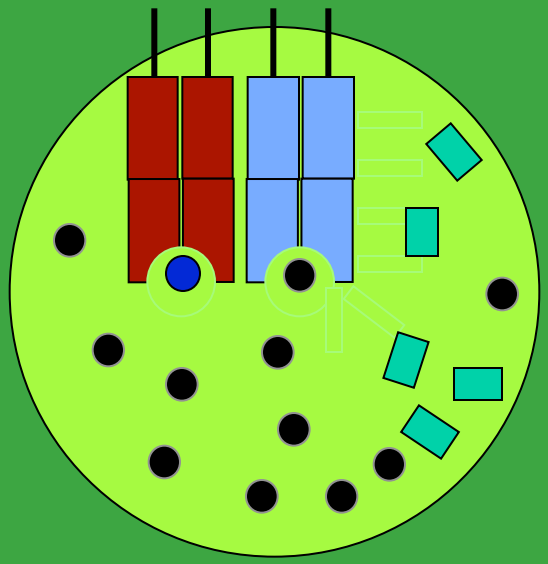
Síntese da molécula de classe II do MHC



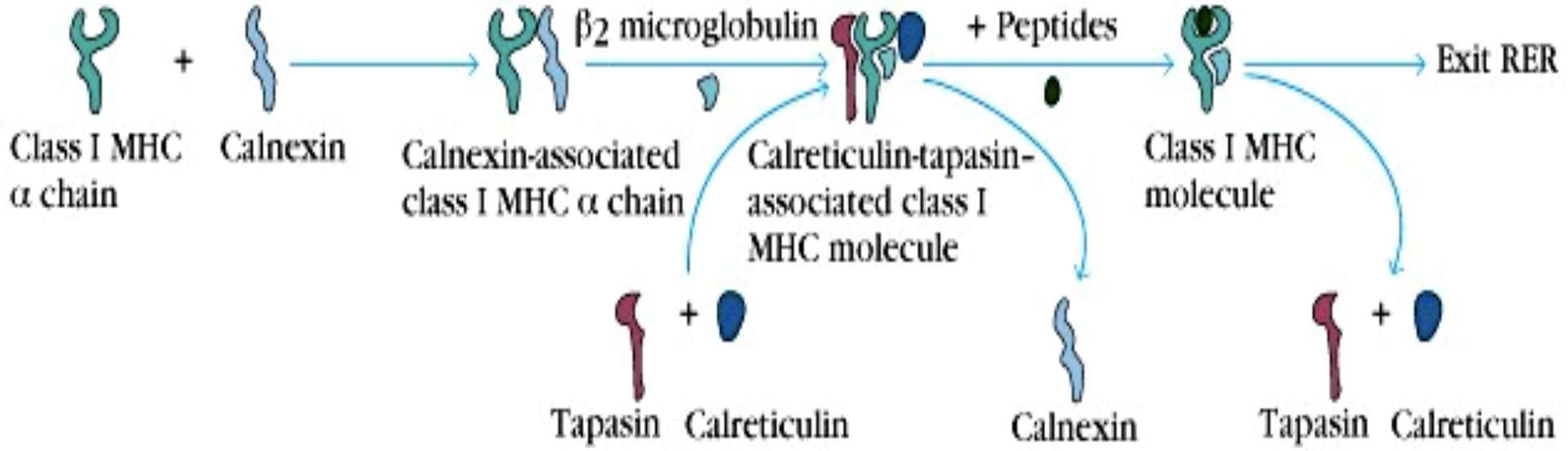
Degradação da cadeia invariante

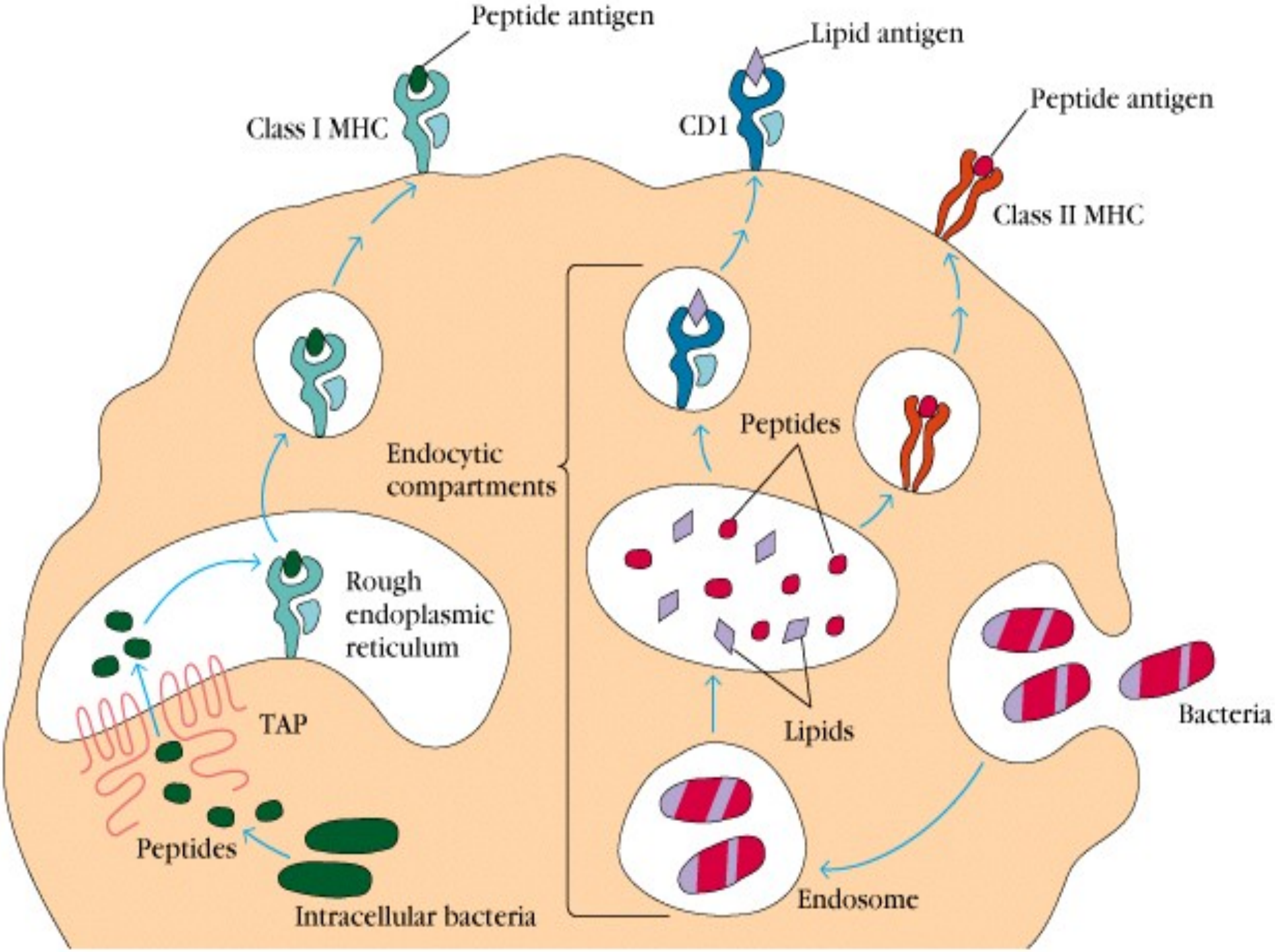


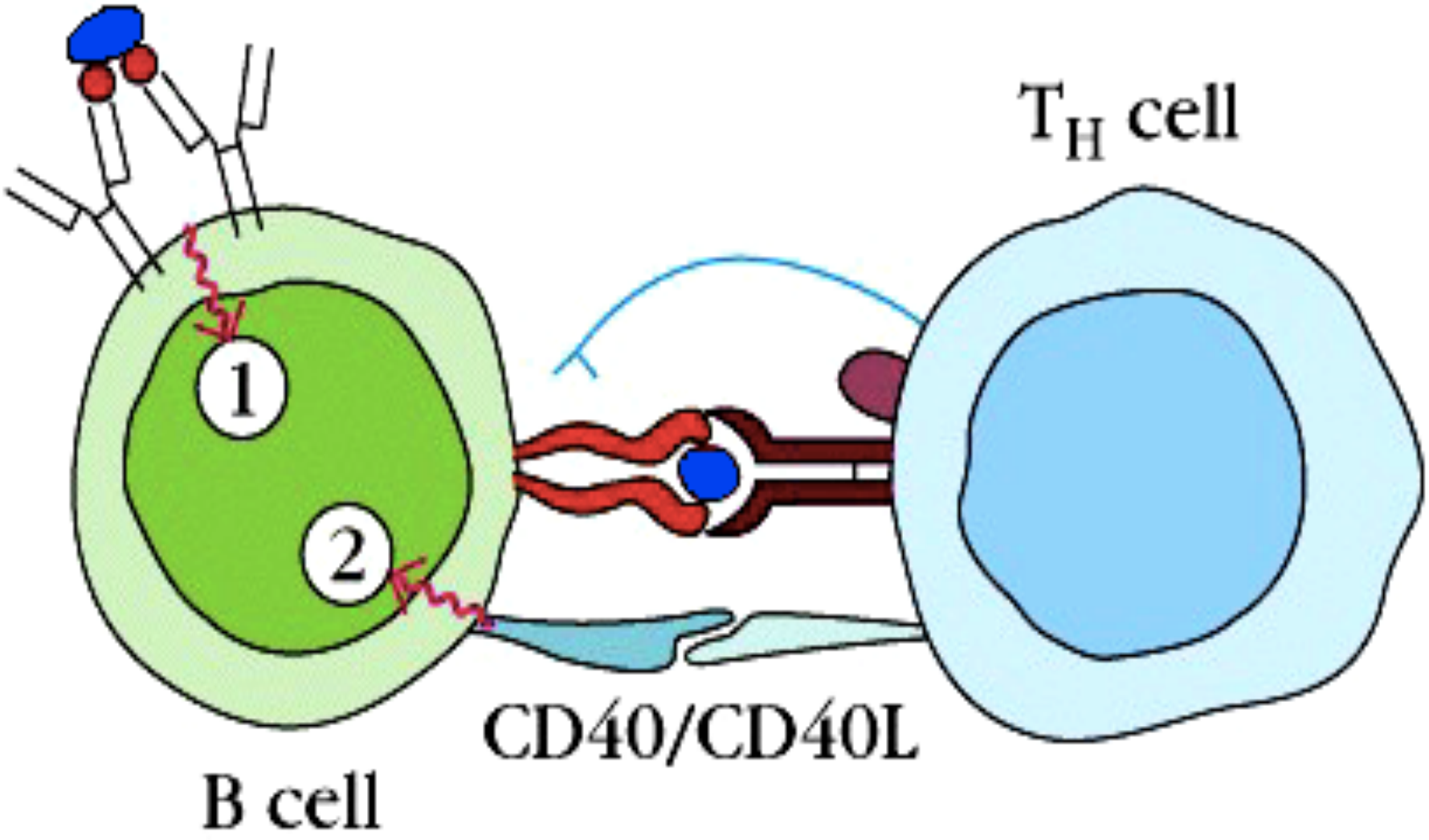
Apresentação do peptídeo na superfície celular

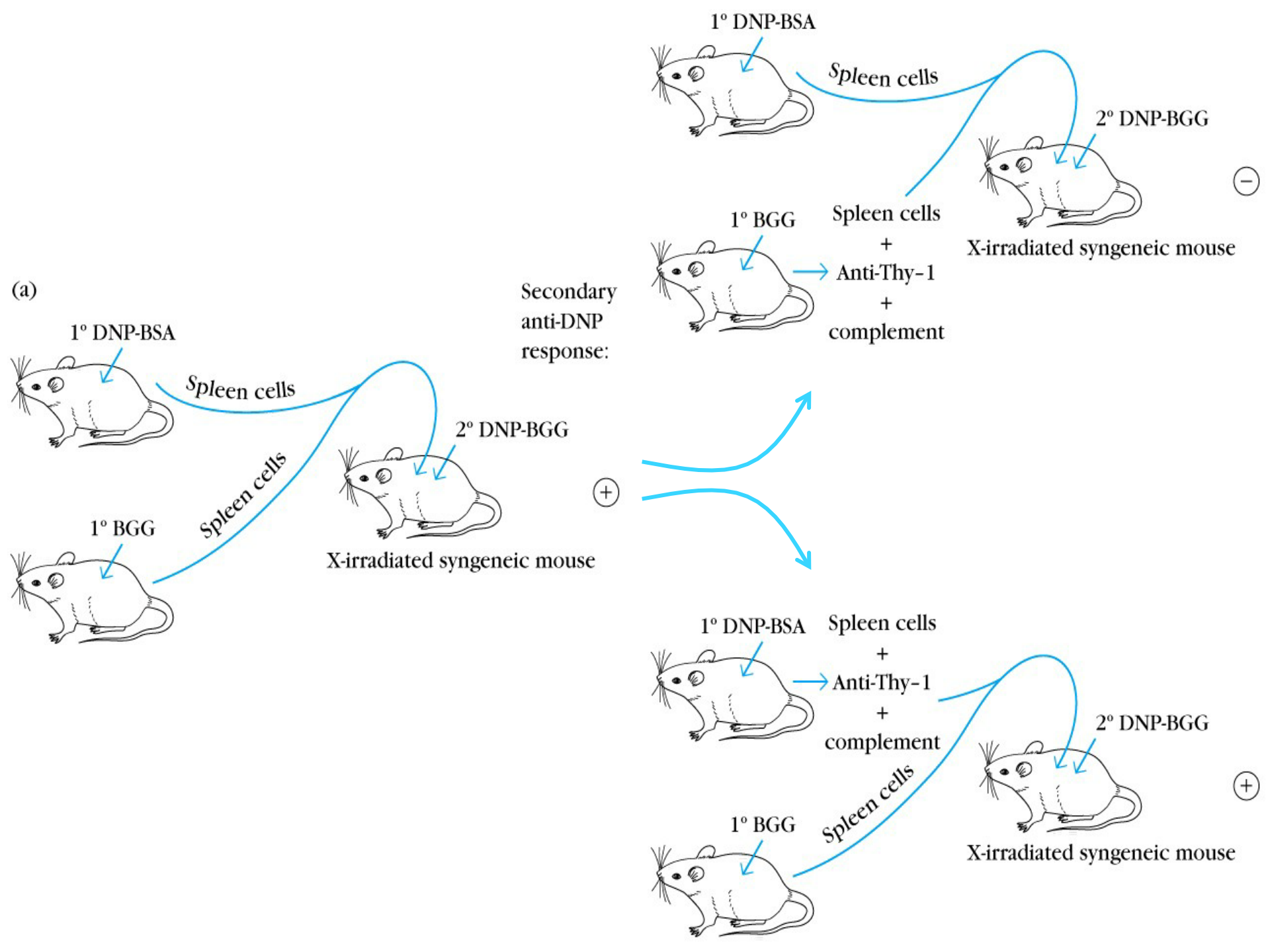


Formação do complexo associado à molécula de MHC classe I

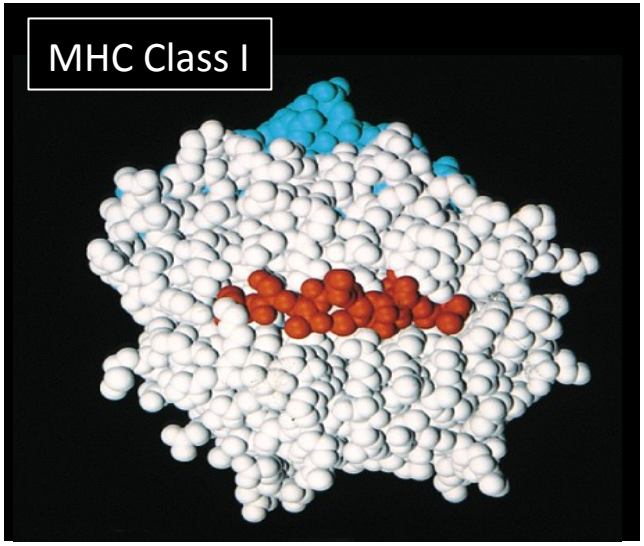


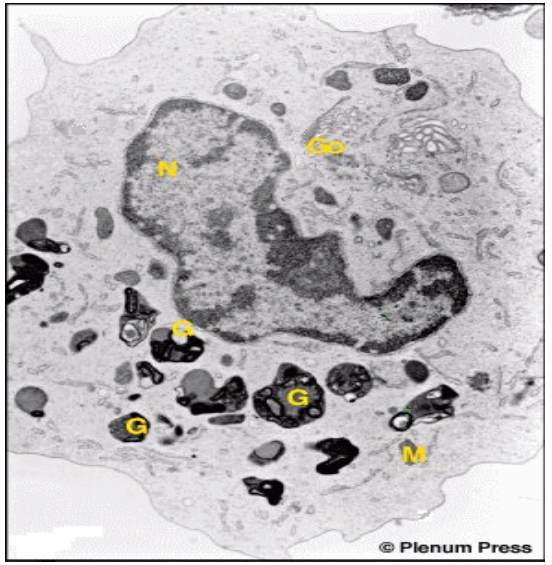

Peptide antigen
Lipid antigen
Peptide antigen
Class I MHC
CD1
Class II MHC
Endocytic compartments
Peptides
Rough endoplasmic reticulum
TAP
Lipids
Bacteria
Peptides
Intracellular bacteria
Endosome


T_H cell
1
2
CD40/CD40L
B cell

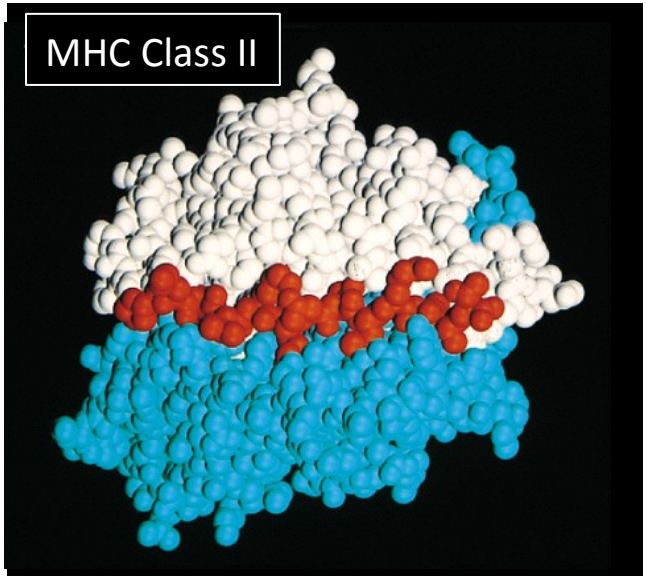

(a)
1° DNP-BSA
Spleen cells
2° DNP-BGG
1° BGG
Spleen cells
X-irradiated syngeneic mouse
+
Secondary anti-DNP response:
1° DNP-BSA
Spleen cells
2° DNP-BGG
−
X-irradiated syngeneic mouse
1° BGG
Spleen cells
+
Anti-Thy-1
+
complement
1° DNP-BSA
Spleen cells
+
Anti-Thy-1
+
complement
2° DNP-BGG
+
X-irradiated syngeneic mouse
1° BGG
Spleen cells

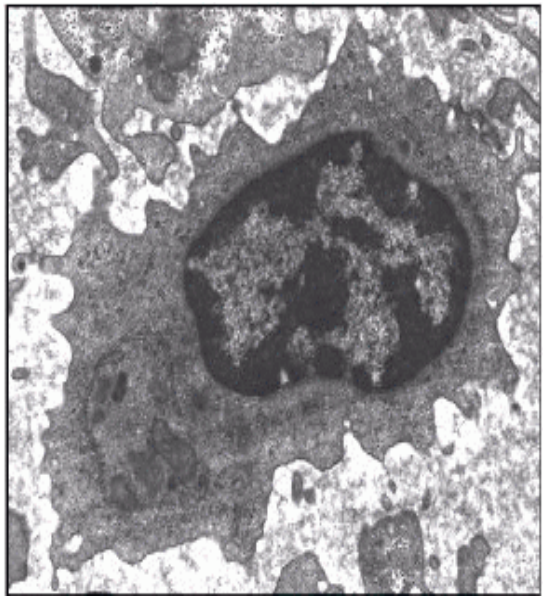
Interação TCR-MHC+peptídeo





Linfócito T CD8+





Linfócito T CD4+

Interação TCR-MHC+peptídeo

Receptores e Co-receptores