THE MEANING OF SELF

MAJOR HISTOCOMPATIBILITY COMPLEX antigens

and their role in the immune system

Role of the IMMUNE SYSTEM:

Hostility towards others

Elimination of pathogens (bacterial and viral infections)
Elimination of toxins and poisons
Elimination of infected and malfunctioning cells
Elimination of malignantly transformed cells

with self-regard

Preservation of healthy self-tissues intact

MUST BE ABLE TO DISCRIMINATE SELF FROM NONSELF

***Subject**: Re: the meaning of self*
***From**: Alan Challoner MA(Phil.) MChS*

1. One of the most important aspects of personal development is the way in which we see ourselves.

2. As a child grows, he becomes aware through his experiences, initially within the family and later also outside in his society, of who and what he is.

3. This reality not only represents his present situation but also acts as a stepping-stone towards his future development.

4. ***This of course includes some degree of self-regard, for as Horney, 1950 and Rogers, 1951 have indicated, unless an individual loves himself, he will feel a basic hostility towards others.***

(random citation from the internet)

MHC antigens (class I and class II) coordinate nearly all pathways of SELF –NONSELF discrimination in the adaptive immune system

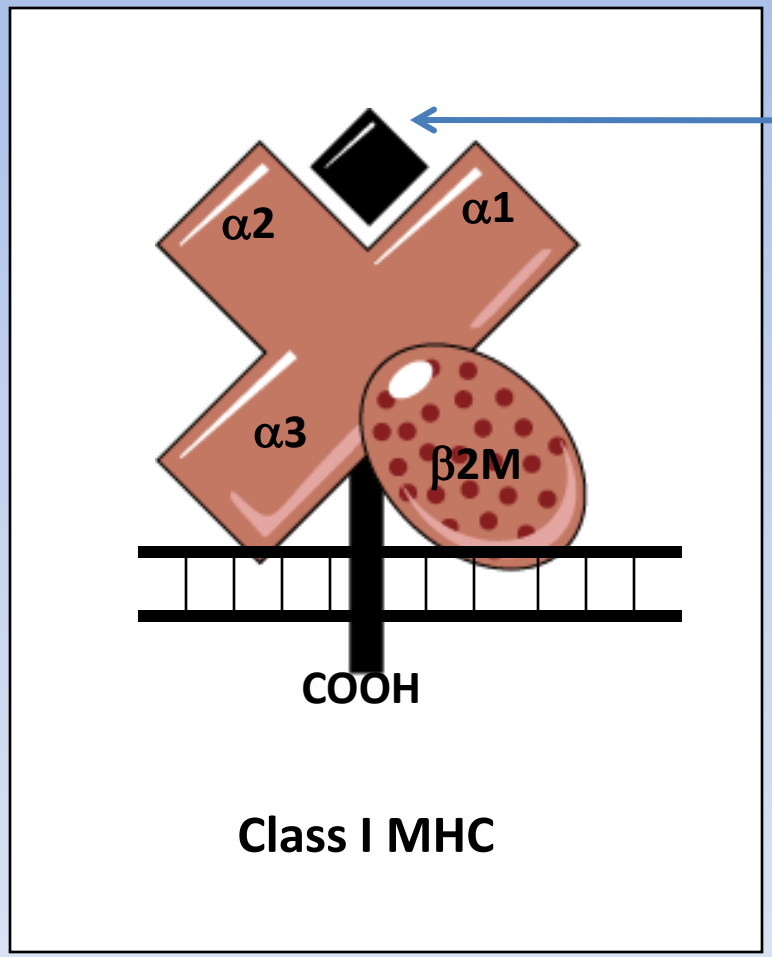
1. During early development MHC antigens educate immune cells how to distinguish foe from friend based on what is present in the host environment

2. This “education” will have lasting effects on how the host will react to “self” and “nonself” in the future

3. MHC instruct immune system to be hostile to pathogens

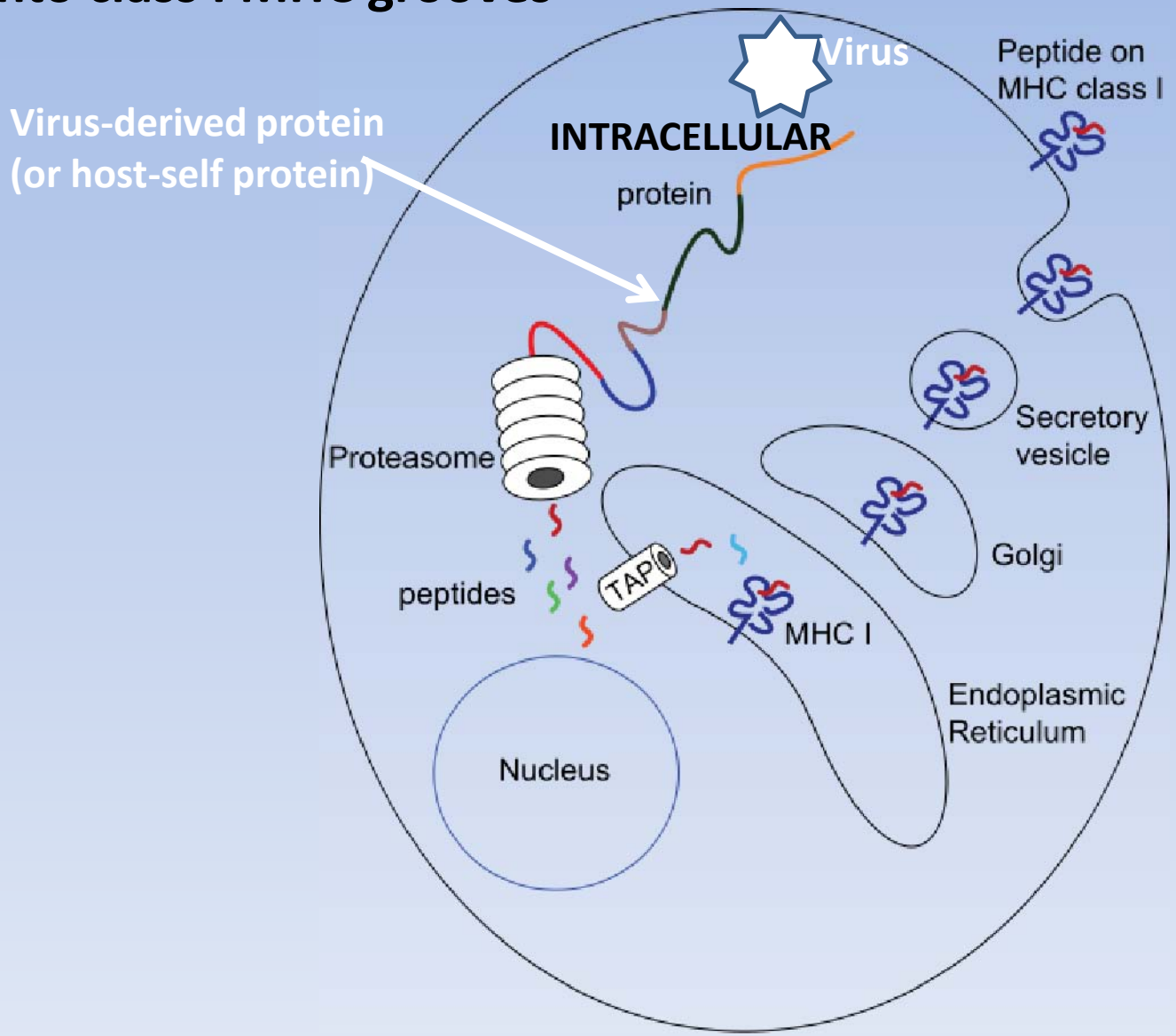
4. MHC teach immune system to be tolerant to healthy tissues of the host

MHC class I proteins act as molecular organizers of “self” and “nonself” peptides. The complexes are displayed on all cells of the body

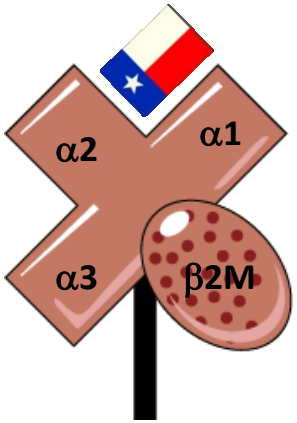


- Multiple, structurally related peptides fit into class I MHC groove
- Self and nonself peptides are always presented to immune system in the context of class I MHC

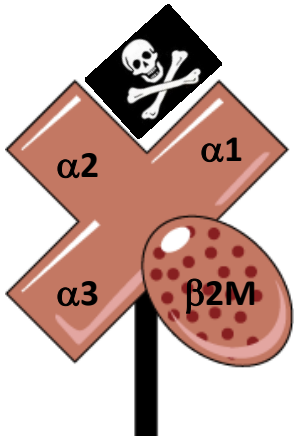
In pathogen infected cells both “self” and “nonself” intracellular proteins are synthesized and degraded: their fragments are loaded into class I MHC grooves



SELF

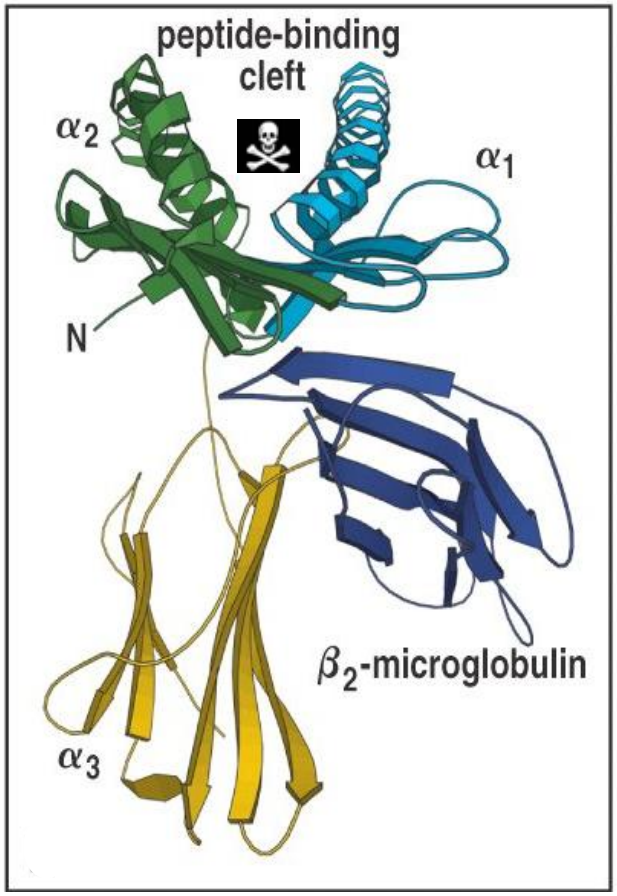


NONSELF

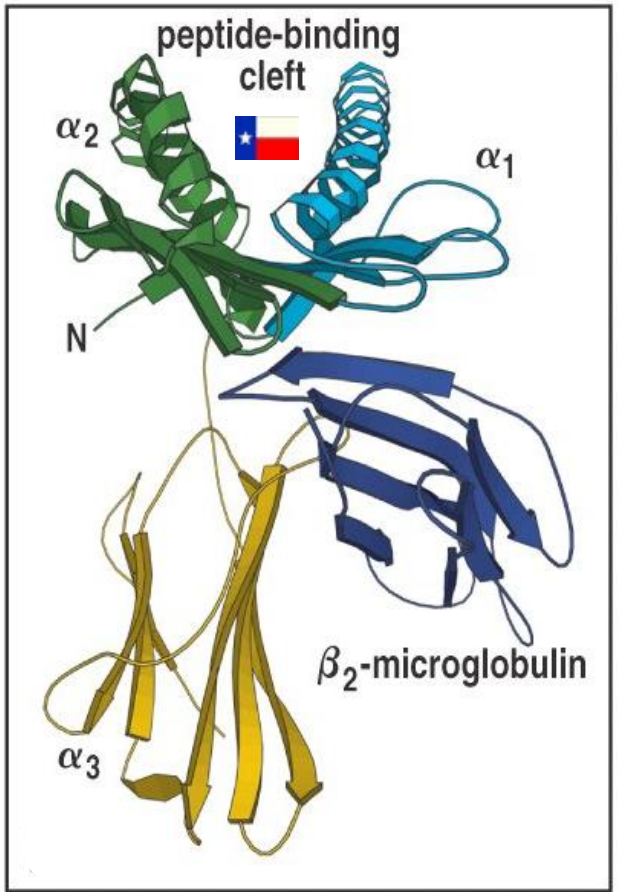


Cell surface MHC molecules are trimolecular complexes

NONSELF

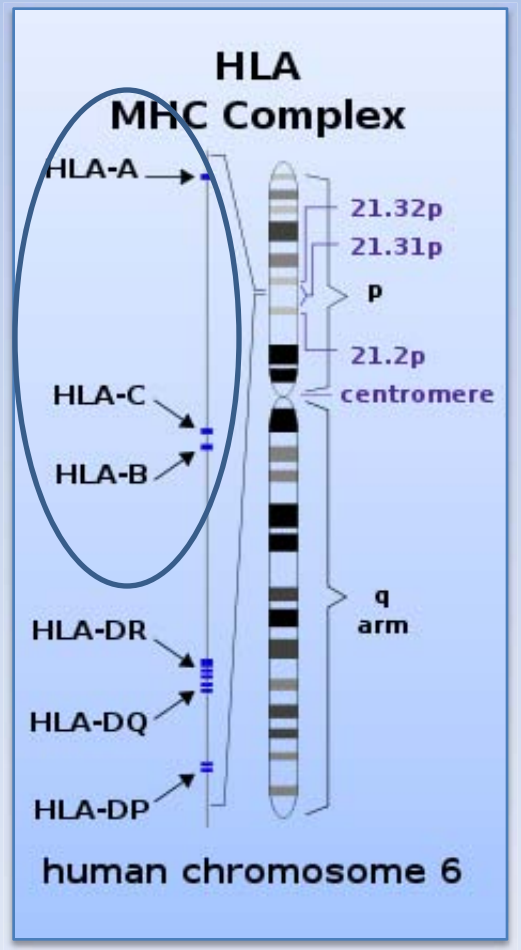


SELF



- Each MHC class I dimer can bind thousands of structurally related “self” and “nonself” peptides
- Each cell expresses thousands of copies of MHC class I trimers

Major Histocompatibility Complex Antigens



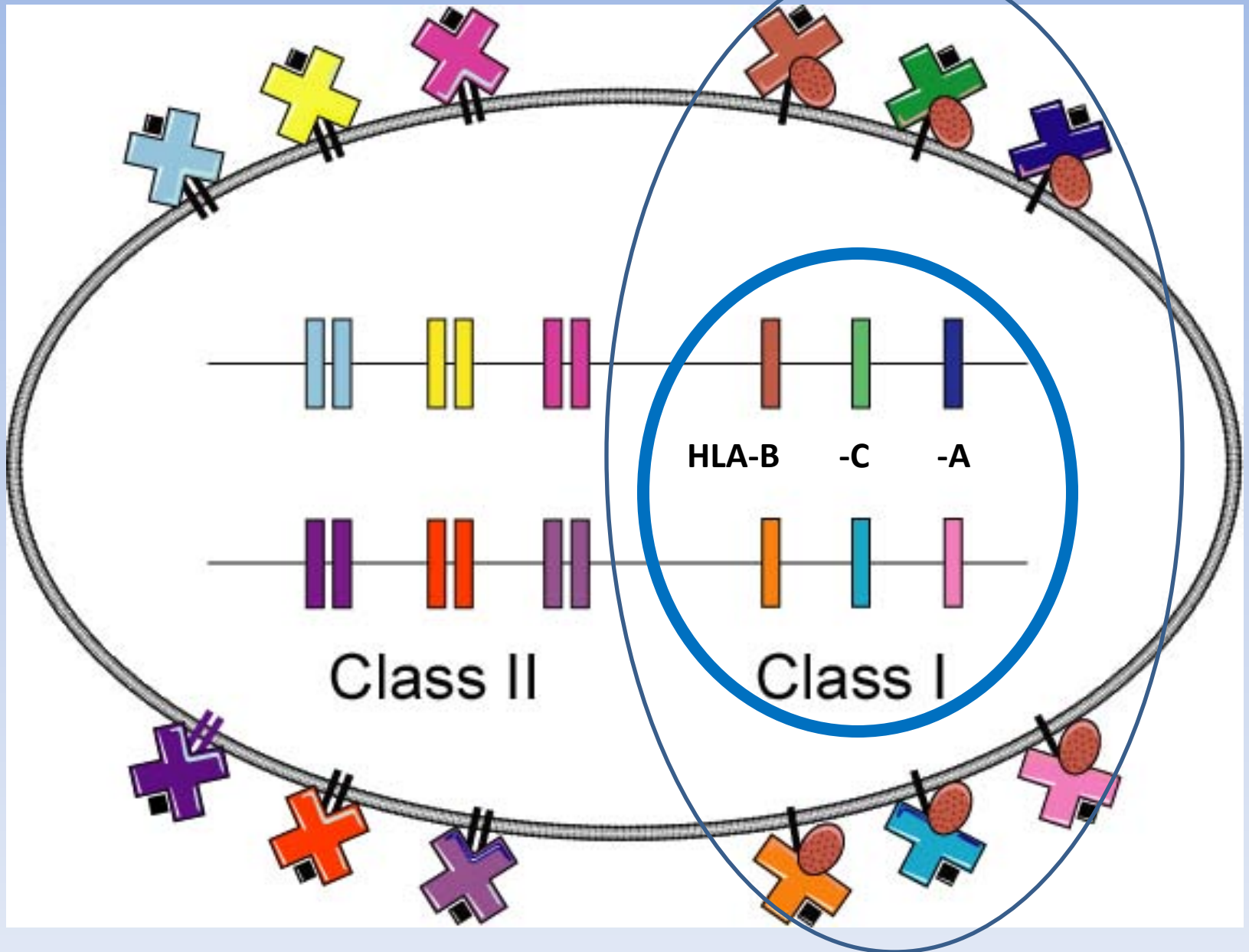
- **MHC** is called **HLA** in human and **H2** in mouse

Numbers of HLA alleles in worlwide populations (2011)

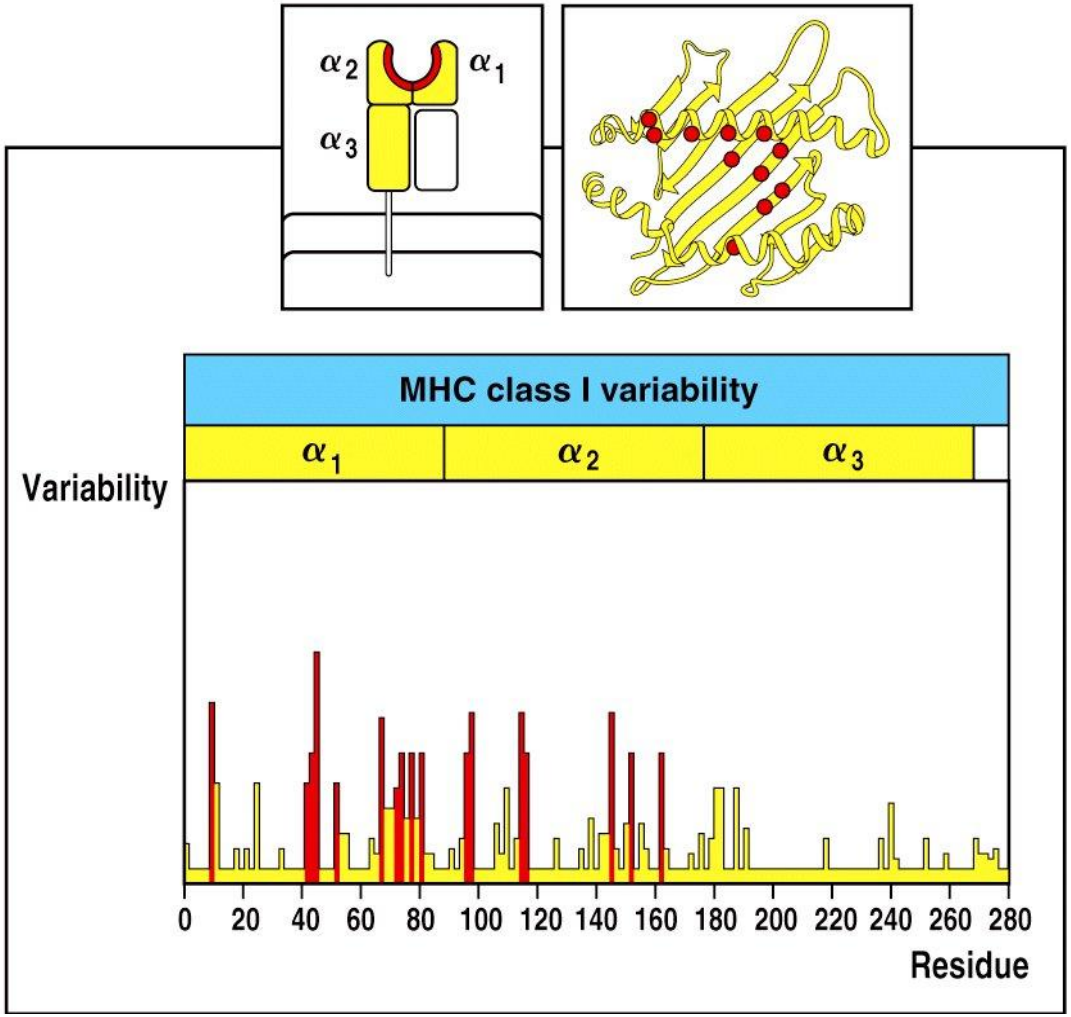
Locus	Number of alleles
HLA-A	1518
HLA-B	2068
HLA-C	1016

http://www.allelefrequencies.net/#

Codominant expression of MHC class I and class II molecules



Polymorphisms are highly focused into the peptide-binding coding regions of MHC genes



Two major consequences of high polymorphism of MHC antigens:

1. **Different individuals have different susceptibilities to pathogens and autoimmune diseases: some MHC alleles are protective , others are predisposing**

2. **The differences at the MHC loci are the main reason for TRANSPLANT REJECTION**

TWO MAIN PHYSIOLOGICAL TASKS OF CLASS I MHC

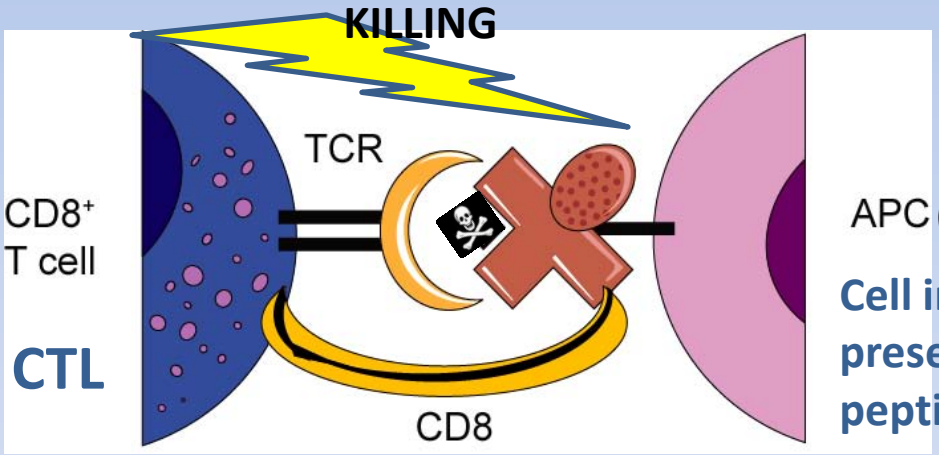
1. To activate different subsets of CTL (cytotoxic T lymphocytes) cells in response to "nonself" peptides

Pathogen elimination: (Hostility to others)

2. To participate in education of CTL (cytotoxic T lymphocytes) cells in response to "self" peptides

Prevention of autoimmunity: (High self-regard)

1. MHC instruct mature Cytotoxic T lymphocytes (CTL) to eliminate aberrant cells

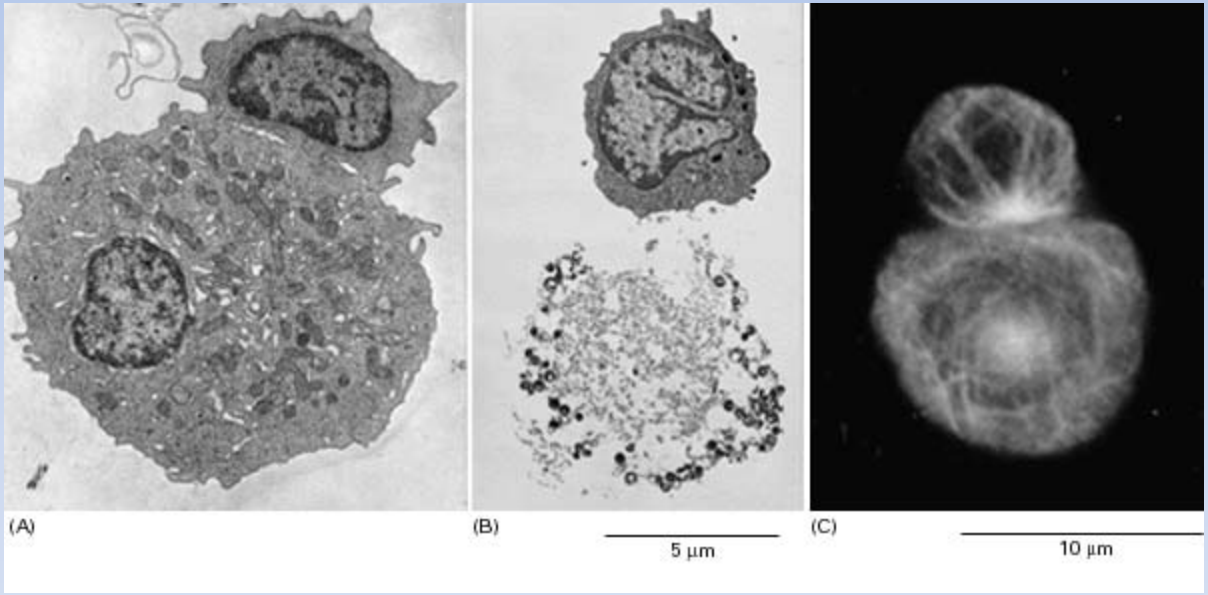


Mature CTL

APC (Antigen Presenting Cell)

Cell infected by a virus presenting pathogen-derived peptide in class I MHC

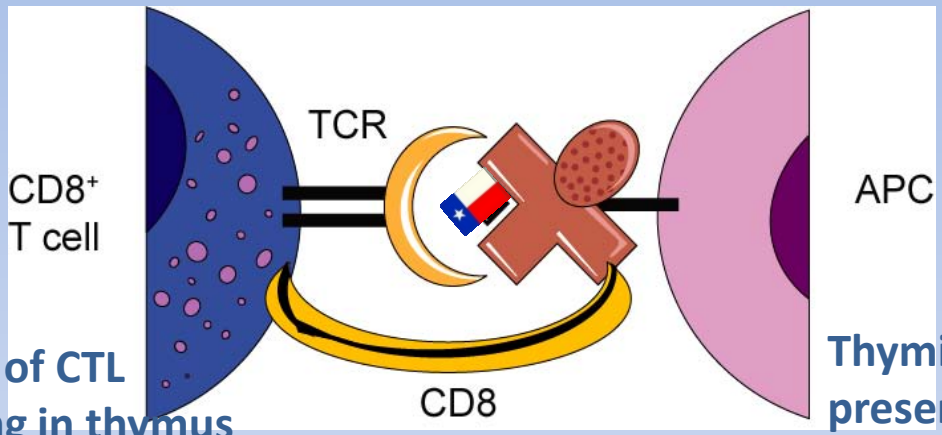
Cytotoxic T lymphocyte killing a target cell



Electron microscopy images

Immunofluorescence microscopy

2. During early development MHC educate CTL precursors in thymus for “self-regard” (tolerance of healthy cells)

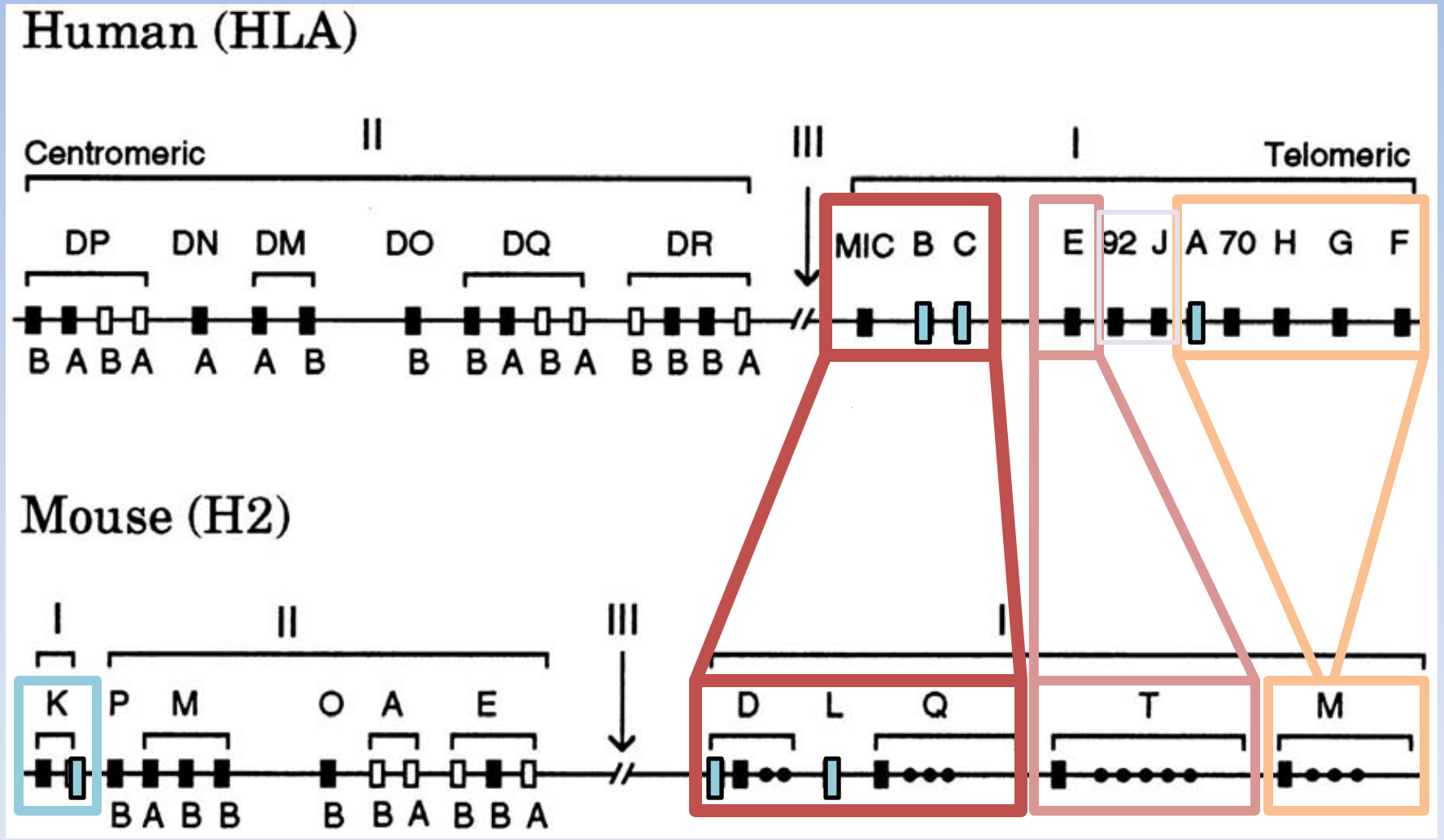


Precursor of CTL
Developing in thymus

Thymic epithelial cell
presenting self peptide

T cells with TCR receptors binding to MHC+”self” die and are absent in mature hosts!

Human and mouse MHC are not co-linear and differ in number of class I genes: Evolutionary relationships are unclear



Class Ia and class Ib MHC antigens

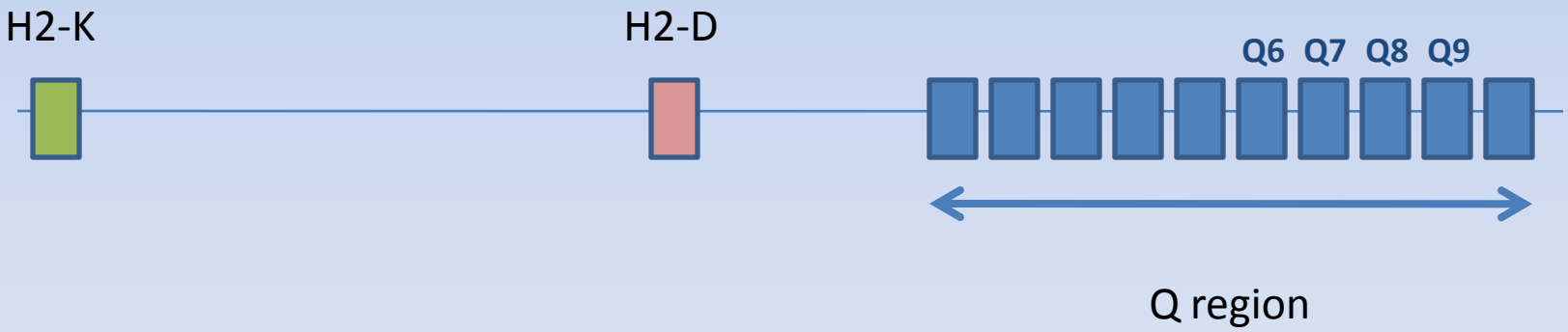
In addition to the three "classical" HIGHLY POLYMORPHIC MHC class I loci (class Ia) the human and mouse genomes encode multiple "non-classical" NON-POLYMORPHIC (class Ib) genes which differ in amino acid sequences of the peptide binding grooves.

The predicted structures of the class Ia and Ib MHC are very similar but the functions of the "non-classical" class Ib proteins in the immune system are largely unknown. Mouse strains may encode dozens of class Ib genes, many of which are clustered in the "Q" subregion of MHC.

The class Ib products of mouse Q region are called Qa-2 proteins or Q proteins. There are ~10 Q genes in common mouse strains.

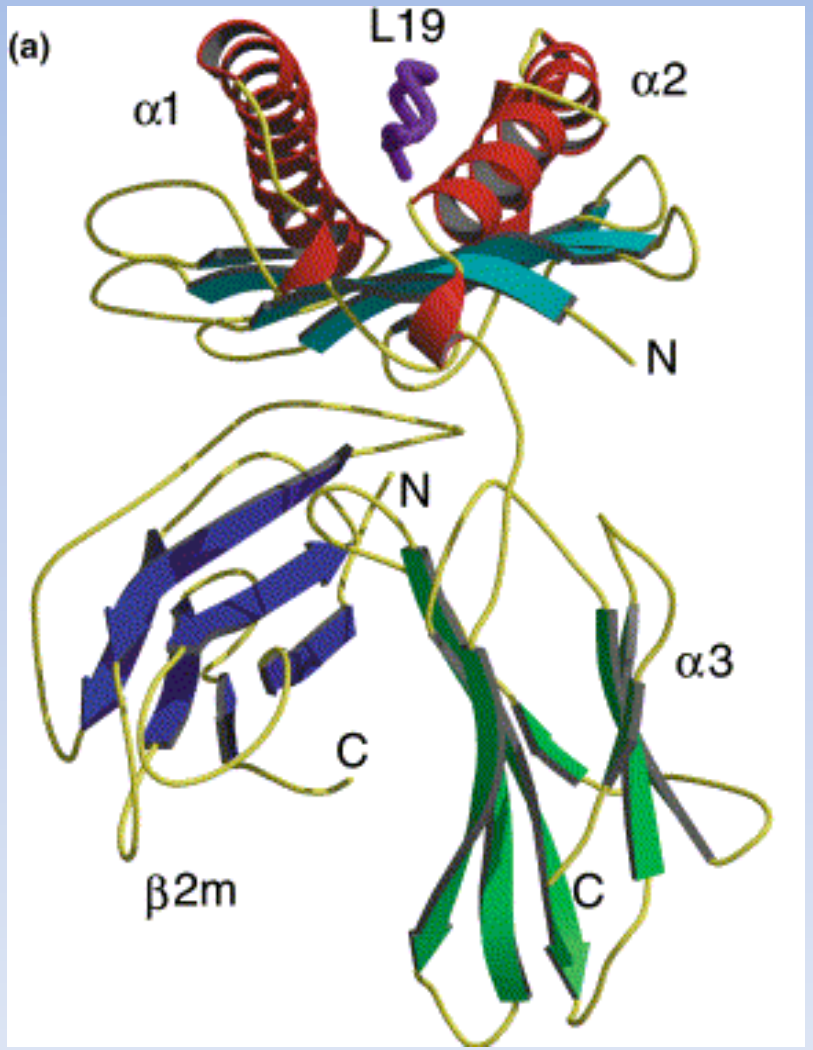
Searching for functions of nonclassical MHC antigens:

What have we learned about highly conserved Q9 MHC properties?

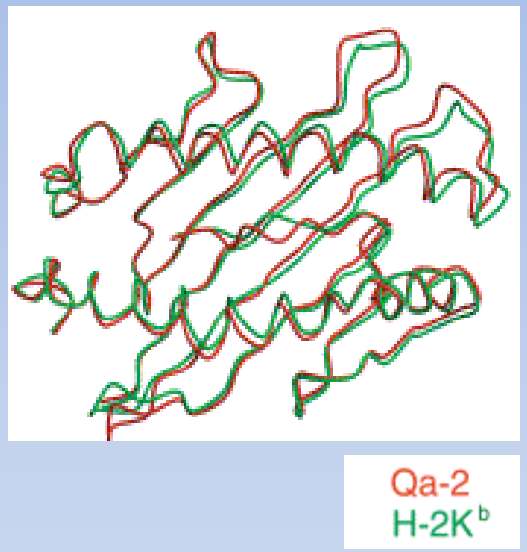


3D structures Q9 class I is nearly identical to “classical” of H2K and H2-D

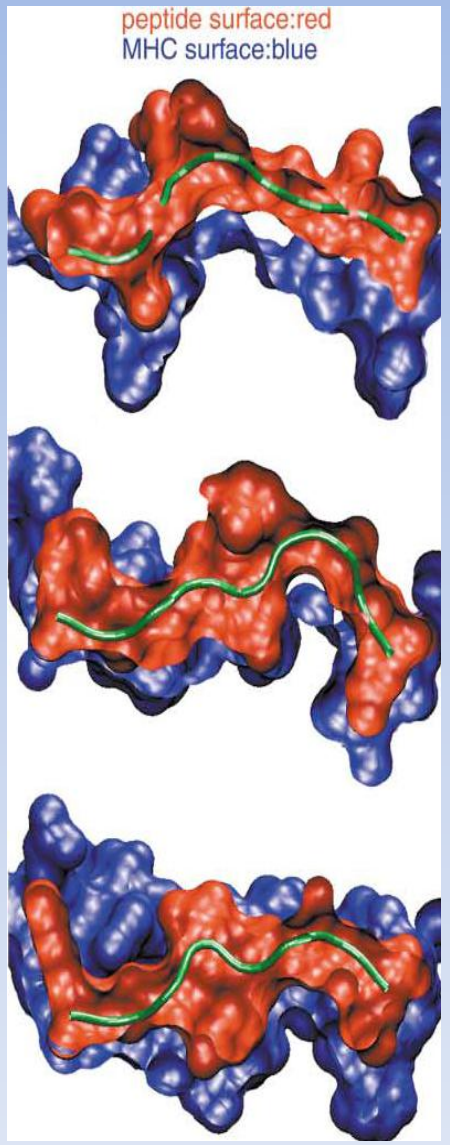
Side view of Q9



Top view of Q9 and H2-K



Classical and nonclassical class I MHC present different “self” and “nonself” to CTL as illustrated by the shapes of their peptide binding grooves

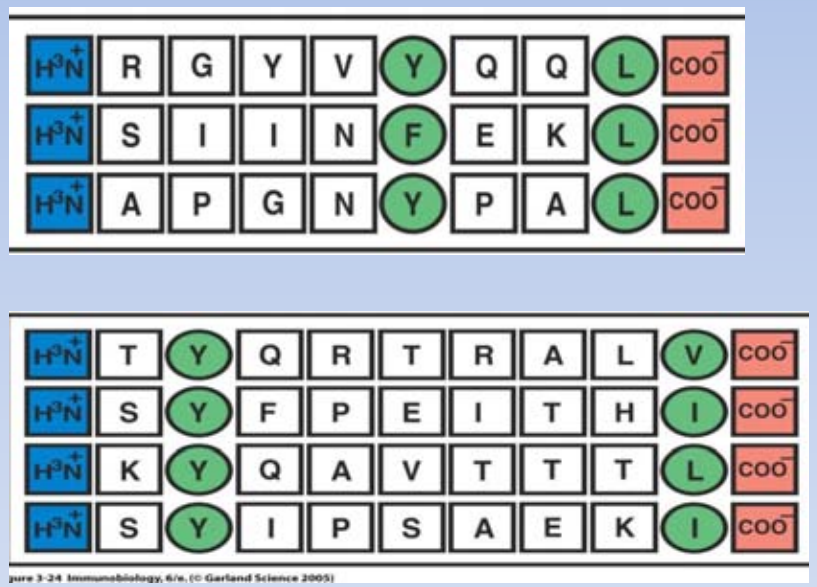


Q9/peptide

H2- D/peptide

H2-K/peptide

Architecture of the MHC groove defines peptide repertoire and “peptide motifs”



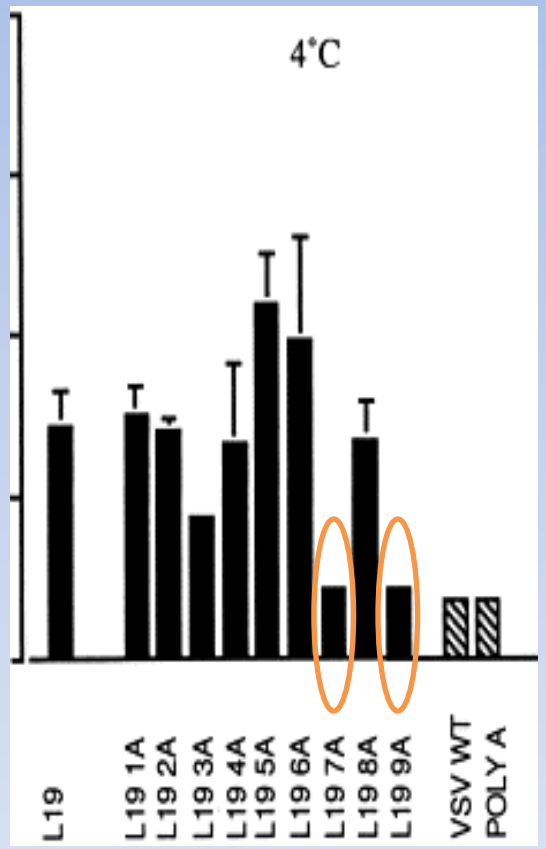
jure 3-24 Immunobiology, 6/e. (© Garland Science 2005)

Peptides eluted from two different class Ia MHC alleles have different anchors

Q9 groove accommodates peptides with a unique binding motif: H at position 7 and L/I/F at position 9

Pool	Position of Residue P1	P2	P3	P4	P5	P6	P7	P8	P9	Comments
Dominant residues							**H**		**L** **I** **F**	
Strong	K	M L Q	N I L	P	V I	K M I		E Q N D		Residues detected in the pool of endogenous peptides eluted from Qa-2[a]
Also detected	**A** E Q (G)		T	E **A** G K **S** D	L T E H M F Y (Q)	L F N Y	R	K **S** T R (V)		
Individual Peptides										
L19	I	L	**M**	E	H	I	**H**	K	**L**	Endogenous peptides[b]
COF	K	L	T	G	I	K	**H**	E	**L**	

Substitution of amino acid residues at “anchor” positions eliminates binding of synthetic L19 peptides to Q9

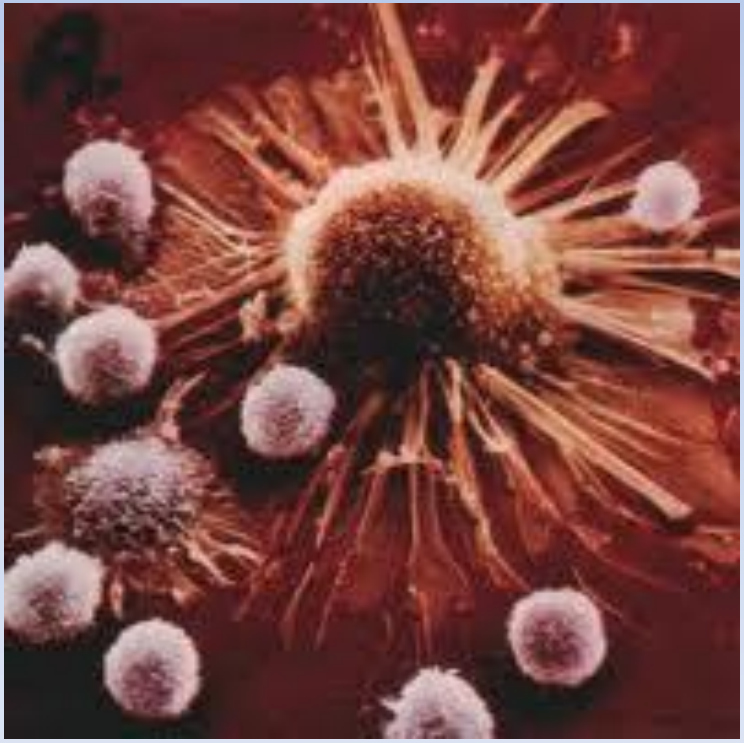


Peptides lacking crucial “anchor” residues cannot bind Q9MHC

All tumors lack Q9 proteins while all normal healthy cells are Q9 positive

Cytotoxic T lymphocytes (CTL) recognize cancer cells as nonself and kill it

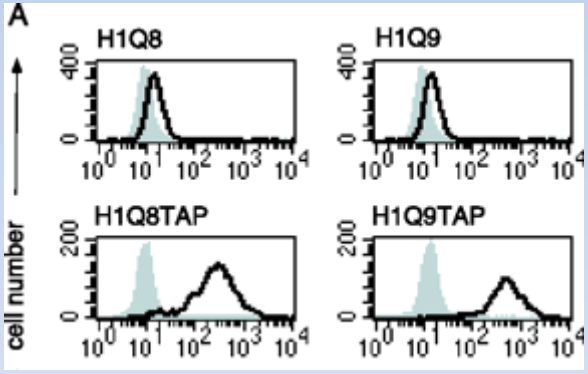
Multiple CTL in physical contact with a tumor cell



Cytoskeleton of a dead tumor cell with live CTL

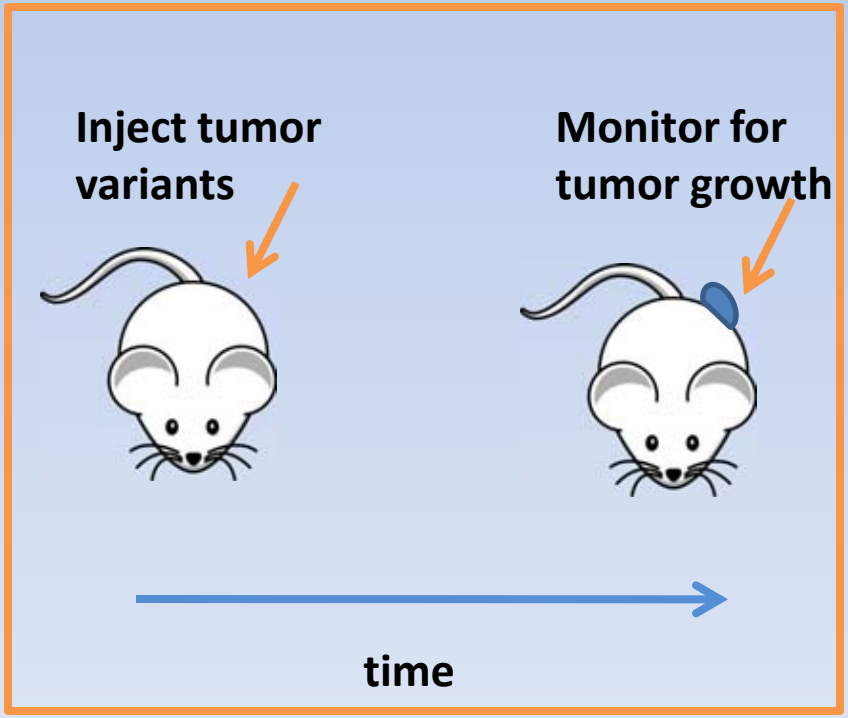
B78H1- melanoma devoid of all class I MHC : a model for studying tumor outgrowth properties

B78H1 melanoma can be transfected with desired class I genes and TAP

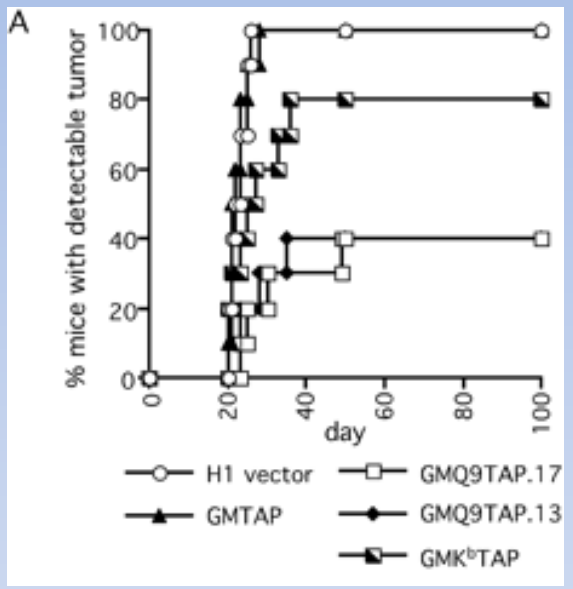


Q8+ tumor peptide

Q9+ tumor peptide



Q9 protects mice against melanoma better than classical MHC



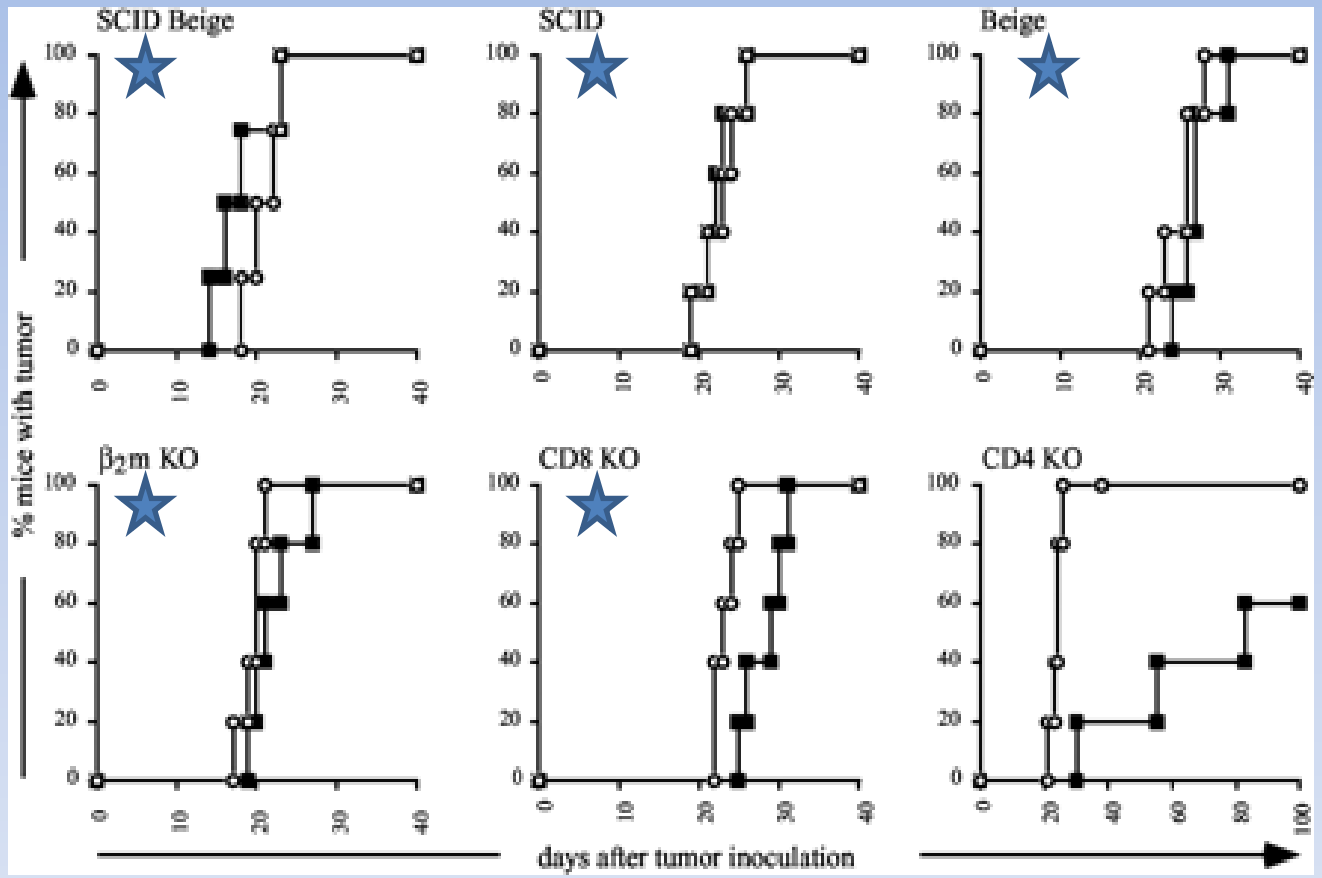
Class I negative tumor grows in 100% of mice

H2-K positive tumor grows in 80% of mice

Q9 positive tumor grows only in 40% of mice

Rejection of Q9 positive tumors is mediated by CTL (CD8 cytotoxic T cells)

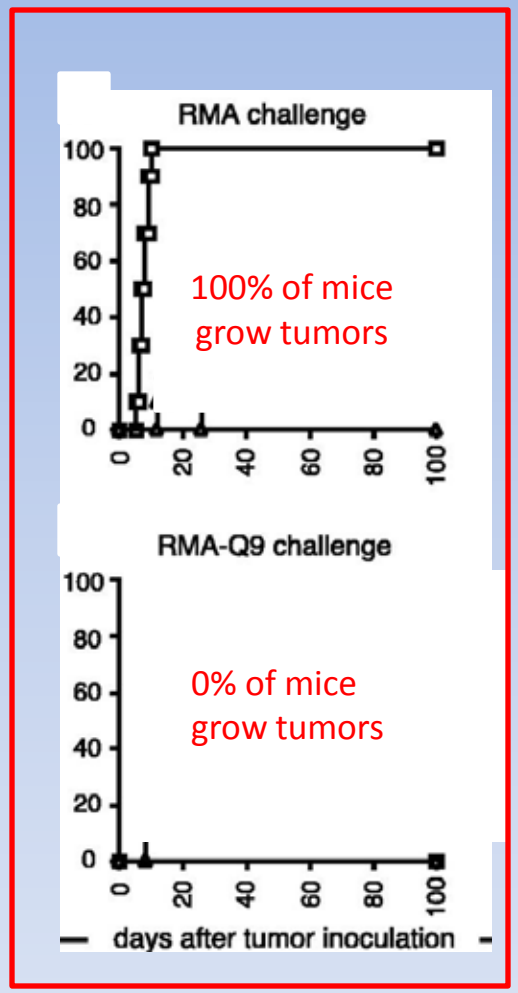
★ Mice lacking CTL

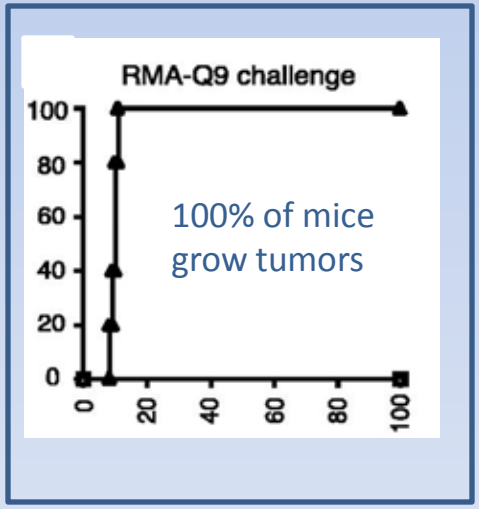


○ Q9 negative melanoma

■ Q9 positive melanoma

Q9 on tumor cells protects B6 mice against RMA thymoma outgrowth





Immunocompetent B6 mice

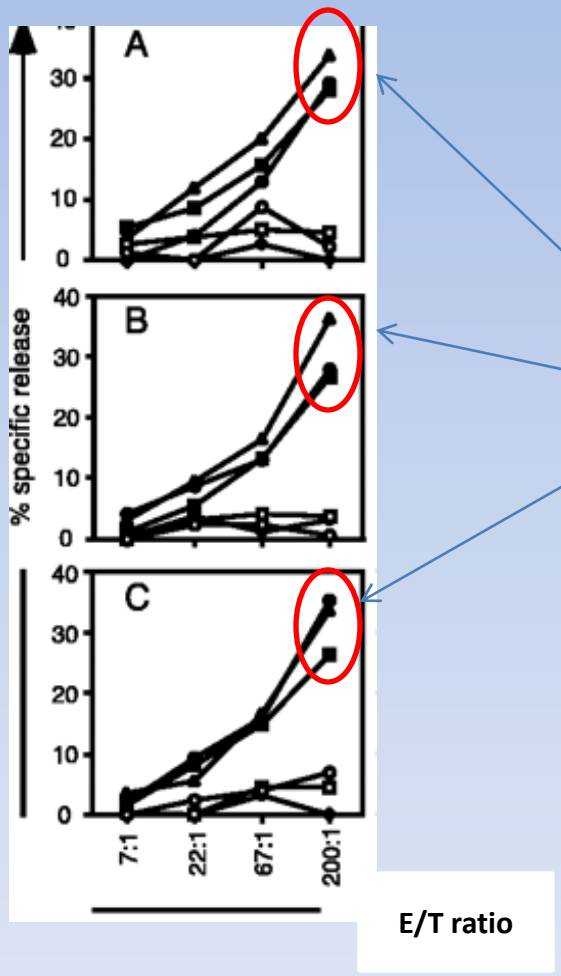
T cell and NK cell deficient B6 mice

CTL from mice immunized with Q9 expressing tumors kill other cancers in vitro

CTL from **Q9** lung cancer survivors

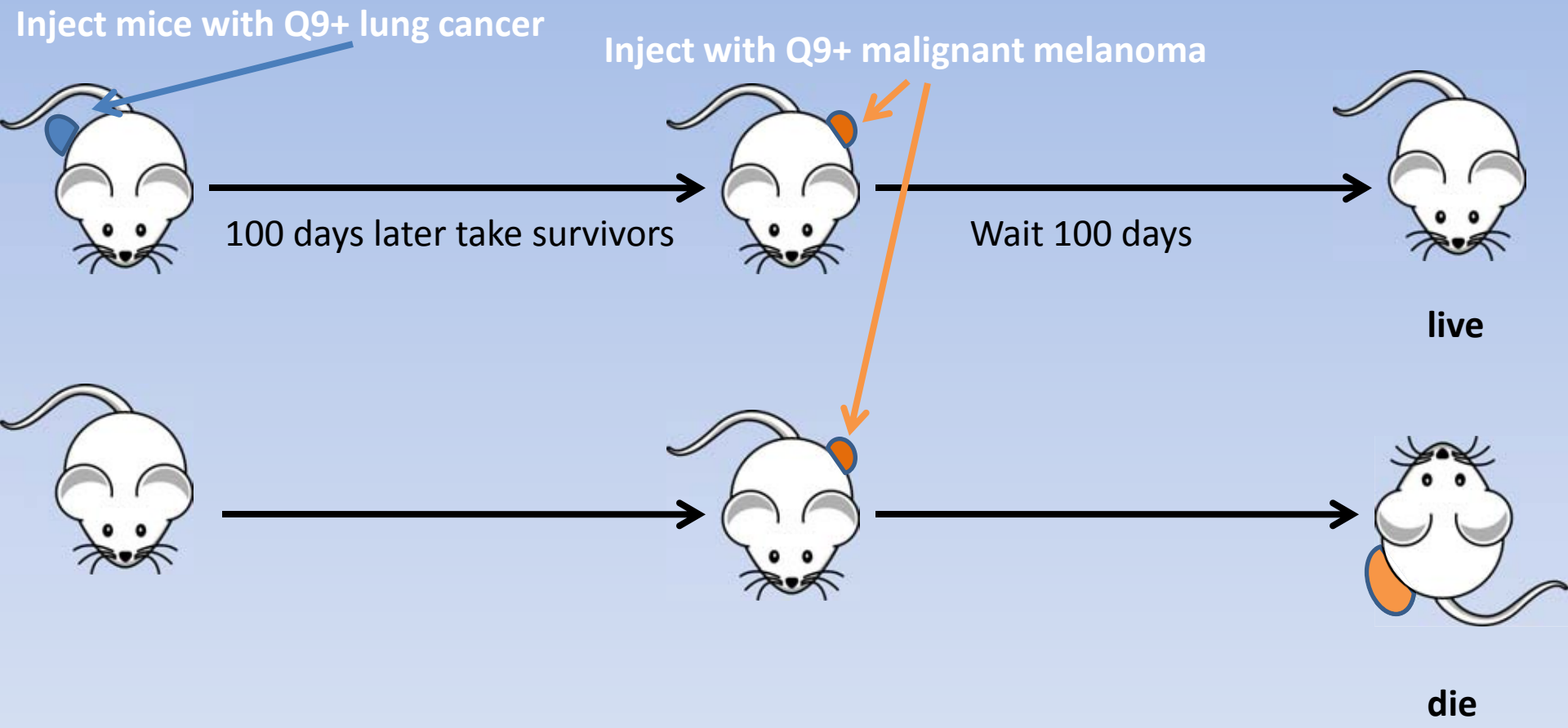
CTL from **Q9** thymoma survivors

CTL from **Q9** Melanoma survivors



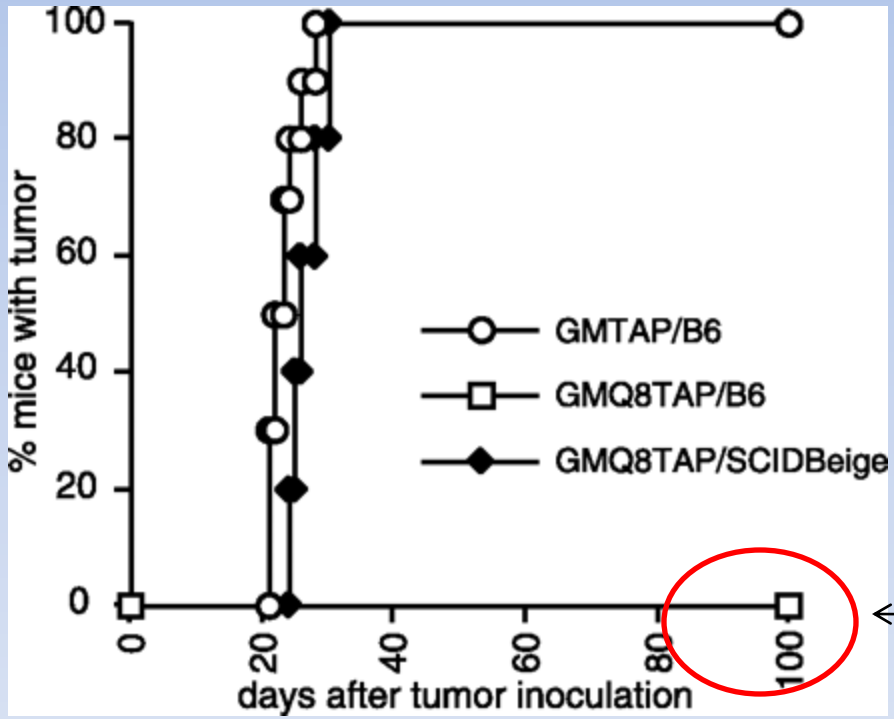
Q9-expressing targets:
lung cancer, thymoma and melanoma

Immunization with Q9 positive lung cancer or thymoma protects from subsequent challenge with a different tumor



Conclusion: Q9 presents CONSERVED ("SHARED") tumor antigens

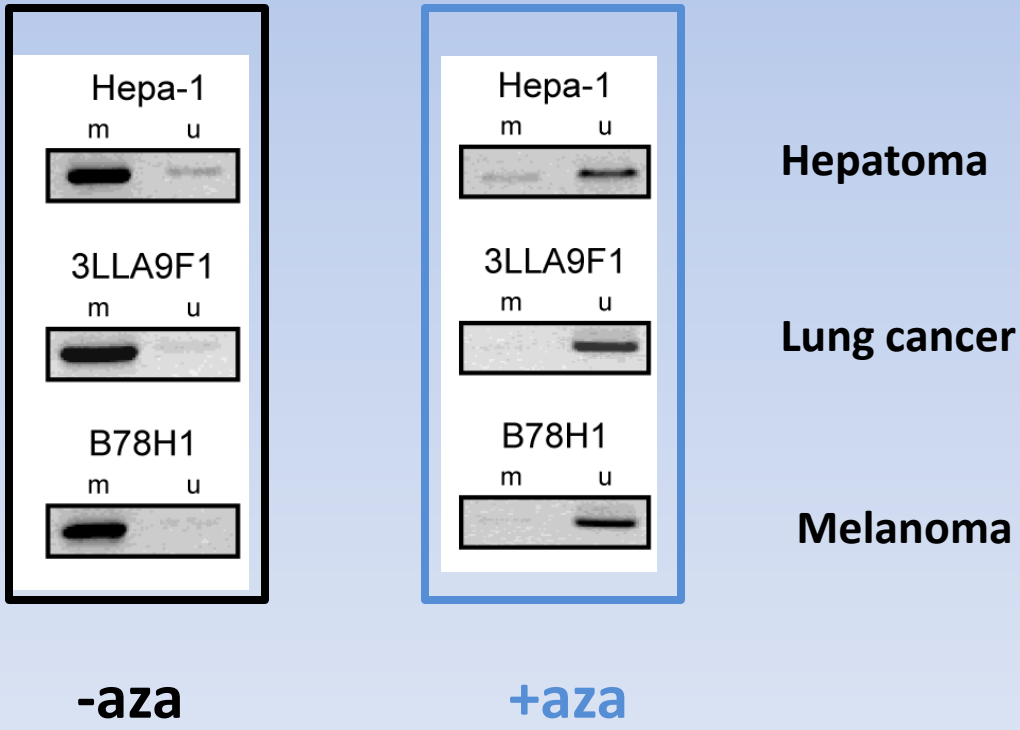
Q8 MHC family member protects immunocompetent B6 mice against malignant melanoma



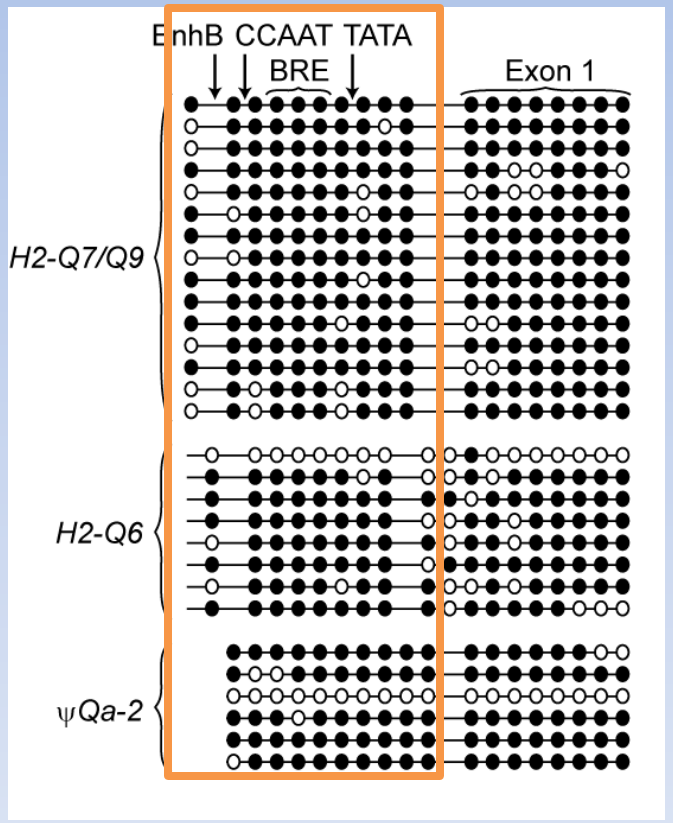
← Protection from tumor

Treatment of tumors with “aza” removes methylathion around MHC (Qa-2)promoters

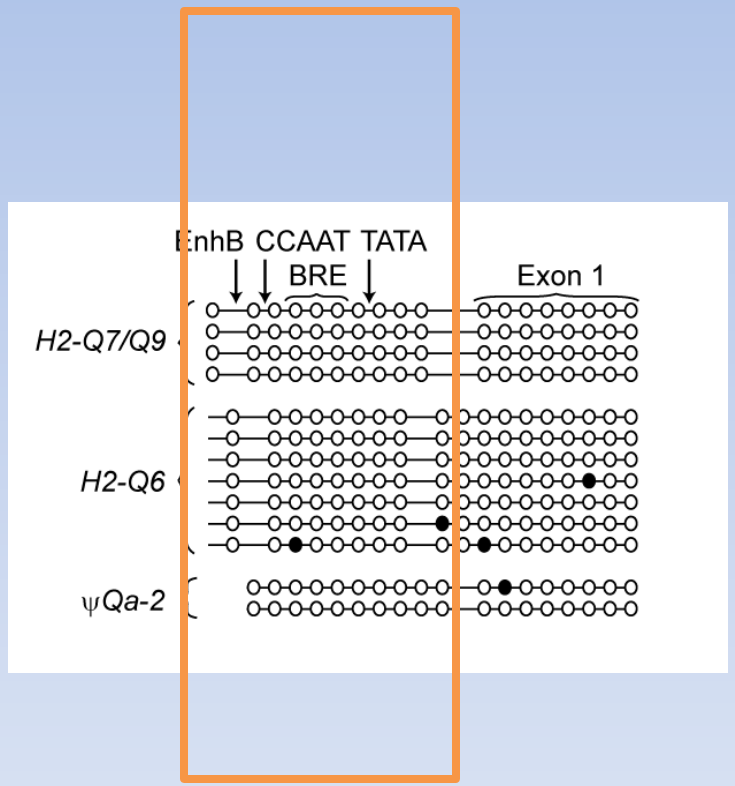
m=methylated, u=unmethylated



Tumor-specific methylation targets multiple CpG sites in the MHC class I promoter

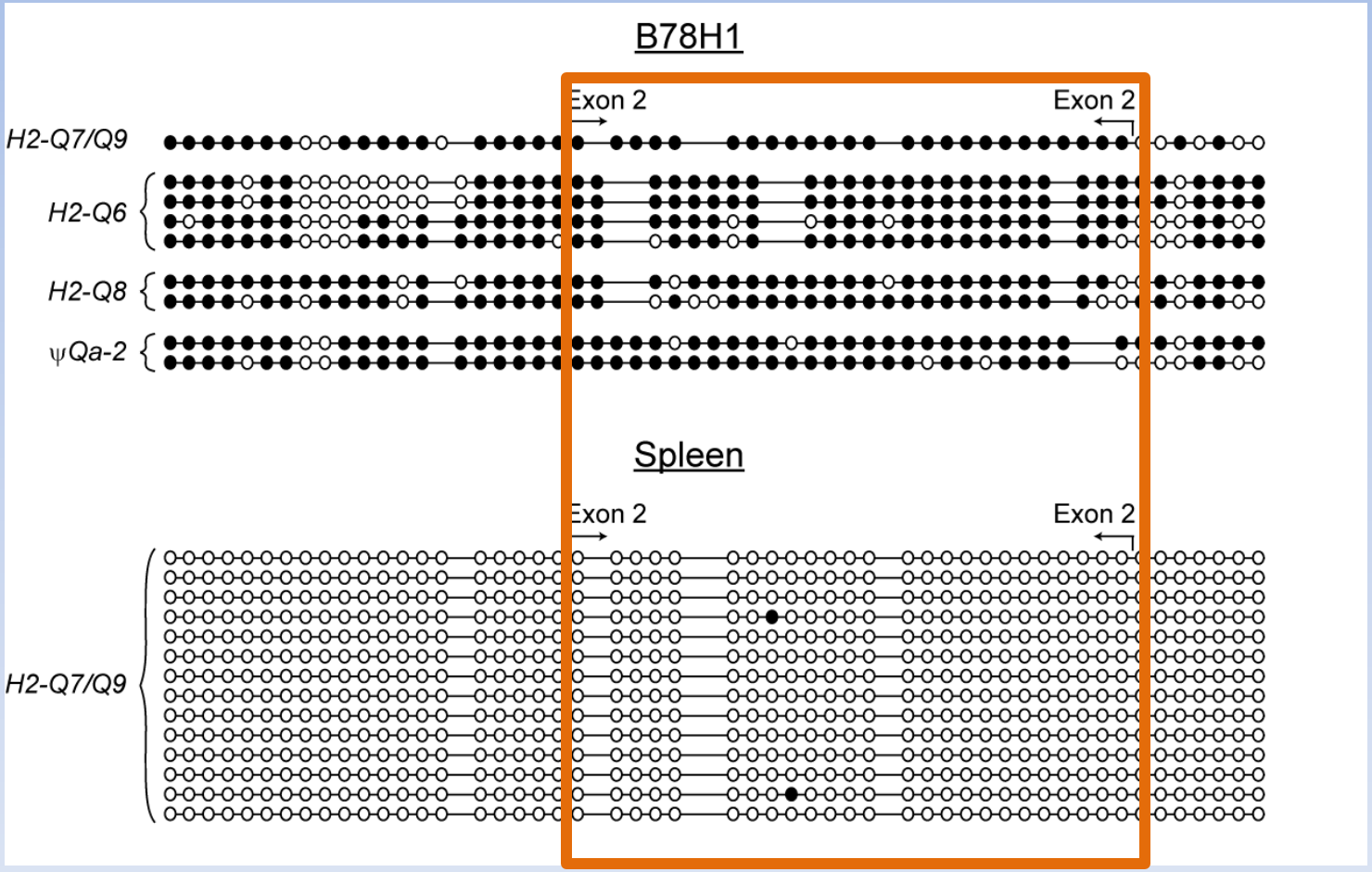


DNA from B78H1 tumor

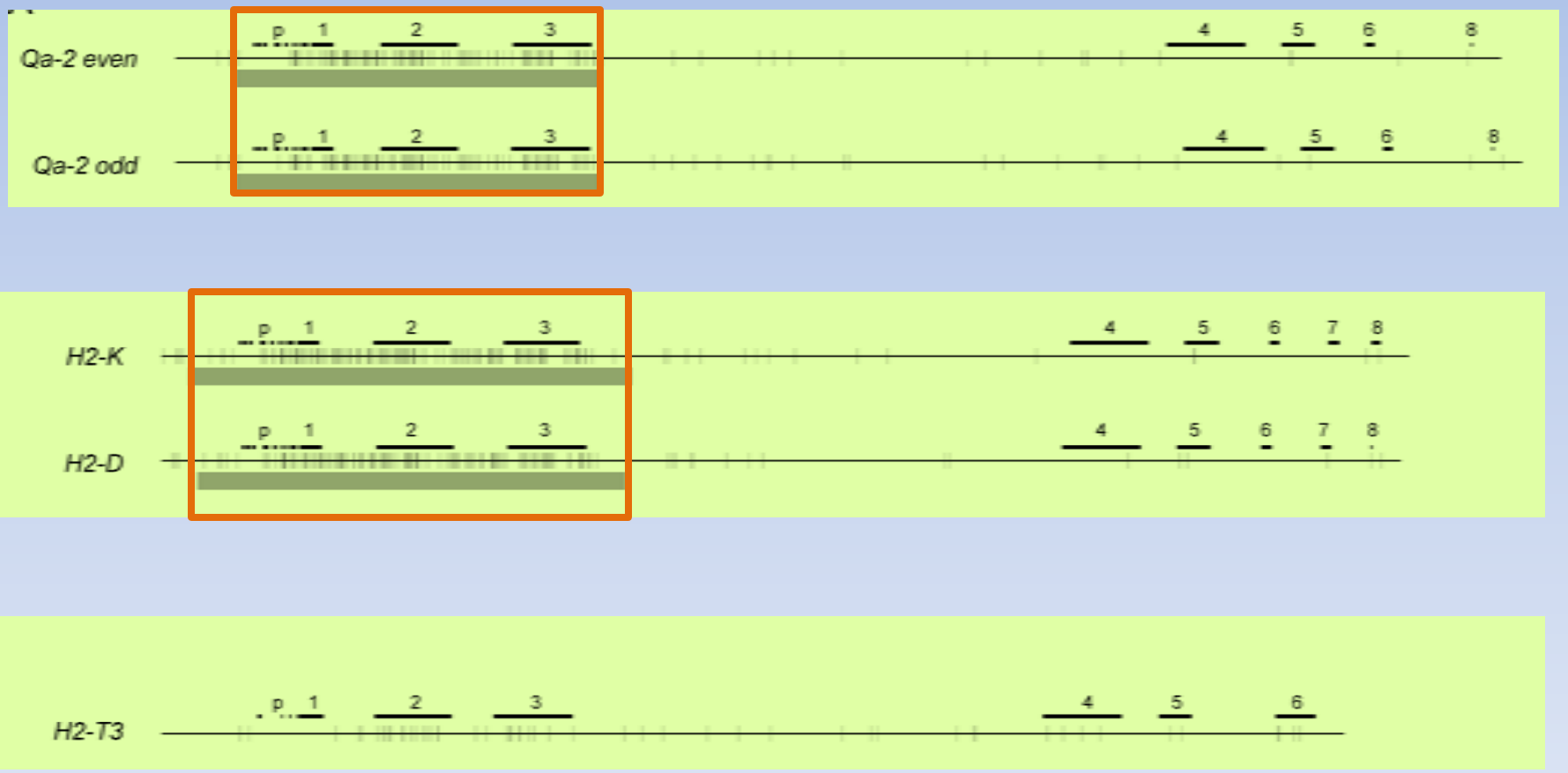


DNA from healthy spleen cells

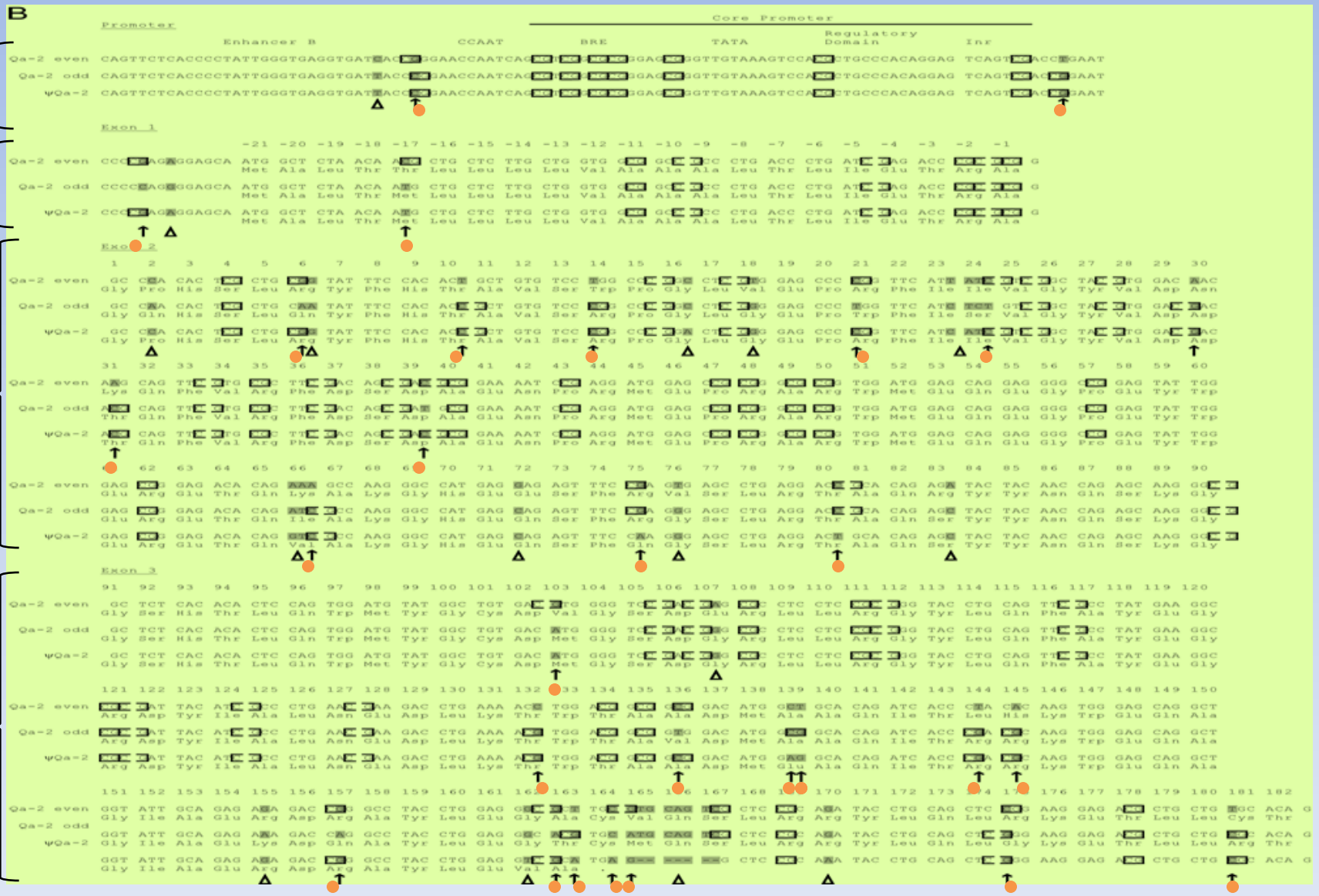
Tumor-specific DNA methylation targets multiple CpG sites in peptide-coding regions



CpG Islands extend into peptide coding regions in most class I MHC genes



DNA polymorphisms in Qa-2 genes occur predominantly at the CpG sites



CONCLUSIONS

1. **Some of the nonclassical class I MHC perform unique functions in the immune system. Their roles are defined by the shape of their peptide binding grooves (antigenic peptides that can bind) and their tissue distributions.**

2. **New class Ib genes evolve very fast: they are continuously created by gene duplications followed by gene mutations targeting mutable methylated CpG sites in their peptide binding coding exons.**

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