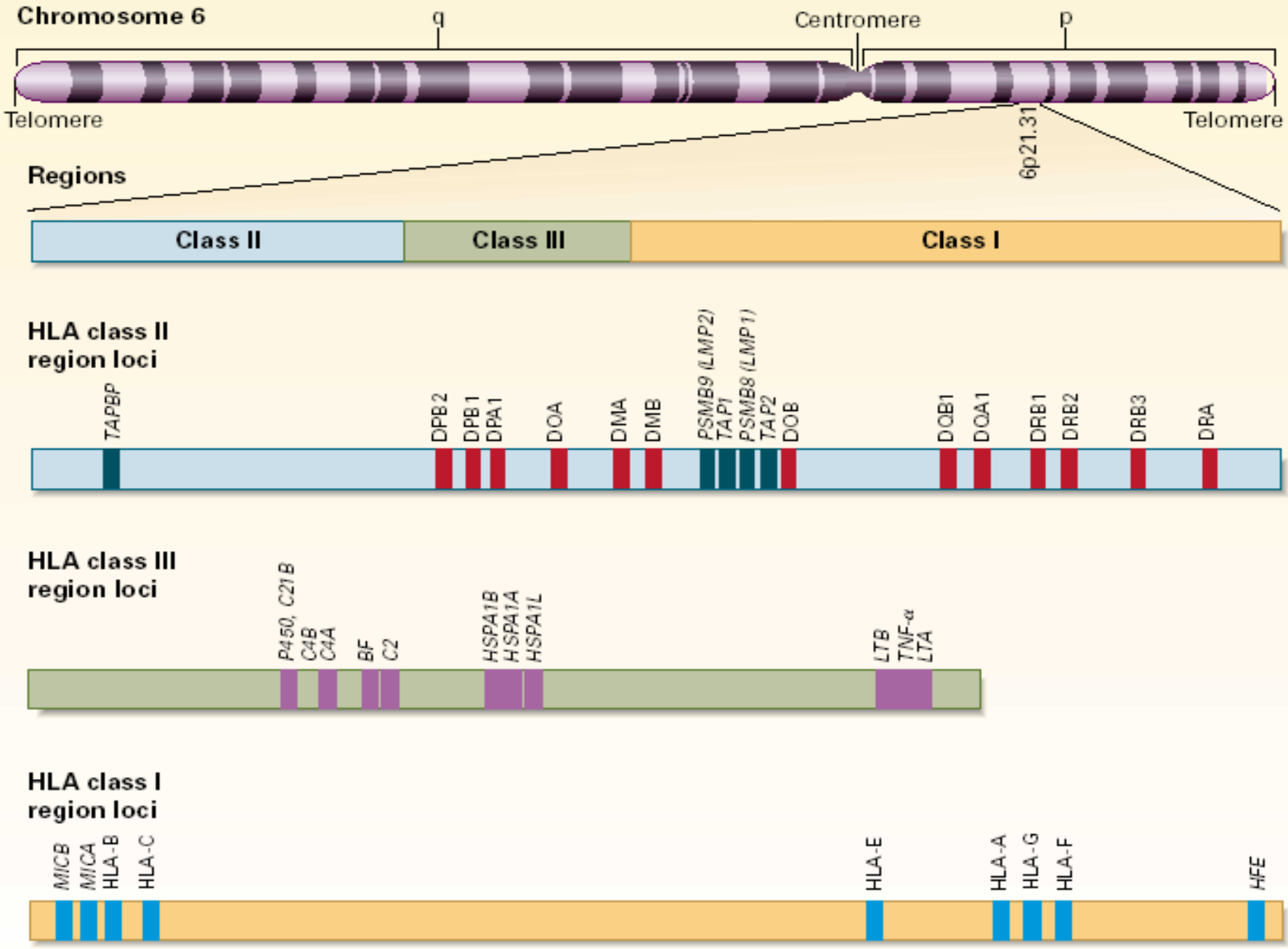
HLA IN HEALTH AND DISEASE

MHC

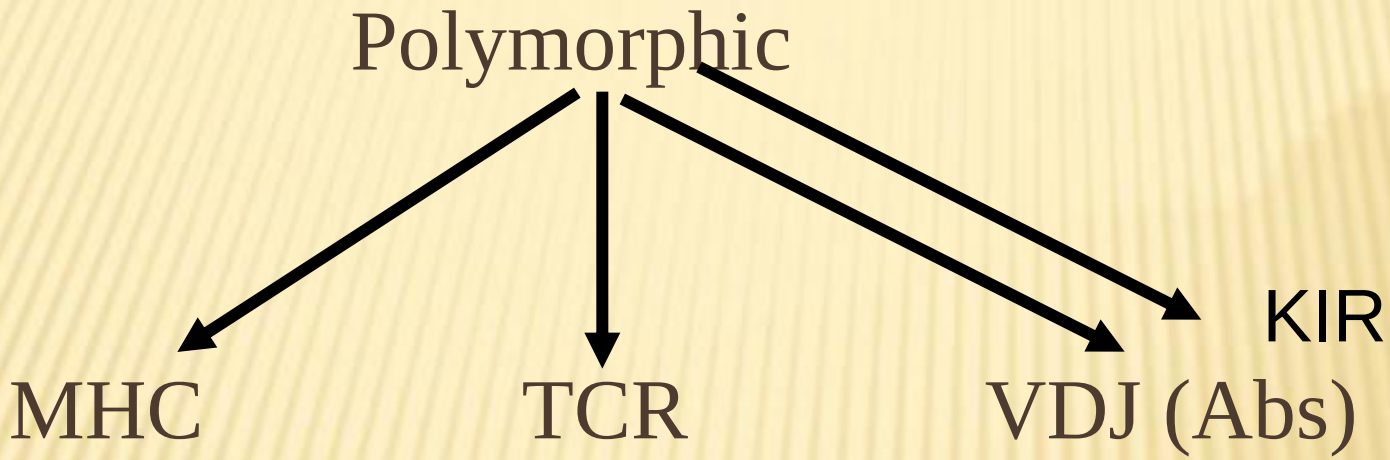
- MHC.(Major histocompatibility complex.)
- The immune system is regulated by molecules coded by some genes.
- These are genes of the histocompatibility system which code for Human leukocyte antigens (HLA).
- HLA : located in the short arm of chromosome 6 (part of MHC).
-


Chromosome 6
q
Centromere
p
Telomere
Telomere
6p21.31
Regions
Class II
Class III
Class I
HLA class II region loci
TAPBP
DPB 2
DPB 1
DPA1
DOA
DMA
DMB
PSMB9 (LMP2)
TAP1
PSMB8 (LMP1)
TAP2
DOB
DQB1
DQA1
DRB1
DRB2
DRB3
DRA
HLA class III region loci
P450, C21B
C4B
C4A
BF
C2
HSPA1B
HSPA1A
HSPA1L
LTB
TNF-α
LTA
HLA class I region loci
MICB
MICA
HLA-B
HLA-C
HLA-E
HLA-A
HLA-G
HLA-F
HFE

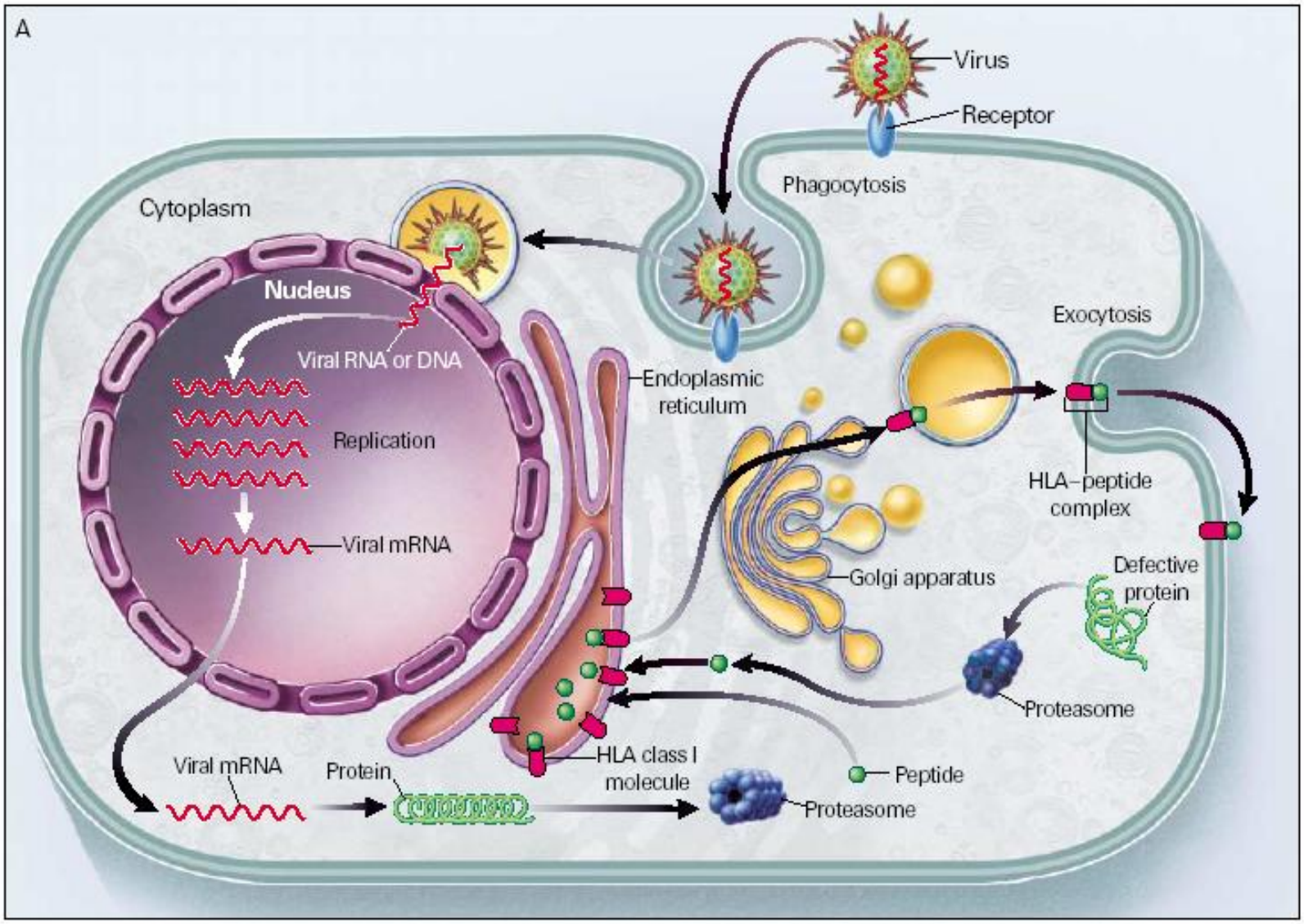
MHC POLYMORPHISM

- Selection pressure
  - Pathogens
  - Hosts (MHC diversity is driven by disassortative mating preferences)
- Cause of MHC polymorphism
  - Heterozygote advantage
    - Different MHC molecules bind different peptides
    - Heterozygous hosts have a broader immune response
    - Degree of MHC heterozygocity correlates with a delayed onset of progress to AIDS
  - Frequency-dependent selection by host-pathogen coevolution
    - Pathogens adapt to the most common MHC alleles
    - Rare alleles have a selective advantage

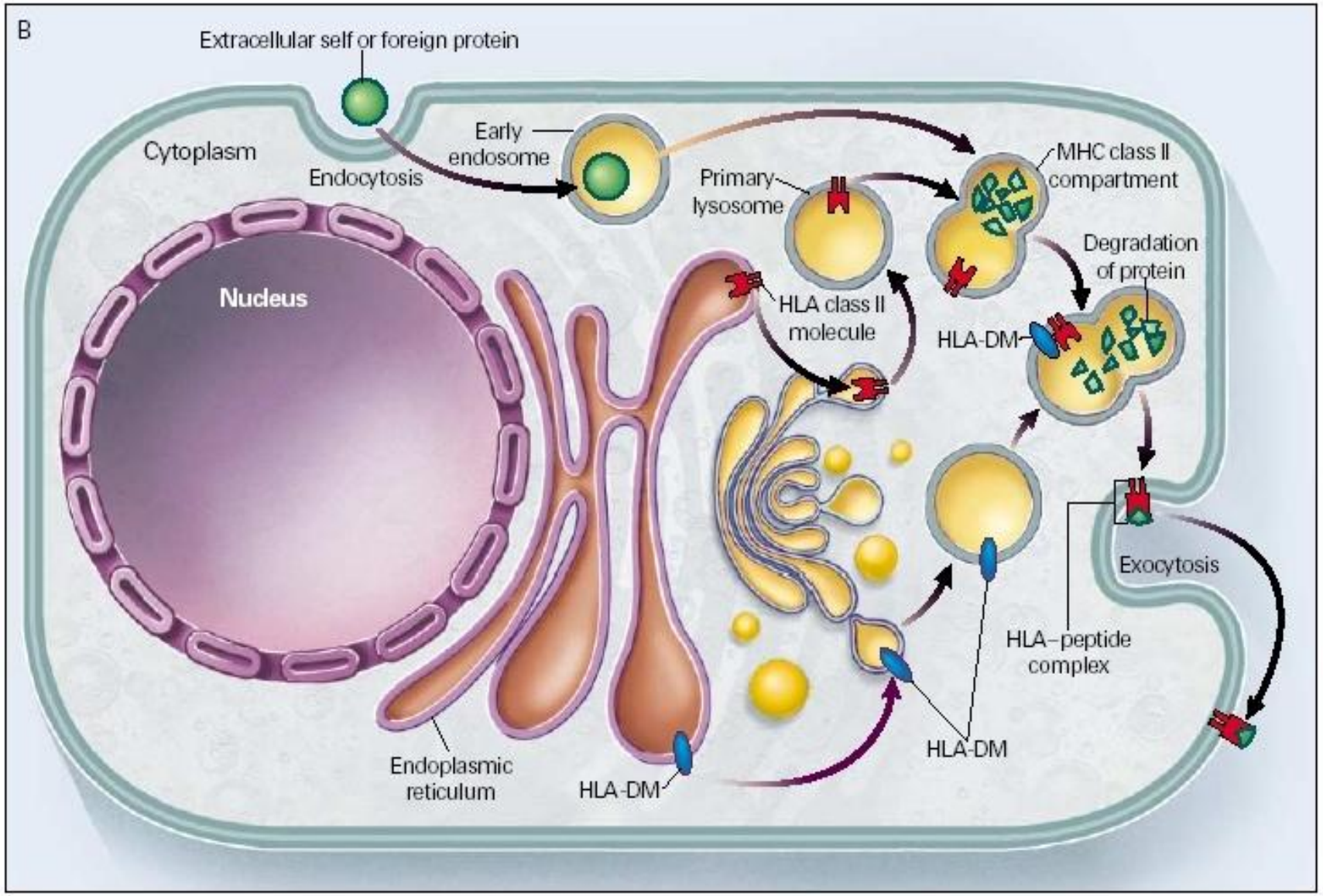
NATURES' MYSTERY



ANTIGEN PRESENTATION BY HLA CLASS I MOLECULES



ANTIGEN PRESENTATION BY HLA CLASS II MOLECULES

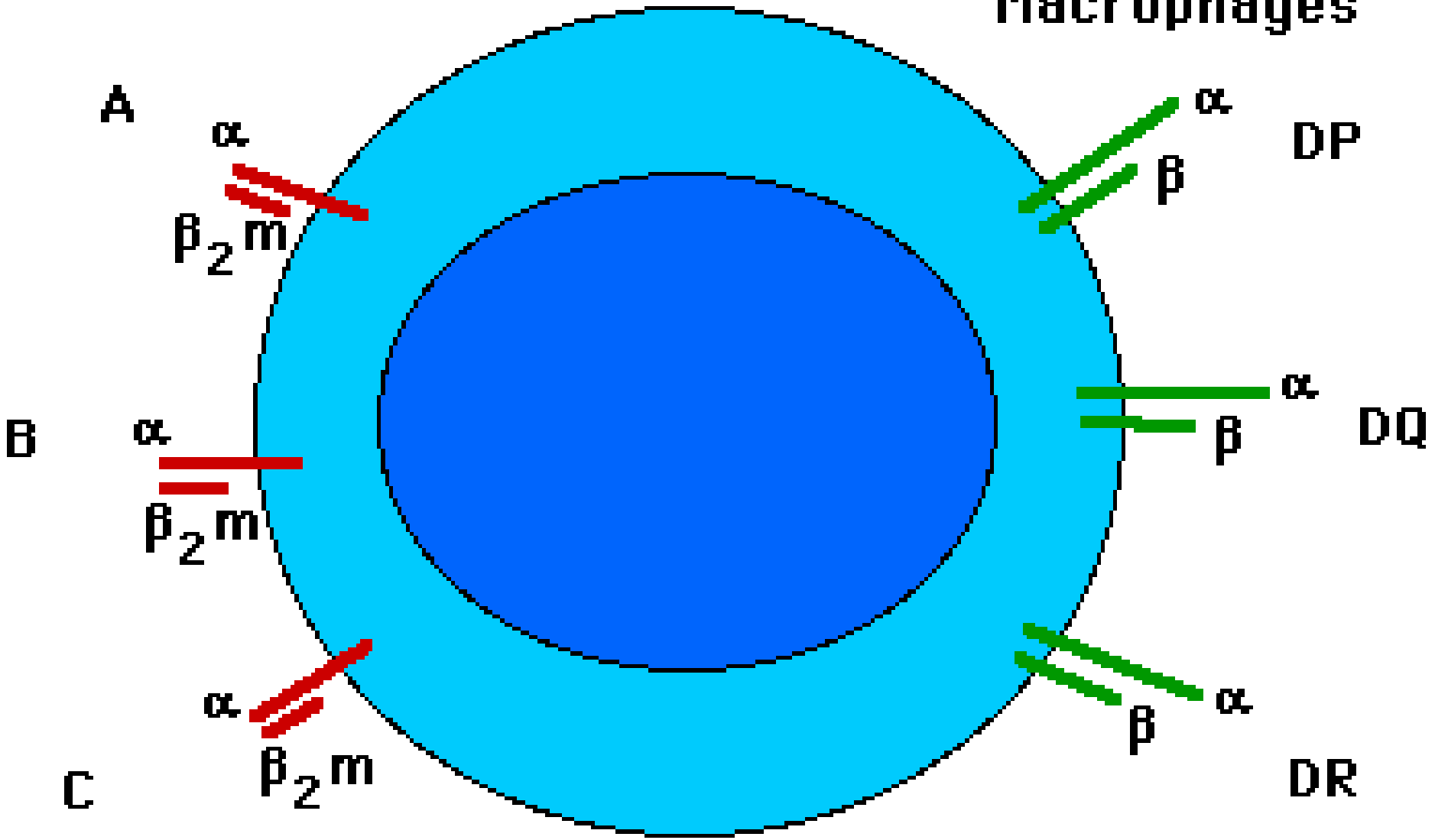


CLASSES

- MHC class 1 : code the molecules
- HLA-A, HLA-B, HLA-C (present in almost all somatic cells)
- MHC class11 : code the molecules
- HLA-DR, HLA-DQ, HLA-DP (expressed in APC , B- cells, activated T-cells, macrophages, dendritic cells, Thymic epithelial cells.)

MHC Class I:
All nucleated cells

MHC Class II:
B cells
APC's
Macrophages



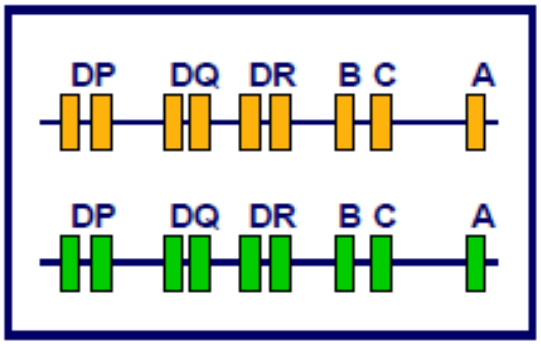
- Each individual have:
- * 2 antigens in each locus.
- * one half inherited from each parent.

- Expression of MHC alleles is Codominant.
- (one haplotype inherited from each parent .)

Inheritance of MHC haplotypes

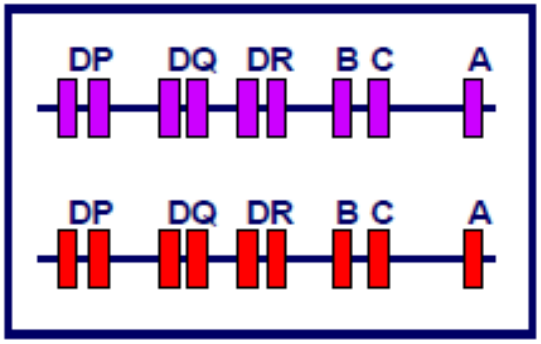
Parents

DP-1,2
DQ-3,4
DR-5,6
B-7,8
C-9,10
A-11,12



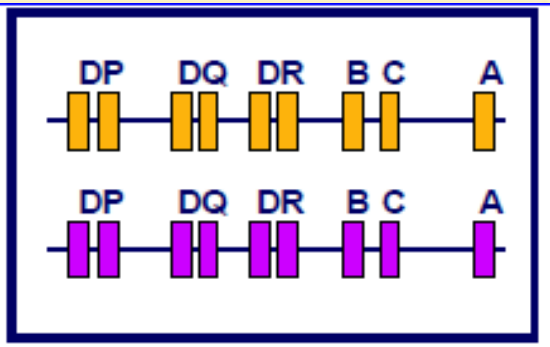
X

DP-9,8
DQ-7,6
DR-5,4
B-3,2
C-1,8
A-9,10

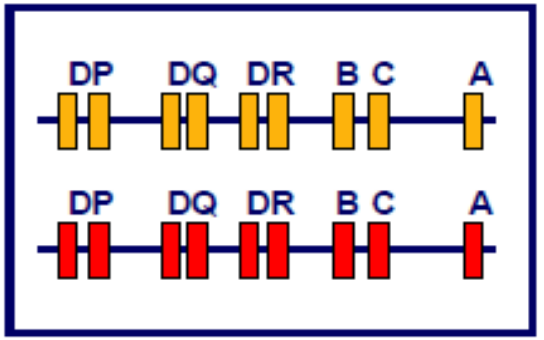


Children

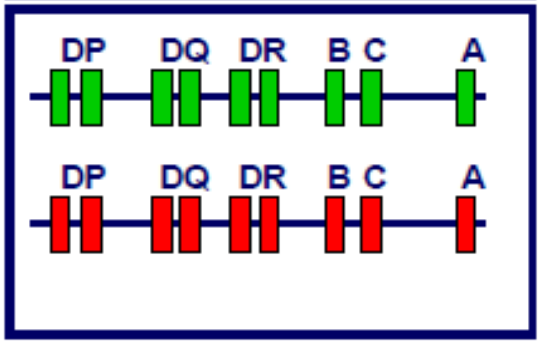
DP-1,9
DQ-3,7
DR-5,5
B-7,3
C-9,1
A-11,9



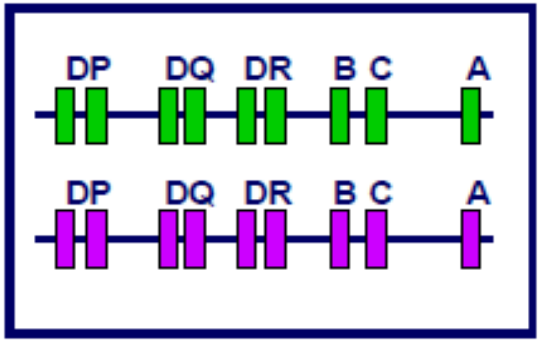
DP-1,8
DQ-3,6
DR-5,4
B-7,2
C-9,8
A-11,10



DP-2,8
DQ-4,6
DR-6,4
B-8,2
C-10,8
A-12,10



DP-2,9
DQ-4,7
DR-6,5
B-8,3
C-10,10
A-12,9



- **HLA: the most polymorphic system in man**
- numerous alleles.
- * various possible combinations.
- * Polymorphism contribute to :
- - the genetic diversity of the species.
- - differences in susceptibility to diseases.
- (among genetically distinct groups.)
- * this make it difficult for large-scale epidemics to occur.

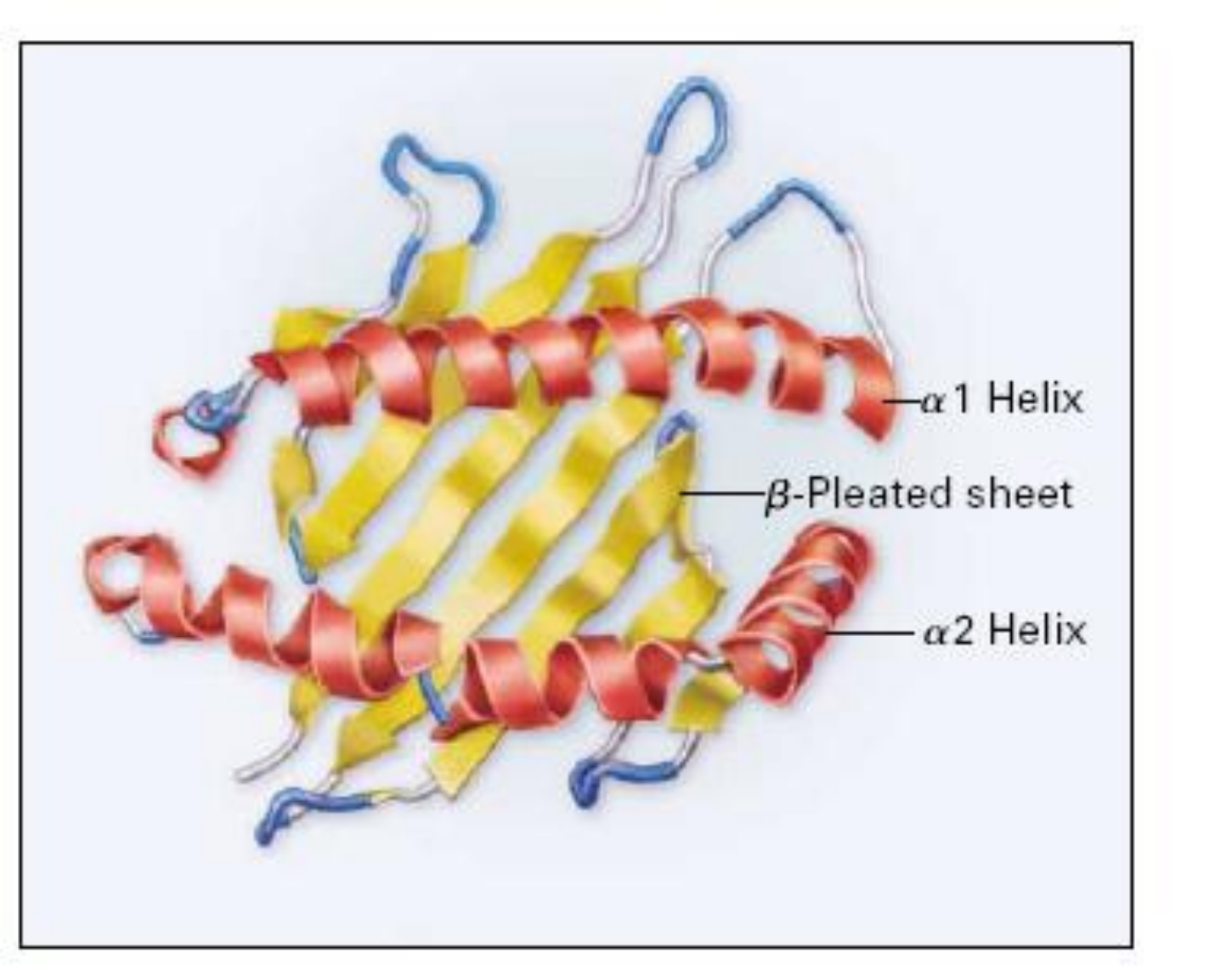
- MHC-binding peptides
- Each human usually expresses:
- 3 types of MHC class I (A, B, C) and
- 3 types of MHC class II (DR, DP,DQ)
- The number of different T cell antigen receptors is estimated to be 1,000,000,000,000,000
- Each of which may potentially recognize a different peptide antigen
- How can 6 invariant molecules have the capacity to bind to 1,000,000,000,000,000 different peptides?

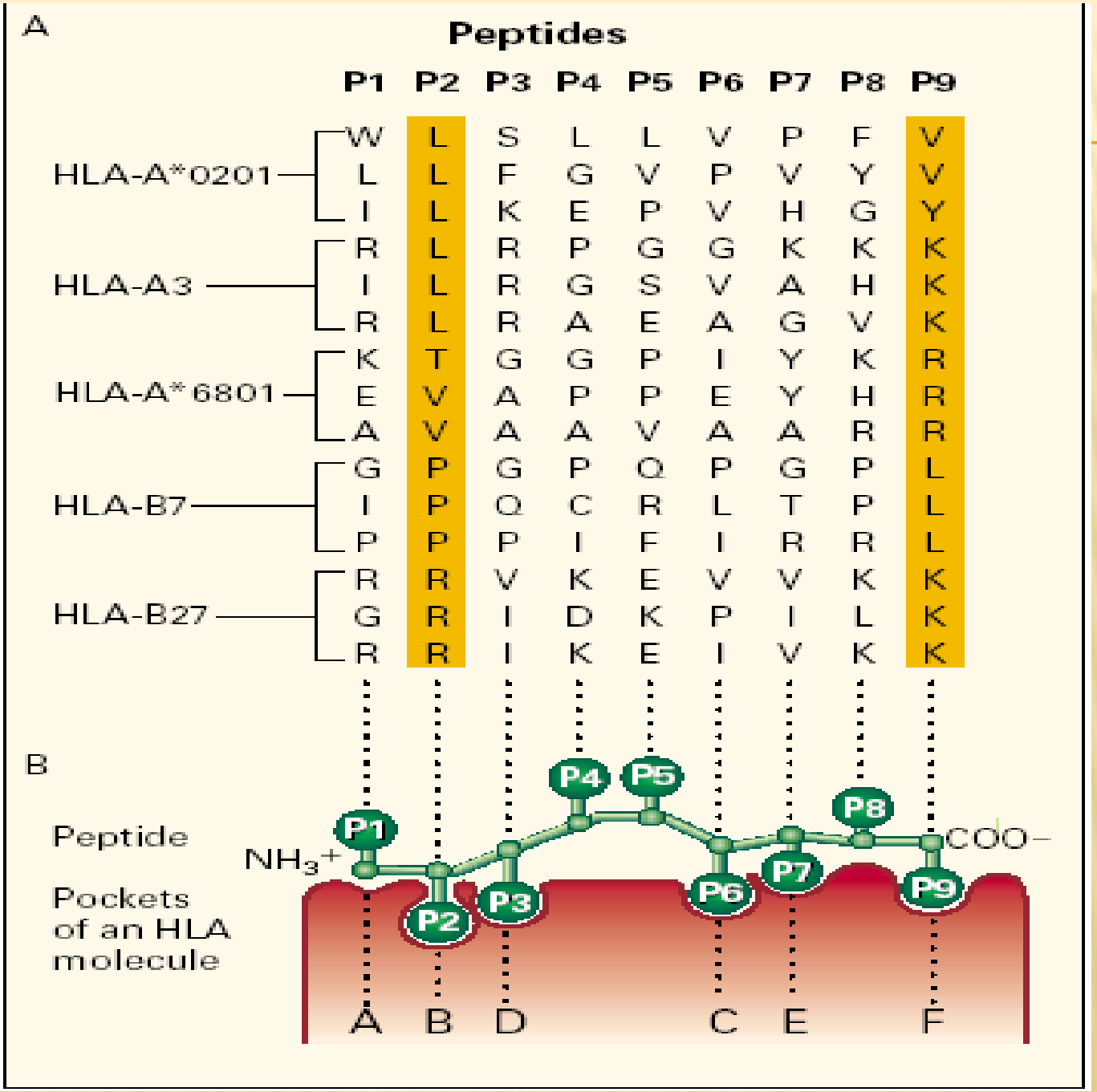
- **“The antigenic universe”.**
- Scientists estimate that the antigenic universe contain between 10^6 -10^7 epitopes.(antigens.)
- This mean that there are at least 10^6 -10^7 epitope –specific T-cell and B-cell. (specific mean that there is a cell, T or B for each of the 10^6 -10^7 epitopes.)
- T-cells only recognize microbial peptides in association with MHC.(restricted)

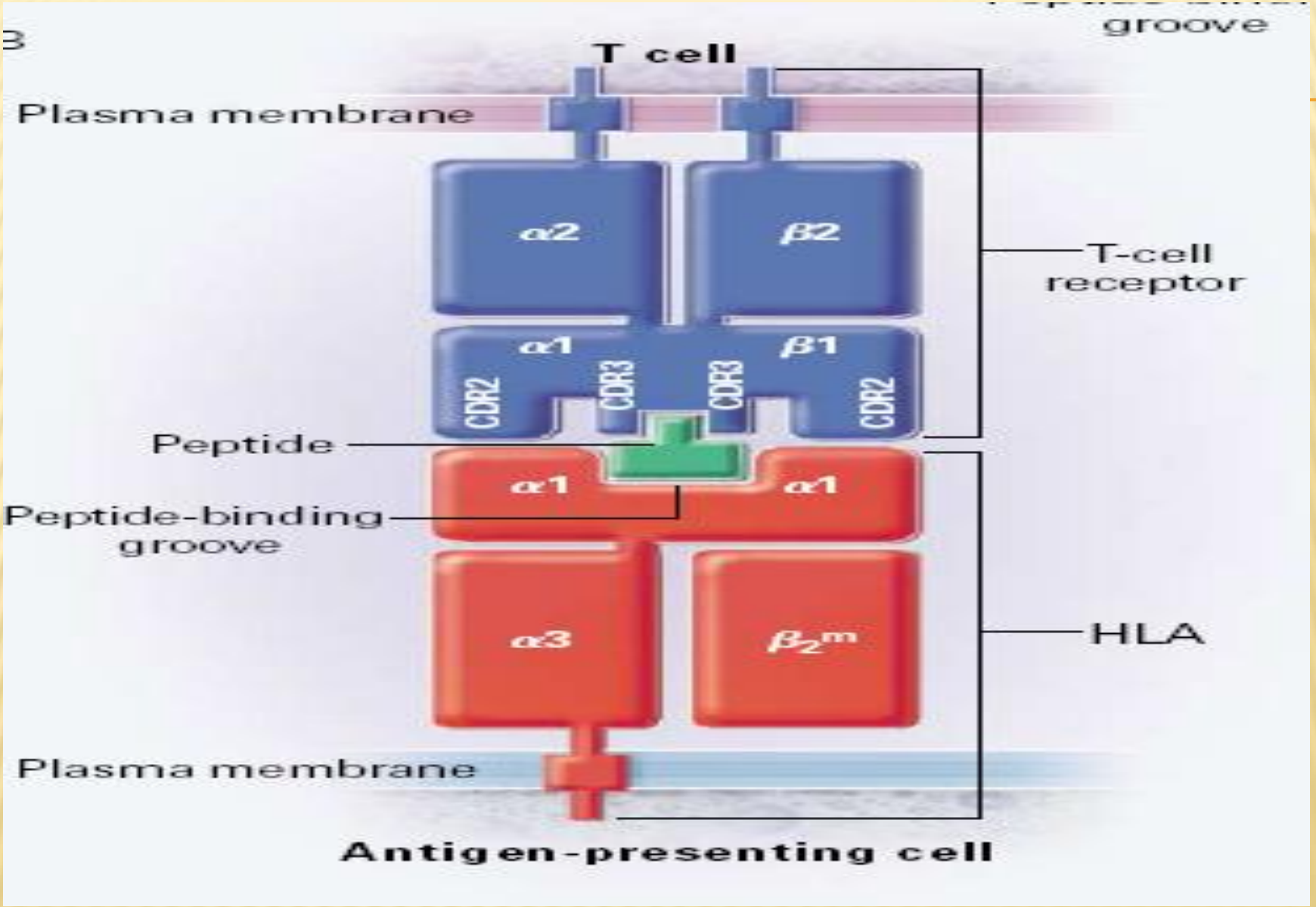
- T-cells only recognize microbial peptides in association with MHC.(restricted)
- * MHC control :
- -resistance to infections.
- -susceptibility to infections.

- Stimulation require 2 signals.
- *Antigen peptide.
- * Co-stimulatory signal.
- (2 key system .)

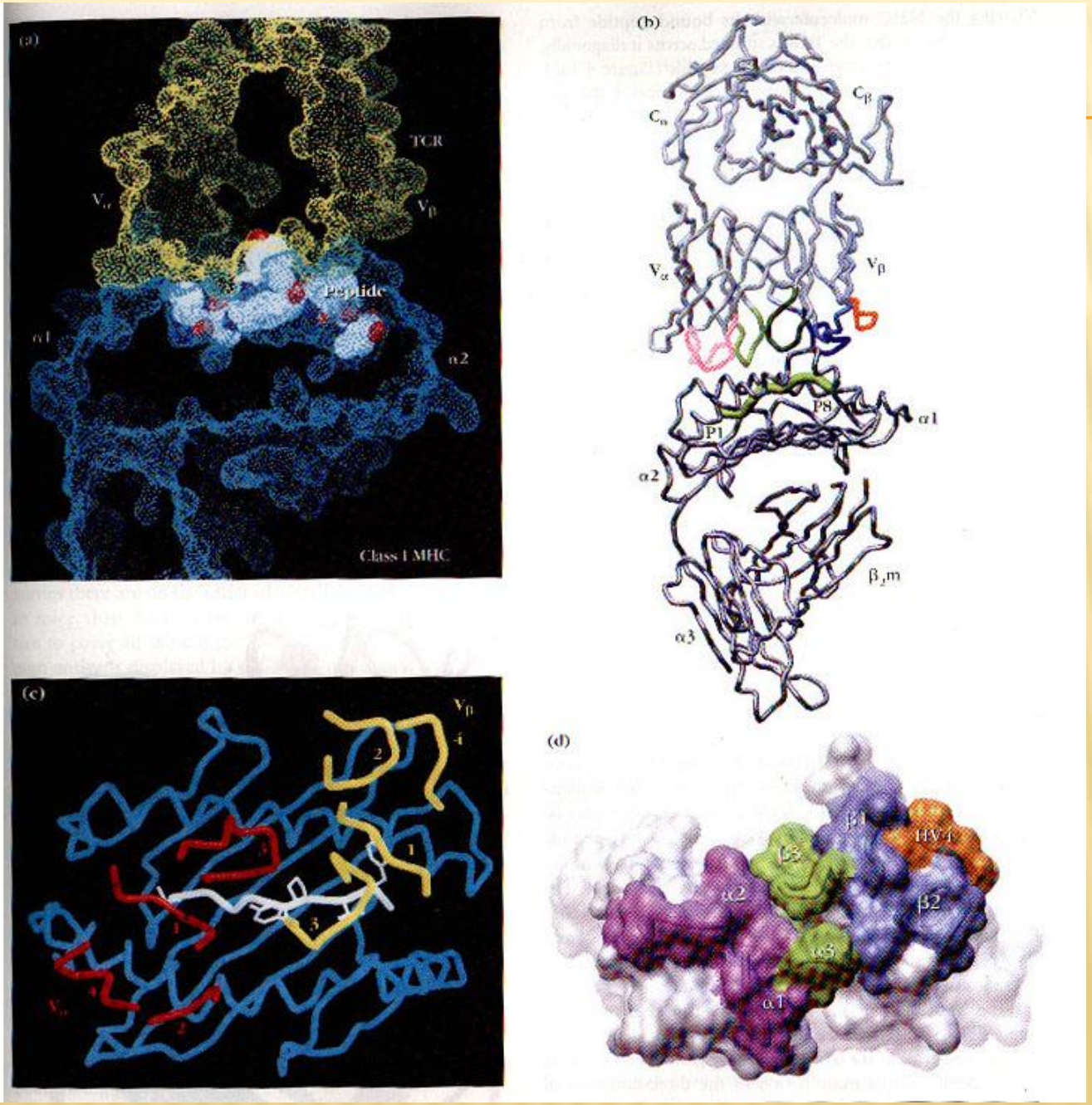
TERTIARY STRUCTURE OF HLA CLASS I BINDING MODULE



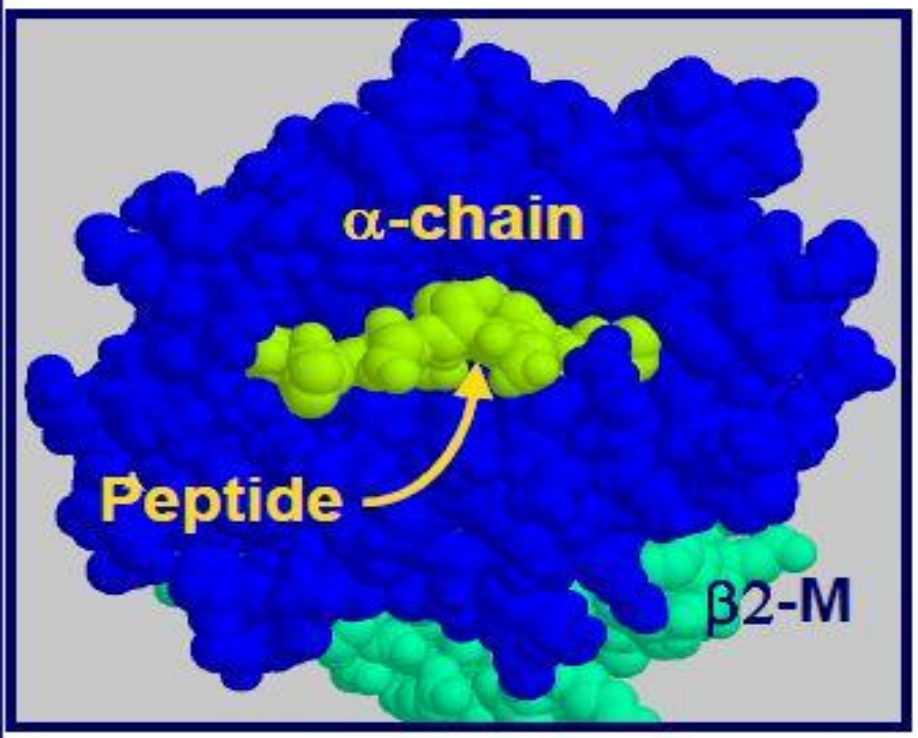

A
Peptides
P1 P2 P3 P4 P5 P6 P7 P8 P9
HLA-A*0201
W L S L L V P F V
L L F G V P V Y V
I L K E P V H G Y
HLA-A3
R L R P G G K K K
I L R G S V A H K
R L R A E A G V K
HLA-A*6801
K T G G P I Y K R
E V A P P E Y H R
A V A A V A A R R
HLA-B7
G P G P Q P G P L
I P Q C R L T P L
P P P I F I R R L
HLA-B27
R R V K E V V K K
G R I D K P I L K
R R I K E I V K K
B
Peptide
Pockets of an HLA molecule
NH3+
COO−
P1
P2
P3
P4
P5
P6
P7
P8
P9
A
B
D
C
E
F

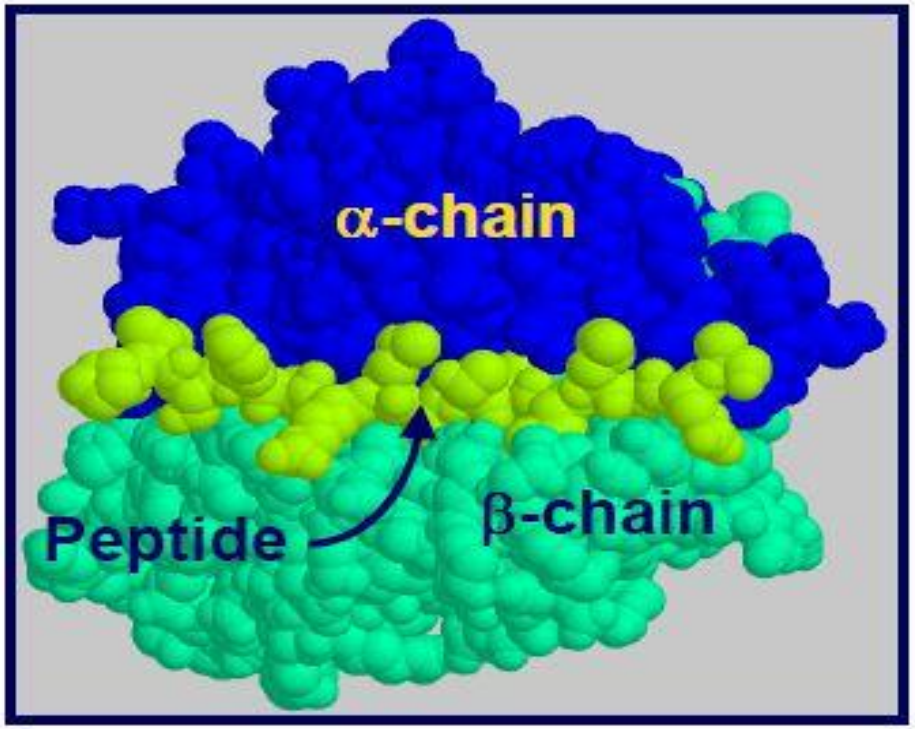

groove
T cell
Plasma membrane
α2
β2
T-cell receptor
α1
β1
CDR2
CDR3
CDR3
CDR2
Peptide
α1
α1
Peptide-binding groove
α3
β2m
HLA
Plasma membrane
Antigen-presenting cell

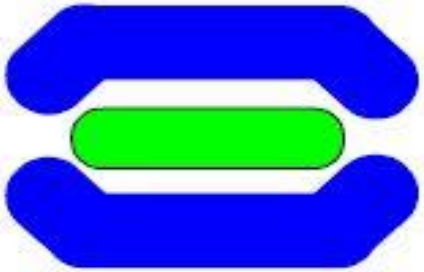
TERNARY COMPLEX



Cleft geometry







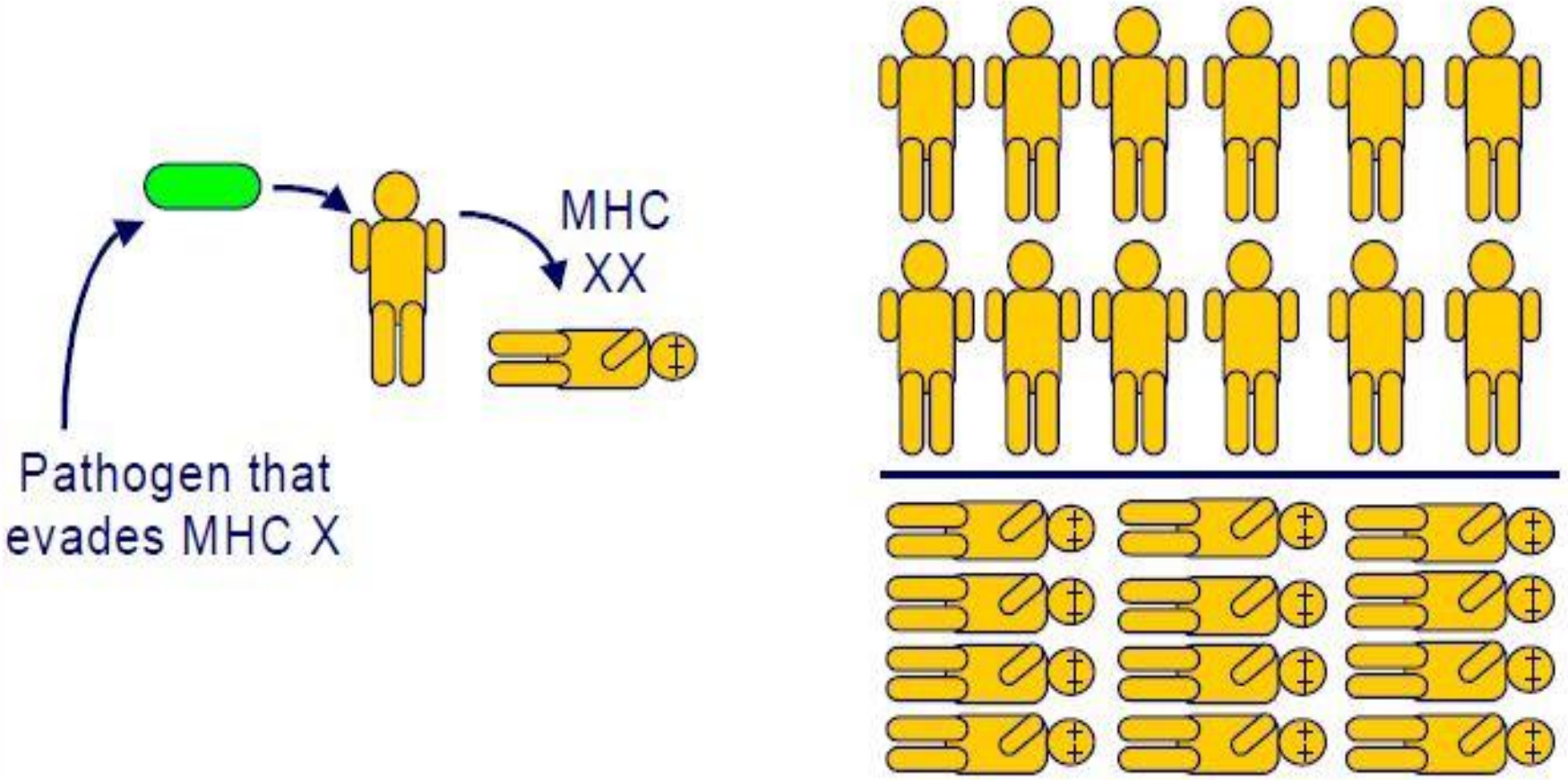
MHC class I accommodate peptides of 8-10 amino acids

MHC class II accommodate peptides of >13 amino acids

- How diverse are MHC molecules in the population?
- ~6 x 1015 unique combinations
- IF • each individual had 6 types of MHC
- • the alleles of each MHC type were randomly distributed in the population
- • any of the 1,200 alleles could be present with any other allele
- In reality MHC alleles are NOT randomly distributed in the population
- Alleles segregate with lineage and race

	Frequency (%)		
Group of alleles	CAU	AFR	ASI
HLA-A1	15.18	5.72	4.48
HLA- A2	28.65	18.88	24.63
HLA- A3	13.38	8.44	2.64
HLA- A28	4.46	9.92	1.76
HLA- A36	0.02	1.88	0.01

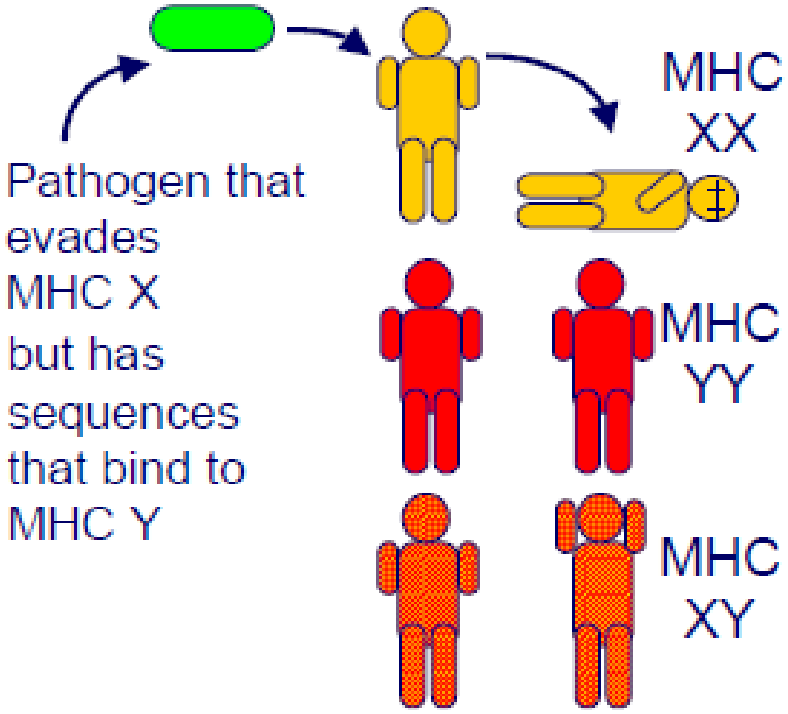
Example: If MHC X was the only type of MHC molecule



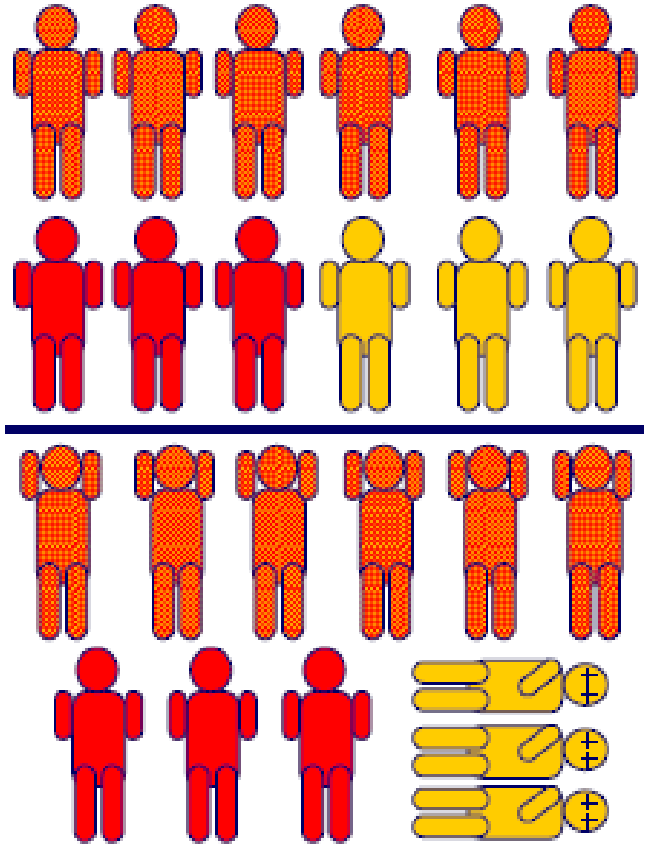
Survival of individual threatened

Population threatened with extinction

Example: If each individual could make two MHC molecules, MHC X and Y

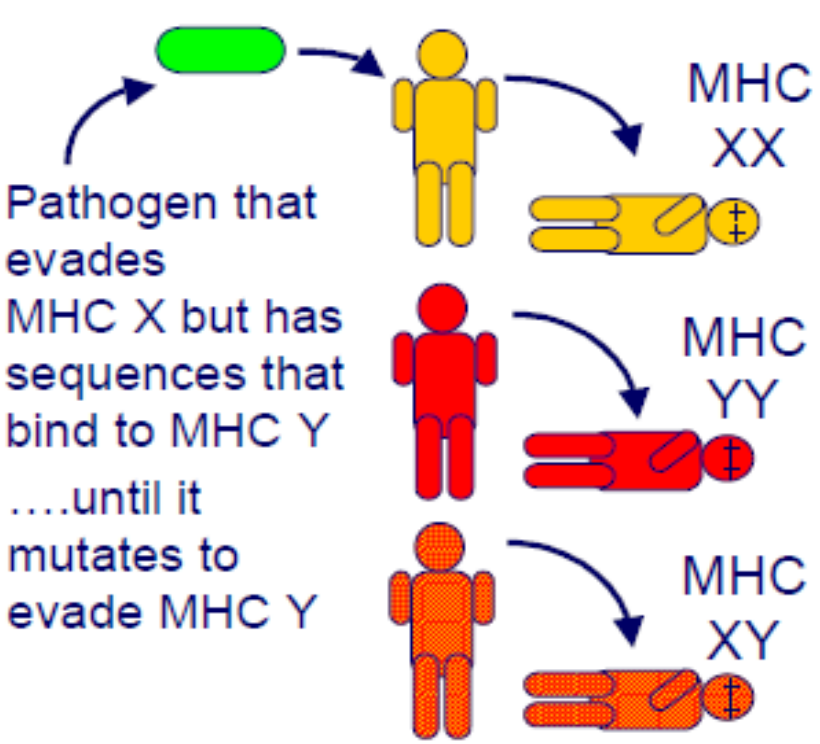


Impact on the individual depends upon genotype

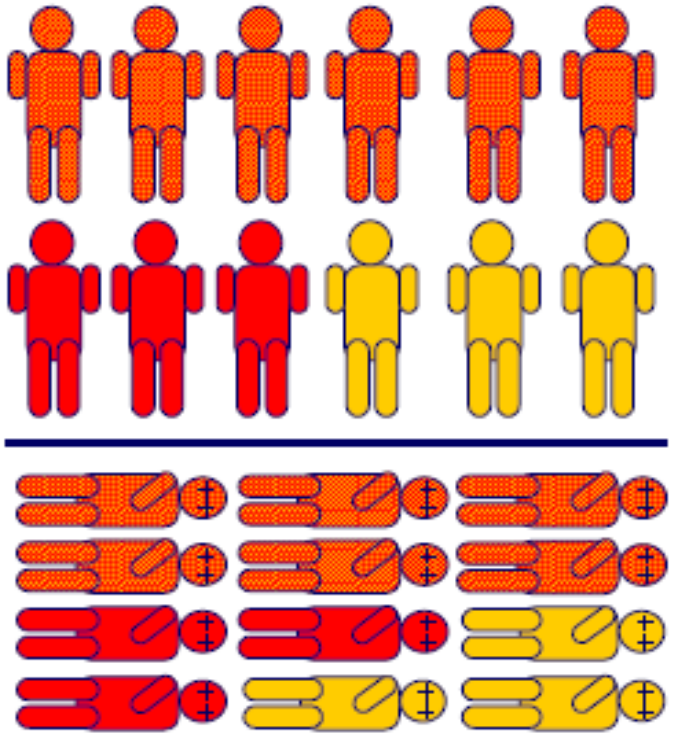


Population survives

Example: If each individual could make two MHC molecules, MHC X and Y……and the pathogen mutates



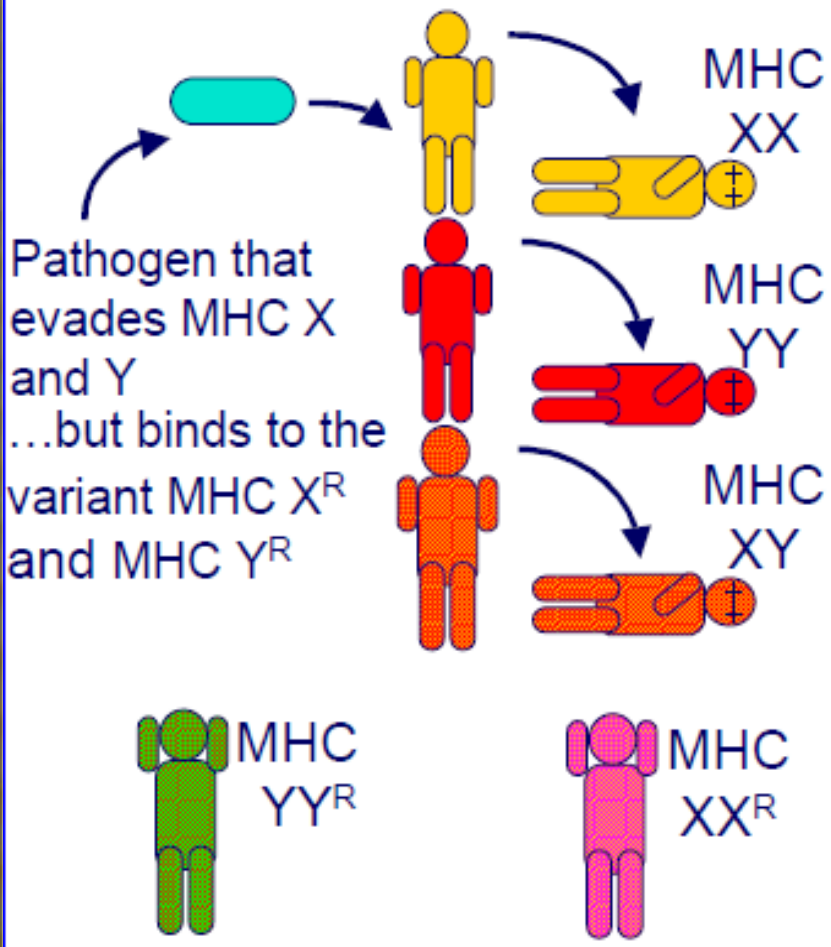
Survival of individual threatened

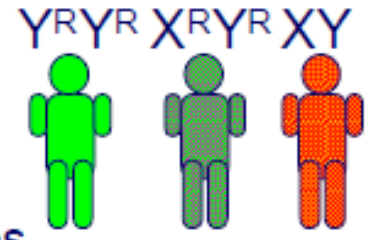


Population threatened with extinction

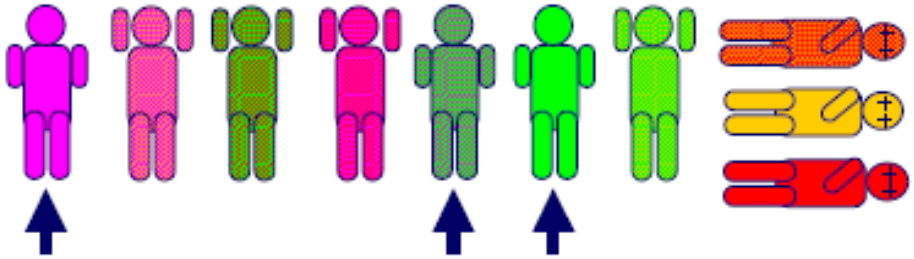
The number of types of MHC molecule can not be increased *ad infinitum*

Variant MHC molecules protect the population



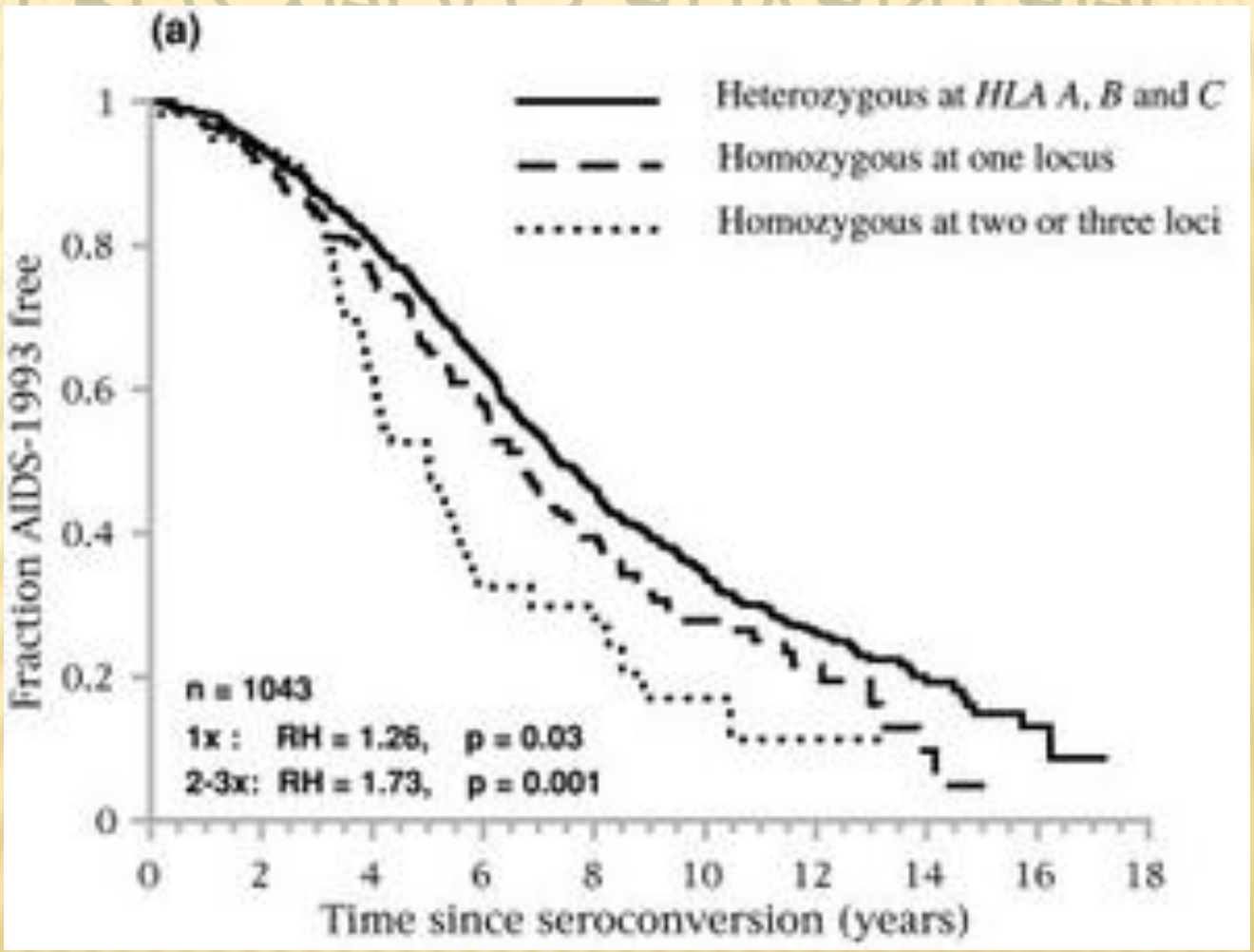


From 2 MHC types
and 2 variants…….
10 different genotypes



Variants – alleles - of each type of MHC gene encode proteins that increase the resistance of the population from rapidly mutating or newly encountered pathogens without increasing the number of types of MHC molecule

HETEROZYGOUS ADVANTAGE



- Genetic factors are one of the main determinants of susceptibility to infectious diseases.
- The same infectious agent may cause different immune responses in different infected individuals.
- The HLA is responsible for the varied clinical forms of some diseases.

TUBERCULOSIS:

- Organ susceptibility appear to have a genetic basis related to the polymorphism of the HLA region. HLA-DR2 (expressed by the alleles
- HLA-DRB2*1501 & HLA-DRB1*1502),

- * Associated with severe multibacillary T.B. greater prevalence of forms resistant to drug therapy.

Disease	HLA Antigen	Relative risk
Rheumatic Ankylosing Spondylitis	B27	69.1
Hematologic		
-Idiopathic	A3	6.7
-Hemochromatosis	B14	26.7
	A3,B14	90.0
Neurology		
-Narcolepsy	DR2	130.0
TB MKU	DRB1*1501	
PSORIASIS MKU	A1-B57	

- HLA alleles vary in ethnically different populations.
- * alleles that confer resistance to certain pathogens are prevalent in areas where they cause endemic diseases.
    - **e.g. In Poles :**
- HLA-DR16 increase risk of T.B.
- HLA-DR 13 protect against T.B.
    - **In India:**
- HLA-A10, -B8 &-DR2 increase risk of T.B.

MALARIA :

- In Thailand,

  HLA-B46, -B56 & HLA-DRB1*1001,

- Are found in patients with severe non-cerebral & cerebral malaria.

- * An association with HLA-B53 and protection is well established.

HLA ASSOCIATION WITH MALARIA
HILL ET AL., 1991, NATURE (OXFORD)

	Serology		PCR	
	No.	HLA-Bw53(%)	NO.	HLA-Bw53(%)
Severe Malaria	306	15.7	307	16.9
Mild controls	144	24.3	364	25.4
Mild malaria	_	_	353	22.6
Healthy adults	112	25.0	106	26.4

HLA AND HIV CO-EVOLUTION?

ALLELES:

HLA-A	No=309
HLA-B	No=563
HLA-C	No=167

$CD8^+$ T cells → HLA-B Restricted

HIV Ag Variation ← HLA-B
(nef & gag)

↓

25 Polymorphism –HLA-B
12Polymorphism-HLA-A
9 Polymorphism-HLA-C

HLA IN PHARMACOGENOMICS

Immune Mediated Adverse Drug Effects (IMADE):

- MHC Gene polymorphism - drug allergy.

- ↑HLA DRB1*0401 & HLA DRB1*0404 - RA.

- ↑HLA-A3,B52,DR16,DQ5m,DQ8 & DQ9

  ↓HLA-A24,B35,B44,DQ6 & DQ7 -NSAID intolerance.

- HLA-B*1502-carbamazapine -Stevens-Jhonson syndrome.

- HLA-B*5701-hypersensitivity to Abacavir(RT inhibitor).

MATING & MHC

- Mating pattern is seminatural
- Populations of mice influenced by MHC genotype
- Seminatural population genotyped♀
- Extra territorial Sires ♂
- Pups genotyped (Paternity identified)
- Homozygous reduction
- Heterozygous advantage
- (Pathogen driven?) MHC polymorphism.

Potts et al., 1991. Nature.352.p.619.

IMMUNOINFORMATICS

- Epitope driven vaccines-‘Reverse Immunogenetics’
- T & B EPITOPES
- Promiscous epitopes!!!
- EPITOPE MAPPING
- BlastiMer for putative epitopes
- Patent Blast
- EpiMatrix, Conservatrix, TEPITOPE
- EpiAssembler – EpiVax
- *In silico* vaccine design

EPITOPE MAPPING &VACCINE DESIGN

- Traditional barriers in vaccines design & development
- Two global epidemics
- HIV / TB
- Phase I human clinical trial
- Informatics tool required

NEW TOOLS?

- Microarrays
- Bio-informatics
- Immunoinformatics
- Immunogenomics
- Immunomics

IMMUNOME

Set of immunogenic epitopes derived from pathogens
= ‘Immunome’
Epitope favouring HI → Pathogenicity???
Epitopes favouring CMI → Immunogenicity
To predict secretory signal peptide (SignalP – Menne et al.,2000)
To predict transmembrane domains
(TMpred - Suhan & Hovde, 1998)
To predict lipoprotein attachment sites
(Prosite Scan - Falquet et al., 2002)

EPITOPE – DRIVEN VACCINES

- T/B/ T-B/CTL epitopes based vaccines (An &Whitton,1997; An et al., 2000)
- Mix several plasmids together, each of which contains given epitope (either T/B/T-B/CTL) from different protein or different mini-gene epitope that induce only Th1 type immune response.

HLA TRANSGENICS

- A number of transgenic mouse strains that express the most common HLA-A, B and DR molecule has been developed to mimic the human host ("HLA transgenes")
  (Ishioka et al.,1999; Charo et al., 2001)

HLA transgenics are now routinely used to access and optimize vaccines in preclinical studies

"The Race Factor"

LA Times, Sept 8, 2003

"Some racial differences are encoded in the genes, and those differences can make people of one skin color inherently more or less susceptible to certain diseases than people whose complexion is different.

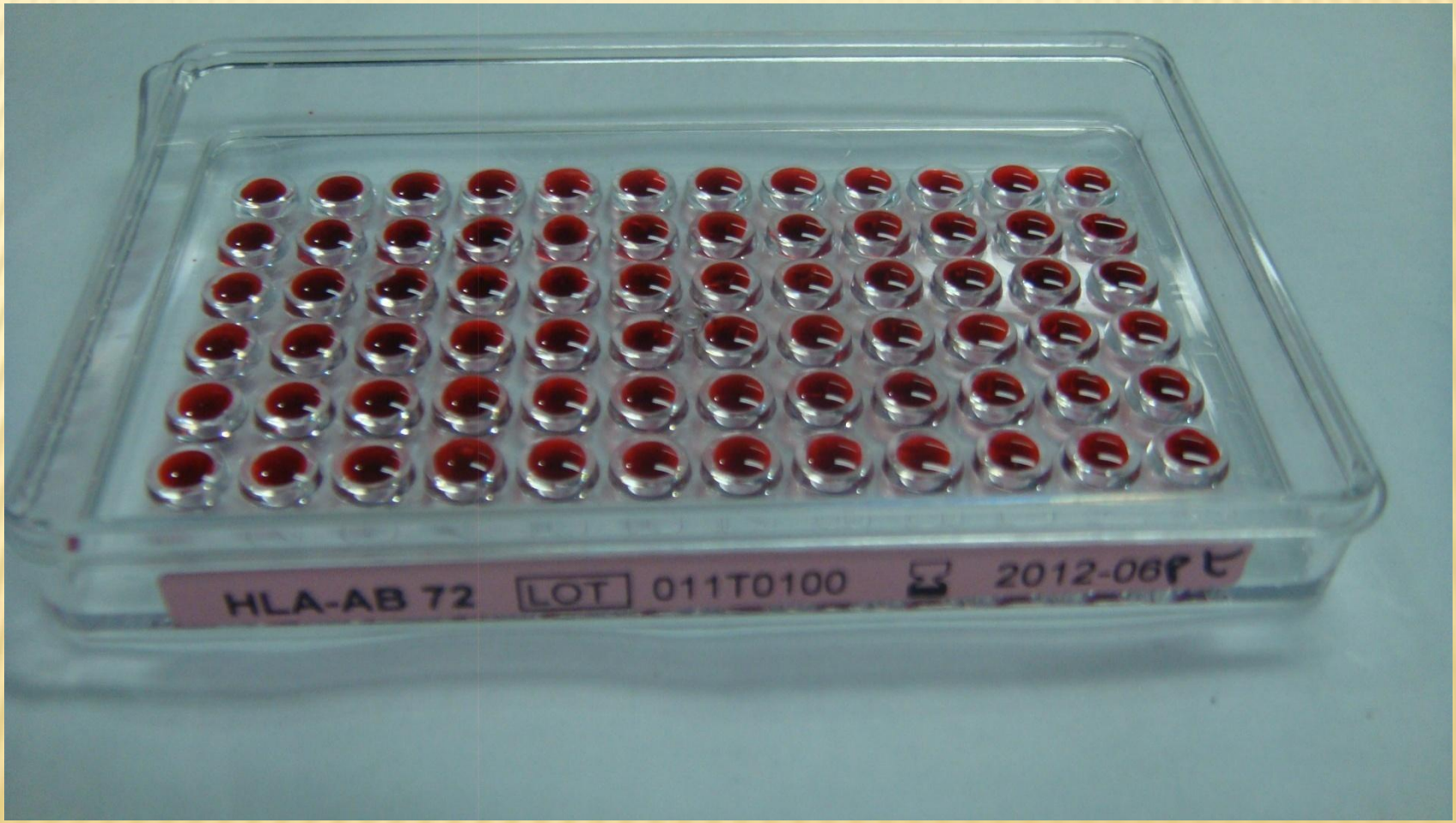
In short, in matters of health, race matters."

CONCLUSION

- * HLA may act alone (or with other genes) in conferring susceptibility to, or protection
- against, infectious diseases.

- * The mechanism of immune responses to infections that are influenced by HLA & may be the key to future vaccines.
- Future vaccines aim to use peptides of the organisms that mimic the HLA antigens.

SEROLOGY-TYPING



PCR-SSP TYPING OF HLA