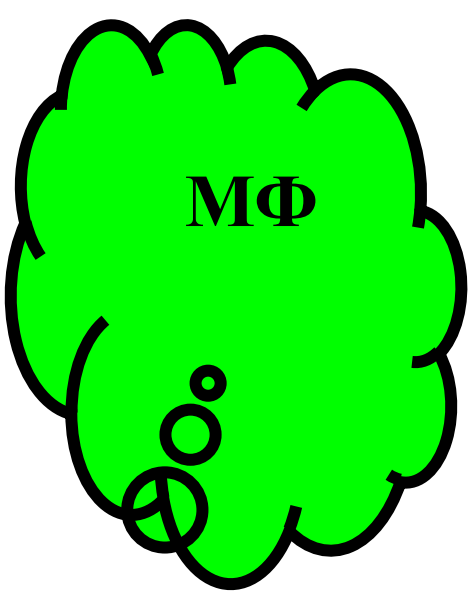
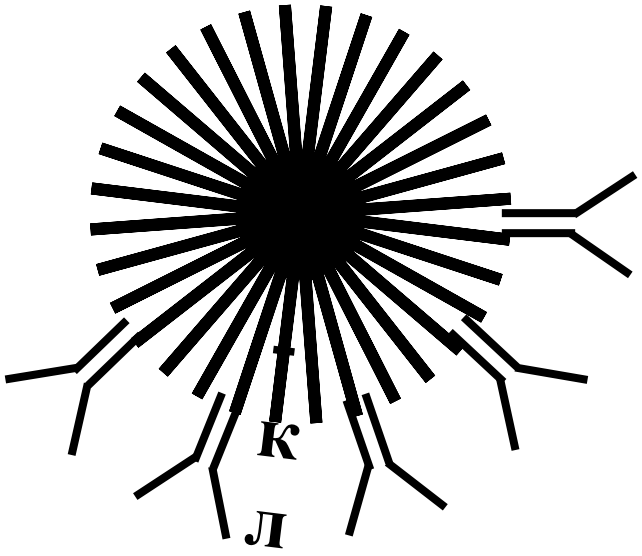
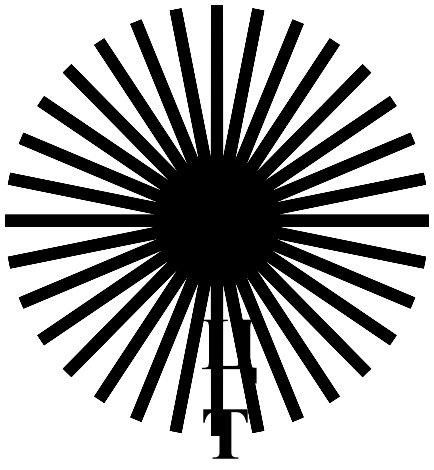
Біологічна роль головного комплексу гістосумісності MHC

(MHC - від англ. – *major histocompatibility complex*).

1.Вкажіть стрілочками активаційні зв'язки між клітинами ІС







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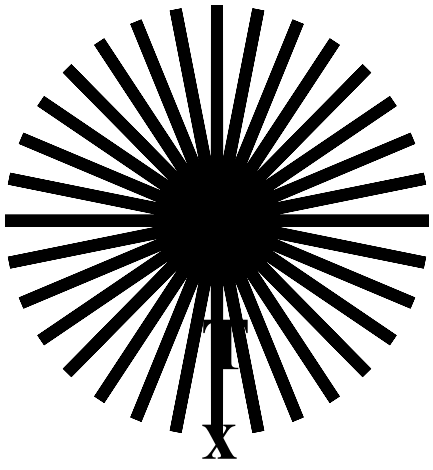

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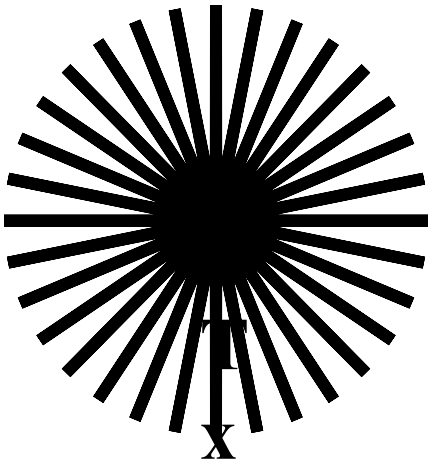
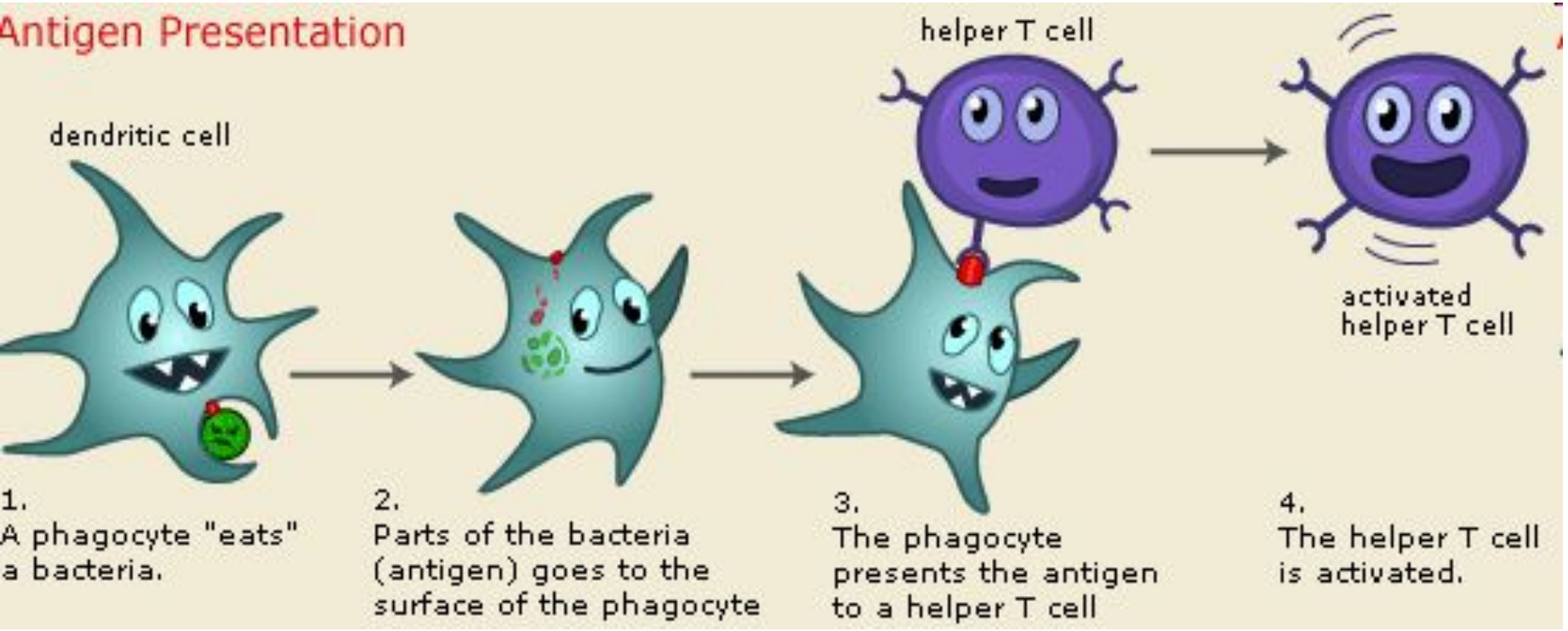


2

Презентація антигенів



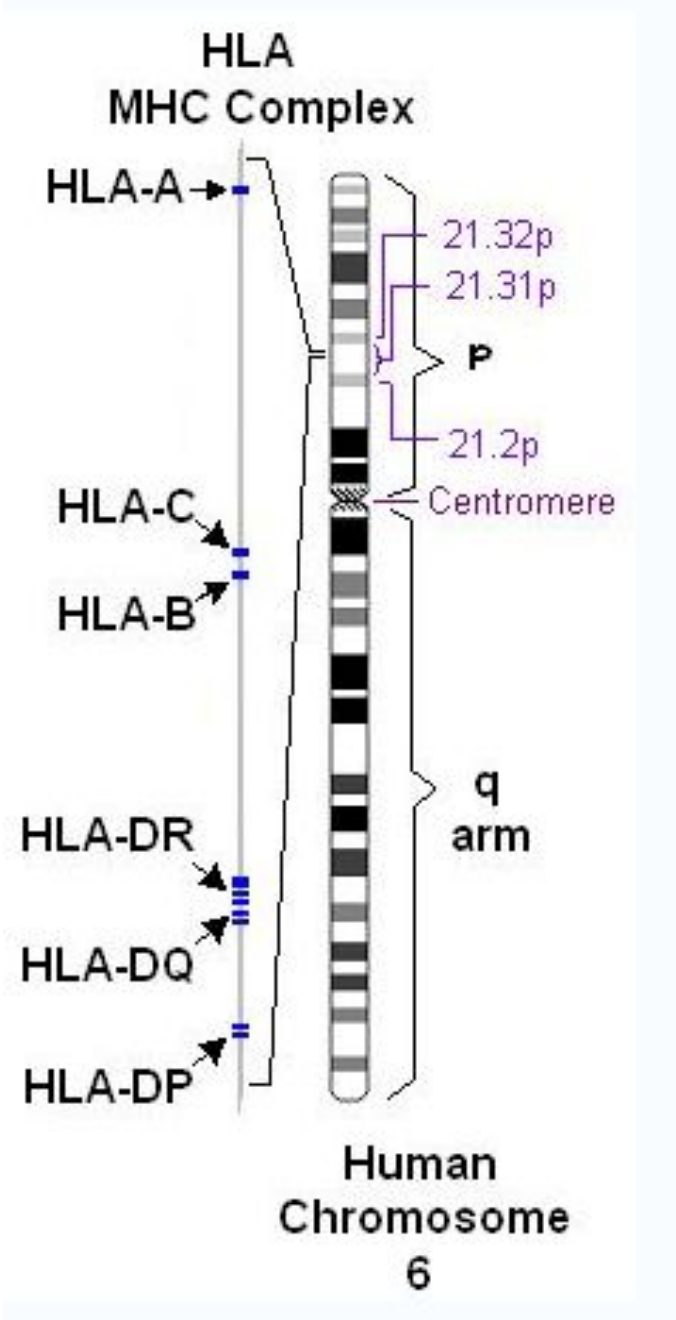
http://nobelprize.org/educational_games/medicine/immunity/immune-detail.html

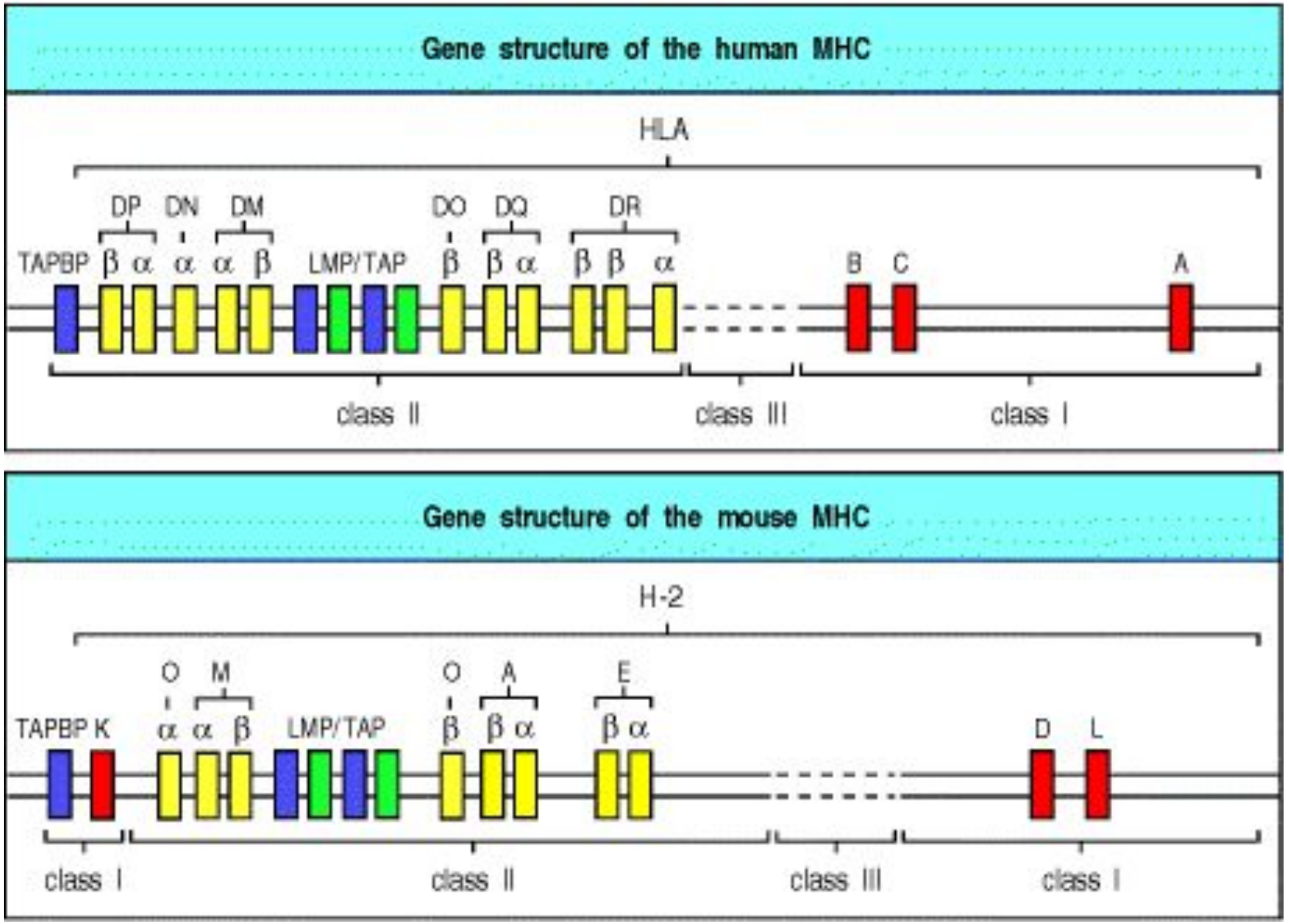
Бару Бенецераф, Жан Доссе і Джордж Снелл

1920 р.н. 1916 р.н. 1903-1996

Нобелівська премія (1980 р)

за відкриття головного комплексу гістосумісності


HLA
MHC Complex
HLA-A
HLA-C
HLA-B
HLA-DR
HLA-DQ
HLA-DP
21.32p
21.31p
p
21.2p
Centromere
q
arm
Human
Chromosome
6

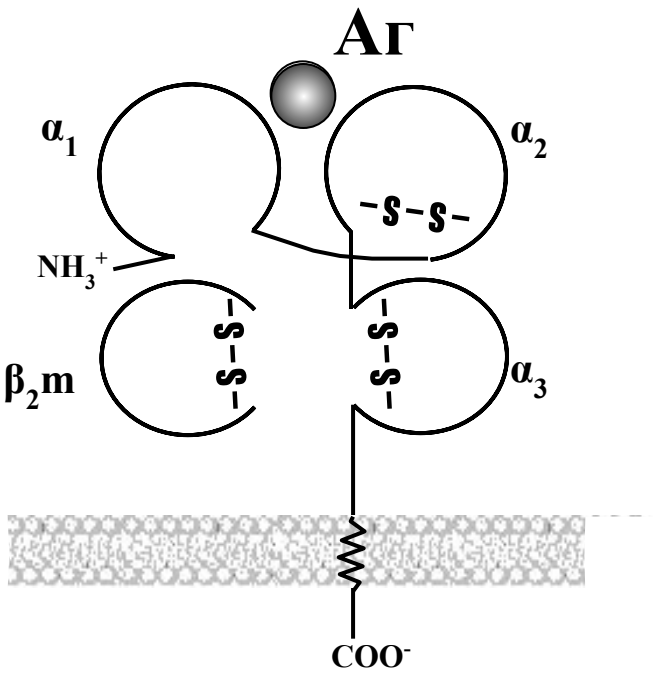

Gene structure of the human MHC
HLA
DP
DN
DM
DO
DQ
DR
TAPBP
β α
α
α β
LMP/TAP
β
β α
β β α
B C
A
class II
class III
class I
Gene structure of the mouse MHC
H-2
O
M
O
A
E
TAPBP K
α α β
LMP/TAP
β
β α
β α
D L
class I
class II
class III
class I

Пітер Догерті і Рольф Цинкернагель

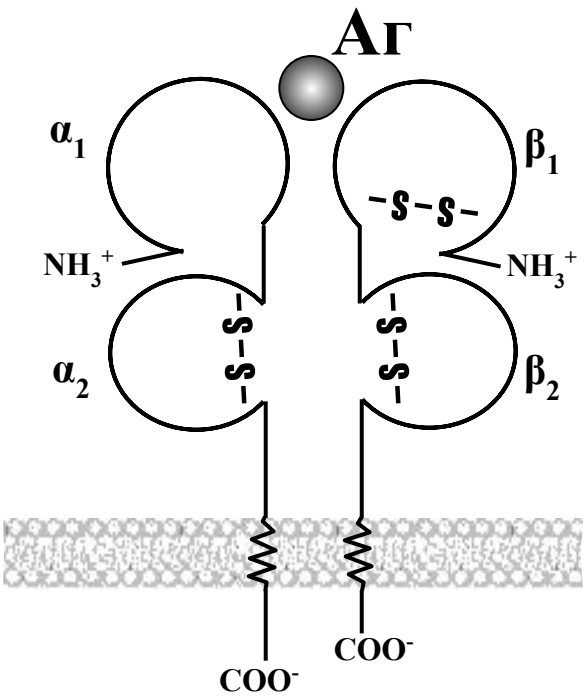
Нобелівська премія (1996 р)

за відкриття MHC-рестрикції імунної відповіді

Схематична будова білків MHC I і MHC II

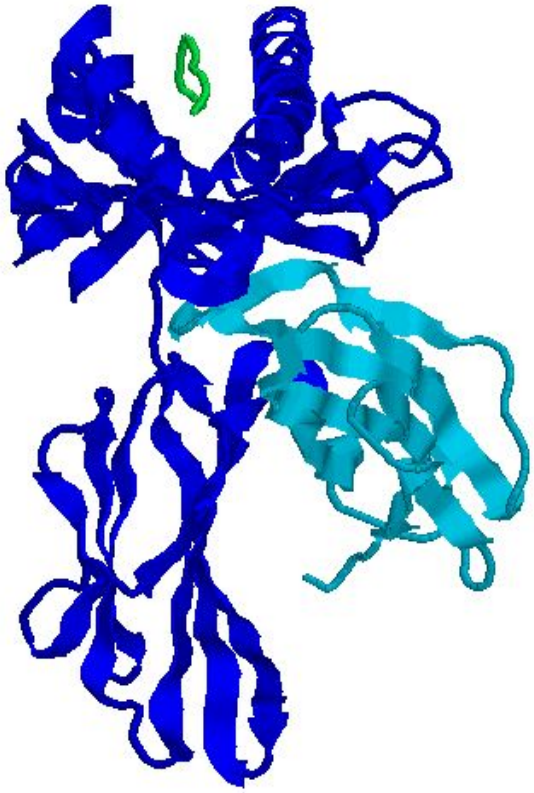


MHC I

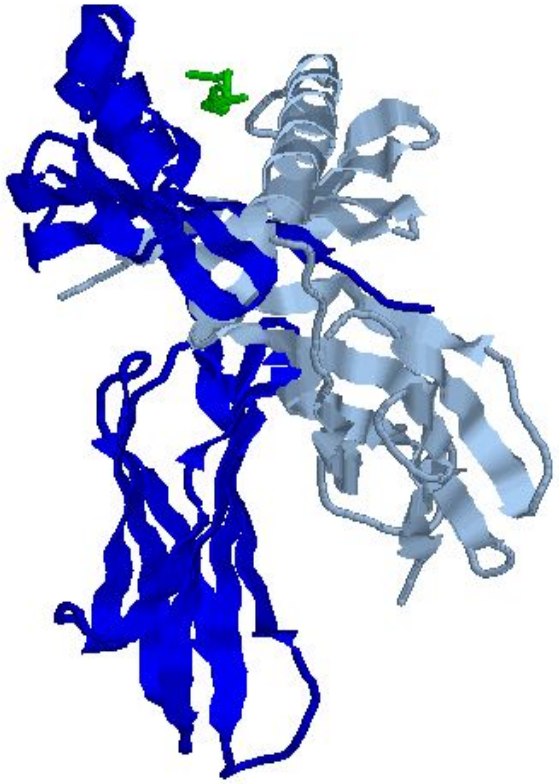


MHC II

Трьохмірна будова білків MHC I і MHC II

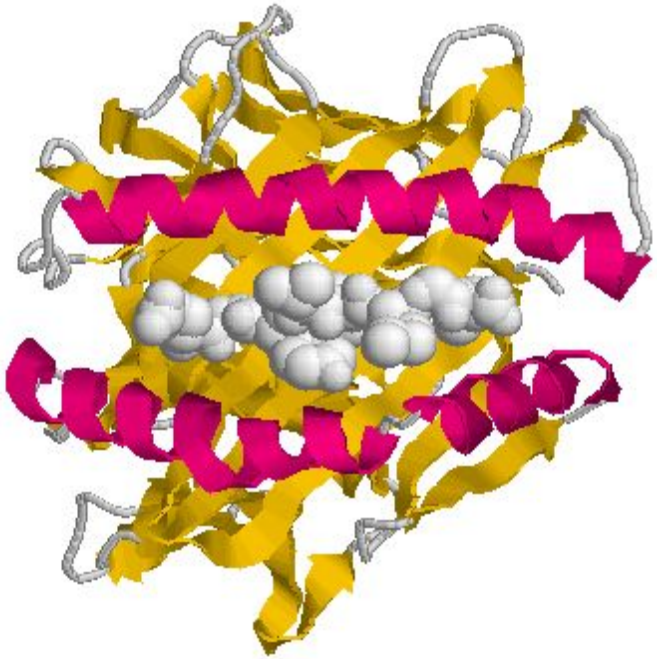


MHC I

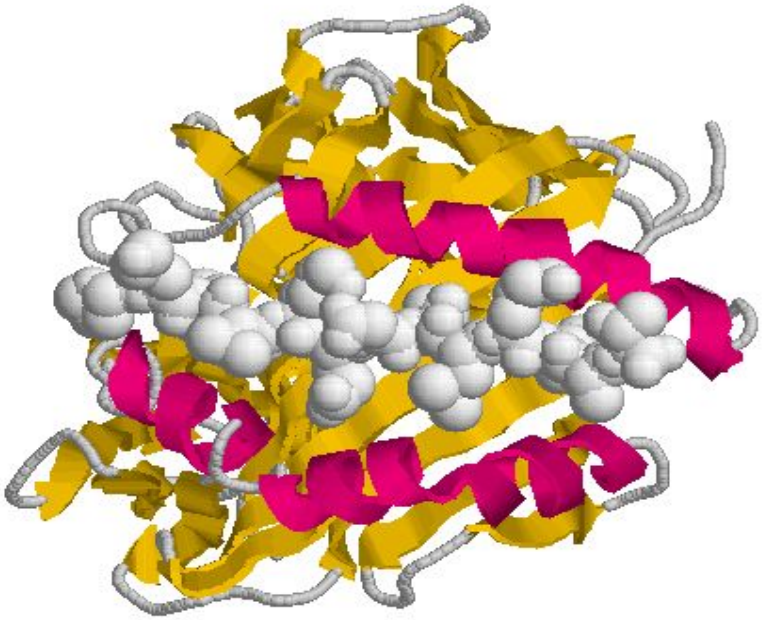


MHC II

Будова “активних центрів” MHC I і MHC II

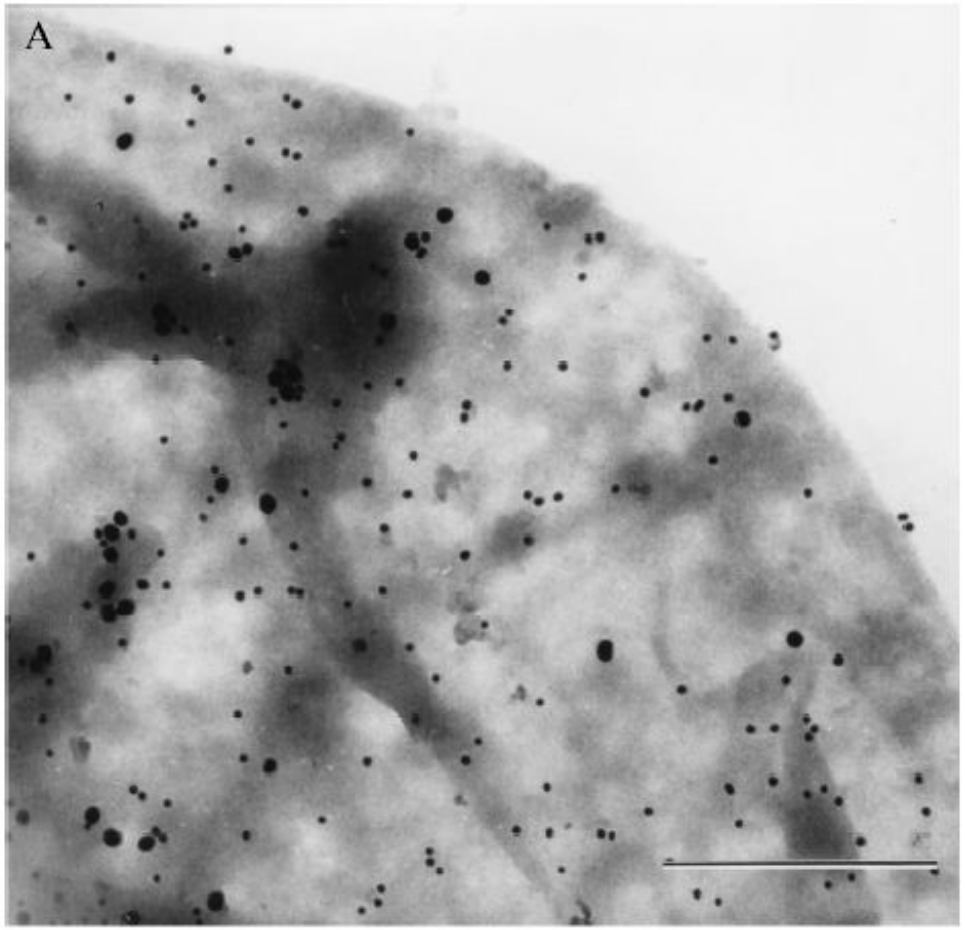


MHC I



MHC II

Розміщення MHC I і MHC II на мембрані клітин



Антитіла до MHC I – мічені 15 нм. кол. золотом (маленькі кульки)

Антитіла до MHC II – мічені 30 нм. кол. золотом (великі кульки)

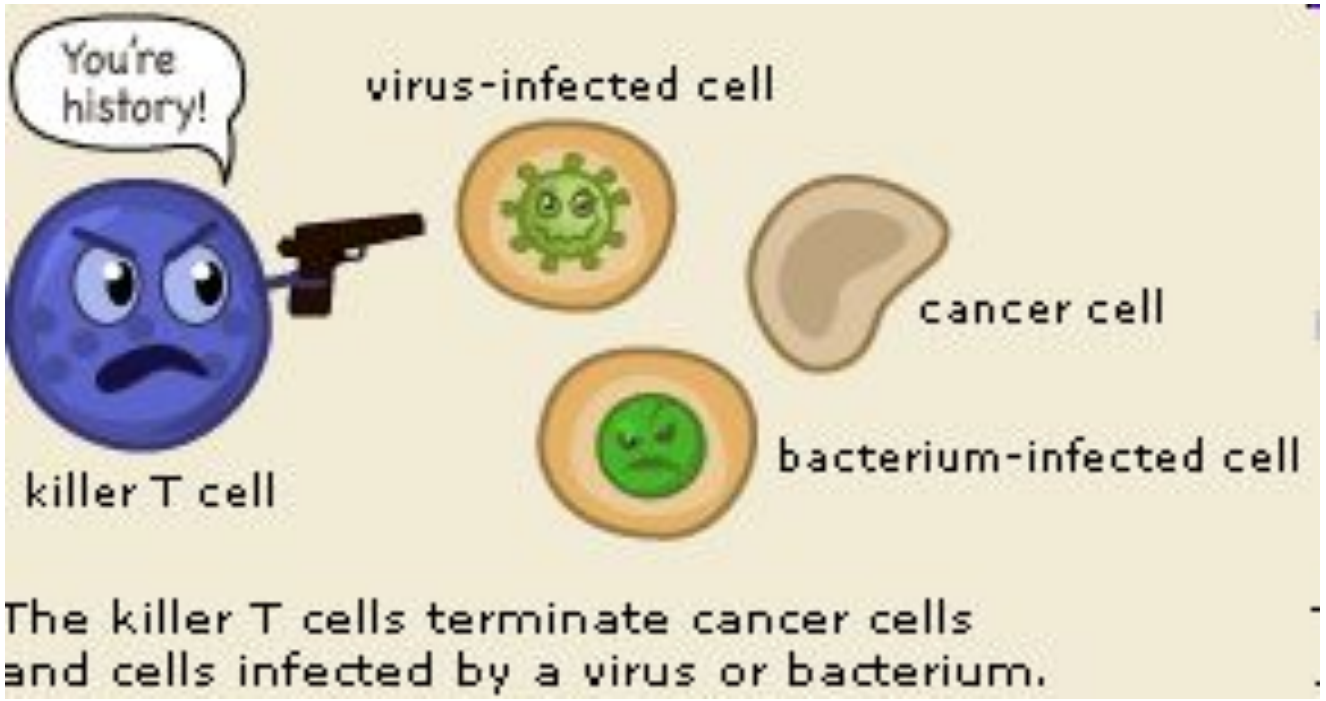
Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 7269–7274, July 1997
Biophysics

Біологічна роль антигенів MHC I

Будь-яка клітина організму може бути місцем перебування внутрішньоклітинних патогенів

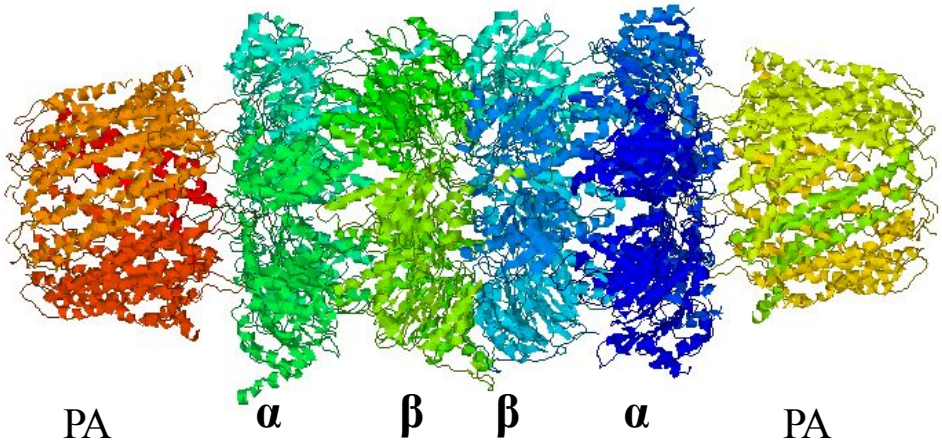
- Імунна система повинна мати доступ до інформації про те, що робиться в середині кожної клітини
- Цю інформацію забезпечують антигени MHC I-го класу, які присутні майже на всіх клітинах організму

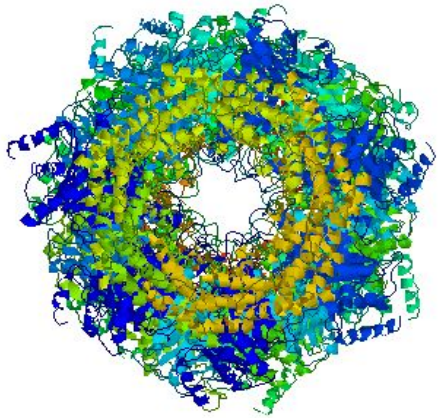
Вбивство уражених клітин Т-кілерами

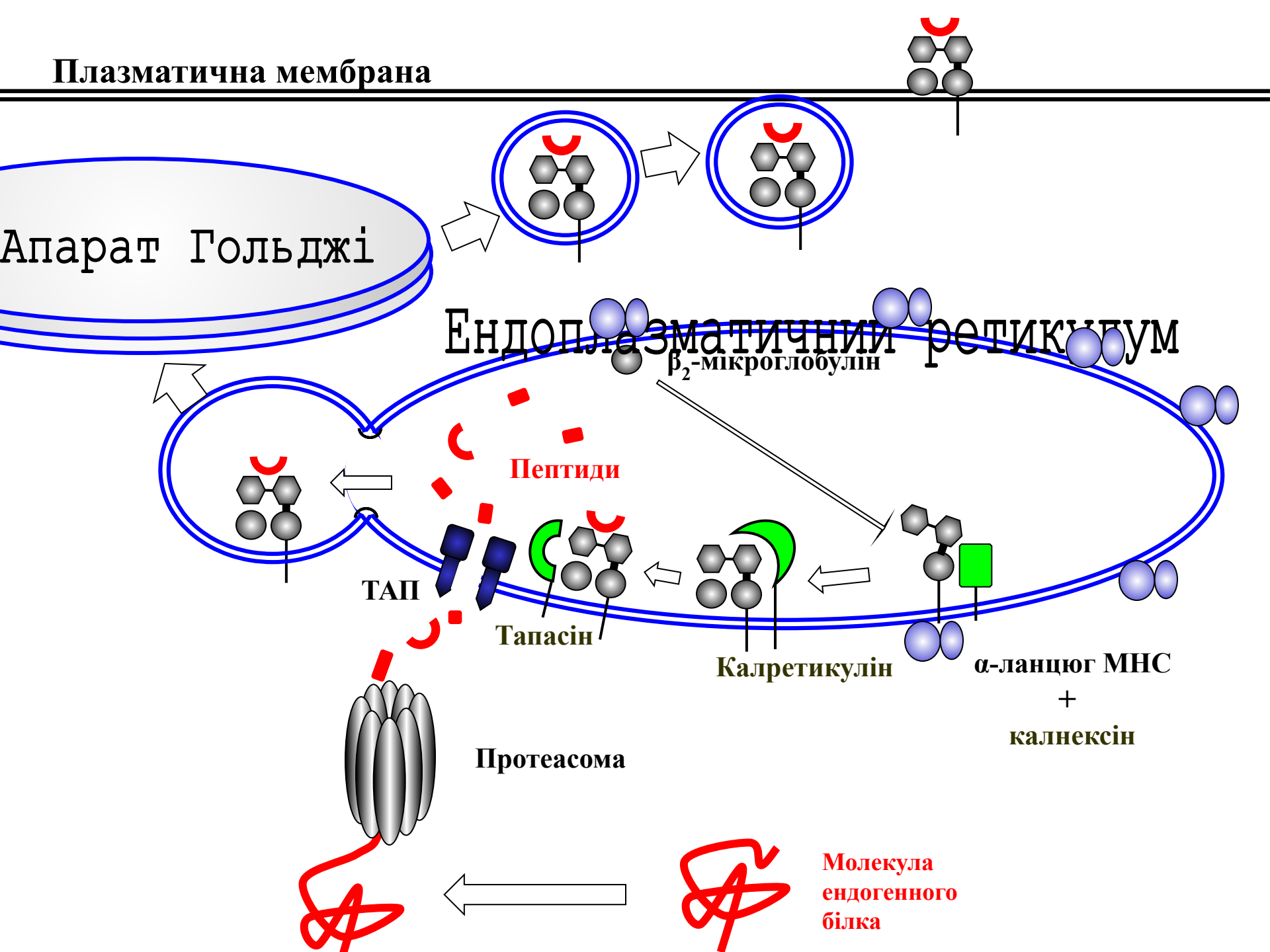


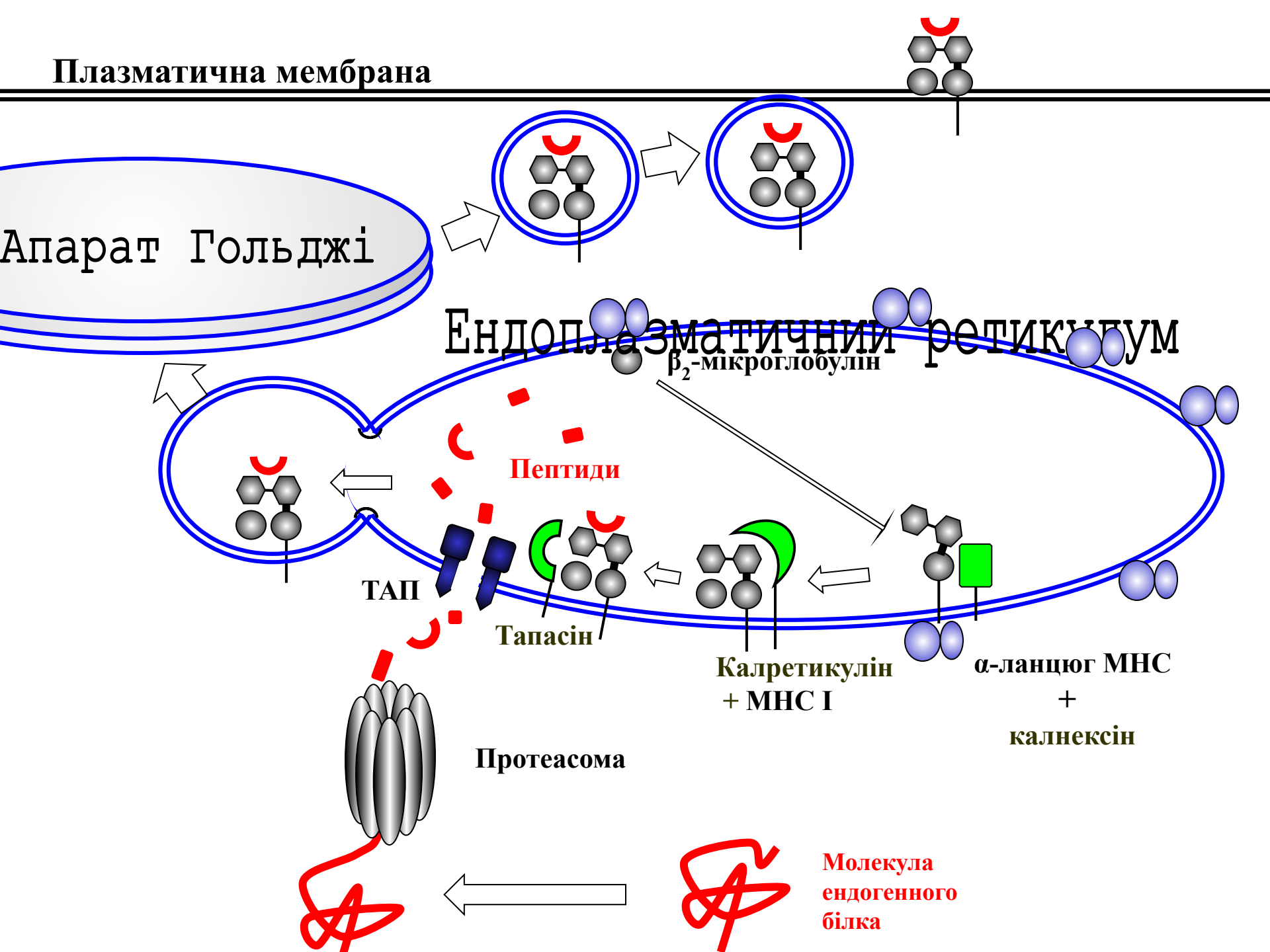
http://nobelprize.org/educational_games/medicine/immunity/immune-detail.html

Структура протеосоми





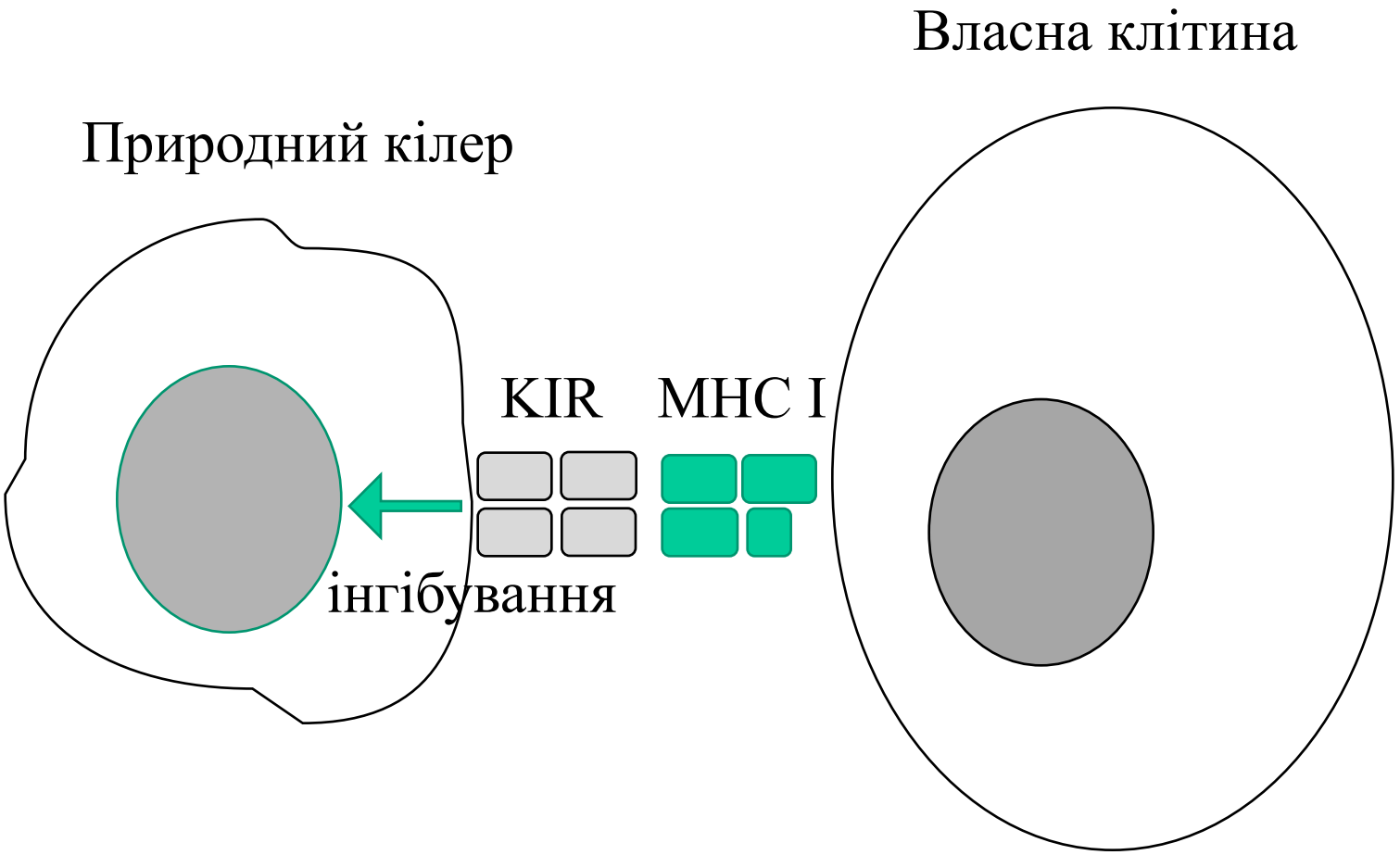

Плазматична мембрана
Апарат Гольджі
Ендоплазматичний ретикулум
β2-мікроглобулін
Пептиди
ТАП
Тапасін
Калретикулін
α-ланцюг МНС
+
калнексін
Протеасома
Молекула
ендогенного
білка


Апарат Гольджі
Ендоплазматичний ретикулум
β2-мікроглобулін
Пептиди
ТАП
Тапасін
Калретикулін
+ MHC I
α-ланцюг MHC
+
калнексін
Протеасома
Молекула
ендогенного
білка

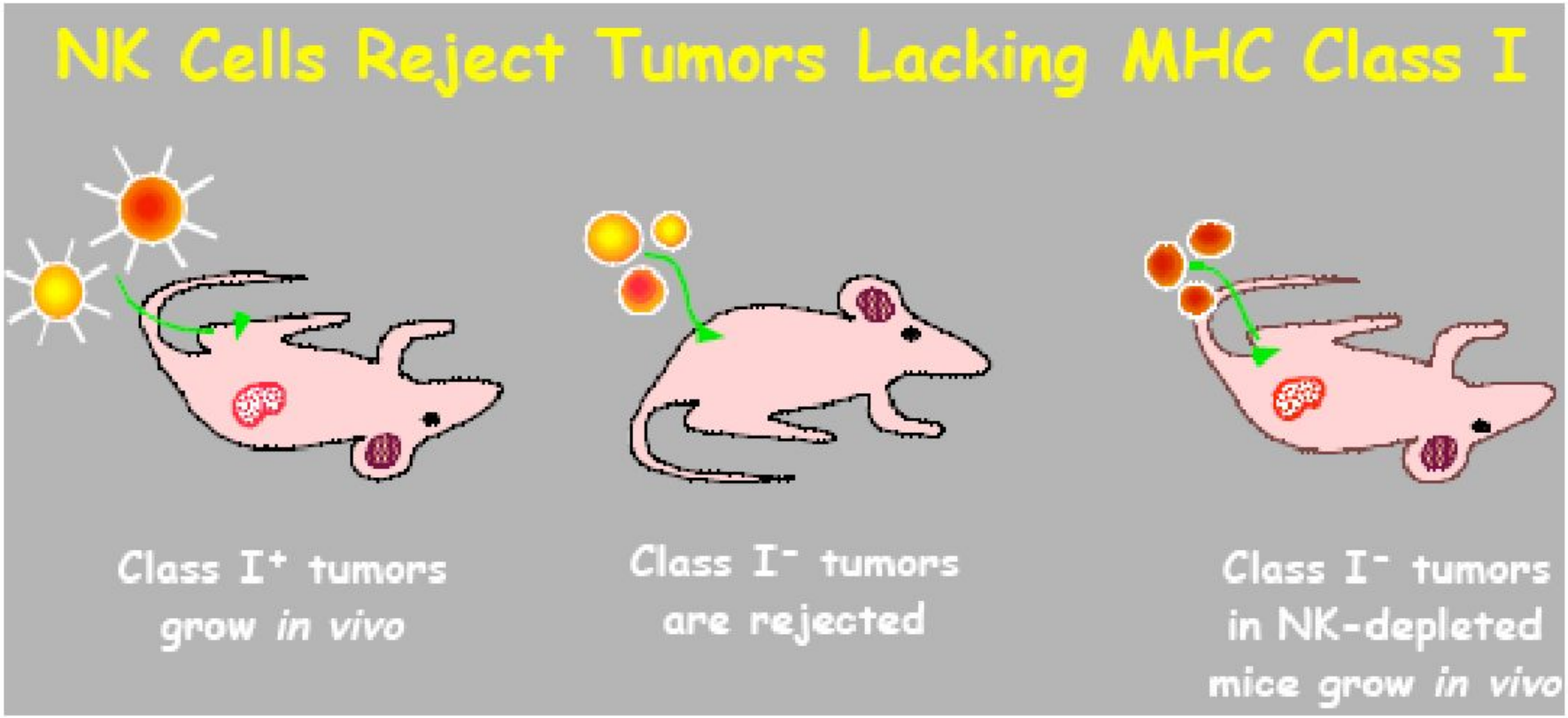
Деякі віруси виробили засоби впливу на систему MHC I

Virus	Protein	Effect on class I
Adenovirus	E3-k19	Retain in ER
HSV-1,2	ICP47	Blocks TAP
EBV	EBNA1	Block peptide generation
HCMV	US2, US11	ER to cytosol
HCMV	US3	Retain in ER
HCMV	US6	Blocks TAP
HCMV	US10	Degrades HLA-G
MCMV	m152	Retain in ER
MCMV	m04	Associates with H-2
MCMV	m06	Lysosomal degradation
HHV8	K3, K5	Endocytosis
HIV-1	Nef	Endocytosis

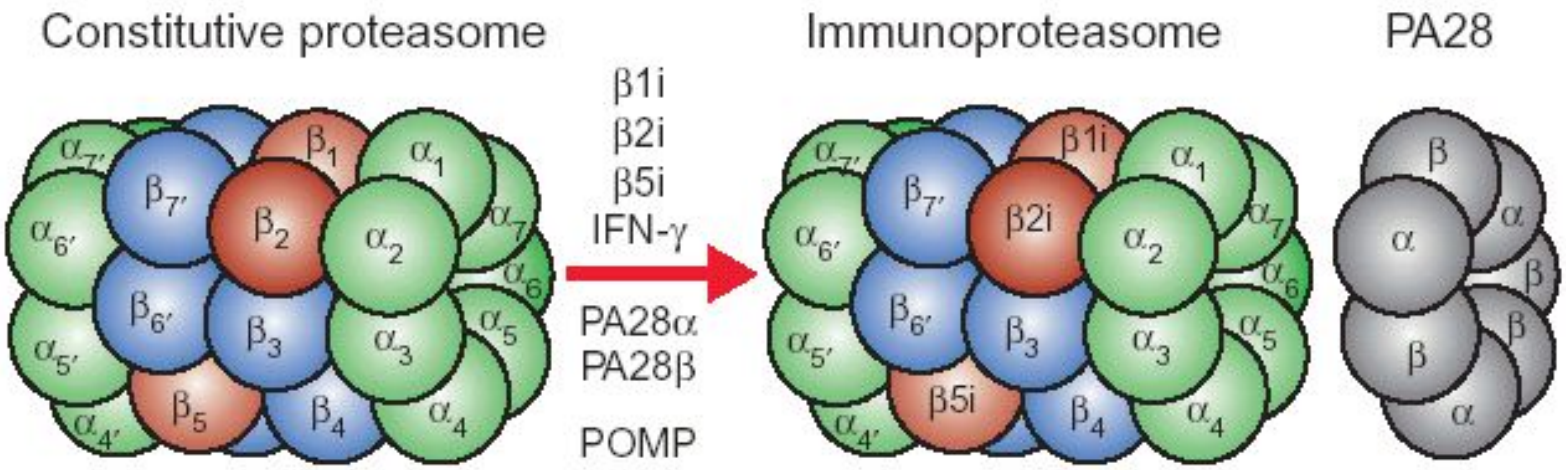
Схема інгібування активності природних кілерів



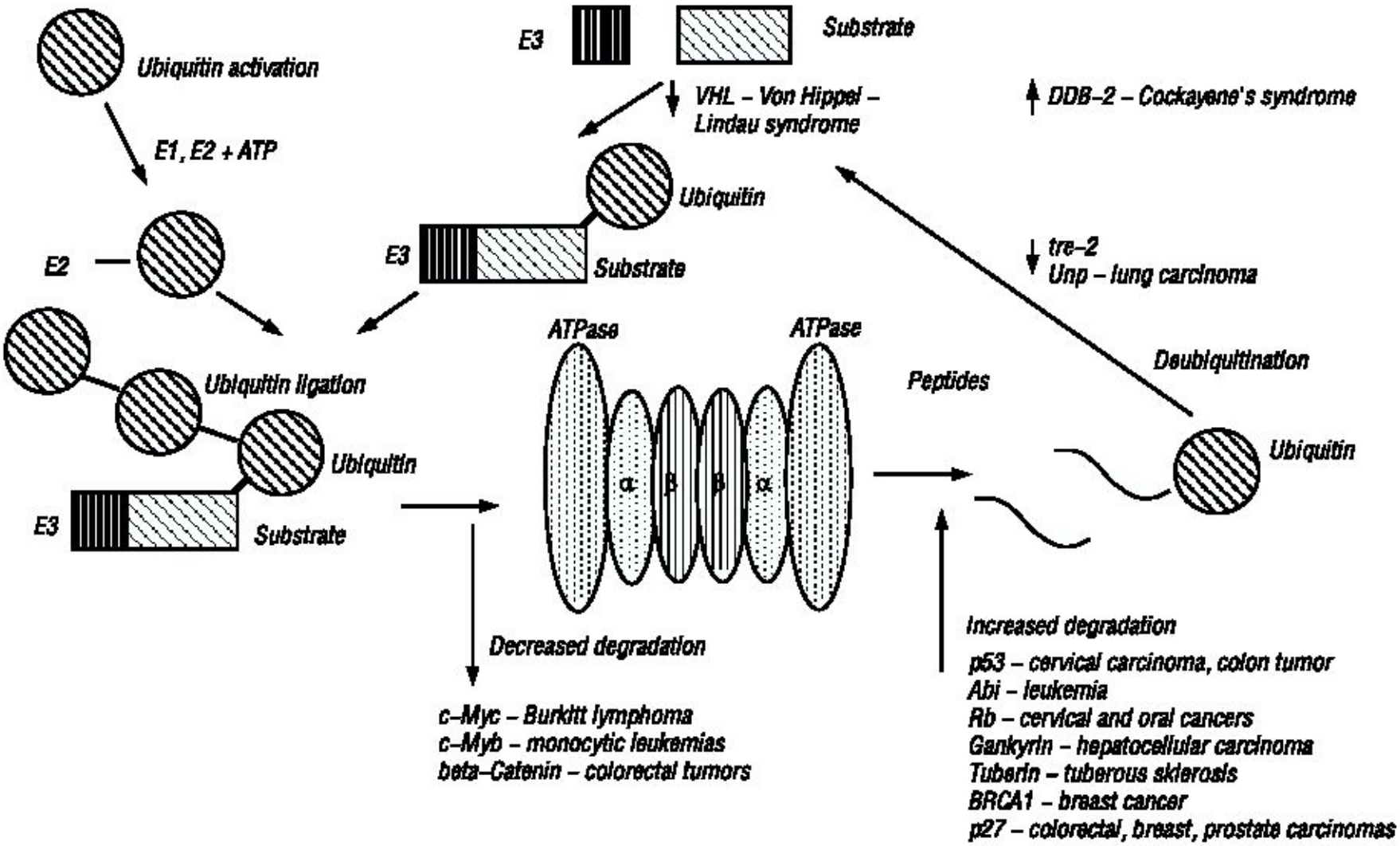
NK cells like to kill cells lacking MHC class I – "missing-self"



Karre et *al. 1986* Nature 319:675



low molecular weight protein LMP 2, LMP7
multicatalytic endopeptidase complex-like 1 (MECL1)


Ubiquitin activation
E1, E2 + ATP
E2
E3
Substrate
Ubiquitin ligation
Ubiquitin
E3
Substrate
E3
Substrate
VHL – Von Hippel – Lindau syndrome
Ubiquitin
E3
Substrate
ATPase
ATPase
α
β
β
α
Decreased degradation
c–Myc – Burkitt lymphoma
c–Myb – monocytic leukemias
beta–Catenin – colorectal tumors
Peptides
DDB–2 – Cockayene's syndrome
tre–2
Unp – lung carcinoma
Deubiquitination
Ubiquitin
Increased degradation
p53 – cervical carcinoma, colon tumor
Abi – leukemia
Rb – cervical and oral cancers
Gankyrin – hepatocellular carcinoma
Tuberin – tuberous sklerosis
BRCA1 – braast cancer
p27 – colorectal, breast, prostate carcinomas

Біологічна роль антигенів MHC II

МНС ІІ-го класу відповідають за комунікацію клітин імунної системи під час імунної відповіді

- МНС ІІ-го класу необхідні для обміну інформацією про антиген між різними клітинами
- Тому клітини, що експресують МНС ІІ-го класу, називають Антиген-Презентувальними Клітинами (АПК)

Презентація антигену – представлення антигену на поверхні клітин для розпізнавання іншими клітинами

1. В-клітини
2. макрофаги
3. Дендритні клітини

здатні до поглинання і процесінгу (розрізання) антигену, а також до презентації його фрагментів в комплексі з антигенами гістосумісності II класу (MHCII)

Поглинання антигенів

1.	В-клітини	ендоцитоз АГ
2.	Макрофаги	фагоцитоз
3.	Дендритні клітини	макропіноцитоз

Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 5553–5557, July 1990
Immunology

Functional and ultrastructural evidence for intracellular formation of major histocompatibility complex class II–peptide complexes during antigen processing

(endosomes/immunocytochemistry/endocytosis)

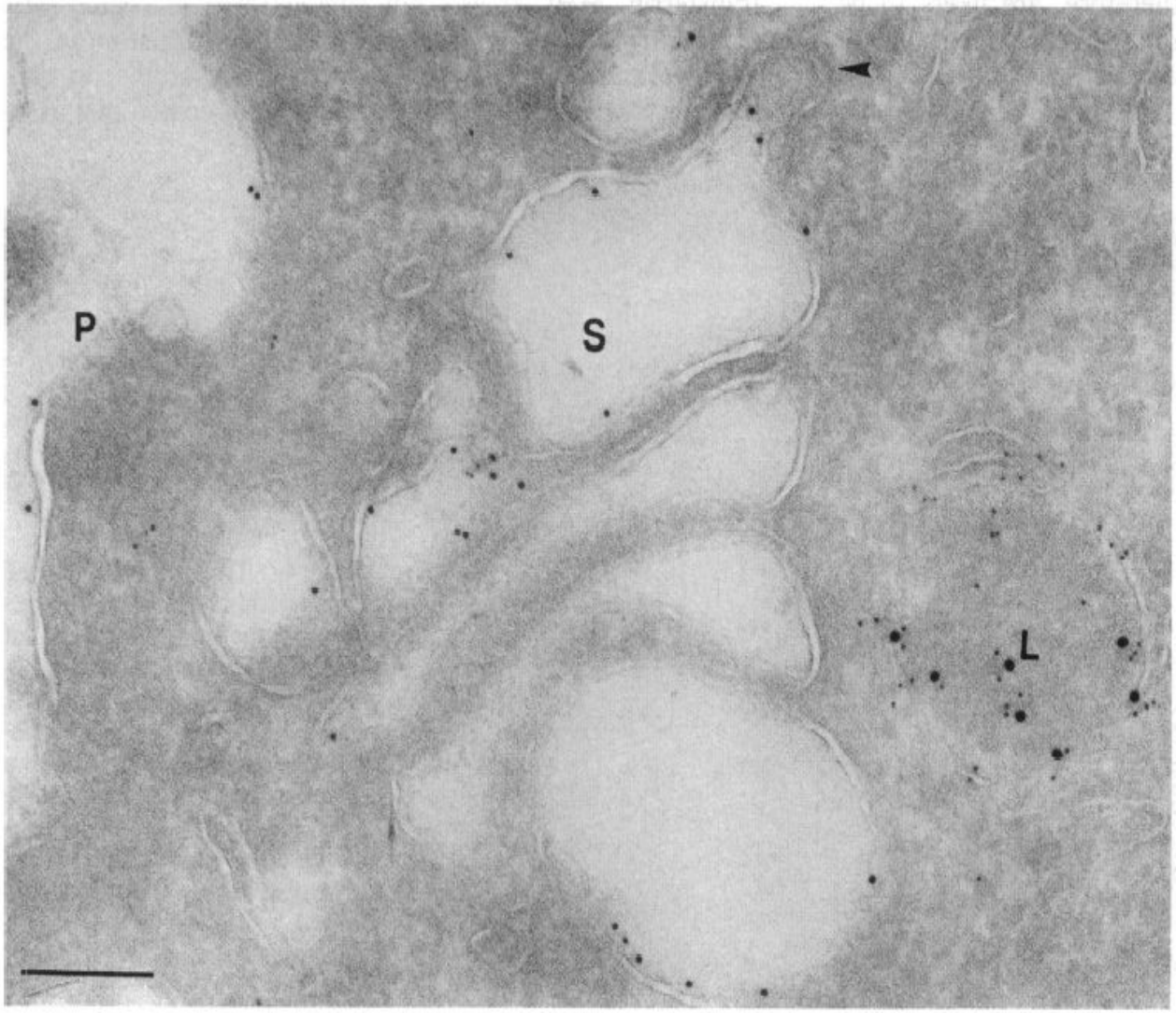
CLIFFORD V. HARDING*, EMIL R. UNANUE*, JAN W. SLOT†, ALAN L. SCHWARTZ‡, AND HANS J. GEUZE†

†Department of Cell Biology, Medical School, University of Utrecht, 3584 CX, Utrecht, The Netherlands; and *Department of Pathology and ‡The Edward Mallinckrodt Departments of Pediatrics and Pharmacology, Washington University School of Medicine, Saint Louis, MO 63110

Contributed by Emil R. Unanue, May 3, 1990

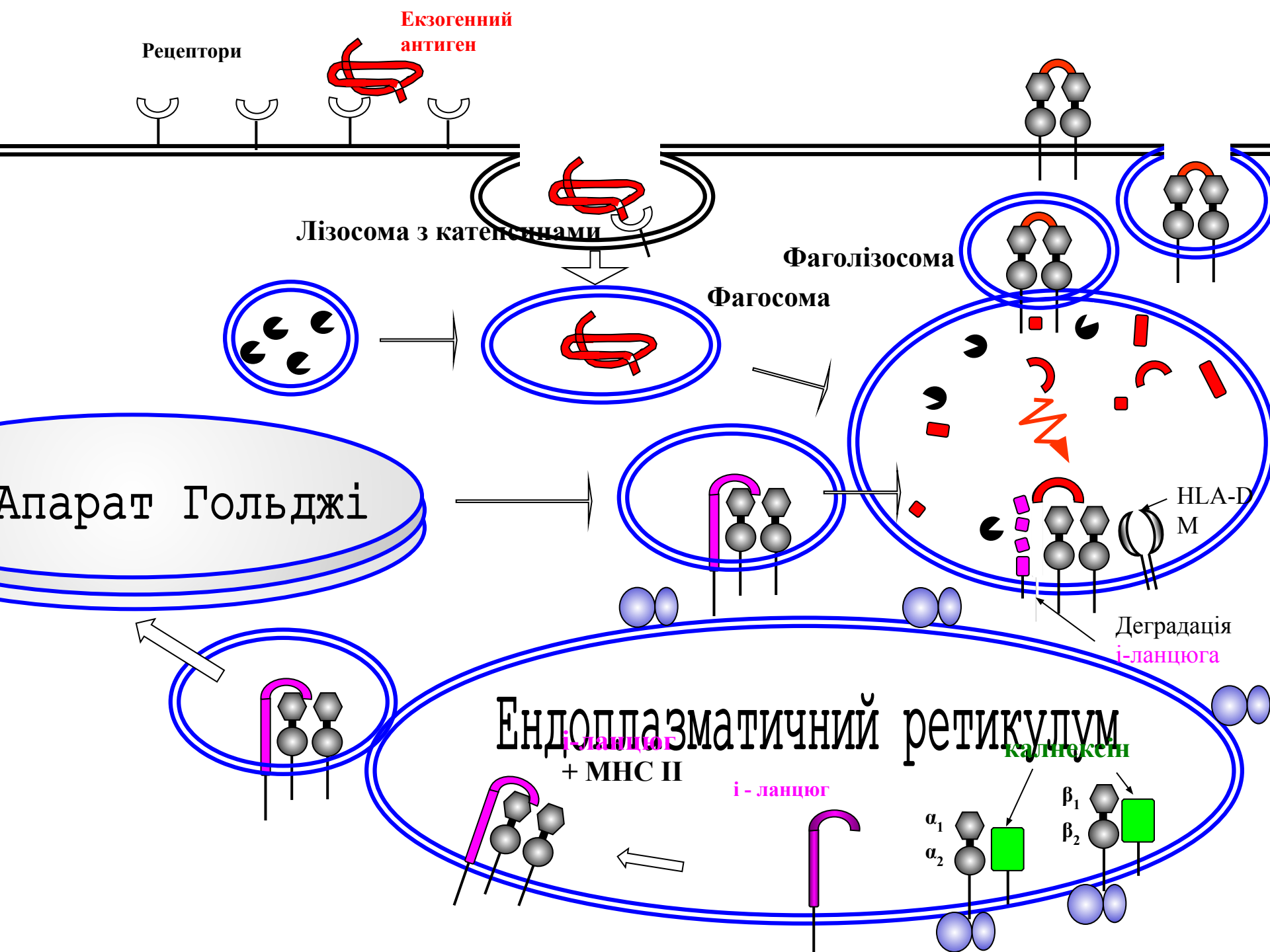
Позаклітинний простір

Ендосома

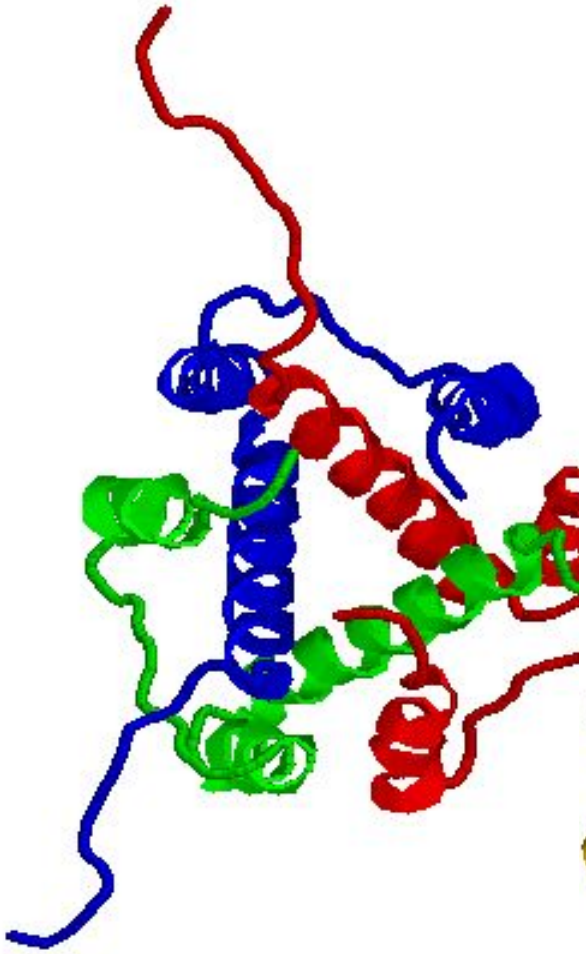


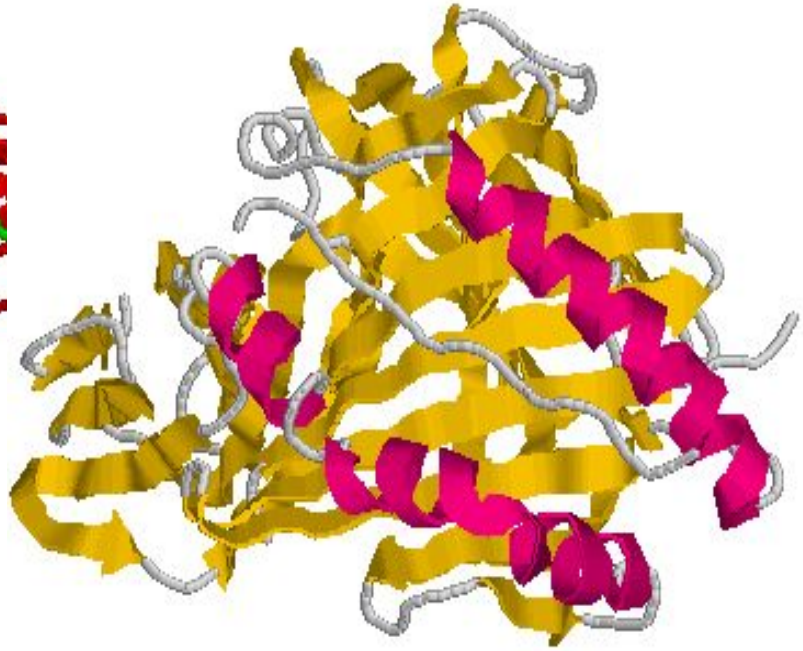
Лізосома

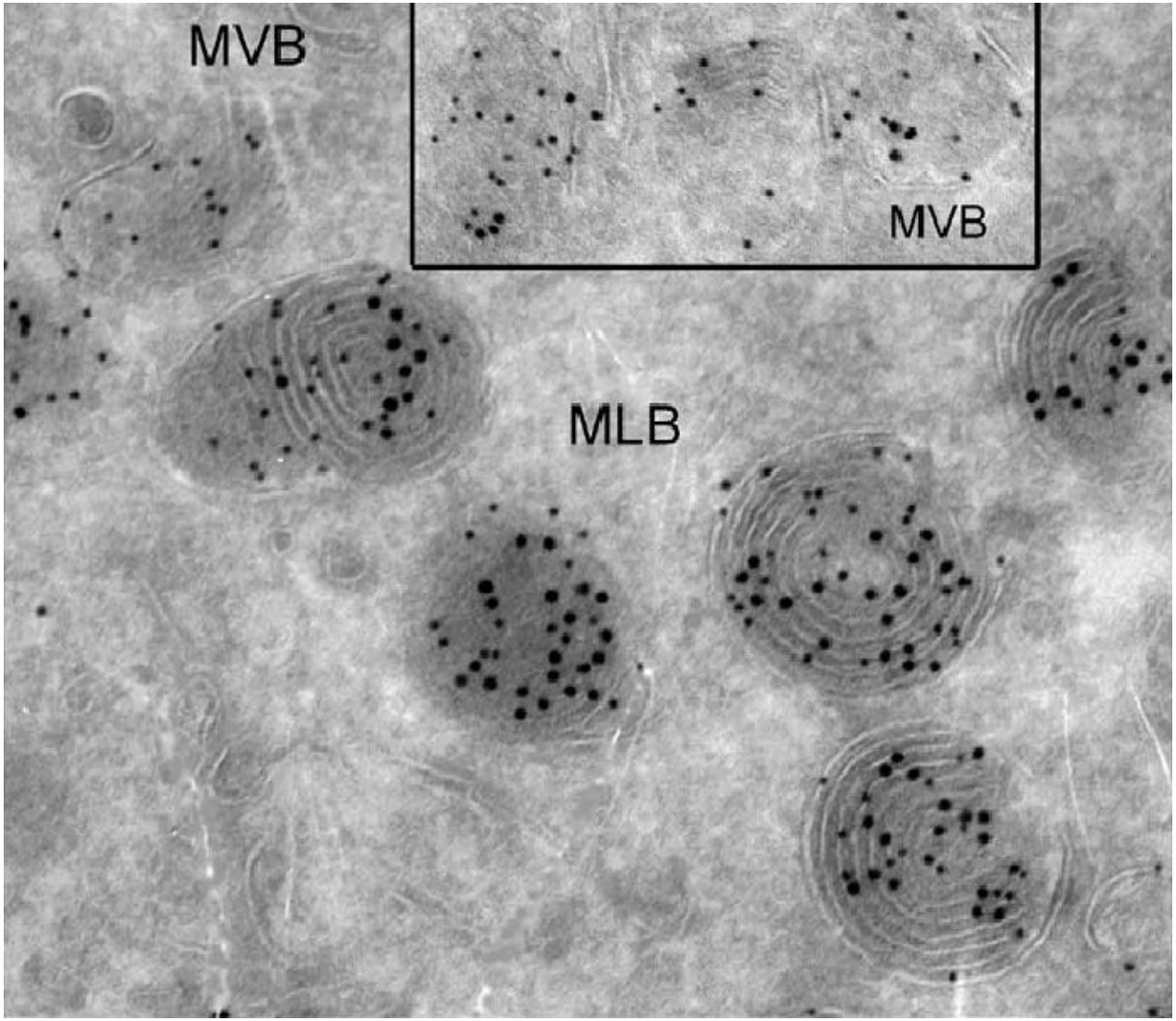
FIG. 2. Triple immunolabeled cryosection of a macrophage to show the presence of MHC-II (10-nm gold) at the plasma membrane (P) and in endocytic sacs (S). MHC-II is absent from a coated pit at the sac membrane (arrowhead) and from the homogeneously dense lysosome (L). The latter shows cathepsin D (15-nm gold) and lamp 1 (5-nm gold), which are both absent from the sacs. (Bar = 0.2 μm; ×72,800.)


Рецептори
Екзогенний антиген
Лізосома з катепсинами
Фагосома
Фаголізосома
Апарат Гольджі
HLA-D M
Деградація і-ланцюга
Ендоплазматичний ретикулум
і-ланцюг + MHC II
і - ланцюг
калнексин
α1
α2
β1
β2

Будова І-ланцюга



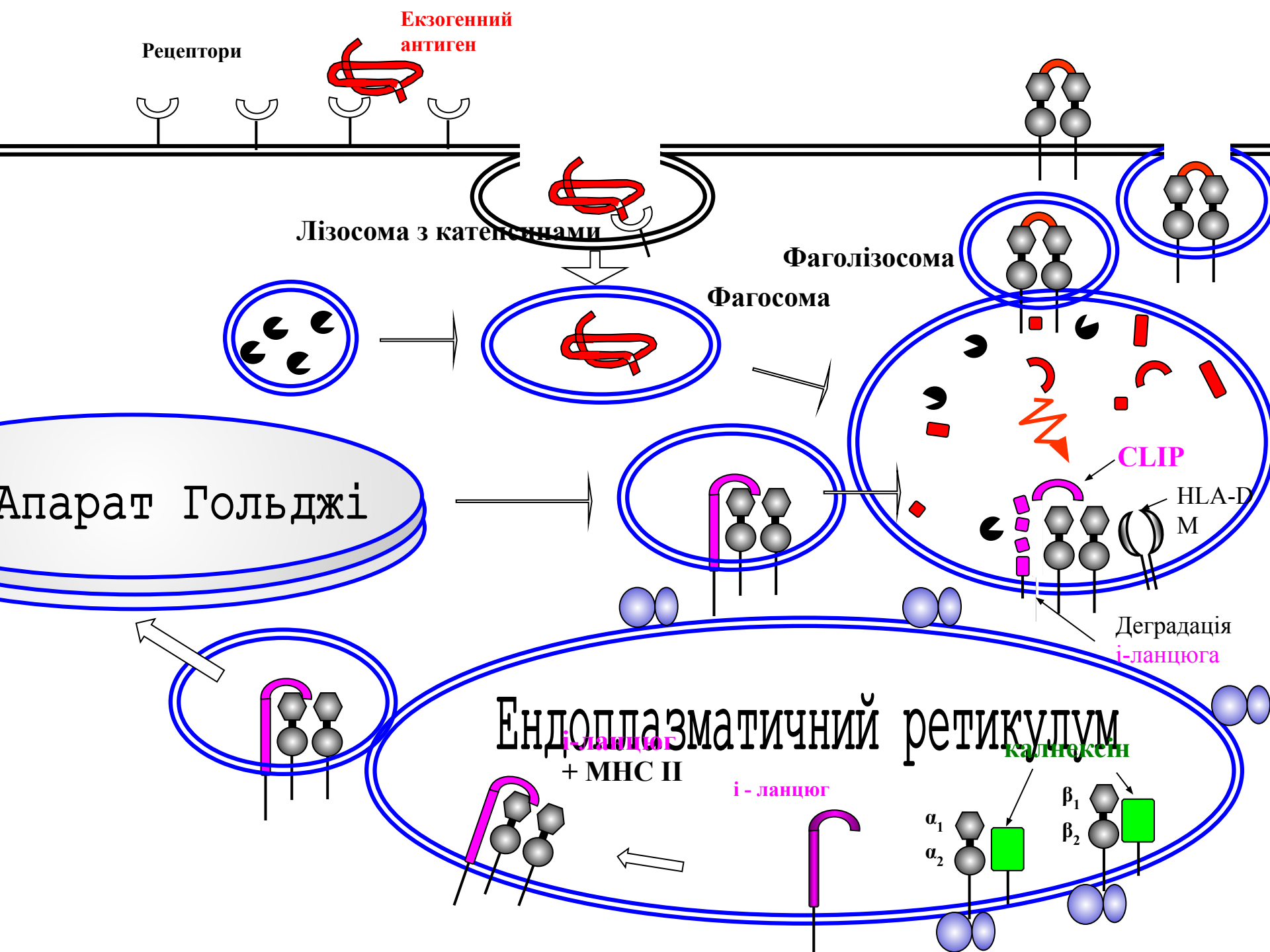




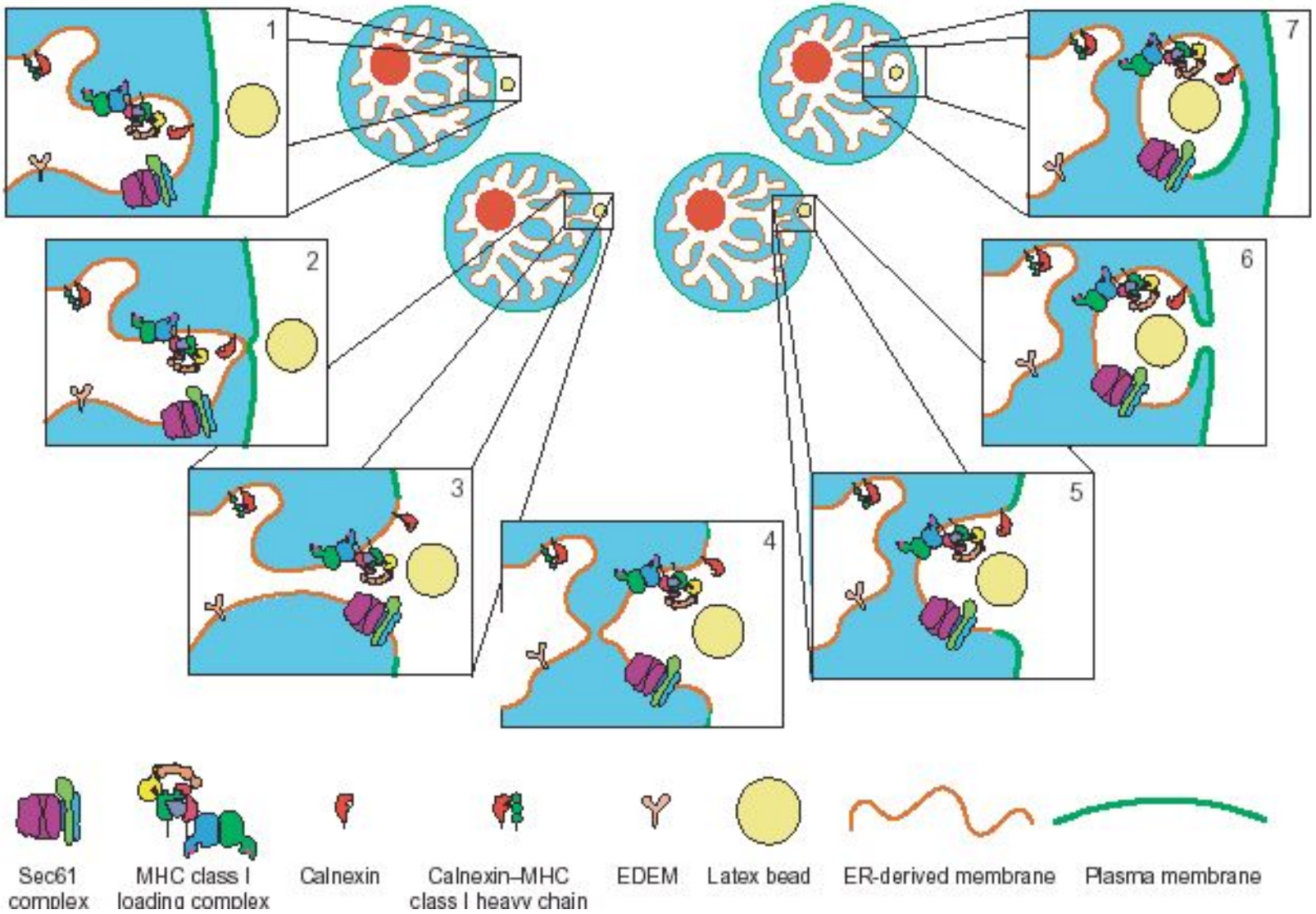
MIIC компартмент

(за Lawrence J Stern, Ilaria Potolicchio and Laura Santambrogio)

MVB-мултивезикулярний, MLB-мултиламелярний

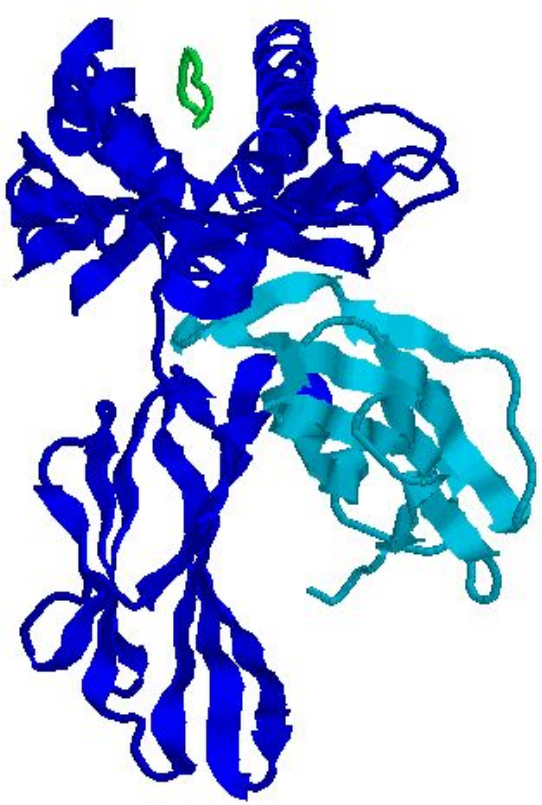

Рецептори
Екзогенний антиген
Лізосома з катепсинами
Фагосома
Фаголізосома
CLIP
HLA-D M
Деградація і-ланцюга
Апарат Гольджі
Ендоплазматичний ретикулум
і-ланцюг + MHC II
і - ланцюг
кальнексин
α1
α2
β1
β2

Перехресна презентація антигенів

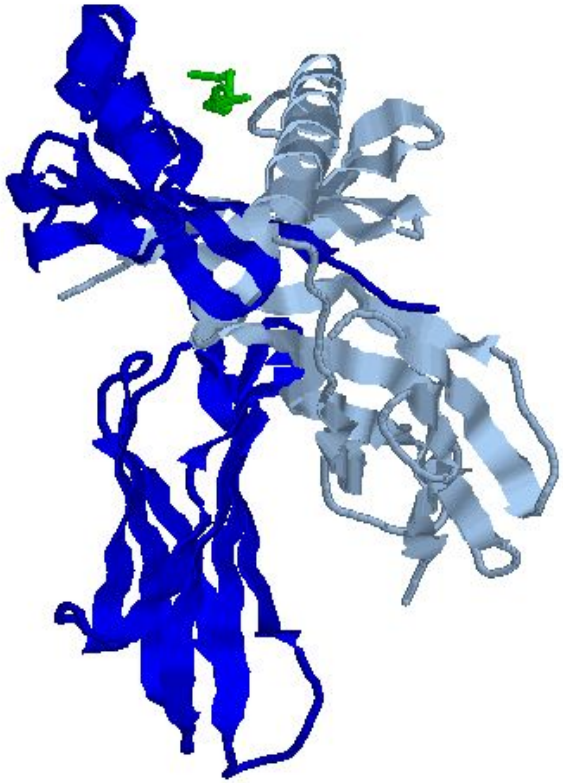


Дендритні клітини також здатні презентувати поглинутий антиген з антигенами гістосумісності І-го класу і активувати Т-кілери

- Всі інші клітини в організмі здатні презентувати внутрішньоклітинні білки разом з МНС І, але не здатні активувати Т-кілери (вони можуть лише знищуватись, у разі небезпеки, активованими Т-кілерами)

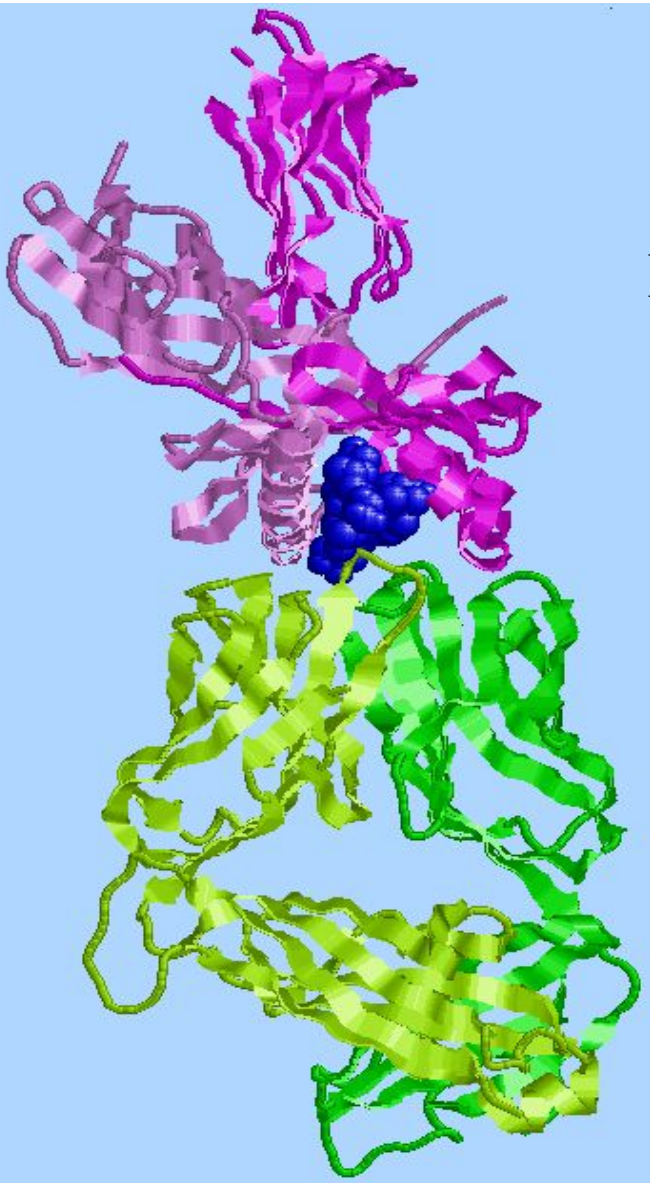


MHC I



MHC II

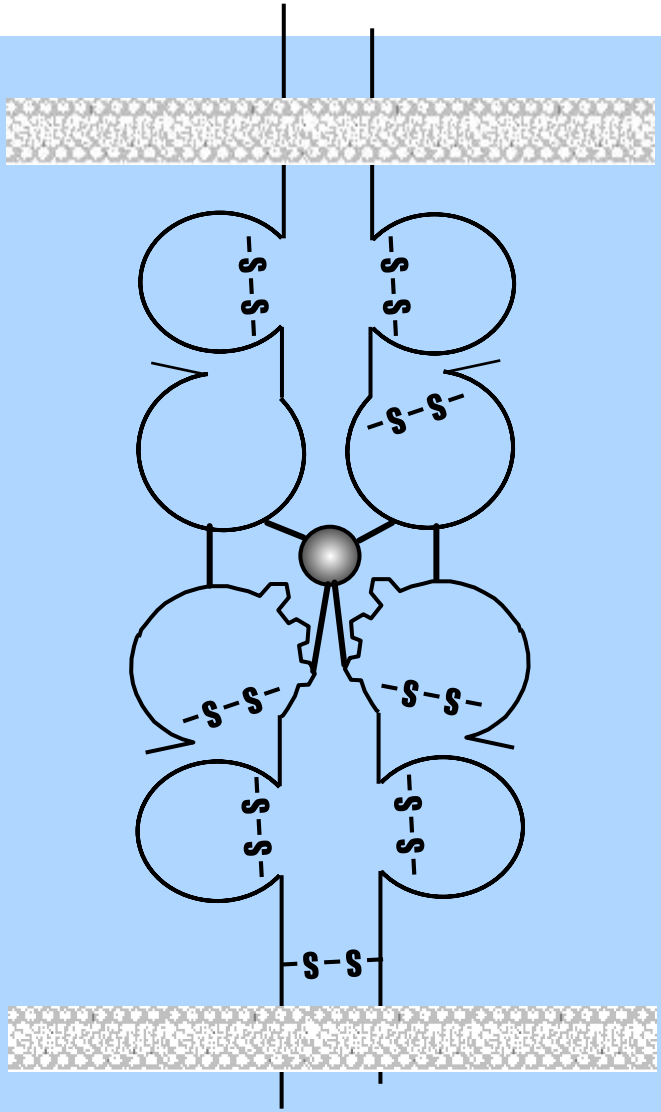
Розпізнавання антигену з МНС



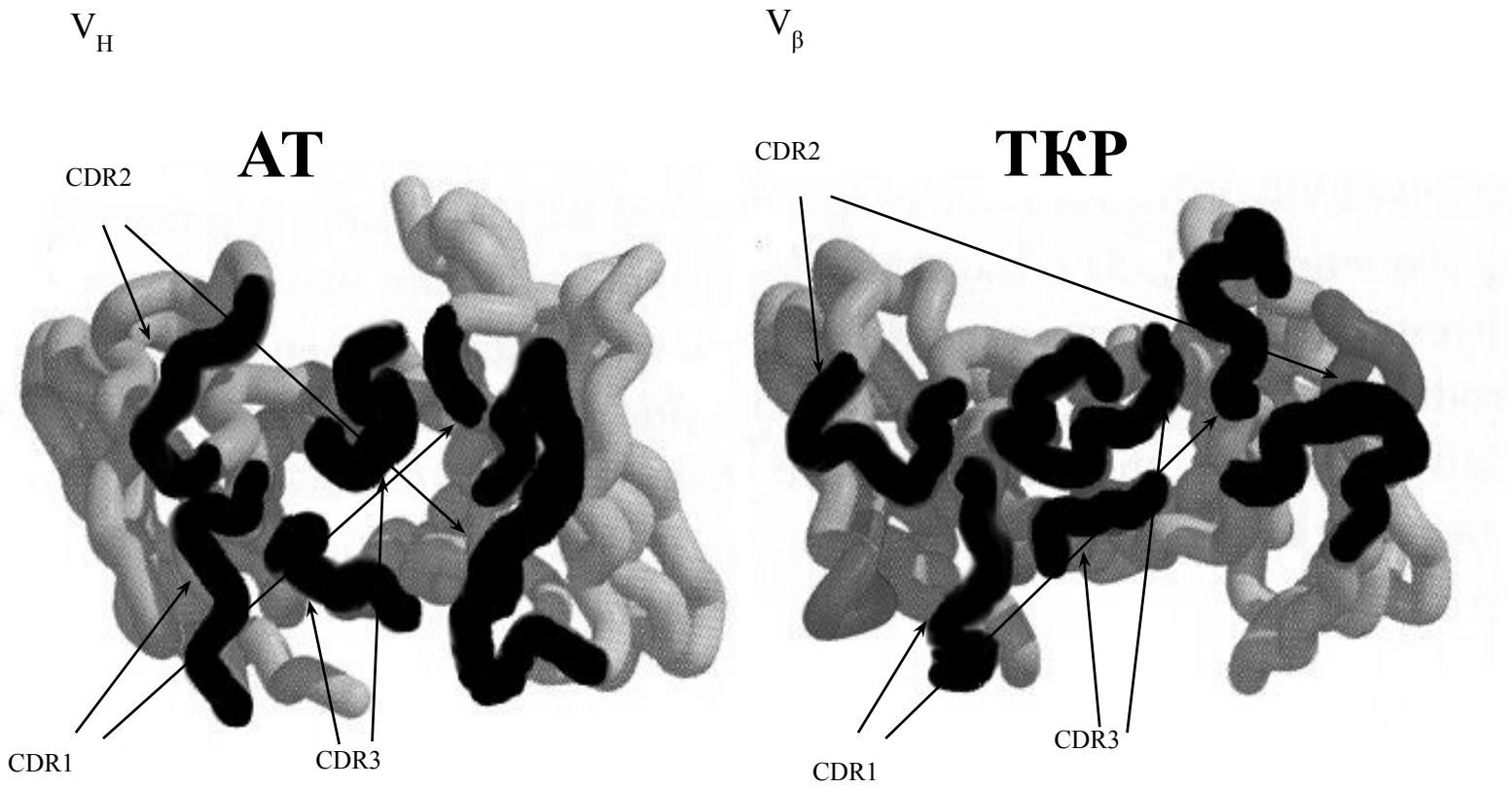
МНС

АГ

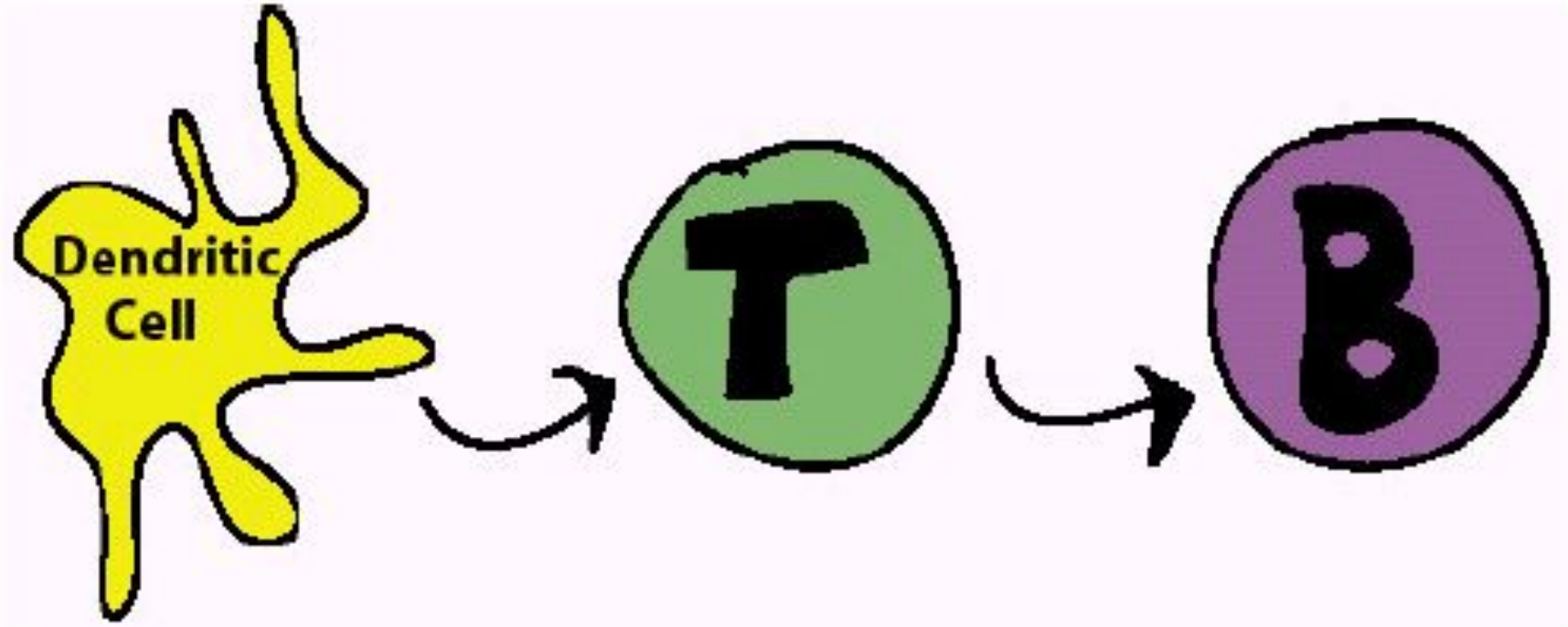
ТКР

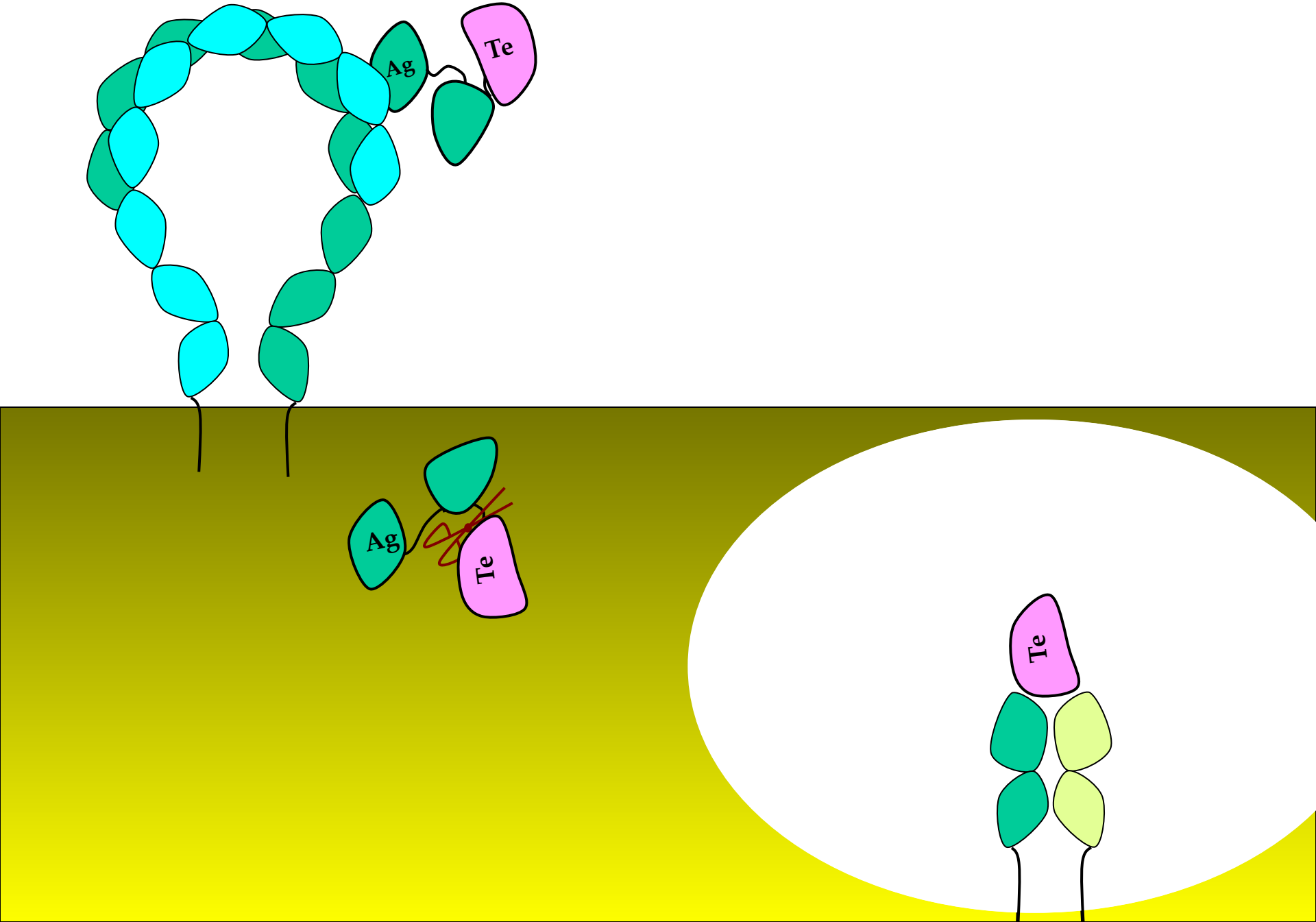


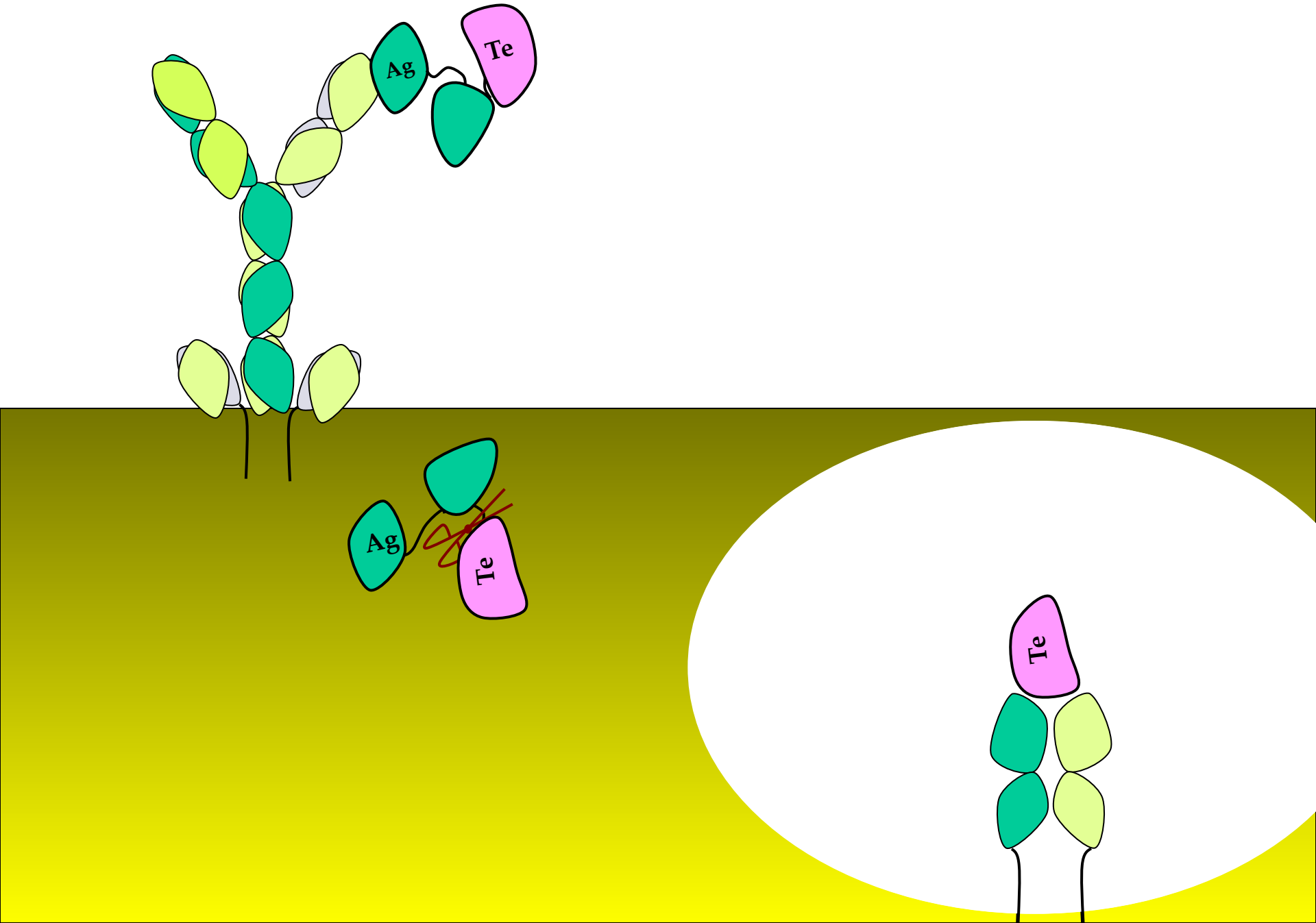
Порівняння будови активних центрів антитіла та ТКР.

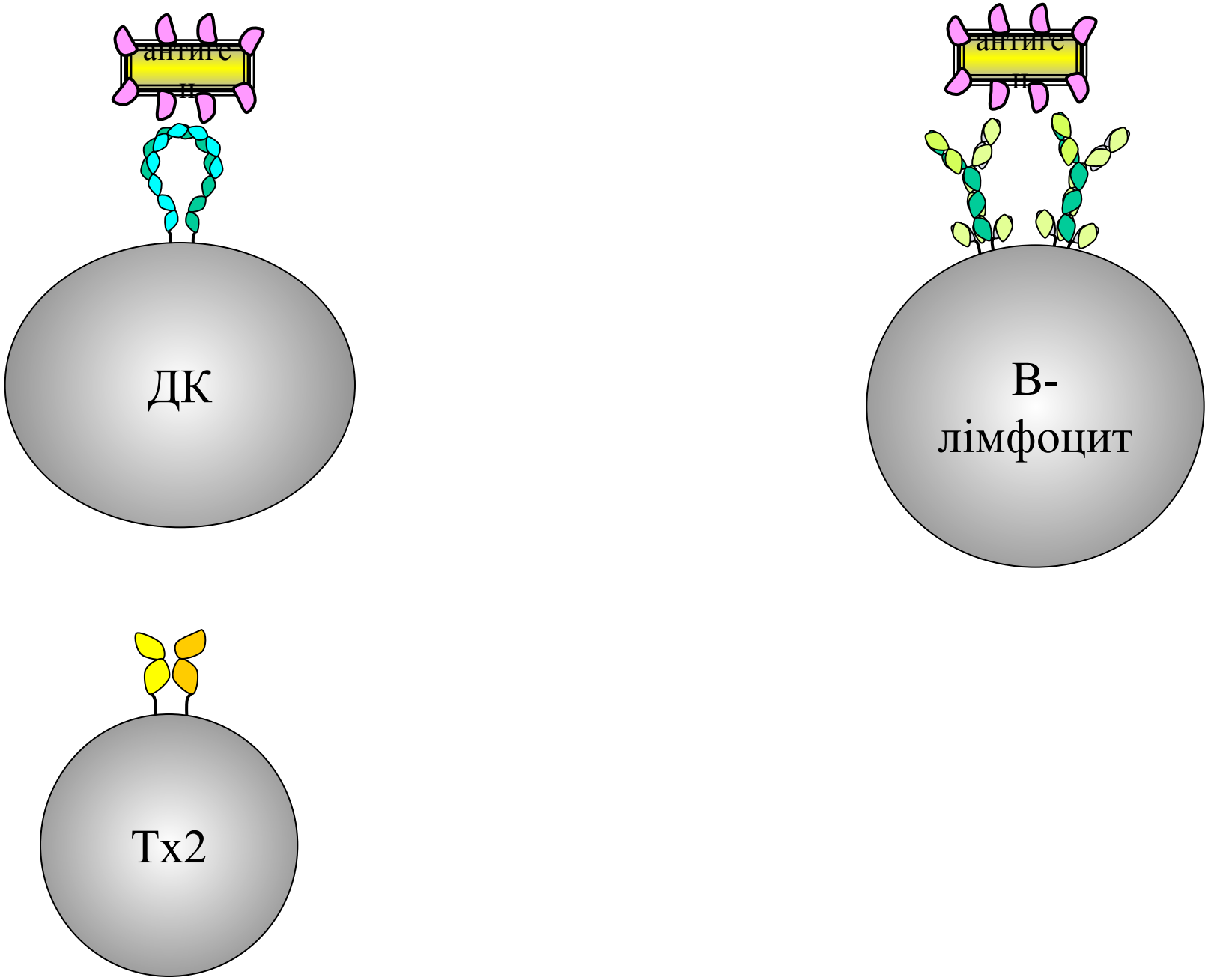


Logic of the RAG immune response

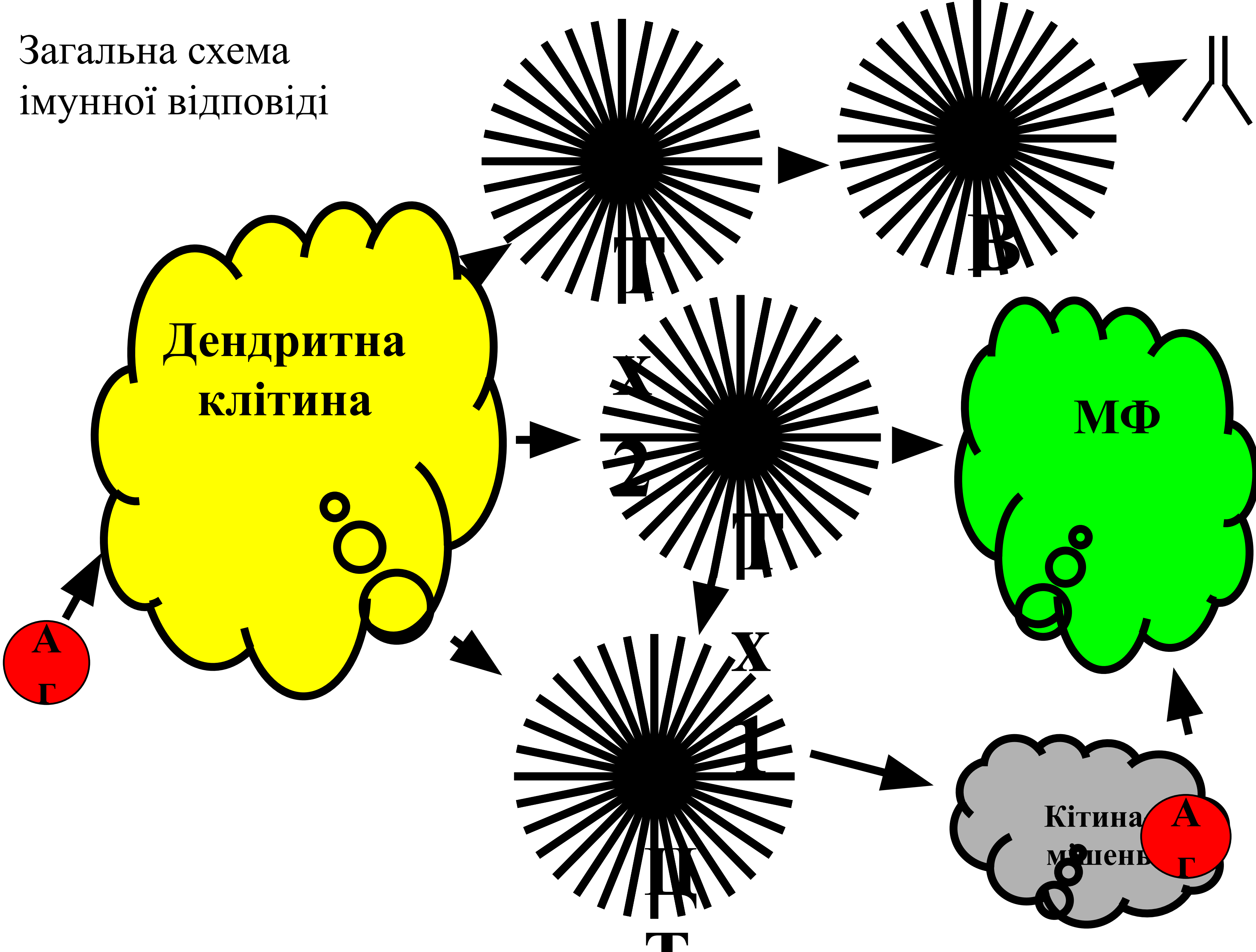



Ag
Te
Ag
Te
Te

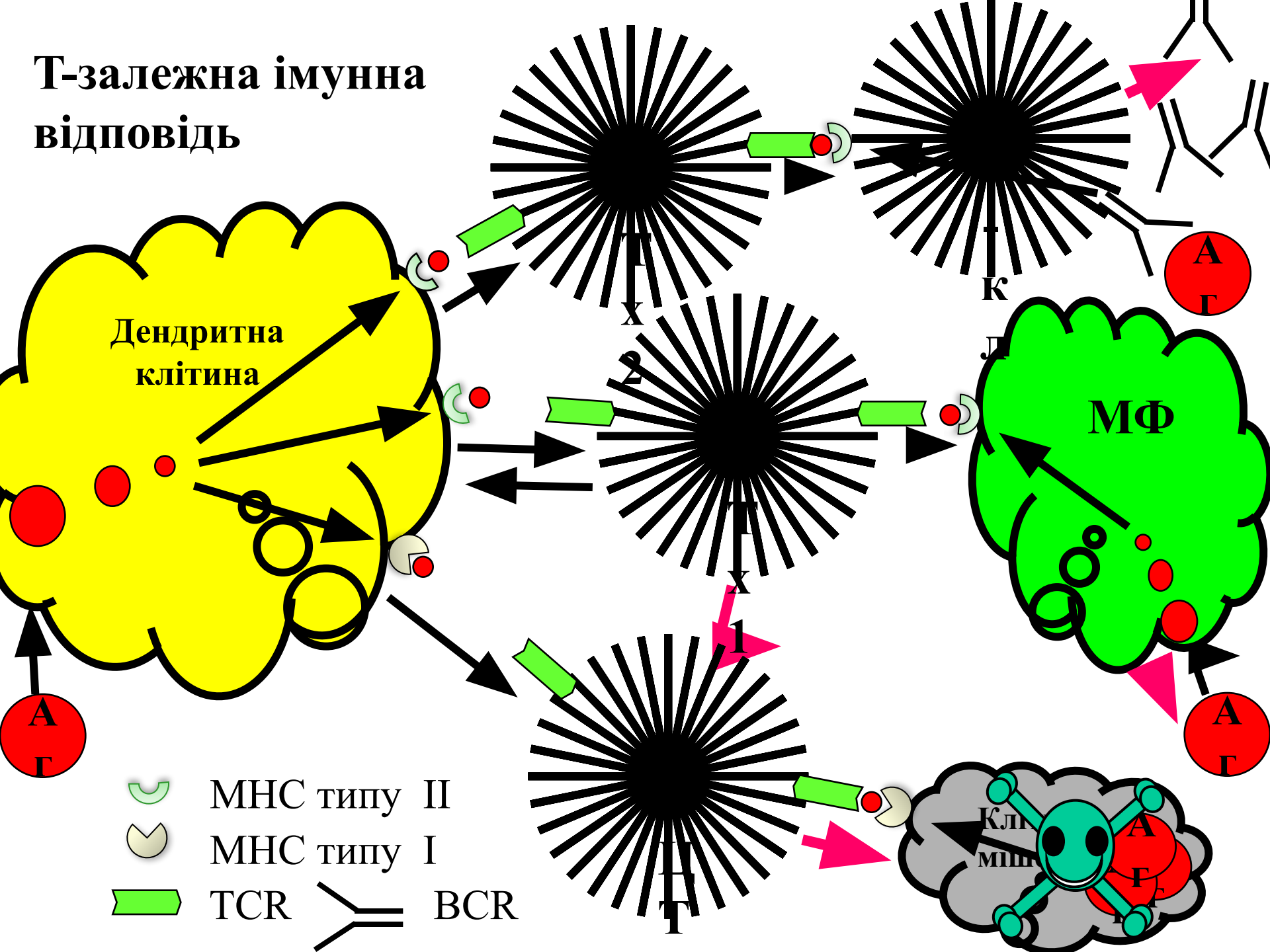

Ag
Te
Ag
Te
Te


антиге
н
ДК
антиге
н
В-
лімфоцит
Тх2

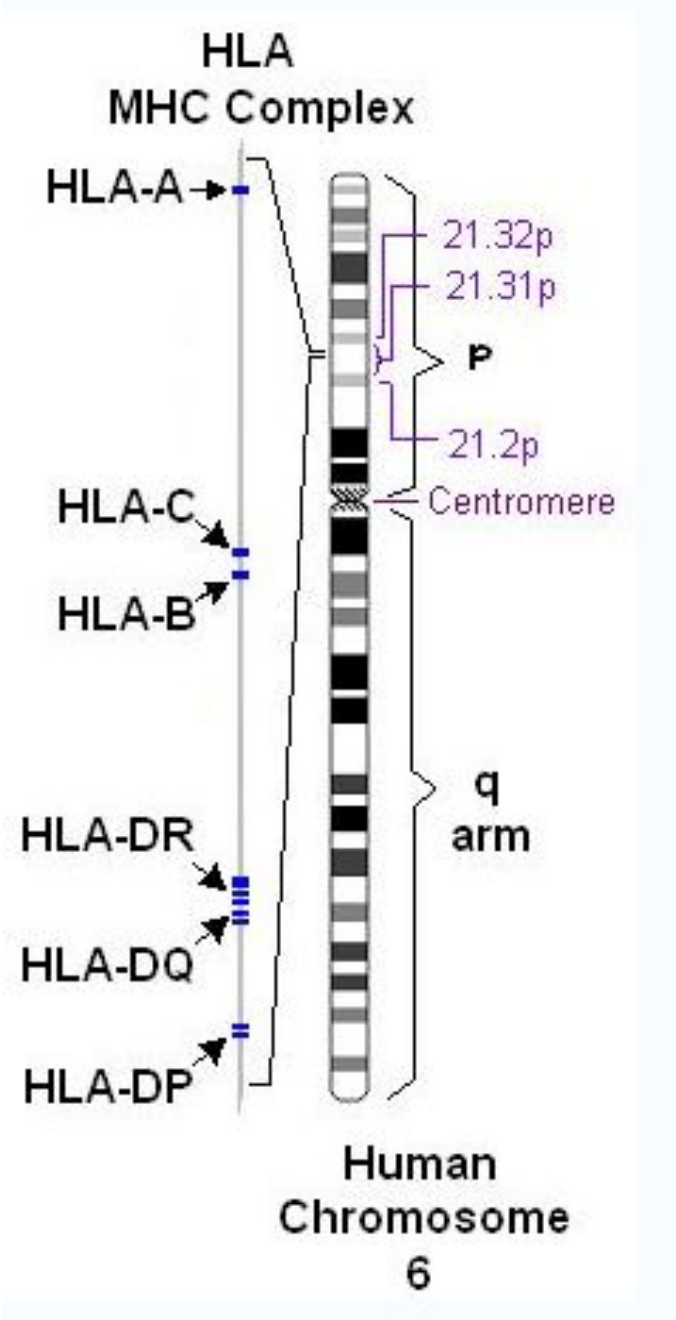
Загальна схема
імунної відповіді

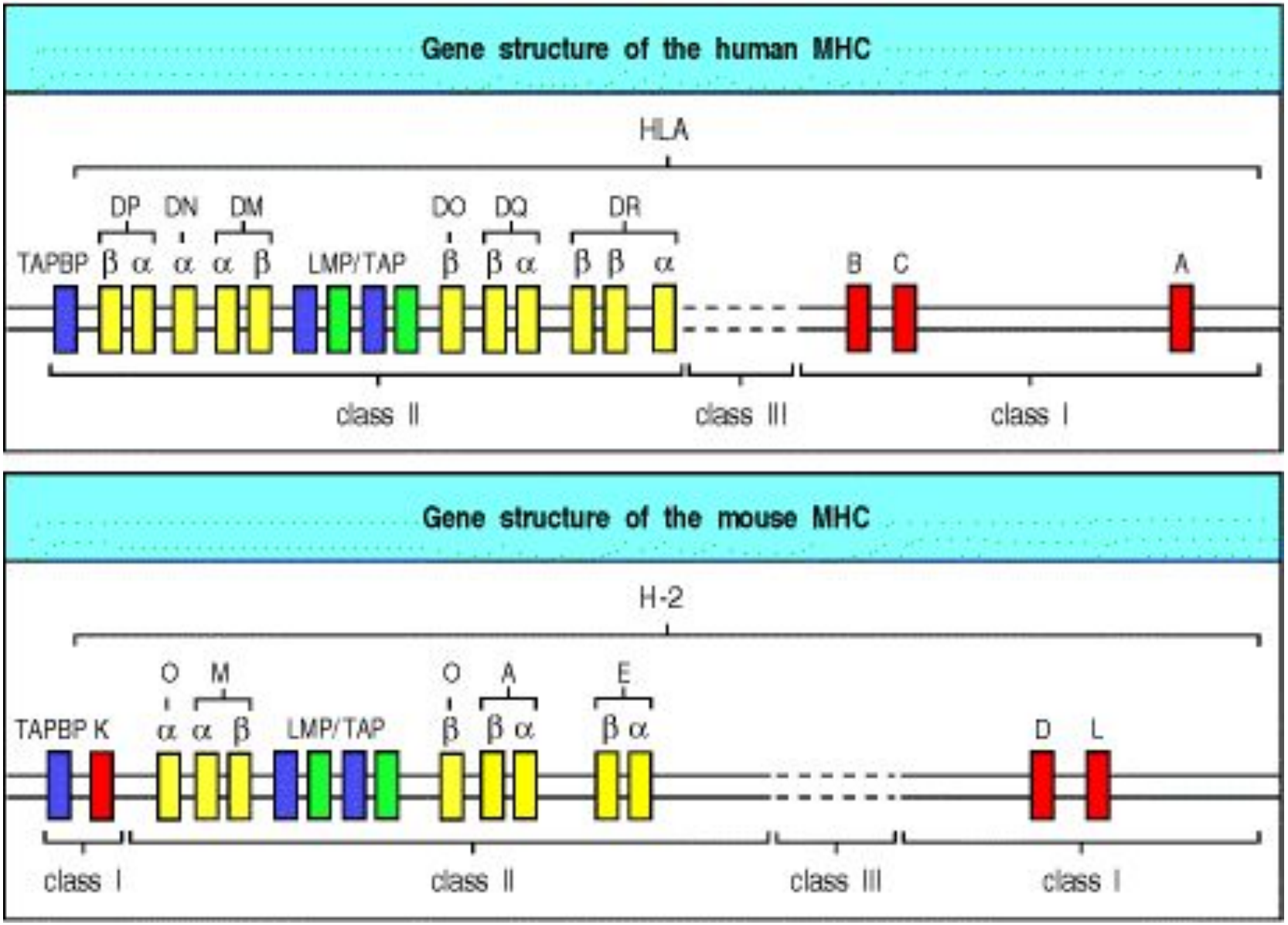


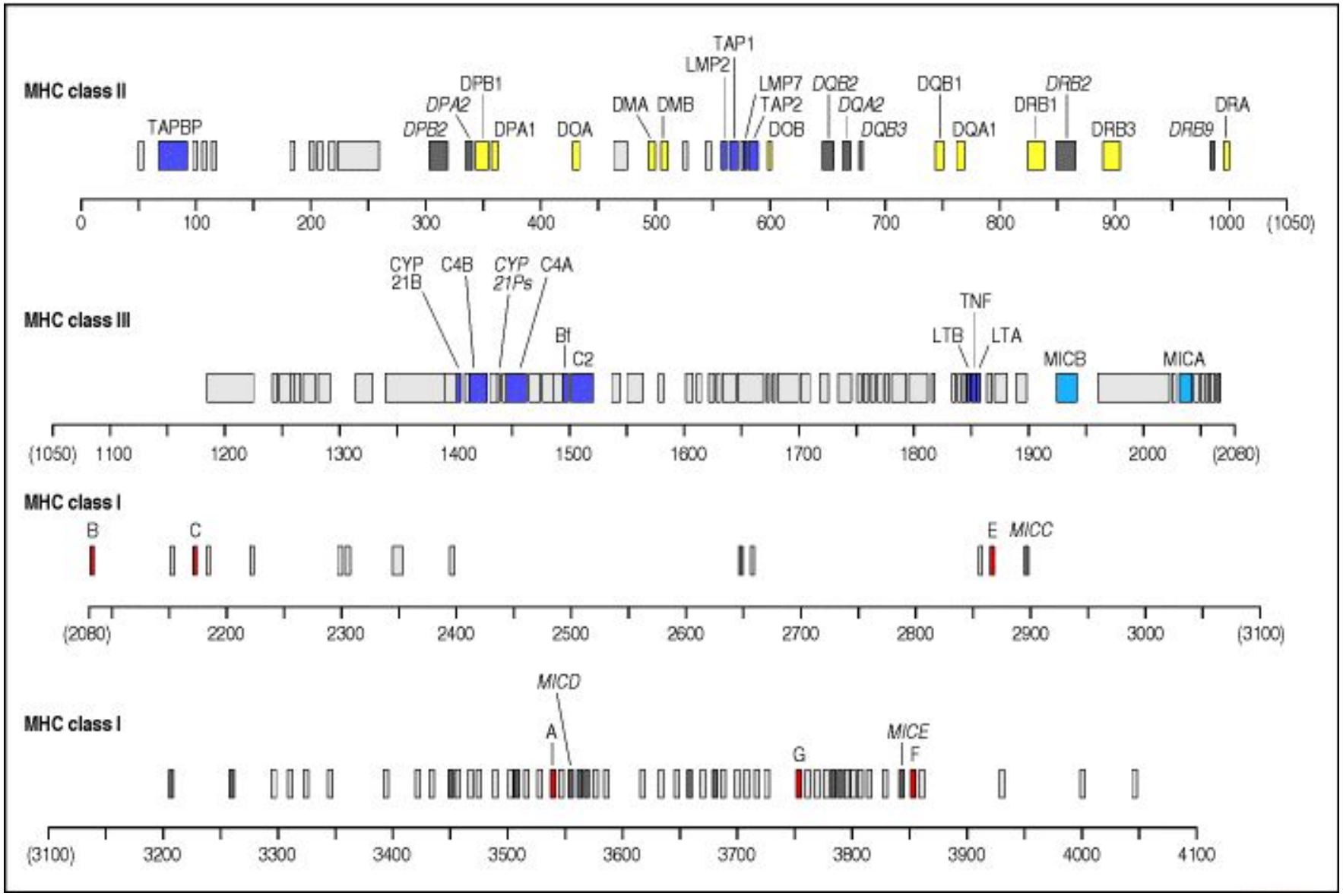
Т-залежна імунна відповідь



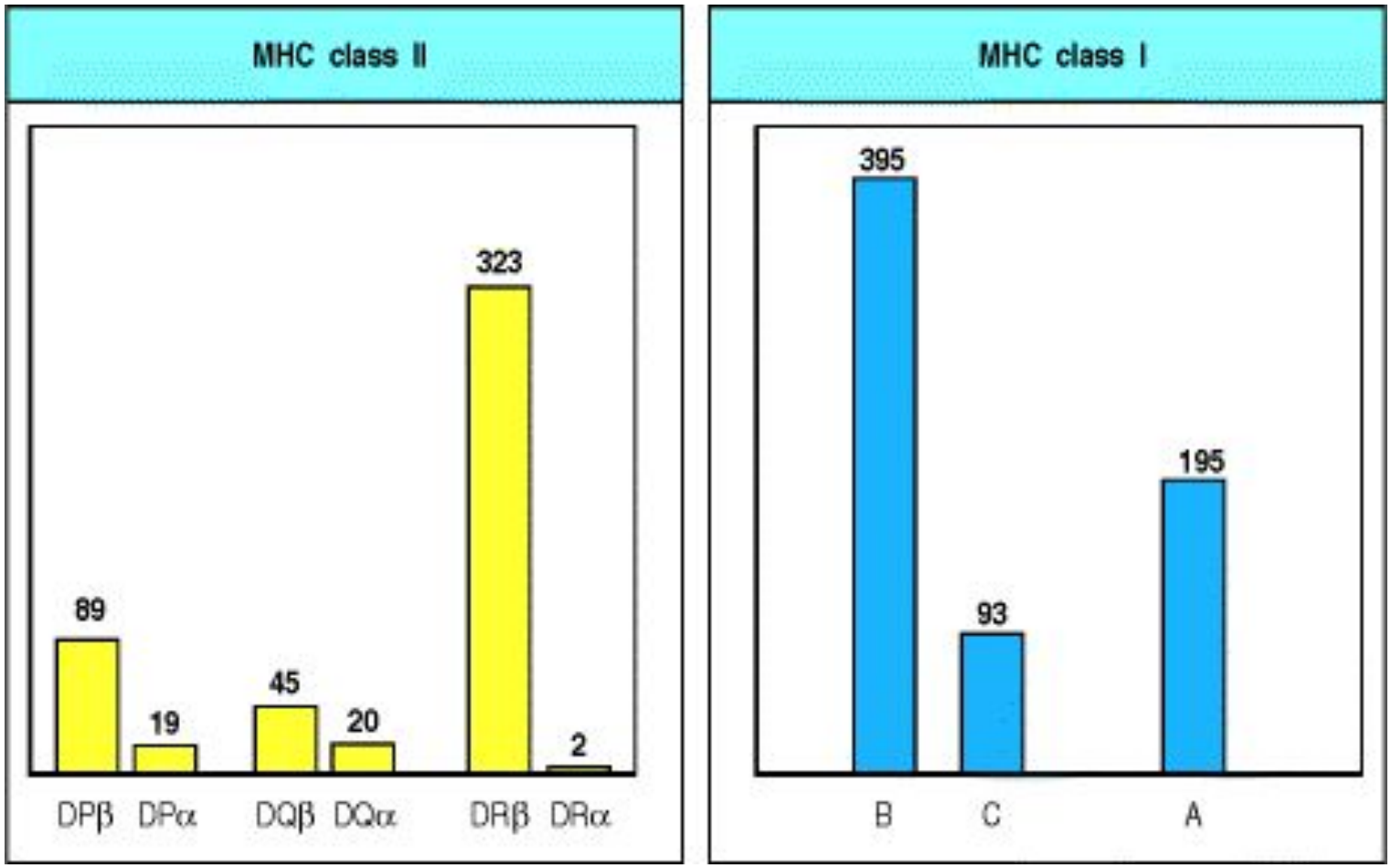
Генетика МНС

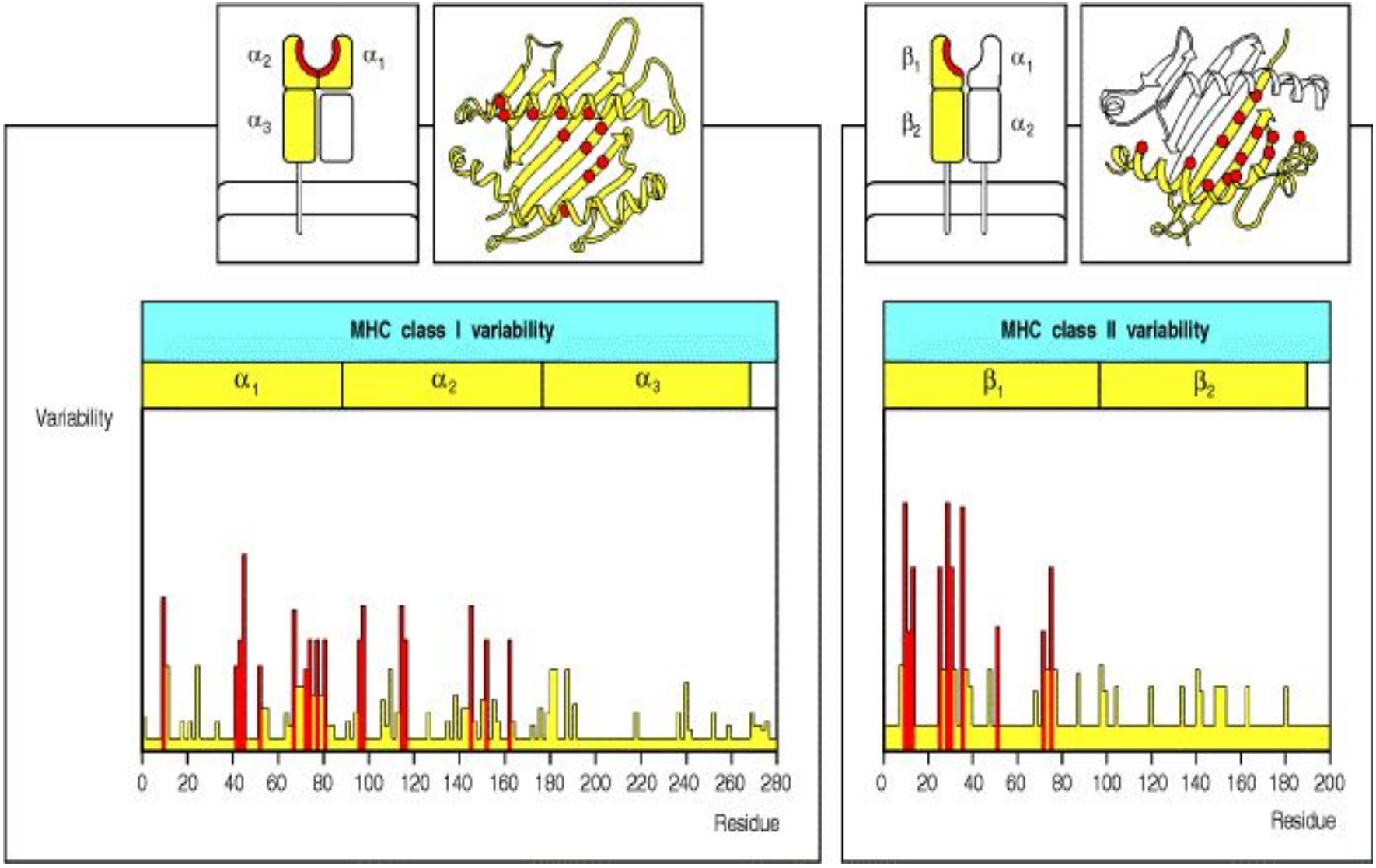

HLA
MHC Complex
HLA-A
HLA-C
HLA-B
HLA-DR
HLA-DQ
HLA-DP
21.32p
21.31p
p
21.2p
Centromere
q
arm
Human
Chromosome
6


Gene structure of the human MHC
HLA
DP
DN
DM
DO
DQ
DR
TAPBP
β α
α
α β
LMP/TAP
β
β α
β β α
B
C
A
class II
class III
class I
Gene structure of the mouse MHC
H-2
O
M
O
A
E
TAPBP K
α α β
LMP/TAP
β
β α
β α
D
L
class I
class II
class III
class I


MHC class II
TAPBP
DPB1
DPA2
DPB2
DPA1
DOA
DMA
DMB
TAP1
LMP2
LMP7
TAP2
DOB
DQB2
DQA2
DQB3
DQB1
DQA1
DRB2
DRB1
DRB3
DRB9
DRA
0
100
200
300
400
500
600
700
800
900
1000
(1050)
MHC class III
CYP 21B
C4B
CYP 21Ps
C4A
Bf
C2
TNF
LTB
LTA
MICB
MICA
(1050)
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
(2080)
MHC class I
B
C
E
MICC
(2080)
2200
2300
2400
2500
2600
2700
2800
2900
3000
(3100)
MHC class I
MICD
A
G
MICE
F
(3100)
3200
3300
3400
3500
3600
3700
3800
3900
4000
4100

Гени HLA дуже поліморфні




α2
α1
α3
β1
α1
β2
α2
MHC class I variability
α1
α2
α3
Variability
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280
Residue
MHC class II variability
β1
β2
0 20 40 60 80 100 120 140 160 180 200
Residue

Ще про біологічну роль MHC…

CONTROL OF MATING PREFERENCES IN MICE BY GENES IN THE MAJOR HISTOCOMPATIBILITY COMPLEX*

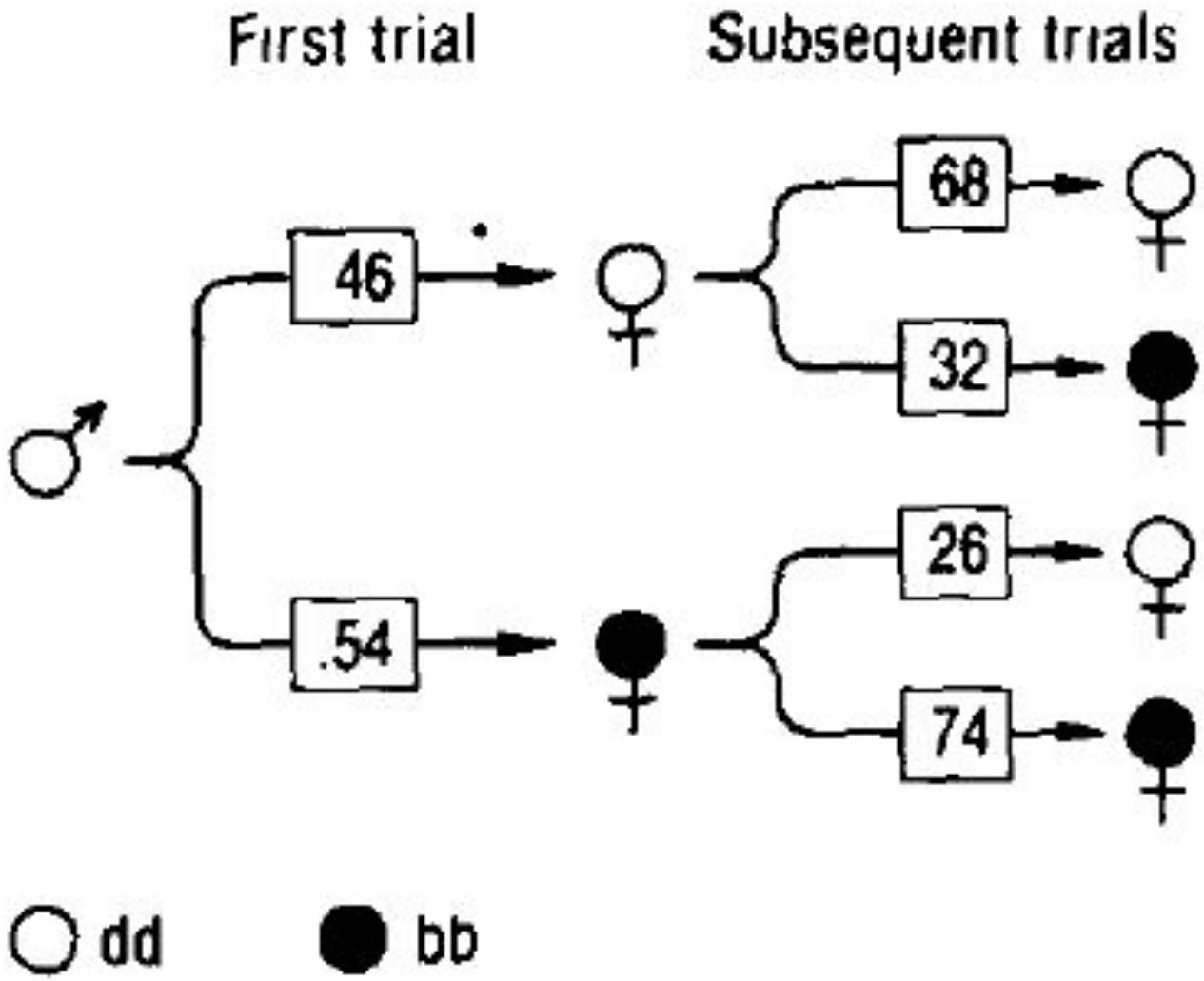
By K. YAMAZAKI, E. A. BOYSE, V. MIKÉ, H. T. THALER, B. J. MATHIESON,‡ J. ABBOTT, J. BOYSE, Z. A. ZAYAS, AND L. THOMAS

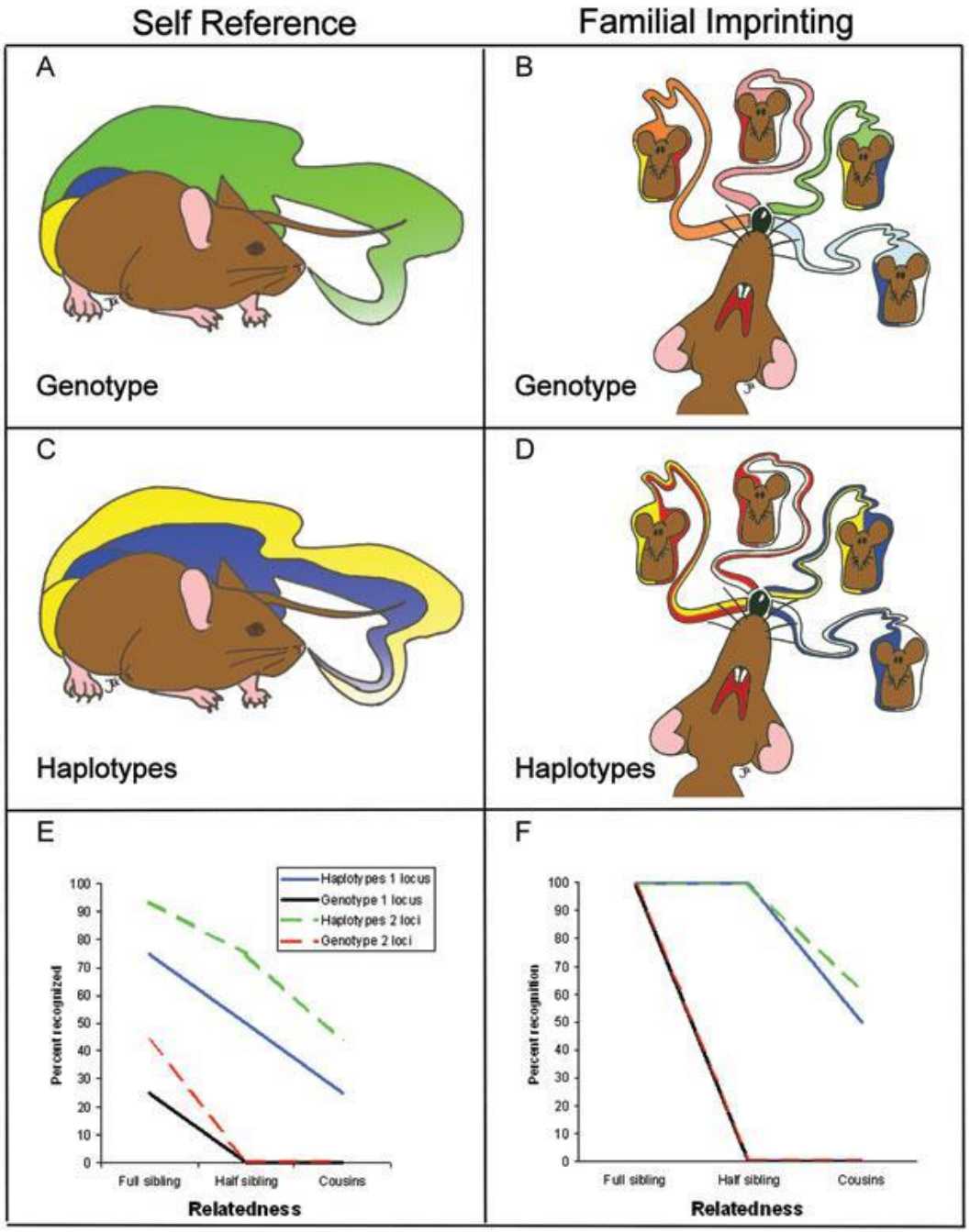
(From the Memorial Sloan-Kettering Cancer Center, New York 10021)

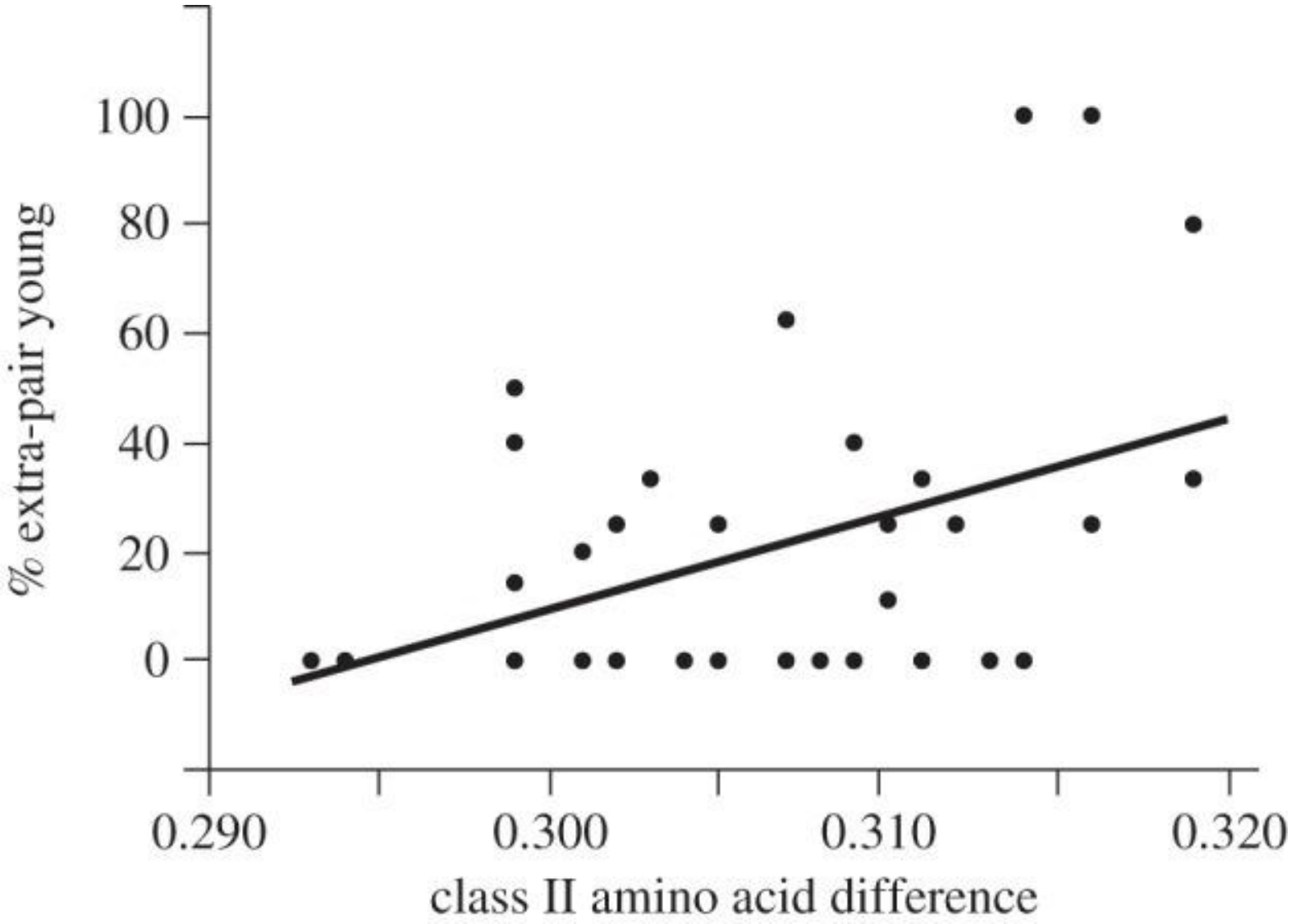
While observing AKR and AKR backcross mice being bred to produce an AKR-*H-2*^{b} congenic mouse strain, one of us (J. B.) noticed that homozygous *H-2*^{b} ♂♂ were more attracted to heterozygous *H-2*^{b}:*H-2*^{k} ♀♀ than to *H-2*^{b} homozygous ♀♀. Meanwhile another of us (L. T.), unaware of these observations, arrived at the theoretical conclusion that histocompatibility antigens might act as olfactory self-markers distinguishing different members of a population from one another (1).

This article is an account of our study of *H-2*-associated "mating preference." By "*H-2*" we imply the chromosomal region including *H-2* which differentiates congenic stocks from their partner strains. We used a straightforward experimental design: A ♂ mouse (e.g., **"bb"**) was caged with two *H-2* congenic ♀♀ (e.g., **"bb"** and **"kk"**), in estrus, and the trio was observed continuously until the ♂ successfully mated with one of the ♀♀.

J Exp Med. 1976 Nov 2;144(5):1324-35.


First trial
Subsequent trials
46
.54
68
32
26
74
dd
bb


Self Reference
Familial Imprinting
A
Genotype
B
Genotype
C
Haplotypes
D
Haplotypes
E
Haplotypes 1 locus
Genotype 1 locus
Haplotypes 2 loci
Genotype 2 loci
Percent recognized
100
90
80
70
60
50
40
30
20
10
0
Full sibling
Half sibling
Cousins
Relatedness
F
Percent recognition
100
90
80
70
60
50
40
30
20
10
0
Full sibling
Half sibling
Cousins
Relatedness


% extra-pair young
100
80
60
40
20
0
0.290
0.300
0.310
0.320
class II amino acid difference

MHC-dependent mate preferences in humans

CLAUS WEDEKIND[1], THOMAS SEEBECK[2], FLORENCE BETTENS[3] AND ALEXANDER J. PAEPKE[1]

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SUMMARY

One substantial benefit of sexual reproduction could be that it allows animals (including humans) to react rapidly to a continuously changing environmental selection pressure such as coevolving parasites. This counteraction would be most efficient if the females were able to provide their progeny with certain allele combinations for loci which may be crucial in the parasite-host arms race, for example the MHC (major histocompatibility complex). Here we show that the MHC influences both body odours and body odour preferences in humans, and that the women's preferences depend on their hormonal status. Female and male students were typed for their HLA-A, -B and -DR. Each male student wore a T-shirt for two consecutive nights. The next day, each female student was asked to rate the odours of six T-shirts. They scored male body odours as more pleasant when they differed from the men in their MHC than when they were more similar. This difference in odour assessment was reversed when the women rating the odours were taking oral contraceptives. Furthermore, the odours of MHC-dissimilar men remind the test women more often of their own actual or former mates than do the odours of MHC-similar men. This suggests that the MHC or linked genes influence human mate choice today.

ELSEVIER

Evolution and Human Behavior 26 (2005) 213–226

Evolution and Human Behavior

MHC-heterozygosity and human facial attractiveness

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Major histocompatibility complex and sexual selection

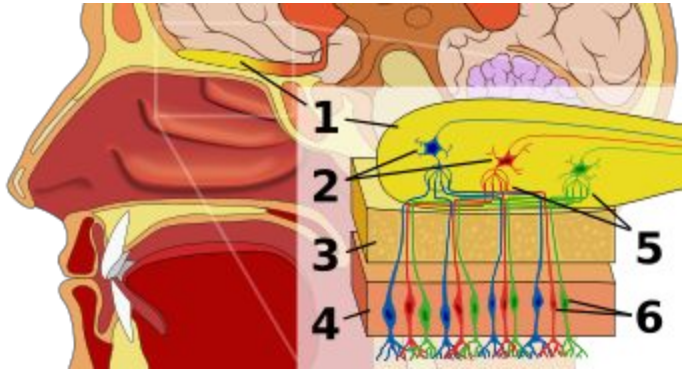
From Wikipedia, the free encyclopedia

A pathogen is any agent that causes disease. The body has two defense mechanisms for dealing with pathogenic microorganisms and other harmful substances: the inflammatory reaction and the development of an acquired immunity. Acquired immunity consists of humoral or cell-mediated immunity, and develops after initial contact with a pathogen; it is manifested by the ability of one's immune system to fight foreign antigens.[1]

All living cells have structures called antigens present on their cell surface. Antigens are either a polysaccharide or a protein that reacts specifically with a cell surface receptor or an antibody. For each person and each type of cell there are different antigens on the cell's surface. The unique, genetically-determined antigens present on cell surfaces are determined by a cluster of genes on chromosome 6 at loci 6p21.3 called the **major histocompatibility complex** (**MHC**).[2] In humans, these antigens were first identified on a type of white blood cell (leukocyte) and were therefore named human leukocyte antigens (HLA antigens). As a result, the human major histocompatibility complex can also be called the HLA system. Often in reference to these antigens and the set of genes responsible for these antigens the terms MHC and HLA are used interchangeably.[1]

The antigens on cell surfaces are processed by the cells of the body's immune system depending on their antigenicity. Specifically, the antigenicity of the HLA surface proteins depends on whether they are one's own proteins (self-antigens) or whether they are the foreign proteins of another person (non-self-antigens). The HLA proteins on a person's own cells are recognized by their immune system as such, while non-self-antigens will incite an immune response. Originally, MHC proteins were considered of interest only in regards to organ transplantation because transplants in which the donor and recipient cells contained different MHC proteins resulted in organ rejection unless the immune system was suppressed. Further studies have shown MHC to actually have a much larger role in the immune system than just organ transplantation. The MHC region of genes contains extremely high levels of gene density and diversity; genetic variation within this region plays a vital role in susceptibility to autoimmune, infectious, and other diseases.[2] MHC genes are also involved in various non-immune functions such as olfaction[2] and self/non-self-recognition.[1][3]

Contents [hide]



MHC Class I, II, and III proteins [edit]