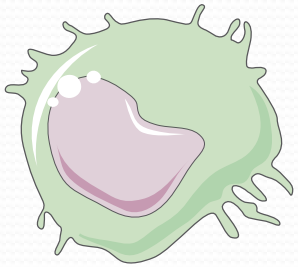
Transplantační imunologie pro kliniky

Ilja Stříž

IKEM

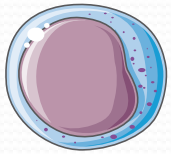
Přirozená imunita

epitel



makrofág

granulocyt

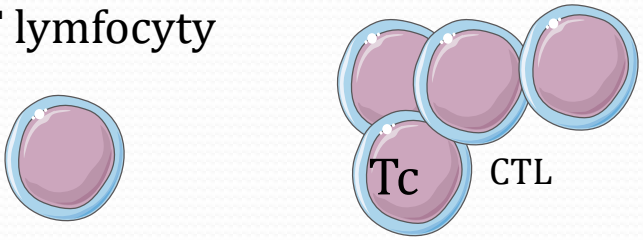


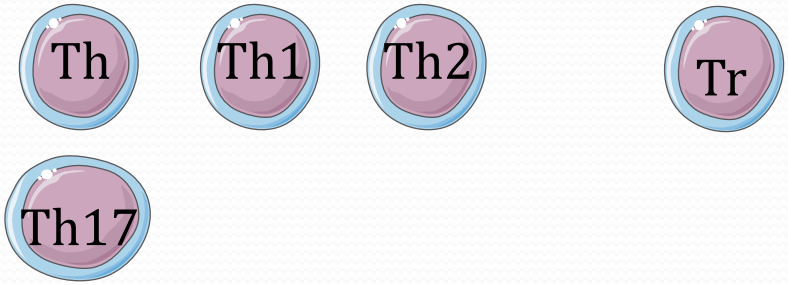
přirozené lymfoidní buňky (NK, NKT, nuocyty, NHC iH2,…)

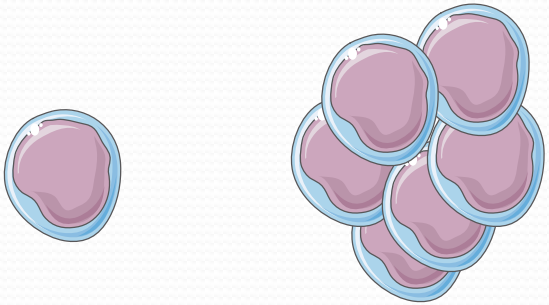
hodiny

Adaptivní imunita

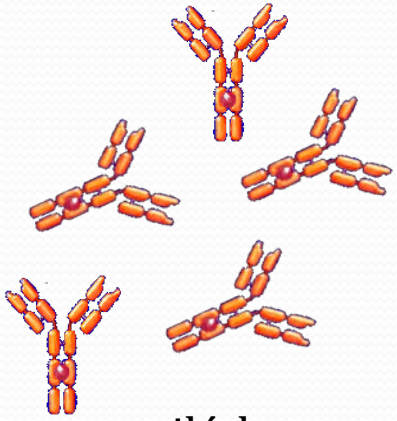
T lymfocyty







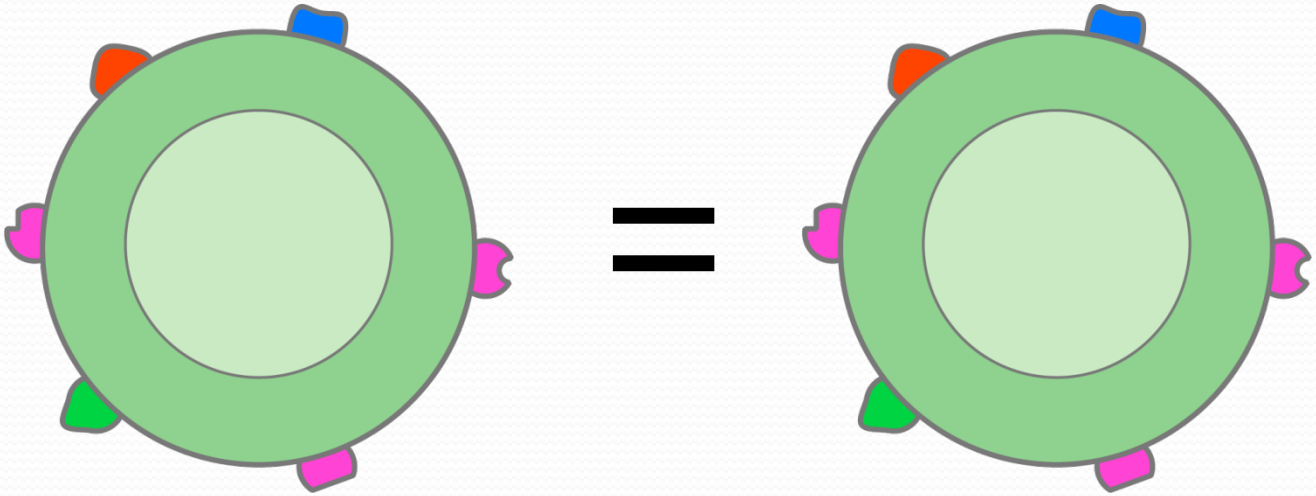
B lymfocyty



protilátky

dny

Cíl transplantačních reakcí - vlastní („self“) antigeny

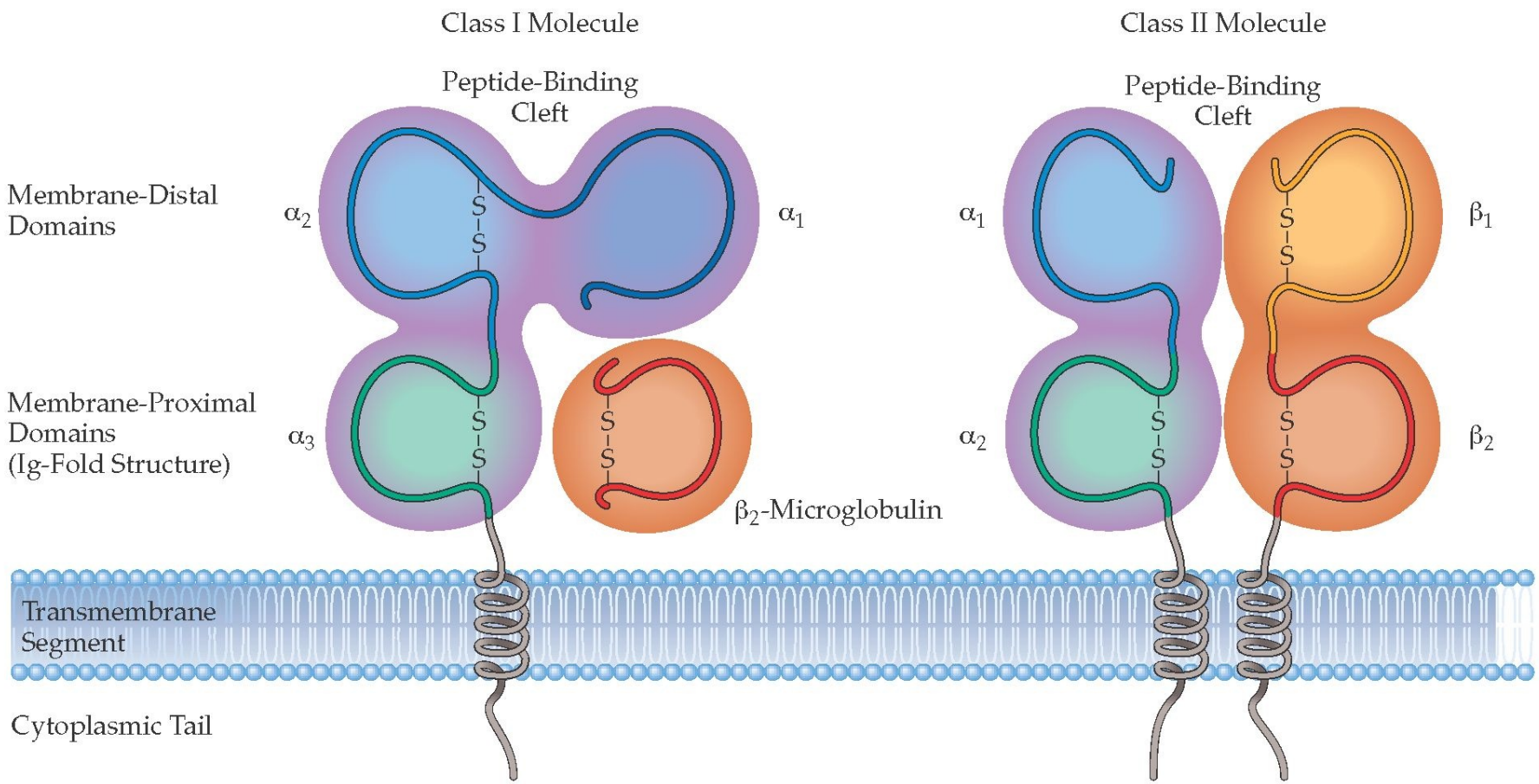


Hlavní histokompatibilní komplex

MHC

Lidské leukocytární antigeny

HLA



I.třída (A, B, C)

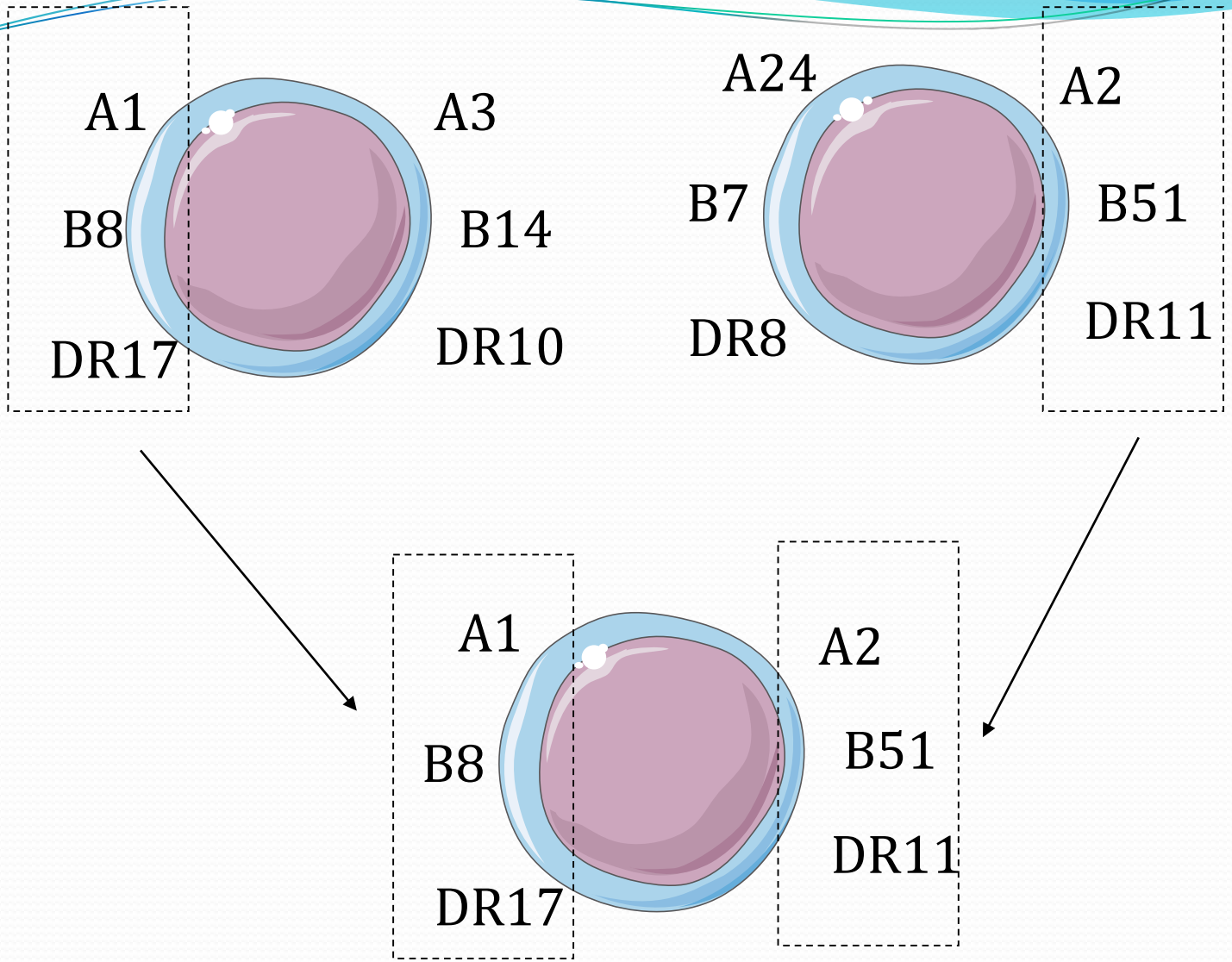
na všech jaderných buňkách

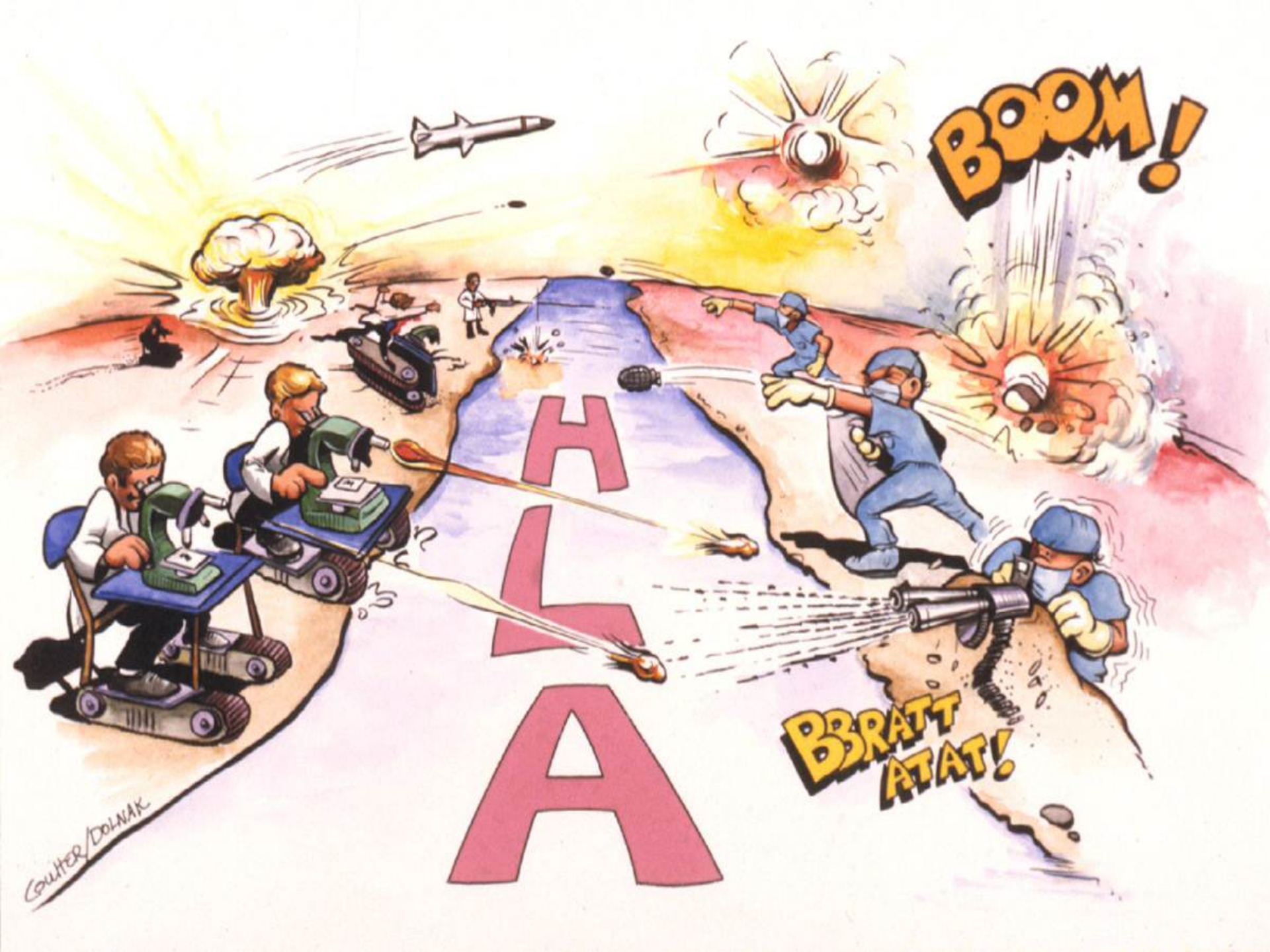
II.třída (DR, DP, DQ)

na antigen-presentujících buňkách

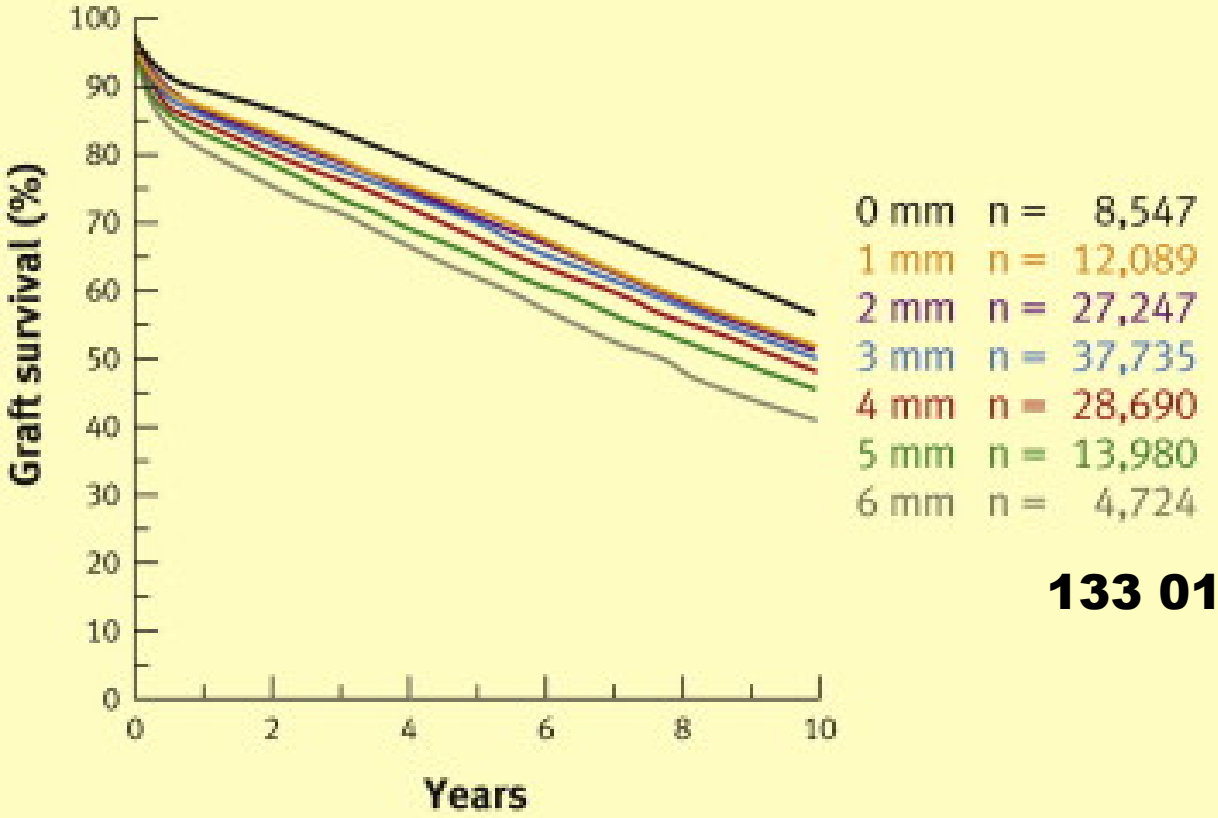
Antigenní frekvence HLA lokusů I.tř. v české populaci

- A*02 (45%), A*03 (28%), A*01 (25%), A*24 (17%)
- B*07 (20%), B*44 (17%) B*08 (15%)
- C*07 (44%), C *0602 (26%), C*03 a C*12 (obojí 20%)
- u kombinace A1B8 C7 je 6,4%


A1
A3
B8
B14
DR17
DR10
A24
A2
B7
B51
DR8
DR11
A1
A2
B8
B51
DR11
DR17


BOOM!
HLA
BBRATT ATAT!
GOULTER/DOLNAK

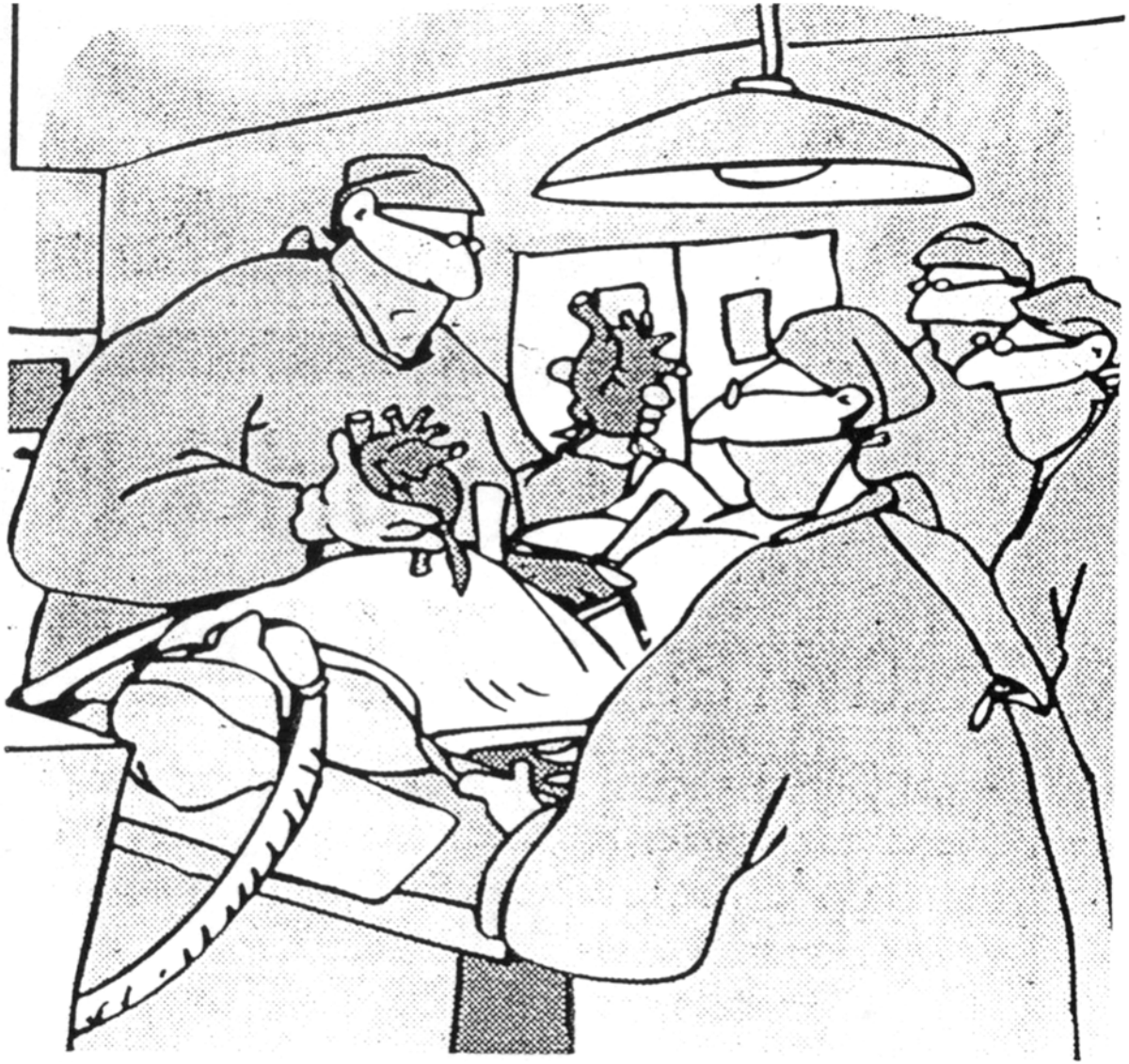
Influence of the number of HLA mismatches at -*A*, -*B* and -*DR* HLA loci on graft survival after kidney transplantation from deceased donors



133 012 pacientů

HLA, human leukocyte antigen; mm, mismatches.

Copyright: Collaborative Transplant Study, K-211101-0211



Tak znovu .. to od dárce mám v levé ruce
a to staré srdce v pravé … je to tak?

Imunitní odpověď proti štěpu

operační trauma
ischemie/reperfuze

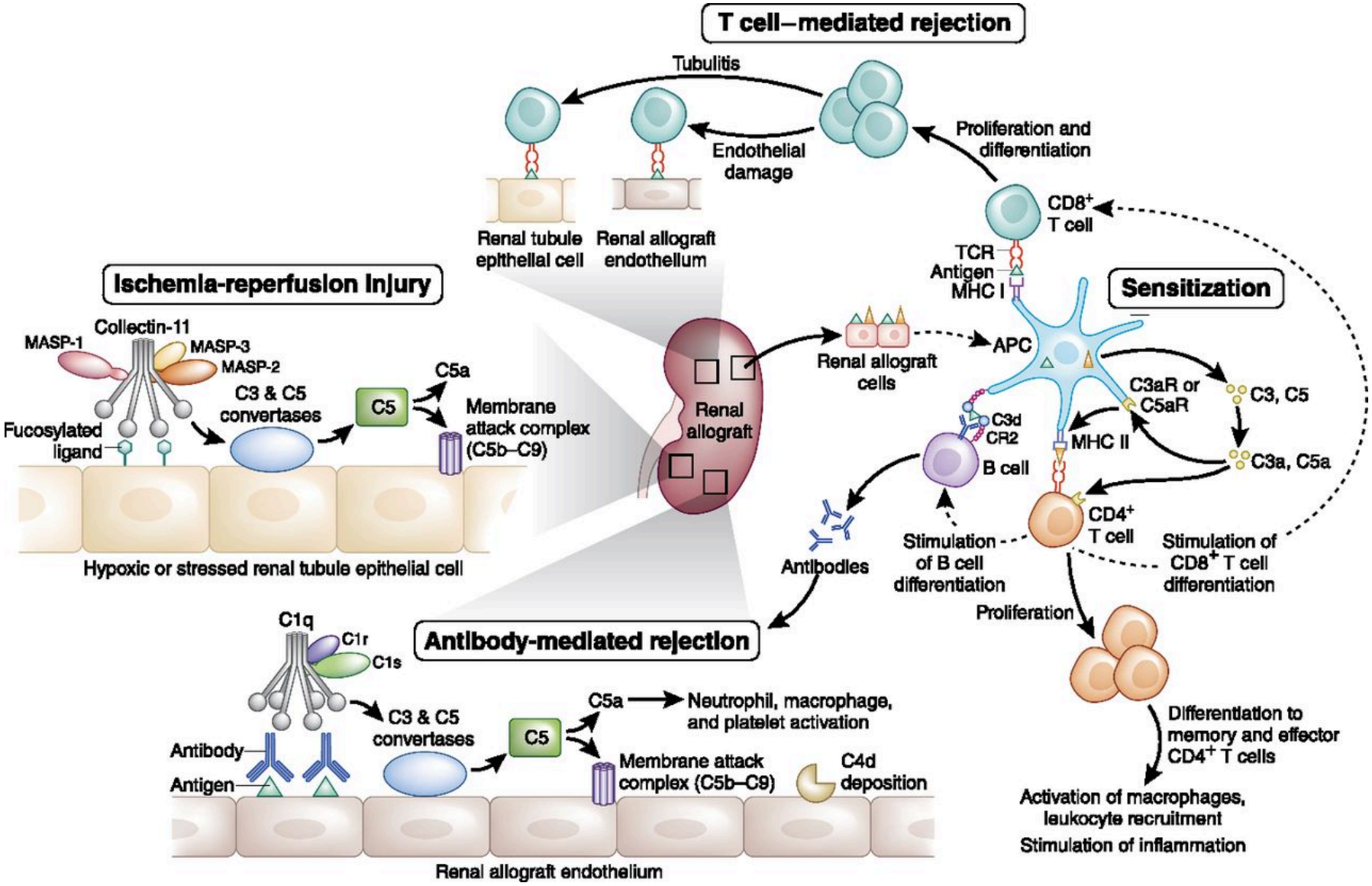
prozánětlivé cytokiny
(TNFα, IL-6, IL-1β, IL-18...)
alarminy
(IL-1α, IL-33, HMGB, ...)

indukce chemokinů
(CXCL8, CXCL5, CCL5, CXCL10,...)
a adhezivních molekul
(ICAM-1, VCAM-1, ...)

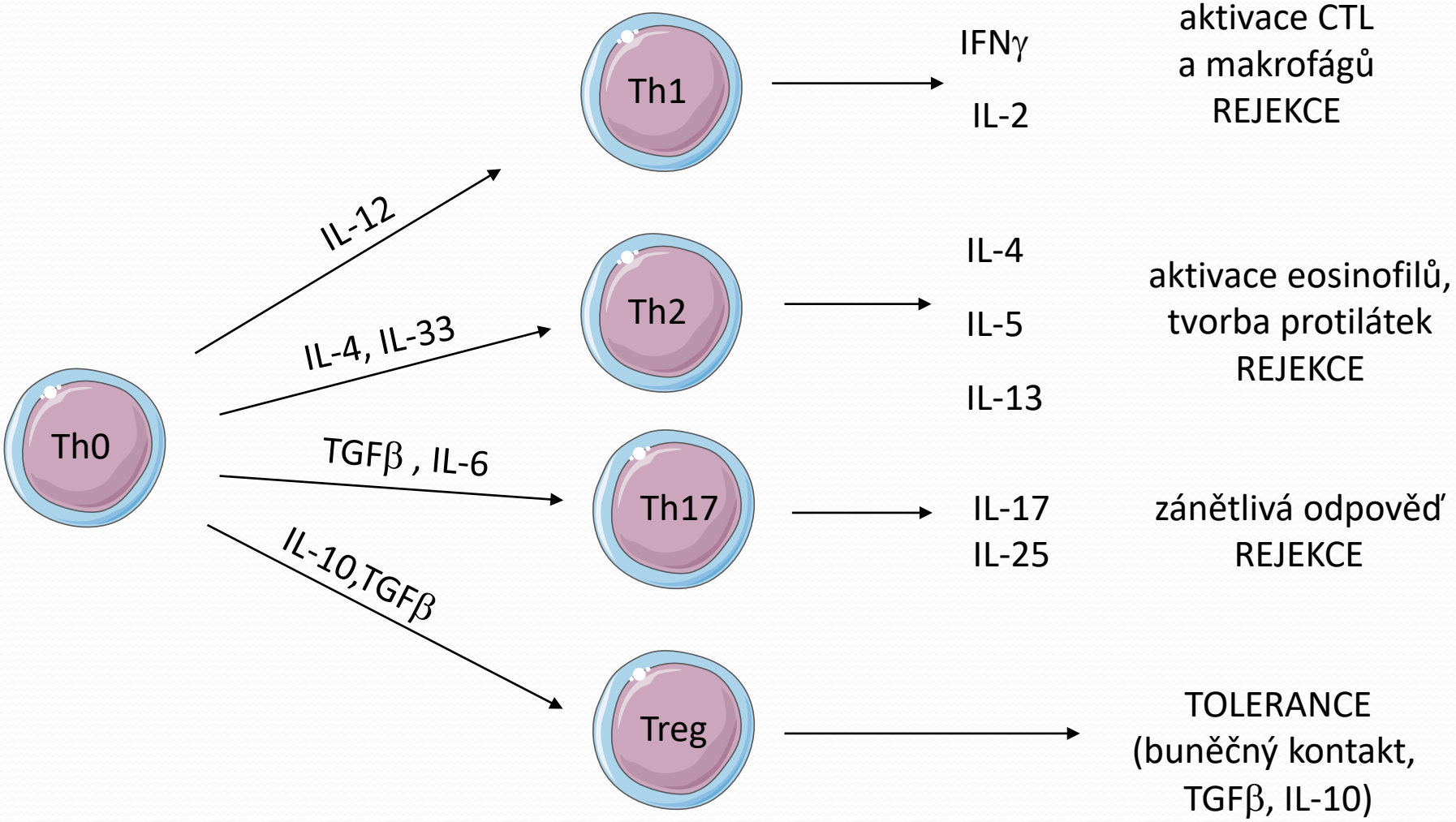
infiltrace efektorových buněk
(neutrofily, monocyty, T lymfocyty)

Stříž I. Postgraduální Medicína 19: 141-6, 2017

Imunitní odpověď proti alotransplantátu

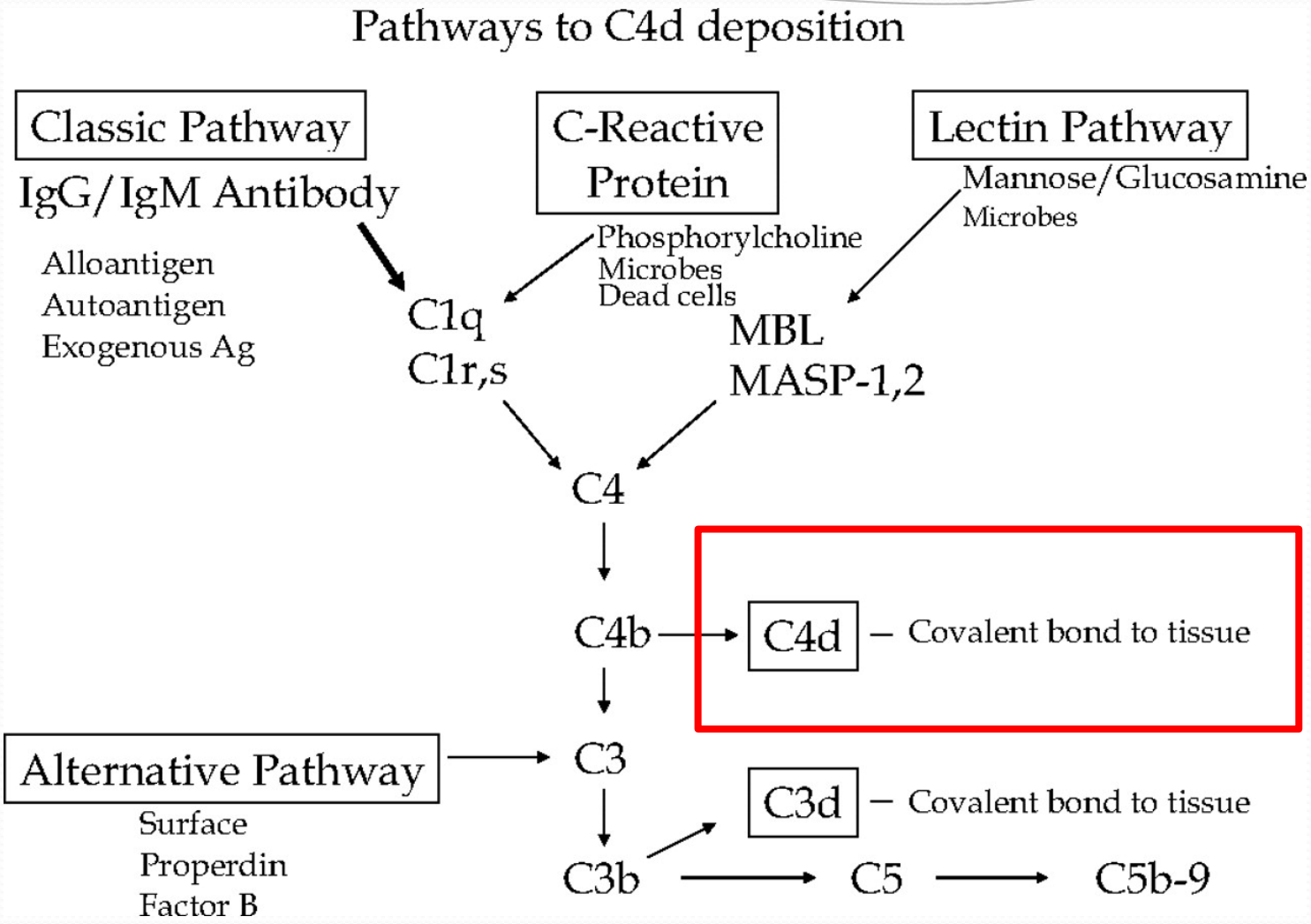


Nauser CL et al. JASN 28:2571-2578, 2017


Th0
IL-12
IL-4, IL-33
TGFβ , IL-6
IL-10,TGFβ
Th1
Th2
Th17
Treg
IFNγ
IL-2
IL-4
IL-5
IL-13
IL-17
IL-25
aktivace CTL
a makrofágů
REJEKCE
aktivace eosinofilů,
tvorba protilátek
REJEKCE
zánětlivá odpověď
REJEKCE
TOLERANCE
(buněčný kontakt,
TGFβ, IL-10)

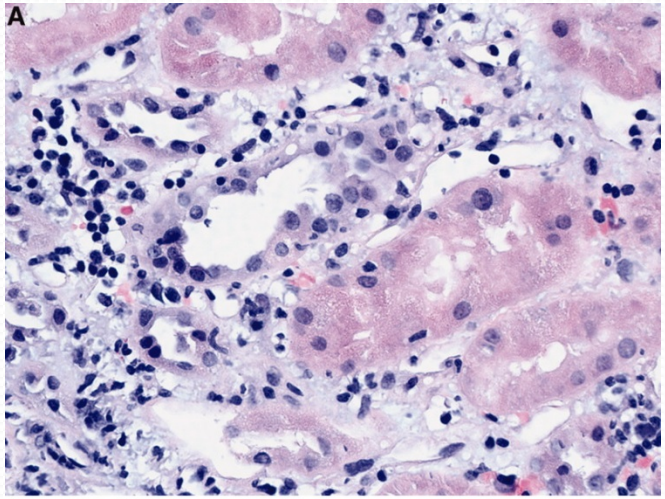
Jak zjistíme, že došlo k protilátkovému poškození štěpu?

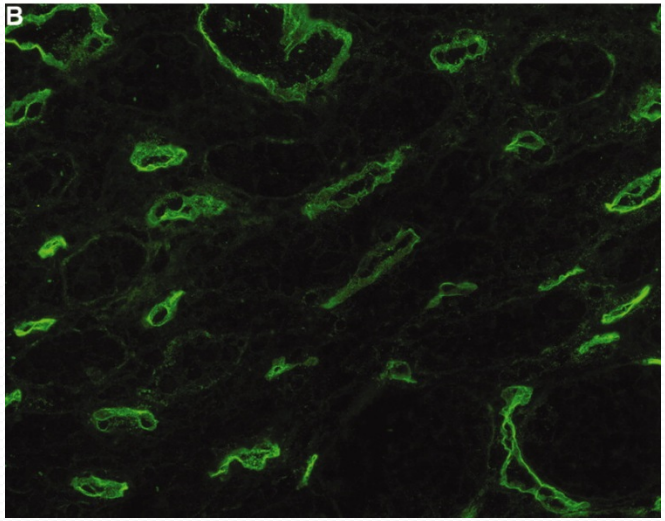
CZXXXXXXXXXX/MM/RRRR



Colvin R B JASN 2007;18:1046-1056

Obraz akutní humorální rejekce





Colvin R B JASN 2007;18:1046-1056

CZXXXXXXXXXX/NM/RRRR

Jak zjistit přítomnost protilátek proti HLA antigenům dárce ?

Detekce alospecifických protilátek

buněčné testy

komplement dependentní cytotoxický test (CDC)

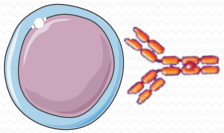
FCXM

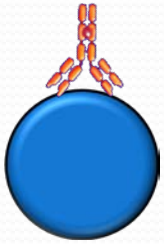
metodiky pevné fáze

ELISA

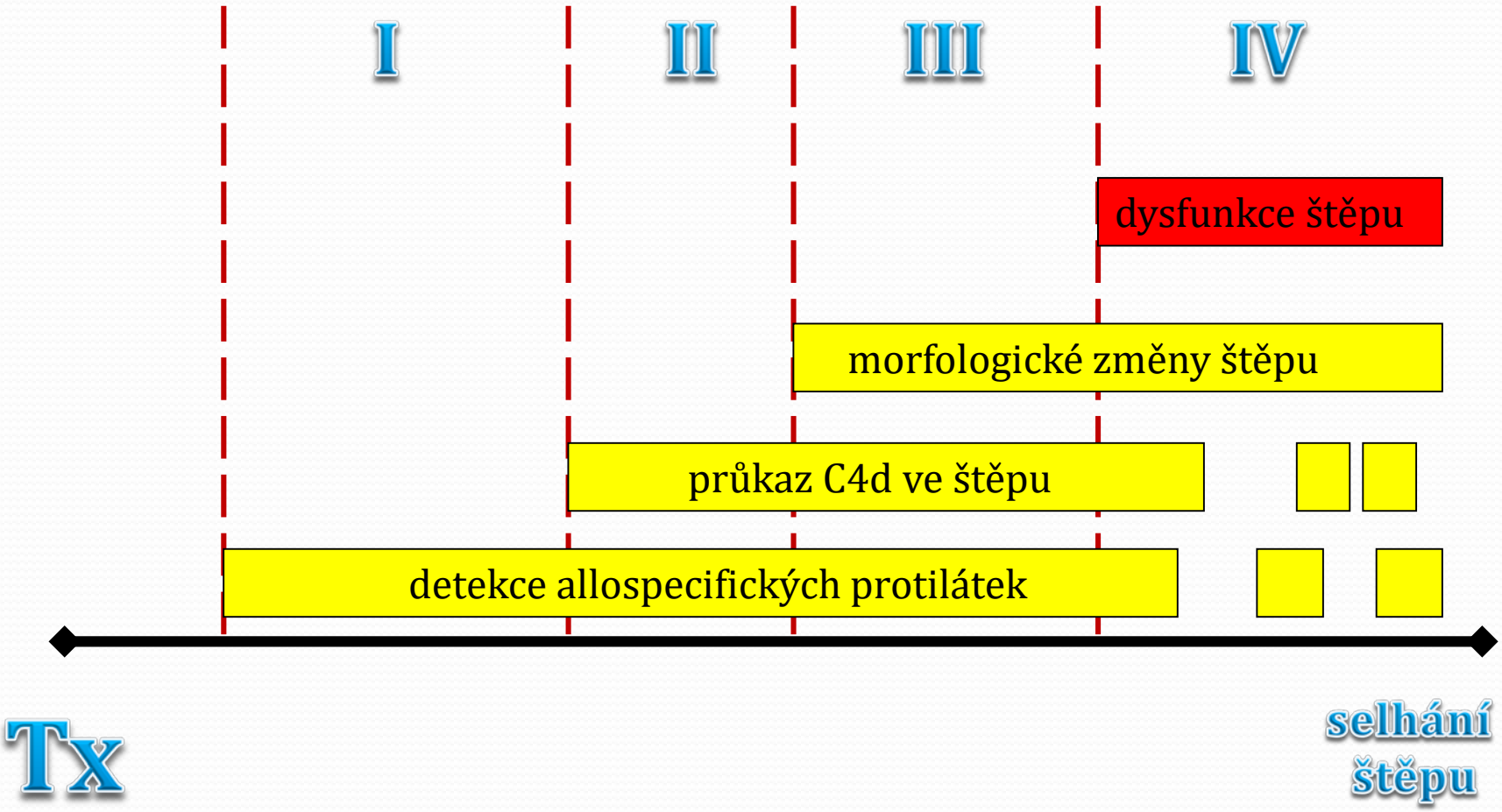
Luminex

1960 1970 1980 1990 2000 2010

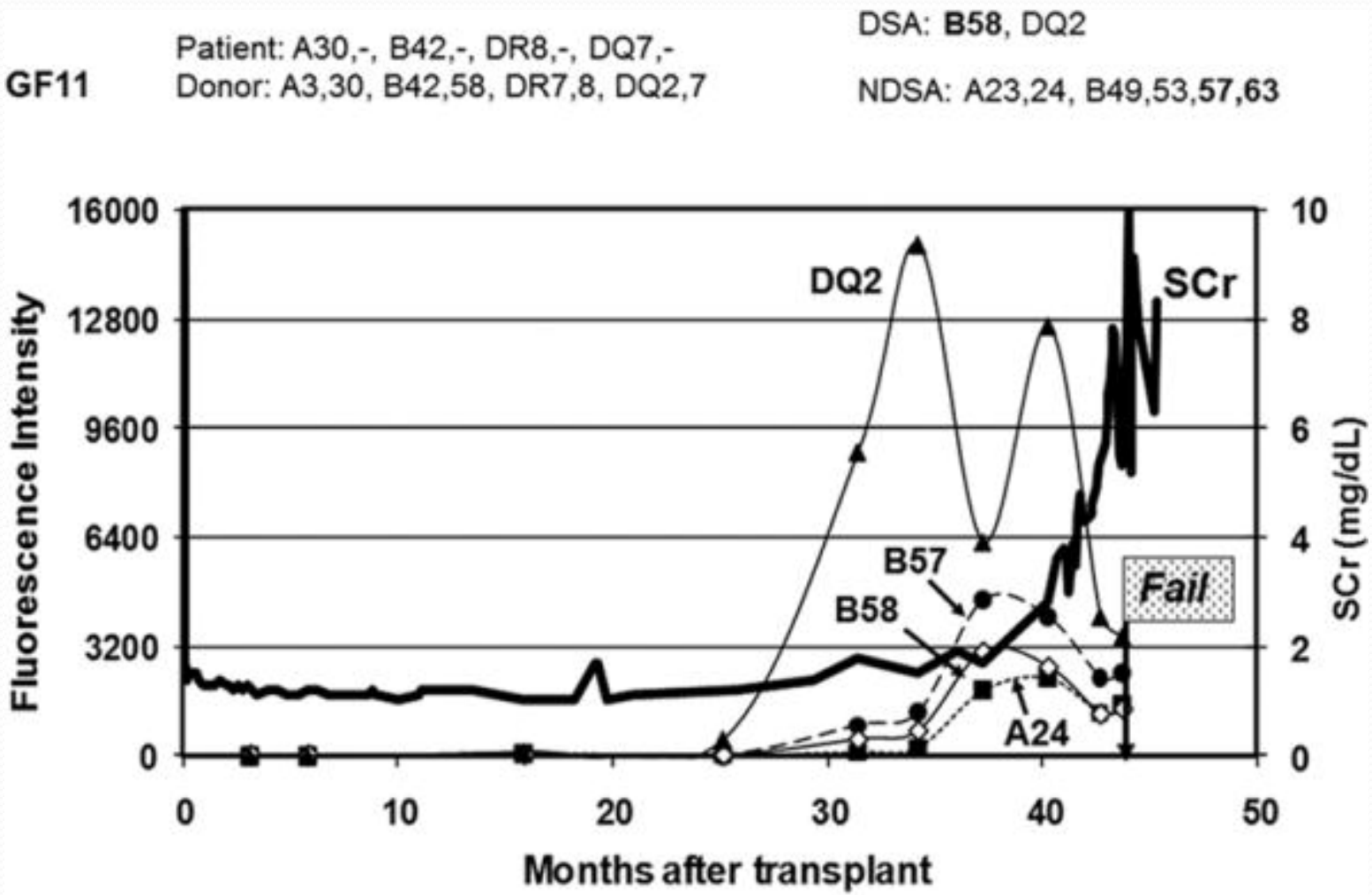




Stadia humorální rejekce



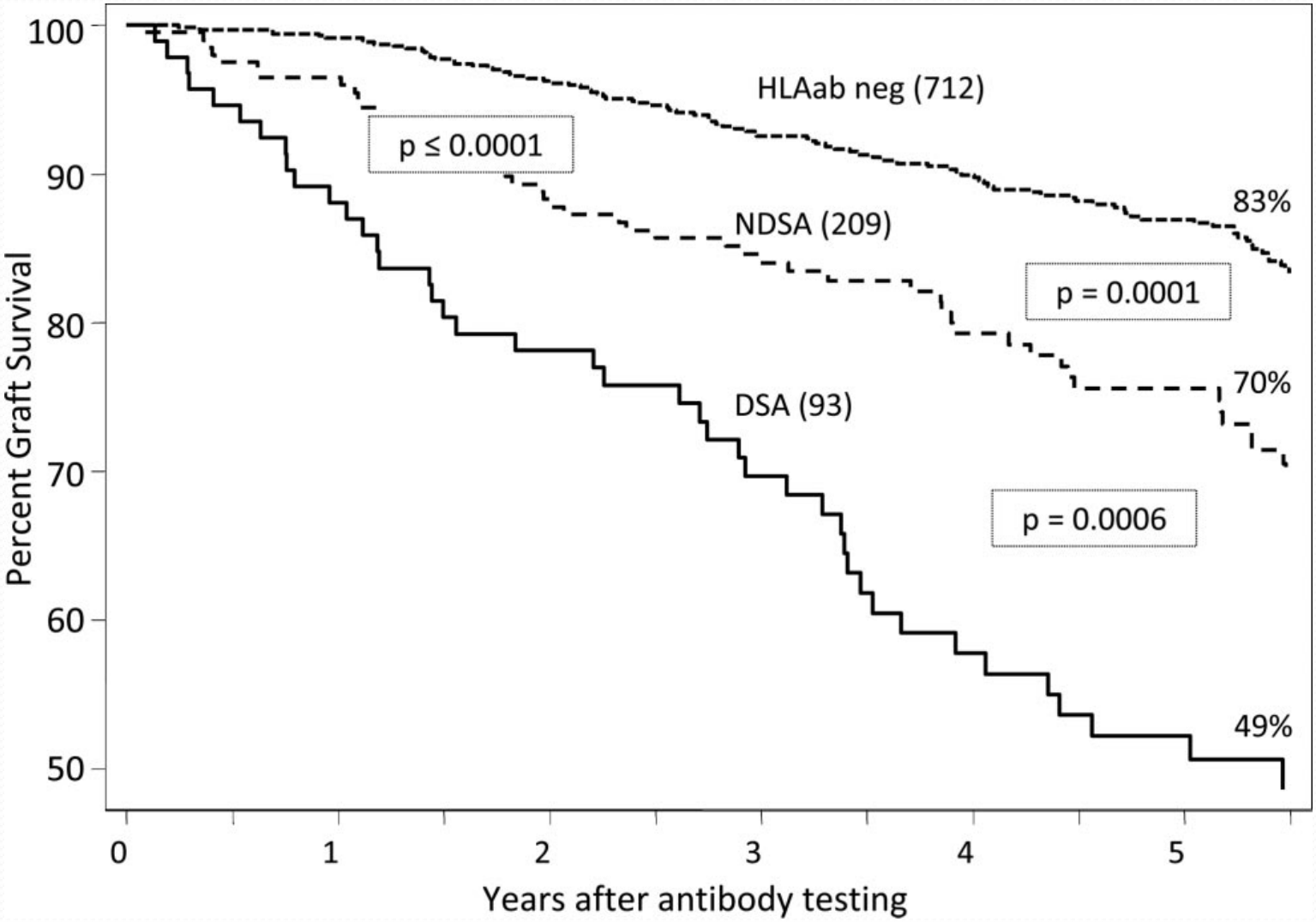
Ke vzestupu donor-specifických protilátek dochází relativně dlouho před vzestupem kreatininu



Ozawa M, et al. Clin Transplant. 2006; 265-290

Mají klinický význam i protilátky proti jiným HLA antigenům než dárcovským?

Přítomnost anti-HLA (i bez specifity proti Ag dárce) omezuje přežití štěpu



Lachmann N et al. Transplantation 87(10): 1505-13, 2009

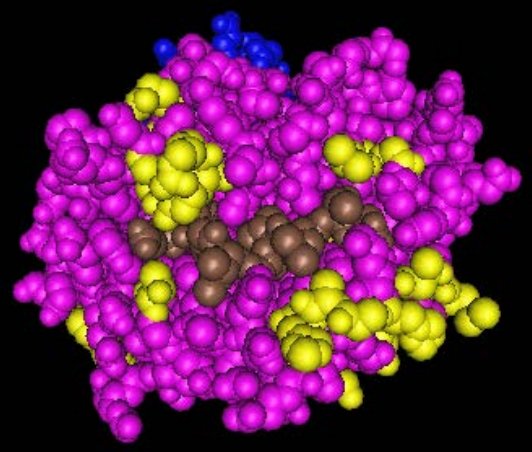
TABLE II. Histocompatibility Antigens of the HLA-A and HLA-B Loci and Their Most Common Cross-Reactive Specificities

HLA-A antigens	Cross-reactive specificities	HLA-B antigens	Cross-reactive specificities[a]
1	3 11	5	35 15 17 21 18
2	28	7	22 27 40
3	1 11	8	14
9	24 23 (2)[b]	12	21
10	25 26 11 32	13	40 7
11	3 26 1	14	8 18
23	24 9 (2)[b]	15	35 5 17 21 18
24	23 9 (2)[b]	16	38 39 22
25	10 26 32 33	17	15 5 35 21 18
26	10 25 11	18	5 35 15 14 17
28	2	21	15 5 35 17
29		22	7 27 40 16 38
30	31 32 33	27	7 22 40
31	30 32 33	35	5 15 17 18 21
32	30 25 33 31	37	
33	32 31 30 25	38	16 39 22
		39	16 38 22
		40	13 7

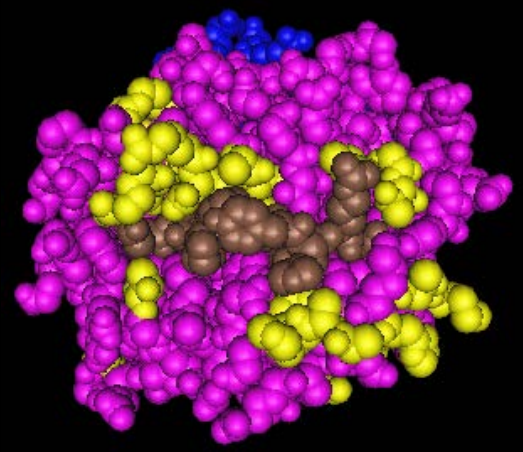
Duquesnoy et al. Am J Haematol 2:219-226, 1977

HLA antigeny sdílejí řadu epitopů, proti kterým jsou tvořeny protilátky

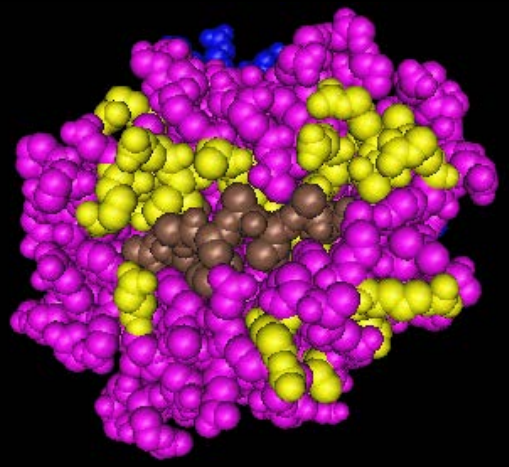
HLA-A2



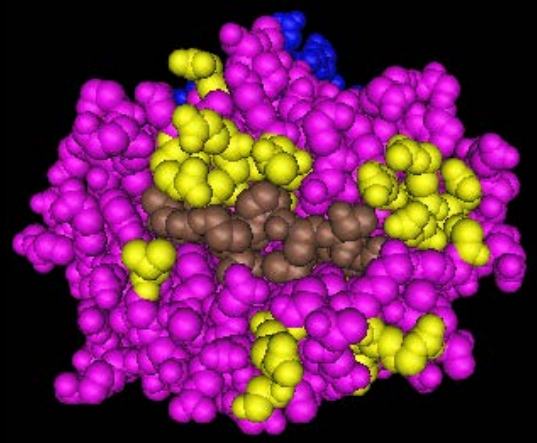
HLA-A68



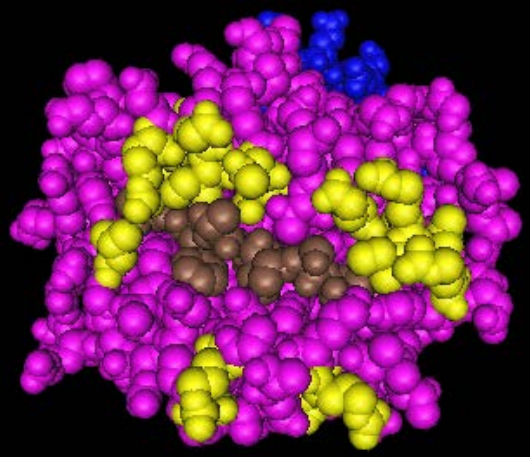
HLA-B27



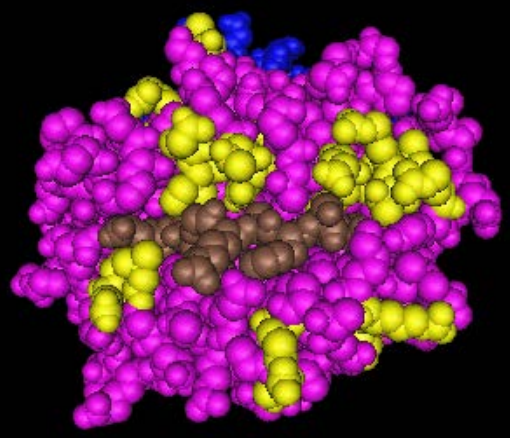
HLA-B35

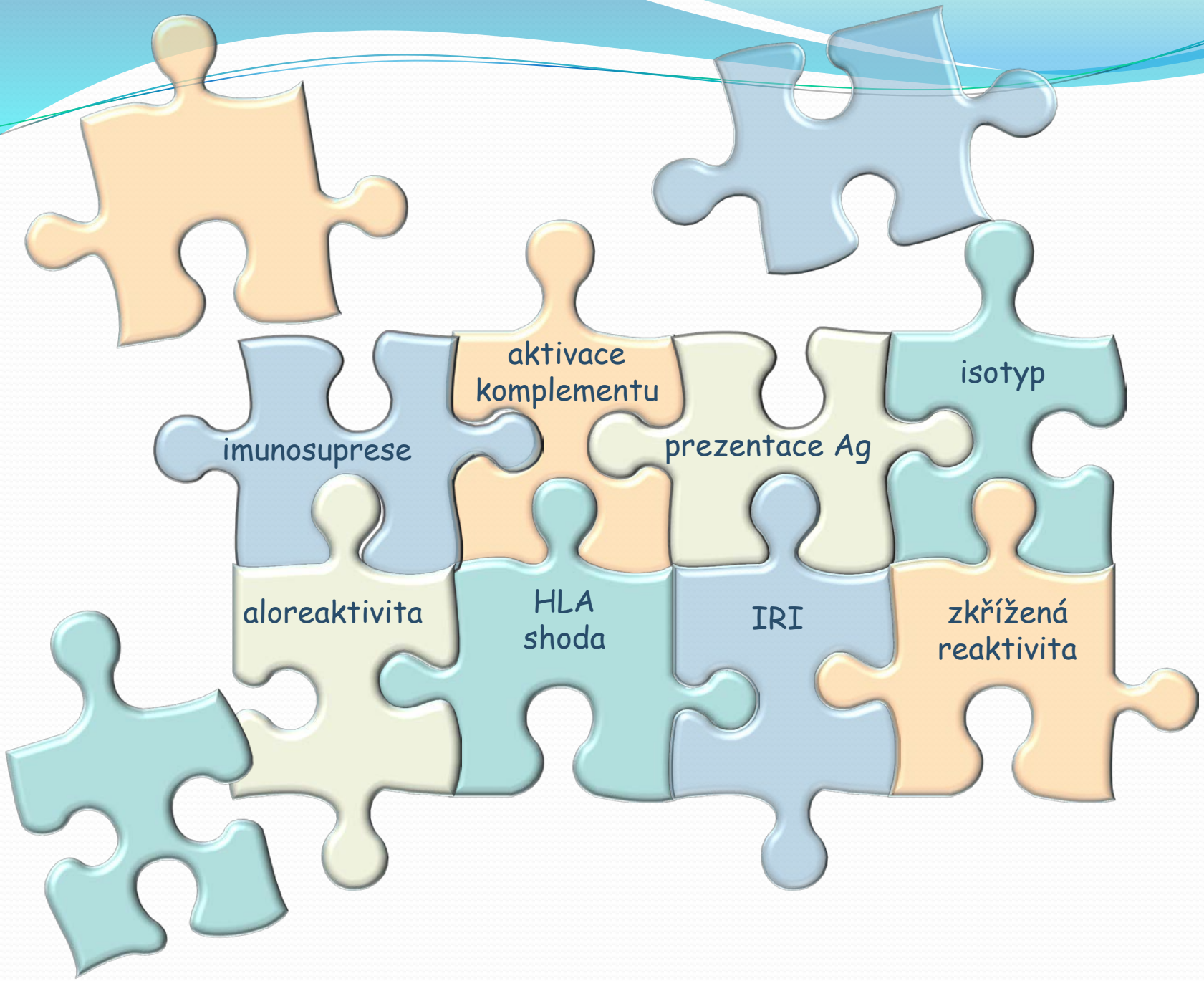


HLA-B51



HLA-B44




aktivace komplementu
isotyp
imunosuprese
prezentace Ag
aloreaktivita
HLA shoda
IRI
zkřížená reaktivita

Děkuji za pozornost !