THE INFLUENCE OF TISSUE (IN)COMPATIBILITY IN UMBILICAL CORD BLOOD TRANSPLANTATION

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ADVANTAGES OF UCB

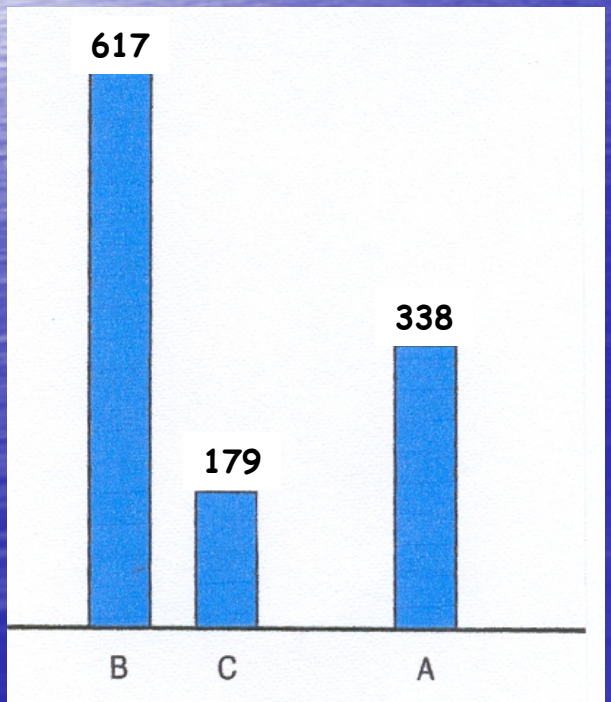
- practically limitless supply with adequate representation of various races and ethnicities;
- no donor attrition (ageing, loss of interest, relocation, ...);
- ease and safety of collection and long-term preservation, allowing rapid availability;
- reduced viral contamination of grafts;
- ex vivo expansion of HSC possible (high proliferative potential)
- immaturity of T cells, diminished capacity of APCs and unique cytokine profiles;
- reduced incidence of acute & chronic GvHD in spite of 1 or more HLA antigen mismatches between donors and recipients.

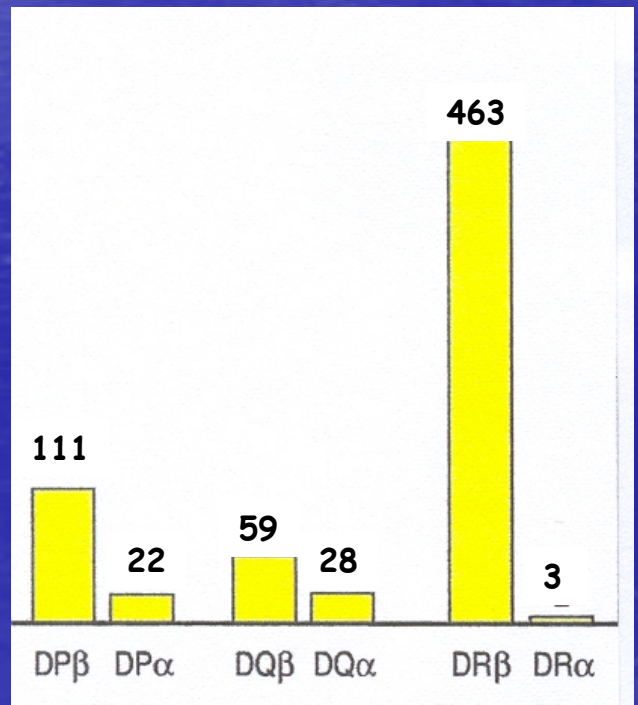
DISADVANTAGES OF UCB

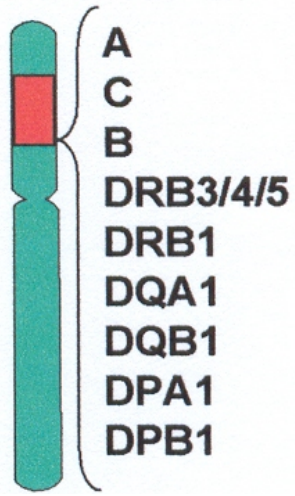
- insufficient nucleated cell dose resulting in delayed engraftment and increased rates of graft failure in larger paediatric and adult patients; possible solutions: *ex vivo* expansion of UCB HSC and the use of multiple units of UCB;
- uncertain GvL activity and long-term graft durability; possible solution: the use of *ex vivo* expanded UCB derived NK cells.
- risk of EBV-associated posttransplantation lymphoproliferative disorder (PTLD);
- inability to obtain donor leukocytes in case of relapse, PTLD or other possible complications.

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

- highly polymorphic HLA genes: A, B, C, DRB1/3/4/5, DQA1, DQB1, DPA1, DPB1
- linkage disequilibrium: when 2 or more genes on the same chromosome are found closely together more often than expected regarding to their individual frequencies in a given population.



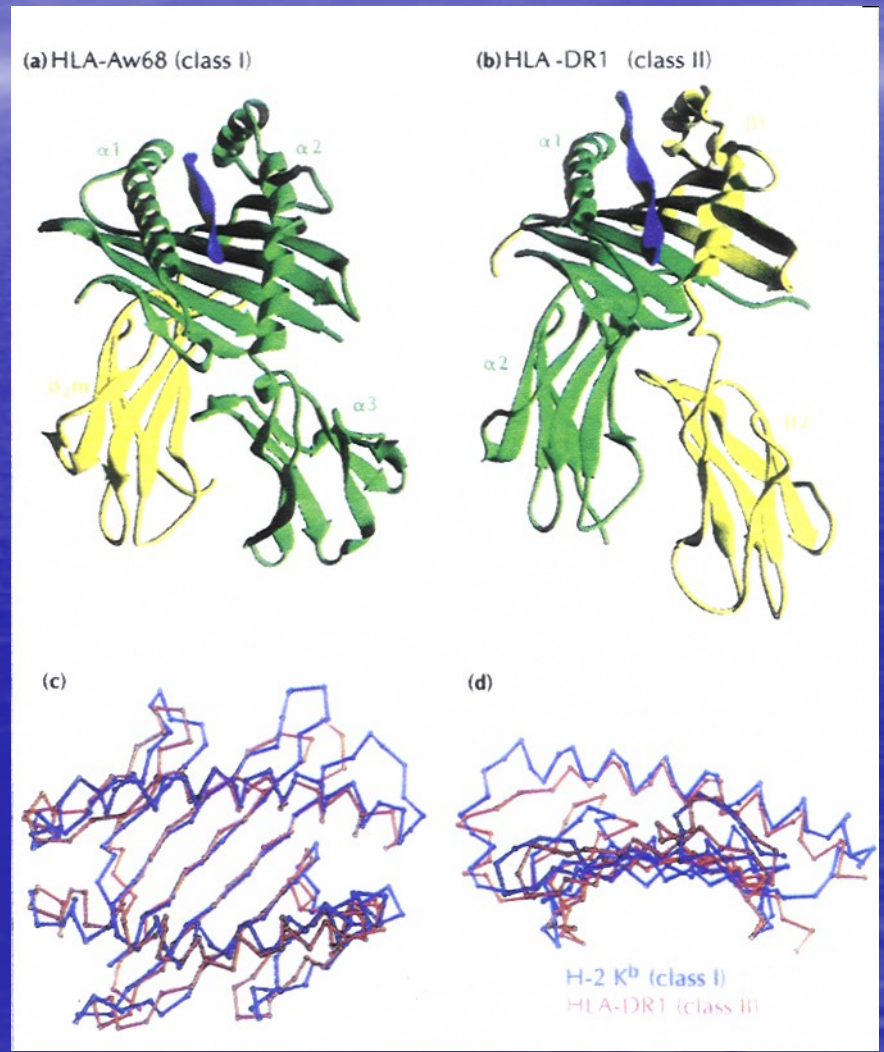




Frequency of recombinantion across MHC: 2 – 2.5 %

STRUCTURE OF HLA CLASS I AND CLASS II MOLECULES

- HLA class I antigens: A, B and C - presenting i.c. antigens (peptides).
- HLA class II antigens: DR, DQ and DP – presenting e.c. antigens (peptides).
- both are strong alloantigens.



WHO HLA NOMENCLATURE

Nomenclature	Indicates
HLA	the HLA region and prefix for an HLA gene
HLA-DRB1	a particular HLA locus
HLA-DRB1*13	a group of alleles which encode DR13 antigen
HLA-DRB1*1301	a specific HLA allele
HLA-DRB1*1301N	a null allele
HLA-DRB1*130102	an allele which differs by a synonimous mutation
HLA-DRB1*13010102	an allele which contains a mutation outside the coding region
HLA-DRB1*13010102N	a null allele which contains a mutation outside the coding region

DIFFERENT LEVELS OF HLA TYPING

Serology/antigen	DNA typing/allele
A2	A*0201 A*0205 …
B7	B*0702 B*0703 …
DR4	DRB1*0401 DRB1*0402 …

Designates allele groups defined by low resolution DNA typing

DEFINITION OF HLA "MATCH"

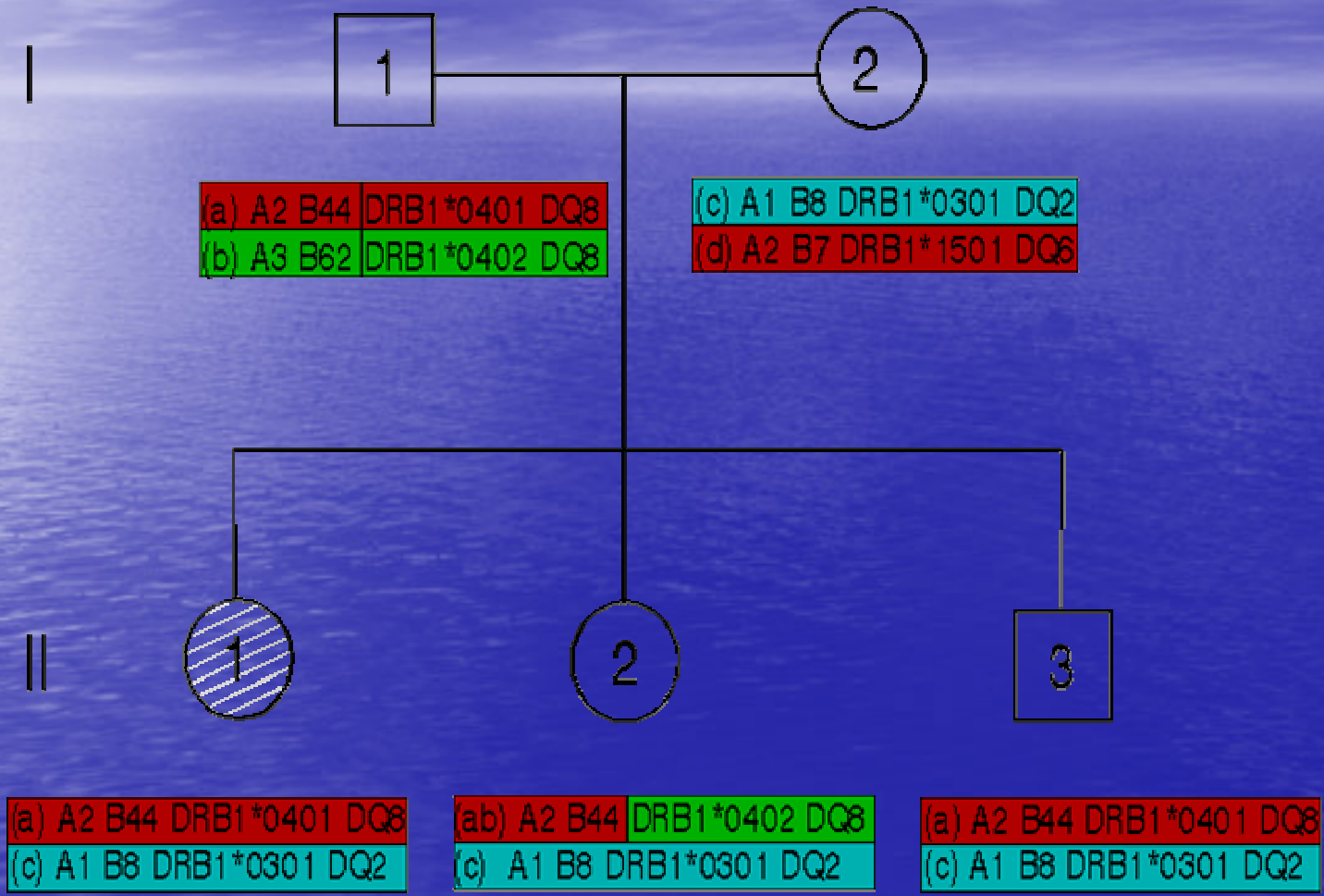
A*2301 Patient

Match level	Donor
Allele match	A*2301
Low resolution DNA typing	A*23
Serology defined split antigen	A23(9)
Serology defined broad antigen	A9
Serologic mismatch	A2

Potential allele match

Antigen & allele mismatch

INHERITANCE OF HLA HAPLOTYPES



THE OPTIMAL MATCH IN UBMT

- still not known exactly (8/8, 10/10, 12/12);
- studies evaluating survival regarding the influence of alleles within different HLA loci – lack of exclusive HLA-DQ and/or –DP impact on survival;
- may depend on age, disease, stem cell source, blood groups, etc. as well;

HLA Gene	Match
A	allele
B	allele
C	allele
DRB1	allele
DRB3/4/5	-
DQ(A1+B1)	(allele)
DP(A1+B1)	-

DETECTION OF HLA MATCHED UNRELATED HSC DONORS

HLA TYPING OF UNRELATED INDIVIDUALS

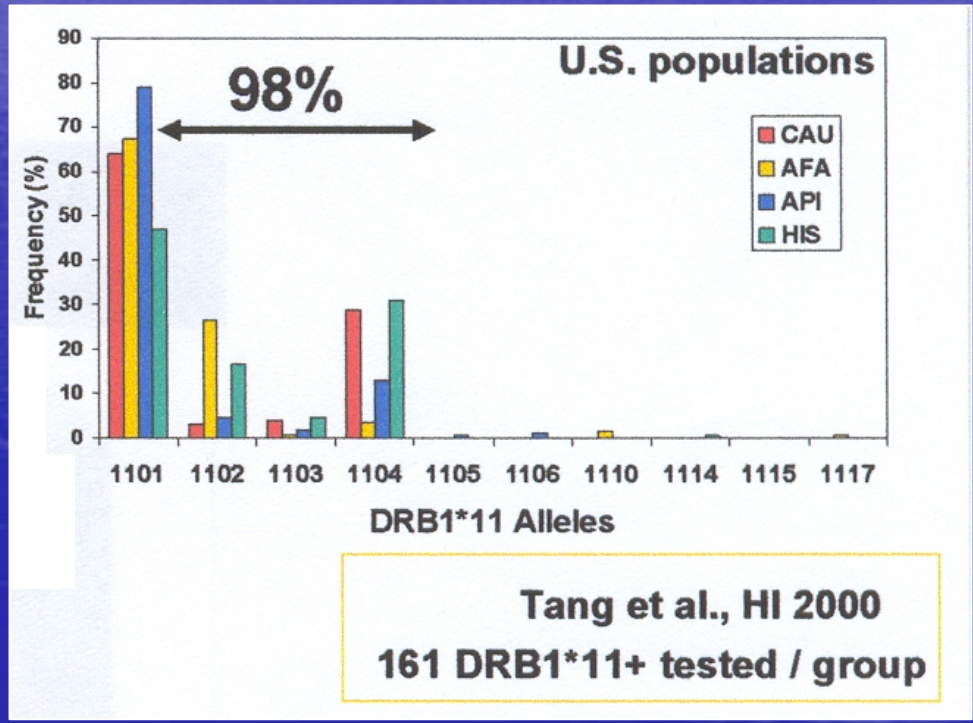
Haplotype				Haplotype		
A2	B7	DR15		A2	B44	DR11
0201	0701	1501		0201	4402	1101
0202	0702	1502		0202	4403	1102
0203	0703	1503		0203	4404	1103
0204	0704	1504		0204	4405	1104
0205	0705			0205	4406	1105
0206				0206		1106
0207				0207		1107
0208			340 possible combinations	0208		1108
0209				0209		1109
0210				0210		1110
0211				0211		1111
0212				0212		1112
0213				0213		1113
0214				0214		1114
0215				0215		1115
0216				0216		1116
0217				0217		1117
						1118
						1119

1615 possible combinations

[Nomenclature for factors of the HLA system, 1995. Tissue Antigens 46: 1-18, 1995]

HLA ALLELES AND HAPLOTYPES ARE ETHNICALLY SPECIFIC

- some alleles are frequent within a given population but others are extremely rare (gene and haplotype frequencies should be carefully considered)



MISMATCHED TRANSPLANTS

- should be considered for patients with rare alleles/haplotypes that have a slim chance for finding an unrelated HLA identical donor;
- acceptable in terms of the type and the stage of disease, age of the patient, transplant protocol, stem cell source, etc.
- are all HLA mismatches equal (different loci, antigens, alleles)?
- mismatches are risk factors (GvHD) but carefully selected ones can result in good transplantation outcome;
- but then, which mismatches are really acceptable?
- special situation in UCBT

THEORETICAL APROACH TO ALLELIC MISMATCH IMPACTS

Table 1. Variations in amino acid sequences of the α1 and α2 domains

Allele	1	3	9	62	65	70	76	79	80	81	82	83	95	97	99	105	107	114	116	127	144	151	152	156	158	161	163	166	167
A*2301	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	**Q**	**R**	V	**L**	A	E	T	D	G
A*2302	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	**Q**	**R**	V	**W**	A	E	T	D	G
A*2303	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	**N**	**Q**	**R**	V	**L**	A	E	T	D	G
A*2402	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2403	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	**E**	**W**
A*2404	G	H	S	E	G	H	**A**	**G**	**T**	**L**	**R**	**G**	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2405	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	**Q**	H	V	Q	A	E	T	D	G
A*2406	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	**W**	A	E	T	D	G
A*2407	G	H	S	E	G	**Q**	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2408	G	**Q**	S	**G**	**R**	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2410	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	**R**	**E**	**W**
A*2413	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	**L**	A	E	T	D	G
A*2414	G	H	S	E	G	H	E	R	I	A	L	R	**V**	**R**	**Y**	S	**W**	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2415	G	H	S	E	G	H	E	R	I	A	L	R	L	M	**Y**	**P**	G	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2416	G	H	**T**	E	G	H	E	R	I	A	L	R	**I**	M	**Y**	S	G	**Q**	**D**	**N**	**Q**	**R**	V	**L**	A	E	T	**E**	**W**
A*2417	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	**R**	**D**	K	K	H	V	Q	A	E	T	D	G
A*2418	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	**E**	**L**	A	**D**	T	**E**	**W**
A*2420	G	**Q**	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	D	G
A*2422	G	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	**W**	**V**	E	T	**E**	**W**
A*2423	**S**	H	S	E	G	H	E	R	I	A	L	R	L	M	F	S	G	H	Y	K	K	H	V	Q	A	E	T	D	**W**
Peptide binding	–	–	+	–	–	+	+	–	+	+	–	–	–	+	+	–	–	+	+	–	–	–	+	+	–	–	+	–	+
TCR binding	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	+	–	+	+	+

Numbers in the first line refer to the position within the HLA-A molecule. Amino acid residues are represented by the one-letter code. Bold text represents those residues that differ from the residue that is present at this position in the majority of HLA-A9 variants. + represents involvement of residues in TCR or peptide binding; – represents no involvement.

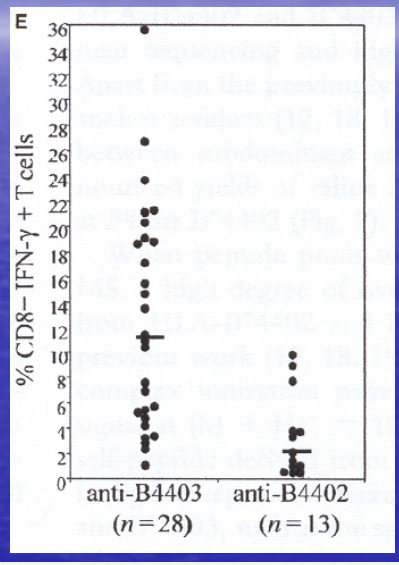
Dissimilarity index (position and (dis)similarity of aa disparities between compared alleles are considered) - *Eur J Immunogenetics 2002; 29: 229-36.*

* aa disparities at position 116 of HLA class I heavy chain increase risk for GvHD and TRM in UBMT (100 D/R pairs) – *Blood 2001; 98(10): 3150-55.*

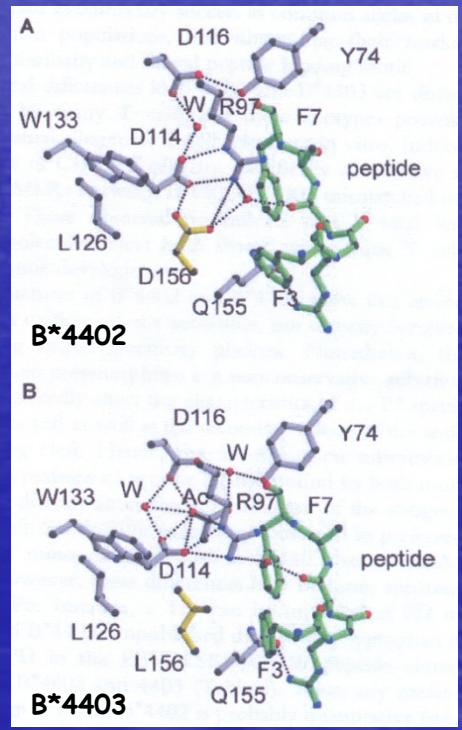
STUDIES OF ALLELIC MISMATCH IMPACT ON PEPTIDE BINDING AND ALLOREACTIVITY *IN VITRO*

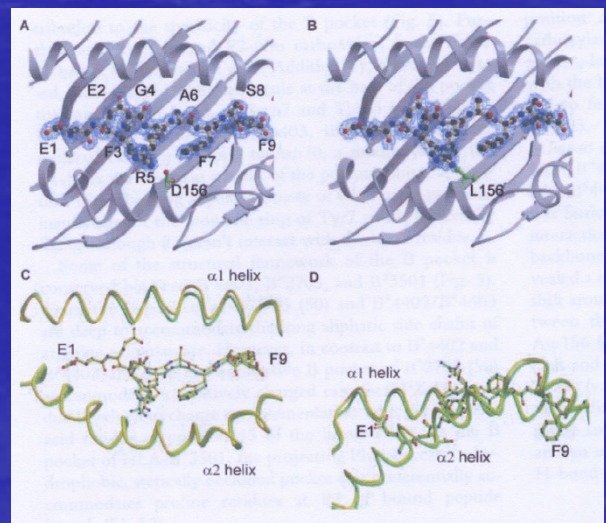
- the only difference between B*4402 and B*4403 (Asp156/Leu156)
- although they share > 95 % of their peptide repertoire B*4403 presents more unique peptides than B*4402 – stronger alloreactivity toward B*4403
- the minimal plymorphism between the two alleles modifies both peptide repertoire and T cell recognition resulting in paradoxically powerful alloreactivity

J Exp Med 2003; 198(5): 679-91



B*4402: *Cw*0501* or *Cw*0704
B*4403: *Cw*0401*, *Cw*1403* or *Cw*1601

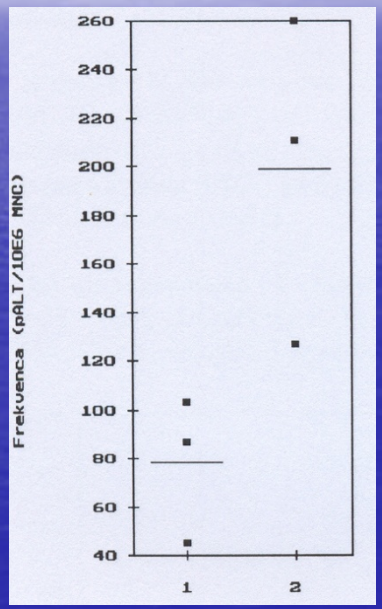




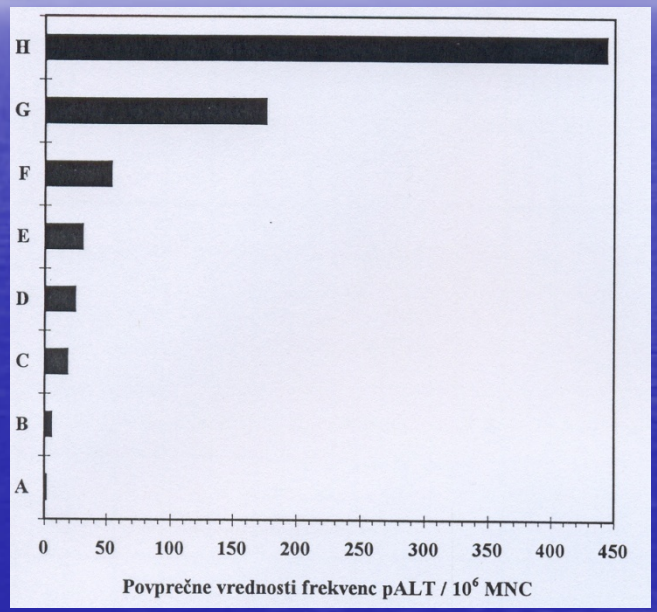
B44 allele matched pairs: 12 % mm at the C-locus !!!

IN VITRO STUDIES OF SINGLE AND COMBINED HLA MISMATCH DRIVEN ALLOREACTIVITY

- HTLp frequencies – *in vitro* assessment of HLA class II – driven alloreactivity
- DRB1*0401 and DRB1*0404 differ in two aa residues at positions 71 (Lys/Arg) and 86 (Gly/Val) respectively
- Combined intra- and inter-locus mismatches are generating higher alloreactivity



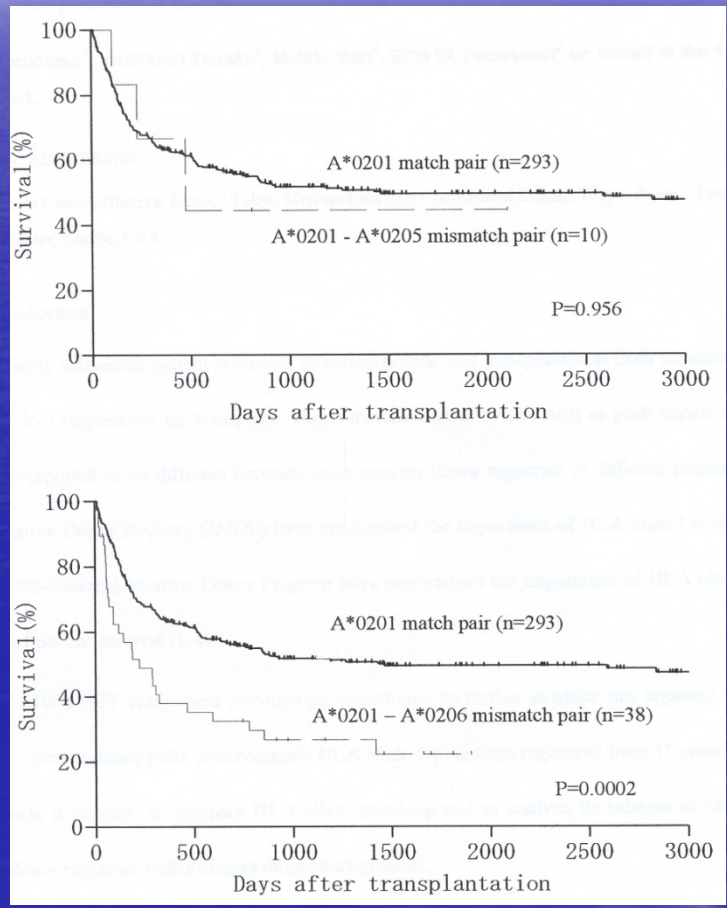
1 – S: DRB1*0401
R: DRB1*0404
2 – S: DRB1*0404
R: DRB1*0401



A: 0 (n=4)
B: 1B+2B (n=3)
C: 1DQ+1B,1DQ (n=5)
D: 1DP (n=29)
E: 1B,1DP+1DP,1DQ+1B,1DP,1DQ (n=5)
F: 2DP+2DP,1DQ (n=5)
G: 1B,1DR+1B,1DR,1DQ+
1B,1DR,1DQ,1DP (n=7)
H: All

SINGLE ALLELE MISMATCH CAN INFLUENCE PATIENT SURVIVAL IN UBMT

- A*0201 and A*0205 frequent, A*0206 rare in caucasoid population
- the influence of single allele mismatch on survival of CML patients



Morishima et al., 13th IHWC: Preliminary data

IMPACT OF HLA CLASS I AND II MATCHING ON OUTCOMES OF UBMT

- *Flomenberg et al. Blood 2004; 104(7): 1923-30* : retrospective study of effects of low and/or high resolution HLA matching on engraftment, GvHD and mortality in 1874 donor recipient pairs. Overall results: high-resolution (allele) mismatches (mm) at HLA-A,-B,-C and DRB1 adversely affect the outcome, but less so than low-resolution mm; mm at HLA-DQ or –DP did not significantly affect the outcome.
- *Petersdorf et al. Blood 2004; 104(9): 2976-80* : association of mortality with HLA-A,-B,-C,-DRB1 and DQB1 mismatching in 948 donor recipient pairs. Overall results: single allele or antigen mm, in particular HLA-C, is associated with increased mortality among transplanted CML patients; increased mortality was also observed with multiple mm involving HLA-DQB1 compared to multiple mm not involving DQB1.

UMBILICAL CORD BLOOD TRANSPLANTS

- UCBT for patients not finding suitable HLA compatible unrelated HSC donor.
- UCB units with 1, 2 or even more different antigenic and allelic HLA inter- or intra-locus mismathes can be chosen for transplantation;

Human leukocyte antigen typing (recipient/donor)*	Nucleated cells ($x10^7$/kg)	CD34-positive cells ($x 10^5$/kg)	GM-CSU† ($x 10^4$/kg)
A 2, 31 / A 2, 2 B 60 / B 60 DR 12, 12 / DRB1 0901, 12	2.46	2.8	4.38
A 2, 2 / A 2, 2 B 13, 6701 / B 13, 60 DRB1 12, 14 / DRB1 12, 16	2.6	0.72	4.58
A 1101, 33 / A 1101, 33 B 5801, 39 / B 5201, 5801 DRB1 03, 04 / DRB1 03, 1410	11.2	10.3	18.0
A 23, 33 / A 24, 33 B 5801, 39 / B 5801, 51 DRB1 15, 13 / DRB1 08, 13	16.4	27.4	3.37
A 02, 1101 / A 02, 1101 B 4001, 5603 / B 1502, 4001 DRB1 12, 0901 / DRB1 12, 15	7.37	2.2	5.47
A 24, 33 / A 24, 1101 B 35, 44 / B 35, 5801 DRB1 07, 14 / DRB1 03, 14	24.7	5.73	31.2
A 02, 33 / A 02, 1101 B 13, 4001 / B 13, 4001 DRB1 15, 12 / DRB1 15, 16	6.04	3.97	6.75
A 02, 33 / A 02, 33 B 5801, 4601 / B 5801, 4601 DRB1 0301, 0901 / DRB1 0301, 0901	4.58	4.02	2.1

Patient No.	Day neutrophil >0.5 x 10^9/L	Day platelet >20 x 10^9/L	Acute GVHD* (onset time)	Chronic GVHD
1	13	39	Grade I: skin (day 43)	Limited skin, off GVHD treatment
2	18	98	Grade II: skin (day 7)	Extensive skin, off GVHD treatment
3	12	24	Grade III: skin, liver (day 6)	Extensive skin, given mycophenonate
4	14	41	Grade II: skin (day 10)	Extensive skin, given prednisolone and cyclosporin
5	19	Not achieved before death	Grade II: skin, liver, gut (day 8)	Not applicable
6	11	47	Grade II: skin (day 22)	Extensive skin, given prednisolone and cyclosporin
7	12	38	Grade II: skin (day 8)	Too early to evaluate
8	13	31	Grade I: skin (day 9)	Too early to evaluate

Hong Kong Med J 2004 10(2): 89-95

Patient No. and Blood Unit	Class I (Serologic Typing)		Class II (Low-Resolution Typing)	Class II (High-Resolution Typing)	No. of Mismatched Antigens	
	A	B	DR	DRB1	Low Resolution	High Resolution
	antigens		gene groups	genes		
Patient 1	2,29	**44,60**	4,7	**0401**,0701		
Blood unit	2,29	**44,50**	4,7	**0407**,0701	1	2
Patient 2	**2,25**	50,57	4,7	**04xx†**,0701		
Blood unit	**2,26**	50,57	**blank**,7	0701,0701	1	2
Patient 3	2,28	44,51	8,11	**0801**,1101		
Blood unit	2,28	44,51	7,11	**0701**,1101	1	1
Patient 4	2,blank	**blank**,44	12,13	1201,**1301**		
Blood unit	2,blank	**41**,44	12,13	1201,**1302**	1	2
Patient 5	11,26	**35**,70	2,4	**1503,0401**		
Blood unit	11,26	**38**,70	2,4	**1501,0402**	1	3
Patient 6	2,blank	57,**62**	2,7	**1501**,0701		
Blood unit	2,blank	57,**44**	2,7	**1601**,0701	1	2
Patient 7	24,28	39,**60**	4,blank	**0403**,0407		
Blood unit	24,28	39,**61**	4,blank	**0411**,0407	1	2
Patient 8	**2,32**	**7,blank**	1,2	**0101**,1501		
Blood unit	**2,1**	**7,blank**	1,2	**0103**,1501	1	2
Patient 9	2,3	7,**18**	7,11	0701,1101		
Blood unit	2,3	7,**50**	7,11	0701,1101	1	1
Patient 10	1,30	13,37	7,11	0701,1103		
Blood unit	1,30	13,37	7,11	0701,1103	0	0
Patient 11	11,31	35,**40**	4,blank	**0404**,blank		
Blood unit	11,31	35,**58**	4,blank	**0402**,blank	1	2
Patient 12	2,3	7,**58**	**13,blank**	**1301,1303**		
Blood unit	2,3	7,**39**	**2,8**	**0801,1501**	3	3
Patient 13	28,30	42,**52**	3,8	0302,0804		
Blood unit	28,30	7,42	3,8	0302,0804	1	1
Patient 14	2,blank	27,50	2,7	**1501**,0701		
Blood unit	2,blank	27,50	7,**blank**	**0701**,blank	1	1
Patient 15	11,24	14,51	1,**11**	0102,**1104**		
Blood unit	11,24	14,51	1,**13**	0102,**1301**	1	1
Patient 16	1,2	8,**60**	3,4	0301,**0404**		
Blood unit	1,2	8,**44**	3,4	0301,**0401**	1	2
Patient 17	3,**32**	8,blank	1,2	0101,1501		
Blood unit	3,2	8,blank	1,2	0101,1501	1	1
Patient 18	2,blank	**35**,62	1,**14**	0101,**1402**		
Blood unit	2,blank	**27**,62	1,4	0101,**0401**	2	2
Patient 19	2,**blank**	15,**46**	2,12	1201,**1501**		
Blood unit	2,**11**	15,**13**	2,12	1201,**1502**	2	3
Patient 20	24,**33**	14,62	1,4	0102,0404		
Blood unit	24,**3**	14,62	1,4	0102,0404	1	1
Patient 21	3,**31**	7,14	1,4	0102,0404		
Blood unit	3,**33**	7,14	1,4	0102,0404	1	2
Patient 22	**2,29**	44,62	4,7	0401,0701		
Blood unit	**1,29**	44,62	4,7	0401,0701	1	1
Patient 23	2,30	**13**,52	2,11	**1103,1501**		
Blood unit	2,30	**35**,52	2,11	**1104,1502**	1	3
Patient 24	3,**30**	7,58	2,11	1503,1101		
Blood unit	3,**28**	**49**,58	2,11	1503,1101	2	2
Patient 25	1,3	7,**8**	3,7	0301,0701		
Blood unit	1,3	7,**14**	3,7	0301,0701	1	1

No. of Mismatched Antigens	No. of Transplants Mismatched by Low-Resolution Typing	No. of Transplants Mismatched by High-Resolution Typing
0	1	1
1	20	9
2	3	11
3	1	4

*Mismatches are indicated by boldface type.

†Novel DR4 genotype.

Patient No.	Date of Transplantation	Weight	Cell Dose	No. of Mismatches		TBI*	Engraftment	GVHD Grade†	EFS‡	Cause of Death or Event
				Low Resolution	High Resolution					
		kg	$\times 10^{-7}$/kg						days	
1	8/24/93	14.1	2.7	1	2	+	Yes	0	61	Interstitial pneumonia
2	9/13/93	10.1	3.7	1	2	–	Yes	II	>998	
3	3/9/94	38.5	0.7	1	1	+	No	NE	30	Graft failure
4	8/19/94	12.9	6.8	1	2	–	Yes	II	>658	
5	9/27/94	17.5	2.1	1	3	+§	Yes	II	>619	
6	10/27/94	19.4	4.8	1	2	–	Yes	II	180	Relapse
7	11/9/94	39.1	1.3	1	2	+	Yes	II	46	Pulmonary alveolar hemorrhage
8	11/15/94	16.2	2.1	1	2	+	Yes	NE	15	Aspergillus
9	12/14/94	16.1	2.4	1	1	+	Yes	NE	41	Relapse
10	1/5/95	34.0	1.5	0	0	+	Yes	0	>519	
11¶	1/17/95	30.5	2.0	1	2	+	Yes	0	55	Toxoplasmosis
12‖	2/1/95	40.4	1.6	3	3	+	No	NE	30	Graft failure, interstitial pneumonia
13	2/24/95	43.0	3.7	1	1	+‡	Yes	III	>469	
14	4/28/95	10.0	5.4	1	1	–	Yes	I	>406	
15	6/14/95	21.3	3.0	1	1	+	Yes	I	>359	
16	7/5/95	53.0	3.8	1	2	+	Yes	III	>338	
17	8/7/95	12.7	2.4	1	1	–	Yes	0	35	Interstitial pneumonia
18	8/9/95	24.9	4.3	2	2	+	Yes	I	>303	
19	8/22/95	12.2	7.4	2	3	–	Yes	II	56	CMV
20	8/23/95	7.5	9.8	1	1	–	Yes	I	>289	
21	9/6/95	32.4	3.7	1	2	+	Yes	II	77	Aspergillus
22	10/13/95	8.0	11.0	1	1	–	Yes	I	>238	
23	10/26/95	8.1	4.4	1	3	–	Yes	II	>225	
24	11/8/95	36.4	0.7	2	2	+	Yes	II	162	Pulmonary failure
25	11/8/95	79.0	1.1	1	1	+	Yes	I	103	Adenovirus

*A plus sign indicates that the patient underwent total-body irradiation (TBI), and a minus sign that the patient did not.

†NE denotes not evaluated.

‡Event-free survival (EFS) is given through June 7, 1996.

§The patient received thoracoabdominal irradiation in place of TBI.

¶The placental-blood graft was negative for toxoplasmosis.[21]

‖Patient 12 had persistent chronic myelogenous leukemia and graft failure and received a second placental-blood graft.

N Engl J Med 1996 355(3): 157-66

OUTCOME COMPARISON BETWEEN UCBT AND UBT

Patient- and disease-related characteristics with comparison of outcome after non-manipulated unrelated bone marrow (UBMT), T-cell-depleted unrelated bone marrow donor (TCD-BMT), and umbilical unrelated cord blood transplants (UCBT).[a]

UCBT ($n=99$)	TCD-BMT ($n=180$)	UBMT ($n=262$)	Patient's characteristics and outcome
6 (2.5–10)	8 (6–12)	8 (5–12)	Age, median (years) (range)
3.8	38	42	Cell dose infused ($\times 10^7$/kg)
2.4–36	14–56	30–60	range
			HLA disparity
8%	57%	80.5%	0
43%	34%	17.6%	I
48%	6.5%	0.4%	$\geqslant$ II
80%	90%	96%	Neutrophil recovery at day 60 (%)
32	16	18	Median days
22%	8%	30%	Acute GvHD (III–IV) at day 100
25%	12%	46%	Chronic GvHD at 3 years
39%	14%	19%	Early TRM at day 100
38%	47%	39%	Relapse at 3 years
35%	41%	49%	Survival at 2 years
31%	37%	43%	EFS at 2 years

TRM, transplant related mortality; EFS, event free survival.

[a] Rocha et al.[31].

Comparison between unrelated UCBT and unrelated BMT in adults with acute leukemia in complete remission.[a]

UD-BMT ($n=8$)	UD-CBT ($n=8$)	Patient's characteristics and outcome
23 (17–36)	38.5 (21–51)	Age, median (years) (range)
29.4	2.43	Cell dose ($\times 10^7$/kg)
22–39	2.0–3.0	range
		HLA disparity
100%	0	0
0%	12.5%	1
0	87.5%	$\geqslant$ 2
100%	100%	Neutrophil
15	20	Recovery at day 60
1	0	Median days
2/7	5/8	Acute GvHD (III–IV) at day 100 Chronic GvHD at 3 years
		Chronic GvHD at 3 years
2	1	Relapse
2	0	Death
75%	85.7%	DFS at 2 years

UD, unrelated donor; CBT, cord blood transplantation; BMT, bone marrow transplantation; DFS, disease free survival.

[a] Ooi et al.[32].

Matched pair analysis comparing the results of UD-UCBT versus UD-BMT in adults with acute leukemia.[a]

UD-BMT ($n=162$)	UD-CBT ($n=81$)	Patient's characteristics and outcome
24	24	Age, median (years)
		HLA disparity
100%	0	0
	49%	I
	51%	$\geqslant$ II
19	29	Neutrophil recovery median day 45
54%	35%	Acute GvHD (II–IV) at day 100
38%	47%	Relapse at 2 years
30%	35%	TRM at day 100
47%	54%	Mortality at 2 years
36/33	32/24	Survival/LFS at 2 years

UD, unrelated donor, UCBT, umbilical cord blood transplantation; BMT, bone marrow transplantation, LFS, leukemia free survival; TRM, transplant related mortality.

[a] Rocha et al.[33].

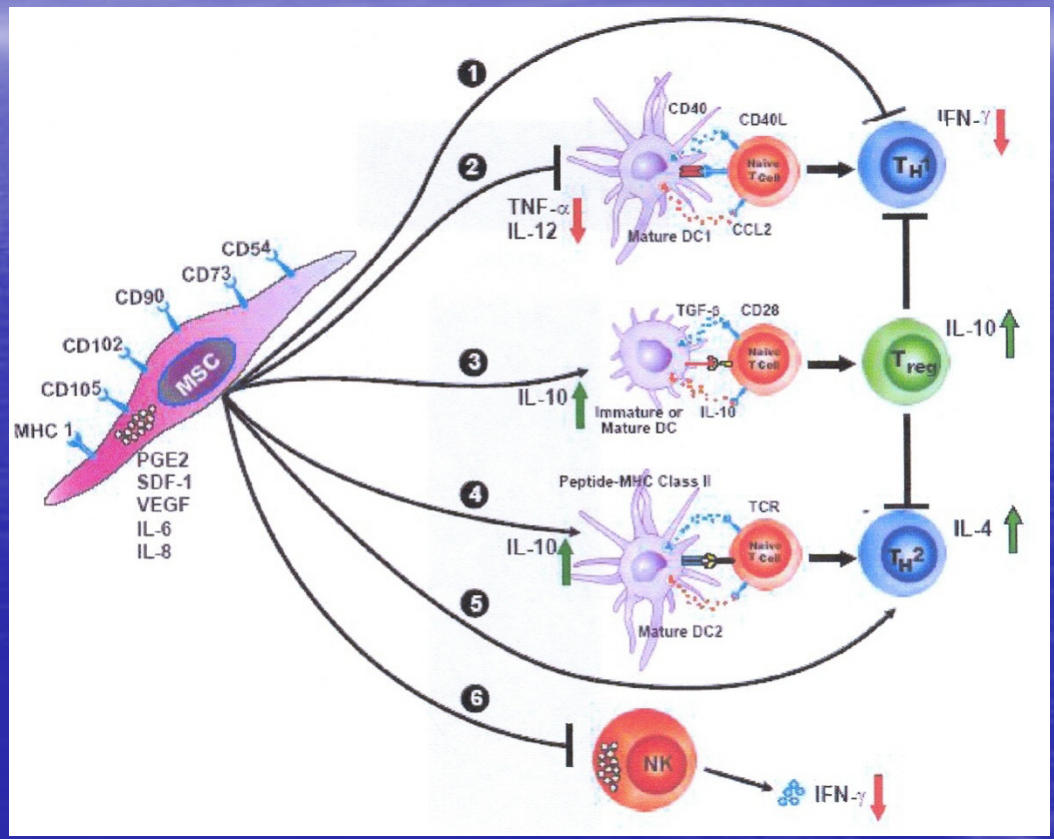
Blood Reviews 2004; 18: 167 -79

POSSIBLE MECHANISMS OF REDUCED ALLOREACTIVITY OF UCB

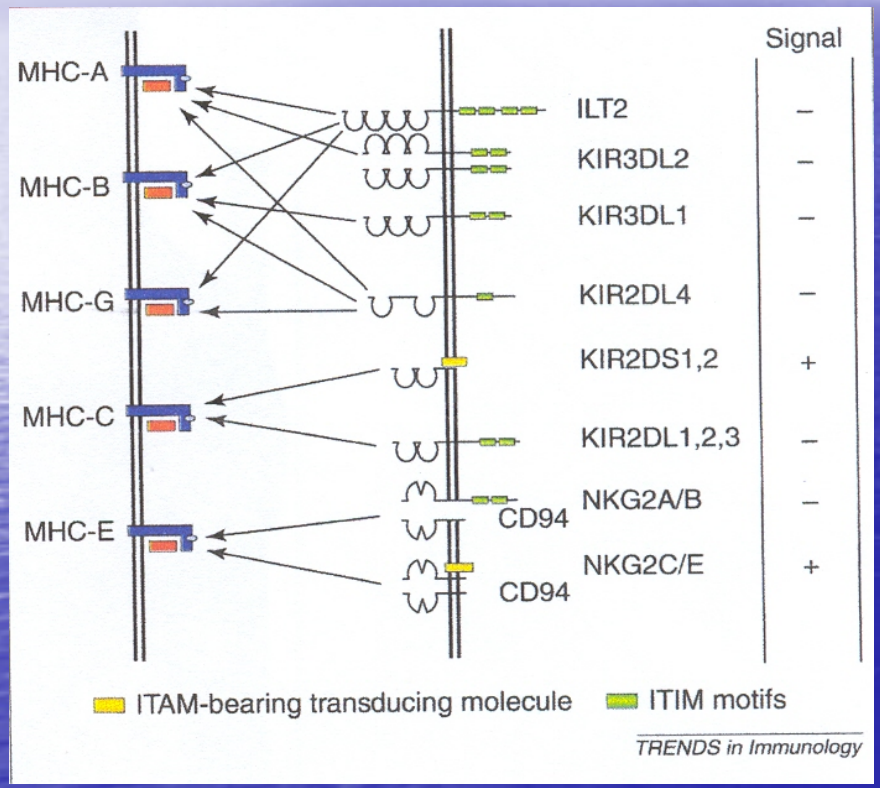
- general immaturity of the neonatal immune system
- high proportion of naive T cells (CD45RA)
- imaturity of APC, especially monocyte function
- different, less proinflamatory cytokine profiles
- immature, less alloreactive nucleated cells in the graft can generate mechanisms of tolerance to alloantigens.

UC AND UCB AS A SOURCE OF OTHER CELLS

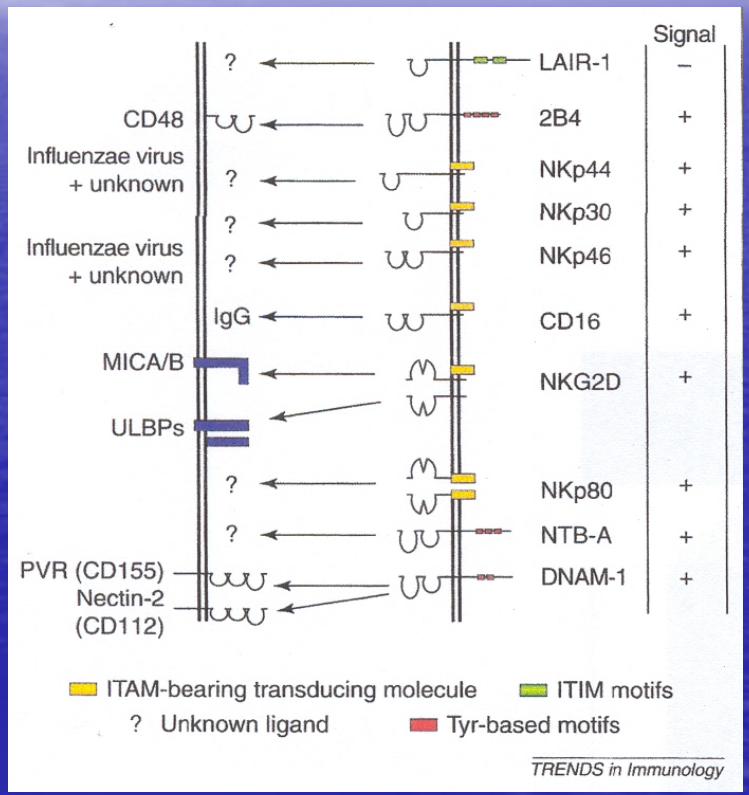
- NK cells can be selectively differentiated out of *in vitro* expanded $CD14^+$ UCB derived stem cells and used for adoptive imunotherapy (GvL without GvHD ?).
- Mesenchymal stem cells (MSC) can be isolated from UCB and/or UC and expanded *in vitro;* they can be used as suppressive modulators of alloimmune responses in UCBT.



NK CELL ACTIVATING AND INHIBITORY RECEPTORS (KIR) AND THEIR LIGANDS



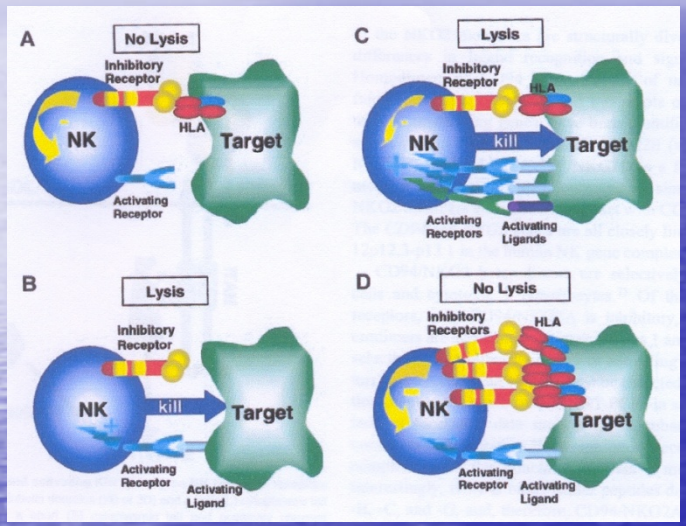
NK-cell MHC specific receptors

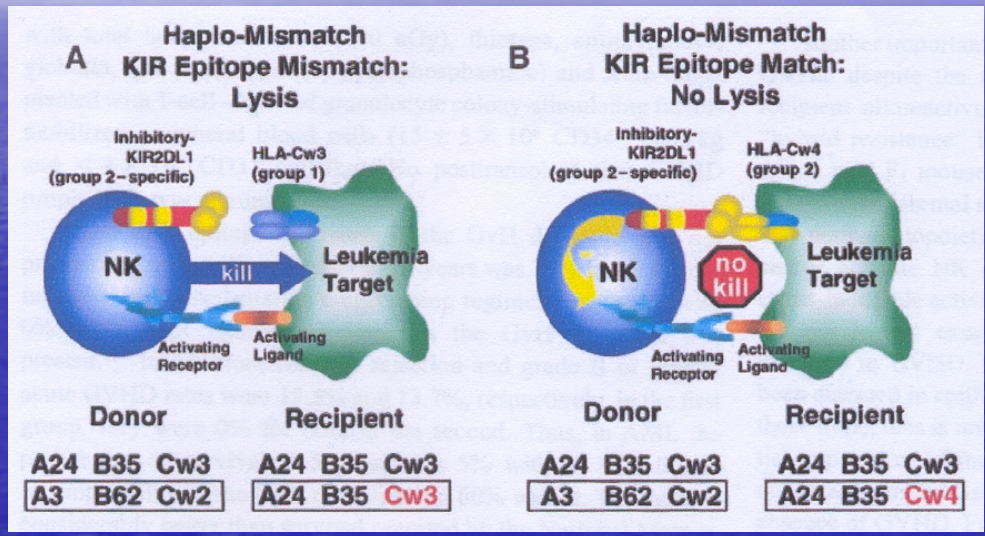


Non-MHC specific NK-cell receptors

Trends in Immunology 2004; 25(6): 328-33

NK CELL TARGET KILLING





Group 1 HLA-C antigens (Ser77Asn80): Cw1, Cw3, Cw7, Cw8 → KIR2DL2, KIR2DL3
Group 2 HLA-C antigens (Asn77Lys80): Cw2, Cw4, Cw5, Cw6 → KIR2DL1
HLA-Bw4 → KIR3DL1
HLA-A3, HLA-A11 → KIR3DL2

Blood 2002; 100(6): 1935-47

CONCLUSION

- regardless the fact that multiple HLA antigenic/allelic mismatches are acceptable in UCBT, whenever possible, the most high-resolution matched UCB units should be chosen for transplantation;
- recently, UCBT has become important also for adult patients - *in vitro* expansion of HSC or the use of two different UCB units to increase the number of transplanted cells and therefore to improve the engraftment;
- potential use of UCB-derived NK (GvL) and mesenchymal stem cells (immunomodulation of alloreactivity).