SUMMER SCHOOL AIBT
Pesaro, 9 – 11 Giugno 2016

I mismatches HLA nel trapianto di cellule staminali ematopoietiche

Manuela Testi

Introduzione

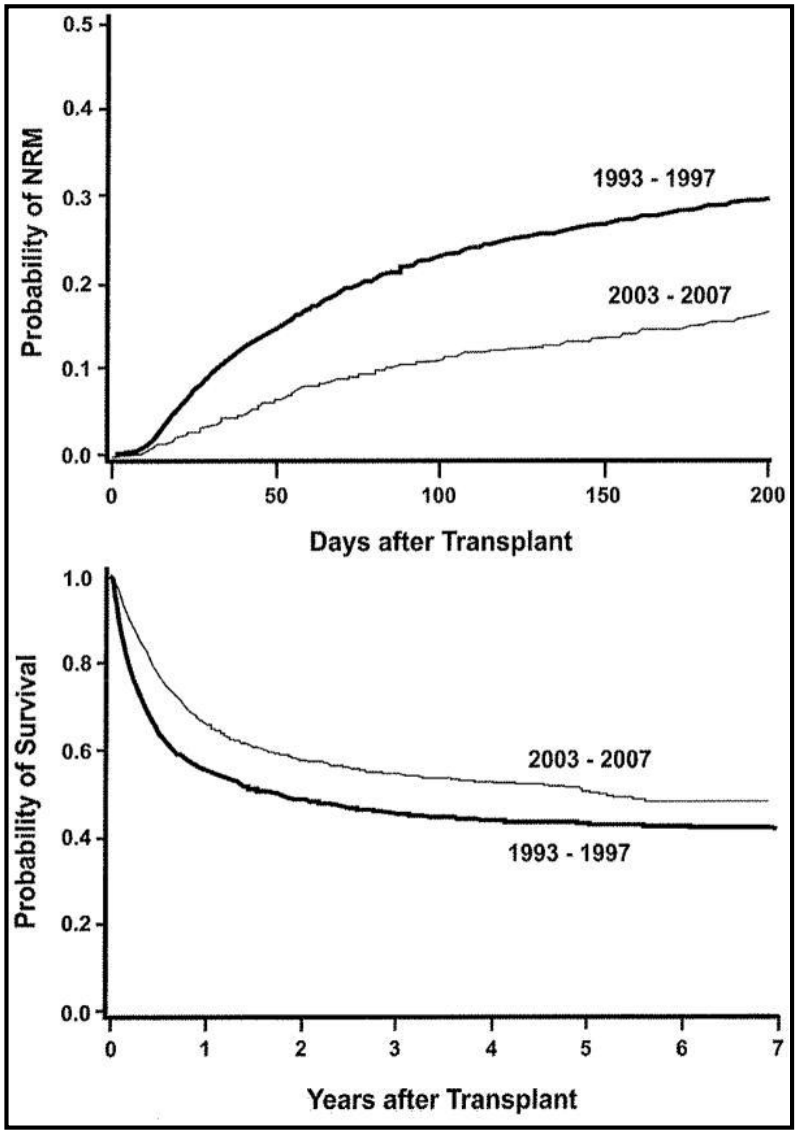
One million haemopoietic stem-cell transplants: a retrospective observational study

Gratwohl A. et al. – Lancet Haematol. volume 2 n°3, e91–e100, March 2015

Il trapianto di cellule staminali ematopoietiche è diventato la "*gold standard care*" per un gran numero di malattie oncoematologiche

Allogeneic HSCT - Outcome

Gooley T. et al. N Engl J Haematol 363:2091, 2010



1418 pazienti trapiantati nel periodo 1993-2007 e valutati per data

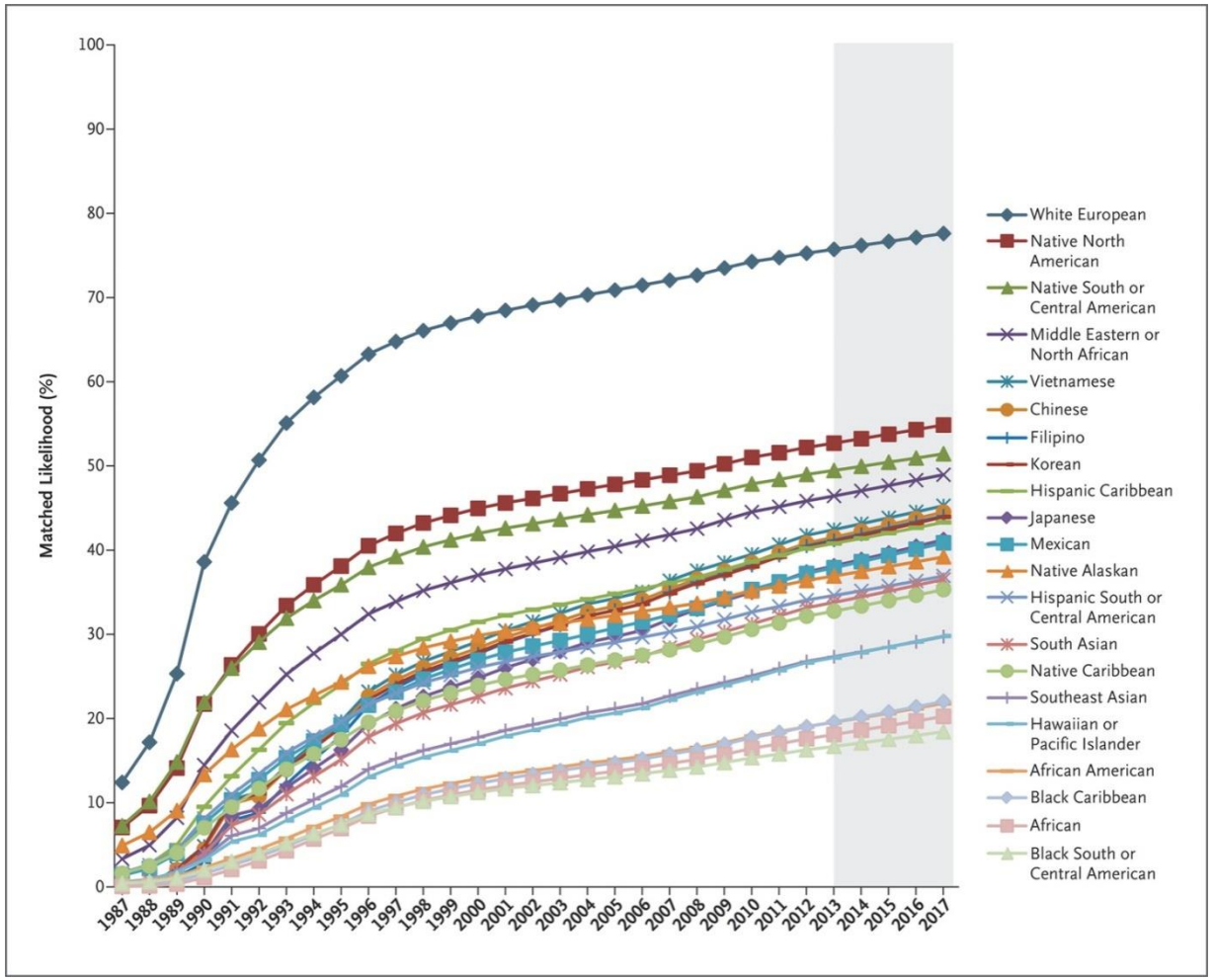
Trapianti più recenti mostrano:
< NRM (-52%)
<Relapse (-21%)
<Mortality (-41%)

La mortalità più bassa è dovuta a:
< aGvHD severa
<Infezioni
<Tossicità d'organo

La selezione del donatore nel HSCT si basa quasi esclusivamente sull'identificazione di un donatore HLA identico o pressocchè identico

Non tutti i pazienti sono in grado di trovare un donatore adatto

Probabilità di trovare un donatore non related 8/8 a seconda dell'origine etnica



Pazienti afroamericani

16% → MUD 8/8

79% → MUD 7/8

Gragert et al N Engl J Med 317:339, 2014

Influence of the HLA characteristics of Italian patients on donor search outcome in unrelated hematopoietic stem cell transplantation

M. Testi, M. Andreani, F. Locatelli et al

Tissue Antigens 2014 Aug;84(2):198-205

HLA matching	Patients	Transplanted patients
10/10	79 (43%) } 75%	55 (70%)
9/10	59 (32%)	25 (42%)
8/10	33 (18%)	10 (30%)
≤7/10	13 (7%)	1 (8%)
	184	**91**

Effetti della disparità HLA

La disparità HLA è associata a

1. Graft failure
2. Ricostituzione immunologica ritardata
3. Graft-versus-host disease (GVHD)
4. Mortalità

I pazienti che non hanno un donatore "matched" possono ……

beneficiare di un trapianto "salva-vita" se noi saremo in grado di capire:

- Quale locus/loci conferisce il rischio più alto
- Quali combinazioni HLA sono più tollerate
- Quali altri fattori HLA dovrebbero essere considerati

Influenza della compatibilità HLA sull'andamento clinico dopo HSCT

- Numero dei mismatches HLA
- Livello di disparità HLA
- Importanza della fase di malattia
- Mismatches HLA permissivi

Influenza della compatibilità HLA sull'andamento clinico dopo HSCT

Numero dei mismatches HLA

Livello di disparità HLA

Importanza della fase di malattia

Mismatches HLA permissivi

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BLOOD, 15 DECEMBER 2007 • VOLUME 110, NUMBER 13

3857 transplantations

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

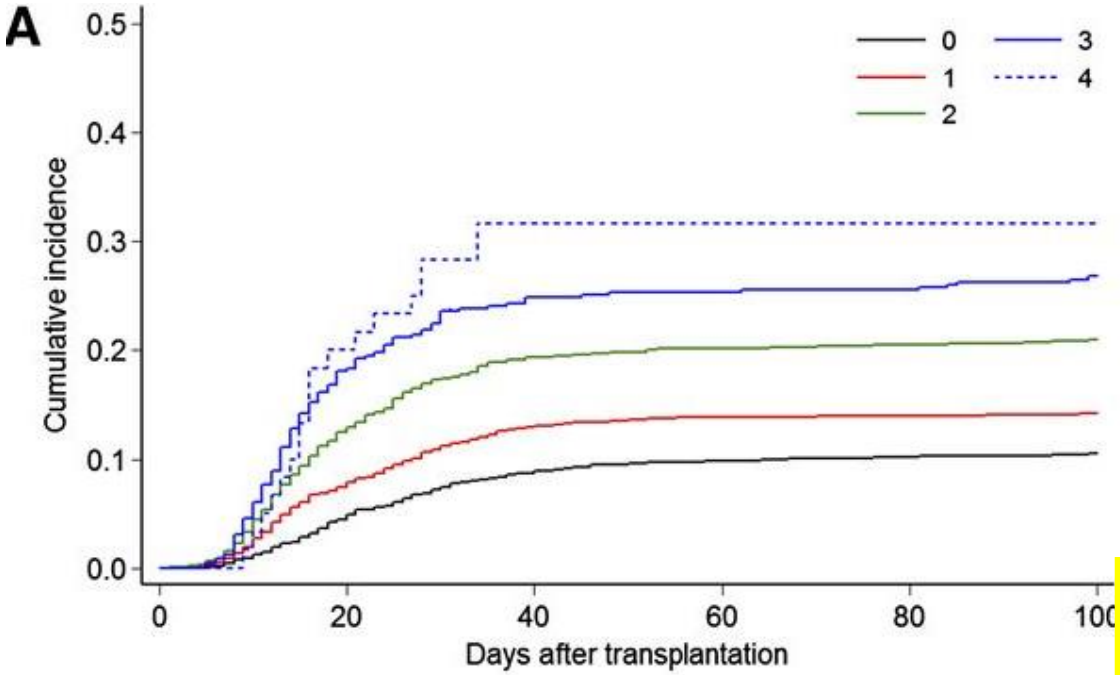
Stephanie J. Lee[1], John Klein[2], Michael Haagenson[3], Lee Ann Baxter-Lowe[4], Dennis L. Confer[5], Mary Eapen[2], Marcelo Fernandez-Vina[6], Neal Flomenberg[7], Mary Horowitz[2], Carolyn K. Hurley[8], Harriet Noreen[9], Machteld Oudshoorn[10], Effie Petersdorf[1], Michelle Setterholm[5], Stephen Spellman[5], Daniel Weisdorf[11], Thomas M. Williams[12], and Claudio Anasetti[13]

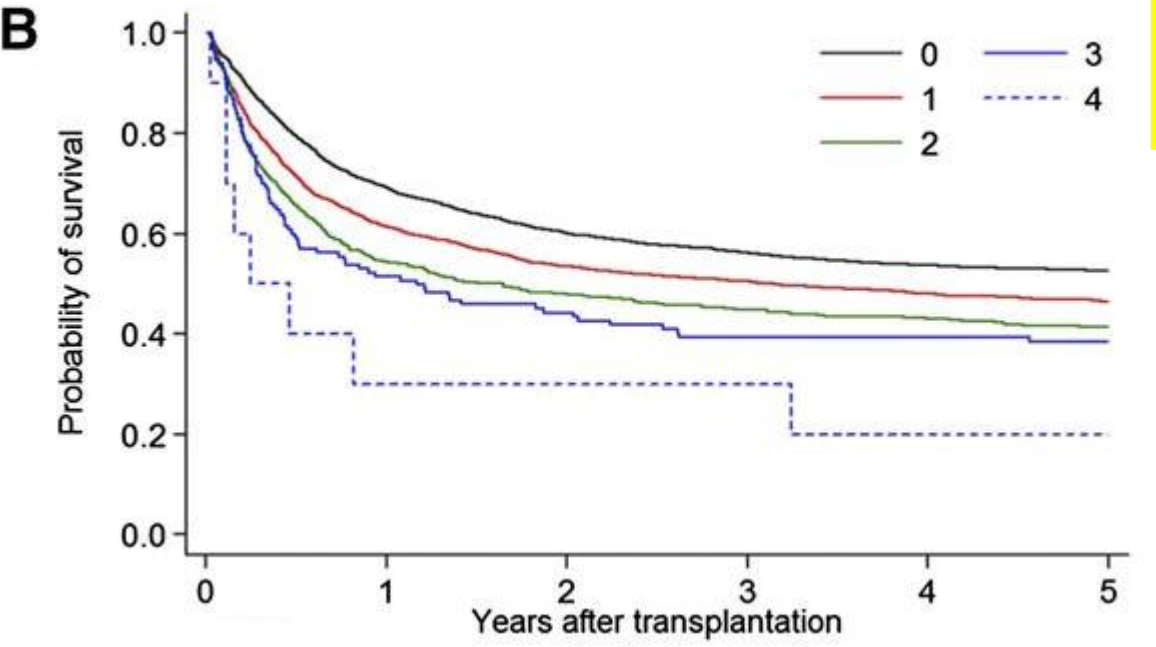
As compared to patients transplanted from a donor matched at the allelic level for HLA-A, -B, -C, and -DRB1,

patients given an allograft from a donor with a single antigenic or allelic disparity

had an increased risk of both acute GVHD and TRM

· Disparities at two or more loci compounded this risk





7898 pairs

Acute GVHD and survival curve by the number of multiple HLA locus mismatches.

Morishima et al. Blood 125,7, 2015

Effetto del locus HLA sulla sopravvivenza

There have been several large-scale analyses on the role of each HLA locus in non-Tcell-depleted UD HSCT (Table 1).

Table 1: Effect of HLA mismatching on survival.

Study	Mismatched HLA locus			
	A	B	C	DRB1
Petersdorf et al. [13]	Merged A, B, and C Decreased			Decreased
Morishima et al. [10]	Decreased	Decreased	None	None
Flomenberg et al. [14]	Decreased	Decreased	Decreased	Decreased
Lee et al. [2]	Decreased	None	Decreased	Decreased
Park et al. [11]	None	Decreased	Decreased	None

Influenza della compatibilità HLA sull'andamento clinico dopo HSCT

Numero dei mismatches HLA

Livello di disparità HLA

Importanza della fase di malattia

Mismatches HLA permissivi

Il livello di disparità HLA influisce sull'outcome del trapianto in maniera differente

→ Definizione

Disparità antigenica

PIU' DI 10 SOSTITUZIONI aa NELLA MOLECOLA HLA

ALLOTIPI CHE PROVOCANO UNA RISPOSTA ANTICORPALE

Disparità allelica

SOLO 1 O POCHE SOSTITUZIONI aa NELLA MOLECOLA HLA

Dati contraddittori sul valore di selezionare un mismatch allelico rispetto ad uno antigenico

- **Lee S al Blood. 2004;110**

  no significant differences in survival depending on whether the mismatch was allelic or antigenic,
  except at HLA-C, in which an antigenic mismatch increased transplant risks while an allelic mismatch did not.

- **EW Petersdorf et al Blood. 2004;104:**

  a single-center study from Seattle **could not find any apparent difference between allele and antigen mismatches** with respect to the number of deaths from transplants, suggesting that donors with a single HLA allele of antigen mismatch may be used for HSCT when a fully MUD is not available for patients with severe diseases not permitting time for a lengthy search

- **N Flomemberg et al Blood. 2004;104:**

  the NMDP study found that *antigenic mismatch was associated with higher mortality compared to allelic mismatch*

Influenza della compatibilità HLA sull'andamento clinico dopo HSCT

Numero dei mismatches HLA

Livello di disparità HLA

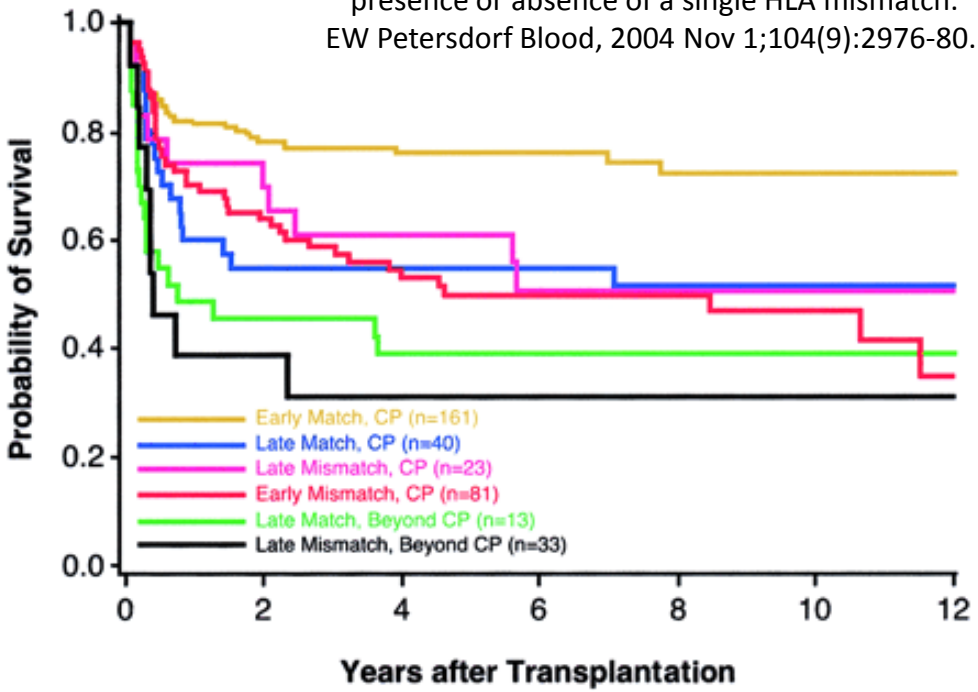
Importanza della fase di malattia

Mismatches HLA permissivi

Importanza della fase di malattia

Alcuni studi hanno dimostrato che un intervallo di tempo più lungo tra la diagnosi ed il trapianto è associato con un aumentato rischio di mortalità.

CML patients according to disease phase and presence or absence of a single HLA mismatch.
EW Petersdorf Blood, 2004 Nov 1;104(9):2976-80.



Un singolo mismatch allelico conferisce un rischio di mortalità più elevato

SI : per i pazienti a basso rischio

NO: per i pazienti a rischio più alto

Influenza della compatibilità HLA sull'andamento clinico dopo HSCT

Numero dei mismatches HLA

Livello di disparità HLA

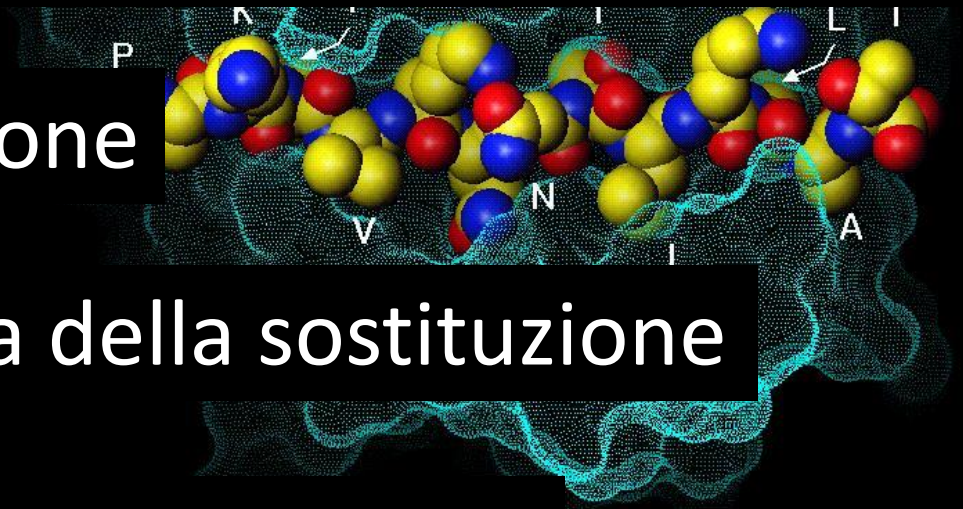
Importanza della fase di malattia

Mismatches HLA permissivi

Non tutti i mismatches HLA conferiscono lo stesso rischio

Per ogni mismatch, tutti i seguenti aspetti influenzano l'alloreattività:

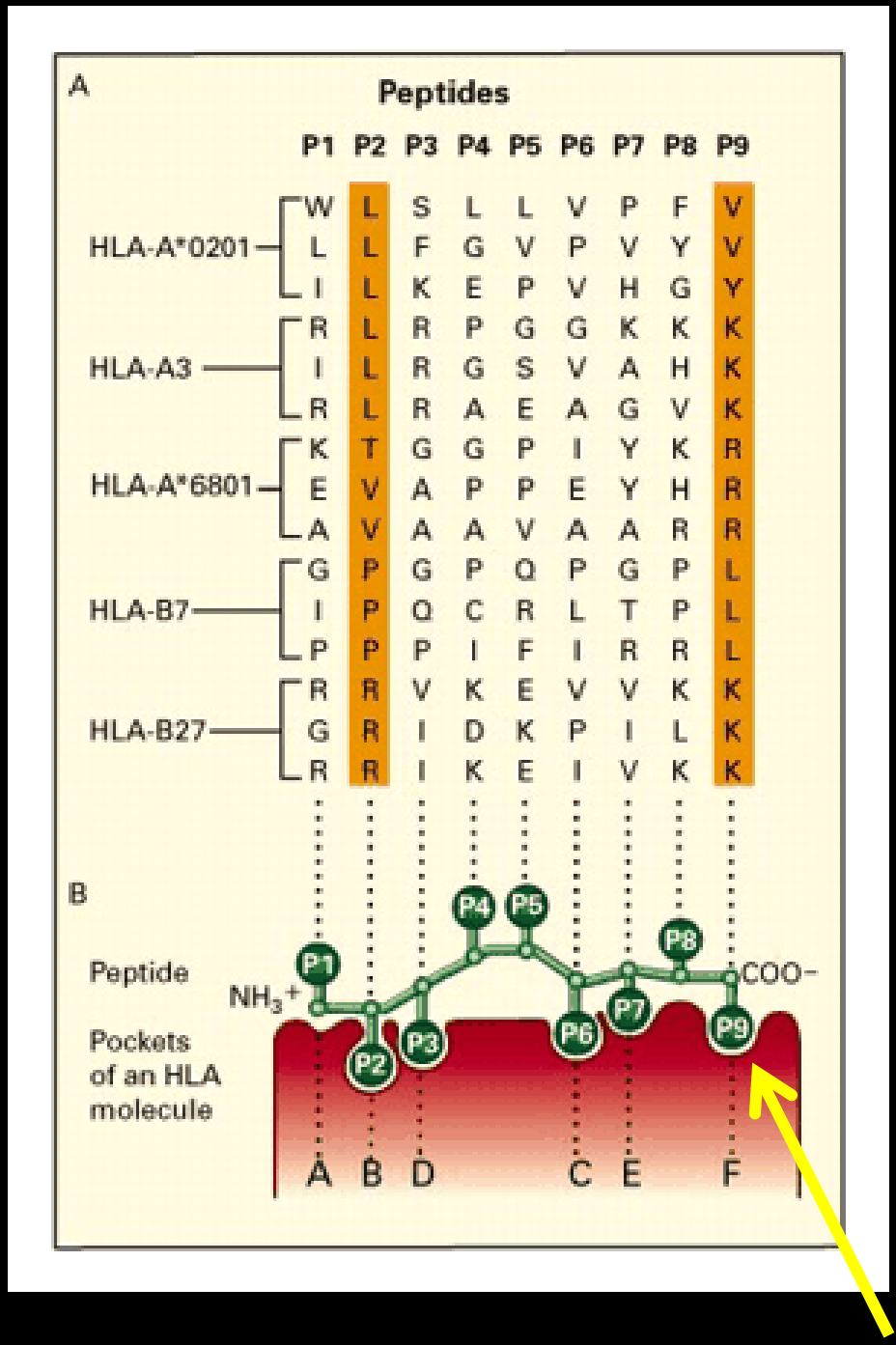
- Il numero delle sostituzioni aminoacidiche
- La posizione
- La natura della sostituzione
- Il livello di espressione



I peptidi interagiscono con le molecole HLA di classe I attraverso specifiche tasche nel sito di legame del peptide

Di particolare rilevanza sono le tasche B e F che alloggiano le estremità N- e C- del peptide

L'amino acido 116 forma il pavimento della tasca F , selezionando la misura del residuo C-terminale del peptide, Interagendo specificamente con il residuo P9 del peptide legato



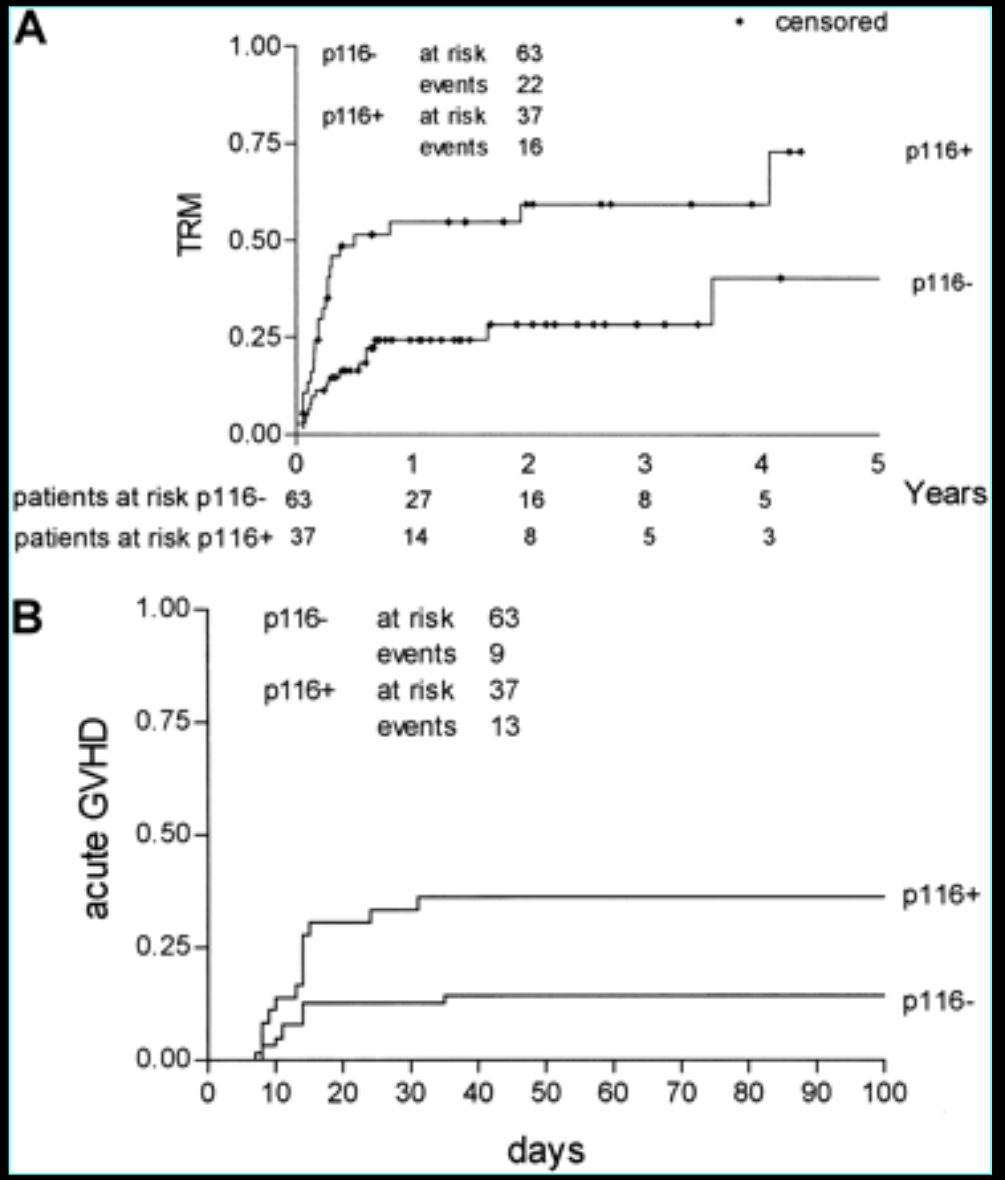
Un mismatch molecolare che coinvolga

la posizione 116

della molecola HLA di classe I può influenzare l'outcome di un trapianto da non correlato

Rischio di aGvHD

Rischio di TRM



Ferrara GB, et al - Blood,98: 3150-3155, 2001

Mismatches allelici rilevanti per aGvHD

High-risk HLA allele mismatch combinations responsible for severe acute graft-versus-host disease and implication for its molecular mechanism

Takakazu Kawase,[1] Yasuo Morishima,[2] Keitaro Matsuo,[3] Koichi Kashiwase,[4] Hidetoshi Inoko,[5] Hiroh Saji,[6] Shunichi Kato,[7] Takeo Juji,[8] Yoshihisa Kodera,[9] and Takehiko Sasazuki,[10] for The Japan Marrow Donor Program

BLOOD, 1 OCTOBER 2007 • VOLUME 110, NUMBER 7

Table 2. Nonpermissive allele mismatch combinations for severe aGVHD

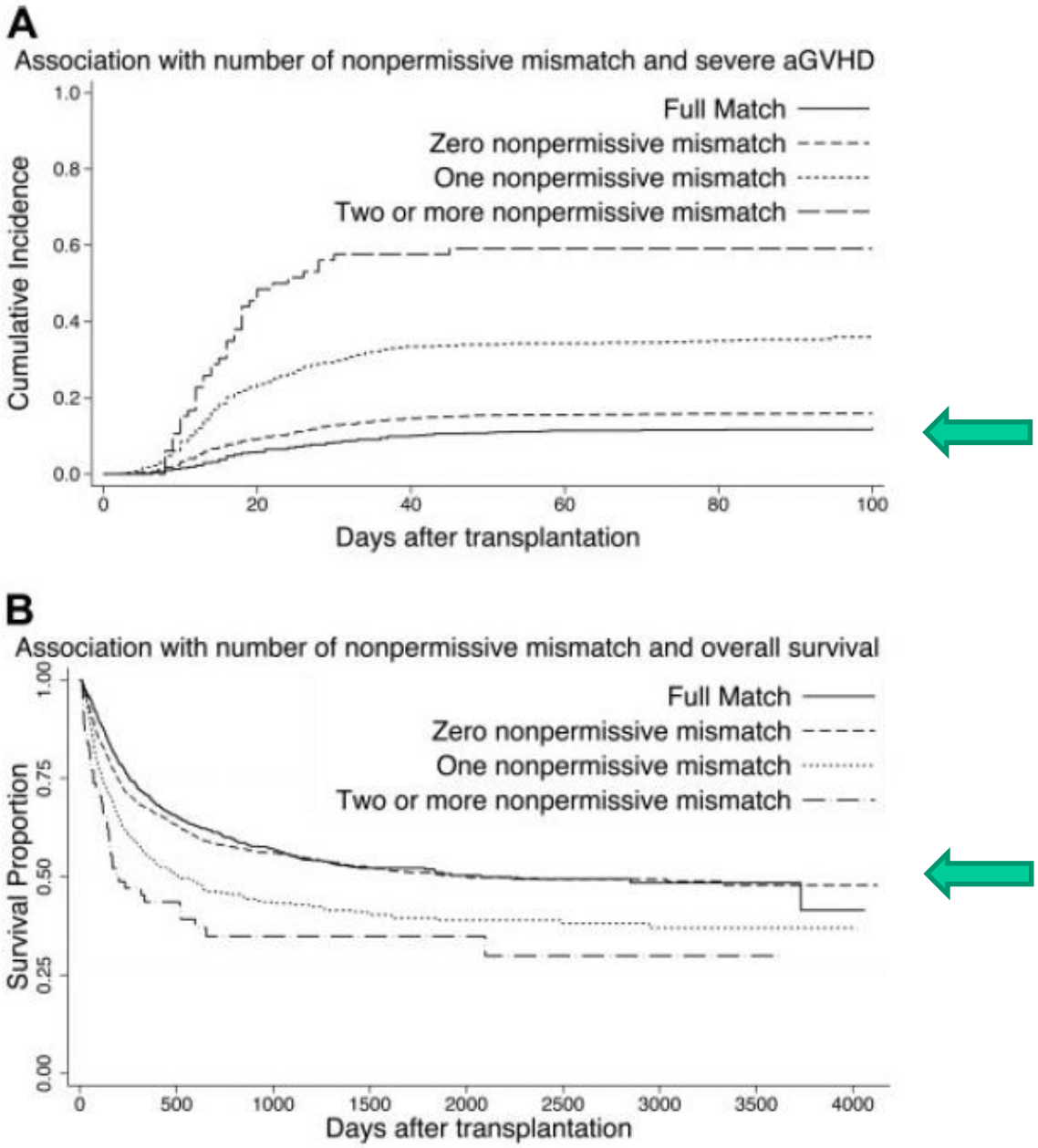
Mismatch combination, donor-patient	N	HR (95% CI)	*P*
A0206-A0201	131	1.78 (1.32-2.41)	< .001
A0206-A0207	27	3.45 (2.09-5.70)	< .001
A2602-A2601	21	3.35 (1.89-5.91)	< .001
A2603-A2601	35	2.17 (1.29-3.64)	.003
B1501-B1507	19	3.34 (1.85-5.99)	< .001
C0303-C1502	25	3.22 (1.75-5.89)	< .001
C0304-C0801	69	2.34 (1.55-3.52)	< .001
C0401-C0303	42	2.81 (1.72-4.60)	< .001
C0801-C0303	80	2.32 (1.58-3.40)	< .001
C1402-C0304	23	3.66 (2.00-6.68)	< .001
C1502-C0304	27	3.77 (2.20-6.47)	< .001
C1502-C1402	50	4.97 (3.41-7.25)	< .001
DR0405-DR0403	53	2.13 (1.28-3.53)	.003
(DR1403-DQ0301)-(DR1401-DQ0502)	19	2.81 (1.44-5.51)	.002
DP0301-DP0501	49	2.41 (1.49-3.89)	< .001
DP0501-DP0901	71	2.03 (1.30-3.16)	.002

5.000 pairs
T cell replete

Table 3. Patient characteristics according to number of nonpermissive mismatches

Group	Total	1 Full match	2 Zero nonpermissive mismatch	3 One nonpermissive mismatch	4 Two or more nonpermissive mismatches
Total	4050	712	2670	602	66
Patient age, median y	30	32	30	29	29
Sex, donor/patient, no. patients					
Male/male	1673	312	1096	237	28
Male/female	785	134	518	119	14
Female/male	769	115	524	117	13
Female/female	823	151	532	129	11
Disease, no. patients					
ALL	981	162	668	139	12
ANLL	1075	196	698	158	23
CML	703	119	453	115	16
Hereditary disease	85	14	56	15	0
MDS	476	91	304	72	9
Malignant lymnphoma	349	69	229	48	3
Multiple myeloma	42	8	29	4	1
Severe aplastic anemia	247	33	175	37	2
Other disease	92	20	58	14	0
Risk of leukemia relapse,* no. patients					
Standard risk	1308	249	857	181	21
High risk	1451	228	962	231	30
Diseases other than leukemia	1291	235	851	190	15
GVHD prophylaxis, no. patients					
Cyclosporin-based	2198	402	1444	319	33
Tacrolimus-based	1852	310	1226	283	33
ATG, no. patients					
ATG	323	48	215	53	7
Non-ATG	3727	664	2455	549	59
Preconditioning, no. patients					
TBI regimen	3117	539	2071	449	58
Non-TBI regimen	933	173	599	153	8

Kawase et al, Blood 2007, 110 (7)



Kawase et al, Blood 2007, 110 (7)

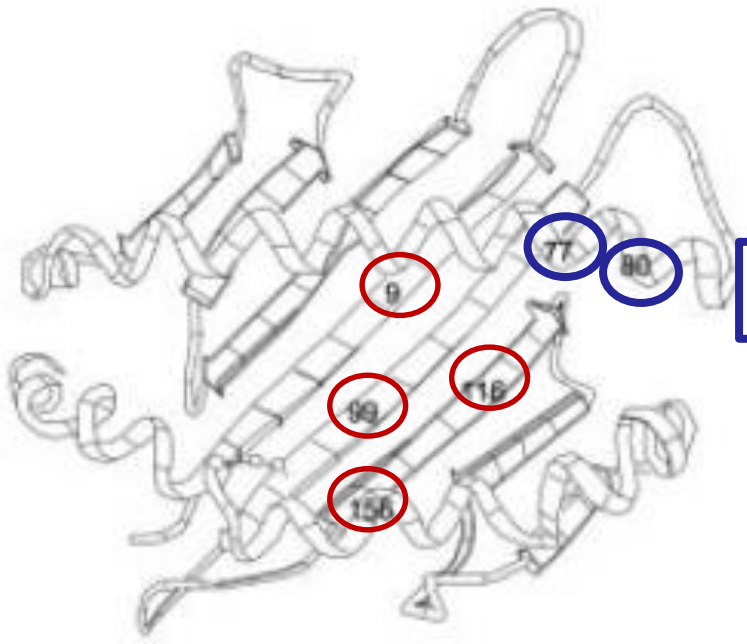
Table 5. Multivariable analysis of impact of amino acid substitution on HLA class I molecules for severe aGVHD

Posisiton and kind of amino acid substitution, donor-recipient	Hydropathy scale HS	N	Event†	HR (95% CI)	*P*
HLA-A locus					
Tyr9A-Phe9A	4.1	163	64	1.66 (1.19-2.32)	.003
Asn116A-Asp116A	0	32	15	2.25 (1.26-4.01)	.005*
HLA-C locus					
Tyr9C-Ser9C	0.5	146	59	1.66 (1.23-2.25)	.001
Asn77C-Ser77C	2.7	205	90	1.87 (1.46-2.39)	< .001
Lys80C-Asn80C	0.4	205	90	1.87 (1.46-2.39)	< .001
Tyr99C-Phe99C	4.1	146	59	1.64 (1.21-2.22)	.001
Leu116C-Ser116C	4.6	53	30	3.40 (2.20-5.25)	< .001
Arg156C-Leu156C	8.3	251	88	1.48 (1.15-1.90)	.002

Sostituzioni di specifici aminoacidi nelle posizioni **9, 77**, **80**, **99**, **116** e **156** sono state identificate come fattori di rischio significativi per lo sviluppo di aGVHD severa.
Il ruolo delle posizioni **77** e **80** nelle molecole HLA-C era associato al matching per i ligandi dei recettori KIR.

Kawase et al, Blood 2007, 110 (7)

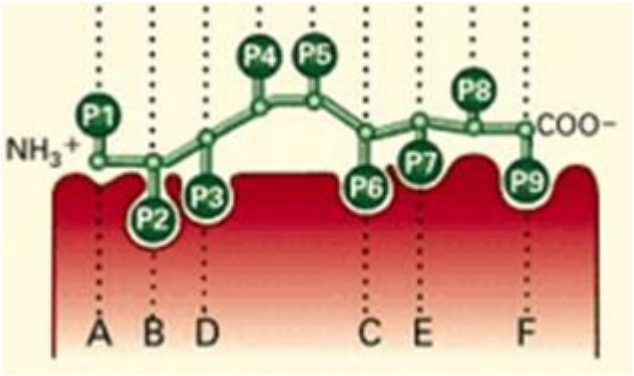
aGvHD



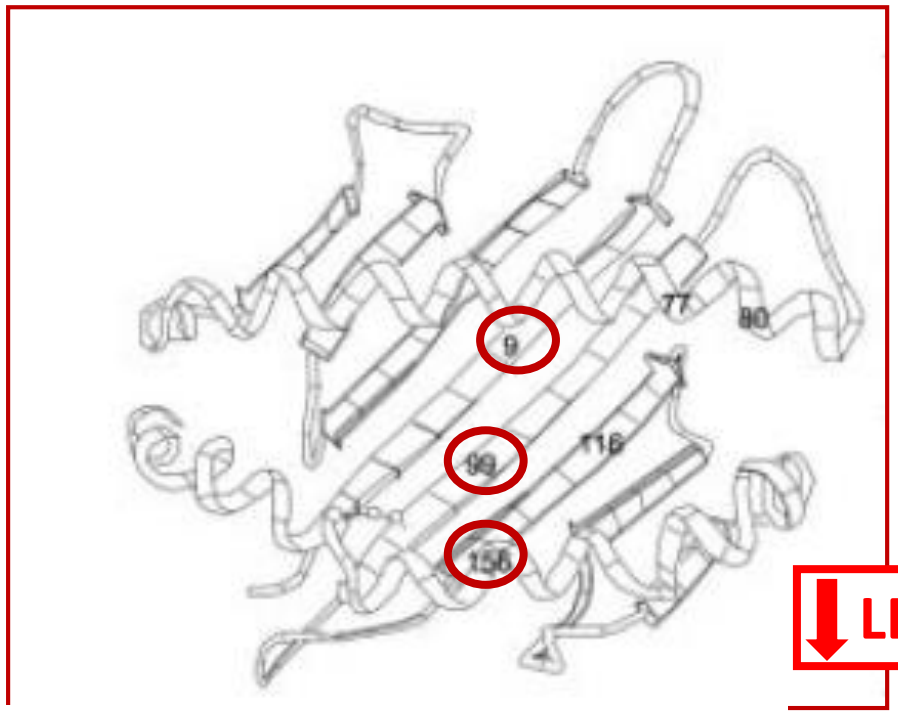
KIR2DL1 LIGAND

KIR2DL2/3 LIGAND

	beta-plate sheet			alpha helix
Position of HLA class I	9	99	116	156
Peptide-binding pocket	B C	A B D	F	D E
Amino acid substitution				
HLA-A	Tyr-Phe		Asn-Asp*	
HLA-C	Tyr-Ser	Tyr-Phe	Leu-Ser	Arg-Leu

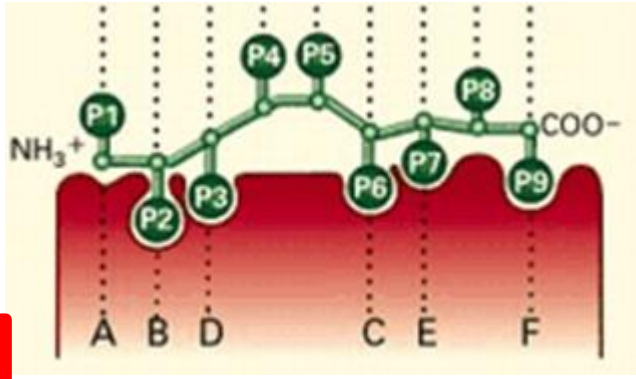


Kawase et al, Blood 2007, 110 (7)



LEUKEMIA RELAPSE

	beta-plate sheet			alpha helix
Position of HLA class I	9	99	116	156
Peptide-binding pocket	B C	A B D	F	D E
Amino acid substitution				
HLA-A	Tyr-Phe		Asn-Asp*	
HLA-C	Tyr-Ser	Tyr-Phe	Leu-Ser	Arg-Leu



Kawase et al, Blood 2007, 110 (7)

Kawase et al, Blood 2009, 113 (12)

BLOOD, 21 NOVEMBER 2013 • VOLUME 122, NUMBER 22

Amino acid substitution at peptide-binding pockets of HLA class I molecules increases risk of severe acute GVHD and mortality

Joseph Pidala,[1] Tao Wang,[2] Michael Haagenson,[3] Stephen R. Spellman,[3] Medhat Askar,[4] Minoo Battiwalla,[5] Lee Ann Baxter-Lowe,[6] Menachem Bitan,[7] Marcelo Fernandez-Viña,[8] Manish Gandhi,[9] Ann A. Jakubowski,[10] Martin Maiers,[11] Susana R. Marino,[12] Steven G. E. Marsh,[13] Machteld Oudshoorn,[14] Jeanne Palmer,[15] Vinod K. Prasad,[16] Vijay Reddy,[17] Olle Ringden,[18] Wael Saber,[2] Stella Santarone,[19] Kirk R. Schultz,[20] Michelle Setterholm,[11] Elizabeth Trachtenberg,[21] E. Victoria Turner,[22] Ann E. Woolfrey,[23] Stephanie J. Lee,[23] and Claudio Anasetti[1]

Relationship between the presence of AAS in position

9, **77**, **99**, **116** e **156**

in pairs 7/8 and HSCT outcome

Table 3. Results of HLA class I restricted multivariate analyses

HLA class I locus	AAS considered	Outcome	N	HR	95% CI	*P*
HLA-A	AAS 116 absent	OS	433	1.00	—	
HLA-A	AAS 116 present	OS	265	0.96	(0.78-1.18)	.70
HLA-B	AAS 116 absent	OS	153	1.00	—	
HLA-B	AAS 116 present	OS	164	0.98	(0.72-1.32)	.88
HLA-C	AAS 116 absent	OS	453	1.00	—	
HLA-C	AAS 116 present	OS	563	1.20	(1.01-1.41)	.03
HLA-A	AAS 99 absent	TRM	612	1.00	—	
HLA-A	AAS 99 present	TRM	85	0.86	(0.58-1.30)	.48
HLA-B	AAS 99 absent	TRM	308	1.00	—	
HLA-B	AAS 99 present	TRM	9	0.53	(0.13-2.24)	.39
HLA-C	AAS 99 absent	TRM	534	1.00	—	
HLA-C	AAS 99 present	TRM	482	1.37	(1.11-1.69)	.0038
HLA-A	AAS 116 absent	Grades III-IV acute GVHD	450	1.00	—	
HLA-A	AAS 116 present	Grades III-IV acute GVHD	247	1.18	(0.90-1.56)	.23
HLA-B	AAS 116 absent	Grades III-IV acute GVHD	159	1.00	—	
HLA-B	AAS 116 present	Grades III-IV acute GVHD	157	1.20	(0.82-1.75)	.35
HLA-C	AAS 116 absent	Grades III-IV acute GVHD	484	1.00	—	
HLA-C	AAS 116 present	Grades III-IV acute GVHD	531	1.45	(1.15-1.82)	.0016
HLA-A	AAS 9 absent	Chronic GVHD	291	1.00	—	
HLA-A	AAS 9 present	Chronic GVHD	374	1.18	(0.91-1.53)	.20
HLA-B	AAS 9 absent	Chronic GVHD	269	1.00	—	
HLA-B	AAS 9 present	Chronic GVHD	40	2.28	(1.36-3.82)	.0018
HLA-C	AAS 9 absent	Chronic GVHD	434	1.00	—	
HLA-C	AAS 9 present	Chronic GVHD	552	1.12	(0.91-1.39)	.28

(*Blood*. 2014;123(8):1270-1278)

Identification of a permissible HLA mismatch in hematopoietic stem cell transplantation

Marcelo A. Fernandez-Viña,[1] Tao Wang,[2] Stephanie J. Lee,[3] Michael Haagenson,[4] Mahmoud Aljurf,[5] Medhat Askar,[6] Minoo Battiwalla,[7] Lee-Ann Baxter-Lowe,[8] James Gajewski,[9] Ann A. Jakubowski,[10] Susana Marino,[11] Machteld Oudshoorn,[12] Steven G. E. Marsh,[13] Effie W. Petersdorf,[3] Kirk Schultz,[14] E. Victoria Turner,[15] Edmund K. Waller,[16] Ann Woolfrey,[3] John Umejiego,[4] Stephen R. Spellman,[4] and Michelle Setterholm[17]

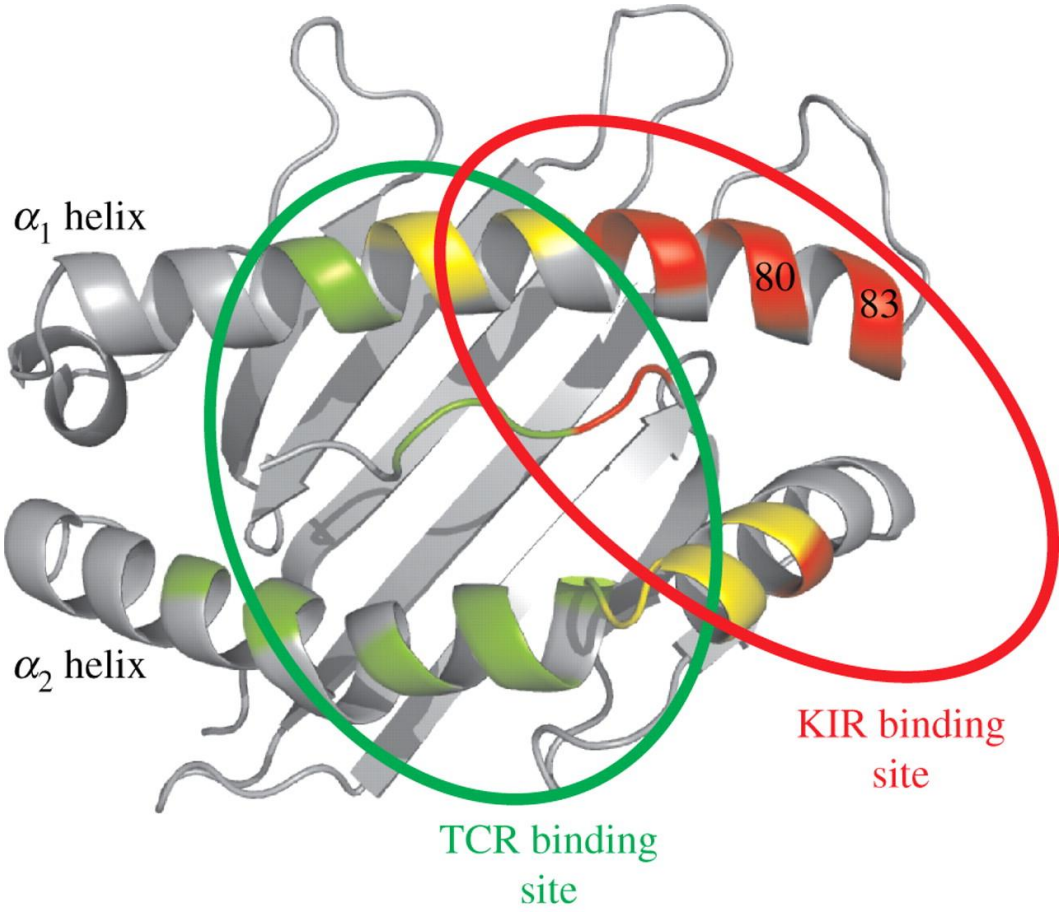
Key Points

- Mismatches in alleles C*03:03/C*03:04 were most frequent (68.7%) among the transplants with a single allele level mismatch in HLA-C.
- The 7/8 C*03:03/C*03:04 mismatch group was not significantly different from the 8/8 HLA matched transplants in any transplant outcome.

Table 2. Multivariate model evaluating transplant outcomes classified according to allele and antigen mismatches at HLA-C

	8/8 Match	7/8 C*03:03/C*03:04 mismatch			7/8 HLA-A, -B, or -DRB1 mismatch			7/8 C-antigen mismatch			7/8 Other C-allele mismatch			Overall comparison
	n = 4779	n = 134			n = 959			n = 700			n = 61			
	HR	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	*P*
OS*	1.00	0.98	(0.78-1.23)	.85	**1.30**	(1.19-1.43)	**<.0001**	**1.37**	(1.24-1.51)	**<.0001**	1.43	(1.06-1.92)	.02	<.0001
DFS†	1.00	1.00	(0.80-1.25)	.99	**1.27**	(1.17-1.38)	**<.0001**	**1.33**	(1.20-1.46)	**<.0001**	1.34	(0.99-1.80)	.06	<.0001
TRM‡	1.00	1.05	(0.79-1.40)	.73	**1.54**	(1.39-1.71)	**<.0001**	**1.54**	(1.39-1.74)	**<.0001**	1.60	(1.10-2.33)	.02	<.0001
3-4 aGVHD§	1.00	0.96	(0.67-1.38)	.83	**1.77**	(1.56-2.01)	**<.0001**	**1.49**	(1.28-1.73)	**<.0001**	1.72	(1.11-2.69)	.02	<.0001
2-4 aGVHD‖	1.00	0.97	(0.76-1.25)	.83	**1.30**	(1.18-1.43)	**<.0001**	1.15	(1.02-1.28)	.02	**1.56**	(1.11-2.19)	**.01**	<.0001
Absence of neutrophil engraftment at day 28¶	1.00	0.63	(0.29-1.33)	.23	1.19	(0.97-1.47)	.10	1.28	(1.02-1.61)	.03	1.19	(0.51-2.78)	.68	.09
Relapse#	1.00	0.94	(0.66-1.32)	.71	0.93	(0.81-1.08)	.35	1.03	(0.88-1.20)	.76	1.00	(0.62-1.64)	.99	.88
cGvHD**	1.00	0.92	(0.72-1.19)	.53	1.04	(0.94-1.16)	.44	1.02	(0.90-1.16)	.76	1.08	(0.75-1.57)	.91	.67

The HLA alleles C*03:03 and C*03:04 differ by a single amino acid substitution at residue 91. The initial crystallographic analyses of HLA class I molecules[29] showed that this residue is located in a loop connecting the second α helix of the α-1 domain with the first β-pleated sheet of the α-2 domain; residue 91 is a contact site with neither peptide[30] nor with the T-cell receptor.



7 residues of the peptide binding site are reported to be key positions influencing T-cell allorecognition

HLA-C MM	Nb pat[a]	Residues in the PBS							Nb
		9	97	99	116	152	156	163	MM[b]
03:03–03:04	22	–	–	–	–	–	–	–	0

[a] *Number of patient/donor pairs.*

[b] *Number of mismatched residues in the PBS (out of the seven key amino acids reported to be associated with outcome).*

J.M.Tiercy, Frontiers in Immunology, May 2014, v.5,216

7 residues of the peptide binding site are reported to be key positions influencing T-cell allorecognition

HLA-C MM	Nb pat[a]	Residues in the PBS							Nb
		9	97	99	116	152	156	163	MM[b]
03:03–03:04	22	–	–	–	–	–	–	–	0
07:01–07:02	14	–	–	Y/S	–	–	–	–	1
15:02–14:02	13	Y/S	R/W	Y/F	L/S	–	L/R	–	5
04:01–16:01	10	S/Y	R/W	F/Y	F/S	E/A	R/Q	–	6
01:02–02:02	9	F/Y	W/R	C/Y	Y/S	–	R/W	–	5
05:01–07:04	8	Y/D	–	–	–	E/A	R/D	–	4
07:02–03:04	8	D/Y	–	S/Y	S/Y	A/E	–	T/L	5
14:02–01:02	7	S/F	–	F/C	S/Y	–	–	–	3
12:03–07:01	9	Y/D	–	W/R	–	E/A	W/L	–	4
02:02–15:02	7	–	–	–	S/L	–	W/L	E/T	3
12:03–04:01	5	Y/S	W/R	Y/F	S/F	–	W/R	–	6
03:04–04:01	5	Y/S	–	Y/F	–	–	L/R	L/T	4
01:02–15:02	5	F/Y	W/R	C/Y	Y/L	–	R/L	–	5

[a] *Number of patient/donor pairs.*

[b] *Number of mismatched residues in the PBS (out of the seven key amino acids reported to be associated with outcome).*

Più alto è il numero di mismatches in queste posizioni maggiore sarà l'influenza sull' outcome clinico

7 residues of the peptide binding site are reported to be key positions influencing T-cell allorecognition

HLA-C MM	Nb pat[a]	Residues in the PBS							Nb
		9	97	99	116	152	156	163	MM[b]
03:03–03:04	22	–	–	–	–	–	–	–	0
07:01–07:02	14	–	–	Y/S	–	–	–	–	1
15:02–14:02	13	Y/S	R/W	Y/F	L/S	–	L/R	–	5
04:01–16:01	10	S/Y	R/W	F/Y	F/S	E/A	R/Q	–	6
01:02–02:02	9	F/Y	W/R	C/Y	Y/S	–	R/W	–	5
05:01–07:04	8	Y/D	–	–	–	E/A	R/D	–	4
07:02–03:04	8	D/Y	–	S/Y	S/Y	A/E	–	T/L	5
14:02–01:02	7	S/F	–	F/C	S/Y	–	–	–	3
12:03–07:01	9	Y/D	–	W/R	–	E/A	W/L	–	4
02:02–15:02	7	–	–	–	S/L	–	W/L	E/T	3
12:03–04:01	5	Y/S	W/R	Y/F	S/F	–	W/R	–	6
03:04–04:01	5	Y/S	–	Y/F	–	–	L/R	L/T	4
01:02–15:02	5	F/Y	W/R	C/Y	Y/L	–	R/L	–	5

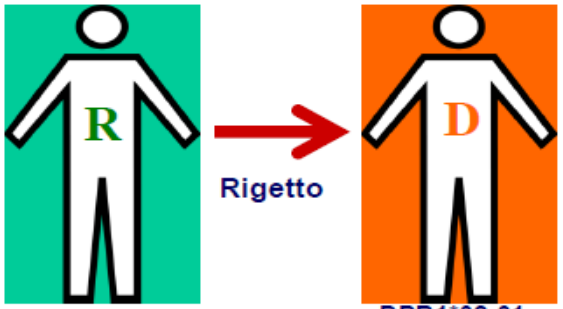
ut of the seven key amino acids reported to be associated with outcome

HLA-B	HLA-C		%
*51:01	*15:02	20	31,75
*51:01	*14:02	13	20,63
*51:01	*16:02	6	9,52
*51:01	*02:02	5	7,94
*51:01	*07:01	4	6,35
*51:01	*12:03	4	6,35
*51:01	*01:02	3	4,76
*51:01	*07:02	2	3,17
*51:01	*15:06	2	3,17
*51:01	*15:13	2	3,17
*51:01	*06:02	1	1,59
*51:01	*15:24	1	1,59
12 C alleles		63	

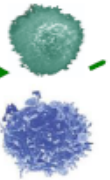
HLA-B	HLA-C		
*44:03	*04:01P	8	36,36
*44:03	*16:01	8	36,36
*44:03	*07:06	3	13,64
*44:03	*02:02	1	4,55
*44:03	*14:03	1	4,55
*44:03	*16:04	1	4,55
6 C alleles		22	

HLA-B	HLA-C		%
*18:01	*07:01	26	42,62
*18:01	*12:03	19	31,15
*18:01	*05:01	10	16,39
*18:01	*01:02	1	1,64
*18:01	*03:03	1	1,64
*18:01	*07:04P	1	1,64
*18:01	*12:02	1	1,64
*18:01	*12:05	1	1,64
*18:01	*15:02	1	1,64
9 C alleles		61	

From the allele to T Cell Epitope (TCE) matching



T cell epitope
K. Fleischhauer et al, 2004



2 cloni alloreattivi che riconoscono in modo DIRETTO, il MM DPB1

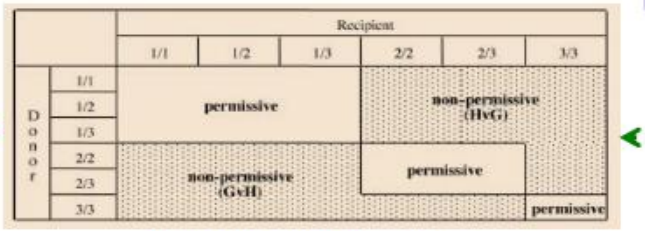
I due cloni sono stati testati con cellule con DPB1 diversi

Table 2. Classification of HLA-DPB1 alleles according to their predicted immunogenicity

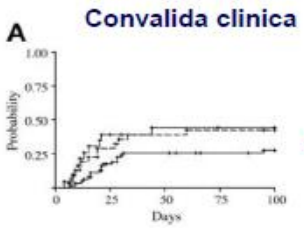
Groups†	HLA-DPB1*	Frequencies		
		White	Asian	African
1	0901, 1001, 1701	0.018	0.025	0.325
2	0301, 1401, 4501	0.143	0.075	0.080
3	0101, 0201, 0202, 0401, 0402, 0501, 0601, 1101, 1301, 1501, 1601, 1901, 2001, 2301, 4601	0.839	0.850	0.575

†Based on the T-cell recognition pattern described in this study, HLA-DPB1 alleles are predicted to be immunogenic (group 1), intermediately immunogenic (group 2), or poorly immunogenic (group 3).

Classificazione degli alleli DPB1 in base all'immunogenicità



Algoritmo di permissività (immunogenicità+educazione timica)



From the allele to T Cell Epitope (TCE) matching

Caratterizzazione dei T Cell Epitopes (TCE) mediante la cross-reattività di cloni T alloreattivi

Predetta tolleranza a T Cell Epitopes (TCE) alloreattivi condivisi

		Polymorphic regions															
		A			B			C			D		E	F			
Groups	HLA-DPB1*	8	9	11	33	35	36	55	56	57	65	69	76	84	85	86	87
1	09:01	V	H	L	E	F	V	D	E	D	I	E	V	D	E	A	V
	10:01	—	—	—	—	—	—	—	—	E	—	—	—	—	—	—	—
	17:01	—	—	—	—	—	—	—	—	—	—	—	M	—	—	—	—
2	03:01	—	Y	—	—	—	—	—	—	—	L	K	—	—	—	—	—
	14:01	—	—	—	—	—	—	—	—	—	L	K	—	—	—	—	—
	45:01	—	—	—	—	—	—	—	—	E	L	K	—	—	—	—	—
3	01:01	—	Y	G	—	Y	A	A	A	E	—	K	—	—	—	—	—
	02:01	L	F	G	—	—	—	—	—	E	—	—	M	G	G	P	M
	02:02	L	F	G	—	L	—	E	A	E	—	—	M	G	G	P	M
	04:01	L	F	G	—	—	A	A	A	E	—	K	M	G	G	P	M
	04:02	L	F	G	—	—	—	—	—	E	—	K	M	G	G	P	M
	05:01	L	F	G	—	L	—	E	A	E	—	K	M	—	—	—	—
	06:01	—	Y	—	—	—	—	—	—	—	L	—	M	—	—	—	—
	11:01	—	Y	—	Q	Y	A	A	A	E	L	R	M	—	—	—	—
	13:01	—	Y	—	—	Y	A	A	A	E	—	—	I	—	—	—	—
	15:01	—	Y	G	Q	Y	A	A	A	E	L	R	M	V	G	P	M
	16:01	L	F	G	—	—	—	—	—	E	—	—	M	—	—	—	—
	19:01	L	F	G	—	—	—	E	A	E	—	—	I	—	—	—	—
	20:01	—	Y	—	—	—	—	—	—	—	L	K	M	—	—	—	—
	23:01	L	F	G	—	—	—	A	A	E	—	K	M	G	G	P	M
	46:01	L	F	G	—	—	—	—	—	—	—	—	M	G	G	P	M

TRANSPLANTATION

Blood. 2014;124(16):2596-2606

Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation

Joseph Pidala,[1] Stephanie J. Lee,[2] Kwang Woo Ahn,[3] Stephen Spellman,[4] Hai-Lin Wang,[3] Mahmoud Aljurf,[5] Medhat Askar,[6] Jason Dehn,[7] Marcelo Fernandez Viña,[8] Alois Gratwohl,[9] Vikas Gupta,[10] Rabi Hanna,[6] Mary M. Horowitz,[3] Carolyn K. Hurley,[11] Yoshihiro Inamoto,[2] Adetola A. Kassim,[12] Taiga Nishihori,[1] Carlheinz Mueller,[13] Machteld Oudshoorn,[14] Effie W. Petersdorf,[2] Vinod Prasad,[15] James Robinson,[16,17] Wael Saber,[3] Kirk R. Schultz,[18] Bronwen Shaw,[16,17,19] Jan Storek,[20] William A. Wood,[21] Ann E. Woolfrey,[2] and Claudio Anasetti[1]

Key Points

- High-resolution matching for HLA-A, -B, -C, and -DRB1 is required for optimal survival in myeloablative-unrelated donor transplantation.
- HLA-DPB1 nonpermissive mismatches should be avoided in otherwise matched transplants to minimize overall mortality.

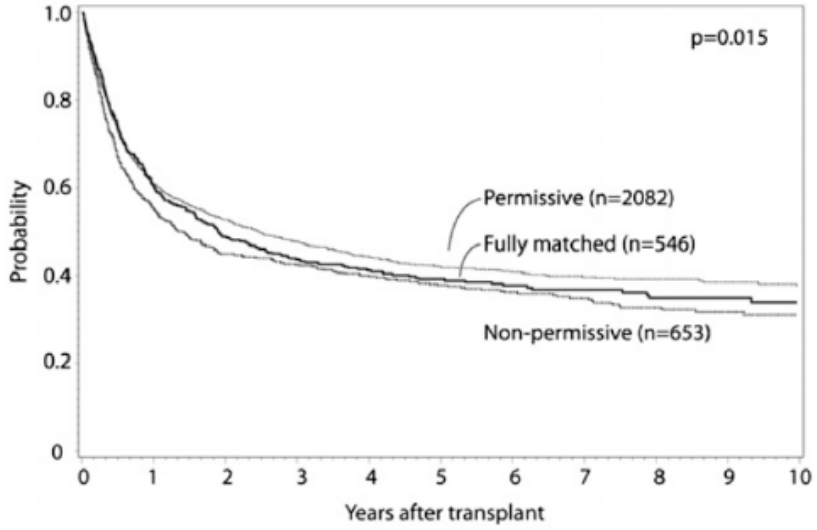
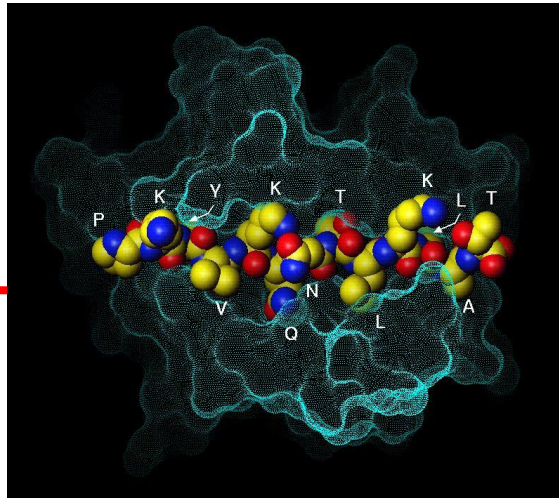


Figure 2. Adjusted OS curves for -DPB1 matched, permissive mismatch, and nonpermissive mismatch cases.

Non tutti i mismatches HLA conferiscono lo stesso rischio



Per ogni mismatch, tutti i seguenti aspetti influenzano l'alloreattività:

- Il numero delle sostituzioni aminoacidiche
- La posizione
- La natura della sostituzione
- Il livello di espressione

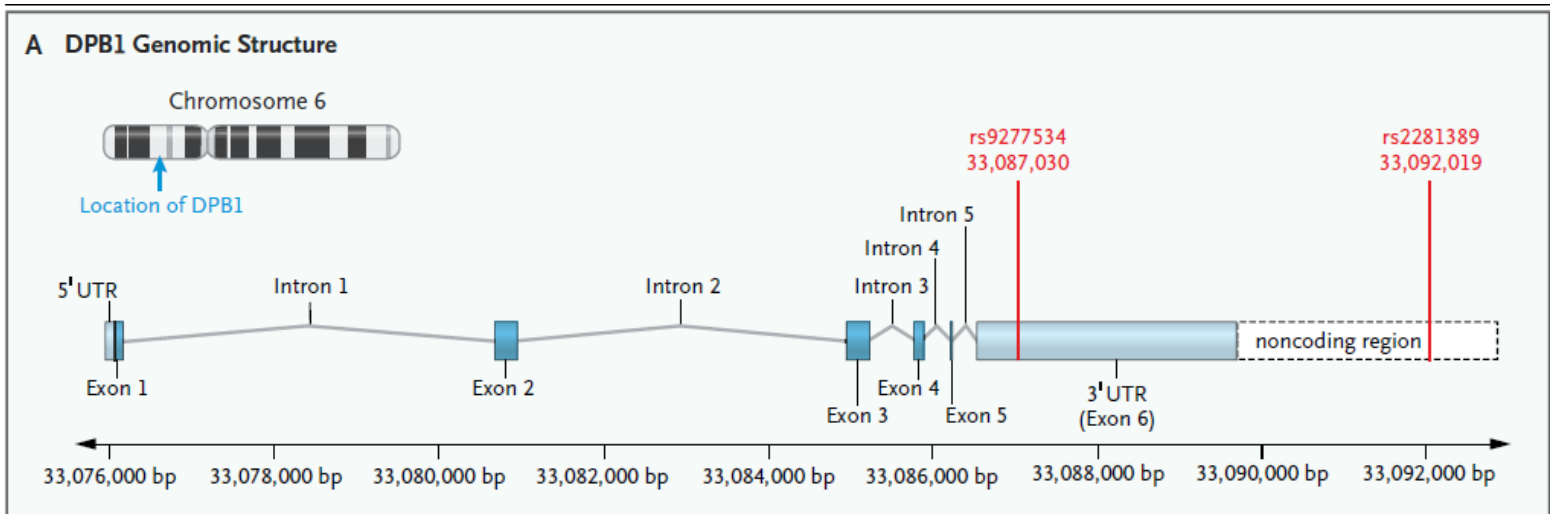
Published in final edited form as:

N Engl J Med. 2015 August 13; 373(7): 599–609. doi:10.1056/NEJMoa1500140.

High HLA-DP Expression and Graft-versus-Host Disease

Effie Petesdorf et al

Fine mapping of the HLA-DP genetic region

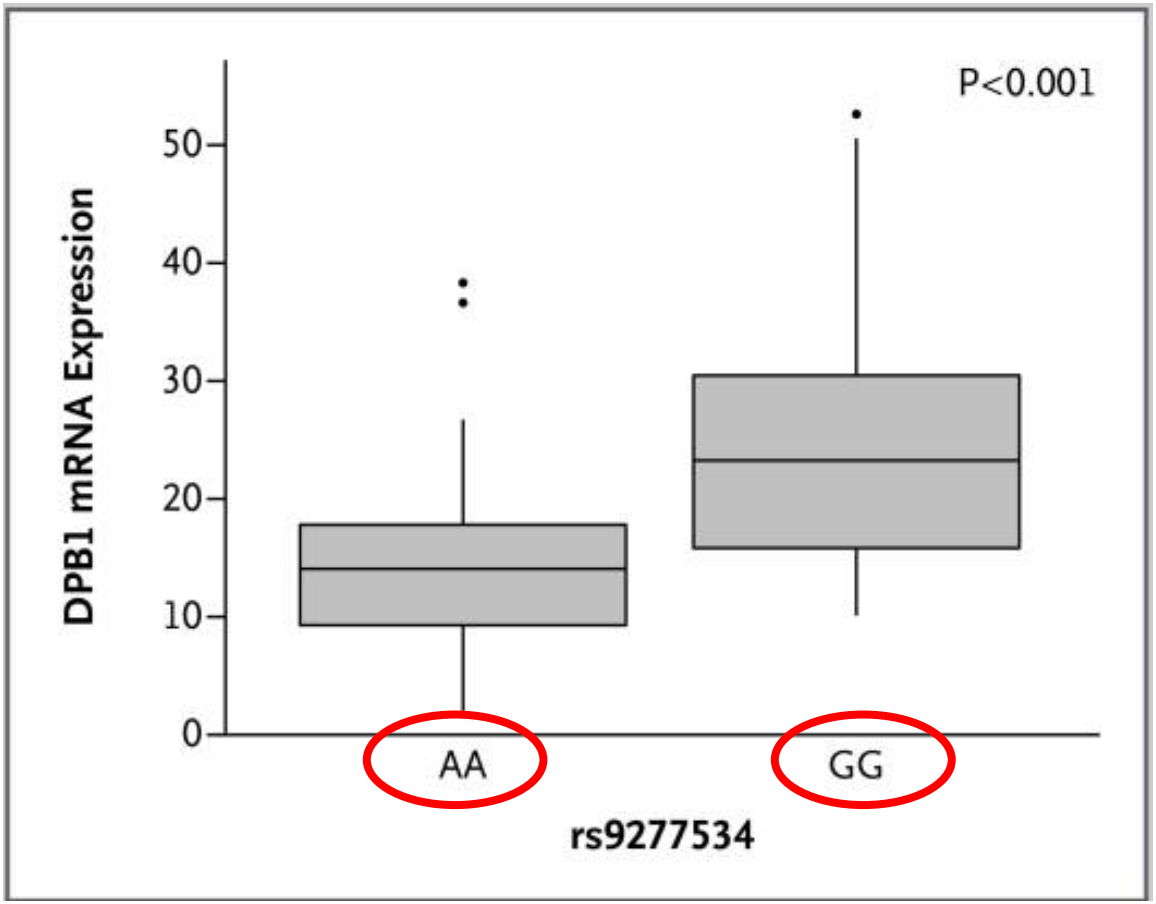


rs2281389 SNP (A/G): marker per rischio di aGvHD in HLA-matched UD-HSCT (Petersdorf et al Sci Trans Med 4:ra101,2012)

rs2281389 SNP (A/G): è collocato fuori dalla regione codificante e quindi non può essere un diretto mediatore di aGvHD

rs2281389 SNP (A/G): è in forte linkage disequilibrium con **rs9277534** (A/G) che a sua volta è legato all'esone 2 del DPB1.

Correlazione dell'espressione di DPB1 con il genotipo rs9277534

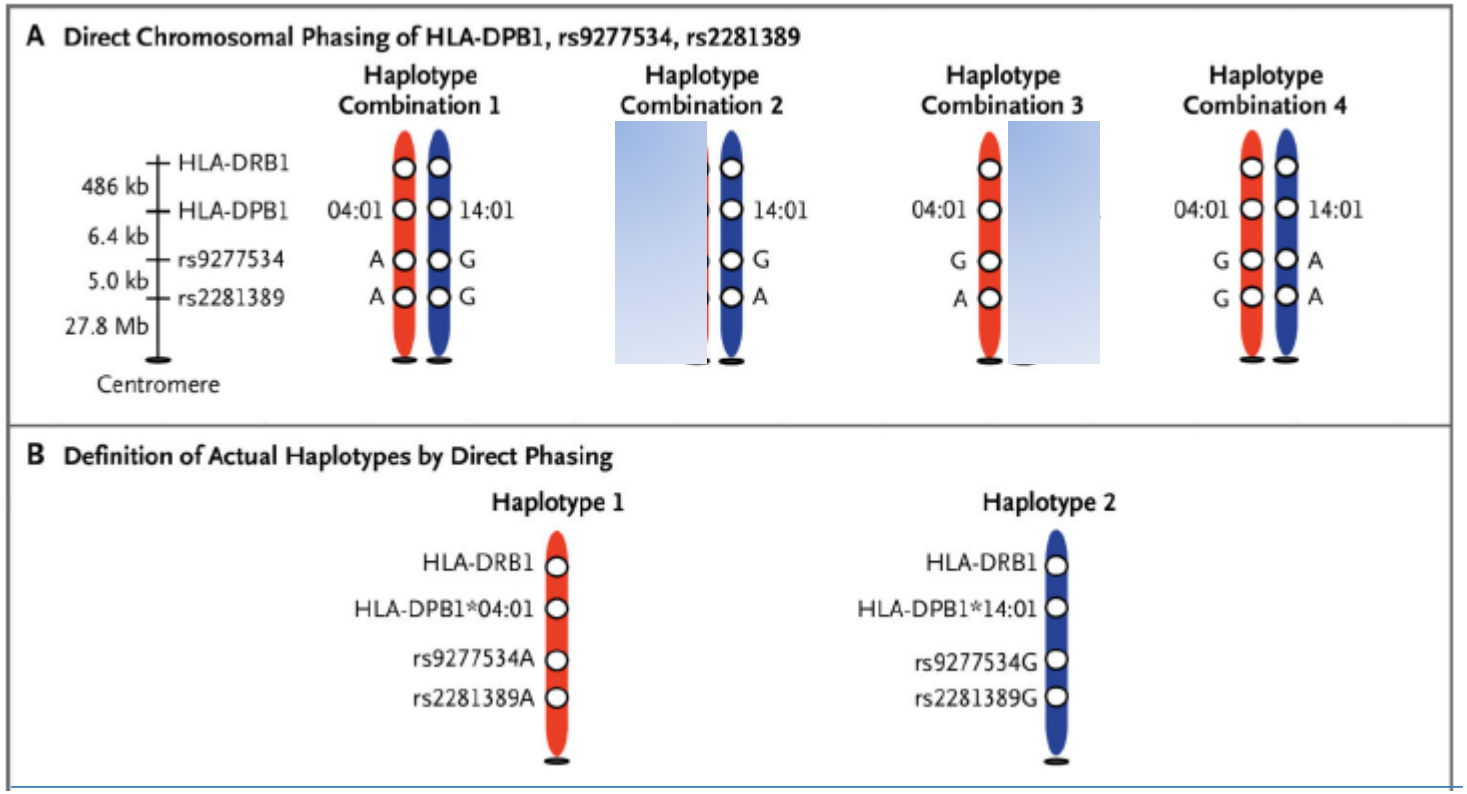


Possibile spiegazione:
Legame preferenziale dei due alleli ai **microRNA**, mediatori dell'RNA silencing

Correlation of HLA-DPB1 Expression with the rs9277534 allele in the 3' Untranslated Region of HLA-DPB1.

Petersdorf et al – New Engl J Med 373:599, 2015

Specifici patterns di linkage disequilibrium tra rs9277534 A/G, rs2281389 A/G e alleli DPB1



Petersdorf et al – New Engl J Med 373:599, 2015

B DPB1*-rs9277534-rs2281389 Haplotypes

DPB1*	rs9277534	rs2281389	HLA-DP Expression Levels
02:01, 02:02, *04:01*, *04:02*, *17:01*, 23:01, 40:01, 46:01, 55:01, 71:01, 94:01, 105:01, 128:01	A	A	Low
01:01, *05:01*, *11:01*, *13:01*, 15:01, 18:01, 19:01, 85:01	G	A	High
03:01, *06:01*, 09:01, *10:01*, *14:01*, 16:01, 20:01	G	G	High

Immunogenetics of HLA-DP — A New View of Permissible Mismatches Katharina Fleischhauer, M.D.
NEJM373:7, 2015

QUALE RUOLO DI QUESTI APLOTIPI NEL TRAPIANTO DA MUD?

Petersdorf et al – New Engl J Med 373:599, 2015

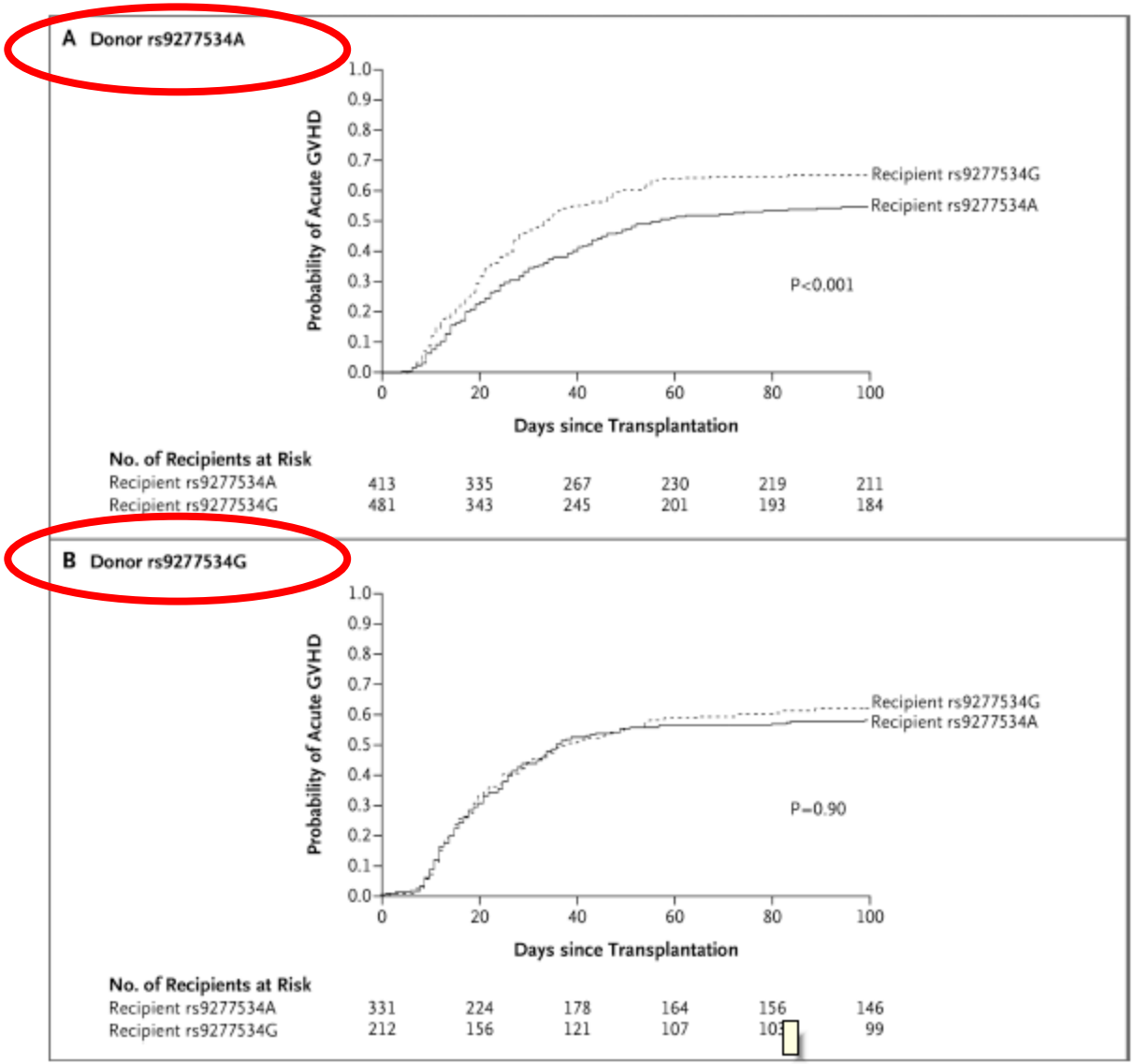
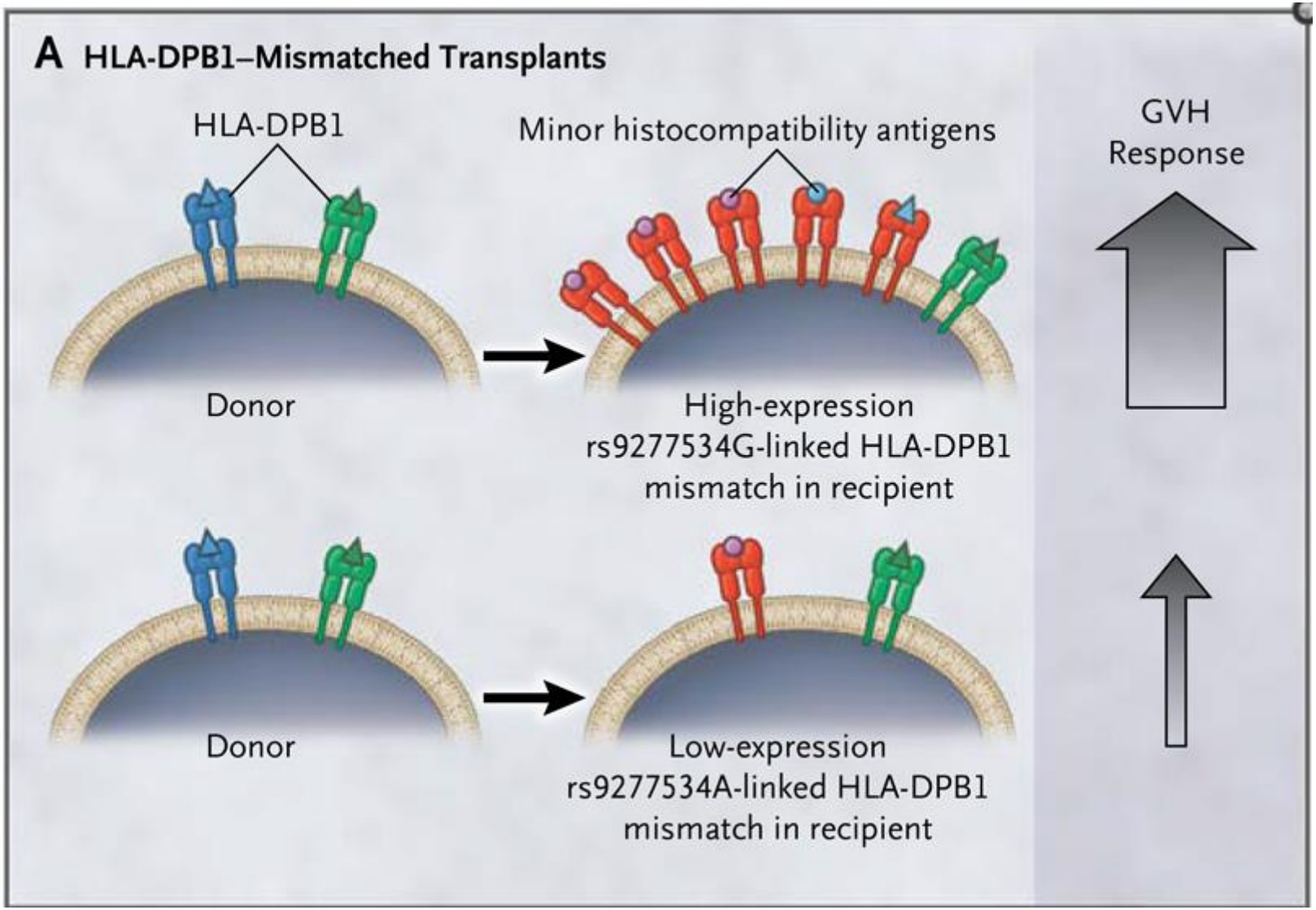


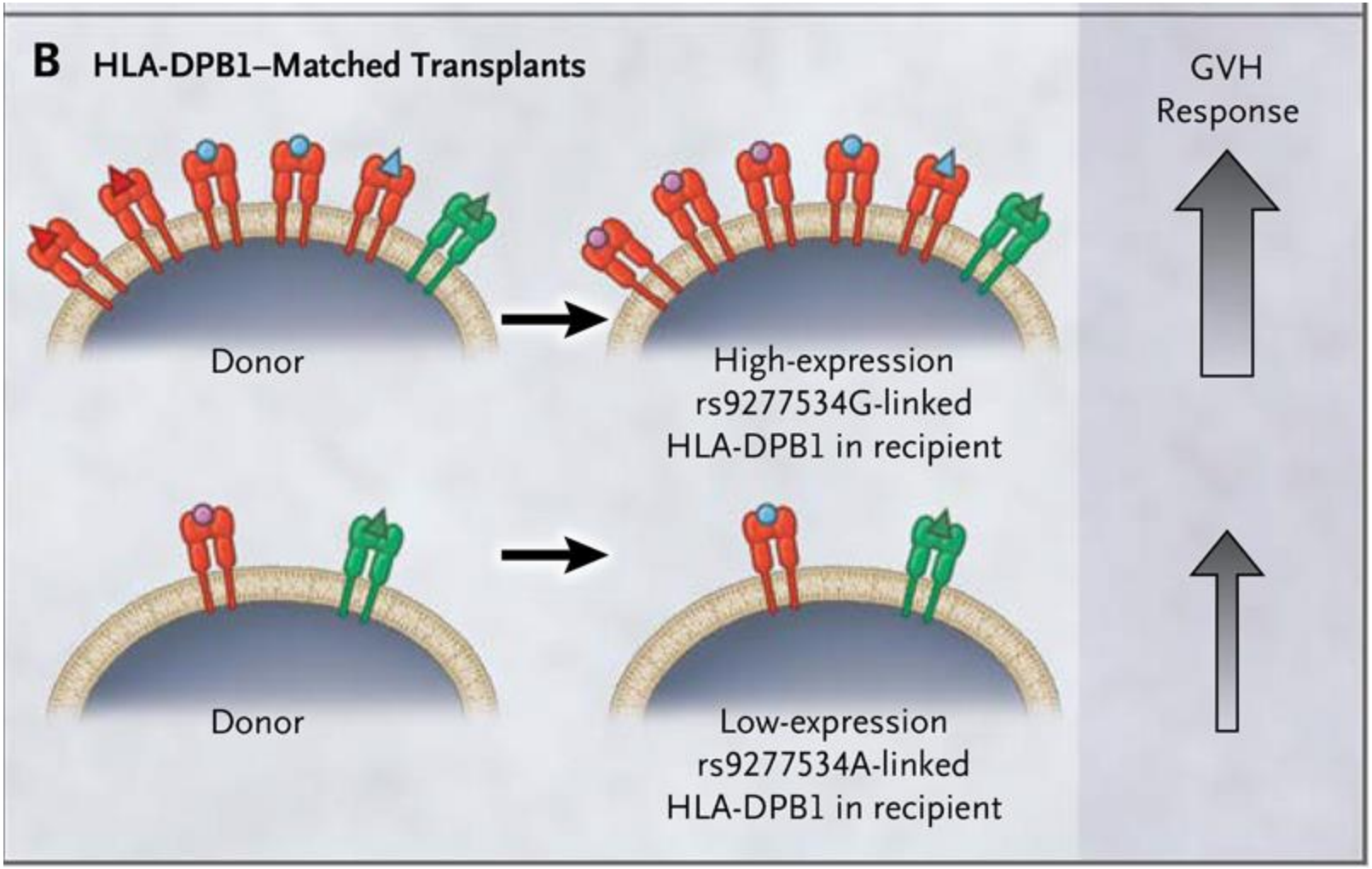
Figure 4. Probability of Grade II, III, or IV Acute Graft-versus-Host Disease

…solo un allele DPB1 di differenza tra ricevente e donatore



Petersdorf et al – New Engl J Med 373:599, 2015

…nessuna differenza DPB1 tra ricevente e donatore



Petersdorf et al – New Engl J Med 373:599, 2015

B DPB1*-rs9277534-rs2281389 Haplotypes

DPB1*	rs9277534	rs2281389	HLA-DP Expression Levels
02:01, 02:02, *04:01*, *04:02*, *17:01*, 23:01, 40:01, 46:01, 55:01, 71:01, 94:01, 105:01, 128:01	A	A	Low
01:01, *05:01*, *11:01*, *13:01*, 15:01, 18:01, 19:01, 85:01	G	A	High
03:01, *06:01*, 09:01, *10:01*, *14:01*, 16:01, 20:01	G	G	High

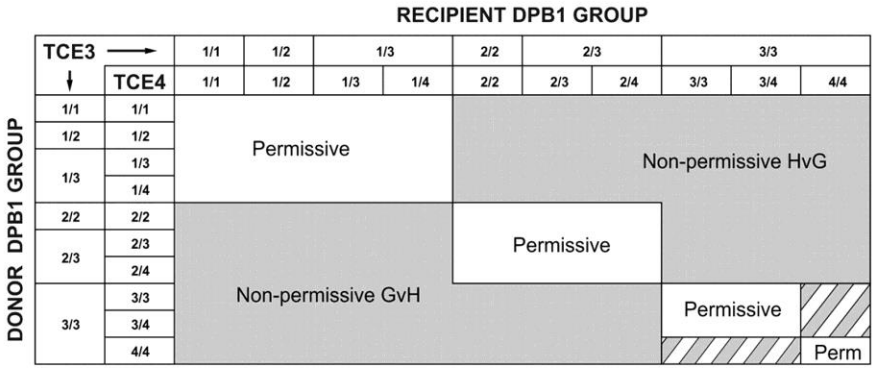
Tutti gli alleli DPB1 appartenenti ai gruppi 1 e 2 sono in linkage con rs9277534 G tranne DPB1*17:01

Tutti gli alleli DPB1 appartenenti al gruppo 3 sono in linkage con rs9277534 A

A

DPB1* alleles	TCE3 group	TCE4 group	Immunogenicity
0901 1001 1701	1	1	
0301 1401 4501	2	2	
0201 0202 0203	3	3	
Others		4	

B



Punti chiave

E’ ipotizzabile che le differenze di immunogenicità dei gruppi definiti dai T Cell Epitopes possano essere in parte legate ad un diverso grado di espressione degli alleli DPB1

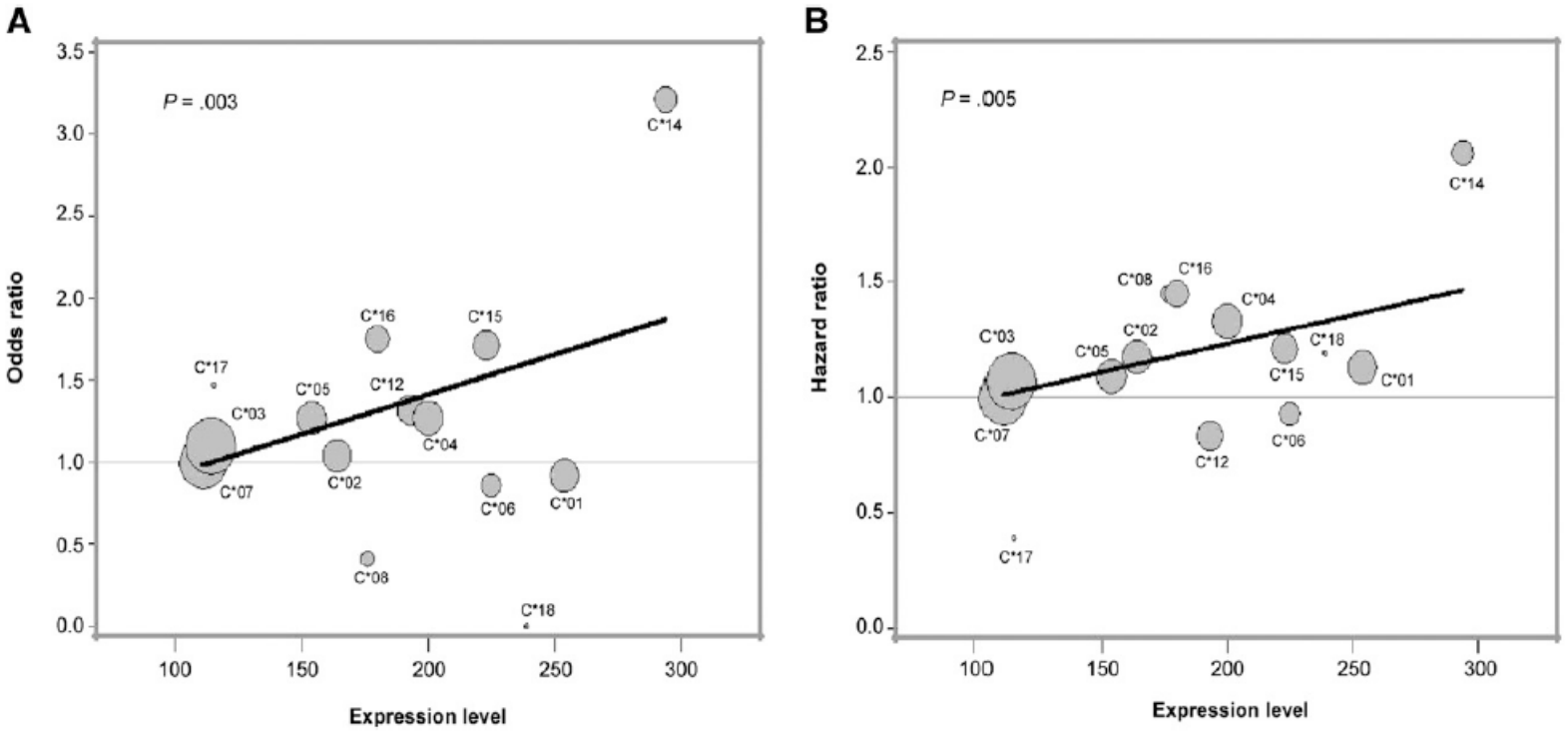
Anche per quanto riguarda il locus HLA-C possono anche essere definiti dei mismatches permissivi in base al livello di espressione

BLOOD, 18 DECEMBER 2014 x VOLUME 124, NUMBER 26

TRANSPLANTATION

HLA-C expression levels define permissible mismatches in hematopoietic cell transplantation

Effie W. Petersdorf,



grades III to IV acute GVHD

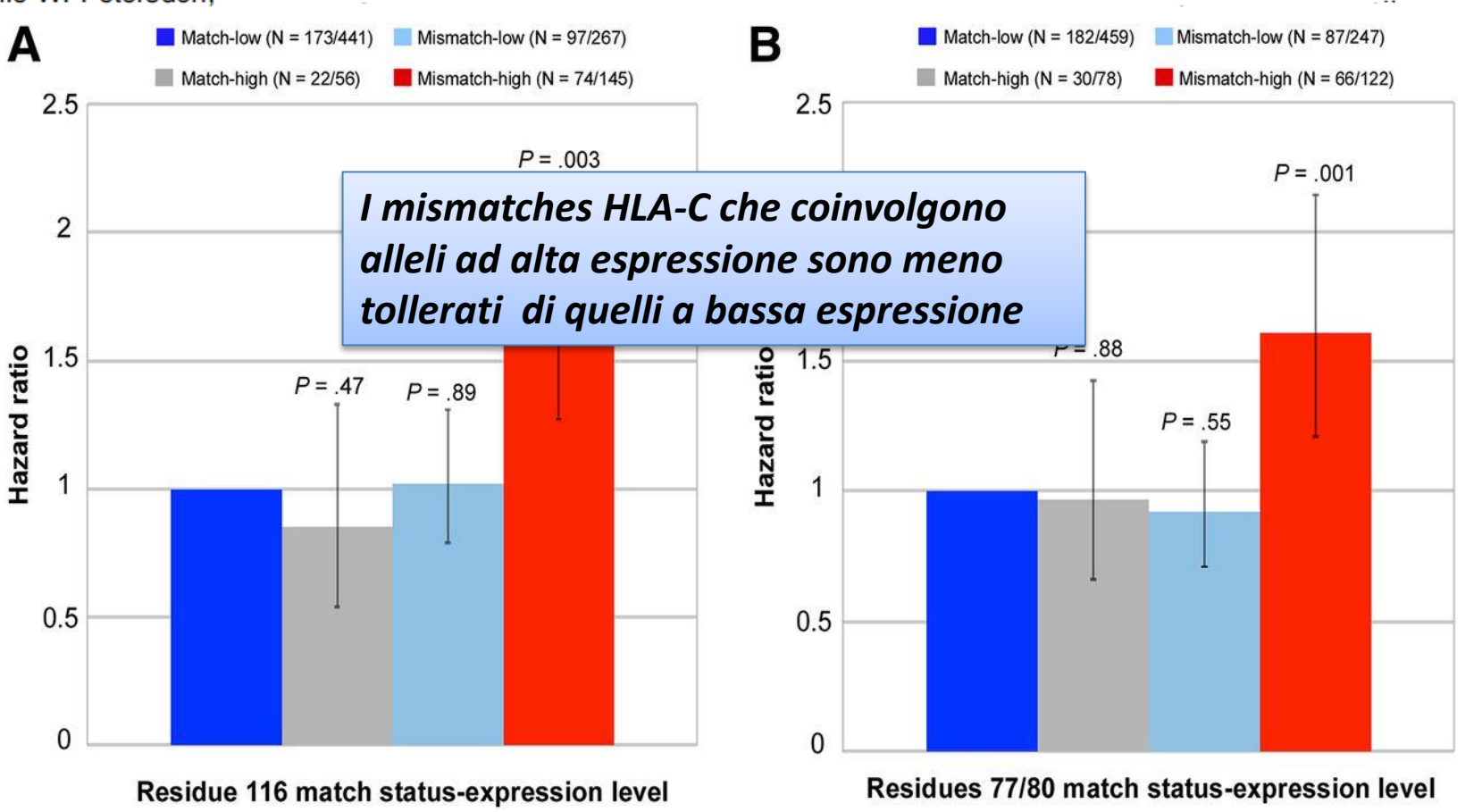
nonrelapse mortality

BLOOD, 18 DECEMBER 2014 x VOLUME 124, NUMBER 26

TRANSPLANTATION

HLA-C expression levels define permissible mismatches in hematopoietic cell transplantation

Effie W. Petersdorf,



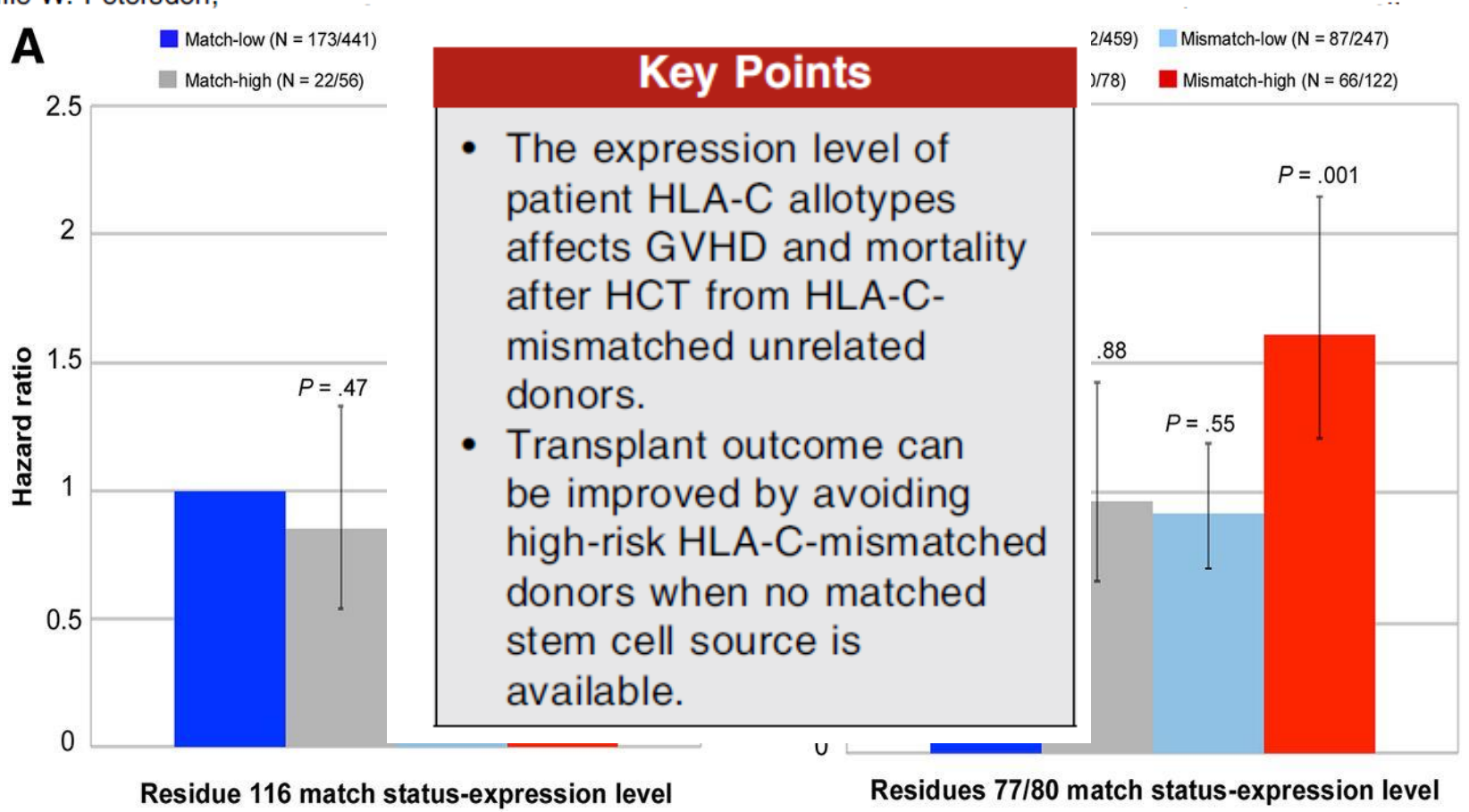
I mismatches HLA-C che coinvolgono alleli ad alta espressione sono meno tollerati di quelli a bassa espressione

BLOOD, 18 DECEMBER 2014 x VOLUME 124, NUMBER 26

TRANSPLANTATION

HLA-C expression levels define permissible mismatches in hematopoietic cell transplantation

Effie W. Petersdorf,



Key Points

- The expression level of patient HLA-C allotypes affects GVHD and mortality after HCT from HLA-C-mismatched unrelated donors.
- Transplant outcome can be improved by avoiding high-risk HLA-C-mismatched donors when no matched stem cell source is available.

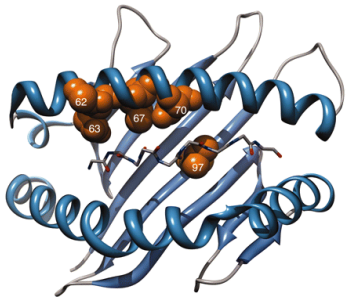
Conclusioni

Esiste una grande complessità nell'analisi della compatibilità tra donatore e ricevente

DIFFERENZE STRUTTURALI

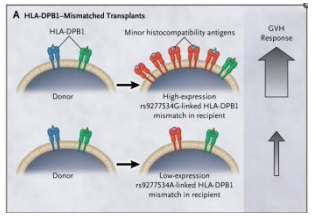
AA

- **numero**
- **posizione**
- **natura**



ASPETTI FUNZIONALI :

LIVELLO DI ESPRESSIONE DELLE PROTEINE



Conclusioni

Esiste una grande complessità nell'analisi della compatibilità tra donatore e ricevente

Si cominciano ad avere nuove indicazioni su quali mismatches dovrebbero essere evitati quando l'HSCT da MUD non completamente compatibile è l'unica possibilità terapeutica e quindi dei criteri di selezione del donatore da trasferire ai clinici

Conclusioni

- ✓Ridurre al minimo il numero totale delle disparità
- ✓Evitare i mismatches per residui amino-acidici chiave
- ✓Evitare mismatches per alleli HLA-C o DPB1 ad alta espressione

GRAZIE PER L'ATTENZIONE!