New trends in donor selection in Europe: "best match" versus haploidentical

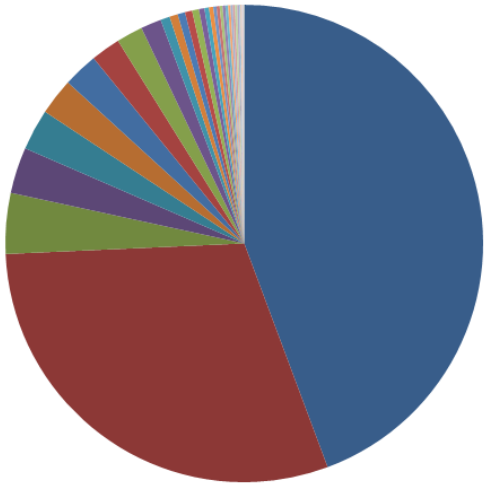
Prof Jakob R Passweg

UNI BASEL

Universitätsspital Basel

SWISS FOUNDATION
Blood stem cells

agence de la biomédecine



USA, Germany, Israel, UK, Japan, Italy, Taiwan, Canada, Portugal, France, Spain, Thailand, Hong Kong, South Africa, Austria, Belgium, Sweden, Netherlands, Poland, Norway, Turkey, Switzerland, Denmark, Greece, Ireland, Czechia, Finland, Croatia, Russia, Slovenia, Mexico, Hungary, Lithuania, India

The ANTHONY NOLAN Trust
Taking back lives from leukaemia

"We search the world to find your perfect match"

MEM' PAS MAL !

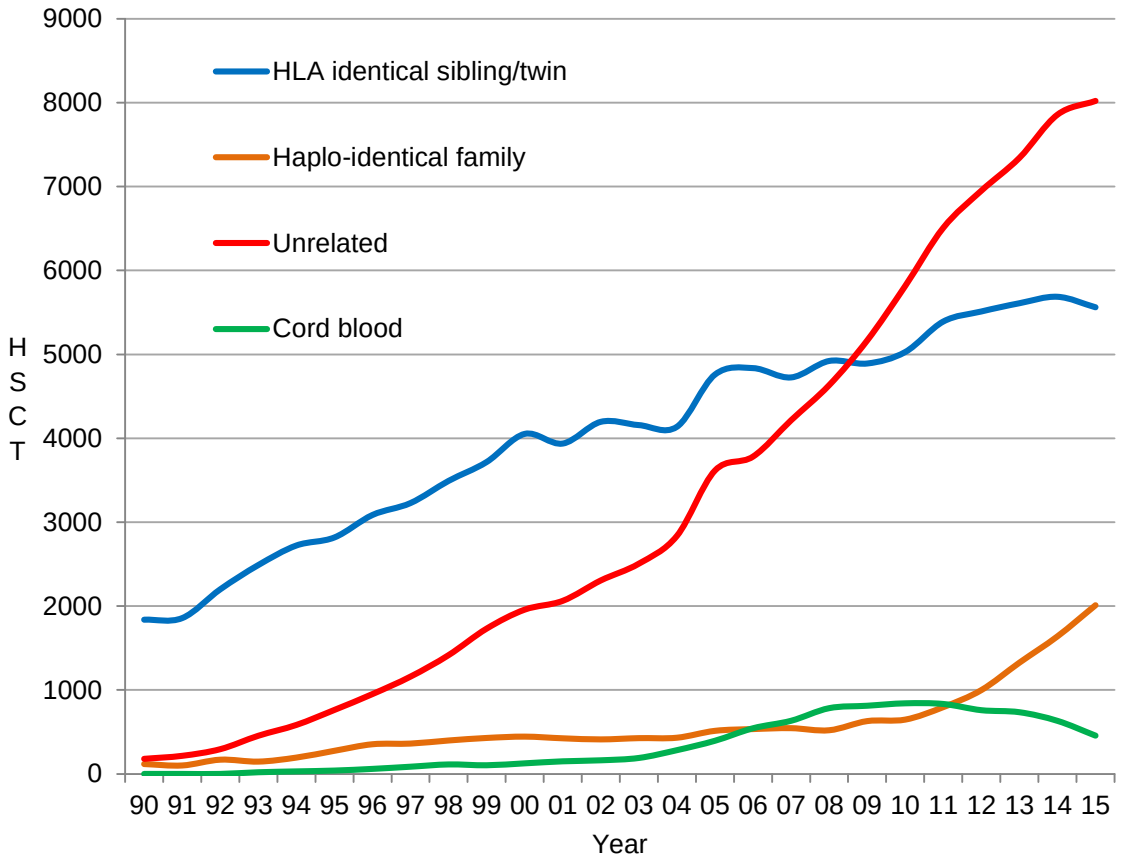
DKMS

Zentrales Knochenmarkspender-Register Deutschland

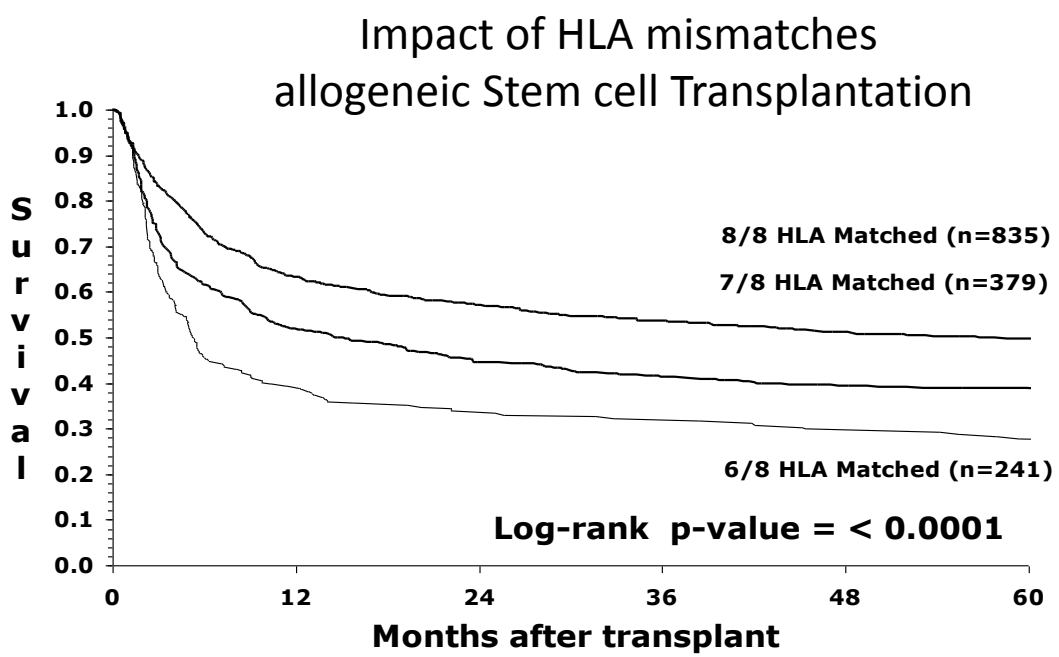
Saudi Stem Cells Donor Registry

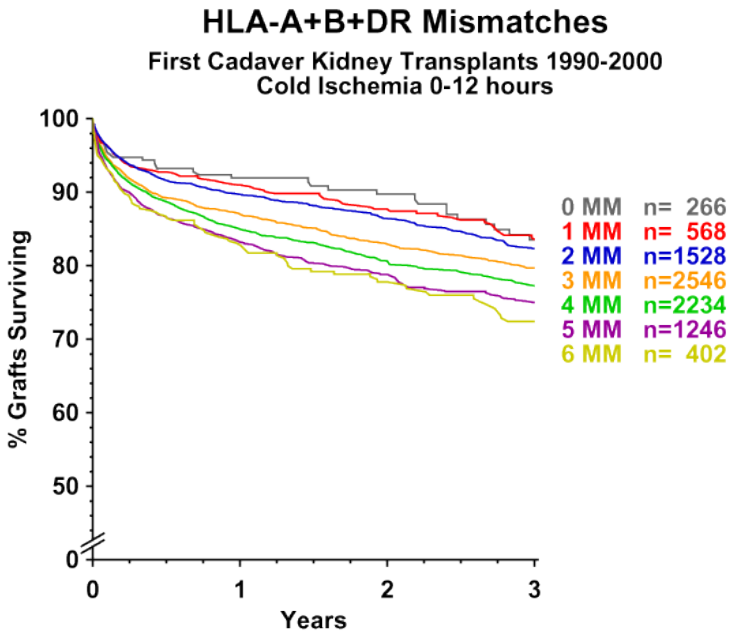
JEDER EINZELNE ZÄHLT

HSCT – change in donor type: 1990-2015



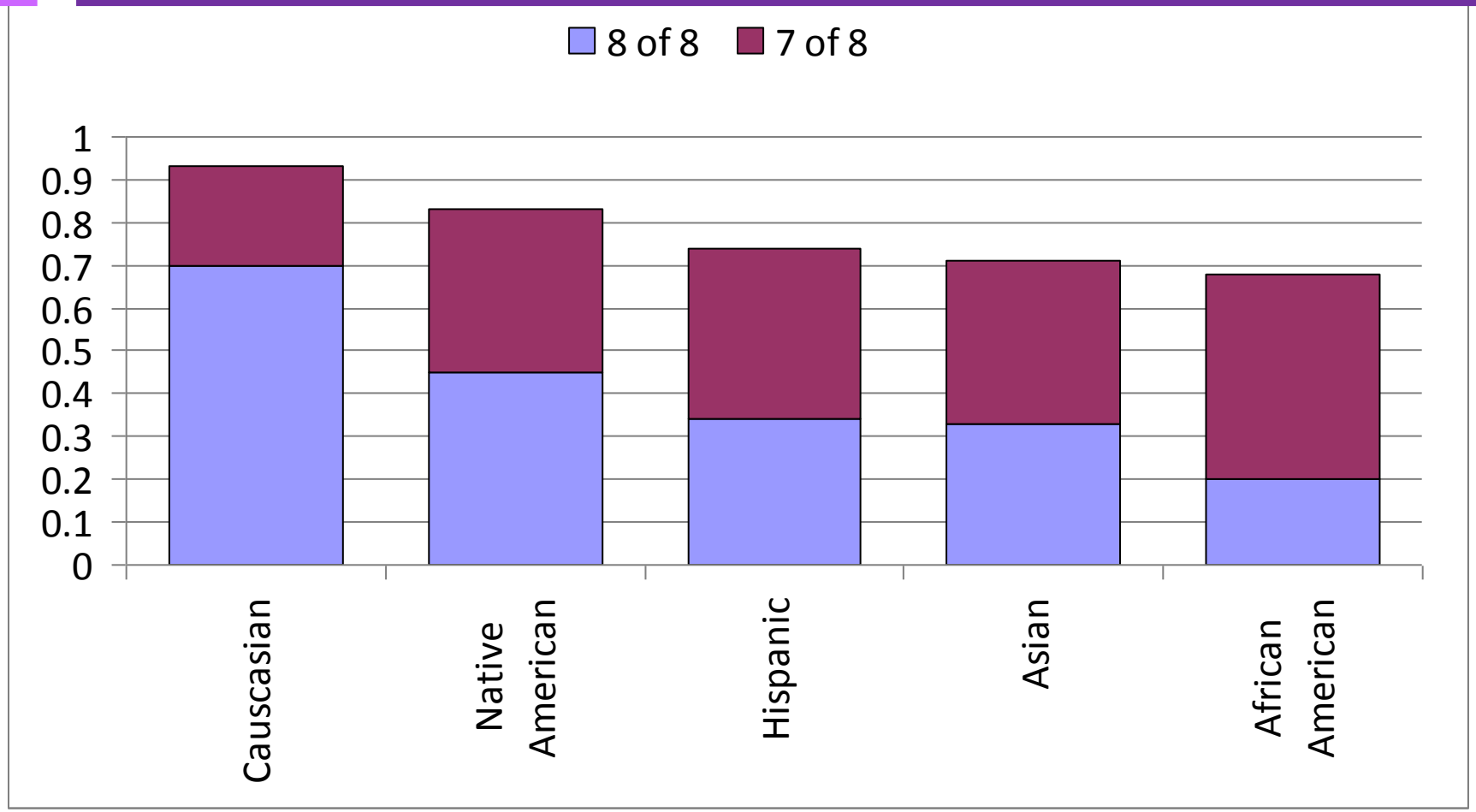
Einfluss HLA match



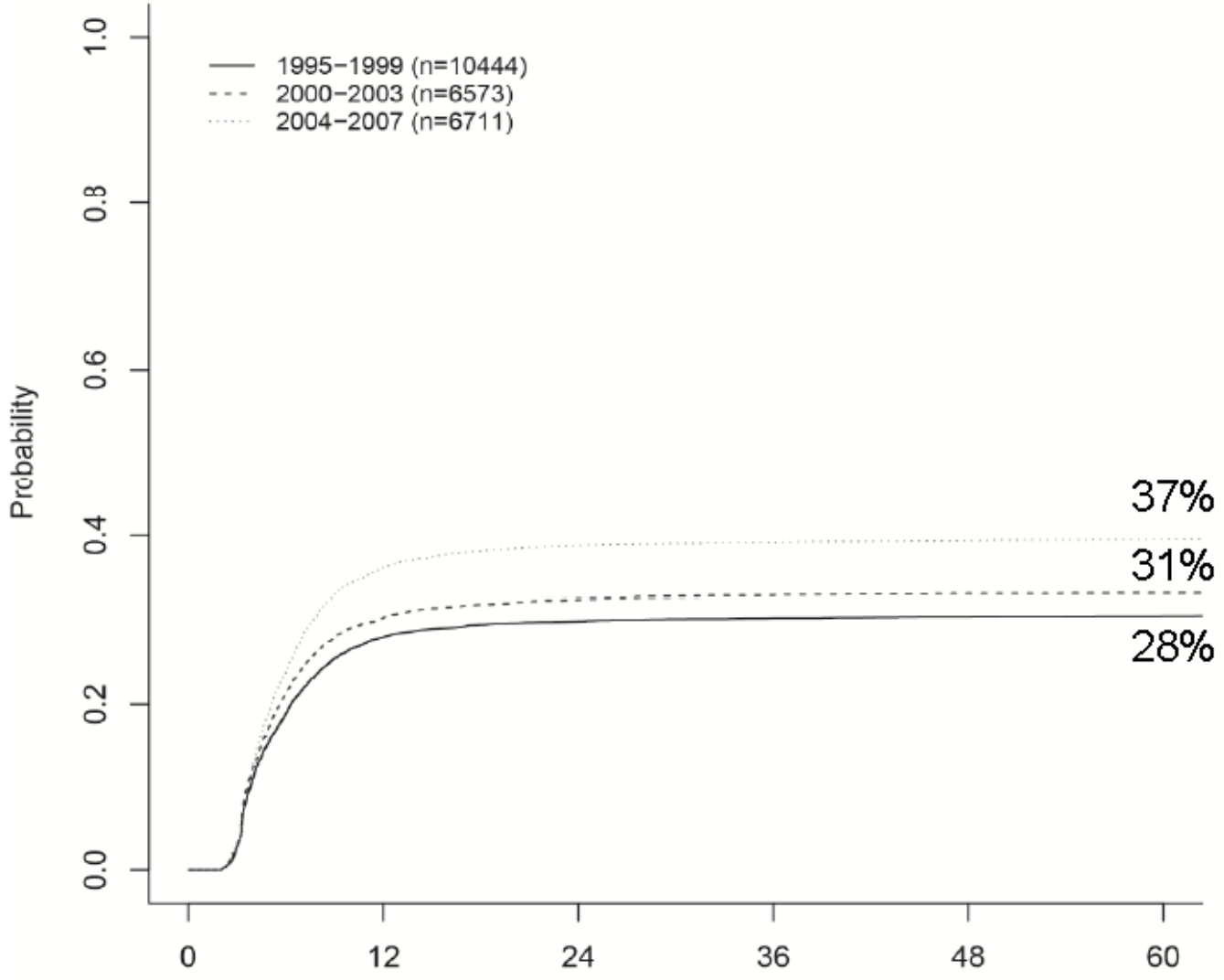


Lee et al	BLood 2007
Pedersdorf et al	PLOS Med 2007
Takakau et al	Blood 2007
Shaw et al	Blood 2008

7/8 and 8/8 Allele, Available-Match Rates in the Adult Donor Registry

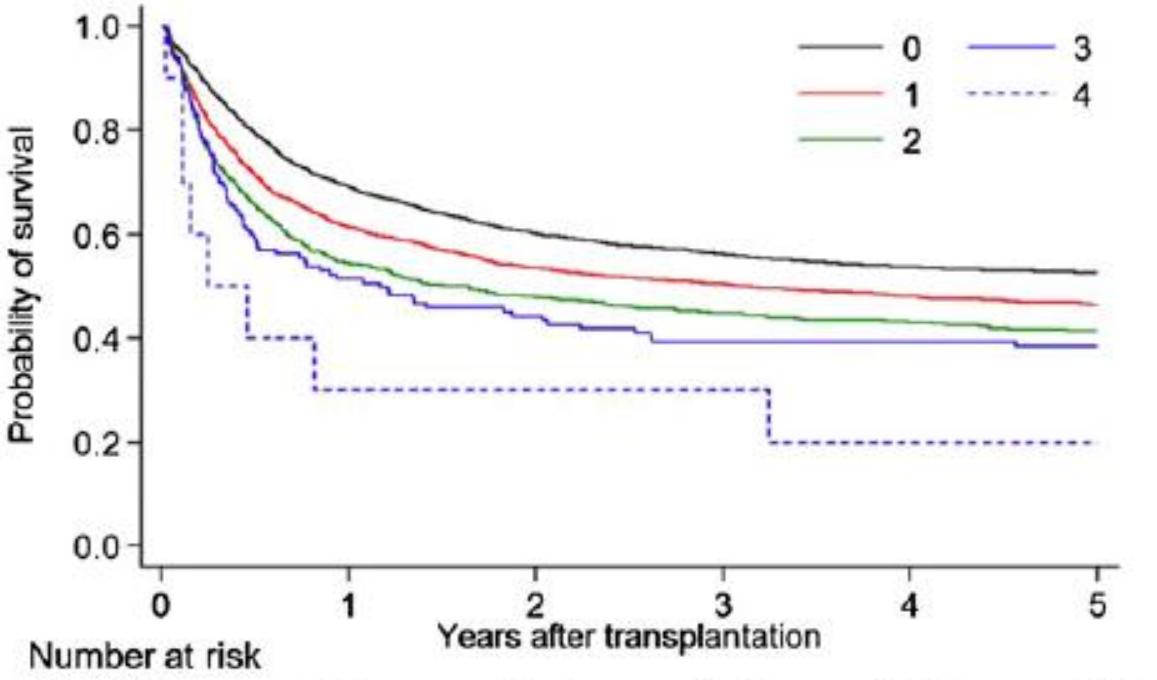


The problem is not going away



Arai S et al. BBMT 2015(2):266-74

number of mismatches at HLA-A, B, C, DRB1/DQB1
Effects cumulate



Number at risk

0	4076	2621	2038	1688	1431	1256
1	2352	1335	1046	878	736	623
2	850	443	359	309	268	218
3	130	65	54	47	46	41
4	10	3	3	3	2	2

Morishima et al. Blood 2015; 125: 1189

HLA-A,B,C,DRB1 mismatches are all relevant

The German multicenter study (2646 patients, 1997-2010)

Locus	n	HR	95% CI	*P*
OS				
Complete match	1511	1.00		
HLA-A MM	282	1.43	1.19-1.72	<.001
HLA-B MM	283	1.52	1.20-1.93	<.001
HLA-C MM	620	1.35	1.17-1.56	<.001
HLA-DRB1 MM	126	1.42	1.10-1.82	.006
HLA-DQB1 MM	191	1.23	1.00-1.51	.050

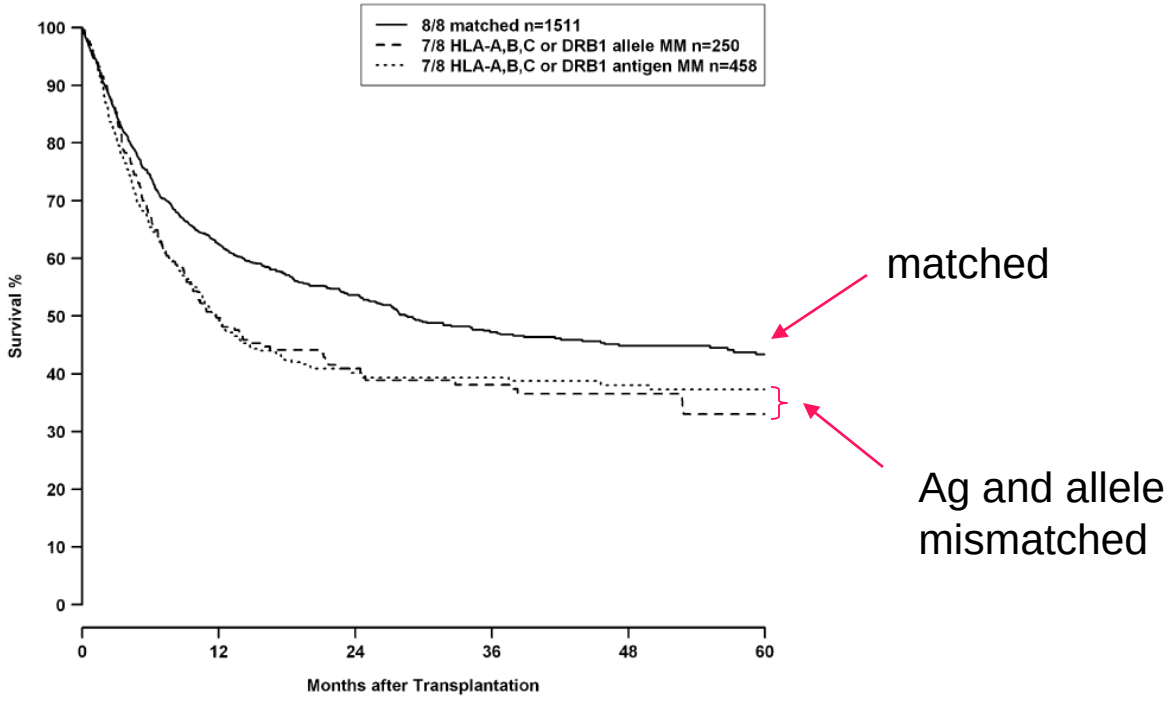
Any single mismatch at HLA-A,B,C or DRB1 loci confers a higher mortality risk

Fürst et al. Blood 2013; 122: 3220

Antigen versus allele (2 vs 4digit) mismatches

Single antigen or allele mismatches at HLA-A,B,C,DRB1 confer the same mortality risk

HLA A 0201 vs 0205
HLA A 0201 vs 0301



Fürst et al. Blood 2013; 122: 3220

in 7/8 transplants: avoid >2 mismatches at the DRB3/4/5, DQ, DP loci

980 patients

LEL

Low Expression Loci

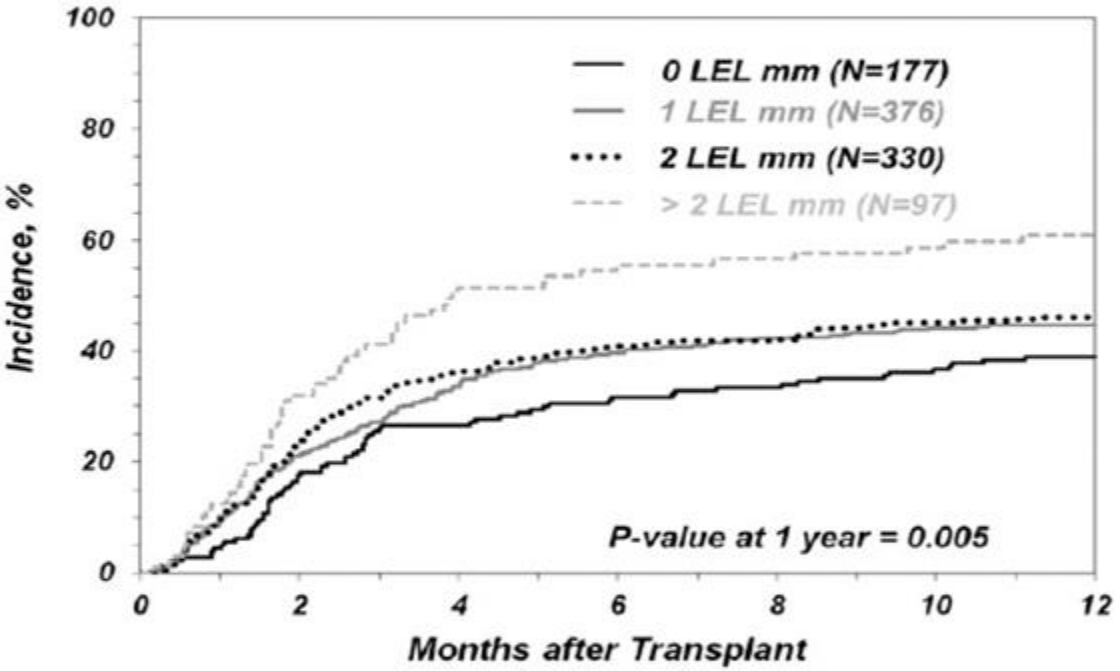


Figure 2. Incidence of TRM as a function of degree of mismatching at HLA-DRB3/4/5, DQ and DP (LEL) loci in transplants matched in 7/8 alleles of HLA HLA-A, -B, -C, and -DRB1 loci.

Fernandez-Vina et al. Blood 2013; 121: 4603-4610

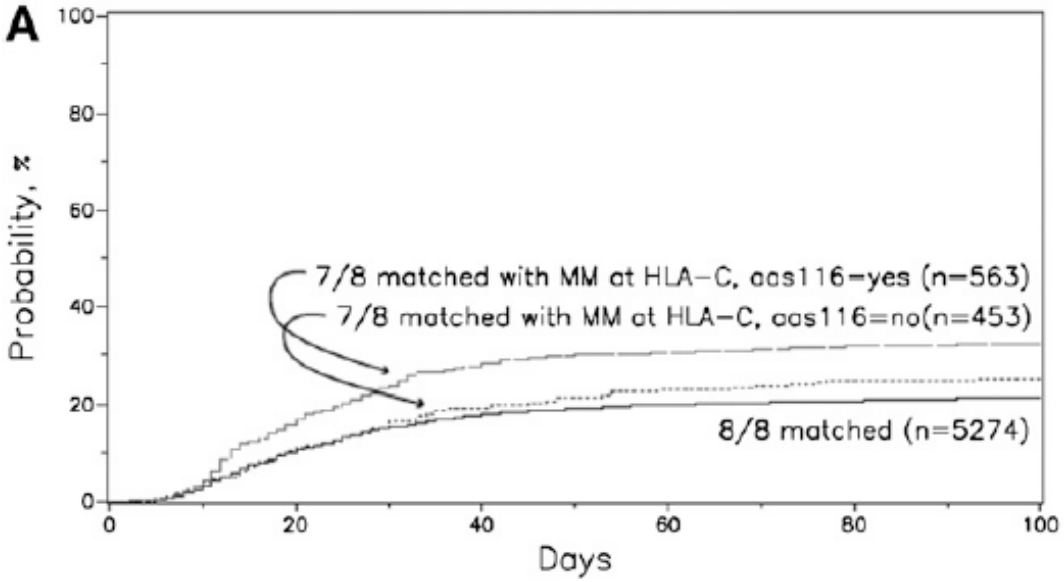
TRANSPLANTATION

(*Blood*. 2013;122(22):3651-3658)

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]

GVHD III-IV

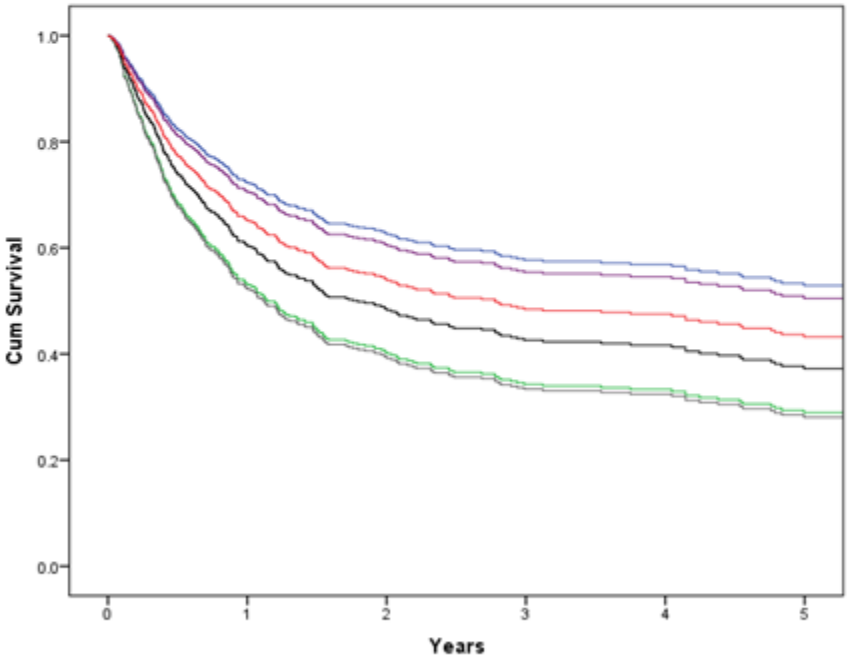


avoid HLA-C MM with aa substitution 116 or 99
avoid HLA-B MM with aa substitution 9

Not all mismatches Are EQUAL

less immunogenic HLA class II mismatches

→ Prospective selection of particular DRB1/DQB1 MM
802 patients (2000-2013), SBST study
10/10 (n=570), 9/10 (n=261), DRB3/4 MM (n=31), 8/10 (n=13)



Passweg et al. BMT 2015, in press

10/10
1 MM DR/DQ → *frequent MM: DRB1*11:01/11:04 DQB1*03:01/03:02*

2 MM

1 MM DRB3/4

1 MM
A,B,C

The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy

Craig Kollman,[1] Stephen R. Spellman,[2] Mei-Jie Zhang,[3,4] Anna Hassebroek,[2] Claudio Anasetti,[5] Joseph H. Antin,[6] Richard E. Champlin,[7] Dennis L. Confer,[2] John F. DiPersio,[8] Marcelo Fernandez-Viña,[9] Robert J. Hartzman,[10] Mary M. Horowitz,[3] Carolyn K. Hurley,[11] Chatchada Karanes,[12] Martin Maiers,[13] Carlheinz R. Mueller,[14] Miguel-Angel Perales,[15] Michelle Setterholm,[13] Ann E. Woolfrey,[16] Neng Yu,[17] and Mary Eapen[3,18]

(*Blood*. 2016;127(2):260-267)

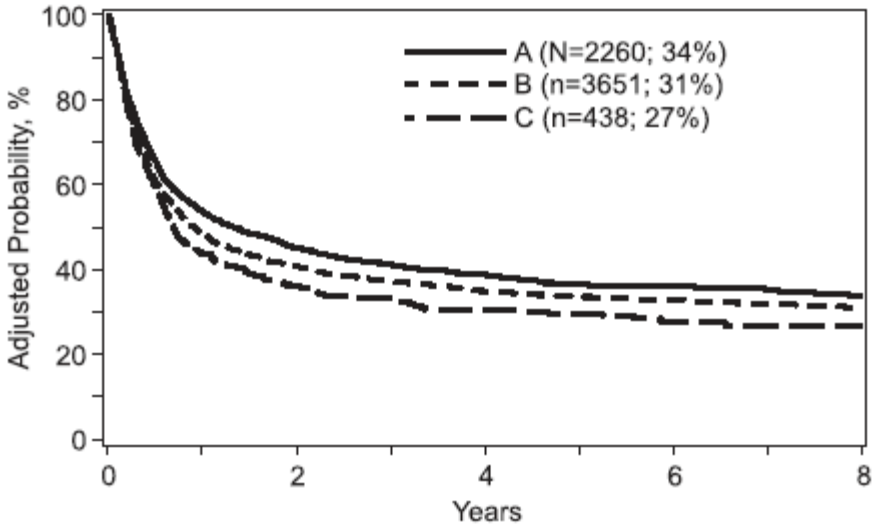
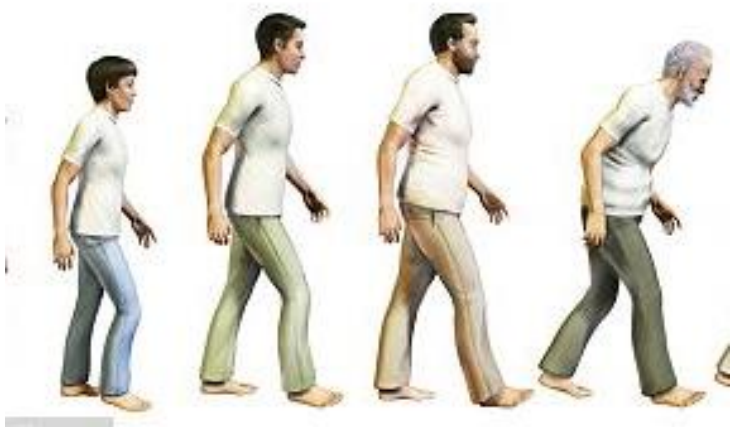


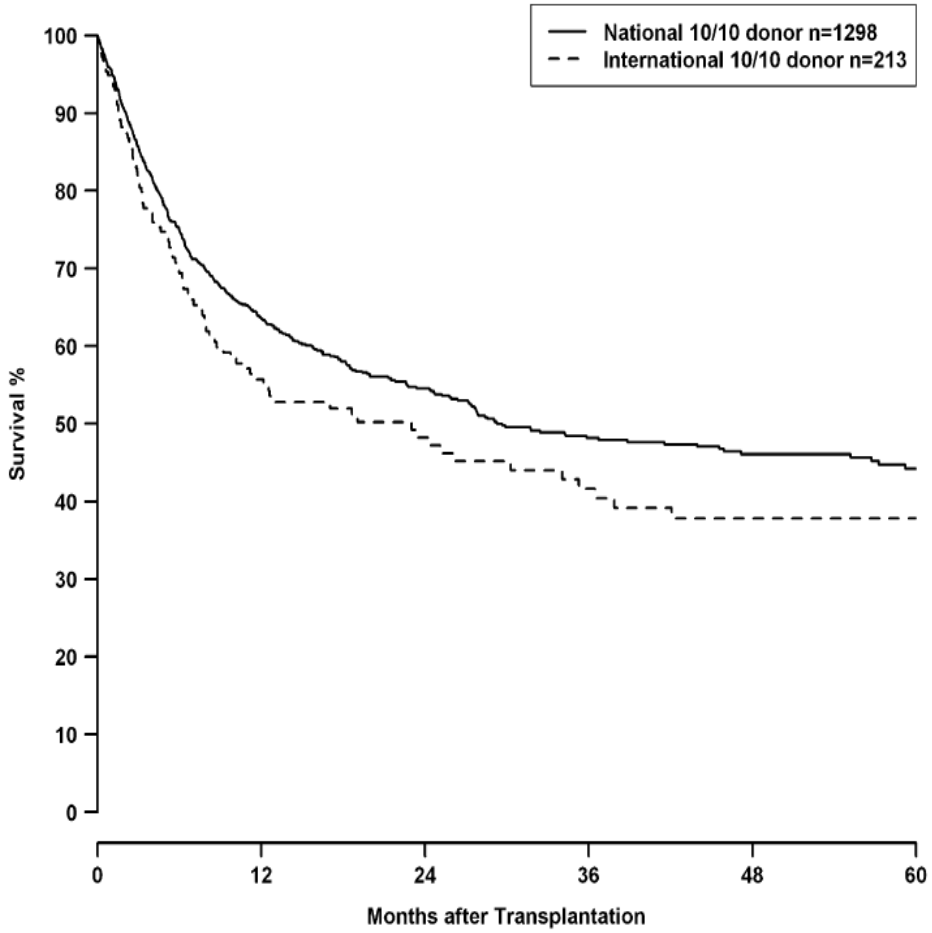
Table 5. Donor characteristics associated with survival for transplantation period 2007 to 2011

Outcome	HR (95% CI)	*P* value
Overall survival*		
Donor age (10-year increments)	1.055 (1.013-1.099)	.01
Donor-recipient HLA-match		
8/8 HLA-match	1.00	
7/8 HLA-match	1.37 (1.25-1.51)	<.001



10,462 8/8 HLA- Matched Unrelated Donor HLA-DQB1, HLA-DPB1 T-cell epitope matching)

HSCT with national donors do better than with international donors (lower proportion of patients with rare HLA phenotypes)



Fürst et al. Blood 2013; 122: 3220

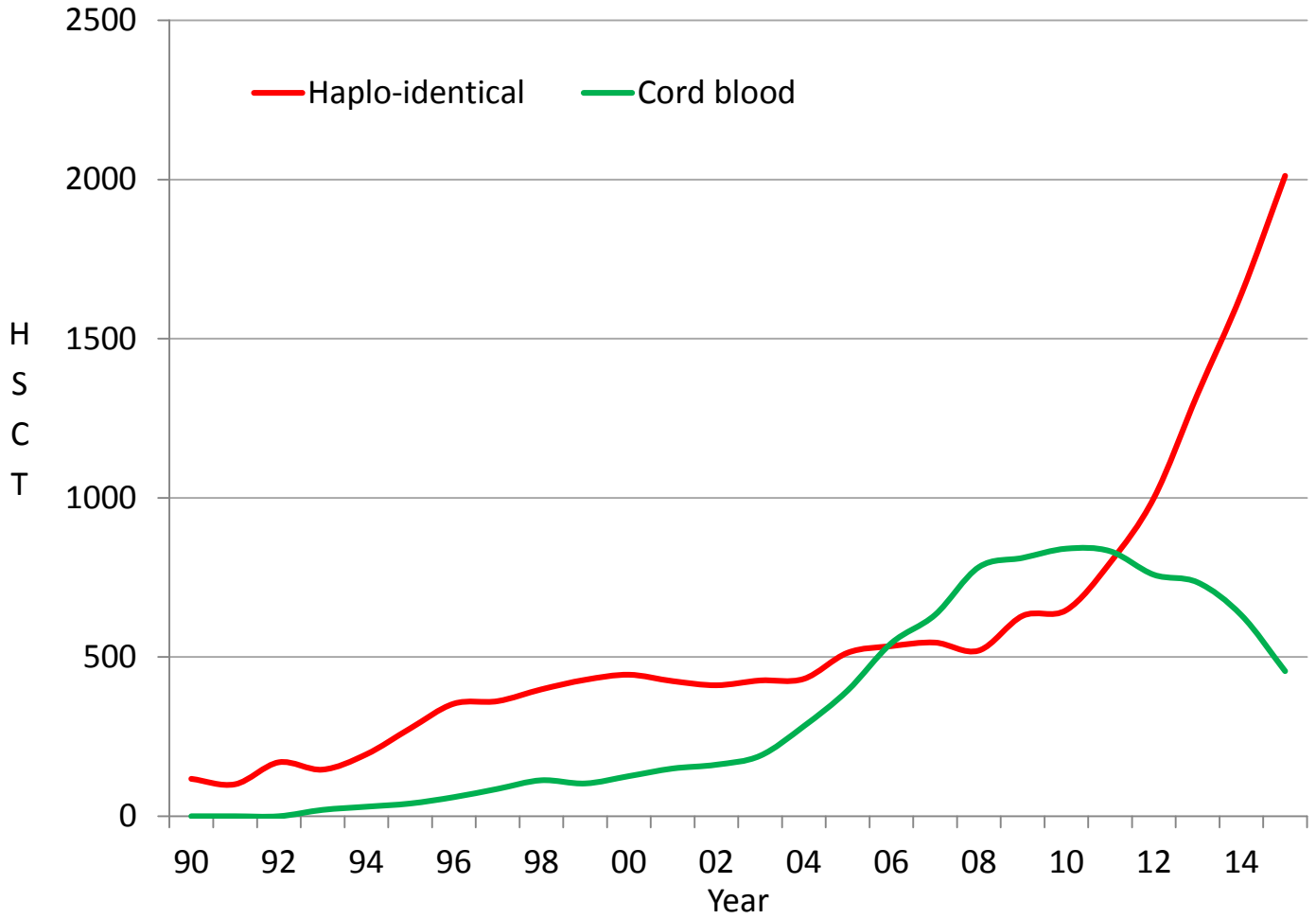
Fürst et al. Blood; 2013, 122: 3220

Progress?

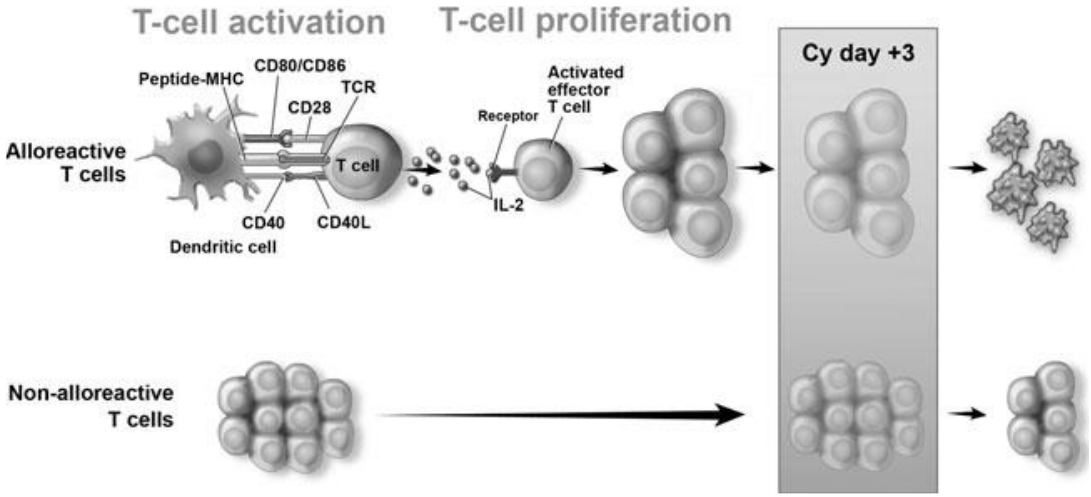
- Haplotype matching?
- NK alloreactivity, activating KIR gene content?
- Matching low expression loci?
- Low expression loci expression regulation?
- T-cell epitope matching algorithms?
- Permissive mismatching e.g. HLA-C 0303 vs 0304?

Statistical Model Fitting = Overfitting

HSCT Activity in Europe 1990-2015: change in donor type

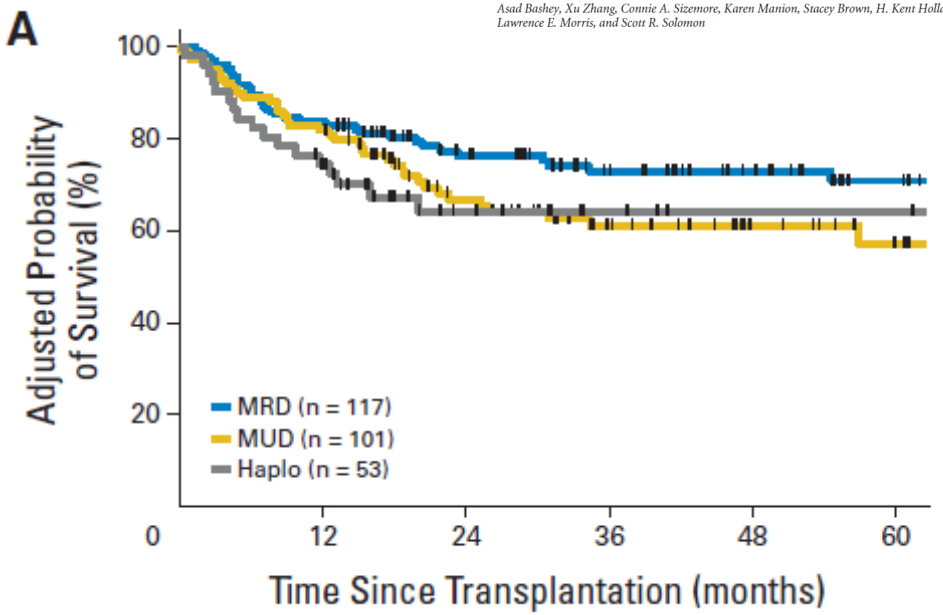


Choice of haploidentical Donors



T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

Asad Bashey, Xu Zhang, Connie A. Sizemore, Karen Manion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon



Results confirmed by many groups?

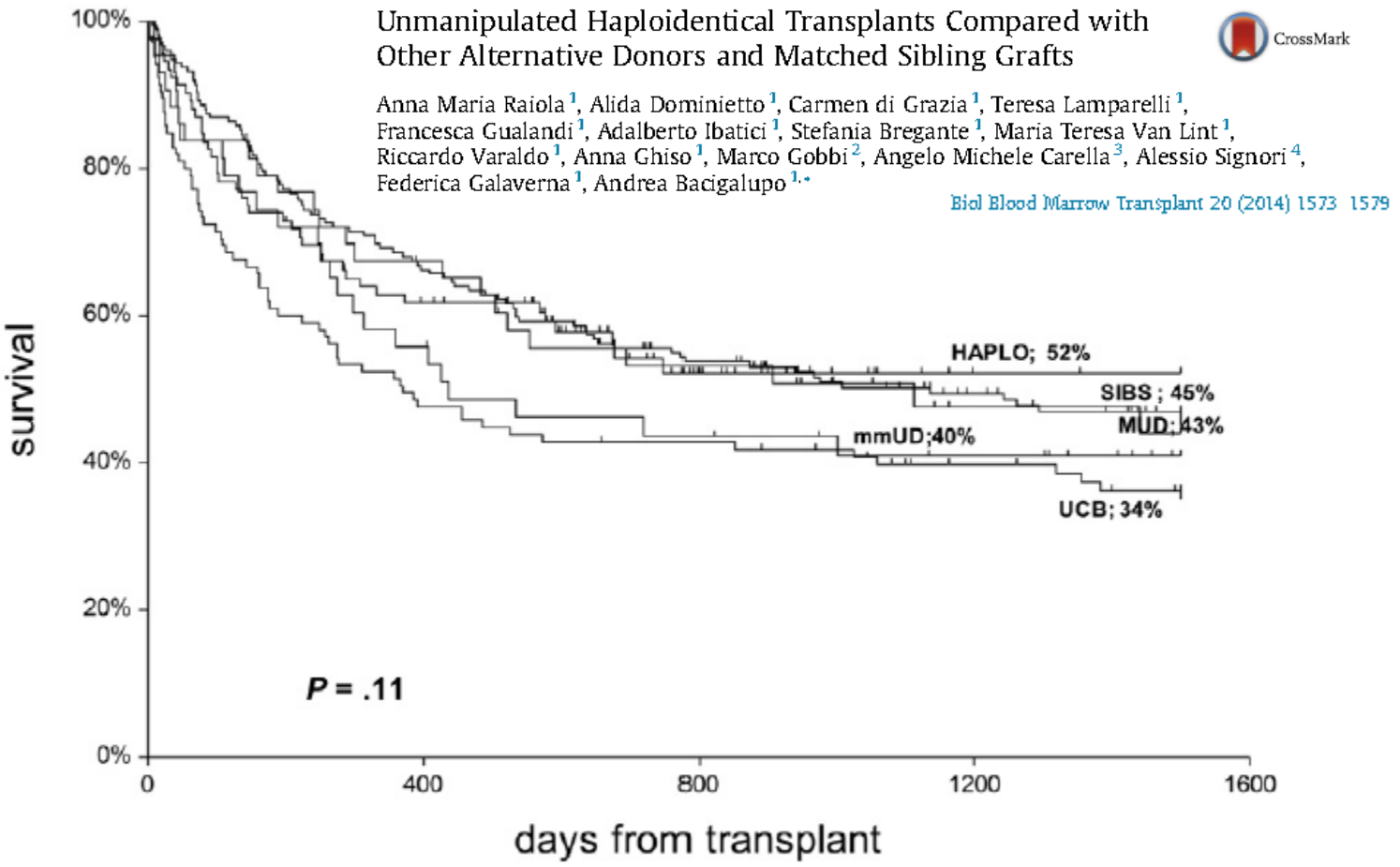
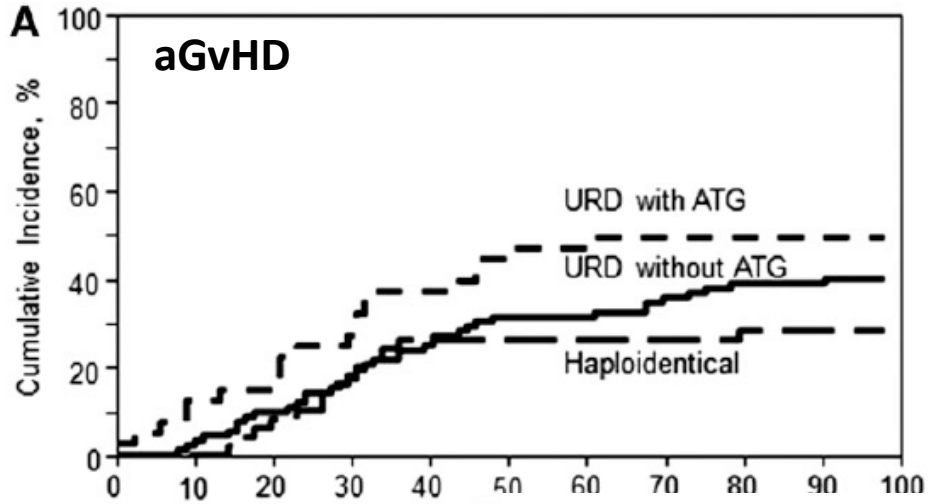


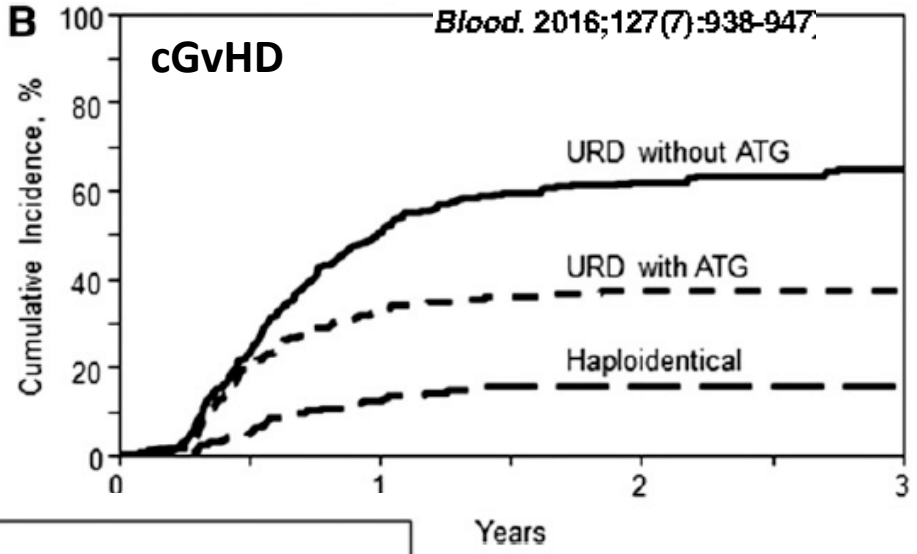
Figure 4. Actuarial survival of patients stratified for donor type. Overall there is no statistically significant difference in survival.

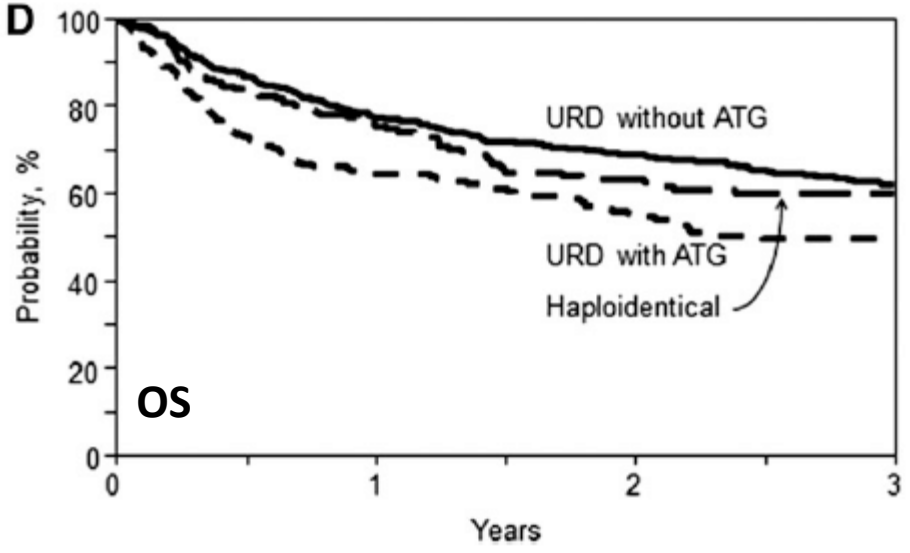
Reduced-intensity transplantation for lymphomas using haploidentical related donors vs HLA-matched unrelated donors

Abraham S. Kanate,[1,*] Alberto Mussetti,[2,*] Mohamed A. Kharfan-Dabaja,[3,*] Kwang W. Ahn,[4,5] Alyssa DiGilio,[4] Amer Beitinjaneh,[6] Saurabh Chhabra,[7] Timothy S. Fenske,[8] Cesar Freytes,[9] Robert Peter Gale,[10] Siddhartha Ganguly,[11] Mark Hertzberg,[12] Evgeny Klyuchnikov,[13] Hillard M. Lazarus,[14] Richard Olsson,[15,16] Miguel-Angel Perales,[17] Andrew Rezvani,[18] Marcie Riches,[19] Ayman Saad,[20] Shimon Slavin,[21] Sonali M. Smith,[22] Anna Sureda,[23] Jean Yared,[24] Stefan Ciurea,[25] Philippe Armand,[26] Rachel Salit,[27] Javier Bolaños-Meade,[28] and Mehdi Hamadani[4]

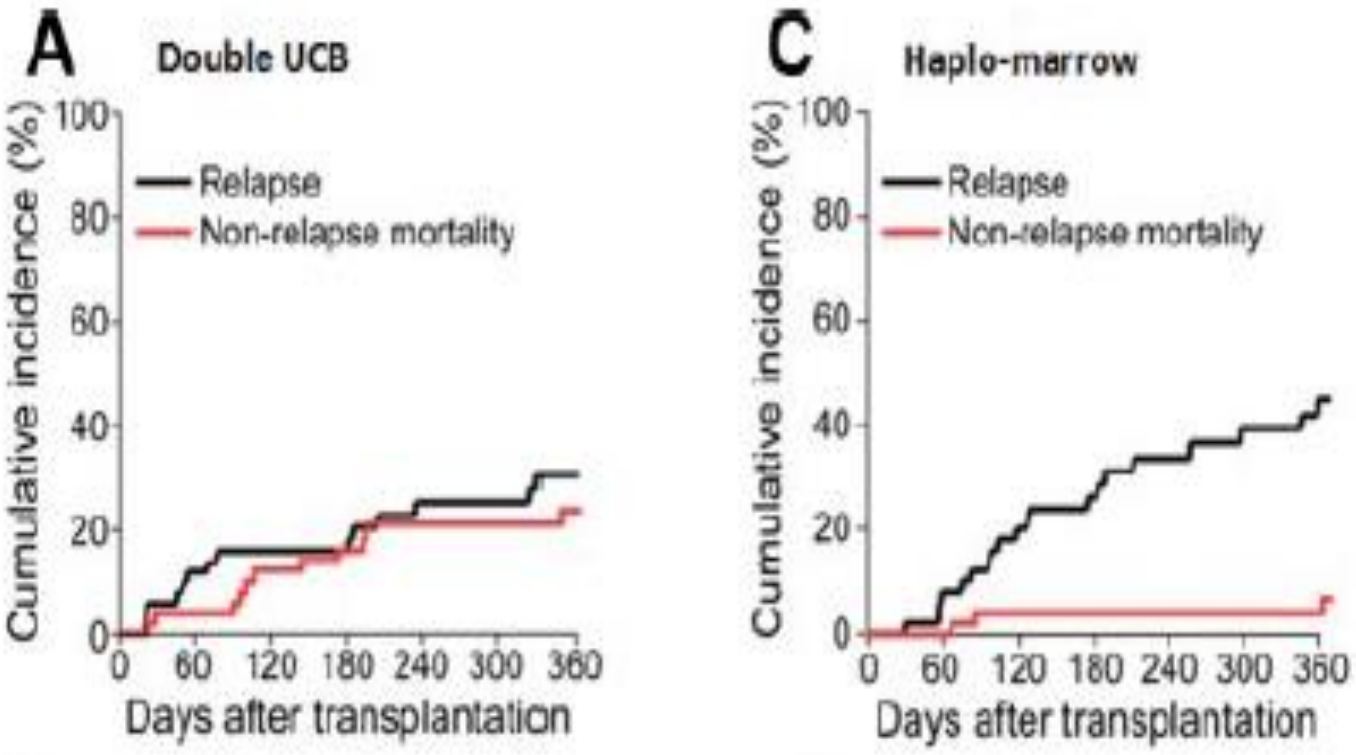
Blood. 2016;127(7):938-947



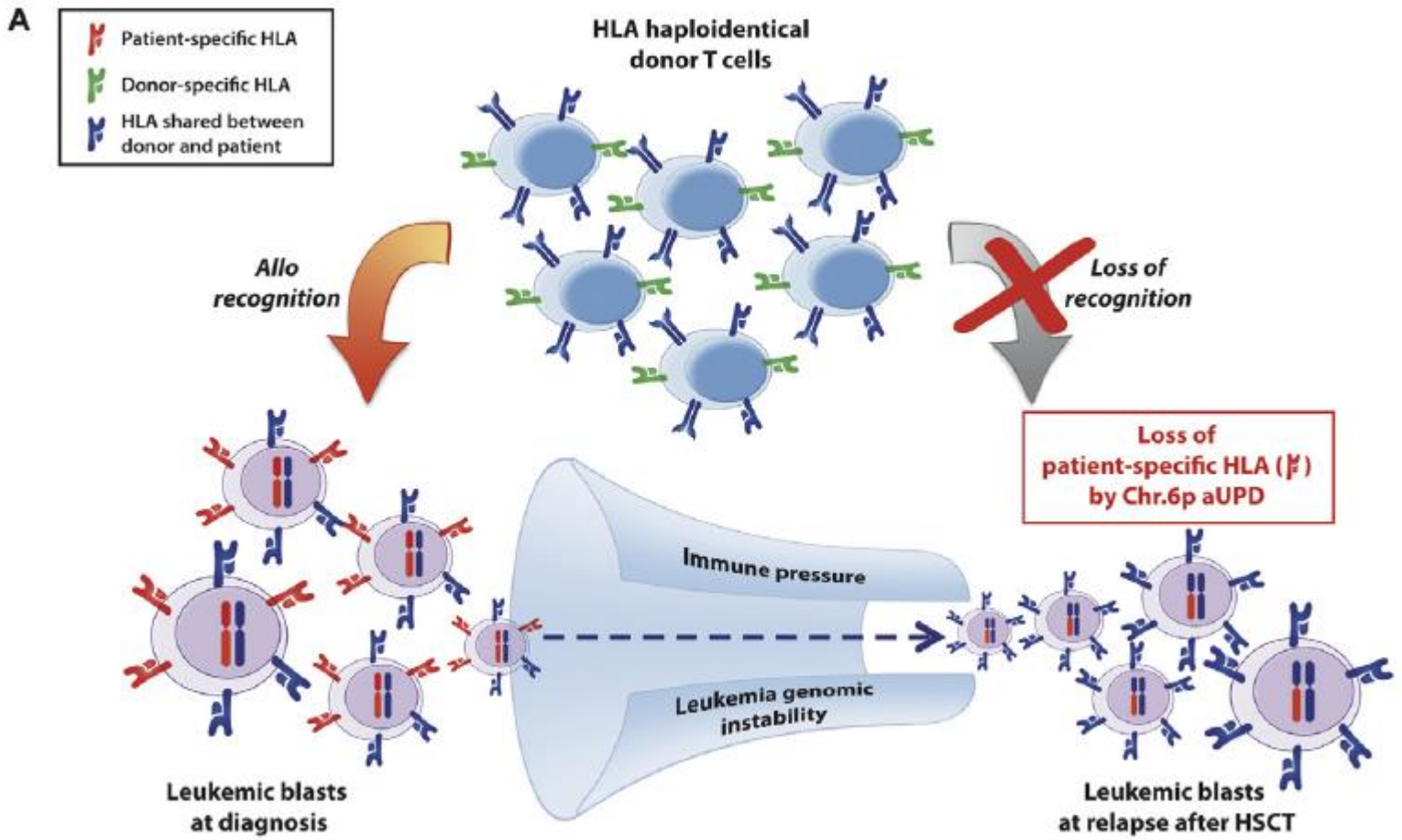




GvL in haploidentical HSCT



GvL in haploidentical HSCT

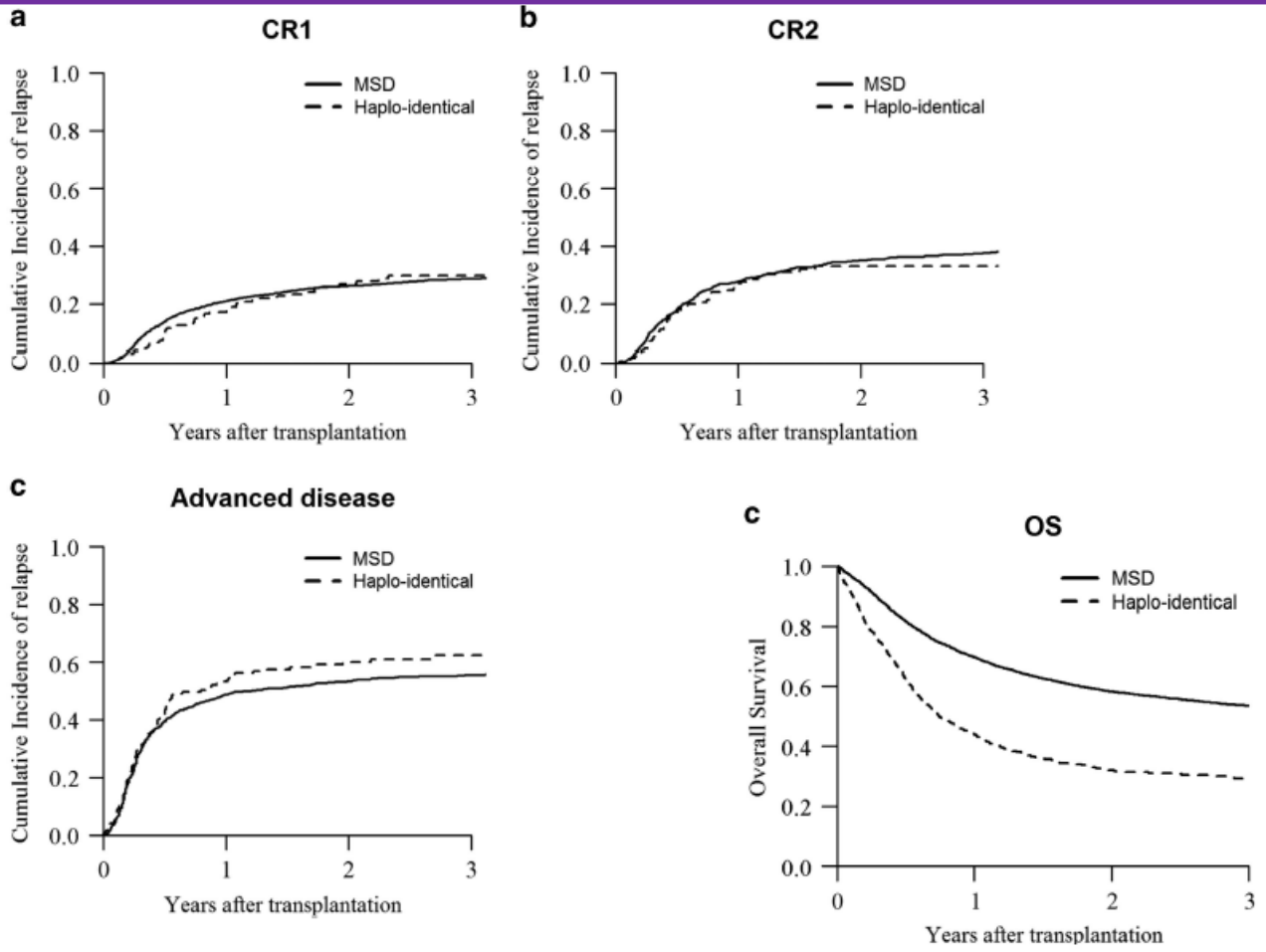


Is there a stronger graft-versus-leukemia effect using HLA-haploidentical donors compared with HLA-identical siblings?

O Ringdén[1], M Labopin[2], F Ciceri[3], A Velardi[4], A Bacigalupo[5], W Arcese[6], A Ghavamzadeh[7], RM Hamladji[8], C Schmid[9], A Nagler[2,10,11] and M Mohty[2,11] for the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

Leukemia (2016) **30,** 447–455;

Relapse Incidence



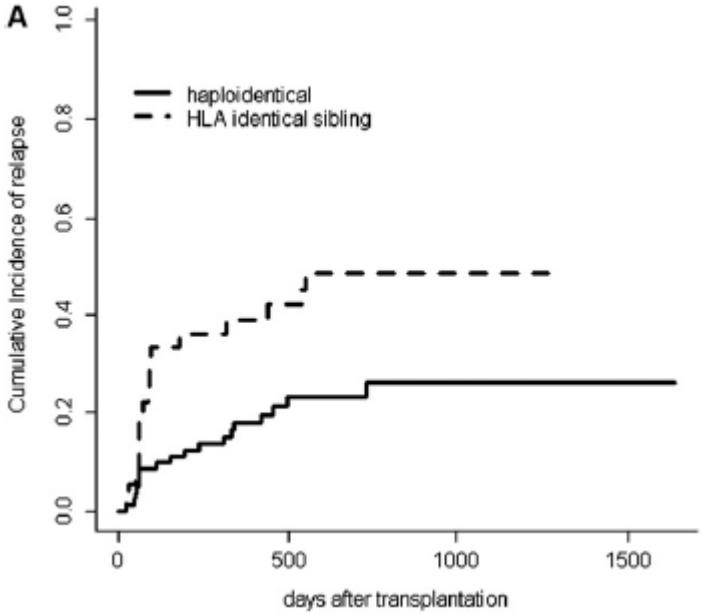
Superior Graft-versus-Leukemia Effect Associated with Transplantation of Haploidentical Compared with HLA-Identical Sibling Donor Grafts for High-Risk Acute Leukemia: An Historic Comparison

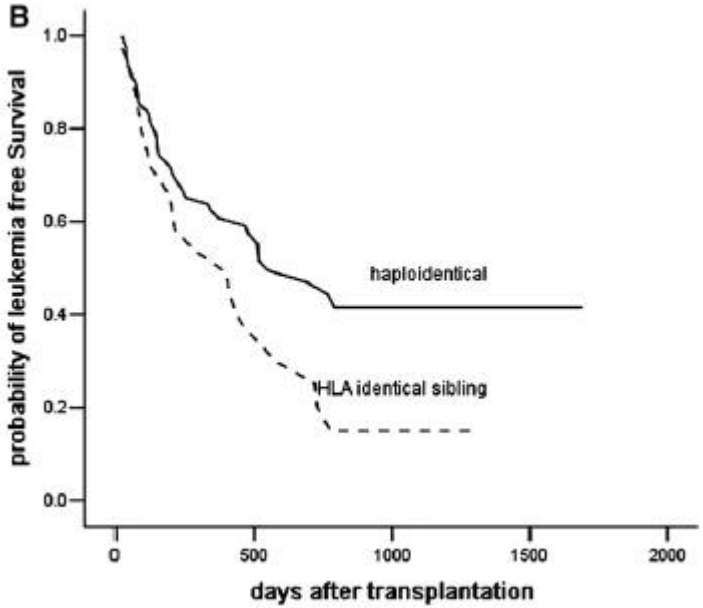
Yu Wang, Dai-Hong Liu, Lan-Ping Xu, Kai-Yan Liu, Huan Chen, Yu-Hong Chen, Wei Han, Hong-Xia Shi, Xiao-Jun Huang

Biol Blood Marrow Transplant 17: 821-830 (2011)

BuCy2
+ ATG in HID

PB + BM in most





Conclusion

- Unrelated donor transplantation -> success story
- Haploidentical HCT without T-cell depletion -> success story

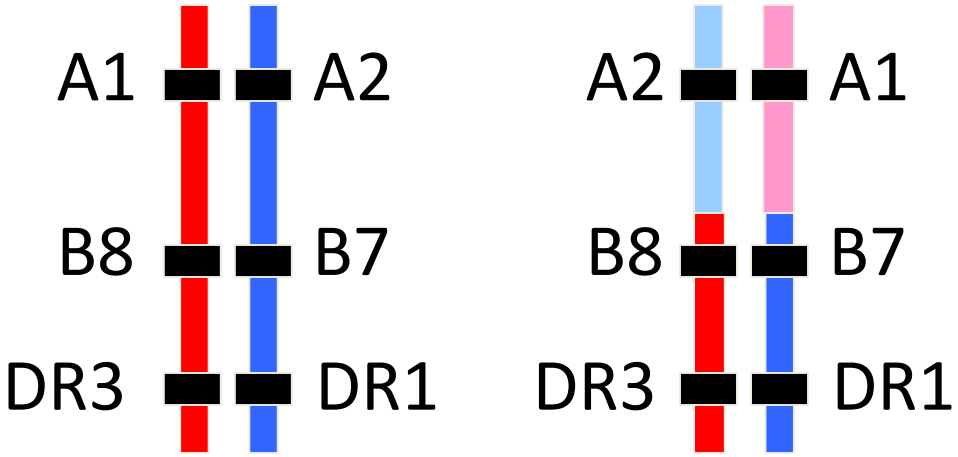
- Progress in MUD, better matching in low risk disease, more GvL in hi risk disease?
- Progress in Haplo, maintain low TRM risks while improving GvL

HLA haplotype matching

Petersdorf et al. PLOS Med 2007; 4: 59-67

Increased risk of GVHD in haplotype-mismatched unrelated HSCT (OR=4.5, p<0.0001)

Haplotypes that share the same HLA alleles may also share discrete segments or blocks of highly conserved sequences in strong positive linkage disequilibrium with those HLA alleles



Donor Selection Unrelated

- Match for A, B, C, DR
- Allele mismatch = antigen mismatch
- Single mismatches > multiple
- HLA DQB1 DRB3/4/5 more permissive
- Some permissive mismatches defined (C:0303 vs 0304)
- Haplotype matching? KIR typing? HLA-DP typing? T-cell epitope matching algorithms? Low expression loci expression regulation?

Characterization of “permissive” mismatches

- MM outside PBS (peptide binding site) or not seen by TCR (ex: A*02:01/2:09, C*03:03/03:04, DRB1*14:01/14:54, …)

  but indirect recognition ??

- MM associated with a negative *in vitro* functional *assay* (MLC, CTLp) (ex: DRB1*11:01/11:04, DQB1*03:01/03:02, …)
- avoid specific aa MM in PBS (aa 9, 99, 116)

Pasi et al. BMT 2011; 46: 916
Jöris et al. Transpl. Immunol. 2014; 30: 59
Fernandez-Vina et al. Blood 2013; 121: 4603
Pidala et al. Blood 2013; 122: 3651

DPB1 matching

HLA-DPB1 mismatches are detrimental

Petersdorf et al. BJH 2001
Loiseau et al. BMT 2002
Shaw et al. Blood 2007 (↗GVHD, no ↘OS)
Ludajic et al. BJH 2008
Crocchiolo et al. Blood 2009
Shaw et al. Leukemia 2010 (TCD, early disease, ↘OS)
Bettens et al. BBMT 2012
Pidala et al. Blood 2014

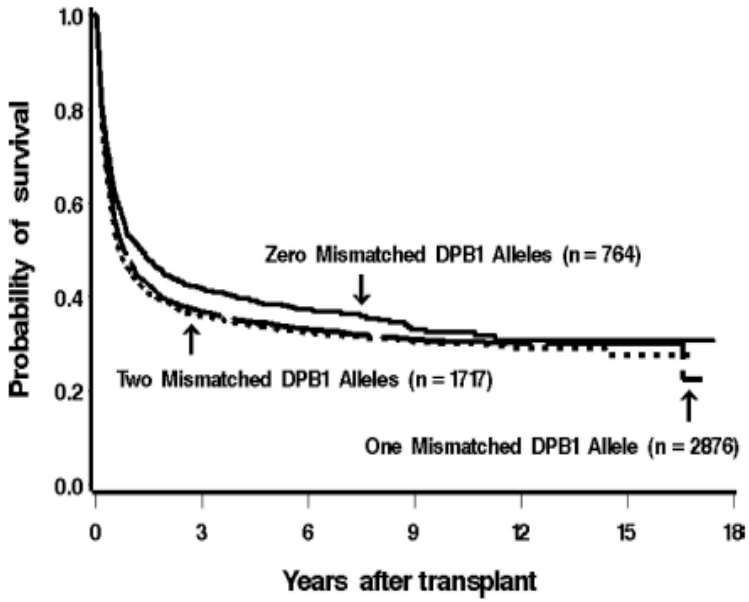
The importance of HLA-DPB1 in unrelated donor hematopoietic cell transplantation

Bronwen E. Shaw,[1,2] Theodore A. Gooley,[3] Mari Malkki,[3] J. Alejandro Madrigal,[1,4] Ann B. Begovich,[5] Mary M. Horowitz,[6] Alois Gratwohl,[7] Olle Ringdén,[8] Steven G. E. Marsh,[1,4] and Effie W. Petersdorf[3,9]

BLOOD, 15 DECEMBER 2007 • VOLUME 110, NUMBER 13

5929 patients (IHWG study)

DPB1 MM: aGVHD II-IV risk
OR = 1.33 (P<0.001)
no impact on OS



Diverging effects of HLA–DPB1 matching status on outcome following unrelated donor transplantation depending on disease stage and the degree of matching for other HLA alleles

BE Shaw[1,2], NP Mayor[1,3], NH Russell[4], JF Apperley[5], RE Clark[6], J Cornish[7], P Darbyshire[8], ME Ethell[2], JM Goldman[1,9], A-M Little[10], S Mackinnon[3], DI Marks[7], A Pagliuca[11], K Thomson[12], SGE Marsh[1,3] and JA Madrigal[1,3]

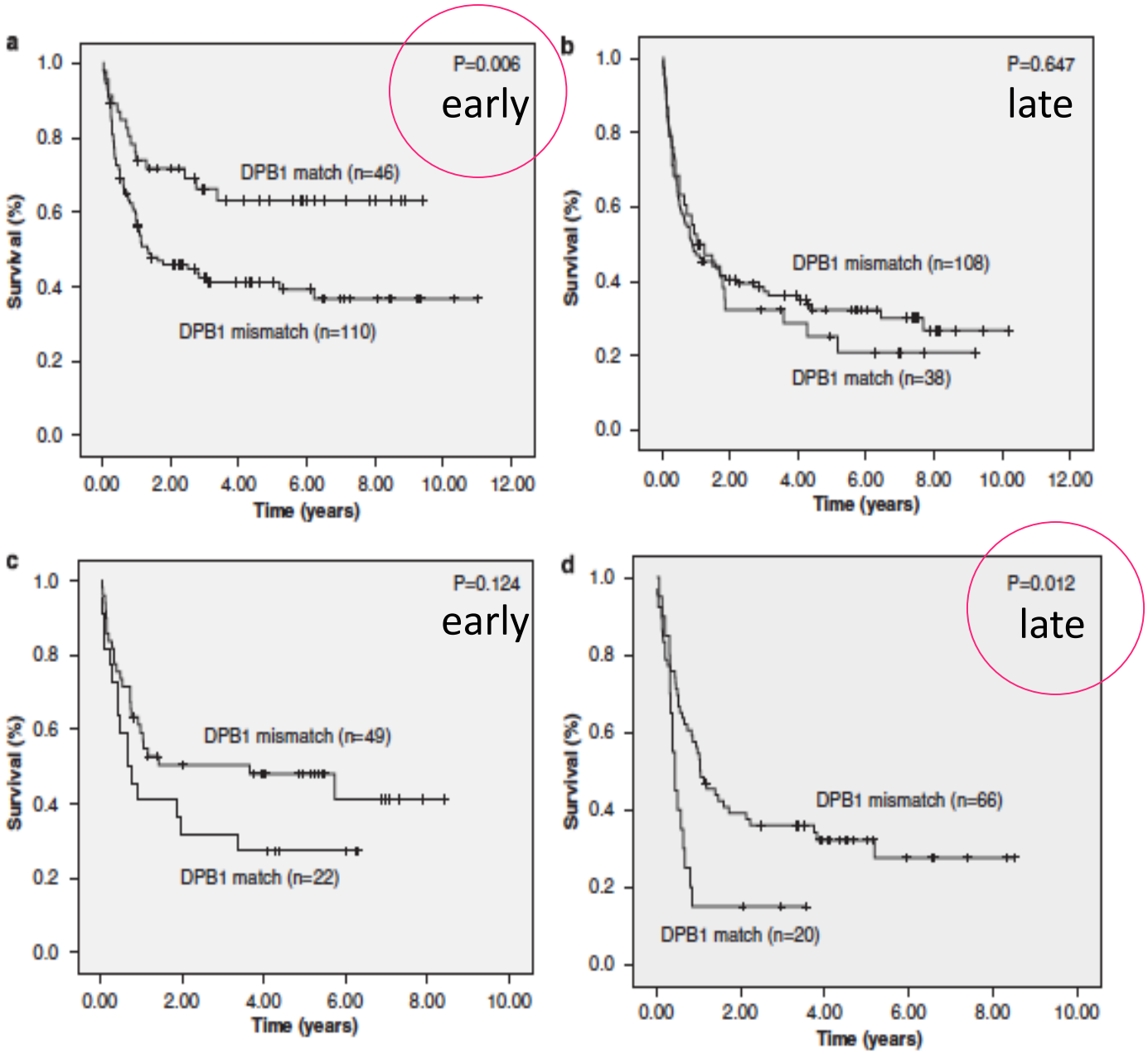
Leukemia (2010) 24, 58–65

488 TCD patients

Differential impact of DPB1 MM in early vs late disease

10/10

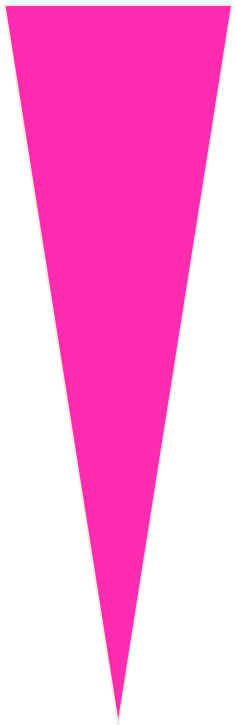
≤9/10


a
P=0.006
early
DPB1 match (n=46)
DPB1 mismatch (n=110)
Survival (%)
Time (years)
b
P=0.647
late
DPB1 mismatch (n=108)
DPB1 match (n=38)
c
P=0.124
early
DPB1 mismatch (n=49)
DPB1 match (n=22)
d
P=0.012
late
DPB1 mismatch (n=66)
DPB1 match (n=20)

The "Italian" matching algorithm

immunogenicity

	DPB1*	TCE
Non-permissive	09:01 10:01 17:01	1
	03:01 14:01 45:01	2
permissive	others	3



adapted from Crocchiolo et al. Blood 2009; 114: 1437

Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study

Katharina Fleischhauer*, Bronwen E Shaw*, Theodore Gooley, Mari Malkki, Peter Bardy, Jean-Denis Bignon, Valérie Dubois, Mary M Horowitz, J Alejandro Madrigal, Yasuo Morishima, Machteld Oudshoorn, Olle Ringden, Stephen Spellman, Andrea Velardi, Elisabetta Zino, and Effie W Petersdorf on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation

Lancet Oncol. 2012 April ; 13(4): . doi:10.1016/S1470-2045(12)70004-9.

IHWG study
5428 10/10 matched patients
3111 9/10 matched patients

DPB1 matched 20%
non-permissive MM (31%)
permissive MM (49%)

10/10

	HLA 10/10 match				
	Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch	
		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	0·96 (0·87–1·06)	0·40	1·15 (1·05–1·25)	0·002
Non-relapse mortality	1 (ref)	0·86 (0·75–0·98)	0·03	1·28 (1·14–1·42)	<0·0001
Relapse *	1 (ref)	1·34 (1·17-1·54)	<0·0001	0·89 (0·77–1·02)	0·10
Grade 3-4 aGvHD	1 (ref)	0·84 (0·69–1·03)	0·09	1·31 (1·11–1·54)	0·001

9/10

	HLA 9/10 match				
	Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch	
		HR or OR	p value	HR or OR	p value
Overall mortality	1(ref)	0·98 (0·85–1·13)	0·80	1·10 (1·00–1·22)	0·06
Non-relapse mortality	1 (ref)	0·98 (0·82–1·17)	0·81	1·19 (1·05-1·36)	0·007
Relapse *	1 (ref)	1·05 (0·84–1·31)	0·68	0·93 (0·78–1·11)	0·44
Grade 3-4 aGvHD	1(ref)	0·93 (0.71–1·21)	0·58	1·37 (1·13–1·66)	0·002

10/10 matched patients
non-perm. MM => overall mortality HR=1.15 (p=0.002) compared with perm. MM

Match vs. perm. MM: ↓non-relapse mortality and ↑relapse, but no impact on overall mortality

9/10 matched patients:
Non-perm. vs. perm. MM: ↑non-relapse mortality and aGVHD

Outcome for 10/10 matched transplantations with non-permissive HLA-DPB1 mismatches did not differ substantially from those for HLA 9/10-matched transplantation with permissive HLA-DPB1 mismatches or HLA-DPB1 matches

If one consider a 9/10 matched donor, look for a donor with a DPB1 match or with a permissive DPB1 MM

BLOOD, 16 OCTOBER 2014 • VOLUME 124, NUMBER 16

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.

8/8

DQB1 MM: no impact

DPB1 MM:
↗aGVHD, ↘relapse
(both permissive and non-perm. MM)

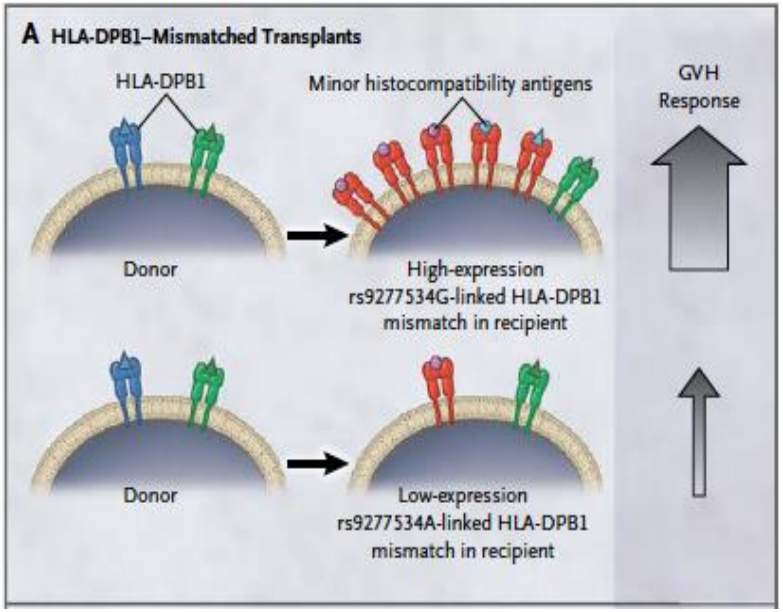
Outcome	HLA 10/10 match (permissive as baseline, N = 1881)			
	Fully matched (N = 514) [RR (95% CI)]	*P* value	Nonpermissive (N = 600) [RR (95% CI)]	*P* value
aGVHD II to IV	0.7 (0.6-0.9)	<.001	1.1 (0.9-1.3)	NS
aGVHD III to IV	0.7 (0.5-0.9)	.006	1.1 (0.9-1.4)	NS
cGVHD	1.0 (0.8-1.1)	NS	1.0 (0.9-1.2)	NS
Relapse	1.4 (1.2-1.7)	<.001	1.0 (0.8-1.2)	NS
TRM	1.0 (0.8-1.2)	NS	1.4 (1.2-1.6)	<.001
Treatment failure	1.2 (1.1-1.4)	.003	1.1 (1.0-1.3)	.03
Overall mortality	1.1 (1.0-1.3)	NS	1.2 (1.1-1.4)	.004

Pidala et al. Blood 2014; 124: 2596

N Engl J Med 2015;373:599-609.

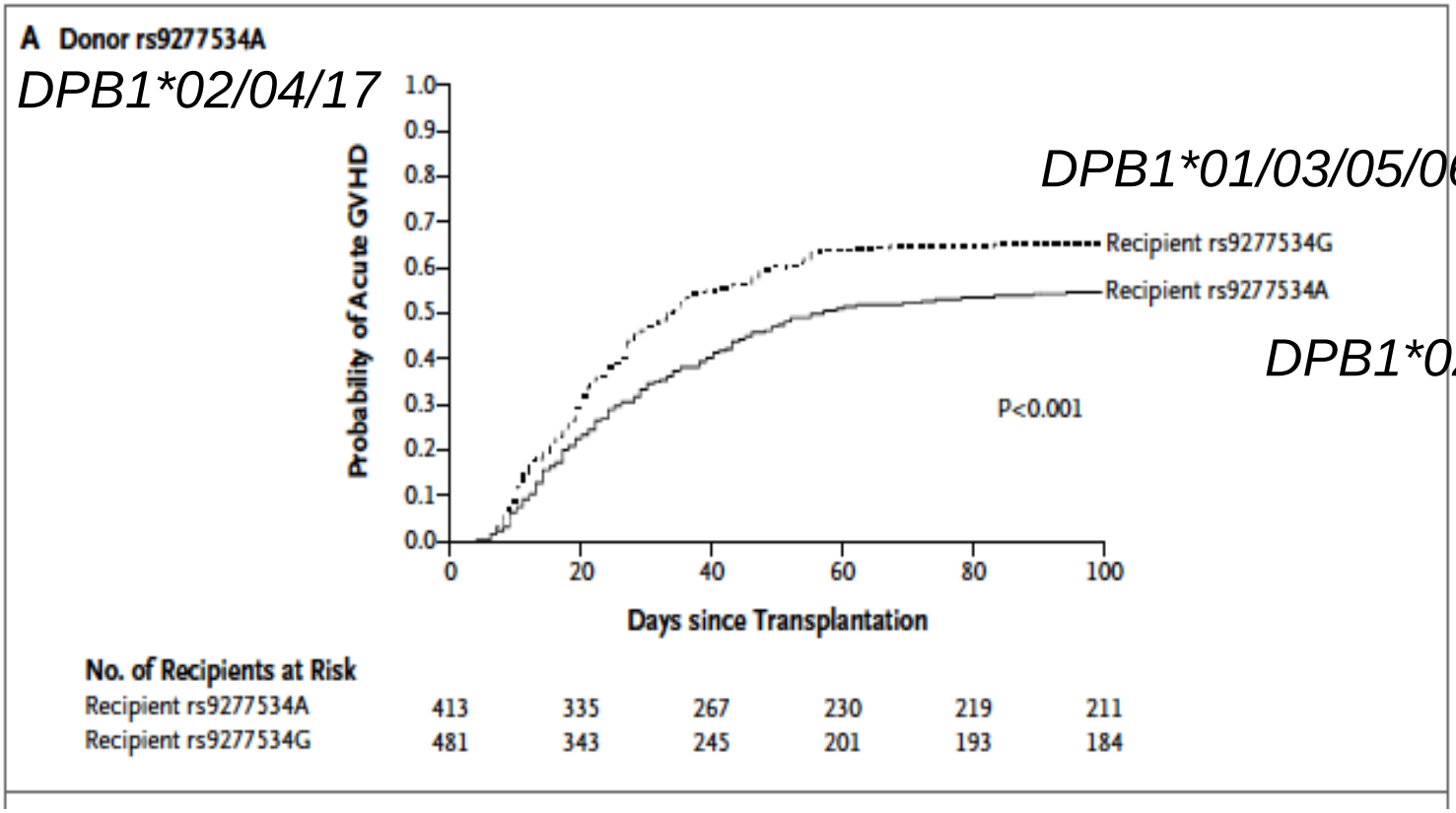
High HLA-DP Expression and Graft-versus-Host Disease

Effie W. Petersdorf, M.D., Mari Malkki, Ph.D., Colm O'hUigin, Ph.D., Mary Carrington, Ph.D., Ted Gooley, Ph.D., Michael D. Haagenson, M.S., Mary M. Horowitz, M.D., Stephen R. Spellman, M.B.S., Tao Wang, Ph.D., and Philip Stevenson, M.S.



rs9277534 in the regulatory region of HLA-DPB1 is associated with DPB1 expression

rs9277534G-linked MM (high DP) => detrimental effect only when MM linked to donor rs9277534A (low DP)

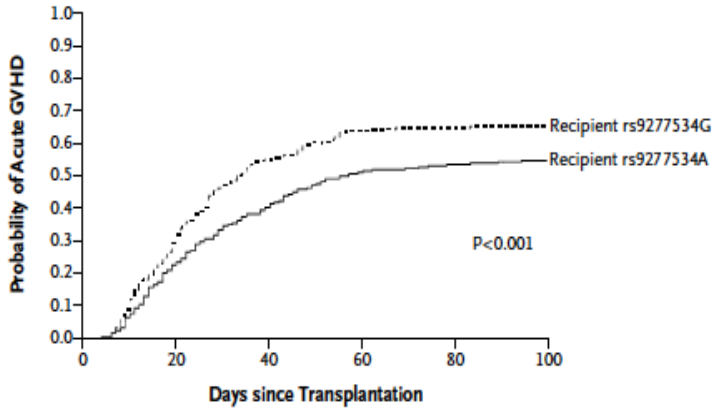


→ Look for donors matched for the high expression allele

low

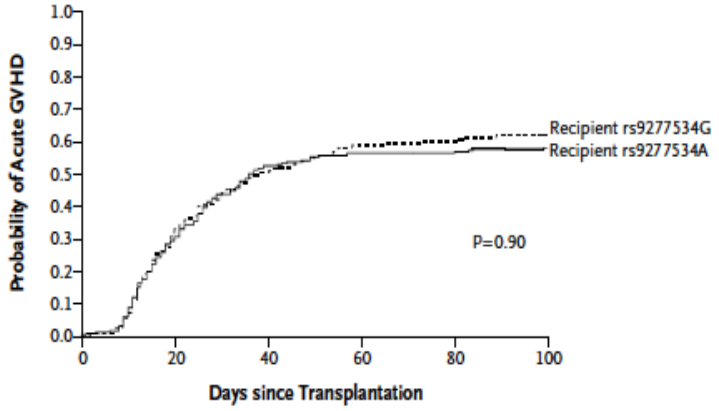
high

A Donor rs9277534A



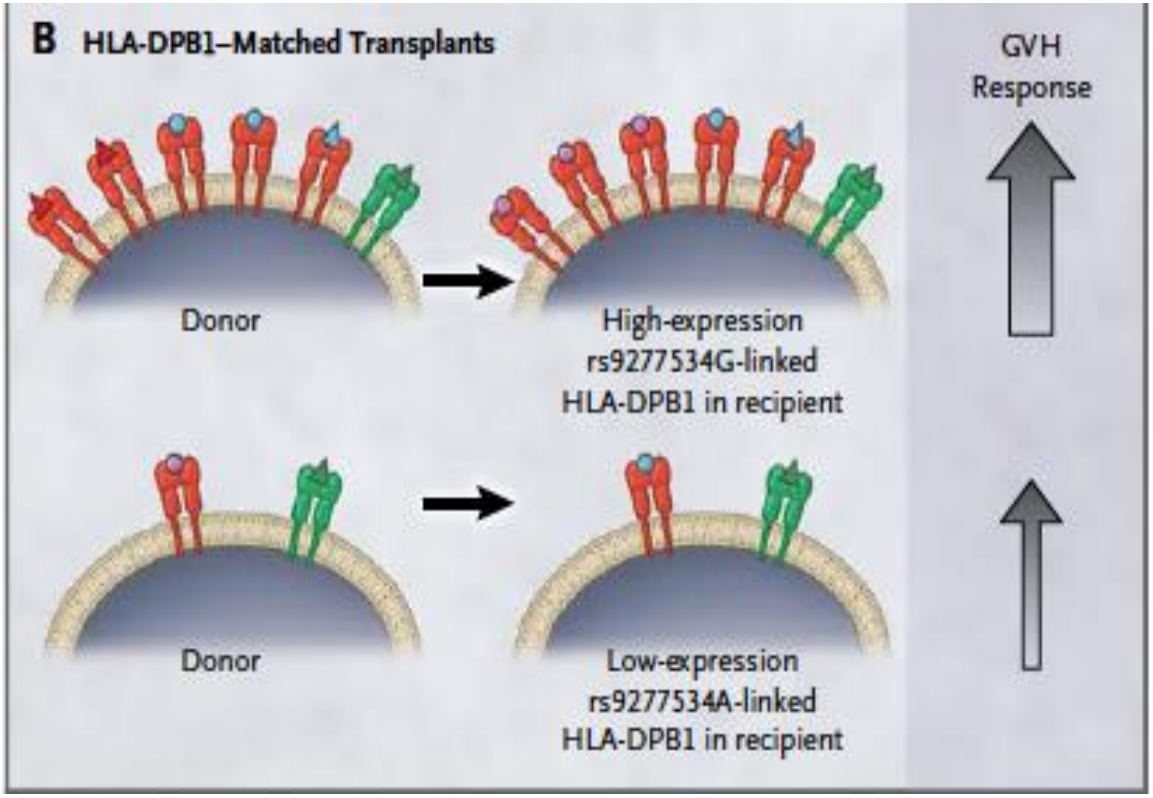
No. of Recipients at Risk						
Recipient rs9277534A	413	335	267	230	219	211
Recipient rs9277534G	481	343	245	201	193	184

B Donor rs9277534G



No. of Recipients at Risk						
Recipient rs9277534A	331	224	178	164	156	146
Recipient rs9277534G	212	156	121	107	103	99

Related/unrelated HSCT with fully matched donors: minor histocompatibility Ag presented by high expression DPB1 alleles may be more efficiently recognized by alloreactive T cells



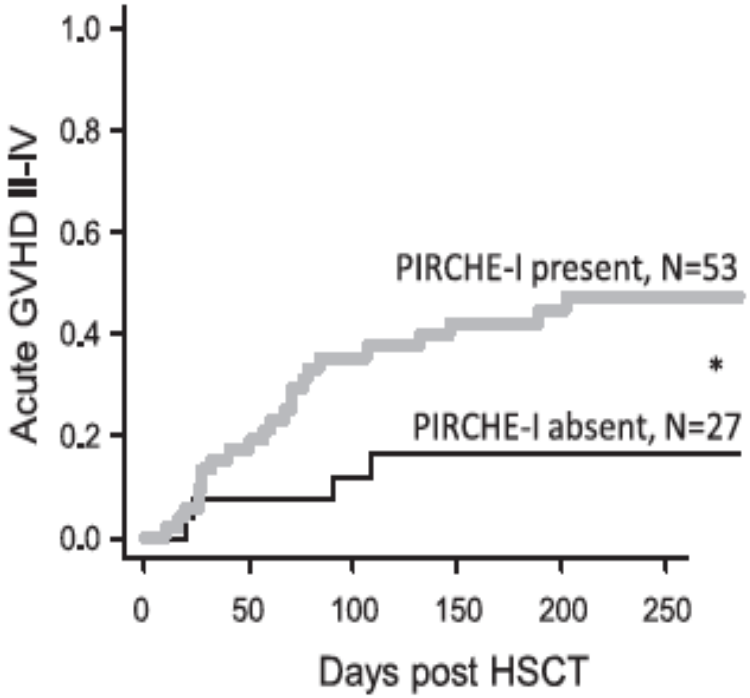
Indirect allorecognition of HLA mismatched alleles: the PIRCHE model

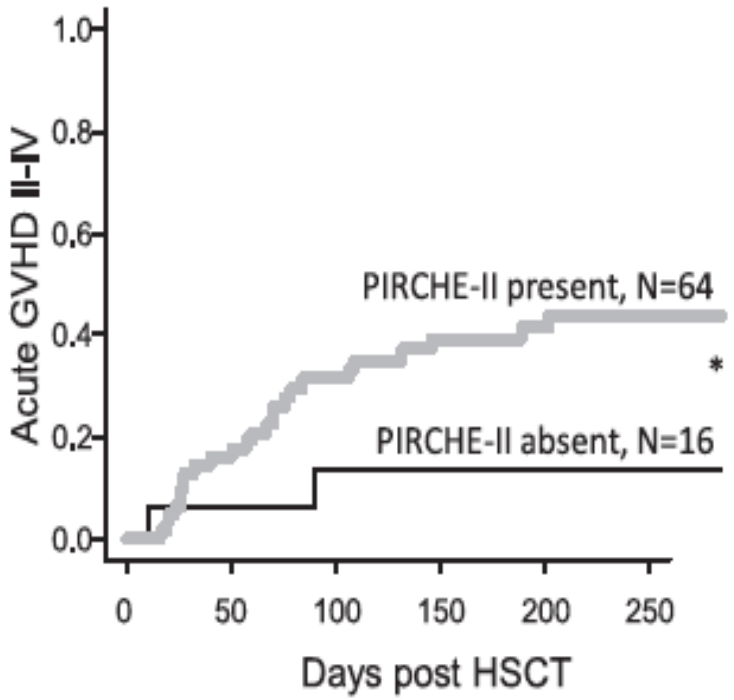
PIRCHE = predicted indirectly recognizable HLA epitopes

In silico prediction of the numbers of peptides derived from mismatched HLA alleles that can be presented by shared HLA antigens, correlation between increasing nb of PIRCHES and increased risk of alloreactivity

Biol Blood Marrow Transplant 20 (2014) 1705–1710

Refinement of the Definition of Permissible HLA-DPB1 Mismatches with Predicted Indirectly ReCognizable HLA-DPB1 Epitopes



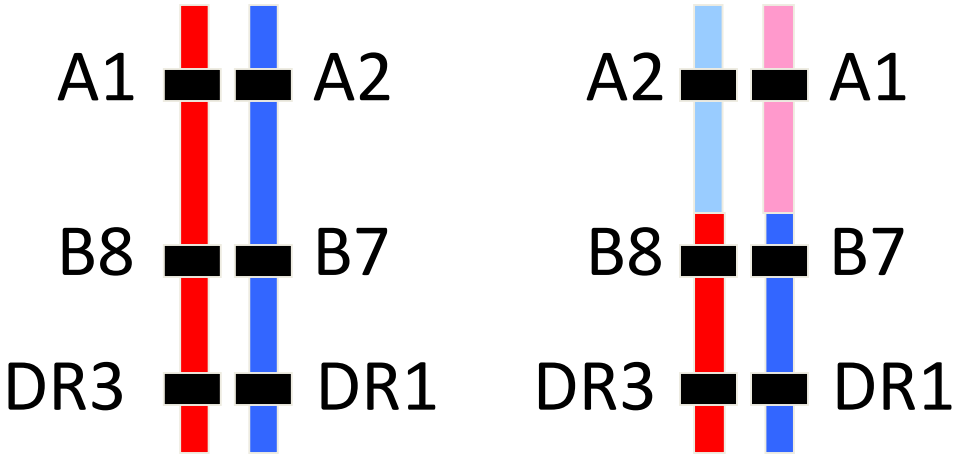


HLA haplotype matching

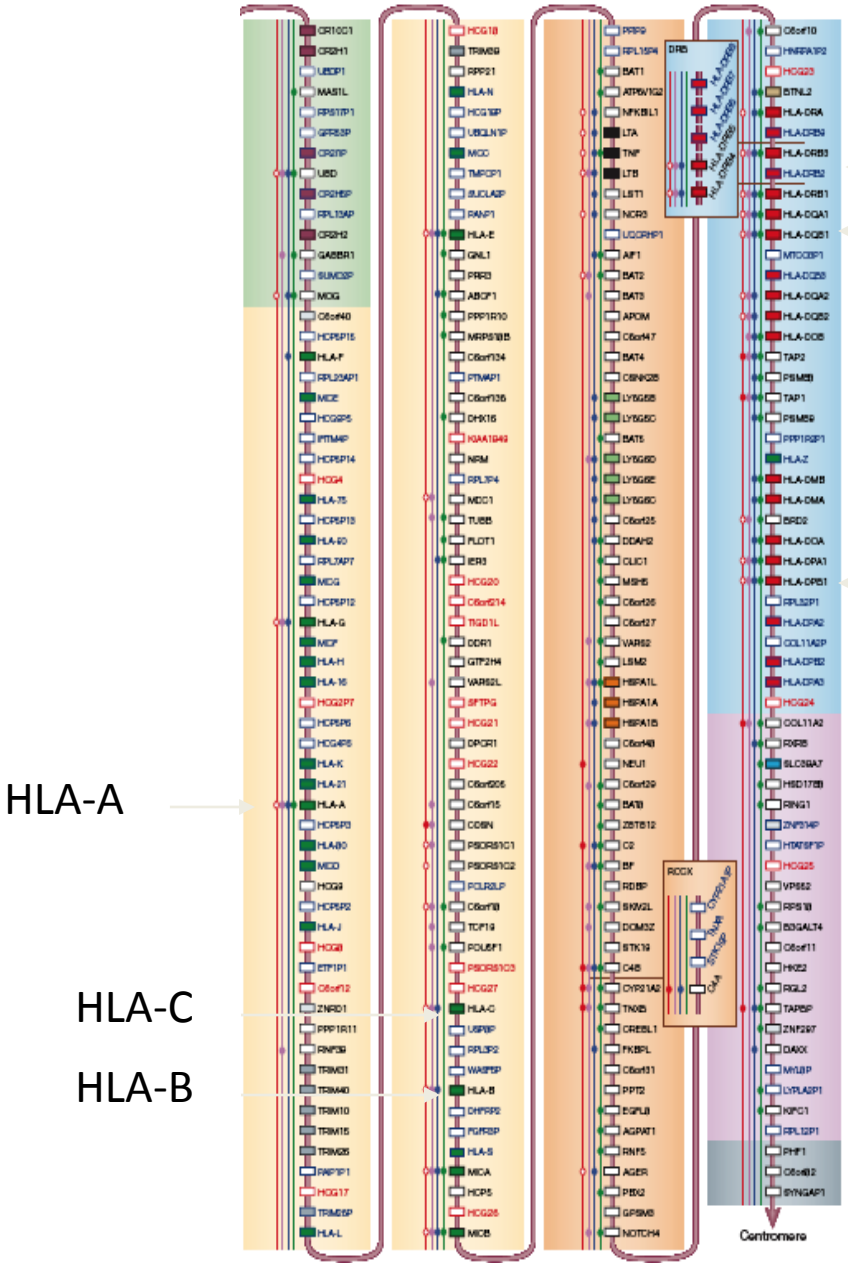
Petersdorf et al. PLOS Med 2007; 4: 59-67

Increased risk of GVHD in haplotype-mismatched unrelated HSCT (OR=4.5, p<0.0001)

Haplotypes that share the same HLA alleles may also share discrete segments or blocks of highly conserved sequences in strong positive linkage disequilibrium with those HLA alleles



MHC=253 genes



Horton et al. Nat. Rev. Genet. 2004; 5: 889

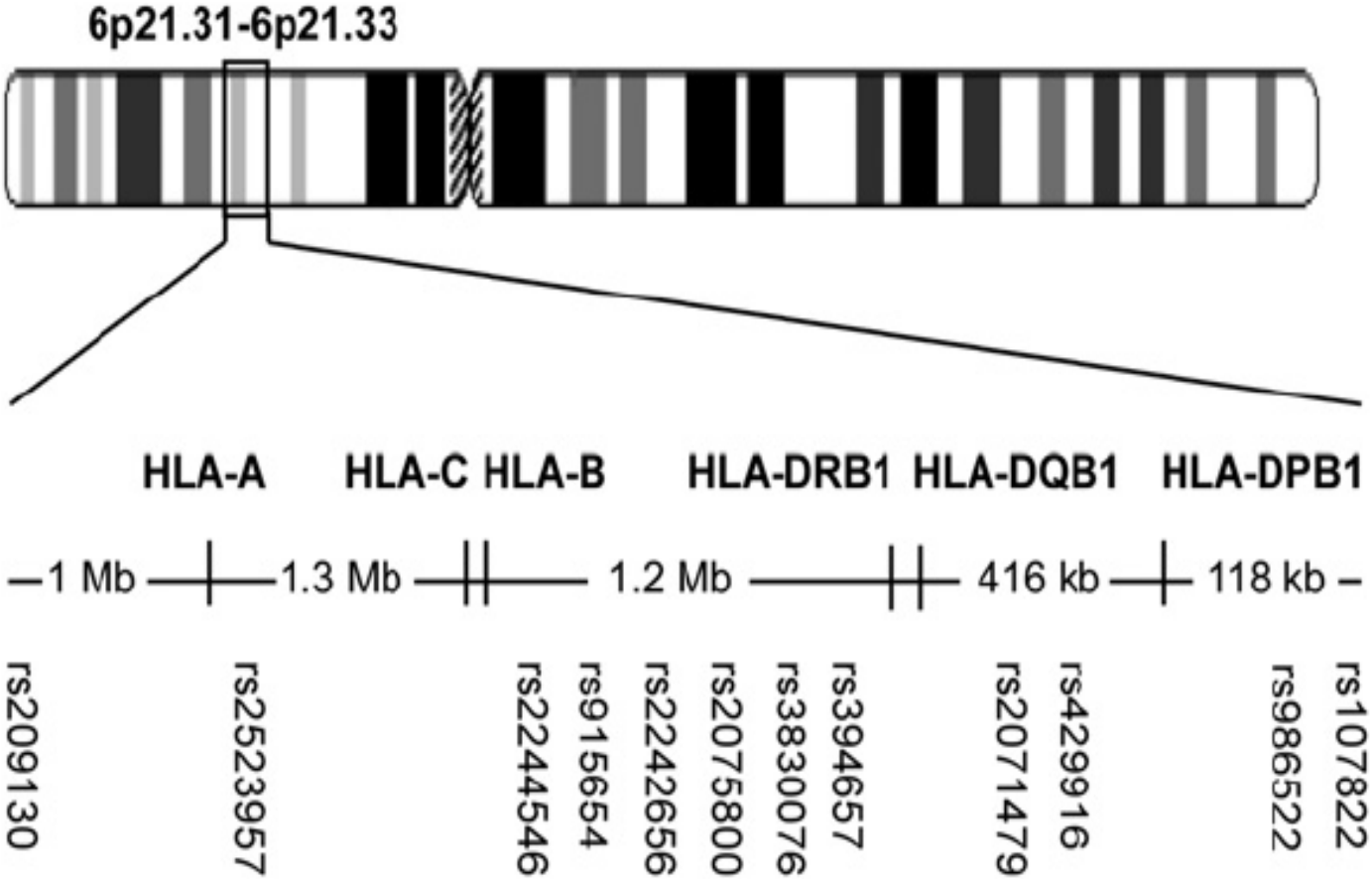
TRANSPLANTATION BLOOD, 7 MARCH 2013 • VOLUME 121, NUMBER 10

Mapping MHC haplotype effects in unrelated donor hematopoietic cell transplantation

Effie W. Petersdorf,[1] Mari Malkki,[1] Mary M. Horowitz,[2] Stephen R. Spellman,[3] Michael D. Haagenson,[3] and Tao Wang[4]

- 2628 HLA mismatched HSCTs
  - 25% HLA-A MM
  - 13% HLA-B MM
  - 38% HLA-C MM
  - 6% HLA-DRB1 MM
  - 17% HLA-DQB1 MM
- Each SNP tested 3 ways: patient genotype, donor genotype, patient/donor SNP mismatching
- Clinical endpoints:
  GVHD II-IV, GVHD II-IV, cGVHD, TRM, relapse (malignancies), DFS, survival

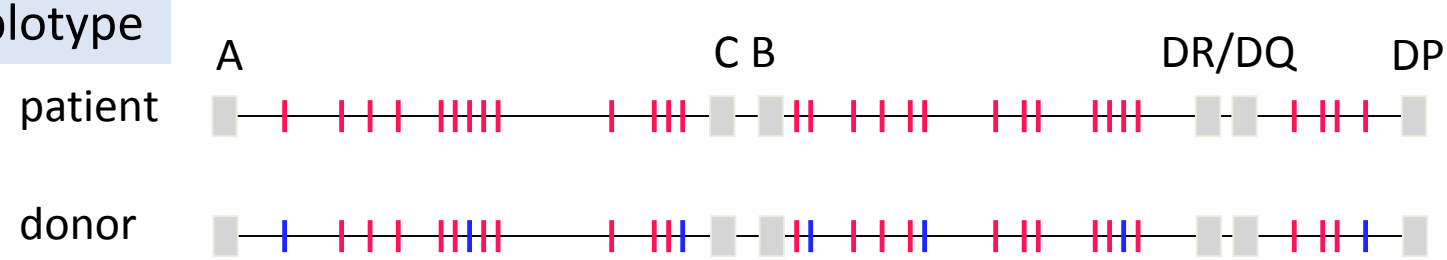
12 SNPs of clinical significance in HLA-mismatched HSCT



HLA-DOA, NOTCH4, TRIM27, FKBPL, HCP5, COL11A2, HSPA1L, BAG6, LTA, RING1

Genetic variation linked to specific HLA haplotypes may impact clinical outcome

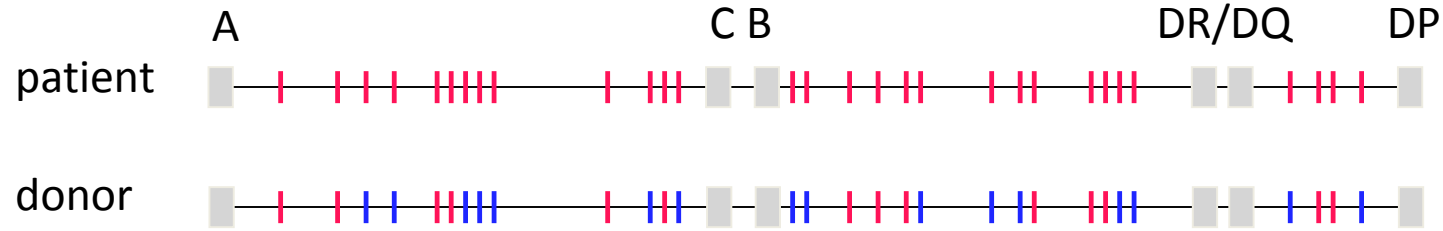
Frequent Haplotype



SNP mismatch

23%

No FH



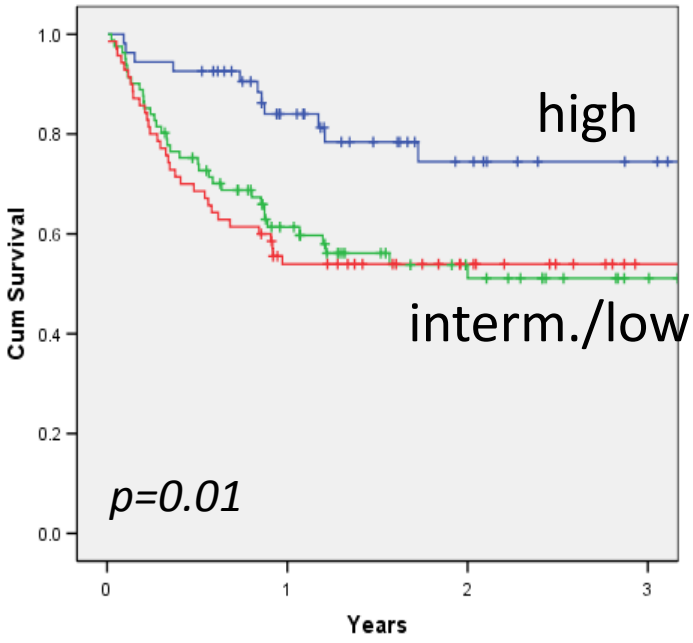
53%

SNP = single nucleotide poylmorphism

patients with frequent/conserved HLA haplotypes (high probability to find a fully compatible unrelated HSC donor)

higher survival

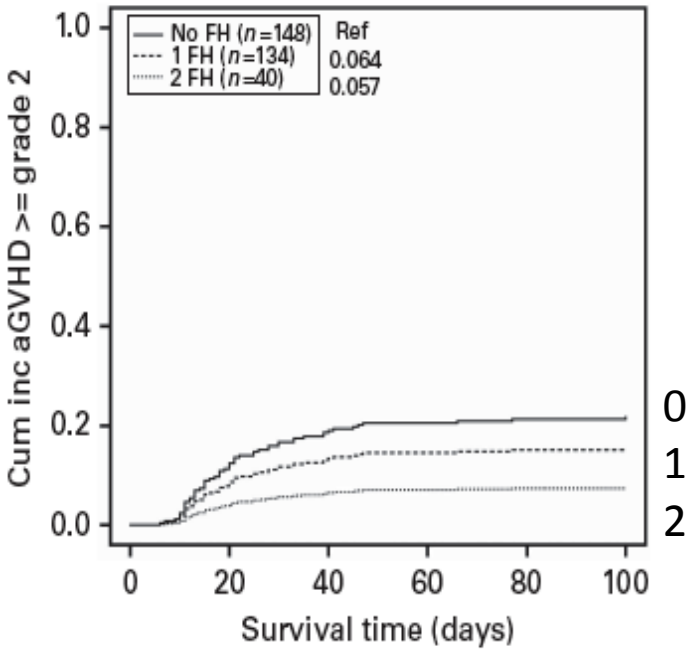
205 p



Tiercy et al. BMT 2007

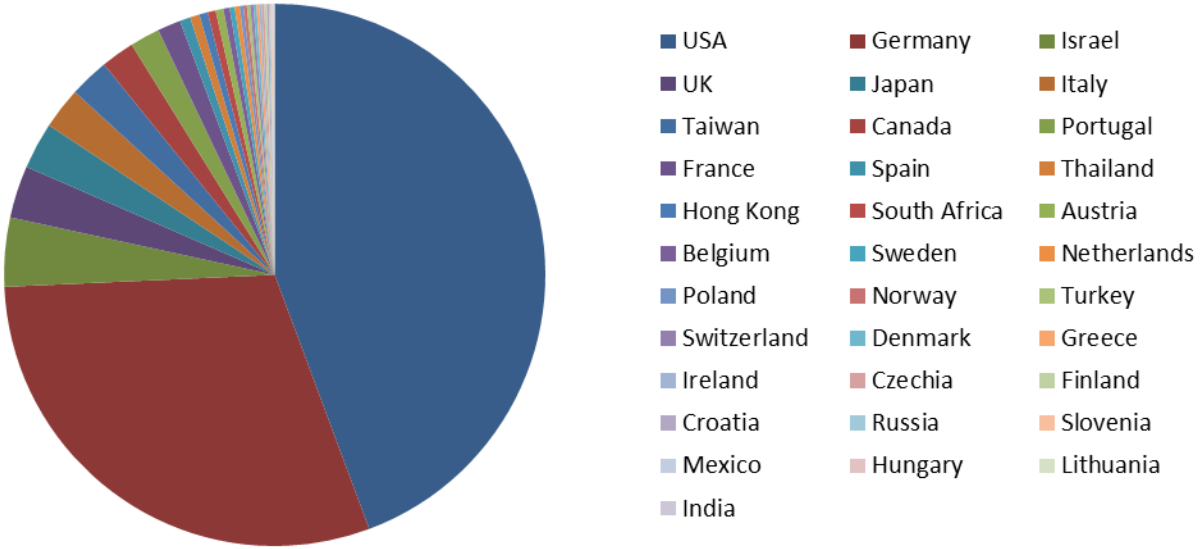
lower GVHD incidence

322 p



Jöris et al. BMT 2013

BONE MARROW DONORS WORLDWIDE

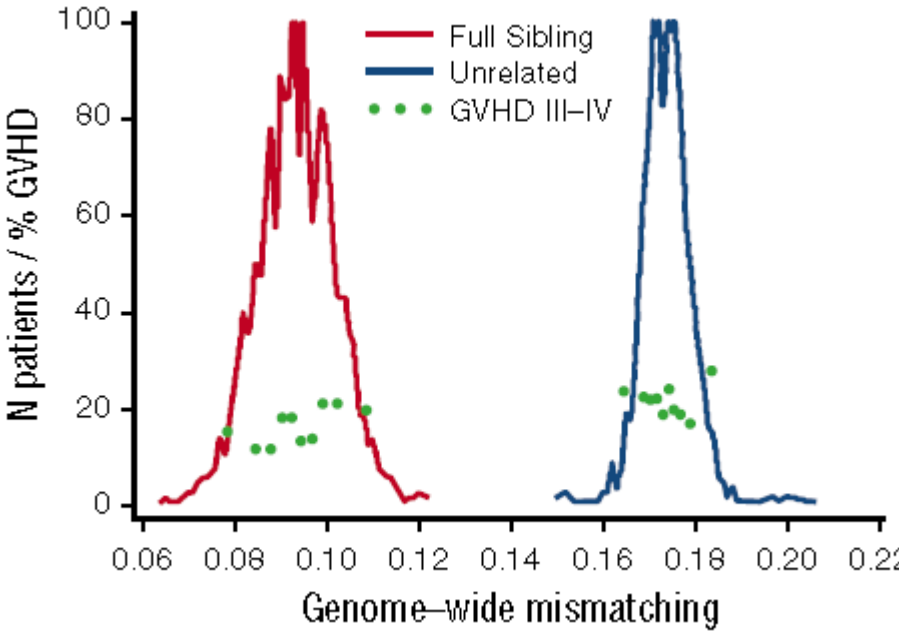


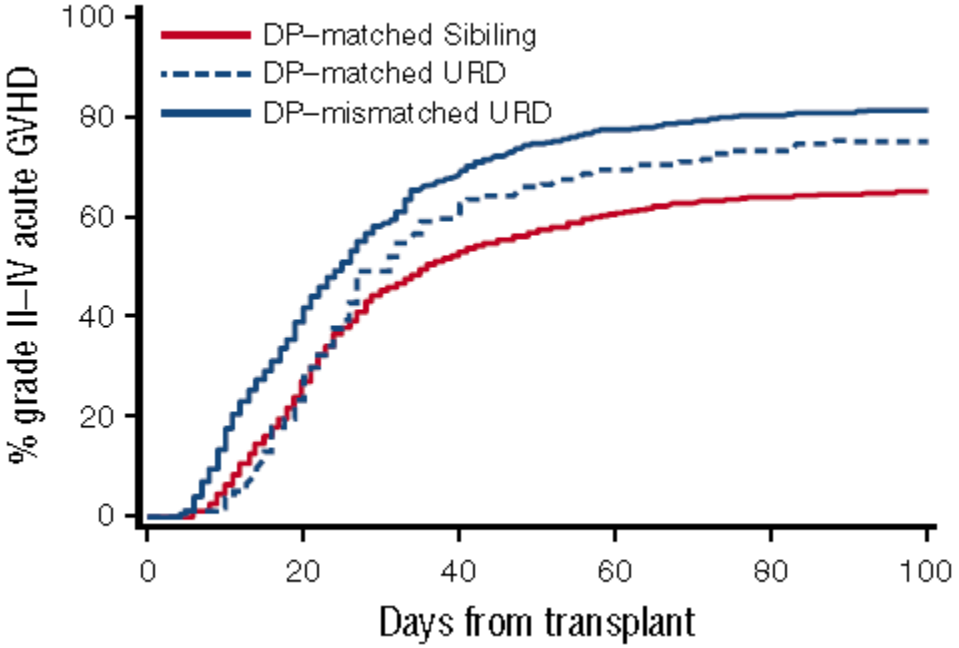
	Einwohner	Spender
Israel	7’600’000	546’851
Schweiz	7’800’000	100‘000

Genome-wide minor histocompatibility matching as related to the risk of graft-versus-host disease

Paul J. Martin,[1,2] David M. Levine,[3] Barry E. Storer,[1] Edus H. Warren,[1,2] Xiuwen Zheng,[3] Sarah C. Nelson,[3] Anajane G. Smith,[1] Bo K. Mortensen,[1] and John A. Hansen[1,2]

Blood. 2017;129(6):791-798)





BLOOD, 4 OCTOBER 2012 • VOLUME 120, NUMBER 14

Evaluation of HLA matching in unrelated hematopoietic stem cell transplantation for nonmalignant disorders

John Horan,[1] Tao Wang,[2] Michael Haagenson,[3] Stephen R. Spellman,[3] Jason Dehn,[4] Mary Eapen,[2] Haydar Frangoul,[5] Vikas Gupta,[6] Gregory A. Hale,[7] Carolyn K. Hurley,[8] Susana Marino,[9] Machteld Oudshoorn,[10] Vijay Reddy,[11] Peter Shaw,[12] Stephanie J. Lee,[13] and Ann Woolfrey[13]

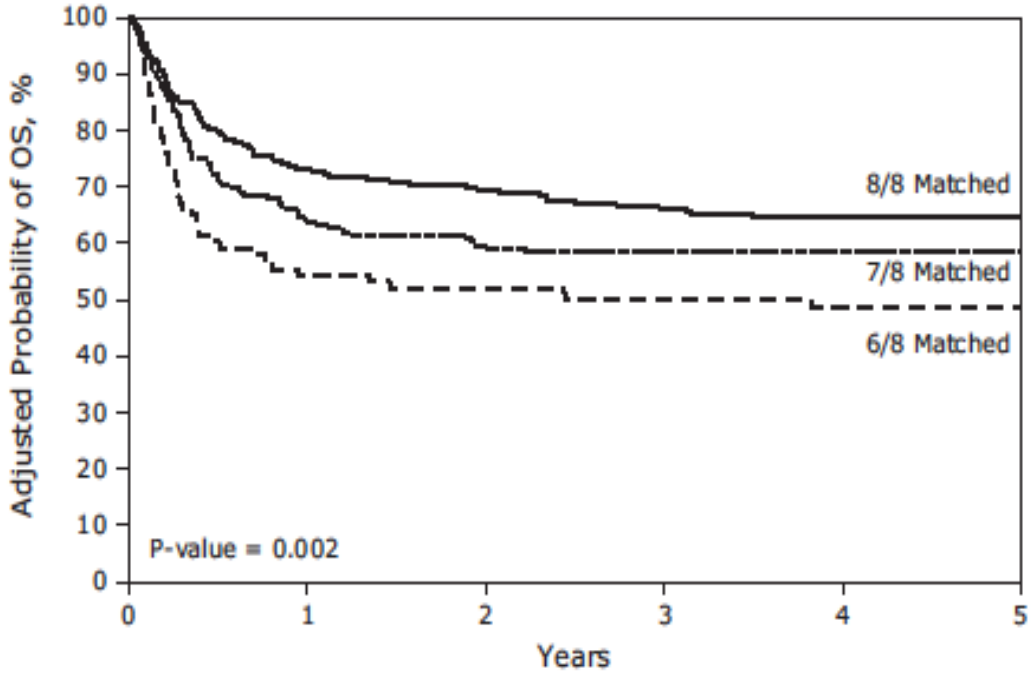
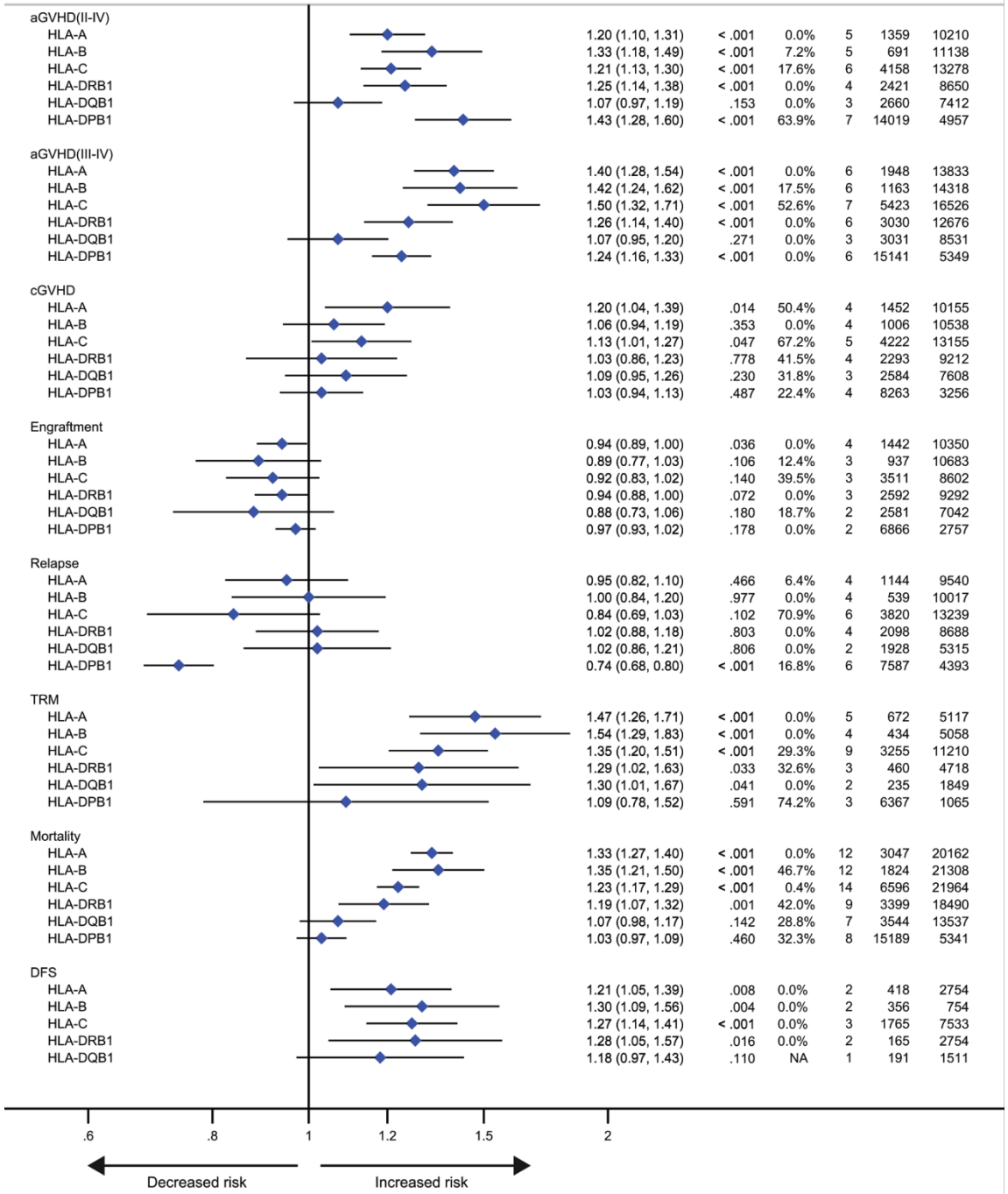


Figure 1. Adjusted probability of overall survival.


Outcomes for individual HLA locus mismatches
HR (95% CI)
P
I²
N0
N1
N2
aGVHD(II-IV)
HLA-A 1.20 (1.10, 1.31) < .001 0.0% 5 1359 10210
HLA-B 1.33 (1.18, 1.49) < .001 7.2% 5 691 11138
HLA-C 1.21 (1.13, 1.30) < .001 17.6% 6 4158 13278
HLA-DRB1 1.25 (1.14, 1.38) < .001 0.0% 4 2421 8650
HLA-DQB1 1.07 (0.97, 1.19) .153 0.0% 3 2660 7412
HLA-DPB1 1.43 (1.28, 1.60) < .001 63.9% 7 14019 4957
aGVHD(III-IV)
HLA-A 1.40 (1.28, 1.54) < .001 0.0% 6 1948 13833
HLA-B 1.42 (1.24, 1.62) < .001 17.5% 6 1163 14318
HLA-C 1.50 (1.32, 1.71) < .001 52.6% 7 5423 16526
HLA-DRB1 1.26 (1.14, 1.40) < .001 0.0% 6 3030 12676
HLA-DQB1 1.07 (0.95, 1.20) .271 0.0% 3 3031 8531
HLA-DPB1 1.24 (1.16, 1.33) < .001 0.0% 6 15141 5349
cGVHD
HLA-A 1.20 (1.04, 1.39) .014 50.4% 4 1452 10155
HLA-B 1.06 (0.94, 1.19) .353 0.0% 4 1006 10538
HLA-C 1.13 (1.01, 1.27) .047 67.2% 5 4222 13155
HLA-DRB1 1.03 (0.86, 1.23) .778 41.5% 4 2293 9212
HLA-DQB1 1.09 (0.95, 1.26) .230 31.8% 3 2584 7608
HLA-DPB1 1.03 (0.94, 1.13) .487 22.4% 4 8263 3256
Engraftment
HLA-A 0.94 (0.89, 1.00) .036 0.0% 4 1442 10350
HLA-B 0.89 (0.77, 1.03) .106 12.4% 3 937 10683
HLA-C 0.92 (0.83, 1.02) .140 39.5% 3 3511 8602
HLA-DRB1 0.94 (0.88, 1.00) .072 0.0% 3 2592 9292
HLA-DQB1 0.88 (0.73, 1.06) .180 18.7% 2 2581 7042
HLA-DPB1 0.97 (0.93, 1.02) .178 0.0% 2 6866 2757
Relapse
HLA-A 0.95 (0.82, 1.10) .466 6.4% 4 1144 9540
HLA-B 1.00 (0.84, 1.20) .977 0.0% 4 539 10017
HLA-C 0.84 (0.69, 1.03) .102 70.9% 6 3820 13239
HLA-DRB1 1.02 (0.88, 1.18) .803 0.0% 4 2098 8688
HLA-DQB1 1.02 (0.86, 1.21) .806 0.0% 2 1928 5315
HLA-DPB1 0.74 (0.68, 0.80) < .001 16.8% 6 7587 4393
TRM
HLA-A 1.47 (1.26, 1.71) < .001 0.0% 5 672 5117
HLA-B 1.54 (1.29, 1.83) < .001 0.0% 4 434 5058
HLA-C 1.35 (1.20, 1.51) < .001 29.3% 9 3255 11210
HLA-DRB1 1.29 (1.02, 1.63) .033 32.6% 3 460 4718
HLA-DQB1 1.30 (1.01, 1.67) .041 0.0% 2 235 1849
HLA-DPB1 1.09 (0.78, 1.52) .591 74.2% 3 6367 1065
Mortality
HLA-A 1.33 (1.27, 1.40) < .001 0.0% 12 3047 20162
HLA-B 1.35 (1.21, 1.50) < .001 46.7% 12 1824 21308
HLA-C 1.23 (1.17, 1.29) < .001 0.4% 14 6596 21964
HLA-DRB1 1.19 (1.07, 1.32) .001 42.0% 9 3399 18490
HLA-DQB1 1.07 (0.98, 1.17) .142 28.8% 7 3544 13537
HLA-DPB1 1.03 (0.97, 1.09) .460 32.3% 8 15189 5341
DFS
HLA-A 1.21 (1.05, 1.39) .008 0.0% 2 418 2754
HLA-B 1.30 (1.09, 1.56) .004 0.0% 2 356 754
HLA-C 1.27 (1.14, 1.41) < .001 0.0% 3 1765 7533
HLA-DRB1 1.28 (1.05, 1.57) .016 0.0% 2 165 2754
HLA-DQB1 1.18 (0.97, 1.43) .110 NA 1 191 1511
.6
.8
1
1.2
1.5
2
Decreased risk
Increased risk

The concept of low expression loci (LEL) mismatches
LEL = DQA1/DQB1, DPA1/DPB1, DRB3/4/5