Choosing a Donor

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February 15, 2013

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Recent Update to Matching Guidelines

blood
2012 120: 259-265
Prepublished online May 17, 2012;
doi:10.1182/blood-2012-03-379032

A perspective on the selection of unrelated donors and cord blood units for transplantation

Stephen R. Spellman, Mary Eapen, Brent R. Logan, Carlheinz Mueller, Pablo Rubinstein, Michelle I. Setterholm, Ann E. Woolfrey, Mary M. Horowitz, Dennis L. Confer and Carolyn K. Hurley

Spellman SR, et al. Blood (2012) 120:259-265

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Questions to Answer

- Which loci should be evaluated for HLA matching?
- How do antigen mismatches compare to allele mismatches?
- Are some loci more important than others?
- Is bone marrow the same as PBSC?
- What about HLA-DP?
- What about anti-HLA antibodies?
- What about cord blood unit transplants?
- Anything about KIR?

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

BLOOD (2007) 110: 4576-83

Stephanie J. Lee, John Klein, Michael Haagenson, Lee Ann Baxter-Lowe, Dennis L. Confer, Mary Eapen, Marcelo Fernandez-Vina, Neal Flomenberg, Mary Horowitz, Carolyn K. Hurley, Harriet Noreen, Machteld Oudshoorn, Effie Petersdorf, Michelle Setterholm, Stephen Spellman, Daniel Weisdorf, Thomas M. Williams and Claudio Anasetti

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Study Population

- N = 3,860 US transplants, 1988-2003
- AML, ALL, CML, MDS
- Myeloablative conditioning
- Calcineurin inhibitor-based GVHD prophylaxis, T replete grafts (79%)
- Bone marrow (94%)
- Median follow-up 6 years

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Any Single Locus Mismatch

9/10 associated with worse survival, DFS, TRM, acute GVHD

	n	RR (95% CI)	P-value
Survival	952	1.17 (1.06-1.329)	0.002
DFS	945	1.16 (1.05-1.28)	0.003
TRM	945	1.31 (1.16-1.47)	<0.0001
Relapse	945	0.90 (0.81-1.00)	0.04
Engraftment	956	OR 0.90 (0.80-1.01)	0.06
Acute GVHD	957	1.35 (1.19-1.56)	<0.0001
Chronic GVHD	910	0.96 (0.91-1.03)	0.25

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Single Antigen vs Allele MM

	Antigen	Allele	P-value
Survival	1.16	1.19	0.69
DFS	1.16	1.17	0.92
TRM	1.34	1.32	0.86
Relapse	0.80	0.93	0.31
Engraftment	0.74	1.08	0.07
Acute GVHD	1.52	1.24	0.06
Chronic GVHD	0.95	0.97	0.84

No statistical difference if mismatched at antigen or allele level, except for C – Antigen worse than Allele

HLA DQ Lacked Impact: As a Single Mismatch

	Survival		TRM		Acute GVHD	
	RR	p	RR	p	RR	p
10/10	1.00		1.00		1.00	
DQ MM	0.97	0.77	1.08	0.50	1.03	0.86

As a Second Mismatch

	8/10	9/10	RR (95% CI)	P-value
DQ MM	191	797	1.14 (0.94-1.38)	0.17

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Specific Single Locus Mismatches

Considering 8/8 as "fully matched"

	Survival		TRM		Acute GVHD	
	RR	p	RR	p	RR	p
8/8	1.00		1.00		1.00	
A MM	1.36	<0.0001	1.47	<0.0001	1.57	<0.0001
B MM	1.16	0.20	1.32	0.03	1.63	0.001
C MM	1.19	0.006	1.32	0.0002	1.43	<0.0001
DR MM	1.48	0.0005	1.56	0.0007	1.27	0.16

Survival: Mismatch at A or DRB1 vs. B or C, RR 1.18 (1.10-1.38), p=0.04

Survival

9-10% lower overall survival with each additional mismatch

Match	n	Survival (CI)	RR (CI)	P-value
8/8	1840	52 (50-54)	1.00	
7/8	988	43 (40-46)	1.25 (1.13-1.37)	<0.0001
6/8	633	33 (30-37)	1.65 (1.48-1.84)	<0.0001

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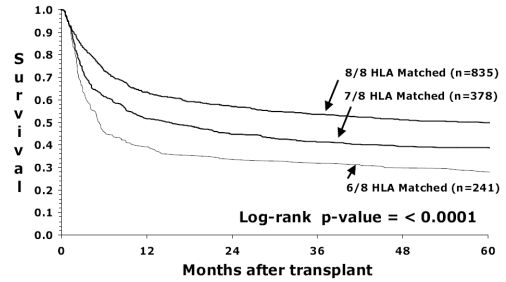
Early stage disease



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Lee SJ, et al. *B lood*.2007;110(13):4576-4583.10.

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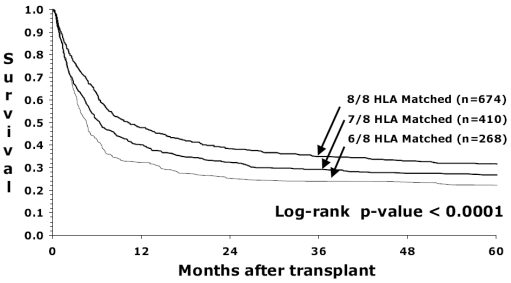
Intermediate stage disease



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Lee SJ, et al. *Blood*.2007;110(13):4576-4583.10

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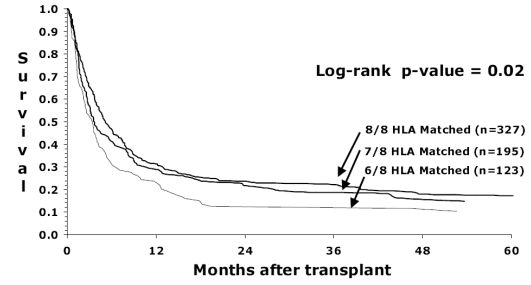
Advanced stage disease



Lee SJ, et al. *Blood*.2007;110(13):4576-4583.10

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Lee Study Conclusions (1)

- High resolution matching of HLA-A, -B, -C, and DRB1 alleles is associated with the best survival
- The adverse effects of allele and antigen mismatches appear equivalent (except at C)
- HLA-DQ matching is not important for survival, TRM or acute GvHD

Lee Study Conclusions (2)

- Single mismatches HLA-A or DRB1 may be more poorly tolerated than at HLA-B and HLA-C
- Each mismatch is associated with a 9-10% decrease in survival, and the absolute decrement in survival is most pronounced in the early stage patients

How do these HLA effects compare with other risk factors?

HLA Match was the Sole Donor Factor

Variable		N	RR	95% CI	P-value
HLA –	8/8 match	1840	1.00		
-	7/8 match	985	1.25	1.13-1.37	<0.0001
-	6/8 match	633	1.65	1.48-1.84	<0.0001

Not significant:
donor age, donor CMV, donor gender, donor parity

Patient Factors

Variable		N	RR	95% CI	P-value
Disease –	AML	969	1.00		
	ALL	834	1.07	0.95-1.20	0.25
	CML	1367	0.78	0.69-0.87	<0.0001
	MDS	288	0.73	0.62-0.86	0.0003
Disease status – Early		1454	1.00		
Intermediate		1352	1.38	1.25-1.53	<0.0001
Late		645	1.90	1.67-2.16	<0.0001

Variable		N	RR	95% CI	P-value
CMV (D/R) –	Neg/Neg	1209	1.00		
	Pos/Neg	555	1.08	0.95-1.23	0.23
	Neg/Pos	969	1.31	1.18-1.45	<0.0001
	Pos/Pos	623	1.36	1.20-1.54	<0.0001
Patient age –	<31	1467	1.00		
	31-45	1263	1.51	1.36-1.67	<0.0001
	>45	728	1.79	1.59-2.0	<0.0001
Patient race –	White	3077	1.00		
	Black	132	1.53	1.26-1.87	<0.0001
	Hispanic	170	1.05	0.87-1.27	0.62
	Other	78	0.68	0.51-0.92	0.01

Lee Study Conclusions (3)

- While HLA-matching is important, patient factors are also critical determinants of outcome
  - Most are not modifiable
  - Only potentially controllable factor is disease stage
  - First determine need for transplant, then proceed with best available donor, even if mismatched

Questions to Answer

- Which loci should be evaluated for HLA matching?
- How do antigen mismatches compare to allele mismatches?
- Are some loci more important than others?
- How important is HLA matching compared to Patient and Donor factors?
- Is bone marrow the same as PBSC?
- What about HLA-DP?
- What if the donor has anti-HLA antibodies?

Evaluation of HLA Matching Requirements for Unrelated PBSC Transplantation

Ann Woolfrey, John Klein, Michael Haagenson, Stephen Spellman, Effie Petersdorf, Machteld Oudshoorn, James Gajewski, Gregory Hale, John Horan, Minoo Battiwalla, Susana Marino, Michelle Setterholm, Craig Kollman, Stephanie Lee
On behalf of the
CIBMTR Immunobiology Working Committee

Patient Characteristics

Variable	(N=1933) N (%)
Age, yrs Median (range)	46 (<1-74)
Male	1078 (56)
KPS ≥ 90	1163 (66)
Disease	
AML	946 (49)
ALL	359 (19)
CML	218 (11)
MDS	410 (21)

New Slide 23

Patient Characteristics

Variable	(N=1933) N (%)
Disease Stage	
Early	682 (35)
Intermediate	453 (24)
Advanced (Late)	798 (41)
Conditioning Regimen	
Myeloablative	1260 (65)
RIC/Non-myeloablative	673 (35)
Year of HCT	
1999-2002	395 (20)
2003-2006	1538 (80)

New Slide 24

Does DQ Matter?

8/8 Match with	N	RR	95% CI	p value
DQB1 match	1125	1.00		
DQB1 allele MM	68	0.97	0.71-1.34	0.87
DQB1 antigen MM	46	1.36	0.95-1.96	0.10

No Significant Effect of DQ Mismatch

New Slide 25

Mortality

	N	RR	95% CI	p value
8/8 match	1243	1.00		
1 allele MM	208	1.11	0.91-1.35	0.30
1 antigen MM	293	1.32	*1.12-1.55*	*0.0007*
2 allele MM	29	1.21	0.77-1.90	0.42
2 antigen MM	31	2.27	*1.55-3.34*	*<0.0001*
2 mixed MM	68	2.32	*1.78-3.02*	*<0.0001*

Mismatch for 1 antigen or >1 allele/antigen increases risk of mortality

New Slide 26

Locus-Specific Analysis — Mortality

	N	RR	95% CI	p value
8/8 match	1243	1.00		
A allele MM	51	1.16	0.80-1.67	0.43
A antigen MM	85	1.17	0.88-1.55	0.29
B allele MM	57	1.29	0.92-1.28	0.14
B antigen MM	16	1.01	0.50-2.04	0.97
C allele MM	61	0.82	0.57-1.19	0.30
C antigen MM	***187***	***1.41***	***1.16-1.70***	***0.0005***
DRB1 MM	39	1.30	0.87-1.94	0.20
C allele vs. antigen		*0.58*	*0.39-0.88*	*0.009*

C antigen mismatch increases risk for mortality, DFS, TRM & GVHD III-IV

New Slide 27

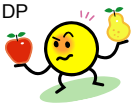
Unrelated Donor PBSC Transplantation Conclusions

- C antigen mismatch confers the greatest risk for poor outcome
- C antigen mismatch is important in both ablative & non-myeloablative HCT
- A larger sample size may reveal additional associations

New Slide 28

Lee data (marrow) vs. Woolfrey (PBSC)

- Similar findings
  - One antigen level mismatch at A, B, C, or DRB1 leads to worse overall survival
  - Survival not affected by isolated DQ or DP mismatches



- Woolfrey differs
  - Allele mismatches, no significant effect on survival
    - Far fewer patients to evaluate for comparisons than Lee

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DPB1 Matching

- **Additional studies have suggested that a DPB1 matching does not impact overall survival**
- DPB1 mismatch reduces relapse risk
- DPB1 mismatch increases acute GVHD and TRM

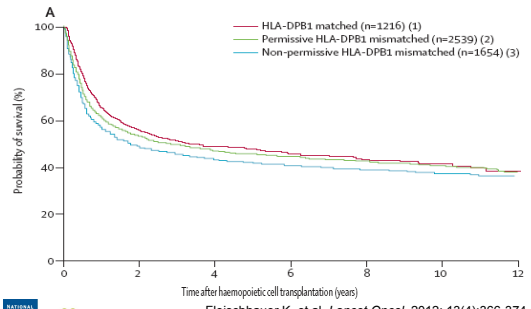
- **Absence of tight DPB1 linkage with other loci decreases the ease of finding a DPB1 match**
- Only ~20% of 10 of 10 matched transplants will be matched for DPB1

DPB1 Permissive Mismatching

- Zino, et al, Blood (2004) 103:1417-1424
  - Grouped DPB1 alleles into groups based on cross-reactive T-cell epitopes
- Created the concept of **permissive** and **non-permissive** mismatches

- DPB1 matches and permissive mismatches are present in ~70% of 10 of 10 matched transplants

10 of 10 HLA-matched with DPB1 Assessment



Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374

DPB1 Permissive Mismatches May Benefit 9 of 10 Matched Transplant

	HLA 10/10 match, non-permissive DPB1 mismatch (n=1654)	HLA 9/10 match, permissive DPB1 mismatch (n=1595)		HLA 9/10 match, DPB1 match (n=500)	
		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	1·04 (0·94–1·14)	0·39	1·02 (0·89–1·18)	0·70
Non-relapse mortality	1 (ref)	1·01 (0·90–1·13)	0·81	1·00 (0·84–1·19)	0·98
Relapse*	1 (ref)	1·12 (0·96–1·31)	0·14	1·16 (0·92–1·45)	0·19
Grade 3–4 aGvHD	1 (ref)	1·00 (0·84–1·19)	0·97	0·93 (0·72–1·21)	0·62

Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374

DPB1 Permissive Mismatches May Benefit 9 of 10 Matched Transplant

	HLA 10/10 match, non-permissive DPB1 mismatch (n=1654)	HLA 9/10 match, non-permissive DPB1 mismatch (n=1001)	
		HR or OR	p value
Overall mortality	1 (ref)	1·13 (1·02–1·26)	0·01
Non-relapse mortality	1 (ref)	1·19 (1·05–1·35)	0·006
Relapse*	1 (ref)	1·04 (0·87–1·24)	0·64
Grade 3–4 aGvHD	1 (ref)	1·36 (1·13–1·65)	0·001

Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374

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THE DETECTION OF DONOR-DIRECTED, HLA-SPECIFIC ALLOANTIBODIES IN RECIPIENTS OF UNRELATED HEMATOPOIETIC CELL TRANSPLANTATION IS PREDICTIVE OF GRAFT FAILURE

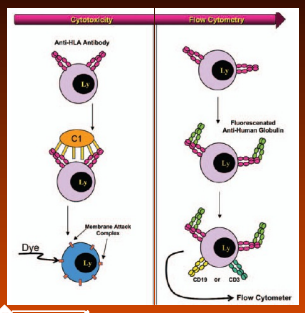
Stephen Spellman, Robert Bray, Sandra Rosen-Bronson, Michael Haagenson, John Klein, Susan Flesch, Cynthia Vierra-Green, and Claudio Anasetti

CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

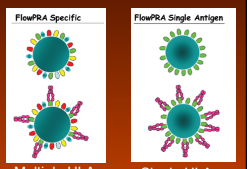
Background

- Alloantibodies directed against mismatched HLA antigens are well established as a significant risk factor in solid organ transplantation (renal, cardiac and pancreas)
- Previous studies in humans and recent animal studies have indicated a role for donor-specific HLA antibodies (DSA) as a risk factor for rejection of hematopoietic stem cell transplants

Evolution of anti-HLA Antibody Detection



HLA Antigen coated micro beads



Bray et al. Immunologic Research 2004;29(1-3):41-53

Study Design

- Retrospective, case-controlled study of recipients who received an unrelated stem cell transplant (SCTx) facilitated through the NMDP
- The study group was selected based on:
  - Preferred mismatched HCT (antigen or allele)
  - Survival past day 28
  - No sustained engraftment
  - Serum samples available in repository
- A total of 37 patients and 78 case-matched controls (2-3 to 1) were tested

Study Design

- Controls were matched for disease, disease status, graft type, age, sex and year of transplant (1990-2002)
- Diseases included AML, CML, ALL, and MDS
- 98% Myeloablative Conditioning
  97% Bone Marrow Stem cells
  97% Calcineurin-Based GvHD Prophylaxis
  100% T-Replete Grafts

Study Design

- Serum samples were tested in two different laboratories (Georgetown University and Emory University) by solid-phase microparticles with 10% of the samples being tested in both labs for QC purposes
- HLA antibody screening was performed on all samples by flow cytometry using FlowPRA® (One Lambda, Inc.)
- For positive samples, HLA specificities were determined by Luminex® LABScreen® Single Antigen Assay or Single Antigen Flow Beads (One Lambda, Inc.)

Study Design

- All donor and recipients were typed for HLA- A, B, Cw, DRB1, DQB1, DQA1, DPB1 and DPA1 to allele-level by high-resolution molecular techniques
  - All matched for DRB1, DQA1 and DQB1
- Antibody specificities were compared to the mismatched HLA antigens (graft rejection direction)
- Patients were considered to possess donor specific HLA antibodies (DSA) if:
  - Antigen or allele mismatch - graft rejection
  - Recipient possessed antibody against MM ag/allele

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Lack of Association Between the Presence of HLA Antibody and Graft Failure

HLA Antibody (Class I and/or II)	Failed Engraftment: YES	Failed Engraftment: NO	
YES	16 (43%)	25 (32%)	N = 41
NO	21 (57%)	53 (68%)	N = 74
	N = 37	N = 78	*p* = 0.2212

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Positive Association Between the Presence of DSA and Graft Failure

Donor Specific HLA Antibody (Class I or II)	Failed Engraftment: YES	Failed Engraftment: NO	
YES	9 (24%)	1 (1%)	N = 10
NO	28 (76%)	77 (99%)	N = 105
	N = 37	N = 78	*p* = 0.0002

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Independent Assessment of Donor-Specific HLA Alloantibody

	OR	*p*-value	95% CI
Class I	11.34	0.0165	1.49 – infinity
Class II	12.00	0.0137	1.46 – 551.97
Class I and/or II	22.84	0.0002	3.57 – infinity

Adjustment for CMV status, cell dose and HLA-C match status did not impact DSA association with graft failure

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Study Conclusions

- Approximately 35% of patients receiving unrelated stem cell transplants possess HLA antibodies
- The presence of donor-specific HLA antibodies against HLA-A, B and/or DP as determined by solid-phase testing, associates with graft failure
- HLA antibody evaluations should be a part of the routine workup for unrelated stem cell transplantation

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NATIONAL MARROW DONOR PROGRAM BE THE MATCH

What Haven't We Covered?

- Role of DRB3, 4, 5
- KIR
- Cord Blood Unit transplantation
  - Role of HLA
  - Non-inherited Maternal Antigen Matching

Q & A

- Thanks for your attention
- Questions?

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