PERFORMING A SEARCH

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- Initiate an effective unrelated donor search

- Select best donors in case of many potential donors

- Select best donors in case of few potential donors

- Select amongst mismatched donors

DATA NEEDED TO START AN UNRELATED DONOR SEARCH

- Collect basic information on patient

- Collect Criteria of Transplant Centre Protocol

- Evaluate patient's HLA assignment

COLLECT INFORMATION ON THE PATIENT

- HLA typing data
- Patient's HLA haplotypes if family members are available
- Date of birth
- Diagnosis and date
- Gender
- Weight
- CMV status and date
- ABO Blood group
- Ethnicity
- Status of sensitization to specific HLA antigens (if mismatched donor needs to be selected)

DONOR SELECTION CRITERIA OF TRANSPLANT CENTER PROTOCOL NEEDED

- PBSC / BM

- CB single / double

- Urgency of search

- Specific HLA loci to be considered 4 or 5?

- Are mismatches acceptable?

- Non-HLA criteria

ELEMENTS OF SEARCH STRATEGY

- Are the patient's HLA assignments sufficient to begin an unrelated search?

- How difficult will it be to find a matched donor?
  - Are any HLA types rare?
  - Are there any unusual HLA associations (B~C or DR~DQ).
  - Are there common HLA associations not found in the patient that might complicate the search?

WHERE IS MY DONOR OR CORD BLOOD UNIT?
WHAT REGISTRY TO SEARCH?

BONE MARROW DONORS WORLDWIDE (www.bmdw.org)

- Central place to identify one or more countries where potential donors or cord blood units can be found

- To register as BMDW user, see BMDW.org : Matching Service

BMDW SEARCH & MATCH SERVICE

Add patient:

- ID

- HLA details (HLA-A, -B, -C, -DRB1, -DQB1, DPB1 etc.)

- Medical details (CMV, ethnicity, d.o.b., Diagnosis, Diagnosis date, Blood group/Rh, Weight, Gender, Urgent Y/N)

- Choose search type (A, B, DR donor search and/or a cord search and/or A, B donor search)

Add patient and Run Search

SELECT BEST DONORS IN CASE OF MANY POTENTIAL DONORS

Patient K: 30 yrs, male, AML, CMV+, Blood group A Rh+

Patient HLA:

A*01:01, 02:01; B*07:02, 44:02; C* 05:01, 07:02;

DRB1*04:01, 15:01; DQB1*03:01, 06:02

DONOR SEARCH RESULT PATIENT K

Search result:

2,988 donors at 10/10 search (HLA-A, -B, -C, -DRB1, DQB1)

Which donors to select?

CUSTOM CRITERIA

Filter donors on non-HLA selection criteria

- **Search setting:**
  - Filter by gender
  - Filter by CMV status

- **Search result list:**
  - Click on ▼
  - Filter by age (give maximum age)
  - Filter by Blood group (A, B, AB, O, unknown)
  - Filter by Registry (choose registry)

PATIENT K: 2,988 10/10 MATCHED DONORS

- Filter on male donors: 1,127 donors

- Filter on CMV positive donors: 62 donors

- Filter on maximum age of 30 yrs: 32 donors

- Filter on ABO match (A): 4 donors

MATCH RESULT FOR PATIENT K AFTER FILTERING

Match results for **Test K.**

10/10 (potential) allele matches

Row	Probability of mismatches 0, 1, 2	A 01:01 02:01	B 07:02 44:02	C 07:02 05:01	DRB1 15:01 04:01	DQB1 06:02 03:01	DPB1	DRB3/4/5	Registry Reg Abbr	Age Gender	Blood group CMV status	Select
2	A A A A A 100% , 0% , 0%	01:01:01:01 02:01:01:01	07:02:01 44:02:01:01	05:01:01:02 07:02:01:03	15:01:01:01 04:01:01	06:02:01 03:01:01:01	04:01:01	4*01:AKJT 5*01:01:01	6354 GB-Anthony	21 Male	A + P (2016-10-28)	★
6	A A A A A 100% , 0% , 0%	01:01 02:01	07:02 44:02	05:01 07:02	04:01:01 15:01:01	03:01:01 06:02:01	04:01:01	4*01:03 5*01:01	6939 DE-ZKRD	25 Male	A - G (2015-02-13)	★
8	A A A A A 100% , 0% , 0%	01:01:01G 02:01:01G	07:02:01G 44:02:01G	05:01:01G 07:02:01G	04:01:01G 15:01:01	03:01:01 06:02:01	04:FNVS 04:HJMR		6939 DE-ZKRD	26 Male	A + H (2016-11-25)	★
30	P A A P P 85% , 15% , 1%	01:VUVN 02:VUVU	07:SNFD 44:JGMU	05:JEAU 07:SNFN	04:UZPN 15:UZTD				5103 CA-One Match	23 Male	A + P	★

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SELECT BEST DONORS IN CASE OF FEW POTENTIAL DONORS

Patient X: South Asian Indian, 22 yrs, M, AML, CMV-, Blood group B Rh+

Patient HLA:

A*02:11, 11:01; B*40:06, 40:50; C*15:02; DRB1*03:01, 11:01; DQB1*02:01, 03:01

Remark: the search is given as urgent

PATIENT X

A*02:11, 11:01; B*40:06, 40:50; C*15:02;

DRB1*03:01, 11:01, DQB1*02:01, 03:01

A*02:11: highest frequency in Asians

B*40:06: highest frequency in Asians

B*40:50: rare allele, highest frequency in South Asian Indians (0.025)

HLA-B-C associations are as expected

HLA-DRB1 – DQB1 association are as expected

DONOR MATCH RESULT FOR PATIENT X

Match results for X.

Mismatches are shown in brackets. **(Bold)** are antigen mismatches, <u>(underlined)</u> are allele mismatches and italics indicate uncertainty.

Row	Probability of mismatches 0, 1, 2	A 02:11 11:01	B 40:06 40:50	C 15:02	DRB1 03:01 11:01	DQB1 02:01 03:01	DPB1	DRB3/4/5	Registry Reg Abbr	Age Gender	Blood group CMV status	Select
	10/10 (potential) allele matches											
1	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:XX 11:XX				5391 PL-Poltranspl	31 Female		★
2	P P P P 1% , 1% , 2%	11:XX 02:XX	40:XX		11:APB 03:BPP			3*02:BRZ	3553 US-NMDP	46 Female		★
3	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:XX 11:XX				3785 SG-BMDP	53 Female	B +	★
4	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:XX 11:XX				8766 BR-REDOME			★
5	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:BACP 11:XX				3458 TW-Tzu Chi			★
6	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:XX 11:XX				3458 TW-Tzu Chi			★
7	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:XX 11:XX				3458 TW-Tzu Chi			★
8	P P P P 1% , 1% , 2%	02:XX 11:XX	40:XX 40:XX		03:XX 11:XX				3458 TW-Tzu Chi			★

DONOR MATCH RESULT FOR PATIENT X

8 potential 10/10 allele matches:

- All donors typed at low resolution

- 4 from Taiwan, 1 from Singapore, 1 from NMDP,
  1 from Brazil and 1 from Poland

Based on the haplotype frequency of the entire BMDW donors:

- Probability of 10/10 match   : 1%
- Probability of 9/10 match   : 1%

Based on Southeast Asian frequency:

- Probability of 10/10 match   : 1%
- Probability of 9/10 match   : 11%

DONOR MISMATCH RESULTS FOR PATIENT X

9/10 (potential) allele matches

10	M A A A A 0% , 100% , 0%	(11:AETSW) 11:AETSW	40:06 40:50	15:ADPFE 15:ADPFE	03:01 11:CTPB	02:ADPFF 03:AFXPP			8486 IN-Datri	29 Male	B +	★
11	P M P P P 0% , 99% , 1%	11:KPUN 02:KJSH	40:06 (27:EHNV)	15:MCFU 15:MCFS	11:KAKV 03:JZMU				3553 US-NMDP	35 Male		★

PATIENT X: SEARCH IS URGENT

Possible donors:

- Potential 10/10 donors with 1% chance. These donors have a low chance of 9/10 match (1% - 11%)

- Two 9/10 donors with 99 – 100%

Conclusion: select mismatched donors

SELECT AMONGST MISMATCHED DONORS

No potential 10/10 matched donor available

How to prioritizes and rank mismatched donors?

SELECTING HLA MISMATCHES

- Check if the patient has IgG antibodies directed to specific HLA antigens.

- Prior sensitization to specific HLA antigens may result in rejection of grafts expressing those antigens.

  Spellman et al. (2010) Blood 115:2704-2708

  Ottinger et al. (2002) Transplantation 73:1280-1285

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HLA-DQB1 MATCHING AND TRANSPLANT OUTCOME

HLA-DQB1 as single mismatch

- No significant impact on survival

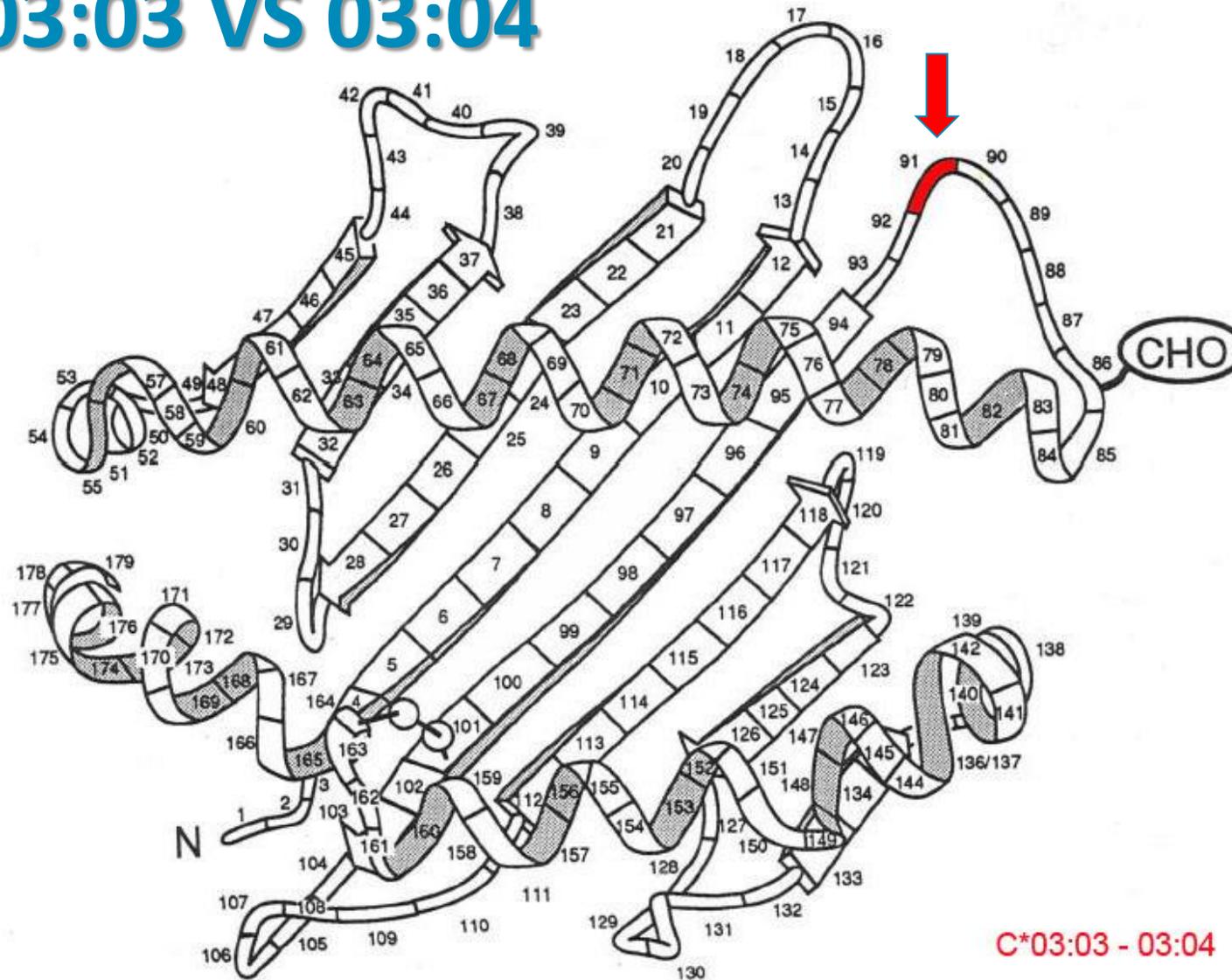## HLA-DQB1 as a second mismatch

- Small, but not significant, adverse effect on survival

Ref: Petersdorf et al 2004, Blood 104; 2976

Lee et al 2007, Blood 110: 4576

Fürst et al 2013, Blood 122: 3220

HLA-C*03:03 VS 03:04

C*03:03 - 03:04

Identification of a permissible HLA mismatch in hematopoietic stem cell transplantation
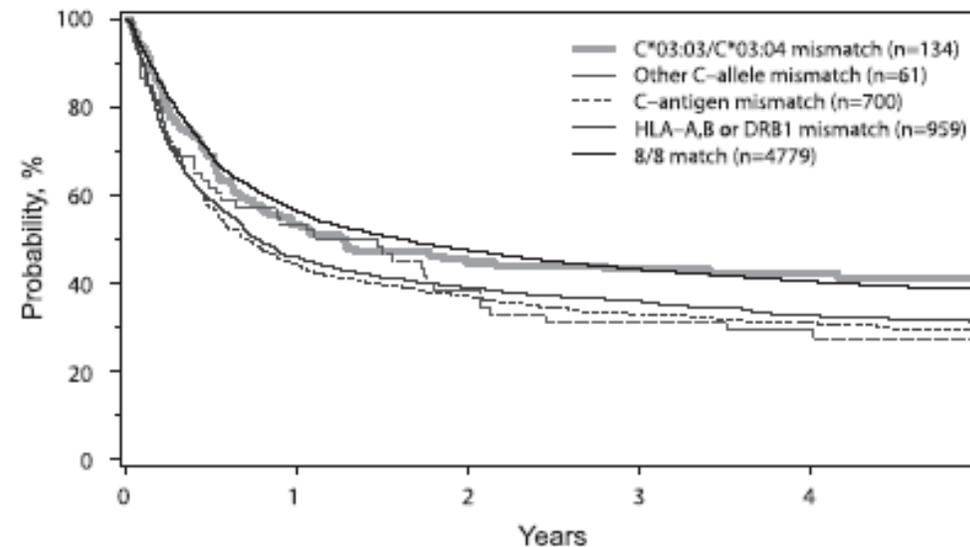
Marcelo A. Fernandez-Viña,[1] Tao Wang,[2] Stephanie J. Lee,[3] Michael Haagenson,[4] Mahmoud Aljurf,[5] Medhat Askar,[6] Minoo Battiwalla,[7] Lee-Ann Baxter-Lowe,[8] James Gajewski,[9] Ann A. Jakubowski,[10] Susana Marino,[11] Machteld Oudshoorn,[12] Steven G. E. Marsh,[13] Effie W. Petersdorf,[3] Kirk 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.

Similar Survival to 8/8 matched

Legend:
- C*03:03/C*03:04 mismatch (n=134)
- Other C-allele mismatch (n=61)
- C-antigen mismatch (n=700)
- HLA-A,B or DRB1 mismatch (n=959)
- 8/8 match (n=4779)

DIRECTION OF HLA MISMATCH AND TRANSPLANT OUTCOME

Outcome	7/8 HvG	7/8 GvH	7/8 Bidirectional
Overall survival	1.37 (1.04 – 1.81), p=0.03	1.67 (1.27 – 2.18), **p=0.0002**	1.29 (1.15 – 1.46), **p<0.0001**
TRM	1.44 (1.05 – 1.97), p=0.025	1.82 (1.37 – 2.42), **p<0.0001**	1.56 (1.36 – 1.79), **p<0.0001**
Relapse	1.38 (0.97 – 1.95), p=0.07	1.11 (0.76 – 1.63), p=0.60	0.98 (0.84 – 1.16), p=0.83
Graft failure	1.21 (0.43 – 3.40), p=0.71	1.97 (0.88 – 4.41), p=0.10	1.66 (1.12 – 2.45), p<0.011

(8/8 matched = Reference value): P< 0.01 threshold for statistical significance.
HR (95% CI), p value.

Hurley et al. 2013, Blood, 121: 4800

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CONCLUSION I

- Inspect patient's HLA assignment carefully. HLA assignment likely?; Rare alleles?; unusual associations?

- Use custom criteria to filter on non-HLA selection criteria in case of many potential donors.

- In case of few potential donors carefully look at probabilities, beware that probabilities in BMDW are based in the entire BMDW donors.

- In some cases directly selecting a 9/10 donor instead of potential 10/10 donors may be the best option.

CONCLUSION II

- Limit HLA mismatches.

- Avoid mismatches to which the patient is sensitized.

- In case of mismatches choose HLA-DQB1 mismatch or HLA-C*03:03 vs 03:04 mismatch

- For patients HLA homozygous at a locus select single HvG mismatch over bi-directional mismatch.

DO NOT HESITATE TO ASK SEARCH ADVICE

- See BMDW Matching Service

QUESTIONS?