Matches and Mismatches in HSCT

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Historical Data

- **1965** HLA-identical sibling donor Bone Marrow SCT
- **1979** HLA-identical unrelated donor Bone Marrow SCT
- **1994** haploidentical family donor megadose CD34+ SCT
- **1995** HLA-identical unrelated donor PBSC SCT
- **1996** HLA-A,B,DR identical unrelated Cord Blood SCT
- **1997** Reduced Intensity Conditioning unrelated SCT
- **1995** Molecular HLA Typing Class 1+2
- **2013** Number of known HLA alleles risen to >6000
Factors influencing outcome of HSCT

Stem Cell Source – D
BM/PBSC/CB

Disease Stage – R
Early/Intermediate/Advanced

HLA Matching D/R
8/8, <8/8, DQ, DP

Conditioning – R
RIC/T-cell depletion

Immunogenetics – D/R
mHag/KIR/Cytokine/NOD

Serology – D/R
CMV, EBV?

AB0 Group – D/R

Age, Sex – D/R
## Donor Matching and T cell Alloreactivity

<table>
<thead>
<tr>
<th>HSCT</th>
<th>Target Ags</th>
<th>GvHD/GvL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-id. Sibling</td>
<td>Minor Ags (12/12)</td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>Minor Ags; HLA-DP (10/10)</td>
<td></td>
</tr>
<tr>
<td>Cord Blood</td>
<td>Minor Ags; HLA-DP; HLA A,B,C,DR,DQ (&gt;6/10)</td>
<td></td>
</tr>
<tr>
<td>Haploidentical</td>
<td>Minor Ags; One full HLA-haplotype (&gt;5/10)</td>
<td></td>
</tr>
</tbody>
</table>
Disease Stage and HLA Matching

• 3857 MUD Tx from unrelated adult volunteer donors (Lee, Blood 2007)

<table>
<thead>
<tr>
<th>Stage</th>
<th>HLA Match</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Stage</td>
<td>8/8 HLA Matched (n = 835)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>7/8 HLA Matched (n = 378)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>6/8 HLA Matched (n = 241)</td>
<td>Log-rank P = &lt; 0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8/8 HLA Matched (n = 674)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>7/8 HLA Matched (n = 410)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>6/8 HLA Matched (n = 268)</td>
<td>Log-rank P = &lt; 0.001</td>
</tr>
<tr>
<td>Late Stage</td>
<td>8/8 HLA Matched (n = 327)</td>
<td>Log-rank P = 0.02</td>
</tr>
<tr>
<td></td>
<td>7/8 HLA Matched (n = 195)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/8 HLA Matched (n = 123)</td>
<td></td>
</tr>
</tbody>
</table>
HLA Matching, Stem Cell Source, Disease Stage

- 8/8 matched BM and PBSC have similar survival (Eapen, Lancet Onc 2010)
- Superior to 7/8 BM/PBSC which are similar to 4-6/6 UCB

...ONLY IN PATIENTS WITH EARLY DISEASE!
Outcome of 4-6/6 double UCB Tx

- HLA matching is far less stringent (4/6 alleles)
- Cell dose $>2.5 \times 10^7$/kg TNC and $>1.7 \times 10^5$/kg CD34+
- Higher NRM but lower relapse than adult donors

B. Causes of Death

...mismatched HLA may be target of GvL!

(Brunstein, Blood 2010)
Donor-specific HLA alloantibodies (DSA)

- Graft failure in HLA-mm unrelated SCT (*Spellman, Blood 2009*)
- Engraftment and survival in unrelated cord SCT (*Takanashi, Blood 2010*)

**HLA-mismatched unrelated SCT**

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I DSA</td>
<td>11.34</td>
<td>1.49-∞</td>
<td>.017</td>
</tr>
<tr>
<td>Class II DSA</td>
<td>12.00</td>
<td>1.46-511.97</td>
<td>.014</td>
</tr>
<tr>
<td>Class I and/or II DSA</td>
<td>22.84</td>
<td>3.57-∞</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

>3-fold higher risk of graft failure

**Unrelated Cord Blood SCT**

P<0.0001

...donor crossmatches in HLA-mismatched SCT!
T Cell Epitope Matching in Unrelated HSCT
Structural versus Functional

**Structural Matching**

- Nucleotide Sequencing
- Allelic Matching or Disparity
- Sequence Identity for A,B,C,DRB1 (8/8)
- Classical Approach for SCT

**Functional Matching**

- Shared T cell epitopes (TCE)
- TCE matching or disparity
- Functional Identity for TCE groups
- In use for Solid Organ TX
  - Innovative for SCT
The three-group model TCE3

- Cross-reactivity of T cell clones from a patient with rejection
- Patient: DPB1*0201,*0401; Donor: DPB1*0201,*0901

Nominal Ag: DPB1*0901

**Group 1:** DPB1*0901,1001,1701

**Group 2:** DPB1*0301,1401,4501

**Group 3:** Others

Zino, Blood 2004
Functional matching by TCE3

<table>
<thead>
<tr>
<th>DPB1* alleles</th>
<th>TCE3 group</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0901</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1701</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0301</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1401</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4501</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td></td>
</tr>
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The Algorithm: 60% permissive
40% non-perm.

Zino, Blood 2004
From Allele to T cell epitope (TCE) matching for DPB1

Retrospective Analysis of 5428 UD-HSCT (10/10)

<table>
<thead>
<tr>
<th>HLA 10/10 match</th>
<th>Permissive HLA-DPB1 mismatch</th>
<th>HLA-DPB1 match</th>
<th>Non-permissive HLA-DPB1 mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>1 (ref)</td>
<td>0.96 (0.87-1.06)</td>
<td>1.15 (1.05-1.25)</td>
</tr>
<tr>
<td>Non-relapse mortality</td>
<td>1 (ref)</td>
<td>0.86 (0.75-0.98)</td>
<td>1.28 (1.14-1.47)</td>
</tr>
<tr>
<td>Relapse*</td>
<td>1 (ref)</td>
<td>1.34 (1.17-1.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3-4 aGVHD</td>
<td>1 (ref)</td>
<td>0.84 (0.69-1.03)</td>
<td>1.31 (1.11-1.54)</td>
</tr>
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NRM

Non-permissive TCE Mismatch

Permissive TCE Match

Allelic DPB1 Match

DPB1 Allele Mismatch

### Predicted Immunogenecity

**Patient Typings: PROSPECTIVEPATIENT1**

<table>
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<th>TCE Group</th>
<th>Predicted Immunogenecity</th>
<th>Comments</th>
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<tr>
<td>DPB1*04:01</td>
<td>3</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>DPB1*04:02</td>
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**Donor Typings: PROSPECTIVEDONOR1**

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The predicted immunogenecity of the DPB1 matching for this pair is: **Permissive**

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http://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/dpb.cgi

*Shaw et al., BMT in press*
Refined Guidelines for unrelated donor searches

Patient Search

Uncommon Haplotypes
Only \( \leq 8/10 \)

- DP not relevant

Common Haplotypes
Several 9-10/10

- Ask Upfront for HLA-DP

- Allele DP-Matched (12/12)
  - Low Relapse Risk

- DP TCE Perm. (9-10/10)
  - Low Relapse Risk

- DP TCE Non-Perm. (9-10/10)
  - High Relapse Risk

X
HLA Mismatching
Tracking Host Chimerism by HLA Typing

HLA typing is sensitive (1%) in detecting re-appearance of host hematopoiesis after SCT from mismatched donors

Mazzi, Leukemia, 2008
In 13/36 (36%) acute myeloid leukemia relapses after haplo-SCT, HLA typing failed to detect leukemic blasts.
HLA Mismatching
UPD of chromosome 6p

HLA Mismatching

Specific evasion from anti-leukemia T cell response

Impact of HLA mismatches in allo-SCT is dependent on
- Disease Stage – Transplant as early as possible!
- Stem Cell Source (BM=PBMC 8/8; UCB 4-6/6)

Permissible mismatches can be functionally defined
- Concept of epitope matching
- Added predictive value for HLA-DP in the 9-10/10 context
- DRB? DQB1? Class 1??

HLA loss relapses limiting factor in HLA-mismatched SCT
- 30% of relapses after haplo-SCT; occurs also after unrelated SCT
- Important impact on clinical treatment of relapse