Donor and stem cell source selection

TRAINING COURSE 2013-2015
E. Baudoux
S. Servais
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• Introduction
• HPC sources and donor types
• HLA and matching
• Unrelated donor searches
• Donor choice and eligibility
• Search strategies (Sibling, UD, CB, no Haplo)
Hematopoietic stem cell transplantation (HSCT) has become an accepted therapy for many congenital or acquired disorders of the hematopoietic system and has seen major changes in indications and use of transplant techniques over the years.

**Figure 3:** shows the continued increase in the numbers of unrelated donor transplantation compared to HLA identical sibling donors and the gradual increase in alternative family donor transplantation (haploididentical donors.)
Trend over 5 years: Donor type

- Unrelated stem cell source: 50% increase since 2006
- Family: 11% increase since 2006

Pie chart showing:
- Peripheral blood: 58%
- Bone marrow: 23%
- Cord blood: 19%

09/10 preliminary data

Worldwide Network for Blood and Marrow Transplantation
NGO in official relations with the World Health Organization

not for publication
Challenges of allogeneic hematopoietic stem cell transplantation

**Patient**
- Age, performance status, comorbidity
  - Diagnosis, status, prior treatments

**Disease**
- Disease control
  - Conditioning regimen, GVHD prophylaxis

**Transplant procedures**
- Graft
  - Immune reconstitution
  - ↓GVHD
  - ↓Transplant-related mortality (TRM)

**AlloHSCT**

- Engraftment
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• **HPC sources and donor types**
  • HLA and matching
  • Unrelated donor searches
  • Donor choice and eligibility
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Hematopoietic Stem Cell (HPC) sources

BM

PBSC

CB
DONOR TYPES

- Matched Sibling Donor
- Matched Unrelated Donor
- Unrelated CB Donor
- (Haploidentical Donor)
## DONOR

### Adult versus CB unrelated donor

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<th>Adult volunteer</th>
<th>Cord blood</th>
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<tr>
<td>Supply</td>
<td>10% loss/year</td>
<td>unlimited</td>
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<tr>
<td>Delay</td>
<td>6 months</td>
<td>Immediately available</td>
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<tr>
<td>Risk to donor</td>
<td>anesthesia (BM)</td>
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<tr>
<td>NC dose</td>
<td>OK</td>
<td>OK for children</td>
</tr>
<tr>
<td>Engraftment</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Risk of GVHD</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>HLA compatibility</td>
<td>8+ out of 8</td>
<td>4-5 out of 6</td>
</tr>
<tr>
<td>Probability</td>
<td>65%</td>
<td>100%</td>
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<tr>
<td><strong>LIMITATION</strong></td>
<td>HLA</td>
<td><strong>CELLULARITY</strong></td>
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Number of stem cell donors and cord blood units worldwide

Data from BMDW - Bone Marrow Donors Worldwide

- Any available donor, if any
- Best available donor or CB
- No alternative to donors

1950: \( \approx 22M \) stem cell donors

2012: 588,958 CBU’s

Data from BMDW - Bone Marrow Donors Worldwide
# Donor/source of HPC

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<th>Allogeneic</th>
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<td>Family</td>
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<td>Sibling ➔</td>
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<td>Donor registries</td>
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<td></td>
<td>PBSC (HPC, A)</td>
<td>Sibling ➔</td>
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<td></td>
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<td>Donor registries</td>
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<tr>
<td></td>
<td>Cord Blood (HPC, CB)</td>
<td>Sibling ➔</td>
</tr>
<tr>
<td></td>
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<td>CB Banks Donor registries</td>
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</table>
Table of contents

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• **HLA and matching**
  • Unrelated donor searches
  • Donor choice and eligibility
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Human Leucocyte Antigen
DONOR
HLA system

• 12 genes on short arm of chromosome 6:
  – 3 HLA class 1 gene (A, B, C) : monomeric Ag (A, B, C)
  – 9 HLA class 2 genes (DRA1, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1) : heterodimeric Ag (DRA1/DRB1, DQA1/DQB1, DPA1/DPB1)
  – DRB3, DRB4, DRB5 genes are mutually exclusive, are present only on certain haplotypes, in relation with particular DR Ag (DR52, DR53, DR51)

• Extreme polymorphism:
  – Antigenic level : A, B, C, DR, DQ antigens
  – Allelic level : A, B, C, DRA1, DRB1, DRB3, DRB4, DRB5, DQA1, DQB1, DPA1, DPB1 genes.
    Number of identified alleles increases constantly
HLA alleles of importance for HSCT
Assigned April 2012

- Range: $10^{23}$ genotypes
- Most frequent haplotype: A 01-B 08-DRB 0301 (6% of caucasians)
Over $10^{23}$ genotypes

Some alleles and some combinations of HLA alleles (haplotypes) are rare and others frequent

**Most frequent haplotype**: A01-B08-DRB0301 (6% of caucasians)

To make sure 2 siblings are genotypically identical, parental typing is necessary to identify haplotypes

If one of the parents is homozygous at Ag level, low resolution typing does not allow verification of genotypic identity between donor and recipient
DONOR

HLA incompatibility

• Level of incompatibility:
  – Antigenic (2-digit): A*02 vs A*03
  – Allelic (4-digit): A*02:01 vs A*02:02

• Direction of incompatibility:
  – GVH direction
  – Rejection direction
  – Both directions (most frequent)
DONOR
HLA compatibility

• Degree of compatibility :
  – 12/12 : A-B-C-DRB1-DQB1-DPB1 (not much used)
  – 10/10 : A-B-C-DRB1-DQB1 (generally by high resolution typing)
  – 8/8 : A-B-DRB1-DQB1 (not much used)
  – 6/6 : A-B-DRB1 (generally by low resolution typing)

• Type of compatibility :
  – Genotypic : donor and recipient have received same 2 haplotypes from their parents (twins, siblings)
  – Phenotypic : donor and recipient have inherited one haplotype but not the other or are unrelated
**Donor**

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<thead>
<tr>
<th>Ag</th>
<th>Allele</th>
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<tr>
<td>B</td>
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<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>DRB1</td>
<td>0</td>
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<tr>
<td>DQB1</td>
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**Patient**

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<th>Allele</th>
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<td>B</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>DRB1</td>
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<tr>
<td>DQB1</td>
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</table>

**Rejection**

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<td>C</td>
<td>0</td>
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<tr>
<td>DRB1</td>
<td>0</td>
</tr>
<tr>
<td>DQB1</td>
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</table>

**GVHD**

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<tr>
<td>B</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
</tr>
<tr>
<td>DRB1</td>
<td>0</td>
</tr>
<tr>
<td>DQB1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total**

- **Donor**: 0.5
- **Patient**: 1

- **Donor** Rejection Score: 9.5/10
- **Patient** GVHD Score: 8.5/10
DONOR

HLA compatibility : genotypic

Mother

A 2
B 44
DR 3

A 1
B 15
DR 11

Father

A 3
B 27
DR 15

A 31
B 16
DR 9

Sibling 1

A 2
B 44
DR 3

A 3
B 27
DR 15

Sibling 2

A 2
B 44
DR 3

A 31
B 16
DR 9

Patient

A 2
B 44
DR 3

A 3
B 27
DR 15
DONOR

HLA compatibility: phenotypic

Mother

- A2
- B44
- DR3

- A31
- B16
- DR9

Father

- A3
- B27
- DR15

- A31
- B16
- DR9

Sibling 1

- A2
- B44
- DR3

- A3
- B27
- DR15

Sibling 2

- A31
- B16
- DR9

- A31
- B16
- DR9

Sibling 3

- A31
- B16
- DR9

- A3
- B27
- DR15

Patient

- A2
- B44
- DR3

- A31
- B16
- DR9
## DONOR

**Minimal and ideal compatibility**

<table>
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<tr>
<th>DONOR TYPE</th>
<th>MATCH LEVEL</th>
<th>REMARK</th>
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</thead>
<tbody>
<tr>
<td><strong>IDENTAL</strong></td>
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<td></td>
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<tr>
<td>Identical twin</td>
<td>By definition genotypically identical</td>
<td></td>
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<tr>
<td>Brother/sister (sibling) or other family donor</td>
<td>6/6</td>
<td>5/6 IF one haplotype is genotypically identical. If not, see MUD</td>
</tr>
<tr>
<td>Unrelated (MUD)</td>
<td>10/10</td>
<td>8/10 allelic*</td>
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<tr>
<td>Cord blood</td>
<td>6/6</td>
<td>4/6 antigenic</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>1 haplotype identical</td>
<td>Other haplotype: any</td>
</tr>
</tbody>
</table>

(*) Minimum 8/10 allelic:

- 1 antigenic MM (9/10)
- 2 allelic MM (9/10)
- 1 allelic + 1 antigenic MM (8.5/10)
- 1 antigenic + 1 antigenic DQB1 (8/10)
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DONOR
Search for unrelated donors

• Simultaneous VUD and CB search: based on type of HSCT (mini vs conventional) and criteria in document TB0201M02-Eligibilité et choix donneur.
• BMDW (Bone Marrow Donor Worldwide): all UD/CB listed by HLA compatibility with patient.
• MDP-B (Marrow Donor Program-Belgium): Syrenad IT system and EMDIS network connecting with foreign registries including NMDP-USA.
• Netcord: CBB network, global search with NMDP-USA. Belgian hub is MDP-B.
• Confirmatory HLA typing (CT) in TC on each donor before start of conditioning.
2011 MDP-B Registry (Syrenad)

Unrelated donors
Belgian Patients

7 donor centers
>60 000 Donors

5 Cord blood banks
>16 000 CBUs

Internet

EMDIS

Internet

10 Transplant centers
(national patients)

Searching for national donors

Searching for International donors

65 INTERNATIONAL REGISTRIES
44 CB BANKS

>23 M DONORS
>600 000 CBUS
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DONOR
Donor choice & eligibility

• Choice: donor selection among a potential donors, based on:
  – HLA
  – Age, sex, CMV, ABO …
  – Donor preferences

• Eligibility: donor acceptance, based on absence of contra-indication (non-conformity):
  – Donor safety
  – Patient safety
DONOR

Donor eligibility : non-conformity

• Donor non-conformity with any eligibility criteria may constitute:
  – Absolute contraindication to cell donation: in this case, UMN (Urgent Medical Need) is not possible
  – Relative contraindication to cell donation: in this case, UMN (Urgent Medical Need) is possible after decision of transplant committee and eventual specialized opinions
  – Precaution: cell donation is acceptable, but measures may be necessary during the process of collection/transplantation
<table>
<thead>
<tr>
<th>Critère</th>
<th>Type</th>
<th>Eligibilité</th>
<th>Avis avant UMN</th>
<th>Document référence</th>
<th>Remarques</th>
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<td>Moelle : CI relative</td>
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<td></td>
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<td>Lympho : CI relative</td>
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<tr>
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<td>A voir selon cause</td>
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</tr>
<tr>
<td>Maladie thrombotique, coronarienne ou vasculaire</td>
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<td>Remarques</td>
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## DONOR
Donor eligibility: patient safety

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<th>Type</th>
<th>Eligibilité</th>
<th>Document référence</th>
<th>Remarques</th>
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<td>HC</td>
<td>Anamnèse</td>
<td>CI relative temp/perm</td>
<td>Avis hépatologie SN</td>
<td>TB0202A01</td>
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<td>CI relative permanente</td>
<td>Avis hépatologie SN</td>
<td>TB0601A03</td>
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<td>IgM</td>
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<tr>
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<td>Test biologique</td>
<td>CI relative</td>
<td>Moelle &amp; bio</td>
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<td>Gammapathie monoclonale</td>
<td>Test biologique</td>
<td>CI relative</td>
<td>Moelle &amp; bio</td>
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<tr>
<td>Etat ferriprive inexpliqué</td>
<td>Test biologique</td>
<td>CI relative</td>
<td>Gastro &amp; colono</td>
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<tr>
<td>Anomalie hépatique</td>
<td>Test biologique</td>
<td>CI relative</td>
<td>HB-HC-EBV-HHV6-Adeno Avis hépato</td>
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<td>Autre pathologie</td>
<td>Anamnèse</td>
<td>A voir</td>
<td>A voir</td>
<td></td>
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<td></td>
<td>Clinique</td>
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<td></td>
<td>Examens</td>
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</tr>
</tbody>
</table>

TB0201M02-Eligibilité & choix donneur.doc
Donor age

Donor type/age

Univariate analysis

N=36
5y-OS: 6% (SE 6%)
Donor age

kumulierte Entnahmewahrscheinlichkeit
cumulated probability for harvest

Alter / Age
UD CBT in patients with malignant diseases

Neutrophils engraftment according to the class of NC infused x10^7/kg (CI)

- >5.2: 78% ± 3
- 3.2-5.2: 76% ± 3
- 2.1-3.2: 72% ± 3
- <2.1: 63% ± 3

p < .00001
↑ UCB cell dose $\rightarrow$ ↑ engraftment / ↓ TRM / ↑ survival

- **Total nucleated cell dose** (per kg recipient weight)

Barker et al. Blood 2010
↑ UCB cell dose → ↑ engraftment / ↓ TRM / ↑ survival

- **Total nucleated cell dose** (per kg recipient weight)
- **CD34+ cell dose** (per kg recipient weight)
- **Progenitor cell dose** (per kg recipient weight)

---

**CD34 dose** ($\times 10^5$/kg)

- $P < 0.01$
- $<1.7$
- $1.7-2.7$
- $2.8-5.4$
- $>5.4$

**CFU** ($\times 10^4$/kg)

- Platelets engraftment

---

*Wagner et al. Blood 2002*

*Page et al. BBMT 2011*
Impact of donor-recipient HLA-matching at HLA-A, -B, -C and –DRB1 on outcomes after umbilical cord blood transplantation for leukemia and myelodysplastic syndrome: a retrospective analysis

Eapen, Lancet Oncol. 2011

- MM HLA-C is an independent risk factor for transplant-related mortality when transplants are matched at HLA-A, -B, -DRB1 or mismatched at a single HLA-A, -B or -DRB1 locus
- MM HLA-DRB1 when transplants are mismatched at a single HLA-A, -B or –C locus is an independent risk factor for transplant-related mortality
- If a unit matched at HLA-A, -B, -C and –DRB1 is not available, selecting a unit matched at HLA-C is preferred; in particular avoiding a mismatch at HLA-C in the presence of a single mismatch at HLA-DRB1 significantly lowers mortality risks.
The NIMA effect
(Non Inherited Maternal Antigen)
Rocha et al, 2012

- Fetal exposure induces lasting tolerance to NIMA (better outcome in renal Tx)
- HLA MM CBT with NIMA match show lower TRM (A) and better OS (B)
- When HLA MM CBT, preferably NIMA match
Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

Eapen et Al. Blood 2013

USA (180,000 CBU inventory)

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th>Non-Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full allele match UD CBU</td>
<td>33%</td>
<td>5-10%</td>
</tr>
<tr>
<td>1 allele MM</td>
<td>80%</td>
<td>33-45%</td>
</tr>
<tr>
<td>2 allele MM</td>
<td>98%</td>
<td>80-85</td>
</tr>
</tbody>
</table>

- Low or IR level match without HLA-C match \(\Rightarrow\) selection of UD CBU not optimal
- If full allele match not available:
  - 1-2 allele MM better tolerated than 3+ allele MM (10-15% difference in NRM)
  - Single MM HLA A, C, DRB1 \(\Rightarrow\) NRM x 3
Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

Figure 1. Nonrelapse mortality and overall survival. (A) The cumulative incidence of nonrelapse mortality by HLA match: the 3-year incidence of nonrelapse mortality after HLA-matched, 1-allele mismatch, 2-allele mismatch, 3-allele mismatch, 4-allele mismatch, and 5-allele mismatch transplants were 9% (95% CI 4-14), 26% (95% CI 20-32), 26% (95% CI 22-30), 34% (95% CI 30-39), 37% (95% CI 31-43), and 41% (95% CI 30-51), respectively. (B) The probability of overall survival by HLA match: the 3-year probability of overall survival after HLA-matched, 1-allele mismatch, 2-allele mismatch, 3-allele mismatch, 4-allele mismatch, and 5-allele mismatch transplants were 52% (95% CI 42-62), 42% (95% CI 36-49), 47% (95% CI 42-52), 42% (95% CI 37-47), 41% (95% CI 35-47), and 34% (95% CI 23-45), respectively.
Table of contents

• Introduction
• HPC sources and donor types
• HLA and matching
• Unrelated donor searches
• Donor choice and eligibility

• **Search strategies (Sibling, UD, CB, no Haplo)**
Finding a MUD

Search success rates and duration

- Search success rates (>23 million VUDs)
  - 8/8 match: 40 – 60%
  - 1 antigen mismatch: 60 – 90%
- Median search duration: 22 d – 2.5 mo
- Median time to transplant: 2 – 4 mo
Actuarial probability of finding a 7/8 or 8/8 MUD

in Spain (Memoria REDMO 2009)
## Alternative donor allogeneic transplantation: criteria for choosing MUD vs. CBT vs. Haplo

<table>
<thead>
<tr>
<th>Information on A+B+DRB1 (DNA) typing (%)</th>
<th>UBMT</th>
<th>UCBT</th>
<th>Haplo-HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median search time (months)</td>
<td>16-56</td>
<td>~80</td>
<td>100</td>
</tr>
<tr>
<td>Donors identified but not available (%)</td>
<td>3-6</td>
<td>&lt;1</td>
<td>Nil</td>
</tr>
<tr>
<td>Rare haplotypes represented (%)</td>
<td>20-30</td>
<td>~1</td>
<td>None</td>
</tr>
<tr>
<td>Main limiting factor to graft acquisition</td>
<td>HLA identity</td>
<td>Cell dose</td>
<td>Poor mobilization</td>
</tr>
<tr>
<td>Ease of rearranging the date of cell infusion</td>
<td>Difficult</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Potential for immunotherapy</td>
<td>Yes</td>
<td>No</td>
<td>Yes (limited)</td>
</tr>
<tr>
<td>Potential for viral transmission to recipient</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for congenital disease transmission to recipient</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for the donor</td>
<td>Very low</td>
<td>No</td>
<td>Very low</td>
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<tr>
<td>Main problems to be overcome</td>
<td>GvHD</td>
<td>Graft failure, delayed immune recovery</td>
<td>Delayed immune recovery, lack of T-cell-mediated GVL effect</td>
</tr>
</tbody>
</table>

Abbreviations: Haplo-HSCT=haploidentical hematopoietic stem cell transplantation; UBMT=unrelated donor BM transplantation; UCBT=umbilical cord blood transplantation.

* Modified from Grewal et al. 4

_V. Rocha, F. Locatelli. BMT 41, 207–214; 2008_
Strategy of alternative stem cell donor

High resolution HLA typing of the patient

Schema of how we select CB units.

Evaluate search reports for units 4-6/6 HLA-matched with TNC ≥ 2.0 x 10^7/kg.

Review information & bank of origin for each unit. Obtain missing unit information. Request CT of units of interest. Prepare CB Search Summary Report (Figure 1).

Review CTs: update Search Summary.

Rank units according to HLA-A,-B antigen, -DRB1 allele match (Figure 1). List highest to lowest TNC within each match grade (correct for RBC if needed).

1st choice
6/6 units: Choose largest TNC.

2nd choice
5/6 units: Choose largest TNC.

3rd choice
4/6 units: Choose largest TNC.

Make final selection of unit(s) of graft (units 1a & 1b if double unit graft).

Prepare domestic back-up unit(s).

Plan shipment(s).

HOW TO SELECT THE OPTIMAL GRAFT SOURCE?

1. HLA-matched related donor (MRD)
   - ↑ CD34⁺  ↑ CD3⁺
   - Avoid F→ M
   - Young
   - MUD > Old MRD?

2. 10/10 HLA-matched unrelated donor (MUD)
   - CMV⁻
   - ABO=

3. HLA-mismatched related (MMRD)
   - Similar OS, late infections
   - Early CD4⁺ T-cell reconstitution

3. HLA-mismatched unrelated (MMUD)

3. Umbilical cord blood (UCB)
   - Related/unrelated

No consensus

Similar OS, also if PB

Graph showing survival rates of matched sibling donors compared to unrelated donors.
Upcoming concerns for donor/CBU selection

- **Donor**
  - Consider age!
  - CMV
  - HLA antibodies in recipient
- **CBU**
  - Seek HLA C match
  - Seek max. 1-2 Allele MM
  - Take into account NIMA effect for MM CB units
Thanks

• Sophie Servais
• Yves Beguin
• Carlheinz Muller (ZKRD)