Minor Histocompatibility Antigens in Transplantation

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Minor Histocompatibility Antigens in Transplantation

Background

HSCT and acute GvHD

Minor Histocompatibility Antigens

Characteristics
Role in Transplantation
Our data in Thalassemia
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Success following HCT is ultimately determined by the ability to achieve sustained engraftment and eradication of abnormal or malignant host cells avoiding reactions influenced by the nature and extent of the genetic disparity between donor and recipient such as:

if possible/necessary to obtain a GvL effect
Clinical features of Acute GVHD

Acute GVHD was defined to occur prior to day 100, whereas chronic GVHD occurred after that time.

The clinical manifestations of acute GVHD occur in the skin, gastrointestinal tract and liver.

81% skin involvement
54% GI involvement
50% liver involvement

Pathophysiology of Acute GVHD

Two principles are important to consider regarding the pathophysiology of acute GVHD:

Acute GVHD reflects exaggerated but normal inflammatory mechanisms mediated by donor lymphocytes infused into the recipient.

Second, the recipient tissues that stimulate donor lymphocytes have usually been damaged by underlying disease, prior infections, and the transplant conditioning regimen.
Pathophysiology of Acute GVHD

The development of acute GVHD can be summarized in three sequential steps or phases:

1 - activation of the APCs;
2 - donor T cell activation, proliferation, differentiation and migration;
3 - target tissue destruction
Based largely on experimental models, the development of acute GVHD can be conceptualized in three sequential steps or phases:

1. activation of the APCs;
2. donor T cell activation, proliferation, differentiation and migration;
3. target tissue destruction.
In Phase I the recipient conditioning regimen damages host tissues and causes release of inflammatory cytokines such as TNFα, IL-1 and IL-6. Increased levels of these cytokines leads to activation of host antigen presenting cells (APCs).

Pathophysiology of Acute GVHD

Based largely on experimental models, the development of acute GVHD can be conceptualized in three sequential steps or phases:

1 - activation of the APCs;
2 - donor T cell activation, proliferation, differentiation and migration;
3 - target tissue destruction.
Pathophysiology of Acute GVHD

In Phase II, host APCs activate mature donor cells

Based largely on experimental models, the development of acute GVHD can be conceptualized in three sequential steps or phases:

1 - activation of the APCs;
2 - donor T cell activation, proliferation, differentiation and migration;
3 - target tissue destruction.
The subsequent **proliferation and differentiation of activated donor T cells** produces additional effectors that mediate the tissue damage, including Cytotoxic T Lymphocytes, Natural Killer (NK) cells, TNFα and IL-1.
Donor T-cell activation occurs when donor T cells respond to genetically defined proteins on host cells.

The most important proteins are Human Leukocyte Antigens (HLA) which are highly polymorphic and are encoded by the major histocompatibility complex (MHC).

It is well known that HLA matching reduces, but does not prevent the development of graft versus host disease.
Despite HLA identity between a patient and donor, approximately 30% of patients receiving HLA-identical grafts develop acute GVHD due to genetic differences that lie outside the HLA loci.
Non-HLA Genetics as risk factors associated with GvHD

Many other genetic factors, besides HLA, are involved in GvHD occurrence.

Polymorphisms in both donors and recipients for cytokines
- Tumor Necrosis Factor (TNF)-α,
- Interleukin 10 (IL-10),
- Interferon-γ (IFNγ)

Genetic polymorphisms of proteins involved in innate immunity
- Nucleotide oligomerization domain 2
- Keratin 18 receptors
- HLA-G 14 bp transcript presence
- KIR receptors and ligands
- Minor histocompatibility antigens (mHAgS)
Minor Histocompatibility Antigens in Transplantation

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Minor Histocompatibility Antigens

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Minor Histocompatibility Antigens in Transplantation

mHAg are peptides derived from allelic variants of normal cellular proteins

mHAg are generally HLA restricted

some allelic variants has high affinity for specific HLA loci

some allelic variants has low affinity for specific HLA loci
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These protein/peptide variants most often arise due to single nucleotide polymorphisms (SNPs) or deletions.

example:

**HA-1** exists in 2 allelic form:

- **R**: no immunogenic
- **H**: immunogenic

HA-1\(^R\)

```plaintext
GTG TTG CGT GAC GAC CTC CTT GAG GCC
V L R D D L L E A
```

HA-1\(^H\)

```plaintext
GTG CTG CAT GAC GAC CTC CTT GAG GCC
V L H D D L L E A
```

(M. Wilke et al. Tissue Antigens 1998)
When presented by self class I or II MHC antigens, the immunogenic variant induces cellular immune responses in HLA-matched individuals lacking the same allelic variant.
A - Peptides derived from cellular proteins are displayed on the surface of cells complexed to MHC molecules and autologous T cells are tolerant to these self-peptides.
Minor Histocompatibility Antigens in Transplantation

A - Peptides derived from cellular proteins are displayed on the surface of cells complexed to MHC molecules and autologous T cells are tolerant to these self-peptides.

B - After processing T cells of the donor will recognize the unique peptides on recipient cells as foreigner.
Cytotoxic T lymphocytes directed against mHAgs have been isolated from recipients of HLA-matched transplants with aGVHD.

...and cytotoxic T cell clones from such patients have been used to identify and characterize mHAgs.
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There likely exist thousands of protein variants with the potential of functioning as mHAg.

However, only about 2 dozen human mHAg have been identified and mostly extensive studied.

Some mHAg are ubiquitously expressed:
- HA-3, HA-8

Most of the mHAg have more restricted tissue expression:
- HA-1, HA-2 in hematopoietic tissue
- CD31 in platelets and endothelial cells
- HB-1 in B lymphoblastoid cells

May be present both in autosomal or sex chromosomes.
List of mHAgS located in autosomal chromosomes

<table>
<thead>
<tr>
<th>mHGs</th>
<th>HLA restriction</th>
<th>Peptide sequence</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-1</td>
<td>HLA-A *02</td>
<td>VLHDDILLEA</td>
<td>haematopoietic</td>
</tr>
<tr>
<td></td>
<td>HLA-B *60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HA-2</td>
<td>HLA-A *02</td>
<td>YIGEVLVSV</td>
<td>haematopoietic</td>
</tr>
<tr>
<td>HA-3</td>
<td>HLA-A *01</td>
<td>VTEPGTAQY</td>
<td>broad</td>
</tr>
<tr>
<td>HA-8</td>
<td>HLA-A *02</td>
<td>RTLDKVLEV</td>
<td>broad</td>
</tr>
<tr>
<td>HB-1</td>
<td>HLA-B *44</td>
<td>EEKRGSLLHVW</td>
<td>haematopoietic</td>
</tr>
<tr>
<td>ADIR</td>
<td>HLA-A *02</td>
<td>SVAPALALFPA</td>
<td>broad</td>
</tr>
<tr>
<td>ACC-1</td>
<td>HLA-A *24</td>
<td>DYLQYVLQI</td>
<td>haematopoietic</td>
</tr>
<tr>
<td>ACC-2</td>
<td>HLA-B *44</td>
<td>KEFEDDIINW</td>
<td>haematopoietic</td>
</tr>
<tr>
<td>CTSH</td>
<td>HLA-A *31</td>
<td>ATLPLLCAR</td>
<td>broad</td>
</tr>
<tr>
<td>ECGF1</td>
<td>HLA-B *07</td>
<td>RPHAIRRPLAL</td>
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</tr>
<tr>
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<td>TPNQRQNVVC</td>
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<td>PANE-1</td>
<td>HLA-A *03</td>
<td>RVWDLPGPLK</td>
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<td>SP1 10</td>
<td>HLA-A *03</td>
<td>SLPRGTSTPK</td>
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<tr>
<td></td>
<td>HLA-A *29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT2B17</td>
<td>HLA-B *44</td>
<td>AELLNIPFLY</td>
<td>broad</td>
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</table>
# List of mHAgS located in sex chromosomes

<table>
<thead>
<tr>
<th>mHGgs</th>
<th>HLA restriction</th>
<th>Peptide sequence</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRBY</td>
<td>HLA-DQ5</td>
<td>HIE\text{NFSDID}MGE</td>
<td></td>
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<tr>
<td></td>
<td>HLA-DRB1 *1501</td>
<td>AST\text{ASKGRYIPPHLRN} KEA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA-B *2705</td>
<td>SR\text{DSRGKPGY}</td>
<td>haematopoietic</td>
</tr>
<tr>
<td>DFFRY</td>
<td>HLA-A*01:01</td>
<td>IVD\text{CLTEMY}</td>
<td>broad</td>
</tr>
<tr>
<td>RPS4Y</td>
<td>HLA-DRB3 *0301</td>
<td>VIKV\text{NDTVQI}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA-B *5201</td>
<td>TIR\text{YPDPVI}</td>
<td>broad</td>
</tr>
<tr>
<td>SMCY</td>
<td>HLA-B *0702</td>
<td>SPS\text{VDKARAEL}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA-A *0201</td>
<td>FID\text{SYICQV}</td>
<td>broad</td>
</tr>
<tr>
<td>TMSB4Y</td>
<td>HLA-A *3303</td>
<td>EV\text{LLRPGLHFR}</td>
<td>broad</td>
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<tr>
<td>UTY</td>
<td>HLA-B *08</td>
<td>LP\text{HNHTDL}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HLA-B *60</td>
<td>RE\text{SEESVSL}</td>
<td>broad</td>
</tr>
</tbody>
</table>
Kamei introduced an innovative approach for identifying the genes that encode novel T cell-defined human minor histocompatibility antigens (mHags)
Minor Histocompatibility Antigens in Transplantation

Introduction

Acute GvHD: clinical aspects and physiopathology

Minor Histocompatibility Antigens

Characteristics
Role in Transplantation
Our data in Thalassemia
Potential role in GvHD:
Presence of Donor T cells specific for mHAgs broadly expressed by both haematopoietic and epithelial cells of the recipient

Potential role in GvL:
Presence of Donor T cells specific also to the graft-versus leukaemia effect if leukaemic cells express the minor histocompatibility antigens
To be considered in the analysis:

- HLA restriction
- the direction of the mHAg mismatch
- the distribution of mHAg: broad or tissue restricted
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**donor**

- mHAg Immunogenic
  - YES
  - REJECTION
- NO
  - MATCHED

**recipient**

- mHAg Immunogenic
  - NO
  - GVHD
  - NO EVENT
- YES
  - MATCHED
Perform a specific Software mHAg analysis

Assessment of the theoretical potential for mismatches mHAg's, through the analysis with a specific software made available online by the University of Leiden, in the clinical course post-transplant.

DdMinor: http://www.lumc.nl/dbminor
Minor Histocompatibility Antigens in Transplantation

MISMATCHES OF MINOR HISTOCOMPATIBILITY ANTIGENS BETWEEN HLA-IDENTICAL DONORS AND RECIPIENTS AND THE DEVELOPMENT OF GRAFT-VERSUS-HOST DISEASE AFTER BONE MARROW TRANSPLANTATION

ELS GOULMY, PH.D., RONALD SCHIPPER, M.SC., JOS POOL, ELS BLOKLAND, J.H. FREDERIK FALKENBURG, M.D., PH.D., JAAK VOSS, M.D., PH.D., ALOIS GRATWOHL, M.D., PH.D., GEORGIA B. VOGELSANG, M.D., PH.D., HANS C. VAN HOUWELINGEN, PH.D., AND JON J. VAN ROOD, M.D., PH.D.
Minor Histocompatibility Antigens in Transplantation


Effects of mismatching for Minor Histocompatibility Antigens on clinical outcomes in HLA-matched, unrelated hematopoietic stem cell transplants:

Minor antigen mismatching in unrelated donors

Stephen Spellman¹, Melissa B. Warden², Michael Haagenson³, Bradley C. Pietz², Els Goulmy, Ph.D.⁴, Edus H. Warren, M.D., Ph.D.⁵, Tao Wang, Ph.D.⁶, and Thomas M. Ellis, Ph.D.²

¹National Marrow Donor Program, Minneapolis, MN ²BloodCenter of Wisconsin, Milwaukee, WI ³Center for International Blood and Marrow Transplant Research, Minneapolis, MN ⁴Leiden University Medical Center, Leiden, The Netherlands ⁵Fred Hutchinson Cancer Research Center, Seattle, WA ⁶Medical College of Wisconsin, Milwaukee, WI
Minor Histocompatibility Antigens in Transplantation

Recipient/donor pairs from 730 unrelated HLA-A, B, C, DRB1, and DQB1 allele-matched transplants facilitated by the National Marrow Donor Program (NMDP) were studied.

The majority (86%) of the pairs were mismatched at HLA-DP.

Transplants were performed between 1996 and 2003.

Patients had different disease characteristics.
Minor Histocompatibility Antigens in Transplantation

Spellman: Results for Single mHAg mismatches
Results for Multiple mHAg mismatches
Spellman: Results for Single mHAg mismatches (UNRELATED HSCT)

No significant association with any GvH or HvG for single mismatch: HA-1, HA-2, HA-3, HA-8, and HB-1

Reduced risk of grades III–IV GvHD when pairs were mismatched for CD31_{563} in the host versus graft direction (p=0.001) in HLA-A2 positive pairs

No effect of HY mismatching was observed for any outcome
Spellman: Results for Multiple mHAg mismatches (UNRELATED HSCT)

**Reduced risk of acute GvHD** in HLA-A2 positive pairs mismatched for 2 or more mHAg for HA-1, HA-2, HA-8 and/or CD31\(^{(563)}\) in the HvG direction (perhaps reflecting the influence of CD31(563) mismatching on this group)

**Lower survival** in HLA-A2 positive pairs mismatched for 2 or more mHAg (HA-1, HA-2, HA-8, and/or CD31\(^{(563)}\) in the GvH direction (p=0.01).

**Decreased survival and increased TRM** in HLA-A1 positive pairs mismatched for both CD31 and HA-3 in the GvH direction (p=0.02)
Minor Histocompatibility Antigens in Transplantation

Multicenter Analyses Demonstrate Significant Clinical Effects of Minor Histocompatibility Antigens on GvHD and GvL after HLA-Matched Related and Unrelated Hematopoietic Stem Cell Transplantation

Minor Histocompatibility Antigens in Transplantation

Spierings E et al. Biol Blood Marrow Tranplant 2013 Aug

The International Histocompatibility and Immunogenetics Workshops (IHIW)

In collaboration with 20 laboratories of the IHIW, the roles of 10 autosomal and 10 Y chromosome-encoded minor H antigens were investigated on GvHD and relapse incidence in:

- 639 HLA-identical related donor (IRD)
- 210 HLA-matched unrelated donor (MUD)

Donor and recipient DNA samples were genotyped for the minor H antigens:

HA-1, HA-2, HA-3, HA-8, HB-1, ACC-1, ACC-2, SP110, PANE1, UGT2B17 and HY.

The correlations with the primary outcomes GvHD (acute or chronic GvHD), survival, and relapse were statistically analyzed.
Results - of mHAgs disparities in sex chromosome

none of the HLA class I-restricted HY antigens were found to be associated with any of the primary outcomes

Analysis of the overall gender effect:

increased GvHD incidence in the female-to-male transplantations (P<0.005)
decreased GvHD-free survival in the female-to-male transplantations (P< .001)
Minor Histocompatibility Antigens in Transplantation

Spierings E et al. Biol Blood Marrow Transplant 2013 Aug

Results - of mHAgS autosomally encoded

Increased GvHD incidence in IRD HSCT - but not in MUD - only when mismatching for the broadly expressed mHAgS HA-8 P<0.005)

In recipients with GvHD - but not in those without GvHD - mismatching for hematopoietic mHAgS correlated with
- lower relapse rates (P=0.078)
- higher relapse-free survival (P=0.029)
- higher overall survival (P=0.032)

The GvHD-GvL association - demonstrating a significant lower relapse in hematopoietic mHAgS mismatched patient/donor pairs - underlines their clinical applicability for adoptive immunotherapy, enhancing the GvL effect in a GvHD controllable manner
Minor Histocompatibility Antigens in Transplantation

Blood. 2013 Aug 1

Human regulatory T cells against minor histocompatibility antigens: ex vivo expansion for prevention of graft-versus-host disease.

Veerapathran A, Pidala J, Beato F, Betts B, Kim J, Turner JG, Hellerstein MK, Yu XZ, Janssen W, Anasetti C. Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL, USA

They identified and expanded regulatory CD4 T cells (Treg) specific for human mHAs

Cultured Treg produced allospecific suppression, maintained demethylation of the Treg-specific Foxp3 gene promoter, Foxp3 expression and TGF-β production

This is the first report of detection and expansion of potent mHA-specific Treg from HLA-matched siblings in sufficient numbers for application in human transplant trials
Minor Histocompatibility Antigens in Transplantation

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HSCT and acute GvHD

Minor Histocompatibility Antigens

Characteristics
Role in Transplantation
Our data in Thalassemia
We investigate the impact of mHAg matching on the outcome of HSCT for Thalassemia in a retrospective study of 146 12/12 HLA identical related donor-recipient Thalassemic HSCT Patients.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>aGvHD (III-IV)</td>
<td>8</td>
<td>5.4%</td>
</tr>
<tr>
<td>Rejection</td>
<td>18</td>
<td>12.3%</td>
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### Obtain donor and patients mHAg data

<table>
<thead>
<tr>
<th></th>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR</td>
</tr>
<tr>
<td>HA-1</td>
<td>□ H</td>
<td>✓ R</td>
</tr>
<tr>
<td>HA-2</td>
<td>✓ V</td>
<td>□ M</td>
</tr>
<tr>
<td>HA-3</td>
<td>✓ T</td>
<td>□ M</td>
</tr>
<tr>
<td>HA-8</td>
<td>□ R</td>
<td>✓ P</td>
</tr>
<tr>
<td>HB-1</td>
<td>✓ H</td>
<td>□ Y</td>
</tr>
<tr>
<td>ACC-1</td>
<td>□ Y</td>
<td>✓ C</td>
</tr>
<tr>
<td>ACC-2</td>
<td>□ D</td>
<td>✓ G</td>
</tr>
<tr>
<td>SP110</td>
<td>✓ R</td>
<td>□ G</td>
</tr>
<tr>
<td>PANE-1</td>
<td>✓ R</td>
<td>□ *</td>
</tr>
<tr>
<td>UGT2B17</td>
<td>✓ +</td>
<td>□ -</td>
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<tr>
<td>LRH-1</td>
<td>□ 4C</td>
<td>□ 5C</td>
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<td>ECGF-1</td>
<td>□ H</td>
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<td>□ R</td>
<td>□ G</td>
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<tr>
<td>LB-ADIR</td>
<td>□ F</td>
<td>□ S</td>
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<tr>
<td>HY</td>
<td>□ +</td>
<td>✓ -</td>
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# HLA Typing

<table>
<thead>
<tr>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*01</td>
<td>B*44</td>
<td>Cw*01</td>
</tr>
<tr>
<td>A*02</td>
<td>B*55</td>
<td>Cw*07</td>
</tr>
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<table>
<thead>
<tr>
<th>HLA-DRB1</th>
<th>HLA-DRB3</th>
<th>HLA-DRB4</th>
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<tbody>
<tr>
<td>DRB1*07</td>
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<td>Select</td>
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<td>DRB1*10</td>
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<th>HLA-DPA1</th>
<th>HLA-DPB1</th>
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<td>DPB1*02</td>
</tr>
<tr>
<td>Select</td>
<td>Select</td>
<td>DPB1*09</td>
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<tr>
<td>Select</td>
<td>DQB1*05</td>
</tr>
</tbody>
</table>
Correlation between donor / patient mHAg disparities and aGvHD (III-IV)

No statistical significant influence on aGvHD due to donor – recipient disparities for mHAg in Thalassemic transplanted patients was observed
**Influence of mHAgS on rejection after HSCT in Thalassemia**

<table>
<thead>
<tr>
<th>Total number of patients = 49</th>
<th>HA-8 with A*02 restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA-8 disparities = 5</td>
</tr>
<tr>
<td>Rejection YES – 7 pts</td>
<td>2</td>
</tr>
<tr>
<td>Rejection NO – 42 pts</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total number of patients = 146</th>
<th>HA-8 NO A*02 restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HA-8 disparities = 15</td>
</tr>
<tr>
<td>Rejection YES – 18 pts</td>
<td>5</td>
</tr>
<tr>
<td>Rejection NO – 128 pts</td>
<td>10</td>
</tr>
</tbody>
</table>
CONCLUSION

The analysis of the minor histocompatibility antigens differences between donor and recipient represents an important element in the occurrence of complications after HLA-identical related donor HSCT, although up to date many contrasting results are still reported in different studies.
Acknowledgments

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Marco Marziali
Antonella Isgrò
Michela Ribersani

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Maria Grazia Roncarolo
Federico Sizzano

LIBT Fondazione IME
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Maria Troiano
Mariarosa Battarra
Tiziana Galluccio
Rossella Condello
Annalisa Guagnano
Giuseppe Testa
Chiara Stellitano
Renata Rosati
Andrea Di Luzio
Simona De Petris
Eleonora Palladini
Martina Mangione
The role for mHAg disparities in HSCT outcomes has been supported by studies showing higher rates of acute GvH and lower survival in HLA-identical sibling transplant recipients who are mHAg disparate.

Marijt WA et al. Proc Natl Acad Sci U S A 2003
Grumet FC et al. Biol Blood Marrow Transplant 2001

increased rates of GvHD and lower rates of leukemia recurrence observed in pairs who are disparate at HA-1 or HA-2

Tseng et al Blood 1999

....although this last is disputed by other studies
Cavanagh G et al. Transplantation 2005
Additionally, disparities in HA-8 and CD31 were associated with decreased patient survival
Tseng et al Blood 1999
Marijt WA et al. Proc Natl Acad Sci U S A 2003
Grumet FC et al. Biol Blood Marrow Transplant 2001