Pre-Transplant Immunogenetic and Immunological assessment for Hematopoietic Stem Cell Transplantation

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January 2018
Bone Marrow Transplantation
Hematopoietic Stem Cell Transplantation

Recognized curative therapy

**Indications**

- Leukemia, lymphoma
- Aplastic anemia
- Hemoglobinopathies
- MDS myeloproliferative
- Thalassemia
- Metabolic disorders
- Immunodeficiencies
- MS, Rheumatologic disorders

Rapid strides – understanding intricacies of HSCT
The Nobel Prize in Physiology or Medicine 1990

Joseph E. Murray, E. Donnall Thomas

The Nobel Prize in Physiology or Medicine 1990 was awarded jointly to Joseph E. Murray and E. Donnall Thomas "for their discoveries concerning organ and cell transplantation in the treatment of human disease"

15th March 1920 - Oct 20th 2012

1950: First Transplant Between identical twins LEUKEMIA

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Hematopoietic Stem Cell Transplantation

Despite good HLA match, milder conditioning, better immunosuppression

Major cause of morbidity and mortality is GVHD??

Patient Improved, now on GVHD prophylaxis

16/01/2018
Annual Number of HCT Recipients in the US by Transplant Type

- Autologous
- Allogeneic

Number of Transplants


CIBMTR

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Sources of Stem Cells

BONE MARROW HARVEST

CORD BLOOD

PERIPHERAL BLOOD STEM CELLS

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Factors Influencing HSCT Outcome

- Original disease - malignant / non-malignant
- Pre-Transplant conditioning regimen
- *Recipient – donor Genetic disparity*
- Hematopoietic Stem Cell Dose
- Presence / absence of donor T cells
- Immunosuppression
Genomic Organization of the HLA Complex

Chromosome 6

- Highly polymorphic genomic region
- Immunologically relevant - Antigen presentation
- Polymorphism restricted to functionally crucial peptide binding regions
- Crucial in Organ and Stem Cell transplantation
- Many diseases associated with genes encoding HLA molecules
Polymorphism of the HLA System

(2017- IMGT/HLA)
Numbers of HLA Alleles
Class I - 12544 + Class II - 4622
= 17166
HLA-typing at the DNA level requires nomenclature for specific DNA sequences.

**Gene region**

**Subregion**

**Allele family 15**

HLA-DRB1*15:03

**α-or β-chain polypeptide**

**Gene locus**

**WHO Nomenclature Committee HLA-Nomenclature System 2010**
## HLA Typing for BMT/PBSCT

<table>
<thead>
<tr>
<th>Low resolution methods</th>
<th>Intermediate resolution methods</th>
<th>High resolution methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC (Serology)</td>
<td>PCR-SSP</td>
<td>PCR-SSP</td>
</tr>
<tr>
<td>PCR-SSP</td>
<td>PCR-RLS</td>
<td>PCR-SSOP</td>
</tr>
<tr>
<td>PCR-SSOP</td>
<td>PCR-SSOP</td>
<td>Sequenced Based Typing (SBT)</td>
</tr>
</tbody>
</table>

- **CDC-Complement Dependent Cytotoxicity**
- **SSP- Sequence Specific Primer**
- **SSOP-Sequence Specific Oligonucleotide Probes**
- **RLS- Reverse Line Strips**

- **Next Generation Sequencing (NGS)**
Serological Typing: *Microlymphocytotoxicity*

Limitations

**Fresh blood, viable lymphocytes, in CML patients-Blasts??**

**Cross reactivity**

**Surface expression of antigens- heterozygous/ homozygous**

Throughput - Low

Resolution - Low

10-15 samples/day

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Molecular methods – DNA based HLA typing

**SSP-PCR** Sequence-specific PCR - allele-specific primers

SSP= Sequence-specific primer

- Amplification
- No amplification

Amplification internal controls
Allele-specific product

SSP does not match allele

Throughput - Low  4-8 samples/ day
Resolution - Low and High

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PCR-SSO: Reverse Hybridization

Reverse SSOP

Amplified DNA

Specific probes on membrane

Processing

Detection

Throughput- intermediate 16 A,B,DR / run  Resolution - Low / intermediate

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通过 - 高 32 样品 (A,B,DR)/天
分辨率 - 低/中间/高

PCR-SSO on the Chip

 userName, nearest, AIIMS, NDelhi, Jan 2018
Luminex Based assay- PCR-SSO Genotyping and Antibody

- Controls + 96 specificities (class I) or 76 specificities (class II)/well
- Performed in a 96-well format (8 well strips)
- Assay time = 2 hours
- Higher sensitivity than flow SA beads

Throughput- High 32 samples/day (A,B,DR)
Resolution - Low and High

Class I beads: HLA-A, -B, -C loci
Class II beads: HLA-DR, -DQ, -DP

Laser 1
Laser 2

Tells the instrument which bead is being examined
Tells the instrument how much antigen is bound to the bead
Sequence Based Typing

Exon 2

HLA-B

Exon 3

Forward PCR primer

Reverse PCR primer

Sequencing primers

Applied Bio-systems 3130xl Genetic Analyzer

Throughput - 12 samples/day (A,B,DR)
Resolution - High

17

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HLA Allele assignment- Sequencing Technologies

**Sanger**
- Allele 1/2
  - SNP1: G/A
  - SNP2: G/A
  - SNP3: G/A

**Next-Generation**
- Allele 1
  - SNP1: A
  - SNP2: A
  - SNP3: G/A?
- Allele 2
  - SNP1: G
  - SNP2: G
  - SNP3: G/A?

**Third-Generation**
- Allele 1
  - SNP1: A
  - SNP2: A
  - SNP3: G
- Allele 2
  - SNP1: G
  - SNP2: G
  - SNP3: A
HLA- Next Generation Sequencing - NGS

- **Roche**
  - 454

- **Illumina**
  - MiSeq
  - HiSeq
  - NextSeq
  - MiniSeq
  - NovaSeq

- **Thermo Fisher**
  - Ion Proton
  - Ion PGM
  - Ion S5

- **PacBio**
  - RS II
  - Sequel

- **Oxford Nanopore**
  - MinION
  - Promethion

**HLA-NGS Technologies**

- Long reads (>10 kb)
- Short reads (<1 kb)
Applications in Clinical Histocompatibility Testing

- Gene Segments Covered - detects all intragenic mutations
- Accuracy and Reproducibility - Ability to get correct types
- Extremely high resolution. No secondary tests needed
- Ability to find errors and novel alleles
- TAT similar or better than Sanger SBT
- Automatic Genotype assignment and Less analysis time
- Loci Tested (in HSCT and in solid organ transplantation)
Donor Selection based on HLA match

Parents: Both 50% Match

50% Sibs: 50% Match
25% Sibs: 0% Match
25% Sibs: 100% Match

Brother: Haploidentical
Sister: Haploidentical
Patient
HLA matched
Sister: Unidentical
What if no HLA compatible donor in the family?

OPTIONS??

- Within family – parents?
- Extended family search
- Ante Natal HLA typing
- Unrelated Donors through registries
Extended family testing

A*26-B*08-DRB1*03
A*02-B*27-DRB1*15

A*26-B*08-DRB1*03
A*02-B*27-DRB1*15

A*24-B*27-DRB1*11
A*23-B*41-DRB1*04

A*02-B*15-DRB1*07
A*23-B*41-DRB1*04

A*26-B*08-DRB1*03
A*31-B*35-DRB1*11

Matched with Uncle

ad = fg
Possibility of additional HLA compatible family donors

Parental Sharing of HLA

Father | A | B | DR
---|---|---|---
a | A23 | B41 | DR4
b | A1 | B8 | DR3

Mother | a | b | c | d
---|---|---|---|---
a | A11 | A11 | A1
b | B35 | B35 | B8
 c | DR7 | DR7 | DR3

donor: Mother

HLA Homozygous Parent

Father | A | B | DR
---|---|---|---
a | A11 | B35 | DR7
b | A11 | B35 | DR7

donor: Sibling

Father | a | b | c | d
---|---|---|---|---
a | A11 | A11 | A33 | A33
b | B35 | B35 | B44 | B44
 c | DR7 | DR7 | DR11 | DR11

donor: Sibling

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The patient and the father share 10 of the 10 alleles tested at class I and II loci.

Tx done in Dec 2013

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CML patient- H-YYYYY/13, HLA No. -------

Tested

<table>
<thead>
<tr>
<th>a</th>
<th>A*02:01</th>
<th>B*40:02</th>
<th>DR*14</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td>A*24:07</td>
<td>B*35:03</td>
<td>DR*11</td>
</tr>
</tbody>
</table>

Tested

<table>
<thead>
<tr>
<th>c</th>
<th>A*02:01</th>
<th>B*40:02</th>
<th>DR*14</th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td>A*02:11</td>
<td>B*40:06</td>
<td>DR*15</td>
</tr>
</tbody>
</table>

4 out of 4 match- LR (A,B)

- ad

5 out of 6 match - LR (A,B,DRB1)

3 out of 6 match- HR (A,B,DRB1)

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Alternate Donor: Antenatal Typing

A*01 B*15
A*32 B*52

A*33 B*44
A*03 B*18

A*03 B*18
A*32 B*52

A*01 B*15
A*33 B*44

A*32 B*52
A*33 B*44

A*01 B*15
A*33 B*44

HLA-unidentical

HLA-haploidentical

HLA-match

Benefit of testing: Nearly 30% of referrals, CVS was HLA identical
Parents: Both 50% Match
50% Sibs: 50% Match
25% Sibs: 0% Match
25% Sibs: 100% Match

Matched Unrelated Donor
A26, B8, DR3
A2, B44, DR4

Haploidentical

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Bone Marrow Donors Worldwide is celebrating a momentous milestone

Bone Marrow Donors Worldwide is celebrating a momentous milestone: 25 million people are currently listed as potential marrow donors on worldwide donor registries. This record number of registry members gives greater hope to blood cancer patients, caregivers and healthcare professionals around the world.

Welcome to Bone Marrow Donors Worldwide

Bone Marrow Donors Worldwide (BMDW) is the continuing effort to collect the HLA phenotypes and other relevant data of volunteer stem cell donors and cord blood units, and is responsible for the co-ordination of their worldwide distribution. Participants are 75 stem cell donor registries from 53 countries, and 53 cord blood registries from 36 countries.

The current number of donors and cord blood units in the BMDW database is: 27,145,900 (26,470,574 donors and 675,326 CBUs)
Bone Marrow Donors Worldwide - 53 countries (Aug 2017)

- **Australia**: Bone Marrow Donor Registry 170,680
- **France Greffe de Moelle**: 273,027
- **Austrian Bone Marrow Donors**: 67,059
- **Be the Match NMDP**: 8,403,592
- **Anthony Nolan Trust**: 659,486
- **German Registry of Bone Marrow Donors**: 7,542,435
- **BM Donors + CBUs**: 28,935,264
- **India**:
  - IN1- 9580
  - IN2- 223,067
  - IN3- 6225
  - IN4- 5200
  - IN5- 33,977

**Total BM Donors Worldwide**: 28.9 M Donors

**Registries**: 75
**CB Banks**: 53
**CBUs**: 28,935,264

**India Donor Registry**: 278,053

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Allogeneic HCT Recipients in the US, by Donor Type

- HLA-identical Sibling
- Other Relative
- URD-BM / PB
- URD / UCB

Number of Transplants


Centre for International Blood and Marrow Transplant Research
Matched and mismatched unrelated donor transplantation: is the outcome the same as for matched sibling donor transplantation?

Andrea Bacigalupo

Hematology 2012

Improved overall 1 year survival rates:

- Improvement in HLA-matching techniques
- Better donor selection
- Better overall patient selection for transplantation
- Improvements in supportive care
Survival among HLA-A,B and DRB1 allele matched pairs by number of mismatched class I loci

Flomenberg et al, Blood 2004

0 Mismatches (n=791)
1 Mismatch (n=317)
2 Mismatches (n=117)
Overall Survival after allo HSCT from ISDs, MFDs and MUDs

Ottinger et al, Blood 2003
Impact of mismatched HLA Loci on the risk of Ac GvHD

Ottinger et al, Blood 2003

Days after Transplantation
SCT Workshop Component: Survival among matched pairs

- 0 Alleles (n=78)
- 1 Allele (n=67)
- 2 Alleles (n=49)
- 3 Alleles (n=16)
- 4 Alleles (n=10)
- 5 or More Alleles (n=7)

Probability vs Years after Transplant
How to select the best available related or unrelated donor of hematopoietic stem cells?

Jean-Marie Tiercy

National Reference Laboratory for Histocompatibility, Department of Genetic and Laboratory Medicine, University Hospitals Geneva, Switzerland

Overall probabilities of identifying a 7/8, 8/8, 9/10 and 10/10 matched unrelated donor.

<table>
<thead>
<tr>
<th>Ethnic origin (country)</th>
<th>Match 8/8</th>
<th>Match ≥7/8</th>
<th>Match 9/10</th>
<th>Match 10/10</th>
<th>Match 9-10/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>European (NL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>69%†</td>
</tr>
<tr>
<td>European (UK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>European (A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80%†</td>
</tr>
<tr>
<td>European (D)</td>
<td></td>
<td>20%</td>
<td>61%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European (CH)</td>
<td></td>
<td>24%</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European (NL)</td>
<td></td>
<td>31%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European (IT)</td>
<td></td>
<td>32%</td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European (HR)</td>
<td></td>
<td>30%</td>
<td>65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European (USA)</td>
<td>75%</td>
<td>97%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African (USA)</td>
<td>18%</td>
<td>71%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ME/NA (USA)</td>
<td>46%</td>
<td>90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (USA)</td>
<td>27-42%</td>
<td>76-88%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic (USA)</td>
<td>34%</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aNL: the Netherlands; UK: United Kingdom; A: Austria; D: Germany; CH: Switzerland; HR: Croatia; USA: United States of America; bME: Middle Eastern; NA: North African; cAsian: Chinese, Korean, South Asian, Japanese, Southeast Asian, Vietnamese; dHispanic: South/Central American; e<9/10 in 13% patients; fexceptionally 8/10 matched donors.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Donor</th>
<th>Compatibility high resolution exons 2+3 (cl.I) exon 2 (cl. II)</th>
<th>Compatibility allele level/ 2nd field</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*02</td>
<td>A*02</td>
<td>potential match</td>
<td>potential match</td>
</tr>
<tr>
<td>A*02:01:01G</td>
<td>A*02:01:01G</td>
<td>potential match</td>
<td>potential match</td>
</tr>
<tr>
<td>A*02:01P</td>
<td>A*02:01P</td>
<td>match</td>
<td>potential match</td>
</tr>
<tr>
<td>A*02:01</td>
<td>A*02:06</td>
<td>mismatch</td>
<td>mismatch</td>
</tr>
<tr>
<td>A*02:06</td>
<td>A*02:126</td>
<td>match</td>
<td>mismatch</td>
</tr>
<tr>
<td>A*02:01:01G</td>
<td>A*02:09</td>
<td>potential match</td>
<td>potential match</td>
</tr>
<tr>
<td>A*02:01</td>
<td>A*02:09</td>
<td>match</td>
<td>mismatch</td>
</tr>
<tr>
<td>DRB1*14:01:01</td>
<td>DRB1*14:54:01</td>
<td>match</td>
<td>mismatch</td>
</tr>
<tr>
<td>A*02:01:01:01</td>
<td>A*02:01:01:01</td>
<td>match</td>
<td>match</td>
</tr>
<tr>
<td>A*02:01:01:01</td>
<td>A*02:26</td>
<td>mismatch</td>
<td>mismatch</td>
</tr>
<tr>
<td>A*02:01:01:01</td>
<td>A*02:01:01:02N</td>
<td>mismatch</td>
<td>mismatch</td>
</tr>
<tr>
<td>DRB1*11:BYCC</td>
<td>DRB1*11:RDPB</td>
<td>potential match</td>
<td>potential match</td>
</tr>
<tr>
<td>(11:01/11:09/11:28)</td>
<td>(11:01/11:95/11:97/11:100/11:117)</td>
<td>potential match</td>
<td>potential match</td>
</tr>
<tr>
<td>DRB1*04:04</td>
<td>DRB1*04:VN</td>
<td>mismatch</td>
<td>mismatch</td>
</tr>
<tr>
<td>C*07:02:01G</td>
<td>C*07:02</td>
<td>match</td>
<td>potential match</td>
</tr>
<tr>
<td>C*07:02:01G</td>
<td>C*07:FEAU</td>
<td>match</td>
<td>potential match</td>
</tr>
</tbody>
</table>
## Impact of specific HLA locus or allele mismatches as reported in a multicenter studies of unrelated HSCT.

<table>
<thead>
<tr>
<th>No. of pts</th>
<th>Main conclusions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,646</td>
<td>Single HLA-A,B,C,DRB1 MM (either antigen or allele) associated with increased mortality, additional risk with &lt;9/10 matched (including DQB1) donors</td>
<td>Furst D, Blood. 2013</td>
</tr>
<tr>
<td>8,539</td>
<td>Non-permissive DPB1 MM associated with increased mortality in 9-10/10 matched HSCT</td>
<td>Lancet Oncol. 2012</td>
</tr>
<tr>
<td>3,853</td>
<td>In 7/8 matched HSCT: &gt;2 MM at DRB3/4/5, DQB1 or DPB1 loci associated with lower survival</td>
<td>Biol Blood Marrow Transplant. 2015</td>
</tr>
<tr>
<td>7,349</td>
<td>C<em>03:03/03:04 MM better tolerated, lower impact of C-locus MM explained by the high frequency of C</em>03:03/03:04 MM in the 7/8 matched group</td>
<td>Fernandez-Vina MA, Blood. 2014</td>
</tr>
<tr>
<td>8,003</td>
<td>Single HLA-A,B,C,DRB1 MM associated with increased mortality, DQB1 MM associated with increased acute GVHD, non-permissive DPB1 MM associated with increased mortality in 10/10 or 8/8 matched cases</td>
<td>Pidala J, Blood. 2014</td>
</tr>
<tr>
<td>7,898</td>
<td>Single HLA-A,B,C and double HLA-DRB1-DQB1 MM associated with increased mortality, HLA-A,B,C,DPB1 MM associated with higher risk of acute GVHD, reduced relapse only with C,DPB1 MM</td>
<td>Morishima Y, Blood. 2015</td>
</tr>
<tr>
<td>2,588</td>
<td>Reduced intensity conditioning HSCT: increased mortality in 7/8 matched HSCT, no impact of C*03:03/03:04 or permissive DPB1 MM</td>
<td>Verneris MR, Biol Blood Marrow Transplant. 2015</td>
</tr>
<tr>
<td>803</td>
<td>Single HLA-A,B,C,DRB1/MM (9/10) associated with higher mortality, HLA-DRB1/DQB1 MM more permissive (high ratio of DRB1<em>11:01/11:04 and DQB1</em>03:01/03:02 MM)</td>
<td>Passweg JR, Bone Marrow Transplant. 2015</td>
</tr>
<tr>
<td>2,029</td>
<td>In 11/12 matched HSCT: single nucleotide polymorphism in the regulatory region of DPB1 locus associated with acute GVHD</td>
<td>Petersdorf EW, N Engl J Med. 2015</td>
</tr>
<tr>
<td>6,967</td>
<td>Patient and/or donor B<em>51:01 and patient C</em>14:02 associated with increased acute GVHD and mortality</td>
<td>Morishima S, Haematologica. 2016</td>
</tr>
<tr>
<td>11,039</td>
<td>Donor age (&gt;32 years) and 7/8, 6/8 mismatched donors associated with lower overall survival</td>
<td>Passweg JR, Bone Marrow Transplant. 2015</td>
</tr>
</tbody>
</table>
Bone Marrow/Stem Cell Transplantation in India

Pictures Curtsey, Dr Khattry, ACTREC
BM/HSC Transplant (centres in India)

High Volume BMT Centres
Other BMT Centres

Information from a presentation at a conference - 2015 data

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Number of Transplants – India (N=8897)

Total centers – 48 centers
Data submitted - 47 centers

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INDIAN STEM CELL TRANSPLANT REGISTRY

Number of Transplants – India (N=8897)

Data submitted - 47 centers

Uma Kanga, AIIMS, NDelhi, Jan 2018
INDIAN STEM CELL TRANSPLANT REGISTRY

Number of Transplants – India (N=8897)

ALLO (N=5325)

- AML 23%
- CML 11%
- AA 16%
- NHL 1%
- Hb disease-Thal 24%
- Cong.BM Failure 3%
- MPS/MPD 0%
- MDS 5%
- Others 4%
- HL 1%
- PCD-Myeloma 1%
- Metabolic disease 0%

Total centers – 48 centers
Data submitted - 47 centers

AUTO (N=3572)

- PCD-Myeloma 50%
- HL 16%
- CML 9%
- AML 15%
- NHL 15%
- Others 1%
- Autoimmune disease 1%
- ALL 0%

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Indications for Hematopoietic Cell Transplant in the US, 2014

- Allogeneic (Total N=8,211)
- Autologous (Total N=12,831)

Bar chart showing the number of transplants for different conditions, such as Myeloma/PCD, NHL, AML, HD, ALL, MDS/MPN, CLL, Other Cancer, CML, Aplastic Anemia, and Other Non-Malignant Dis.
Matched Unrelated and Haplo-identical Donor Transplants in INDIA

personal communication and conf lectures

CMC, Vellore (till Dec 2016-1622)
- First Unrelated Tx: August 2008 (164 till Dec 2016)
- First Haplo-identical Tx: 2003 (128 till Dec 2016)

TMC, Mumbai (till Nov 2015-777)
- First Unrelated Tx: August 2009
- First Haplo-identical Tx: 2003

MUDs in INDIA

Till Nov 2015- approximately ~300 transplants were done

- CMC, Vellore
- TMH, Mumbai
- CMC, Ludhiana
- TMC, Kolkotta

- AIIMS, New Delhi
- R & R, New Delhi
- Apollo, Chennai
- Sahyadiri Hospital, Pune

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Indian Stem Cell Transplantation Registry

SCT- Type of Donor (2012-2016)

Pediatric (N=2220)
- MRD: 73%
- MUD: 11%
- Haplo: 16%

Adult (N=2145)
- MRD: 78%
- MUD: 7%
- Haplo: 15%

<18 years
>18 years

MRD: Matched Related Donor;  MUD: Matched Unrelated Donor  Haplo: Haplo-identical Donor

Information from a presentation at a conference

Uma Kanga, AIIMS, NDelhi, Jan 2018
Stem Cell Transplantation Challenges in India

- BMT centres – Numbers do not match the requirement
- Infrastructure- more BMT wards, Hepa Filter rooms
- Trained medical and para medical staff
- Clinical issues
  - Duration from diagnosis to transplantation: Long
  - Heavily pre-transfused
  - Usually not leuco-depleted/irradiated/directed donor
  - Around 30% patients severely infected
  - More than 90% been exposed to ISA
- Finance- Cost of Transplant- government support
- Public Health Care Programs/Charity Support
- Insurance Schemes
- Lack of large volunteer door pool- ~300,000 donors
Molecular diversity of the HLA-A* 19 group of alleles in North Indians: Possible oriental influence

Caucasians | A Indians | Japanese

A19 frequency

Cauc | NI | Jap

Uma Kanga, AIIMS, NDelhi, Jan 2018
## Cost of BMT/HSCT in INDIA

Variable depending on centre- private or public hospital

<table>
<thead>
<tr>
<th>Registry</th>
<th>Centre I</th>
<th>Centre II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be the Match</td>
<td>USD 45-50,000</td>
<td>USD 50,000</td>
</tr>
<tr>
<td>DKMS/others</td>
<td>USD 12-14,000</td>
<td>USD 35,000</td>
</tr>
<tr>
<td>Datri</td>
<td>USD 12-14,000</td>
<td></td>
</tr>
<tr>
<td>Local -sibling</td>
<td>INR 8-12 Lacs</td>
<td>INR 10-12 Lacs</td>
</tr>
</tbody>
</table>
HSCT- Haploidentical donors

◆ Near universal availability of highly motivated donor
  • Genotypically matched donor: chance is 16-75% depending on ethnicity

◆ Rapid availability
  • 2-3 weeks for donor identification and mobilization
  • Adult unrelated donor is about 25% patients > 3 months

◆ Adequate dose
  • Sufficient HSCs and memory T cells for immune reconstitution
  • CB unit- dose of nucleated cells may be suboptimal for large adult patient

◆ Low cost of graft acquisition
  • MUD and CB very high

◆ Availability and donor for repeated donations
Haploidentical HCT Recipients in the US, by Graft Type
Pre BMT/PBSCT Screening Protocol

New patient For HAPLOIDENTICAL Transplant

PRA Screen

POSITIVE

NEGATIVE

% PRA

De-sensitize

HLA TYPING – SSP /SSO /SBT /NGS

DSA Screen

SAB

POSITIVE

Check status with Alternate donor

Select appropriate donor

TRANSPLANT

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Haploidentical Transplant – applications

To further **improve survival outcomes** after haploidentical SCT  
(Choice of donor within families)
  - To enhance **antileukimic effect** (evaluate **KIR epitope mismatch**)  
  - To reduce transplant related complications –GVHD and TRM  
    (evaluate **NIMA mismatch sibling**)

**Tolerance induction in SCT**  
Combined BM and kidney transplant: sustained donor specific allo-tolerance

**Antitumor effect** in Refractory AML  
Low dose TBI + haplo SCT- leads to graft rejection  
Sequential DLI- enhances antitumor effect

**Haploidentical + graft engineering**  
Deplete cells capable of causing GVHD  
Preserve (or add later) cells responsible for GvT and for restoring T cell immunity  
Infusion of Treg + infusion of tumor/pathogen specific CTLs
Acknowledgments

Prof NK Mehra
TII colleagues

Clinical Colleagues from Hematology and Medical Oncology, AIIMS

Students
Dr Abhishweta Saxena
Dr Manish Mourya
Ms Shweta Tyagi
Dr Nichil Pednekar
Ms Akanksha Sharma

Other lab staff

Funding
DBT/ICMR/AIIMS

Immucor
Dr Ramona Chopra
And Ms Lisa Waltham

Thank you!