Role of NMDP Repository in the Evolution of HLA Matching and Typing for Unrelated Donor HCT

Stephen Spellman, MBS
Director, Immunobiology and Observational Research
Assistant Scientific Director
CIBMTR, Minneapolis

April 19, 2013
Research Repository History

- Established in 1988
- Answer critical questions in hematopoietic stem cell transplantation (HSCT)
  - Blood specimens from transplants facilitated by NMDP
  - Pre-transplant samples from donors and recipients
  - Samples are retrieved and shipped to researchers across the world as requested
  - Collection expanded to related donor/recipient samples in 2007
  - Support for BMT-CTN added in 2009 (6 open protocols)
Repository Usage

- Support hematopoietic stem cell transplant research
- Retrospective transplant outcome analysis
  - Comprehensive collection of clinical outcome data through the CIBMTR
  - Pair clinical data with stored sample testing
  - All data generated on samples submitted to NMDP/CIBMTR

- 233,500 samples shipped since inception
- 143,216 shipped between 2002 and 2012
  - 13,968 samples shipped in 2012
REPOSITORY USAGE
CASE STUDY
Patients and donors were typed and matched serologically.

Mixed lymphocyte cultures (MLC) were performed to test donor/recipient compatibility.

Testing was time consuming and required large amounts of viable cells.
Testing Evolves

• The International Histocompatibility Workshops (IHWS) in the mid 1980s through mid 1990s spent significant energy to refine DNA-based HLA typing methods

• Testing became more accurate and reliable

• DNA testing resulted in identification of new HLA alleles
Donor Recipient Pair Project

• Started in 1994 supported by funding from ONR
• Unanswered questions:
  – What is the importance of matching alleles?
  – If an allele level match is not possible, what is the next best alternative?
  – Are some loci more important than others to match?
• Goals:
  – To provide data so that researchers could determine the impact of allele level matching of HLA-A, B and DRB1 to transplant outcome
  – Determine the contribution of matching at other loci (HLA-C, DPA1, DPB1, DQA1, and DQB1)
Initial sample sets were typed blindly in 2 different laboratories to evaluate the reliability and reproducibility of the results.

As the testing strategies became more robust, typing discrepancies dropped dramatically.

The initial pairs showed that 29% of 6 of 6 antigen matched transplant pairs carried allele mismatches at HLA-A, B, and/or DRB1.

- 92% carried at least 1 allele mismatch at 1 of the 8 HLA loci tested.

A high degree of HLA disparity arises from limited allelic diversity: Analysis of 1775 unrelated bone marrow transplant donor-recipient pairs.

Carolyn K Hurley, et. al. Human Immunology, 68 (1): 30-40
D/R Pair Project Data Utilization

• Donor/Recipient Pair project
  – 15,750 transplant pairs enrolled since 1996
  – Currently, over 15,500 paired typings available for research studies
  – Over 6,000 donors and/or recipients have been presence/absence KIR typed at 16 loci

• Data formed the basis for seminal publications on HLA matching in unrelated donor transplantation
Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome

Study population

- N = 1,874
- US transplants between 1988 - 1996
- AML, ALL, CML, other
- 100% Bone marrow
- 100% Myeloablative transplants
- Median follow-up 9 years

Flomenberg et al., 2004
Mismatching at HLA-A, B, C and DRB1 impacts overall survival

Flomenberg et al., 2004
National Marrow Donor Program HLA-Matching Guidelines for Unrelated Marrow Transplants

Carolyne Katovich Hurley,¹ Lee Ann Baxter Lowe,² Brent Logan,² Chatchada Karanes,³ Claudio Anasetti,⁴ Daniel Weisdorf,⁴,⁶ Dennis L. Confer⁴

Table 3. Typing of Patient HLA Loci

<table>
<thead>
<tr>
<th>HLA Locus</th>
<th>Search Strategy</th>
<th>Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Yes</td>
<td>Recommended</td>
</tr>
<tr>
<td>B</td>
<td>Yes</td>
<td>Recommended</td>
</tr>
<tr>
<td>C</td>
<td>Yes</td>
<td>Recommended</td>
</tr>
<tr>
<td>DRA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DRBI</td>
<td>Yes</td>
<td>Recommended</td>
</tr>
<tr>
<td>DRB3, DRB4, DRB5</td>
<td>Yes (DRB1 association)*</td>
<td>Unknown†</td>
</tr>
<tr>
<td>DQA1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DQB1</td>
<td>Yes (DRB1 association)*</td>
<td>Uncertain†</td>
</tr>
<tr>
<td>DPA1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DPB1</td>
<td>No</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

Table 4. Typing of Potential Donor HLA Loci

<table>
<thead>
<tr>
<th>HLA Locus</th>
<th>Matching</th>
<th>Resolution of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommended</td>
<td>Allele level</td>
</tr>
<tr>
<td>B</td>
<td>Recommended</td>
<td>Allele level</td>
</tr>
<tr>
<td>C</td>
<td>Recommended</td>
<td>Allele level</td>
</tr>
<tr>
<td>DRA</td>
<td>No</td>
<td>Allele level</td>
</tr>
<tr>
<td>DRBI</td>
<td>Recommended</td>
<td>Allele level</td>
</tr>
<tr>
<td>DRB3, DRB4, DRB5</td>
<td>Unknown*</td>
<td>Allele level</td>
</tr>
<tr>
<td>DQA1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DQB1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DPA1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DPB1</td>
<td>Uncertain</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

*Unknown indicates that the effect of matching has not been evaluated; uncertain indicates that studies disagree as to the importance of these loci in matching.
Donor – Recipient Pair Project continues....

• Typing completed on several more sample groups representing thousands of NMDP transplants

• Dataset more than doubled in size for the diseases of interest
  – AML, ALL, CML and MDS

• New analysis undertaken to evaluate the influence of individual loci and the resolution of matching on outcomes
High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

Study population

- N = 3860
- US transplants between 1988 - 2003
- AML, ALL, CML, MDS
- Myeloablative conditioning
- Calcineurin-based GVHD prophylaxis, T replete grafts (79%)
- Bone marrow 94%
- Median follow-up 6 years
Any Single Locus Mismatch

- 9/10 associated with worse survival, DFS, TRM, acute GVHD

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>952</td>
<td>1.17 (1.06-1.329)</td>
<td>0.002</td>
</tr>
<tr>
<td>DFS</td>
<td>945</td>
<td>1.16 (1.05-1.28)</td>
<td>0.003</td>
</tr>
<tr>
<td>TRM</td>
<td>945</td>
<td>1.31 (1.16-1.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relapse</td>
<td>945</td>
<td>0.90 (0.81-1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>Engraftment</td>
<td>956</td>
<td>OR 0.90 (0.80-1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>957</td>
<td>1.35 (1.19-1.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>910</td>
<td>0.96 (0.91-1.03)</td>
<td>0.25</td>
</tr>
</tbody>
</table>
# HLA-DQ Lacked Impact

## As a Single Mismatch

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
<th></th>
<th>TRM</th>
<th></th>
<th>Acute GVHD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
<td>RR</td>
<td>p</td>
</tr>
<tr>
<td>10/10</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>DQ MM</td>
<td>0.97</td>
<td>0.77</td>
<td>1.08</td>
<td>0.50</td>
<td>1.03</td>
<td>0.86</td>
</tr>
</tbody>
</table>

## As a Second Mismatch

<table>
<thead>
<tr>
<th></th>
<th>8/10</th>
<th>9/10</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ MM</td>
<td>191</td>
<td>797</td>
<td>1.14 (0.94-1.38)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Single Antigen vs Allele Mismatch

- No statistical difference if mismatched at antigen or allele level, except for C – Antigen worse than Allele

<table>
<thead>
<tr>
<th></th>
<th>Antigen</th>
<th>Allele</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>1.16</td>
<td>1.19</td>
<td>0.69</td>
</tr>
<tr>
<td>DFS</td>
<td>1.16</td>
<td>1.17</td>
<td>0.92</td>
</tr>
<tr>
<td>TRM</td>
<td>1.34</td>
<td>1.32</td>
<td>0.86</td>
</tr>
<tr>
<td>Relapse</td>
<td>0.80</td>
<td>0.93</td>
<td>0.31</td>
</tr>
<tr>
<td>Engraftment</td>
<td>0.74</td>
<td>1.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>1.52</td>
<td>1.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>0.95</td>
<td>0.97</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Survival

- 9-10% lower overall survival with each additional mismatch

<table>
<thead>
<tr>
<th>Match</th>
<th>n</th>
<th>Survival (CI)</th>
<th>RR (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/8</td>
<td>1840</td>
<td>52 (50-54)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>7/8</td>
<td>988</td>
<td>43 (40-46)</td>
<td>1.25 (1.13-1.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6/8</td>
<td>633</td>
<td>33 (30-37)</td>
<td>1.65 (1.48-1.84)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Impact of HLA Matching varies by disease stage

Early-stage

Intermediate-stage

Late-stage

Benefits of HLA matching diminish as disease progresses

Lee et al., 2007
National Marrow Donor Program HLA Matching Guidelines for Unrelated Adult Donor Hematopoietic Cell Transplants

Robert A. Bray,1 Carolyn K. Hurley,2 Naynesh R. Kamani,3 Ann Woolfrey,4 Carliheinz Müller,5 Stephen Spellman,6 Michelle Setterholm,6 Dennis L. Confer6

<table>
<thead>
<tr>
<th>HLA Locus</th>
<th>Search Strategy</th>
<th>Matching</th>
<th>Resolution of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Yes</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>B</td>
<td>Yes</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>C</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>DRA</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>DRB1</td>
<td>Yes</td>
<td>Recommended</td>
<td>High</td>
</tr>
<tr>
<td>DRB3, DRB4, DRB5</td>
<td>Yes (DRB1 association)*</td>
<td>Unknown†</td>
<td></td>
</tr>
<tr>
<td>DQA1</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>DQB1</td>
<td>Yes (DRB1 association)*</td>
<td>Uncertain‡</td>
<td></td>
</tr>
<tr>
<td>DPB1</td>
<td>No</td>
<td>No</td>
<td>Uncertain</td>
</tr>
<tr>
<td>DPA1</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Typing and Matching of Potential Donor and Patient HLA Loci
Research Results in Clinical Changes

• The typing methods developed through this research study were adopted by the HLA laboratories supporting transplant programs.

• The refinements in high resolution HLA typing have enhanced the ability of transplant centers to more completely characterize patient alleles for a more effective donor search.
HLA Match Grade by Year

Brown et al., Human Immunology 2010

Flomenberg paper published

Lee paper published

Brown et al., Human Immunology 2010
Incorporated further recommendations on:

- **PBSC transplantation** (Woolfrey et al. BBMT 2011)
- **Umbilical cord blood transplantation** (Eapen et al. Lancet Oncology 2011)
- **Transplantation for non-malignant disease** (Horan et al. Blood 2012)
- **Role of anti-HLA antibodies** (Spellman et al. Blood 2010)
REPOSITORY USAGE
CASE STUDIES

Beyond HLA
Investigating the impact of other gene systems on unrelated donor HCT
Natural Killer Cell Program Project Grant

- NK CELLS, THEIR RECEPTORS AND UNRELATED DONOR TRANSPLANTATION
  - PI: Jeff Miller, University of Minnesota, NIH/NCI P01 2005-2015

- Donor NK cell alloreactivity may improve outcomes in HCT by:
  - Preventing relapse
  - Decreasing acute GVHD
  - Promoting engraftment
  - Fighting infection

- Retrospective analyses conducted utilizing research samples from the NMDP Repository and mature outcome data from the CIBMTR
Donor selection for natural killer cell receptor genes leads to superior survival after unrelated transplantation for acute myelogenous leukemia

Sarah Cooley, Daniel J. Weisdorf, Lisbeth A. Guethlein, John P. Klein, Tao Wang, Chap T. Le, Steven G. E. Marsh, Daniel Geraghty, Stephen Spellman, Michael D. Haagenson, Martha Ladner, Elizabeth Trachtenberg, Peter Parham and Jeffrey S. Miller
Study population

- N = 1409
- AML; n = 1086, ALL; n = 323
- US transplants between 1988 - 2006
- Myeloablative conditioning, T replete grafts
- Bone marrow 67%
- Peripheral Blood Stem Cells 33%
- Follow-up 3 years post transplant

Cooley et al., 2010
More B is Better

<table>
<thead>
<tr>
<th></th>
<th>HLA Matched</th>
<th>HLA Mismatched</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Relapse (%)</td>
<td><img src="image" alt="Graph A" /></td>
<td><img src="image" alt="Graph B" /></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><img src="image" alt="Graph C" /></td>
<td><img src="image" alt="Graph D" /></td>
</tr>
<tr>
<td><strong>C</strong> Disease Free Survival (%)</td>
<td><img src="image" alt="Graph E" /></td>
<td><img src="image" alt="Graph F" /></td>
</tr>
<tr>
<td><strong>D</strong></td>
<td><img src="image" alt="Graph G" /></td>
<td><img src="image" alt="Graph H" /></td>
</tr>
<tr>
<td><strong>E</strong> Overall Survival (%)</td>
<td><img src="image" alt="Graph I" /></td>
<td><img src="image" alt="Graph J" /></td>
</tr>
</tbody>
</table>

Time since transplantation (years)

Cooley et al., 2010
Genome Wide Association Study (GWAS)

- ASSESSMENT OF GENETIC POLYMORPHISMS AND TRM IN RELATION TO CONDITIONING REGIMEN BEFORE HLA-MATCHED UNRELATED DONOR HCT
  - PIs: Theresa Hahn and Lara Sucheston, Roswell Park Cancer Institute, NIH/NHLBI RO1 2010-2015

Study Objectives:
- Test for genetic association with transplant-related and overall mortality
- Compare the type of transplant-related mortality (infection, toxicity, GVHD, hemorrhage, etc) by conditioning regimen.
- Test for a genetic association with type of transplant-related mortality by conditioning regimen
GWAS study population
Discovery Set

- N = 2513
- AML, ALL, or MDS
- Myeloablative conditioning 65%
- Non-myeloablative / Reduced intensity conditioning 33%
- Bone marrow 34%
- Peripheral Blood Stem Cells 66%

Study status:
- GWAS testing underway
- Validation dataset (N=1000) to be tested in 2013
What about Autoimmune Disease?

- Research Repository inventory is extremely limited
  - Scleroderma (3 cases)
  - Autoimmune cytopenia (1 case)

- Have to start somewhere!
Acknowledgements

- Transplant Centers, Donor Centers, Cord Blood Banks
- Donor/Recipient Pair Project Typing Laboratories
- CIBMTR Immunobiology Research Team
- NMDP Bioinformatics Research

NMDP/CIBMTR Funding Sources:
- HRSA
- Office of Naval Research
- NHLBI
- NCI
- NIAID
QUESTIONS?