E. Donnall Thomas, MD
(1920 – 2012)

1990 Nobel Prize in Medicine or Physiology with Joseph Murray
Questions for Today

• What is HCT?
• Why is HCT done?
• How is HCT done?
• What are the differences in HCT between humans and mice?
Terminology

- Bone marrow transplant
- Hematopoietic stem cell transplant
- Hematopoietic progenitor cell transplant
- Peripheral blood stem cell transplant

The transfer of hematopoietic progenitor cells for therapeutic purposes
Purpose of Transplant

• To replace hematopoiesis
• To modulate immune response
• Donor source reflects purpose
Transplant Donor Sources

• Autologous transplant – Uses cells from the recipient
• Allogeneic transplant – Uses cells from another individual
• Donor source reflects the purpose of the transplant
Autologous HCT

Patient

Regular Chemo ± XRT

Blood or Marrow Collection

High dose Chemo ± XRT

Freezer

8-14 days
Indications for autoHCT

• Rescue of the patient from side effects of chemotherapy

• Diseases in which cytoreduction is effective therapy and dependent on dose of chemotherapy
  – Germ cell tumors (testicular)
  – Large cell lymphoma
  – Myeloma
Allogeneic HCT

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time
Indications for alloHCT

• Replacement of hematopoiesis (aplastic anemia)
• Graft versus tumor effect
• Disease requiring both
  – Acute leukemia
  – Indolent lymphoma
Donor source reflects purpose

<table>
<thead>
<tr>
<th></th>
<th>Replacement therapy</th>
<th>Immune therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous</td>
<td>XXX</td>
<td>X</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>XXX</td>
<td>XXX</td>
</tr>
</tbody>
</table>
Adjusted probabilities of leukemia-free survival rates after identical twin bone marrow transplantations with high (more than $3 \times 10^8$ cells/kg) versus low (less than or equal to $3 \times 10^8$ cells/kg) cell doses.


©2000 by American Society of Hematology
Immune Cell Populations Before AutoHCT for Myeloma

Hahn, et al. ASH 2013
Allogeneic BMT Survival Outcomes (AML)

- Acute GvHD (15%)
- Infection (10%)
- Other (5%)
- Chronic GvHD, dead (15%)
- Disease relapse (20%)
- Chronic GvHD, alive (15%)
- Alive and well (20%)
A transplant is a bet against the future

Leukemia Therapy

High dose Chemo ± XRT

95%
5%
35%
65%
5%
95%
Genetic Subgroup Analysis: RFS

**NPM1+/FLT3 ITD-**

- **p=0.71**
- donor n=35
- no donor n=92

**Others**

- **p=0.02**
- donor n=45
- no donor n=125

Courtesy of Schlenk R et al, NEJM 2008
MUD Transplantation in Relapsed Patients with Unfavorable Genotype

Survival after relapse (%)

- MUD n=37
- Other strategy n=67

p<0.0001

Time (months)
HOW?
Patient

Donor

Allogeneic BMT

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time
Many cooks, many recipes

- Conditioning intensity
- Donor HLA matching
- Graft sources
- Graft versus host disease prevention
- Modulation of immune therapy
Transplant regimens

**Immunosuppression**

- **Non-myeloablative**
  - Flu-Cy
  - Flu-Cy-ATG
  - Flu-low dose TBI
  - Flu ATG
  - TLI/ATG

- **Reduced Intensity**
  - Flu-Mel
  - Flu-Bu
  - Flu-Mel-TBI

- **Myeloablative**
  - Cy-TBI
  - Bu-Cy
  - Mel 200

**Regimen Related Toxicity**

- Relapse

**Later Graft-versus Disease Effect**

**Earlier Anti-Disease Effect**

**Myelosuppression**
Autologous HCT

1. Regular Chemo ± XRT
2. Blood or Marrow Collection
3. High dose Chemo ± XRT
4. Freezer
5. 8-14 days
Reduced Intensity AlloBMT

Patient

Donor

Regular Therapy

Immunosuppression
± Chemo ± XRT

14-21 days

Time
Many cooks, many recipes

- Conditioning intensity
- *Donor HLA matching*
- Graft sources
- Graft versus host disease prevention
- Modulation of immune therapy
HLA

- $(>1 \times 10^{12} \text{ haplotypes})^2 = > 1 \times 10^{24}$ combinations
- Not all alleles have been identified
- Frequencies are not equally distributed

<table>
<thead>
<tr>
<th>HLA</th>
<th>DRB1</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>DQB1</th>
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<tbody>
<tr>
<td>Alleles</td>
<td>400</td>
<td>370</td>
<td>660</td>
<td>190</td>
<td>62</td>
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</table>
HLA Matching

- Autologous
- Allogeneic
  - Syngeneic
  - Related donors
    - HLA matched (6/6)
    - HLA mismatched (5/6)
    - Haploidentical (3/6-6/6)
  - Unrelated donors
    - HLA matched (10/10)
    - HLA mismatched (9/10)
<table>
<thead>
<tr>
<th>Donor</th>
<th>Maternal Haplotype</th>
<th>Paternal Haplotype</th>
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<tbody>
<tr>
<td></td>
<td>DR</td>
<td>B</td>
</tr>
<tr>
<td>MUD</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRD</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Haplo</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Choice of a matched sibling = 1 − 0.75 \# of siblings
Donor Selection

Related: DRB1 > B > A

Unrelated: DRB1 > B > A > C > DQ > CMV status

After HLA: CMV status, age, gender, parity, and DP - not ABO!
What is a haploidentical transplant?

Transfer of hematopoietic progenitor cells from:

- Parent → Child
- Child → Parent
- Sibling → Sibling *
haplotype – all HLA information from one parent

haplo (Greek)-single
Many cooks, many recipes

- Conditioning intensity
- Donor HLA matching
- *Graft sources*
- Graft versus host disease prevention
- Modulation of immune therapy
- *Areas to apply fundamental discoveries to improve patient outcomes*
Sources of Grafts

• Bone marrow
• Peripheral blood mobilized hematopoietic progenitor cells
• Umbilical cord blood
Many cooks, many recipes

- Conditioning intensity
- Donor HLA matching
- Graft sources
- Graft versus host disease prevention
- Modulation of immune therapy
- Areas to apply fundamental discoveries to improve patient outcomes
Immunologic Effects of Allogeneic Grafts

• Graft-versus-Tumor Effects – Reaction of the donor immune system against the recipient’s malignancy

• Graft-versus-Host Effects – Reaction of the donor immune system against the recipient’s body tissues.

• Different sides of the same coin.
Billingham Criteria (1966)

• The graft must contain immunologically competent cells

• The host must possess important transplantation alloantigens that are lacking in the donor graft, so that the host appears foreign to the graft, and is, therefore, capable of stimulating it antigenically

• The host itself must be incapable of mounting an effective immunological reaction against the graft, at least for sufficient time for the latter to manifest its immunological capabilities; that is, it must have the security of tenure
Transplant Complications

• Acute Graft-versus-Host Disease
• Graft failure/persistent chimerism
• Opportunistic infections
• Chronic Graft-versus-Host Disease
Acute Graft-versus-Host Disease

• Reaction of donor’s immune system against the recipient’s body tissues
• Manifests as diarrhea, skin rash, liver test abnormalities usually within the first 100 days.
• ~20-50% of allogeneic transplants will develop some aGvHD
• Associated with a 15-20% mortality
Acute GvHD Therapy

• Prophylaxis – Attempts to prevent aGvHD development

• Treatment – For therapy of aGvHD once it occurs
# Acute GvHD Prophylaxis Regimens

<table>
<thead>
<tr>
<th></th>
<th>FK</th>
<th>MTX</th>
<th>MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FK/µMTX/MMF</strong></td>
<td>0.01 mg/kg IV BID</td>
<td>2.5 mg/m² days 1, 3, 6</td>
<td>1000 mg PO TID discontinued day 60</td>
</tr>
<tr>
<td></td>
<td>↓10% every week starting day 100</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td><strong>FK/MMF</strong></td>
<td>Not given</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FK/MTX</strong></td>
<td>10 mg/m² days 1, 3, 6, 11</td>
<td></td>
<td>Not given</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>
Acute GvHD Overall Grade 3-4

P = 0.001

Acute GvHD GI Stage 2-4

P = 0.006

Acute GvHD Skin Stage 3-4

P = NS

Acute GvHD Liver Stage 2-4

P = NS
• FK/µMTX/MMF is as effective as FK/MTX for preventing aGvHD. Both are better than FK/MMF.

• FK/µMTX/MMF results in equivalent mucositis as FK/MMF. Both are better than FK/MTX.
T cell depletion

- Prevention of aGvHD, decreased hepatic sinusoidal obstructive syndrome
- Slowed engraftment, increased infectious complications, increased leukemic relapse, increased post transplant lymphoproliferative disorder
- *Ex vivo* and *in vivo* (alemtuzumab, ATG) methods of depletion
# T Cell Depletion vs. Pharmacologic Approaches

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Acute GvHD</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD vs. CSA/MTX</td>
<td>48</td>
<td>23% vs. 12%</td>
<td>LFS: 42 vs 44% @ 3 yrs</td>
</tr>
<tr>
<td>Partial TCD/CSA</td>
<td>400</td>
<td>18% vs. 37%</td>
<td>cGvHD: 18 vs. 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DFS @ 3 years the same</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DFS @ 3 years the same</td>
</tr>
<tr>
<td>TLI/ATG</td>
<td>37</td>
<td>1/37 (3%)</td>
<td>cGvHD: 27% of patients surviving &gt;100d</td>
</tr>
</tbody>
</table>
High dose cyclophosphamide
Post HCT cyclophosphamide (Cy) for GvHD

Day 0
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
Post HCT cyclophosphamide (Cy) for GvHD
# HCT for hematologic malignancy

<table>
<thead>
<tr>
<th></th>
<th>Haplo*</th>
<th>Standard#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning</td>
<td>Flu/Cy/TBI</td>
<td>Flu/Mel/TBI</td>
</tr>
<tr>
<td>aGvHD prophylaxis</td>
<td>Cy/Tac/MMF</td>
<td>uMTX/Tac/MMF</td>
</tr>
<tr>
<td>Graft failure</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>aGvHD Gr. III-IV</td>
<td>6% (day 200)</td>
<td>27% (day 100)</td>
</tr>
<tr>
<td>Progression free</td>
<td>26% (2 years)</td>
<td>44% (2 years)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>36% (2 years)</td>
<td>47% (2 years)</td>
</tr>
</tbody>
</table>

Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia

- Twins (N=70)
- T Cell Depletion (n=401)
- No GVHD (n=433)
- AGVHD Only (n=738)
- CGVHD Only (N=127)
- AGVHD + CGVHD (N=485)

Years

Probability of Relapse, %

Increasing GVT

Increasing GVH
Graft Failure

- Failure to recover leukocytes, platelets, and erythrocytes by day 28
- Causes
  - Anti-HLA antibodies
  - Viral infections – EBV!
  - Inadequate immunosuppression (host versus graft reactions)
  - Infected grafts
  - Large spleen (in myelofibrosis)
- Autologous recovery can occur.
- Treatment is another transplant
KHIMAIRA (Greek) was a three headed, fire-breathing creature with the fore-parts of a lion, the hindquarters of a goat, and the tail of a serpent. The Chimera was slain by Bellerophon astride Pegasus.

http://www.theoi.com/Tartaros/Khimaira.html
Donor Chimerism

- RIC or NMA Rx
- 14-21 days
- Time
- Remove immuno-suppression
- Donor lymphocyte infusion
- Full
- Mixed
- Donor lymphocyte infusion
## Human vs. mouse transplants

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Outbred</td>
<td>Inbred</td>
</tr>
<tr>
<td></td>
<td>Older (40-70) Comorbidities</td>
<td>Young (8-14 weeks/2 years) Healthy</td>
</tr>
<tr>
<td></td>
<td>Thymic involution</td>
<td></td>
</tr>
<tr>
<td>Environment</td>
<td>Not clean Antibiotics</td>
<td>Clean</td>
</tr>
</tbody>
</table>

## Human vs. mouse transplants

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA</strong></td>
<td>MHC matched</td>
<td>Wide variety</td>
</tr>
<tr>
<td><strong>Conditioning</strong></td>
<td>Chemotherapy Radiation</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Radiation Fractionation</td>
<td>Single Dose</td>
</tr>
<tr>
<td><strong>GvHD prophylaxis</strong></td>
<td>Required</td>
<td>Not used</td>
</tr>
<tr>
<td><strong>Cell source</strong></td>
<td>Bone marrow Peripheral blood</td>
<td>Bone marrow + splenocytes</td>
</tr>
</tbody>
</table>
Chronic Graft-versus-Host Disease

• Post transplant complication usually occurring > 100 days characterized by
  – Fibrotic skin disease
  – Dry and gritty mouth eyes due to glandular destruction
  – Gastrointestinal fibrosis with malnutrition

• 50% of long term survivors will develop some form of cGvHD

• Chronic GvHD is the major cause of long term mortality other than relapse after transplant
cGvHD Therapy

• Corticosteroids and a calcineurin inhibitor
• Use of rituximab (clinical grade anti-CD20 monoclonal antibody) has increased in the past 5 years because of evidence suggesting that B-cells are involved in the pathogenesis of cGvHD.
Sex Mismatched AlloHCT

• Female (XX) donors into male (XY) recipients
• H-Y proteins are foreign to XX T and B cells resulting in reactivity, proliferation, and ultimately anti-H-Y antibodies
Quantitation of IgG antibodies specific for H-Y and H-X proteins.

Detection of DBY and UTY antibodies after stem cell transplantation.

The cumulative incidence of chronic GVHD and relapse as a function of H-Y antibody response.

Rituximab for steroid-refractory chronic graft-versus-host disease

- Phase 1/2 trial in 21 patients
- Rituximab 375 mg/m$^2$ weekly x 4 weeks, repeated every 2 months as needed
- Clinical responses in 70%,
- Reduced prednisone dosed by $\geq$ 50% in 68%