The Atomic Bomb Approach to Medicine

• Little Boy bomb dropped on Hiroshima August 6, 1945
• 90-166,000 deaths
• 15-20% death from radiation sickness characterized by anemia, leukopenia, thrombocytopenia, gastrointestinal, and neurologic disturbances
Early Animal Studies

• Spleen shielding rescued otherwise lethally irradiated mice. (Jacobson et al 1949)
• Bone marrow injection rescued otherwise lethally irradiated mice and guinea pigs. (Lorenz et al 1951)
• Secondary disease – A mortal wasting system of skin abnormalities and diarrhea occurring in allogeneically transplanted mice (Barnes & Loutit 1955).
• Methotrexate increased survival and attenuated secondary disease (Uphoff 1958)
E. Donnall Thomas, MD  
(1920 – 2012)  

1990 Nobel Prize in Medicine or Physiology with Joseph Murray
Intravenous Infusion of Bone Marrow In Patients Receiving Radiation and Chemotherapy

- Six terminal patients
- Variety of graft sources and doses: fetal and adult marrow from long bones and ribs
- Short lived engraftment of donor cells in 2 out of 6 patients only.
- Not very promising.

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
WHY?
Purpose of Transplant

• To replace hematopoiesis
• To modulate immune response
• Donor source reflects purpose
Patient

Regular Chemo ± XRT

Blood or Marrow Collection

Freezer

High dose Chemo ± XRT

8-14 days

Autologous HCT
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
Patient

Donor

Allogeneic BMT

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>
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
Genetic Subgroup Analysis: RFS

**NPM1+/FLT3 ITD-**

- Donor n=35
- No donor n=92

- p=0.71

**Others**

- Donor n=45
- No donor n=125

- p=0.02

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

Survival after relapse (%)

Time (months)

MUD n=37

Other strategy n=67

p<0.0001
HOW?
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*
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

Later Graft-versus Disease Effect
Earlier Anti-Disease Effect

Relapse

Auto and Allo
Myeloablative
Autologous HCT

Regular Chemo ± XRT → Blood or Marrow Collection → Freezer

High dose Chemo ± XRT → 8-14 days
Patient

Allogeneic BMT

Donor

Regular Chemo ± XRT

High dose Chemo ± XRT

14-21 days

Time
Reduced Intensity AlloBMT

Regular Therapy

± 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

• *Areas to apply fundamental discoveries to improve patient outcomes*
HLA

- Human Leukocyte Antigen
- On surface of most body cells
- The most important proteins in transplant
- Responsible for graft rejection and GvHD

![Diagram of antigen presentation process](image-url)
HLA

• Normal function is to present antigen to T cells.
• Each allele binds antigen differently.
• More variety in alleles = greater ability to present antigens so that infections can be better controlled*
• * For humans as a species, not as individuals
HLA

\[(>1 \times 10^{12} \text{ haplotypes})^2 = > 1 \times 10^{24} \text{ combinations}\]

• 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)
## HLA

<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>
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</table>
Chance of a matched sibling = $1 - 0.75 \# \text{ of siblings}$
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.
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
<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 survival</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>
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</tbody>
</table>

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

Mixed

Full

- Remove immuno-suppression
- Donor lymphocyte infusion

Donor lymphocyte infusion
## Human vs. mouse transplants

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Mouse</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>Outbred</td>
<td>Inbred</td>
</tr>
<tr>
<td></td>
<td>Older (40-70) Comorbidities Thymic involution</td>
<td>Young (8-14 weeks/2 years) Healthy</td>
</tr>
<tr>
<td>Environment</td>
<td>Not clean</td>
<td>Clean</td>
</tr>
<tr>
<td>Interspecies immune differences</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td>Mouse</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>HLA</td>
<td>MHC matched</td>
<td>Wide variety</td>
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<tr>
<td>Conditioning</td>
<td>Chemotherapy Radiation</td>
<td>Radiation Single Dose</td>
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<tr>
<td></td>
<td>Fractionation</td>
<td></td>
</tr>
<tr>
<td>GvHD prophylaxis</td>
<td>Required</td>
<td>Not used</td>
</tr>
<tr>
<td>Cell source</td>
<td>Bone marrow</td>
<td>Bone marrow + splenocytes</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood</td>
<td></td>
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</table>
Thanks for Listening.