Bone Marrow Transplantation & HLA Typing
Boston doctor shares Nobel for medicine

Transplant work cited

By David L. Chandler
GLOBE STAFF

A doctor at Brigham and Women's Hospital was one of two American physicians awarded the Nobel Prize in Medicine yesterday for pioneering work that paved the way for now-commonplace organ and tissue transplants that have saved thousands of lives.

Joseph E. Murray, 71, of Wellesley, professor emeritus of plastic surgery at Brigham and Women's Hospital, and E. Donnell Thomas, 70, of Bellevue, Wash., received the honor for their work during the 1950s and 1960s on how to reduce the risk of organ rejection by the body's immune system. The two will share a prize worth about $700,000.

Murray performed the world's first successful organ transplant - a kidney from one identical twin to another - at the Peter Bent Brigham Hospital on Dec. 23, 1954.

From unthinkable to commonplace

By Judy Foreman
GLOBE STAFF

It was two days before Christmas 1954.

Richard Herrick, 23, lay at Boston's Peter Bent Brigham Hospital - now called Brigham and Women's - facing death from kidney failure. His twin brother, Ronald, had just agreed to the unthinkable: removal of one of his kidneys to donate to Richard.

Kidney dialysis, so commonplace today, was still so new and clumsy that it was not considered a long-term option. The process had been invented in the Netherlands just after World War II.

Immunosuppressive drugs, the backbone of most of the more than 13,000 organ transplants done today in the United States, were barely a gleam in researchers' eyes.

And the idea that by 1990 Americans in every state would by law be able, more or less casually, to carry organ donor cards or donor stickers on drivers' licenses was too wild even for Dr. Joseph E. Murray, then 35 years old, to imagine.
After a lethal dose of radiation in rodents, canines or primates, the destroyed bone marrow may be repopulated by intravenous infusion of cellular suspensions of marrow taken from healthy isologous, homologous and, in some cases, heterologous donors. Effective cells for these infusions may be stored by the Polge technic of freezing to $-80^\circ$C in glycerol. Hosts seeded with donor marrow have some of the immunologic characteristics of the donors, and

Experimental Considerations

Bone marrow was collected from fetal and adult cadavers, from ribs removed at surgery and from aspiration biopsy of the ilium. Irrespective of source, it was passed repeatedly through a stainless-steel screen and broken into a smooth cellular suspension, and the fat, as a rule, removed by centrifugation. The cells, resuspended in tissue-culture fluid and serum, were administered intravenously or frozen in glycerol and stored at $-80^\circ$C.

One may assess permissible periods of post-mortem

Hematopoietic cell transplantation for bone marrow failure – a simple concept

Bone marrow – the blood cell “factory” in postnatal life

Bone marrow is readily transplantable
Bone Marrow Harvest

PBSC Collection

Cord Blood Unit
First home of the Seattle BMT unit, late 1960’s

Former U. S. Public Health Service Hospital

http://www.ci.seattle.wa.us/neighborhoods/preservation/images/large/PacMed3DON.jpg
First step is to perform HLA Typing

HLA Nomenclature

- **Hyphen used to separate gene name from HLA prefix**
- **Suffix used to denote changes in expression**
- **Separator**
- **Field Separators**
- **HLA Prefix**
- **Gene**
  - **Field 1**: allele group
  - **Field 2**: specific HLA protein
  - **Field 3**: used to show a synonymous DNA substitution within the coding region
  - **Field 4**: used to show differences in a non-coding region
What is involved in HLA typing, anyway?

- Exons 2 and 3 in each gene
- 8 exons total
- ~275 nt each
- TOTAL: 2,200 bp

- Haploid genome: 3.3 x 10^9 bp
- < 1 x 10^-6 of the genome
Hematopoiesis: some numbers

• Each day a typical adult produces:
  – $2 \times 10^{11}$ red blood cells
  – $1 \times 10^{11}$ white blood cells
  – $1 \times 10^{11}$ platelets

• Over a lifetime: $\sim 4-8 \times 10^{15}$ blood cells

• Maintenance of basal hematopoiesis requires each human HSC to divide $\sim 52$ times

• Between the HSC and terminally differentiated circulating blood cells, there are between 17 and 19.5 effective cell divisions, with a net amplification of between $\sim 170,000$ and $\sim 720,000$

Rates of production can increase 10-fold
Annual Number of Transplant Recipients in the US by Transplant Type

- Autologous
- Allogeneic

*2014 Data incomplete
### Diseases commonly treated with allogeneic hematopoietic [stem] cell transplantation

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Non-malignant diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Acute myeloid leukemia</td>
<td>– Aplastic anemia</td>
</tr>
<tr>
<td>– Acute lymphoblastic leukemia</td>
<td>– Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>– Chronic myeloid leukemia</td>
<td>– Fanconi’s anemia</td>
</tr>
<tr>
<td>– Myelodysplastic syndromes</td>
<td>– Blackfan-Diamond anemia</td>
</tr>
<tr>
<td>– Myeloproliferative disorders</td>
<td>– Thalassemia major</td>
</tr>
<tr>
<td>– Non-Hodgkin lymphoma</td>
<td>– Sickle cell anemia</td>
</tr>
<tr>
<td>– Hodgkin lymphoma</td>
<td>– Severe combined immunodeficiency</td>
</tr>
<tr>
<td>– Chronic lymphocytic leukemia</td>
<td>– Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>– Multiple myeloma</td>
<td>– Inborn errors of metabolism</td>
</tr>
<tr>
<td>– Juvenile chronic myeloid leukemia</td>
<td></td>
</tr>
</tbody>
</table>
Indications for Hematopoietic Stem Cell Transplants in the US, 2013

- **Allogeneic (Total N=8,197)**
- **Autologous (Total N=11,258)**

### Number of Transplants by Indication

- **Myeloma / PCD**
- **AML**
- **ALL**
- **CML**
- **NHL**
- **HD**
- **MDS / MPD**
- **CLL**
- **Aplastic Anemia**
- **Other Non-Malignant Disease**
- **Other Cancer**
Trends in Autologous Transplants by Recipient Age*

*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

![Graph showing trends in autologous transplants by recipient age from 1993-1999, 2000-2006, and 2007-2013.](Image)
Trends in Allogeneic Transplants by Recipient Age

*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Causes of Death after Autologous Transplants done in 2012-2013

- Primary Disease: 70%
- Infection: 20%
- Organ Failure: 7%
- Second Malignancy: 2%
- Other: 1%
Causes of Death after HLA Match Sibling Transplants done in 2012-2013

- Primary Disease: 48%
- Infection: 17%
- Organ Failure: 16%
- GVHD: 14%
- Second Malignancy: 4%
- Other: 1%
What is GVHD?

- Graft vs. Host Disease (GVHD)
- Occurs after bone marrow transplantation or any tissue transplantation
- Transplanted immune cells attack host’s body cells
- Symptoms include:
  - Rash
  - Immune-mediated pneumonitis
  - Damage to connective tissue and exocrine glands
  - Sloughing of mucosal membrane
  - Diarrhea
  - Abdominal pain
  - Nausea
  - Vomiting
  - Eye irritation
- Can be fatal
- Treatment includes glucocorticoids such as prednisone
Major sites of graft-versus-host disease

Skin

GI Tract

Liver
Survival after Allogeneic Transplants for Severe Aplastic Anemia, <20 Years, 2003-2013

Probability, %

Years

By Donor Type

HLA Match Sibling (n=1,318)
Unrelated Donor (n=805)

p<0.001
Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥20 Years, 2003-2013

- HLA Match Sibling (n=1,352)
- Unrelated Donor (n=827)

p < 0.001
Summary

- Infusion of autologous and allogeneic hematopoietic stem cells is a standard and quite common procedure in contemporary hematology and oncology.

- Histocompatibility is determined by genetic loci both within the MHC on chromosome 6p and at a large number of minor histocompatibility loci elsewhere in the genome (including the Y chromosome).

- Eradication of malignant cells in recipients of allogeneic HCT is mediated by the donor’s immune system – providing the clearest example of effective cancer immunotherapy.
References

• https://www.cibmtr.org

• https://bethematch.org/

• https://dreamerbiologist.wordpress.com/2013/04/19/hla-complex-in-predictive-medicine/

• Weilin Chen, Ph.D., Institute of Immunology, ZJU, http://slideplayer.com/slide/6086041/


• http://www.ci.seattle.wa.us/neighborhoods/preservation/images/large/PacMed3DON.jpg

• https://en.wikipedia.org/wiki/Graft-versus-host_disease