Transplantation:
Friendly organs in a hostile environment

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How is foreign tissue recognized?
How is the tissue rejected?
What limits transplantation?
What can be done about it?
## Transplants

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acellular tissue</td>
<td>Heart valve</td>
</tr>
<tr>
<td>Cells</td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow</td>
</tr>
<tr>
<td>Living tissue</td>
<td>Cornea</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Islets</td>
</tr>
<tr>
<td>Organs</td>
<td>Kidney, Heart, Liver, Lung, Pancreas, Intestine</td>
</tr>
</tbody>
</table>
## Transplants in USA

### Organs (total 23,985) \(^1\)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Recipients</th>
<th>5 yr graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>14,095</td>
<td>66-78%</td>
</tr>
<tr>
<td>Liver</td>
<td>5,157</td>
<td>64%</td>
</tr>
<tr>
<td>Heart</td>
<td>2,194</td>
<td>70%</td>
</tr>
<tr>
<td>Lung</td>
<td>1,053</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Tissues/Cells

<table>
<thead>
<tr>
<th>Tissue/Cell</th>
<th>Quantity</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea</td>
<td>~40,000</td>
<td>70%</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>23,500</td>
<td>80%</td>
</tr>
</tbody>
</table>

80,617 patients waiting as of 2/15/03 [unos.org](http://unos.org)

17 die each day waiting for transplant
Why are grafts lost?

- Acute rejection
- Chronic rejection
- Infection
- Drug toxicity
- Recurrent disease
- Complications of original disease
<table>
<thead>
<tr>
<th>Graft Source</th>
<th>Graft Source</th>
<th>Graft Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto-</td>
<td>Auto-</td>
<td>Auto-</td>
</tr>
<tr>
<td>Source</td>
<td>Self</td>
<td>Identical twin</td>
</tr>
<tr>
<td>Rejection</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xeno-</td>
<td>Xeno-</td>
<td>Xeno-</td>
</tr>
<tr>
<td>Other species</td>
<td>Other species</td>
<td>Other species</td>
</tr>
<tr>
<td>Rejection</td>
<td>Yes +++</td>
<td>Yes +++</td>
</tr>
</tbody>
</table>
Skin graft to syngeneic recipient

MHC\textsuperscript{a}

Graft is tolerated

Skin graft to allogeneic recipient

MHC\textsuperscript{b}

Graft is rejected rapidly
(first-set rejection)

Second skin graft from same donor to same recipient

MHC\textsuperscript{b}

Graft shows accelerated (second-set) rejection

---

% grafts surviving

Days post transplant

0 10 20

0 50 100

Memory
**Major Histocompatibility Complex determines graft outcome**

- **Parents**
  - Homozygous MHC

- **3rd Party**
  - Grafts rejected

- **F1 Heterozygous MHC**
  - W W
  - B B
  - Graft accepted
  - Graft rejected

- **3rd Party**
  - Y Y

**F1 accepts graft from either parent**

**Parent rejects graft from F1**

**3rd party grafts rejected by all**
Major Histocompatibility Complex

Chromosome 6 human (HLA), 17 mouse (H-2)
HLA loci highly polymorphic
Antigen Presenting Cell

T cell receptor

MHC
Class I or II
antigen

Peptide antigen

T Cell

Antigen Presenting Cell
Class II has 2 polymorphic chains
more open peptide groove
Thymic education for T cells

Eliminated:

- T cells that fail to bind to self MHC
  Nonreactivity
- T cells that bind too avidly to self +self peptides
  Self reactivity

Retained:

- T cells that recognize self-MHC + foreign peptide
  Foreign peptide reactivity
A Normal

Self-MHC molecule presents foreign peptide to T cell selected to recognize self-MHC-foreign peptide complexes

B Allorecognition

The self-MHC-restricted T cell recognizes the allogeneic MHC molecule whose structure resembles the self-MHC-foreign peptide complex
How do the host T cells recognize foreign tissue?

**Direct** (on graft cells)
- Foreign MHC + peptide
- Mimics self MHC + foreign peptide

**Indirect** (on host antigen presenting cells)
- Self MHC + Foreign peptides (e.g. HLA)

The graft looks like a pathogen to the T cell.
Host Antigen Presenting Cell or Graft Cell

T Cell

- TCR α,β
- CD4
- CD3
- CD40L
- CD40
- IL2R
- IL2
- IFNγ
- + other cytokines

Activation...

- ICAM-1
- LFA-1

HLA Class II

- Peptide antigen
Graft Cell

TCR α,β

HLA Class I

Peptide antigen

CD40

CD40L

CD8

CD3

T Cell

Activation...

LFA-1

ICAM-1

ICAM-1

HLA Class I

Cytolysis

Graft Cell
Chances for a sibling being HLA-Identical 25%

Donor Sibling Possibilities
1:4 match

MHC region of each copy of chromosome 6
Chances of a Match from unrelated donor

Recipient

\[
\begin{array}{cc}
A & A \\
B & B \\
DR & DR
\end{array}
\]

Depends on frequency of each allele in population and fineness of distinction

Donors

\[
\begin{array}{cccccc}
B & B & B & B & B & B \\
DR & DR & DR & DR & DR & DR
\end{array}
\]

<table>
<thead>
<tr>
<th>Match</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
</table>

for 6 antigen match of 10, 20, 20 alleles per locus

\(~1/16,000,000\)
HLA Mismatch Reduces Graft Survival

% Grafts Surviving 5 years

Kidneys transplanted in 1994-5

UNOS.org
Acute Rejection

**Cause:** Reactivity to donor alloantigens

- HLA Class I, II
- Non-HLA antigens

**Specific Agents:**
- T Cells
- Antibody

**Secondary Mediators:**
- Macrophages, granulocytes, NK cells
- Complement, clotting system, chemokines
How to diagnose rejection

**Clinical:** Loss of function of organ
  - **Lab tests:** serum creatinine (kidney), bilirubin (liver)

**Imaging:** blood flow, arterial diameter (heart)

**Pathology:** Biopsy
  - Light microscopy, immunofluorescence, markers of function

**Molecular:** PCR/proteomics markers of function
Acute Cellular Rejection (ACR)
<table>
<thead>
<tr>
<th>PAS</th>
<th>Tubulitis</th>
<th>CD3</th>
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Tubulitis

Lymphocytes inside the renal tubules

Chemokines (IL-8, RANTES, MCP-1, fractalkines)
Produced by tubular epithelium in response to IL-1, TNFα

Cytotoxic T cells mostly CD8
Express receptors for E-cadherin
Cytotoxic T Cell

Fas ligand gene

Granule exocytosis, perforin, granzymes

TCR

MHC

FasL

Fas

Target cell

Death
Cytotoxic T cells in tubules with apoptosis

Please see Meehan SM et al. Cytotoxicity and apoptosis in human renal allografts: identification, distribution, and quantitation of cells with a cytotoxic granule protein GMP-17 (TIA-1) and cells with fragmented nuclear DNA. Lab Invest. 1997 May;76(5):639-49.
<table>
<thead>
<tr>
<th></th>
<th>Acute Rejection</th>
<th>Stable</th>
</tr>
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<tbody>
<tr>
<td>Perforin</td>
<td>1.4±0.3*</td>
<td>-0.6±0.2</td>
</tr>
<tr>
<td>Granzyme</td>
<td>1.2±0.3</td>
<td>-0.9±0.2</td>
</tr>
<tr>
<td>Cyclophilin</td>
<td>2.3±0.3</td>
<td>2.5±0.1</td>
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</tbody>
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*fg mRNA/µg RNA ln transform

Li...Suthanthrian NEJM 344:947, 2002
Endarteritis (Type 2 ACR)