**Genetic barriers to transplantation**

**autograft**
from one part of the body to another, e.g. trunk to arm

**isograft**
between genetically identical individuals, e.g. monozygotic twins, or within an inbred strain

**allograft**
between different members of the same species, e.g. Mr Smith to Mr Jones

**xenograft**
between members of different species, e.g. monkey to man
Figure 17-1
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First skin graft, strain A

Naive strain = B mouse

First-set rejection

Time

Second skin graft, strain A

Necrosis

Second-set rejection

Naive strain = B mouse

14 days

6 days

Spleenic T cells

First skin graft, strain A

Necrosis

6 days
Figure 17-3
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Antibody to different HLA-A antigens

Recipient

Donor 1

Donor 2

Figure 17-4b
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Serological tissue typing

complement → HLA-B8 → anti-HLA-B8 → trypan blue
Figure 17-4c

Donor cells

Allele A

Reciprocal cells lacking class II MHC of donor

Activation and proliferation of recipient cells

[3H]thymidine

Incorporation of radioactivity into cell nuclear DNA

No reaction

Recipient cells sharing class II MHC of donor

Irradiation

Allele B
Figure 17-5
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A. Direct allore cognition

- Allogeneic MHC
- Allogeneic antigen-presenting cell in graft
- Alloreactive T cell
- T cell recognizes unprocessed allogeneic MHC molecule on graft APC

B. Indirect alloantigen presentation

- Allogeneic MHC
- Professional APC in recipient
- Self MHC
- Uptake and processing of allogeneic MHC molecules by recipient APC
- Presentation of processed peptide of allogeneic MHC molecule bound to self MHC molecule
- Peptide derived from allogeneic MHC molecule
<table>
<thead>
<tr>
<th>Type of Rejection</th>
<th>Time Taken</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>minutes-hours</td>
<td>preformed anti-donor antibodies and complement</td>
</tr>
<tr>
<td>Accelerated</td>
<td>days</td>
<td>reactivation of sensitized T cells</td>
</tr>
<tr>
<td>Acute</td>
<td>days-weeks</td>
<td>primary activation of T cells</td>
</tr>
<tr>
<td>Chronic</td>
<td>months-years</td>
<td>causes are unclear: antibodies, immune complexes, slow cellular reaction, recurrence of disease</td>
</tr>
</tbody>
</table>
1. Preexisting host antibodies are carried to kidney graft.

2. Antibodies bind to antigens of renal capillaries and activate complement ($C^-$).

   Capillary endothelial walls

3. Complement split products attract neutrophils, which release lytic enzymes.

4. Neutrophil lytic enzymes destroy endothelial cells; platelets adhere to injured tissue, causing vascular blockage.

   Platelets
### Table 16-1. Methods of Immunosuppression in Clinical Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine and FK-506</td>
<td>Block T cell cytokine production by inhibiting activation of the NFAT transcription factor</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Blocks proliferation of lymphocyte precursors</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Blocks lymphocyte proliferation by inhibiting IL-2 signaling</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Reduce inflammation by inhibiting macrophage cytokine secretion</td>
</tr>
<tr>
<td>Anti-CD3 monoclonal antibody</td>
<td>Depletes T cells by binding to CD3 and promoting phagocytosis or complement-mediated lysis (used to treat acute rejection)</td>
</tr>
<tr>
<td>Anti-IL-2 receptor antibody</td>
<td>Inhibits T cell proliferation by blocking IL-2 binding</td>
</tr>
<tr>
<td>CTLA4-Ig</td>
<td>Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28; used to induce tolerance (experimental)</td>
</tr>
<tr>
<td>Anti-CD40 ligand</td>
<td>Inhibits macrophage and endothelial activation by blocking T cell CD40 ligand binding to macrophage CD40 ligand binding to macrophage CD40 (experimental)</td>
</tr>
</tbody>
</table>
Cyclosporine introduced

Five-year survival (%) of cardiac allograft patients

Year of transplant

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Figure 17-8

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T cells that recognize graft antigens become activated

Graft rejected
T cells that recognize graft antigens lack costimulation and become anergic. Graft survives.
Figure 17-10

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**Cornea**
From cadaver
Immunosuppression not required
47,000 transplants in 2005

**Skin**
Mostly autologous (burn victims)
Temporary grafts of nonviable tissue
Allogeneic grafts rare, require immunosuppression

**Lung**
From brain-dead donor
Procedure recently developed;
little data available
1408 transplants in 2005
Often heart/lung transplant (33 in 2005)

**Blood**
Transfused from living donor
ABO and Rh matching required
Complications extremely rare
An estimated 14 million units used each year

**Heart**
From brain-dead donor
HLA matching useful but often impossible
Risk of coronary artery damage, perhaps mediated by host antibody
2127 transplants in 2005

**Pancreas**
From cadaver
Islet cells from organ sufficient
540 transplants in 2005
Increasingly, pancreas/kidney transplant for advanced diabetes (903 in 2005)

**Kidney**
From live donor or cadaver
ABO and HLA matching useful
Immunosuppression usually required
Risk of GVHD very low
16,477 transplants in 2005

**Liver**
From cadaver
Surgical implantation complex
Resistant to hyperacute rejection
Risk of GVHD
6444 transplants in 2005

**Bone marrow**
Needle aspiration from living donor
Implanted by IV injection
ABO and HLA matching required
Rejection rare but GVHD a risk
Digestion with collagenase frees islets from surrounding tissue

Centrifugation isolates islets containing mainly alpha and beta cells

Purified islet

Islets established in sinusoids

Purified islets, transplanted through a catheter into the liver portal vein, move to liver sinusoids, where they become permanently established.
<table>
<thead>
<tr>
<th></th>
<th>HLA-A</th>
<th></th>
<th>HLA-B</th>
<th></th>
<th>HLA-DR</th>
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<tbody>
<tr>
<td>Donor 1</td>
<td><img src="1" alt="Circle" /> <img src="2" alt="Circle" /> <img src="3" alt="Circle" /> <img src="4" alt="Circle" /></td>
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<tr>
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<td>Donor 4</td>
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