Immunotherapies

- **Vaccines** (toxoid, attenuated live, killed cell vaccines, subcellular, DNA, peptide)
- **Adjuvants** (nonspecific immune stimulant)
- **Passive Antibody** (IVIG, humanized monoclonal antibodies or immunotoxins)
- **Cytokines** (IFN, IL-10, IL-12) or **cytokine antagonists** (anti-TNF, soluble cytokine receptors)
Immunotherapies

- Co-stimulator or suppressor signaling molecules (CTLA-4)
- Adoptive transfer of immune cells
  - Immune Tc cells
  - Lymphokine activated NK cells
- Antagonist peptides (inhibit specific T cells by blocking TcR)
- Oral tolerance (ingestion of antigen induces suppressive factors [TGF-β])

Immunosuppressive agents

- **Corticosteroids** (block cellular infiltration, cytokine release, T cell maturation, etc.)
- **Azathioprine** (inhibit lymphocyte proliferation)
- **Cyclosporine** (inhibit IL-2 gene expression)
- **Anti-lymphocyte serum** (causes lymphocyte destruction and removal)
### Immunosuppressive agents

- **Anti-CD3** (causes T cell destruction)
- **Anti-CD4** (causes T cell destruction)
- **Cytotoxic drugs and ionizing radiation**
  (block cell proliferation, lymphopoiesis)

### Immunotherapeutic agents:

**applications: mechanisms of action**

- **Anti-TNF-alpha**: inflammatory bowel disease and rheumatoid arthritis: inhibits inflammatory actions of TNF-alpha
- **Anti-CD20**: non-Hodgkin’s lymphoma:
  ADCC destruction of B cells
- **Anti-lymphocyte globulin**: treatment of acute graft rejection: depletes T cells via ADCC or inhibits of cell function
Immunotherapeutic agents: applications: mechanisms of action

- **Interferon-alpha:**
  - viral hepatitis: anti-viral
  - Hairy cell leukemia: anti-proliferative

- **Interferon-beta:**
  - Gliomas: anti-proliferative?
  - Multiple sclerosis: anti-viral, antagonism of interferon-gamma

### Corticosteroid therapy

<table>
<thead>
<tr>
<th>Effect on</th>
<th>Physiological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ IL-1, TNF-α, GM-CSF ↓ IL-3, IL-4, IL-5, IL-8</td>
<td>↓ Inflammation caused by cytokines</td>
</tr>
<tr>
<td>↓ NOS</td>
<td>↓ NO</td>
</tr>
<tr>
<td>↓ Phospholipase A&lt;sub&gt;2&lt;/sub&gt;</td>
<td>↓ Prostaglandins</td>
</tr>
<tr>
<td>↑ Cyclooxygenase type 2</td>
<td>↓ Leukotrienes</td>
</tr>
<tr>
<td>↑ Lipocortin-1</td>
<td></td>
</tr>
<tr>
<td>↓ Adhesion molecules</td>
<td>Reduced emigration of leukocytes from vessels</td>
</tr>
<tr>
<td>↑ Endonucleases</td>
<td>Induction of apoptosis in lymphocytes and eosinophils</td>
</tr>
</tbody>
</table>

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**Fig 14.17 © 2001 Garland Science**

- **Tumor-specific antibody**
- **Tumor-specific antibody conjugated to toxin**
- **Tumor-specific antibody conjugated to radionuclide**

Antibodies bind to the tumor cell

- **NK cells with Fc receptors (CD16) are activated to kill the tumor cells**

Antibody-toxin conjugates bind to the tumor cell

- **Conjugates are internalized, killing the cell**

Radioactive antibody binds to the tumor cell

- **Radiation kills the tumor cell and neighboring tumor cells**

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- **Malignant tumor cells expressing TRA but no co-stimulatory molecules**
- **Naive CD8 T cells specific for TRA cannot be activated by the tumor cells and may be rendered anergic**
- **Tumor grows progressively**
Humanized monoclonal antibodies

• Use of mouse monoclonal antibodies for immunotherapy in humans is limited by immune responses in humans against the foreign mouse antibody proteins.

• Complementarity determining regions (CDR) of mouse monoclonal antibodies can be grafted onto the framework of a human immunoglobulin. Recombinant antibodies are less immunogenic and induce less allergic reactions.