HST 535

PRINCIPLES AND PRACTICE OF TISSUE ENGINEERING:

Review/Discussion

M. Spector, Ph.D.
The degree to which the implant needs to support immediate function dictates the degree to which the tissue engineered construct needs to be mature before implantation.

Properties cannot degrade with time.

**Vessels**

- Can the tissue engineered vessel be isolated from flow for a certain time period after implantation?

**Musculoskeletal Tissues (e.g., bone and cartilage)**

- Can the tissue/joint be immobilized (unloaded) post-operatively (using metal rods and plates)?
• **Cardiovascular tissues**
  – Endothelium-smooth muscle-connective tissue
• **Genito-urinary tissues**
  – Endothelium-connective tissue -smooth muscle
EXAMPLE OF A HOLLOW, LAYERED STRUCTURE

Epithelial cells
Muscle cells
Connective tissue cells

Diagrams removed for copyright reasons.
Coronary artery structure: from Netter, F. H. Heart (Ciba Collection), 1969.
Diagram removed for copyright reasons.

Diagram removed for copyright reasons.

Urinary Bladder

Diagram removed for copyright reasons.

Urinary Bladder (Relaxed)
http://www.bu.edu/histology/p/16501oca.htm

Images of urinary tract histology removed for copyright reasons. See http://www.bu.edu/histology/p/16501oca.htm
Ureter (Primate)


Courtesy of Lutz Slomianka. Used with permission.
# Tissue Characteristics and Approaches

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Lec.</th>
<th>Hollow (Tube) vs. Solid</th>
<th>Layered Y or N</th>
<th>Immed. Funct. Y or N</th>
<th>Blood Contact Y or N</th>
<th>Cell Type</th>
<th>Scaff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periph Nerve</td>
<td>Yannas Gong</td>
<td>S</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Nerve</td>
<td>Collag. Chitin</td>
</tr>
<tr>
<td>Blood Vessel</td>
<td>Schoen</td>
<td>H</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Ep, CT, Muscle</td>
<td>Collag. PGA</td>
</tr>
<tr>
<td>Heart Valve</td>
<td>Schoen</td>
<td>S</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Ep, CT, Muscle</td>
<td>PGA</td>
</tr>
<tr>
<td>Urin.</td>
<td>Atala</td>
<td>H</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Ep, CT, Muscle</td>
<td>SIS Others</td>
</tr>
<tr>
<td>Bone</td>
<td>Liu/Xu</td>
<td>S</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>CT,stem</td>
<td>Coll/HA</td>
</tr>
<tr>
<td>Cart.</td>
<td>Liu/Spe</td>
<td>S</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>CT</td>
<td>Collag.</td>
</tr>
</tbody>
</table>
How to engineer a layered structure?

- Separately seed layers of a scaffold with different types of cells
- If all the cell types are mixed and added to a scaffold will they segregate eventually to form separate layers?

*Some connective tissues like bone have a lamellar architecture, but these are layers of the same bone materials (i.e., same cell type in each lamella or layer)
TISSUE ENGINEERING VS. REGENERATIVE MEDICINE

**TISSUE ENGINEERING**

Regeneration *In Vitro*

Advantages
- Evaluation of tissue prior to implantation

Disadvantages
- For incorporation, must be remodeling
- Stress-induced architecture cannot yet be produced *in vitro*

**REGENERATIVE MED.**

Regeneration *In Vivo*

Advantages
- Incorporation and formation under the influence of endogenous regulators (including mechanical strains)

Disadvantages
- Dislodgment and degradation by mech. stresses *in vivo*
Define the clinical problem.

- What type of tissue/organ to be engineered (connective, epithelial, muscle, or nerve)?
- Location and specific features of the tissue that distinguish it from other members of the tissue category.
- Function of the tissue at the location at which it has been lost.
- The degree to which the tissue has to be regenerated to restore meaningful clinical function (including histology, biochemistry, and functional properties).
<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Connective Tissues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bone</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Articular Cartilage, Ligament, Intervertebral Disc, Others</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Epithelia (e.g., epidermis)</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cardiac, Skeletal</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>• Smooth</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Nerve</strong></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
### CELL-MATRIX INTERACTIONS REQUIRED FOR TISSUE ENGINEERING

<table>
<thead>
<tr>
<th>Connective Tissues (Musculoskeletal)</th>
<th>Mitosis(^1)</th>
<th>Migration(^2)</th>
<th>Synthesis(^3)</th>
<th>Contract.(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Articular Cartilage</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ligament/Tendon</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Intervertebral Disc</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Meniscus</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>

\(^1\) Inadequate mitosis requires exogenous **cells**.
\(^2\) Inadequate migration may require a **scaffold**.
\(^3\) Inadequate biosynthesis require **growth factors** or their **genes**.
\(^4\) Contraction ?
How the *in vivo* environment differs from that *in vitro*

- Vascular and lymphatic systems
  - blood elements (cells and circulating molecules)
  - fibrin clot
  - endocrine factors
- pH and electrical effects
- Many cell types in the tissue producing paracrine factors
- Complex mechanical loading
- All of the above change with time
FACTORS THAT CAN PREVENT REGENERATION

- Limited vascular invasion of large defects
  - *e.g.*, bone does not regenerate in the central portion of large defects
- Collapse of surrounding tissue into the defect
  - *e.g.*, periodontal defects
- Excessive mechanical strains in the reparative tissue
  - *e.g.*, unstable fractures