HST 535

PRINCIPLES AND PRACTICE OF TISSUE ENGINEERING:

Introduction

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Tissue Engineering Triad*

• **MATRIX (SCAFFOLD)**
  – Porous, absorbable biomaterials
  – Can serve to regulate cell function prior to its absorption

• **CELLS**

• **REGULATORS**
  – Chemical: *e.g.*, cytokines (growth factors)
  – Mechanical: *e.g.*, mechanical loading and flow conditions *in vitro* (bioreactors)

* Used individually or in combination, but often with a matrix (*i.e.*, with a biomaterial)
TISSUE ENGINEERING

Issues to be Addressed

- Should the tissue be produced *in vitro*, for subsequent implantation, or *in vivo*?
- What scaffold should be used?
  - Material of fabrication, pore characteristics, absorbability, mechanical properties?
  - How to be manufactured?
- What cells are to be used?
  - Source of cells?
  - Under what conditions can cells be expanded in number *in vitro* while retaining their phenotype?
- What regulators are required to stimulate cell proliferation and matrix synthesis or to facilitate differentiation of stem cells?
TISSUE ENGINEERING VS. REGENERATIVE MEDICINE

**TISSUE ENGINEERING**

Regeneration *In Vitro*

Produce the fully formed tissue *in vitro* by seeding cells into a biomaterial matrix, and then implant the regenerated tissue into the body.

**REGENERATIVE MEDICINE**

Regeneration *In Vivo*

Implant the biomaterial matrix with, or without seeded cells, into the body to facilitate regeneration of the tissue *in vivo*. 
<table>
<thead>
<tr>
<th>TISSUE ENGINEERING</th>
<th>REGENERATIVE MED.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regeneration</strong></td>
<td><strong>Regeneration</strong></td>
</tr>
<tr>
<td><em>In Vitro</em></td>
<td><em>In Vivo</em></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• Evaluation of tissue prior to implantation</td>
<td>• Incorporation and formation under the influence of endogenous regulators (including mechanical strains)</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>• For incorporation, must be remodeling</td>
<td>• Dislodgment and degrad. by mech. stresses <em>in vivo</em></td>
</tr>
<tr>
<td>• Stress-induced architecture cannot yet be produced <em>in vitro</em></td>
<td></td>
</tr>
</tbody>
</table>
1980 Yannas: Collagen-GAG matrix for dermal regeneration ("artificial skin"); Integra

1984 Wolter/Meyer: 1st use of the term, TE; endothel.-like layer on PMMA in the eye

1991 Cima/Vacanti/Langer: Chondrocytes in a PGA scaffold; the ear on the nude mouse

1993 Langer/Vacanti: Science paper on TE; cells in matrices for tissue formation in vitro; PGA

1994 Brittberg/Peterson: NEJM paper on human autologous chondrocyte implantation; Carticel
## Which Tissues Can Regenerate Spontaneously?

<table>
<thead>
<tr>
<th>Connective Tissues</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<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>Epithelia (e.g., epidermis)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Muscle</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>Nerve</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
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
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ELEMENTS OF TISSUE ENGINEERING/REGENERATIVE MEDICINE

- **MATRIX (SCAFFOLD)**
  - Porous, absorbable synthetic (*e.g.*, polyglycolic acid) and natural (*e.g.*, collagen) biomaterials
- **CELLS (Autologous or Allogeneic)**
  - Differentiated cells of same type as tissue
  - Stem cells (*e.g.*, bone marrow-derived)
  - Other cell types (*e.g.*, dermal cells)
- **REGULATORS**
  - Growth factors or their genes
  - Mechanical loading
  - Static versus dynamic culture ("bioreactor")
### 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 ?