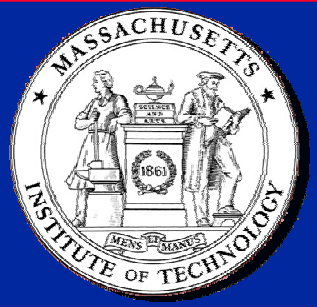
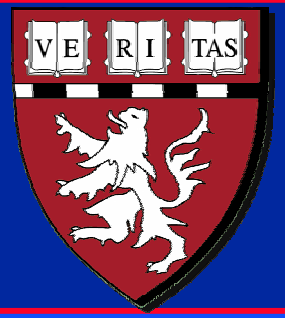


Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



HST 535

PRINCIPLES AND PRACTICE OF TISSUE ENGNEERING:

Introduction

M. Spector, Ph.D. and Fu-Zhai Cui

ELEMENTS FOR TISSUE ENGINEERING

Tissue Engineering Triad*

- MATRIX (SCAFFOLD)
  - Porous, absorbable biomaterials
  - Can serve to regulate cell function prior to is 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 MED.

Regeneration *In Vivo*

Implant the biomaterial matrix with, or without seeded cells, into the body to facilitate regeneration of the tissue *in vivo*.

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 degrad. by mech. stresses *in vivo*

TISSUE ENGINEERING/REGEN. MED. Historical Perspective; Selected Milestones

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?

	Yes	No
Connective Tissues		
• Bone	√	
• Articular Cartilage, Ligament, Intervertebral Disc, Others		√
Epithelia (e.g., epidermis)	√	
Muscle		
• Cardiac, Skeletal		√
• Smooth	√	
Nerve		√

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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  - ***e.g.*, unstable fractures**

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

Connective Tissues (Musculoskeletal)	Mitosis[1]	Migration[2]	Synthesis[3]	Contract.[4]
Bone	+	+	+	+
Articular Cartilage	-	-	-	+
Ligament/Tendon	+	+	?	+
Intervertebral Disc	?	?	?	+
Meniscus	?	?	?	+

[1] Inadequate mitosis requires exogenous cells.

[2] Inadequate migration may require a scaffold.

[3] Inadequate biosynthesis require growth factors or their genes.

[4] Contraction ?