Harvard-MIT Division of Health Sciences and Technology
HST.535: Principles and Practice of Tissue Engineering
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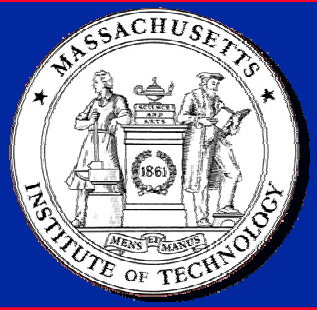

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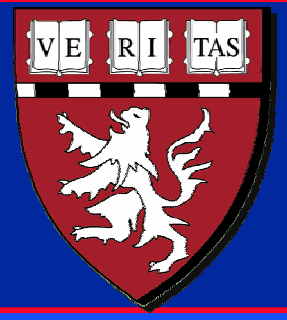

HST 535

PRINCIPLES AND PRACTICE OF TISSUE ENGNEERING:

Clinical Applications

M. Spector, Ph.D.

ELEMENTS FOR TISSUE ENGINEERING

Tissue Engineering Triad

- MATRIX (SCAFFOLD)
  - Porous, absorbable biomaterials
- CELLS
- REGULATORS
  - Chemical: *e.g.*, cytokines (growth factors) or their genes
  - Mechanical: *e.g.*, mechanical loading and flow conditions *in vitro* (bioreactors)

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 ENDPOINTS

- **Morphological/Histological/Biochemical**
  - Match the composition and architecture of the tissue.
  - Problem: A complete analysis is difficult and no clear relationships yet with functional and clinical endpoints.
- **Functional**
  - Achieve certain functions; display certain properties (*e.g.*, mechanical properties).
  - Problem: Difficult to measure all properties; Which properties are the most important?
- **Clinical**
  - Pain relief.
  - Problems: Can only be evaluated in human subjects and the mechanisms (including the placebo effect) and kinetics of pain relief (*e.g.*, how long it will last) are unknown.

TISSUE ENGINEERING CLINICAL APPLICATIONS

Critical Steps

- **Define the clinical problem.**
- **Apply what has been learned *in vitro* to *in vivo* (animal) models.**
- **Apply what has been learned in animal models to clinical (human) trials.**

TISSUE ENGINEERING CLINICAL APPLICATIONS

Define the clinical problem.

- **Know the tissue or organ**
  - Anatomy: size, shape, location, and structure at the mm length scale
  - Physiology: functions
  - Histology: microscopic structure (μm length scale)
  - Pathology: diseases and abnormalities
  - Current clinical treatments
- **Multidisciplinary team**
  - Clinical specialists (consumers)

PARTICIPANTS IN TISSUE ENGINEERING

- **Scientists** (physical and biological)
- **Engineers**
- **Clinicians**
  - Plastic surgeon
  - Orthopaedic surgeon
  - Urologic surgeon
  - Cardiovascular surgeon
  - Neurosurgeon
  - Dermatologist
  - Dental (oral surgeon, periodontist, prosthodontist)

TISSUE ENGINEERING
CLINICAL APPLICATIONS

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 is has been lost.**
- **The degree to which the tissue has to be regenerated to restore meaningful clinical function (including histology, biochemistry, and functional properties).**

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**

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		√

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Which Tissues Can Regenerate Spontaneously?

	Problems
Connective	
• Bone	Lg. Defects: absence of scaffold & osteogenic cells
• Art. Cart. Lig., IVD	Non-vascular: No scaffold & blood-borne regulators Low cell density and mitotic activity
Epithelia	Needs CT on which to migrate and be maintained; Epidermis: dry environment
Muscle	
• Cardiac/ Skel.	No cardiomyocyte and skeletal muscle mitosis
• Smooth	
Nerve	No nerve cell division & scaffold for axon elongation

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 ?

TISSUE ENGINEERING CLINICAL APPLICATIONS

Critical Steps

- Define the clinical problem.
- Apply what has been learned *in vitro* to *in vivo* (animal) models.
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TISSUE ENGINEERING CLINICAL APPLICATIONS

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

TISSUE ENGINEERING
CLINICAL APPLICATIONS

Critical Steps

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TISSUE ENGINEERING
CLINICAL APPLICATIONS

How the human environment may differ from that in the animal model.

- Size and location of the defect
- Chemical and histological make-up of the tissues
- Applied loading and functional demands
- Age and gender
- Disease conditions (including genetic anomalies)
- Tissue/organ performance
- Innervation and pain response

TISSUE ENGINEERING CLINICAL APPLICATIONS

What features of the human condition are to be modeled by the animal experiment?

- **Response of normal or (induced) diseased tissue to implantation of the tissue-engineered construct into a defect**
- **Effects of function (*e.g.*, applied mechanical loading) on the implant**
- **<u>Not</u> the pain response.**

TISSUE ENGINEERING CLINICAL APPLICATIONS

What information is to be obtained from the animal "model?"

Safety

- Local and systemic response to the implant (*i.e.*, the tissue-engineered construct).

Efficacy/Effectiveness

- Function of the tissue/organ being regenerated

TISSUE ENGINEERING CLINICAL APPLICATIONS

Response time of animal models

Same time frame as the human

- Processes in the animal occur on the same time course as in the human

Accelerated

- Processes in the animal occur more rapidly
  - Are certain responses to implants expected to reflect time courses scaled to the life span of the animal?

TISSUE ENGINEERING
CLINICAL APPLICATIONS

How do you know if regeneration has been achieved?

- **Histology**
- **Biochemistry**
- **Functional properties (*e.g.*, mechanical properties).**

TISSUE ENGINEERING CLINICAL APPLICATIONS

Evaluating the outcome from clinical (human) trials

- Pain assessment (semi-quantitative: visual analog scale)
- Psychological assessment
- Function
- Imaging
- Non-destructive testing
  - *e.g.*, indentation probes for mechanical testing
- Biopsies
  - Histology, biochemistry, and functional properties (*e.g.*, mechanical properties).

TISSUE ENGINEERING
CLINICAL APPLICATIONS

To what extent does regeneration have to be achieved to obtain a clinical benefit?

Clinical Benefits

- **Pain relief**
- **Function**

TISSUE ENGINEERING
Current Status

- No one has yet employed Tissue Engineering methods to fully regenerate any tissue that does not have the capability for spontaneous regeneration*.
  - The Integra skin has no hair or glandular structures and its architecture is close to but not identical to normal dermis.
  - The Carticel cartilage is not articular cartilage.
- Experience has taught us that full regeneration may not be necessary to achieve a meaningful clinical result (*e.g.*, pain relief, recovery of function, esthetics)
- How close to regeneration is good enough?

* Many examples of bone regeneration