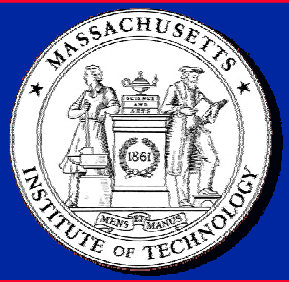
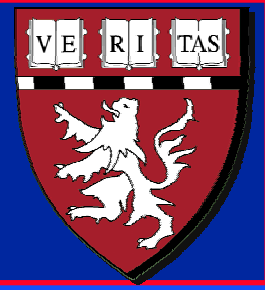


Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



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TISSUE ENGINEERING: OVERVIEW

I.V. Yannas, Ph.D. and M. Spector, Ph.D.

TISSUE ENGINEERING

What is tissue engineering?

- Production of tissue *in vitro* by growing cells in porous, absorbable scaffolds (matrices).

Why is tissue engineering necessary?

- Most tissues cannot regenerate when injured or diseased.
- Even tissues that can regenerate spontaneously may not completely do so in large defects (*e.g.*, bone).
- Replacement of tissue with permanent implants is greatly limited.

TISSUE ENGINEERING

Problems with Tissue Engineering

- Most tissues cannot yet be produced by tissue engineering (*i.e.*, *in vitro*).
- Implantation of tissues produced *in vitro* may not remodel *in vivo* and may not become integrated with (bonded to) host tissue in the body.

Solution

- Use of implants to facilitate formation (regeneration) of tissue *in vivo*.
  - "Regenerative Medicine"
  - Scaffold-based regenerative medicine

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

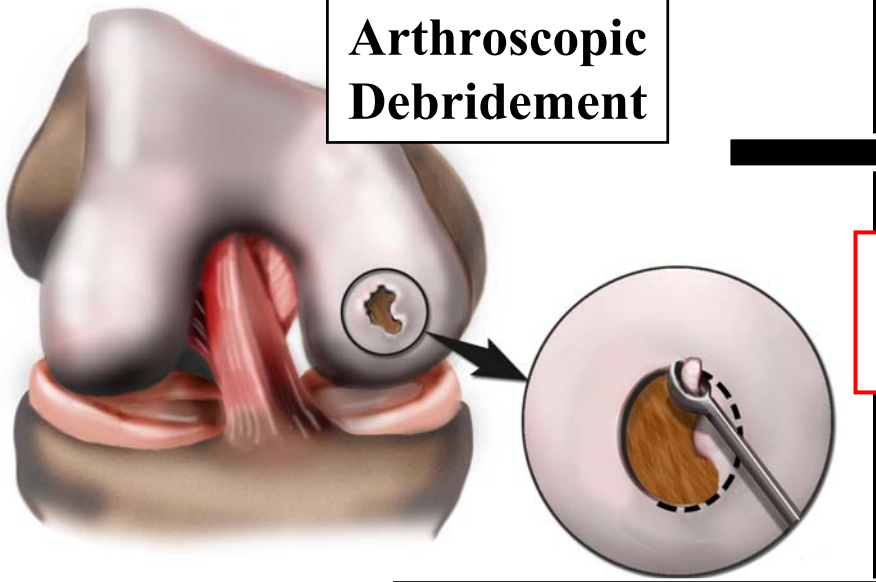
1980 **Yannas**: Collagen-GAG matrix for dermal regeneration ("artificial skin"); Integra

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



Arthroscopic Debridement

"Microfracture"

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Osteochondral Autograft

Current Clinical Practice

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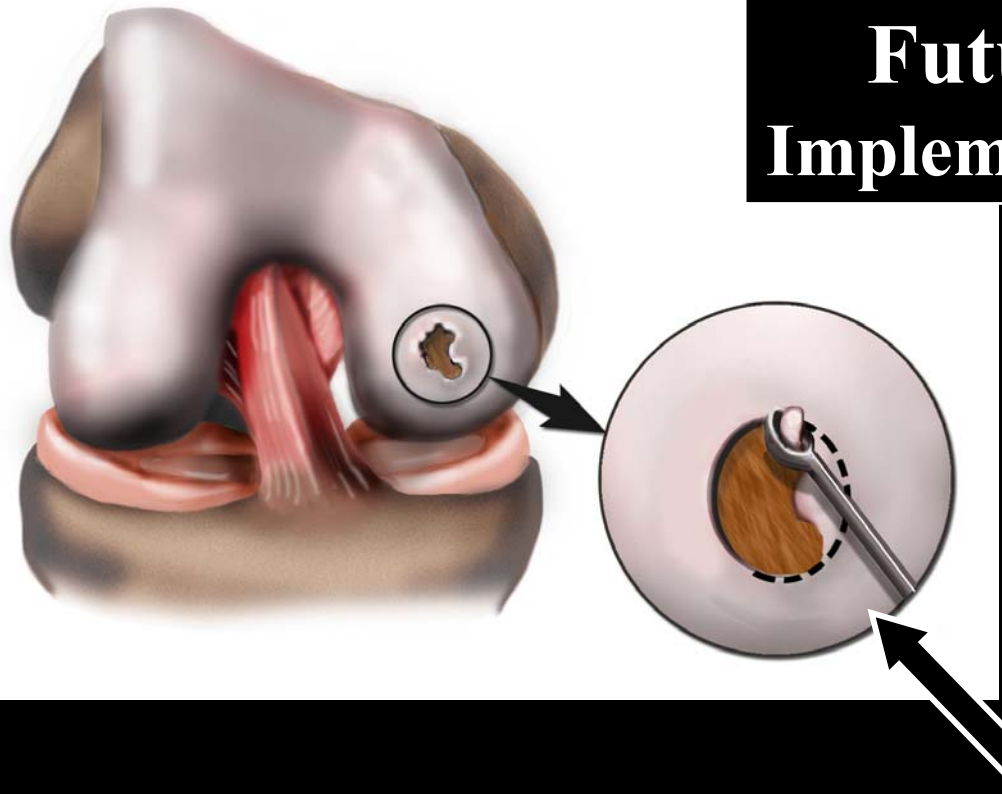
Total Knee Replacement

Autologous chondrocytes injected under a periosteal flap (ACT)

Future Clinical Practice
Implementing Tissue Engineering



Implantation of a cell-seeded matrix

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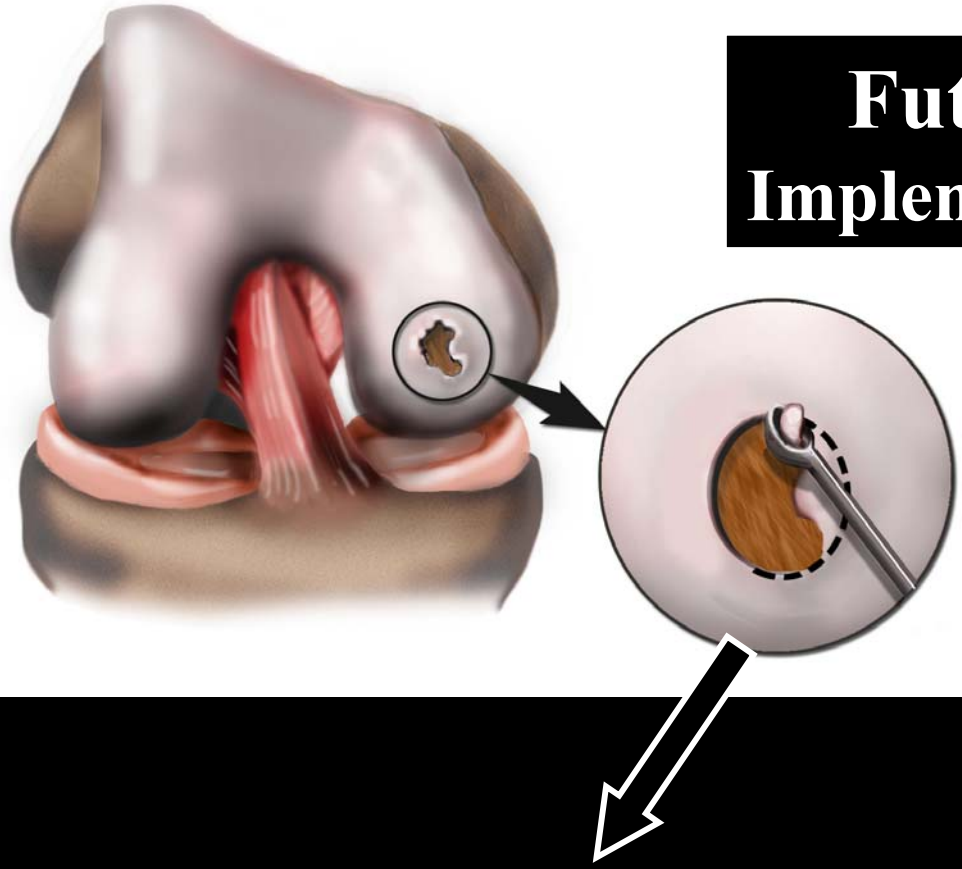
"Tissue engineered" cartilage implanted in a rabbit model did not remodel (Advanced Tissue Sciences, Inc.).

Future Clinical Practice
Implementing Tissue Engineering



Implantation of the matrix alone

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"Microfracture":
Stem cells from bone marrow infiltrate the defect

500µm

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.

Which Tissues Can Regenerate?

	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

- Size of defect
  - *e.g.*, bone does not regenerate in large defects
- Collapse of surrounding tissue into the defect
  - *e.g.*, periodontal defects
- Excessive strains in the reparative tissue
  - *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)
- SOLUBLE REGULATORS
  - Growth factors or their genes
- ENVIRONMENTAL FACTORS
  - Mechanical loading
  - Static versus dynamic (“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 ?

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

TISSUE ENGINEERING
Risks

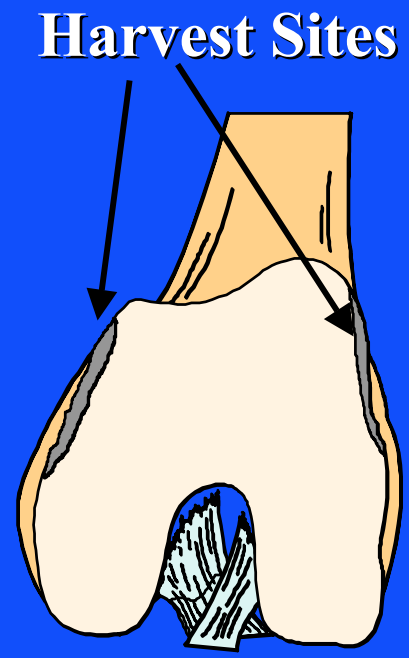
Exercise caution that the tissue engineering solution does not create larger problems that being solved.

- Tissue harvest for the isolation of cells places the donor site and surrounding tissue at risk of degeneration.
- Implants that accelerate the breakdown of surrounding tissues.

EFFECTS OF THE CARTILAGE REPAIR PROCEDURES ON UNINVOLVED CARTILAGE ?

Effects of Harvest (Canine Model)

- Changes in the mechanical properties of AC at sites away from the harvest, 4-mo post-op (up to 3-fold).
- Changes were consistent with hypertrophy, predisposing to osteoarthritis.



CR Lee, *et al.*,
JOR, 2000;18:790-799