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

2.782J/3.961J/BEH.451J/HST524J

TISSUE ENGINEERING
II. Scaffolds

M. Spector, Ph.D.

ELEMENTS* OF TISSUE ENGINEERING/ REGENERATIVE MEDICINE

- MATRIX (SCAFFOLD)
  - Porous, absorbable synthetic or natural polymers
- 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")

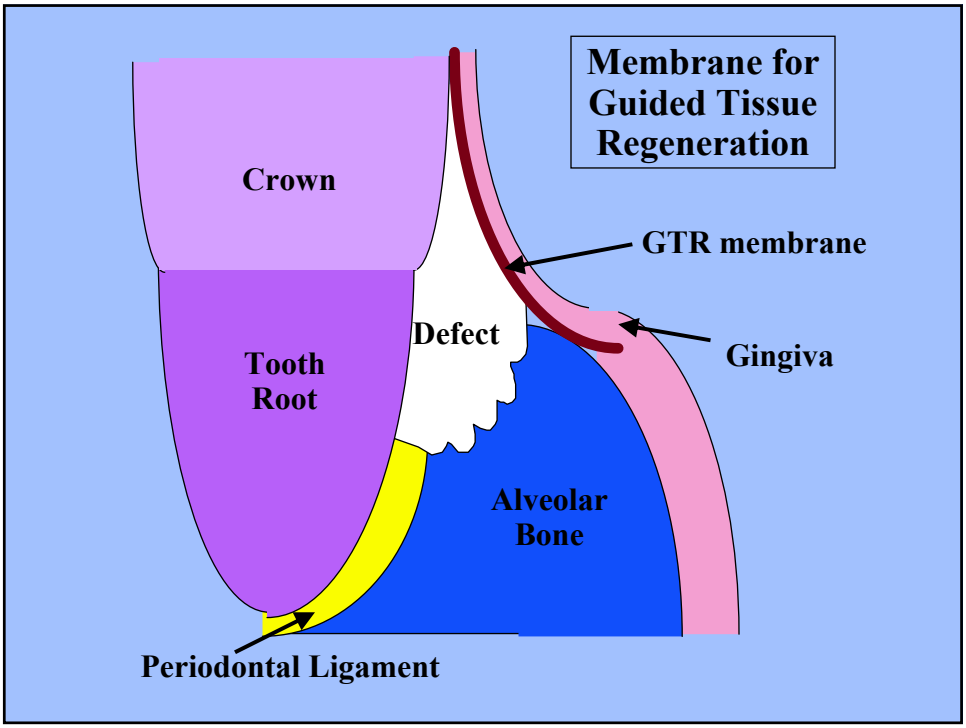
*Used individually or in combination

TISSUE ENGINEERING
The Role of Biomaterials

- Tissue engineering is proving to be a revolution in biomaterials.
- In the last century biomaterials were used for the fabrication of permanent implants to replace tissue function (*e.g.*, total joint replacement prostheses).
- In this century the principal role of biomaterials will likely be to serve as scaffolds/matrices for tissue engineering and cell and gene therapies.
- The challenge in developing biomaterials as scaffolds for tissue engineering appears to exceed the challenges in the recombinant production of growth factors, and cell and gene therapies.

ROLES OF THE BIOMATERIALS/ SCAFFOLDS (MATRICES)

1) the scaffold serves as a framework to support cell migration into the defect from surrounding tissues; especially important when a fibrin clot is absent.
2) serves as a delivery vehicle for exogenous cells, growth factors, and genes; large surface area.
3) before it is absorbed a scaffold can serve as a matrix for cell adhesion to facilitate/"regulate" certain unit cell processes (*e.g.*, mitosis, synthesis, migration) of cells *in vivo* or for cells seeded *in vitro*.
    a) the biomaterial may have ligands for cell receptors (integrins)
    b) the biomaterial may selectively adsorb adhesion proteins to which cells can bind
4) may structurally reinforce the defect to maintain the shape of the defect and prevent distortion of surrounding tissue.
5) serves as a barrier to prevent the infiltration of surrounding tissue that may impede the process of regeneration.



SCAFFOLDS

Concepts Guiding the Development of Scaffolds

Biomaterals

- Existing safe ("biocompatible") absorbable materials; PLA-PGA
- Natural extracellular matrix materials; bone mineral
- Biomimetics and analogs of extracellular matrix; collagen and collagen-hydroxyapatite scaffolds
- Biopolymers for nanoscale matrix; self-assemblying peptides
- New types of biomaterials designed specifically for tissue engineering scaffolds

Methods of Scaffold Production

- Precision (computer) multi-scale control of material, architecture, and cells; solid free-form fabrication technologies

PROPERTIES OF MATRICES
Change of Properties with Degradation

- Physical
  - Overall size and shape
  - Pore characteristics: % porosity, pore size distribution, interconnectivity, pore orientation
- Chemical
  - Biodegradability and moieties released; degradation rate synchronized to the formation rate
  - Provide or bind ligands that affect cell function
- Mechanical
  - Strength (and related prop., *e.g.*, wear resistance)
  - Modulus of elasticity; stiffness
- Electrical and Optical ?

MATRIX (SCAFFOLD) MATERIALS

- Synthetic Polymers
  - *e.g.*, polylactic and polyglycolic acid
  - self-assembling proteins
  - many others
- Natural Polymers
  - fibrin
  - collagen
  - collagen-glycosaminoglycan copolymer
  - many others

SCAFFOLD (MATRIX) MATERIALS
Synthetic

- Polylactic acid and polyglycolic acid
- Polycarbonates
- Polydioxanones
- Polyphosphazenes
- Poly(anhydrides)
- Poly(ortho esters)
- Poly(propylene fumarate)
- Pluronic (polaxomers)
  - Poly(ethylene oxide) and poly(propylene oxide)

SCAFFOLD (MATRIX) MATERIALS
Natural

- Collagen
  - Gelatin and fibrillar sponge
  - Non-cross-linked and cross-linked
- Collagen-GAG copolymer
- Albumin
- Fibrin
- Hyaluronic acid
- Cellulose
  - Most abundant natural polymer
  - Mechanism of absorbability *in vivo*?

SCAFFOLD (MATRIX) MATERIALS
Natural (Continued)

- Chitosan
  - –Derived from chitin, 2nd most abundant natural polymer
  - –Mechanism of absorbability *in vivo*?
- Polyhydroxalkanoates
  - –Naturally occurring polyesters produced by fermentation
- Alginate (polysaccharide extracted from seaweed)
- Agarose
- Polyamino acids

SCAFFOLDS

Structure/Architecture

- Fiber mesh
- Sponge-like
- Fine filament mesh
- Architecture by design; Free Form Fabrication/3-D printing

SCAFFOLDS

Structure/Architecture

- Percentage porosity
  - number of cells that can be contained
  - strength of the material
- Pore diameter
  - surface area and the number of adherent cells
  - ability of cells to infiltrate the pores
- Orientation of pores
  - can direct cell growth
- Overall shape of the device needs to fit the defect

SCAFFOLDS

Methods for Producing Scaffolds*

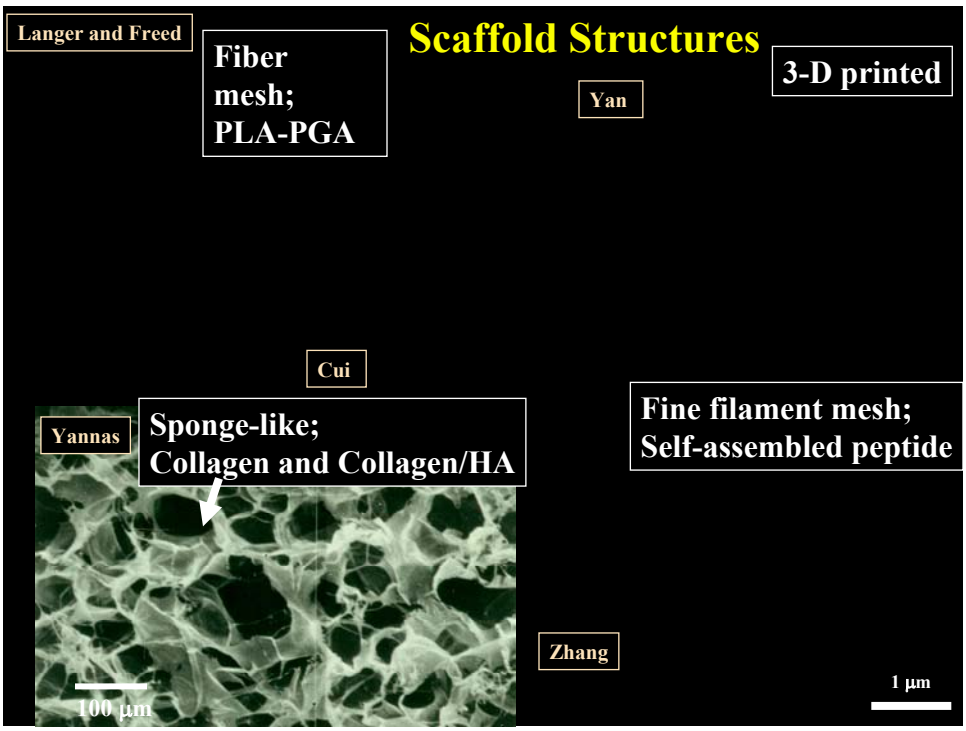
- Treat tissues/organs to remove selected components
- Fibers (non-woven and woven)
- Freeze-drying
- Incorporate porogens into polymers
- Self-assemblying molecules
- Free-form manufacturing

* Need to consider the advantages and disadvantages with respect to the production of scaffolds with selected chemical composition and structure

DE-ORGANIFIED BOVINE TRABECULAR BONE

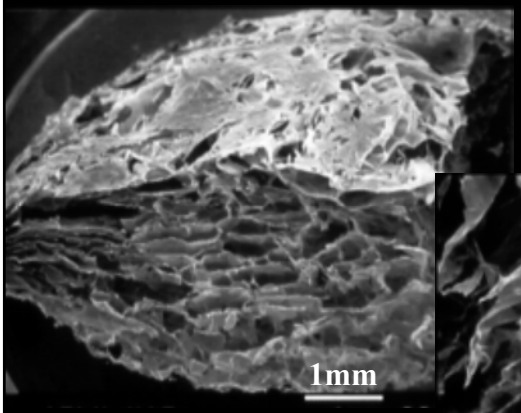
Natural Bone Mineral

Photo removed due to copyright restrictions.

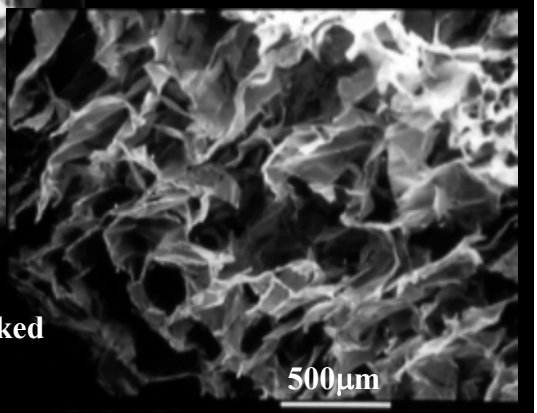


Images removed due to copyright restrictions.

COLLAGEN-GAG SCAFFOLDS

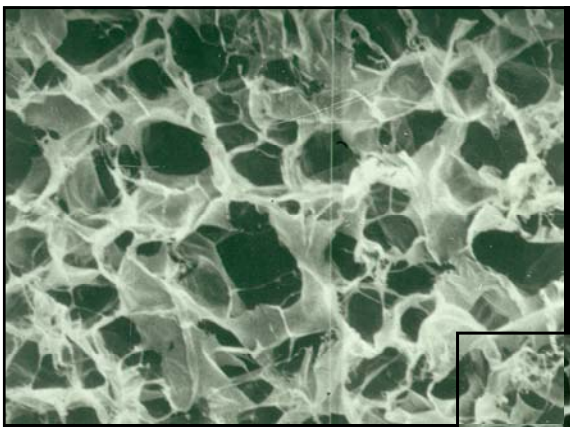


- Type I (bovine and porcine)
- Type II (porcine)
- Chondroitin 6-sulfate



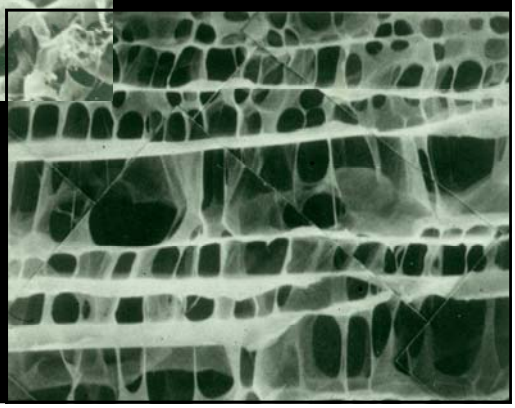
- Freeze-dried
- Dehydrothermally cross-linked
- Additional cross-linking

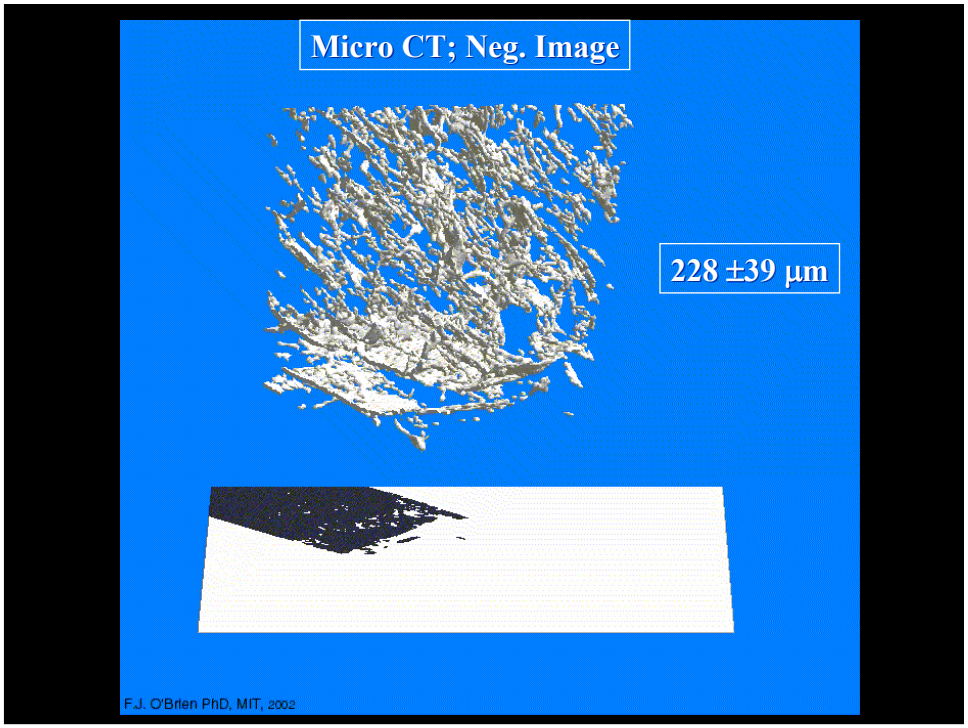
IV Yannas, *et al*. PNAS, 1989



Scaffold Structures: Pore Orientation

(Yannas)





BIOMANUFACTURING

BIOMANUFACTURING:
A US-CHINA NATIONAL SCIENCE FOUNDATION-SPONSORED WORKSHOP

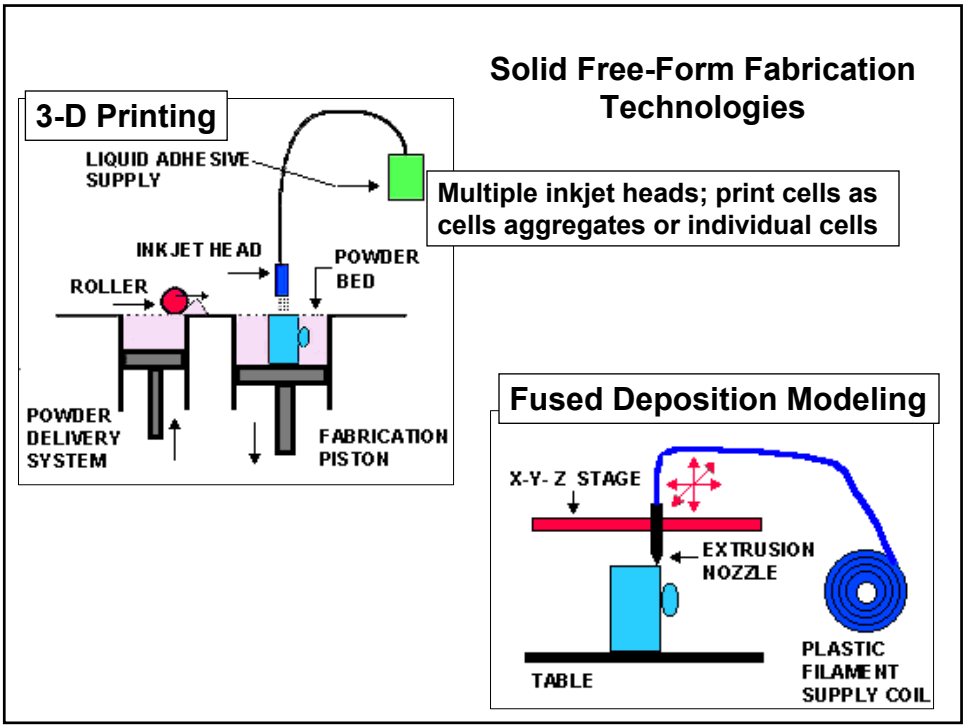
June 29-July 1, 2005, Tsinghua University, Beijing, China

W. Sun, Y. Yan, F. Lin, and M. Spector

New technologies for producing scaffolds with *precision (computer-controlled) multi- scale control of material, architecture, and cells.*

www.mem.drexel.edu/biomanufacturing/index.htm

Tiss. Engr., In Press



Figures removed due to copyright restrictions.

1) Single-nozzle deposition using polylactic acid and tricalcium phosphate.

See Yan, Yongnian, et al. "Layered manufacturing of Tissue Engineering Scaffolds via Multi-nozzle Deposition." *Materials Letters* 57 (2003): 2623-2628.

2) Hepatocyte/gelatin/sodium alginate construct.

See Yan, Yongnian, et al. "Fabrication of Viable Tissue-engineering Constructs with 3D Cell-assembly Technique." *Biomaterials* 26 (2005): 5864-5871.

3) Printing single cells, cell aggregates, and the supportive biodegradable thermosensitive gel according to a computer-generated template.

See Mironov, Vladimir, et al. "Organ Printing: Computer-aided Jet-based 3D Tissue Engineering." *TRENDS in Biotechnology* 21, no. 4 (April 2003).