Biomaterials and Cell-Biomaterial Interactions

Module 3, Lecture 2

20.109 Spring 2008

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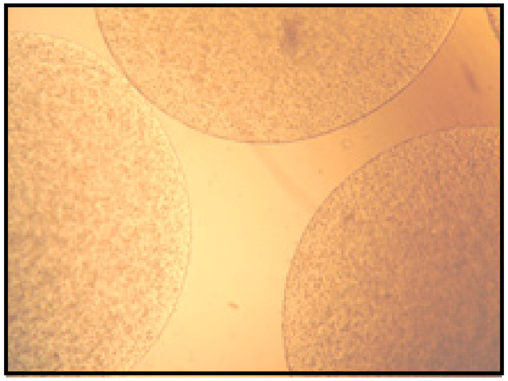
Topics for Lecture 2

- Module 3 goals+assessments
- Introduction to biomaterials
  - properties and types of biomaterials
  - biocompatibility and bioactivity
  - natural vs. synthetic materials
- Examples of TE constructs
  - how do we tailor materials for specific purposes?

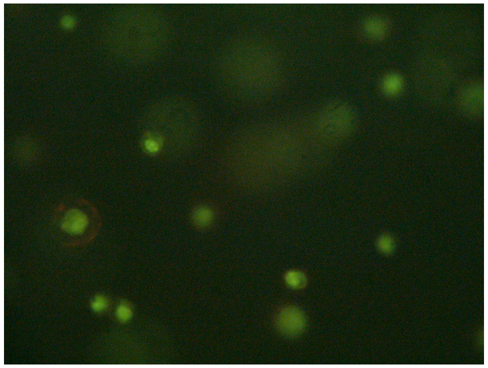
Module overview: lab

Day 1: design

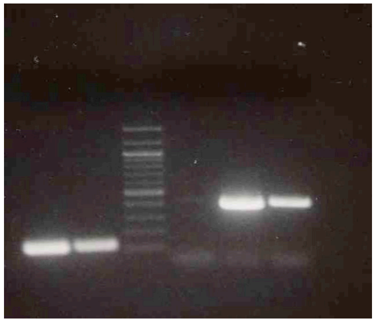
Day 2: seed cultures



Day 3: viability assay



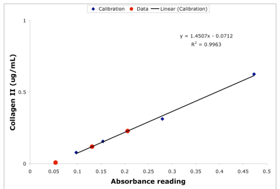
Day 4: prep RNA+cDNA



Day 5: transcript assay

Day 6: protein assay

Day 7: remaining analysis



Overall learning goals:

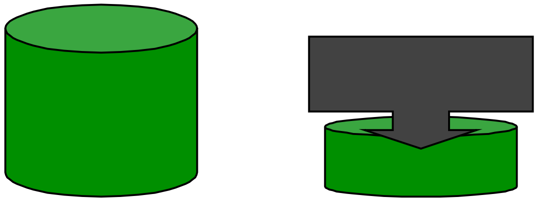
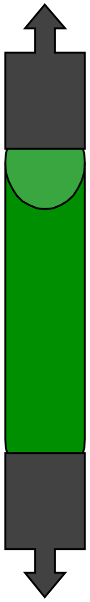
- Extend experience with mammalian cell culture.
- Gain conceptual familiarity and practical experience carrying out and analyzing phenotypic assays.

Module 3 overview: assessments

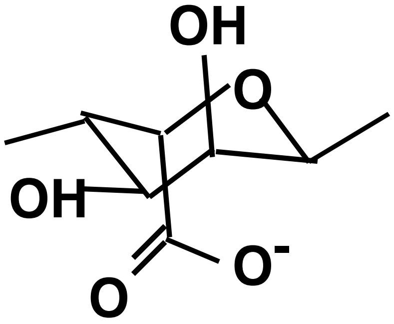
- Essay on standards in TE
  - draft due D4, final due D6
  - learning goals: engage in a modern discussion on a meta-scientific issue

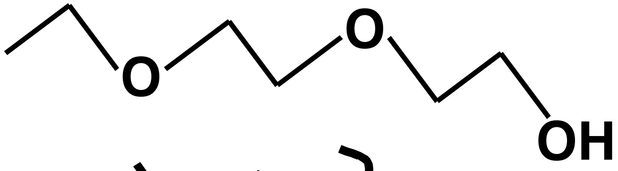
- Presentation of novel research idea
  - final presentation D8
  - learning goals: investigate literature independently, exercise scientific creativity, design experiments to address a specific question/problem

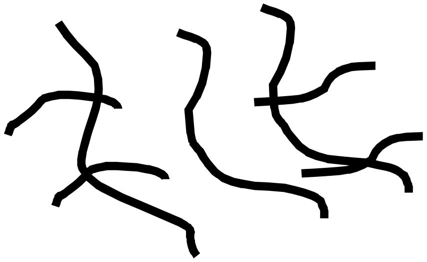
Properties of biomaterials

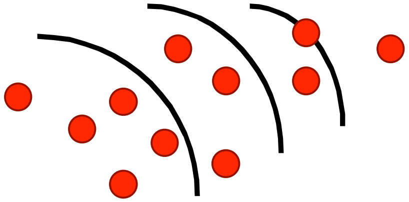
- Physical/mechanical
  - strength (tensile or compressive)
  - elasticity
  - architecture (e.g., pore size)
- Chemical
  - degradability
  - water content
  - toxicity







- Biological
  - motifs that cells recognize
  - release of biological components
- Lifetime



The right material for the job

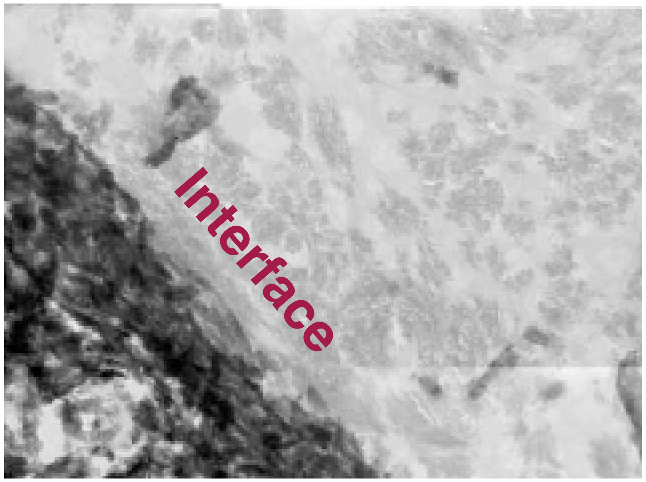
- Metals
  - types: Ti, Co, Mg alloys
  - pros: mechanically robust (E=10's of GPa)
  - applications: orthopedics, dentistry
- Ceramics
  - types: Al_2O_3, Ca-phosphates, sulfates
  - pros: strength, attachment to bone
  - applications: orthopedics, dentistry
- Polymers
  - diverse, tunable properties
  - applications: primarily soft tissues

General: B. Ratner, ed. *Biomaterials Science*, 1996.

Image: Porter et al., *Biomaterials* **25**:3303 (2004).

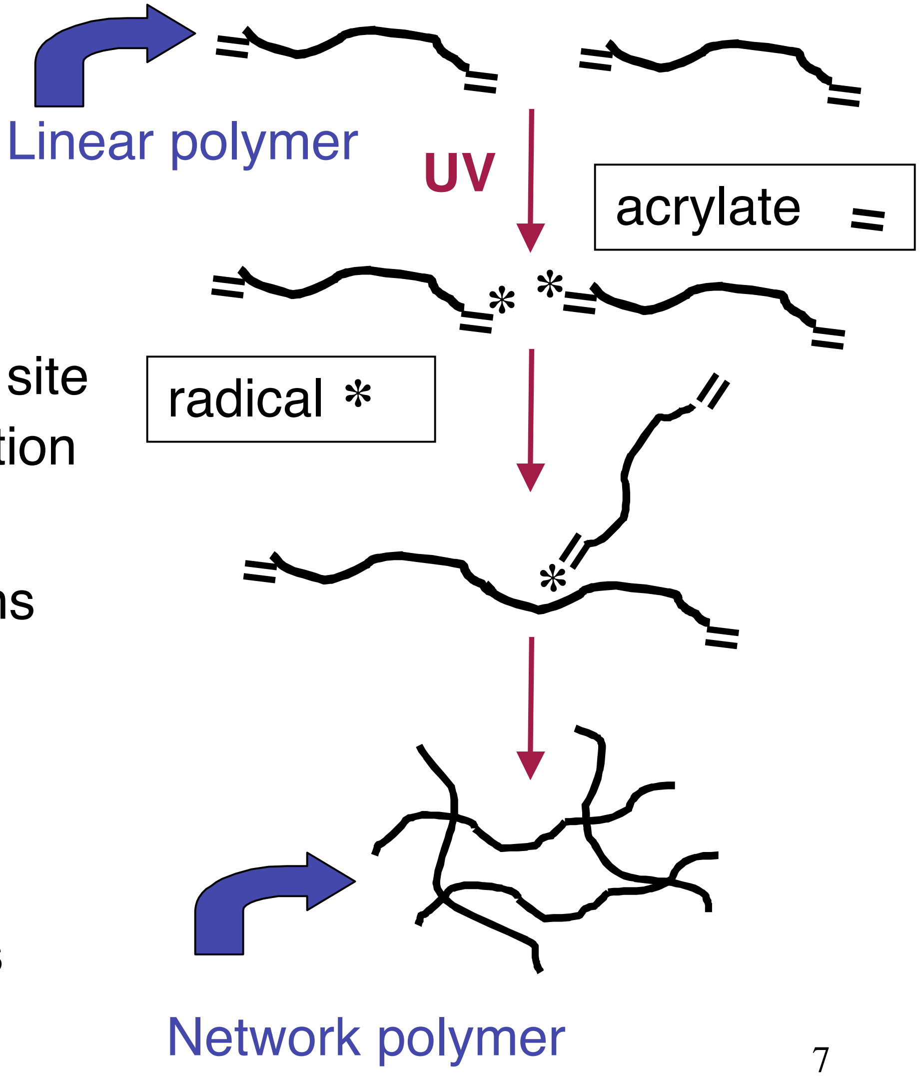
Metal hip implant

http://www.weisshospital.com/joint-university/hip/metal.html



Synthesis and use of hydrogels

- Linear polymer:
  - bifunctional monomers covalently bound together
- Network polymer:
  - multi-functional polymers covalently attached at same site
  - example: radical polymerization
- Network structure
  - covalently cross-linked chains
  - water-swollen (if hydrophilic)
- Advantages
  - mimic tissue water content, elasticity, diffusivity
  - form under gentle conditions



Linear polymer

UV

acrylate =

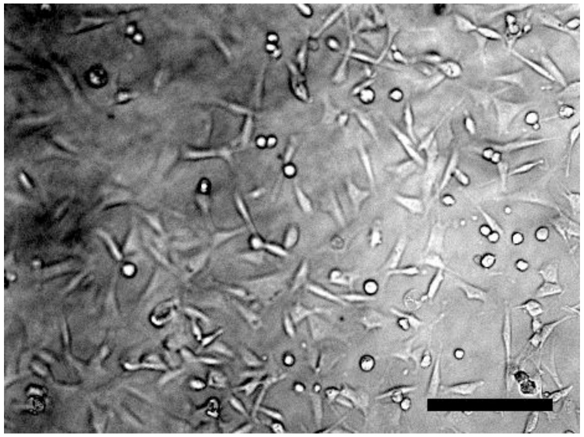
radical *

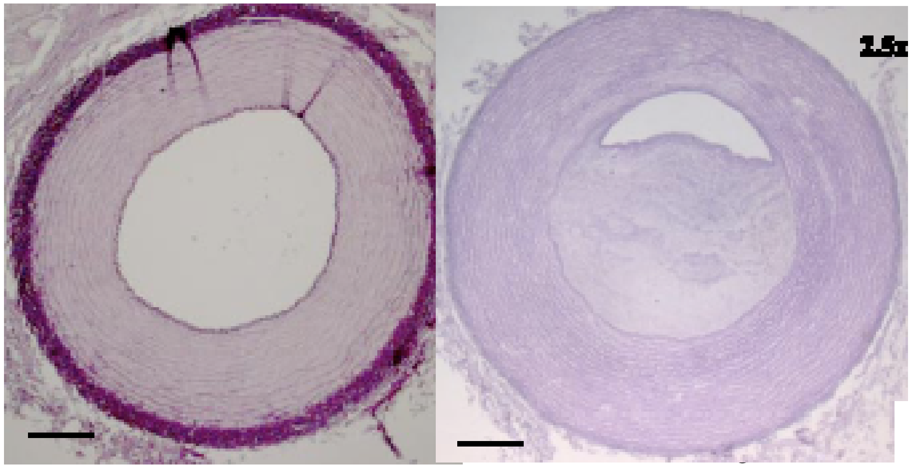
Network polymer

Materials interfacing with cells

- Desire bioactivity
  - cell adhesion
  - cell proliferation/differentiation
- Avoid bio-incompatibility
  - bacterial adhesion
  - clot formation
  - toxicity
  - immunogenicity
- Material properties
  - present adhesion ligands and growth factors
  - manufacture/keep sterile
  - prevent non-specific sticking of blood cells, bacteria

Fibroblasts on polymer-peptide gels (Stachowiak).





Normal artery

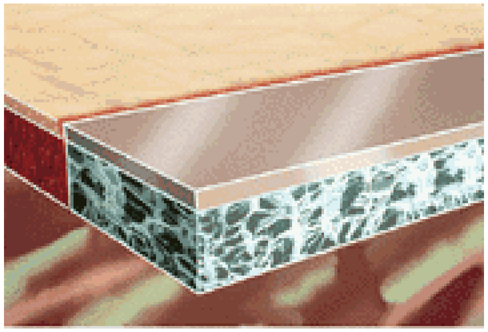
Occluded artery

Zavan et al., *FASEB J* online preview (2008).

Natural vs. synthetic materials

- Natural pros/cons
  - built-in bioactivity
  - poor mechanical strength
  - immunogenicity (xenologous sources)
  - lot-to-lot variation, unpredictable

Natural examples: collagen, alginate



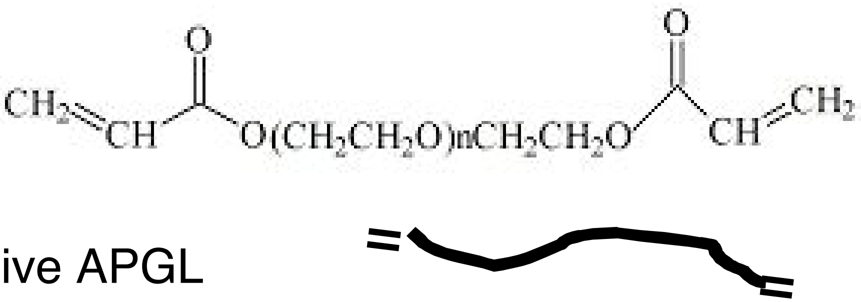
Synthetic examples: silicone rubber, PEG

- Synthetic pros/cons
  - biocompatibility may be difficult to predict, must be tested
  - mechanical and chemical properties readily altered
  - minimal lot-to-lot variation

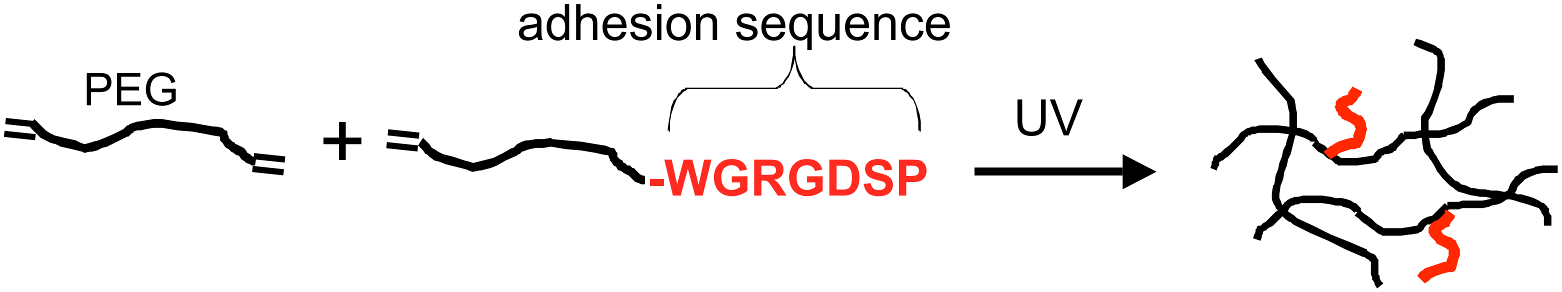
- Synthetic advantages: tuneable and reproducible

Example: bioactive photopolymers

- PEG is poly(ethylene glycol), a bio-inert polymer
- PEG acrylates can be photopolymerized to hydrogel
  - safe for patient
  - temporal and spatial control
  - efficient (wrt energy, conversion)
- Covalent modification with peptides
  - degradability: e.g., collagenase-sensitive APGL
  - adhesion: RGD (general), VAPG (smooth muscle), etc.



laysanbio.com



adhesion sequence

PEG

+

-WGRGDSP

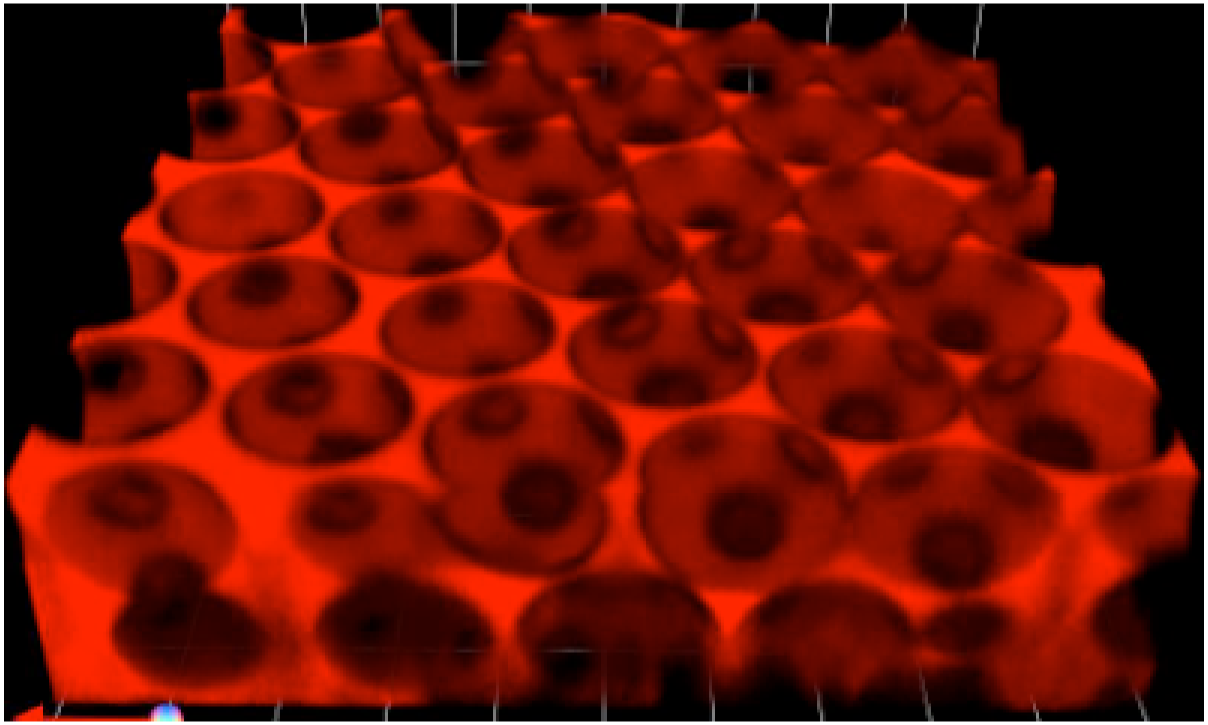
UV

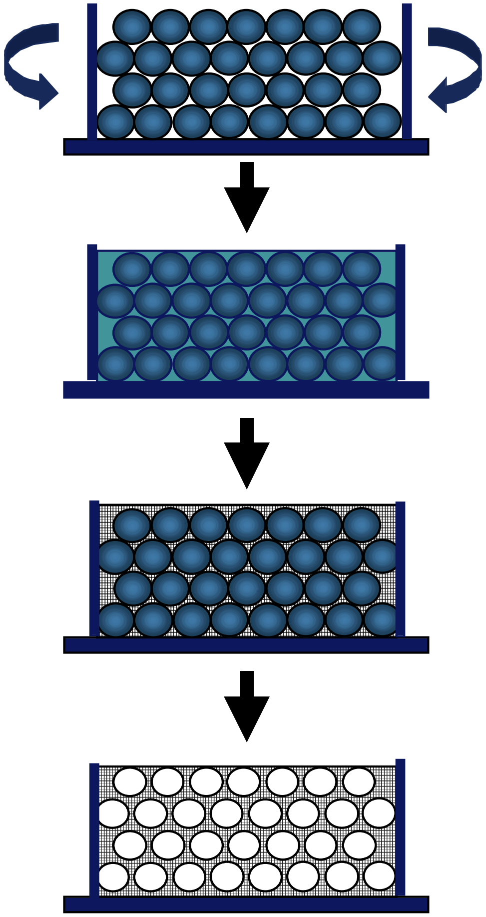
West JL & Hubbell JA, *Macromolecules* **32**:341 (1999)

Gobin AS & West, *J Biomed Mater Res* **67**:255 (2003)

Example: pore-forming strategies

- How to get pore interconnectivity without sacrificing mechanical properties? Colloidal crystal templating





Stachowiak et al., *Adv Mat* **17**:399 (2005), Stachowiak & Irvine, unpublished data

Example: cytokine delivery

- VEGF delivery for angiogenesis, D. Mooney lab
- PLGA = poly(lactic-co-glycolic) acid
- Delivery methods
  - direct mixing of VEGF with hydrophobic PLGA
  - direct mixing with PLGA/alginate mixture
  - release from alginate beads w/in PLGA scaffold
- Results
  - incorporation efficiency: 74% with alginate, else 27%
  - mechanical properties: unchanged
  - protein stability: >80% activity
  - release predictability: similar, ~ 2 weeks long

Peters et al., *J Biomed Mater Res* **60**:668 (2002)

Sheridan et al., *J Cont Rel* **64**:91 (2000)

+VEGF

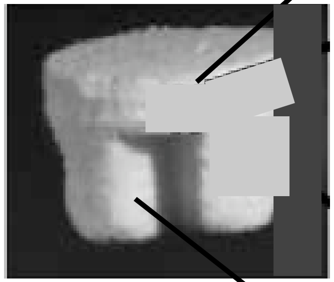
Control

Peters et al.

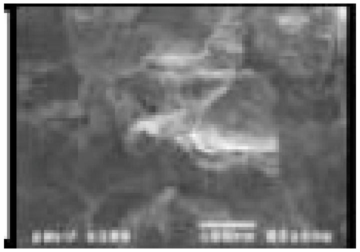
Example: cartilage-bone composite

- 3D-printing (3DP) method, L. Griffith lab:
  - powdered polymer preparation
  - solvent addition by nozzle (or heat) to fuse polymer in precise patterns, layer-by-layer
- PLA/PGA scaffold by 3DP
  - top = cartilage-mimic: high porosity
  - bottom = bone-mimic: low porosity

high porosity



low porosity



- 3DP-like methods for hydrogels (e.g., Bhatia lab)
  - *light* rather than solvent or heat for polymerization
- Limitations of 3DP method
  - large feature size (~100 um), for now…

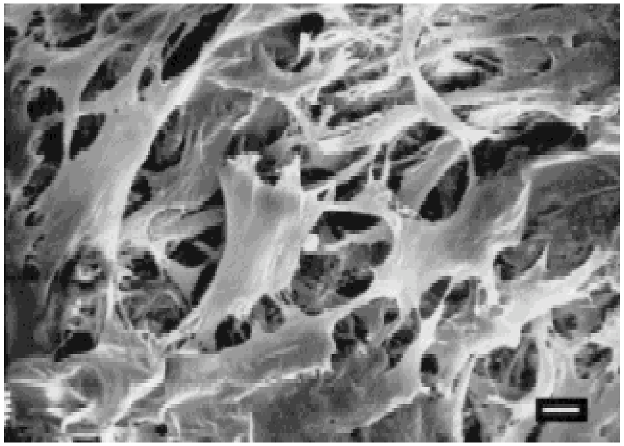
Chondrocytes preferentially attach to top! →

Sherwood et al., *Biomaterials* **23**:4739 (2002)

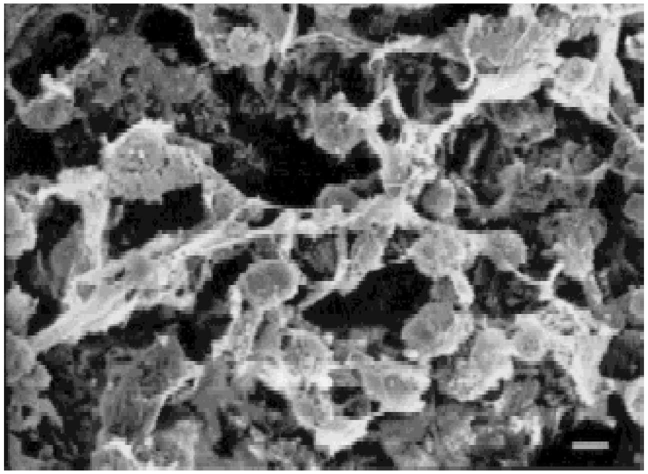
Example: multi-polymer composite

- Porous PLA scaffold + marrow cells
- Cells loaded in medium
  - elongated morphology
- Cells loaded in alginate
  - round morphology
  - improved cell retention
  - somewhat enhanced chondrogenesis

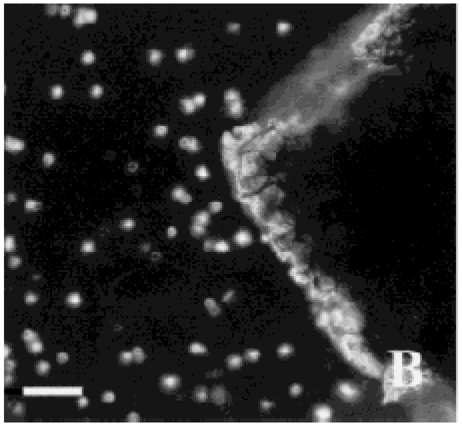
PLA



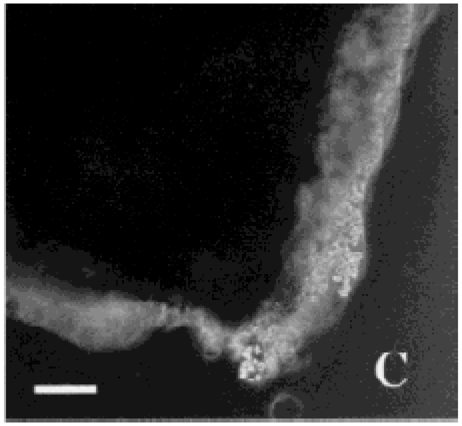
PLA+alginate



PLA



PLA+alginate



Caterson et al., *J Biomed Mater Res* **57**:394 (2001)

Lecture 2: conclusions

- A wide variety of biomaterials can be used in TE.
- Cell-material interactions can be positive, negative, or neutral (cf. bioactivity, biocompatibility, cytotoxicity).
- Optimization of TE constructs for a given purpose may involve trade-offs (e.g., increased porosity for nutrient diffusion vs. sufficient mechanical strength).
- Hydrogels are useful for soft tissue engineering, due to their similarity to tissue and ease of modification.

Next time… standards in tissue engineering and other scientific communities.

Module overview: week 1

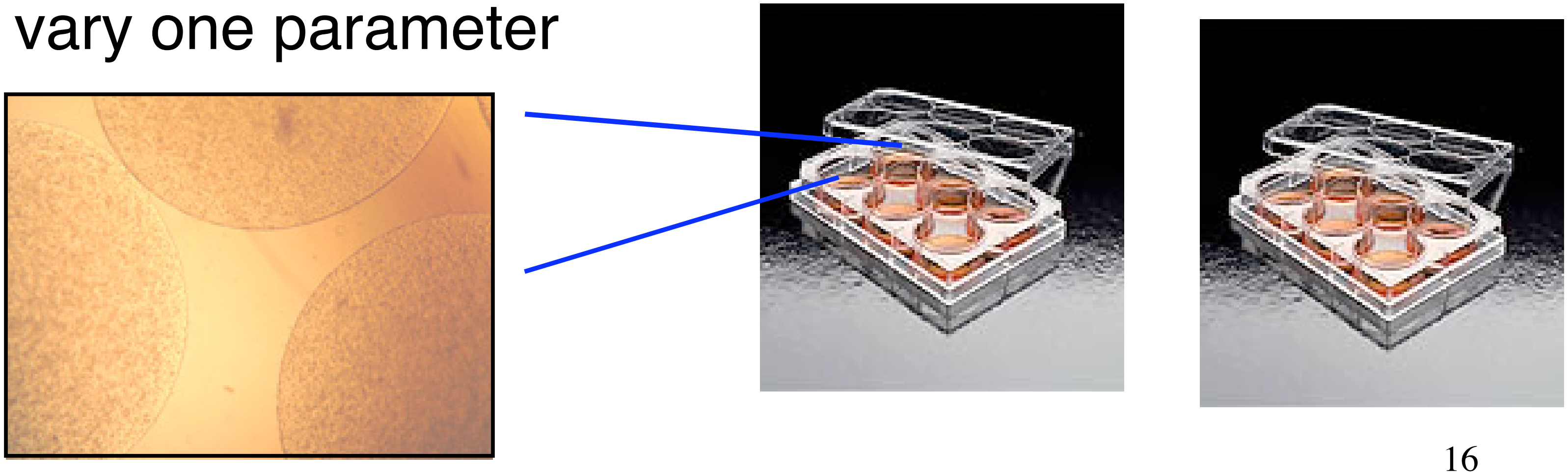
Days 1+2: design and seed cultures

- 2D culture: plastic surface
  - prepare in duplicate
  - design maintenance plan

flask 1 = flask 2

- 3D culture: alginate beads
  - prepare in duplicate wells
  - vary one parameter

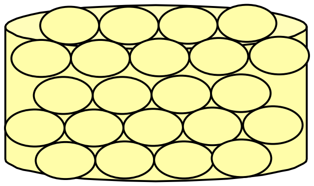
plate 1 ≠ plate 2



What designs did you choose?

scaffold/matrix

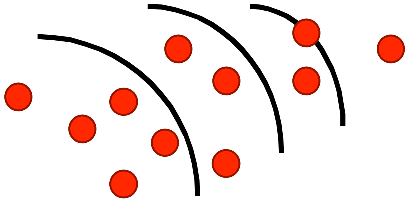
→ usually degradable, porous



soluble factors

→ made by cells or synthetic

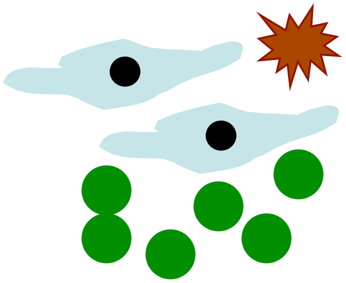
→ various release profiles



cells

→ precursors and/or differentiated

→ usually autologous



integrated implantable or injectable device