Biomaterials and Cell-Biomaterial Interactions

Module 3, Lecture 2

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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: Al₂O₃, Ca-phosphates, sulfates
  – pros: strength, attachment to bone
  – applications: orthopedics, dentistry

• Polymers
  – diverse, tunable properties
  – applications: primarily soft tissues


Metal hip implant

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

  **Synthetic examples: silicone rubber, PEG**

- **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.

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

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

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

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

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

flask 1 = flask 2

plate 1 ≠ plate 2
What designs did you choose?

**scaffold/matrix**
- usually degradable, porous

**cells**
- precursors and/or differentiated
- usually autologous

**soluble factors**
- made by cells or synthetic
- various release profiles

**integrated implantable or injectable device**