Overview of Module 3, Part I

Module 3, Lecture 6

20.109 Spring 2008

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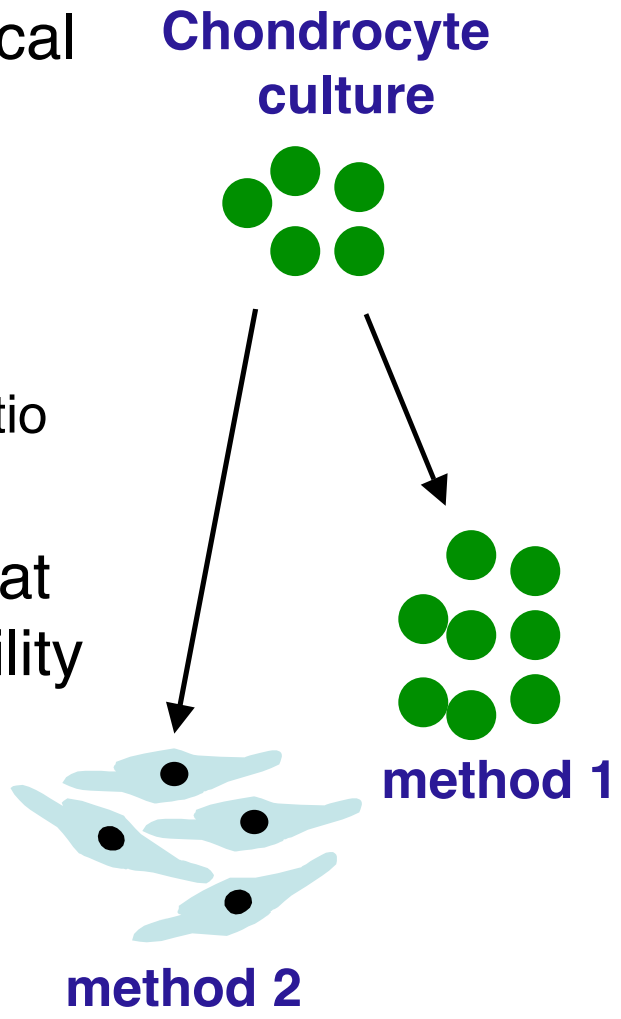
Topics for Lecture 6

- First, a presentation from Atissa Banuazizi
- Review of big picture:
  - brief module 3 overview
  - cartilage tissue engineering concepts
- What does each day of module 3 contribute? (start today, finish next time)

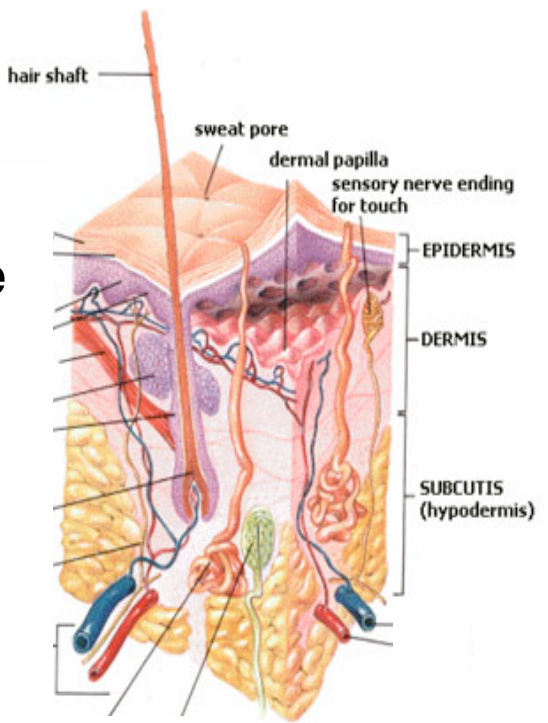
Overall goals of Module 3

- Design experiment to study effects of local environment on cell de-differentiation
  - cell: primary chondrocytes, *in vitro* culture
  - local environment: material properties, cell density, culture medium composition
  - effects: viability, morphology, collagen II:I ratio
- Grander purpose: discovering factors that maintain chondrocyte phenotype has utility for cartilage tissue engineering
  - conditions for *ex vivo* cell expansion
  - conditions for bulk cartilage production



Therapies for damaged tissue

- All tissues have limited regeneration
  - e.g., skin: shallow vs. deep cuts
- Replace with tissue graft
  - donor tissue: limited supply, immune response
  - autologous tissue: donor site damage
- Replace with permanent synthetic substitute (not strictly speaking TE)
  - inflammatory response (chronic)
  - mis-match with natural tissue properties
  - multiple replacements/surgeries
- A new strategy: promote regeneration of ~native tissue = tissue engineering



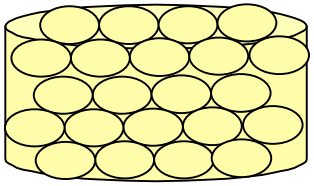
[Public domain image, Wikimedia Commons]

Potential components for cartilage TE

scaffold/matrix

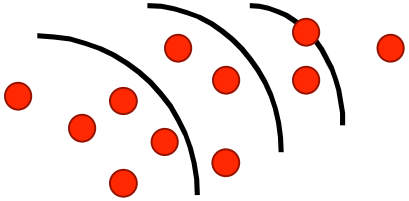
→ usually degradable, porous

→ hydrogel (e.g., alginate)



soluble factors

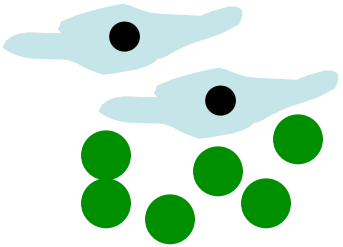
→ TGF, BMP, others

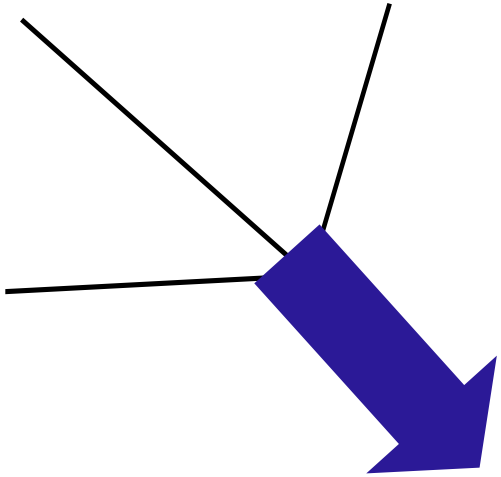


cells

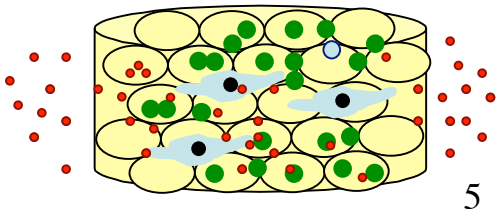
→ stem cells, or

→ chondrocytes



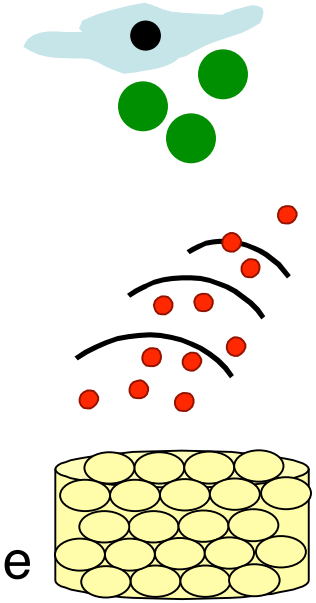


integrated implantable or injectable device



Roles of components in cartilage TE

- Cells
  - contribute to tissue reconstruction (secrete matrix)
- Cytokines
  - stimulate chondrocyte production of fresh matrix
  - simulate stem cell differentiation to chondrocytes
  - attract stem cells to wound site (chemokines)
- Scaffold
  - retain cells and cytokines in needed location
  - provide mechanical support and structure for new tissue

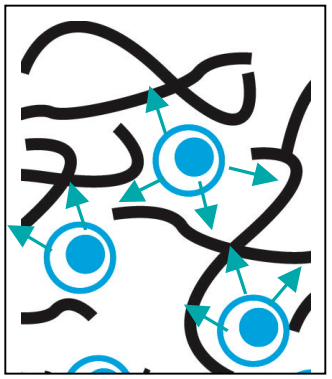


- Any component may be engineered!
  - cells: genetically engineered to express a needed protein
  - cytokine proteins: engineered to have longer half-lives
  - scaffold: engineered to have specific chemical, mechanical, and biological properties that mimic cartilage

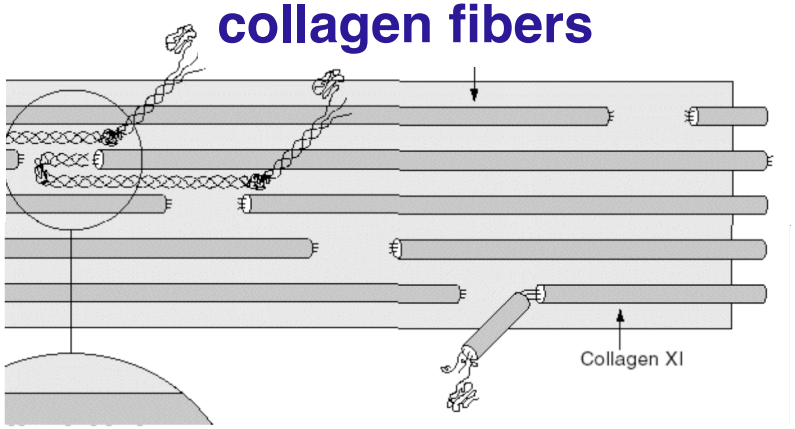
→ e.g., cell-adhesive peptide sequences

Cartilage structure and growth

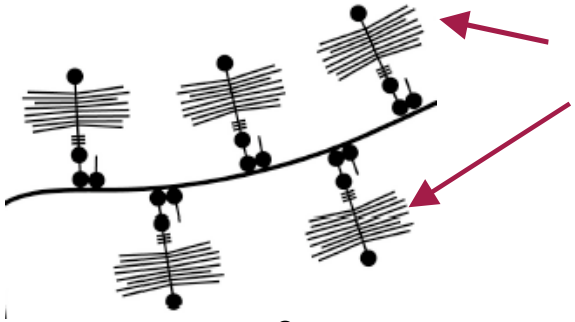
- Cartilage structure
  - chondrocytes make collagen (CN), proteoglycans (PG)
  - CN forms covalently cross-linked fibers
  - PG promote influx of water/ions



collagen fibers



proteoglycans



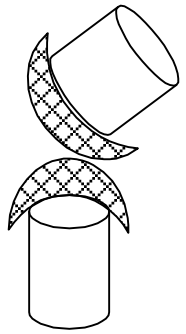
COO^-, SO_3^-

high (-) density

10^8 Da

- Natural cartilage growth
  - very slow turnover of collagen in absence of damage
  - even if damaged, little new extracellular matrix forms
  - atypical wound healing partly because avascular

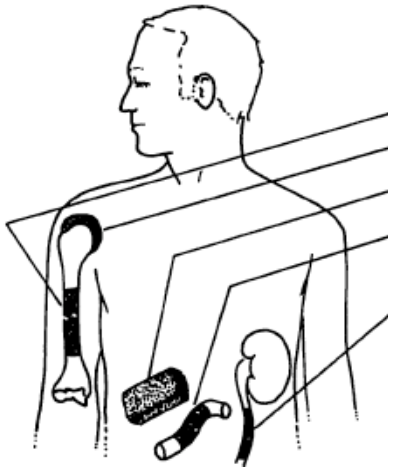
Cartilage replacement



- Specific requirements for replacement
  - sustain compressive loads (done by PG, water)
  - lubricate joint (done by PG, synovial fluid)
  - sustain tensile stresses (done by collagen)
- Ideal replacement has collagen/proteoglycan balance of native tissue
  - option 1: promote native tissue regeneration *in vivo*
  - option 2: grow native tissue-like construct *in vitro*, implant it
  - either option may involve cells and/or scaffold and/or cytokines

T. Nagai et al., *Tissue Eng* **14** (2008)

(option 2)

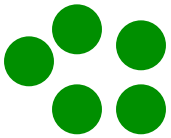


R. Langer & J.P. Vacanti, *Science* **260**:920 (1993)

What can we learn from culture models?

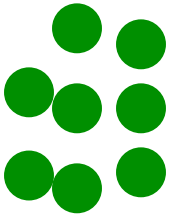
- What cell/cytokine/scaffold/culture combinations stimulate or sustain the chondrocyte phenotype?
- Knowledge can feed into multiple kinds of therapies:

Cell transplantation therapy



1. Biopsy: a few chondrocytes

Conditions for *ex vivo* expansion???

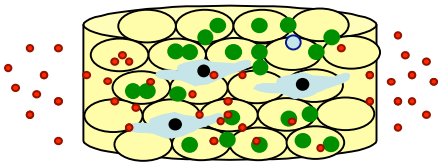


2. Inject many cells into patient

3. Grow fresh tissue *in vivo*

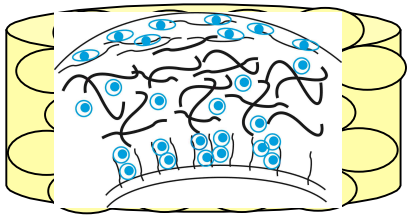
Cartilage replacement therapy

1. Put together cells, scaffold, cytokines



Conditions for cartilage production???

2. Grow cartilage-like tissue *in vitro*



3. Directly implant into patient

… and many other potential alternatives!