Tissue Engineering
BIOE 476

Prof. Gregory Underhill

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http://courses.engr.illinois.edu/bioe476/
Types of Therapies

Boceprevir (Victrelis)
Protease Inhibitor - Hepatitis C

Small Molecule Drug
Hydrophobic
Oral Administration


Insulin
Protein
Large & Hydrophilic
Injected into Bloodstream
What are Cell-Based Therapies?

- Delivering cells as therapeutics instead of drugs

- Examples of cell-based therapies
  - Blood Transfusion
  - Bone Marrow Transplant
  - Organ Transplants
Cell-Based Therapies

- β cells (pancreatic islets)
- Allograft: donor ≠ recipient
- Autograft: donor = recipient

- Immune rejection
The Transplant Problem- Organ Shortage

Patients on the waiting list on December 31st of the year (active listings only)

[Graph showing the number of patients on the waiting list for various organs (Kidney, Liver, Lung, Heart, Kidney-pancreas, Pancreas (PTA & PAK), Intestine) from 1998 to 2008.]

United Network for Organ Sharing
Organ Procurement and Transplantation Network (2010)
The Transplant Problem- Organ Shortage

Liver transplant waiting list activity among adult patients

<table>
<thead>
<tr>
<th>Removal reason</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listings at start of year</td>
<td>16,085</td>
<td>15,990</td>
<td>15,641</td>
</tr>
<tr>
<td>Listings added during year</td>
<td>10,261</td>
<td>10,344</td>
<td>10,478</td>
</tr>
<tr>
<td>Listings removed during year</td>
<td>10,356</td>
<td>10,693</td>
<td>10,494</td>
</tr>
<tr>
<td>Listings at end of year</td>
<td>15,990</td>
<td>15,641</td>
<td>15,625</td>
</tr>
<tr>
<td>Deceased donor transplant</td>
<td>5,951</td>
<td>5,791</td>
<td>5,807</td>
</tr>
<tr>
<td>Living donor transplant</td>
<td>191</td>
<td>173</td>
<td>168</td>
</tr>
<tr>
<td>Patient died</td>
<td>2,336</td>
<td>2,451</td>
<td>2,396</td>
</tr>
<tr>
<td>Trans. to another center</td>
<td>263</td>
<td>190</td>
<td>184</td>
</tr>
<tr>
<td>Too sick to transplant</td>
<td>269</td>
<td>280</td>
<td>327</td>
</tr>
<tr>
<td>Improved, tx not needed</td>
<td>476</td>
<td>585</td>
<td>586</td>
</tr>
<tr>
<td>Other</td>
<td>870</td>
<td>1,223</td>
<td>1,026</td>
</tr>
</tbody>
</table>

Liver transplant waiting list status, new listings (2006)

- Removed from list
- Died
- Transplanted (LD)
- Transplanted (DD)
- Still waiting

United Network for Organ Sharing
Organ Procurement and Transplantation Network (2010)
The Transplant Problem - Organ Shortage

Transplant: A Gift for Life
PBS (2012)

http://www.pbs.org/programs/transplant-gift-life/
The Transplant Problem - Organ Shortage

The Opinion Pages
ROOM for DEBATE

How Much for a Kidney?

INTRODUCTION

According to the World Health Organization, 85,000 kidney transplants are performed worldwide each year. Nicole Bengiveno/The New York Times

The demand for transplantable organs far exceeds the supply. That has led to an increase in the illegal trafficking of kidneys, which represent the majority of living-donor transplants because a person can live with only one.

Should people in need of a kidney transplant be allowed to pay someone to donate one of theirs, or would that let the rich exploit the poor?

READ THE DISCUSSION »
What is Tissue Engineering?

- Charles Vacanti, 1997
- Biodegradable polymer scaffold molded from ear of 3-year-old child
- Seeded with cartilage-producing cells from a calf (chondrocytes).
- Implanted into immune-deficient mouse.
- Extensive cartilage formation at 12 wk

Y. Cao+, Plastic and Reconstructive Surgery, 1997
Tissue Engineering

- Cell expansion and manipulation
- Mechanical and molecular signaling
- Cell sourcing
- Full incorporation into host
- Implantation of construct
- Cell seeding and extracellular matrix expression

- Therapeutics: restore, maintain, improve
  - Implantable
  - Extracorporeal (outside the body)

- In Vitro Models: structure/function
  - Basic science
  - Drug development

Adapted from Van Blitterswijk, Elsevier
Tissue Replacement: Therapeutic Context

Whole Organ Transplantation

Engineered Tissues

Medical Devices

Engineered tissues = biomaterials + cells

Biomaterials that recruit cells (acellular)

Biomaterials that house cells (hybrid)

Biomaterial-free systems (w/ cell-derived ECM)

S. Bhatia
Integra

• Most successfully employed “artificial skin” currently
• Bovine collagen and shark chondroitin sulfate (GAG)
• Silicone surface layer to provide barrier function
• Host cells infiltrate and remodel matrix over 3 weeks
• Silicone is peeled off and replaced by ultra-thin split-thickness graft

Artificial Skin- Hybrid
Apligraf from Organogenesis
Artificial Skin- Hybrid
Apligraf from Organogenesis

- FDA approved for diabetic and venous ulcers
Artificial Skin- Hybrid
Apligraf from Organogenesis

- FDA approved for diabetic and venous ulcers
Designing an Engineered Tissue

• Design considerations
  – **What function are you replacing?**
  – Cell source
    • Somatic
    • Stem cells
  – Biomaterial
    • Natural/ECM vs. Synthetic scaffolds
  – Fabrication
    • Structure-Function relationships
Function of Tissue Replacements

- Fulfill a biomechanical role
- Replace physiological function
- Deliver secretory products
- A combination of the above

<table>
<thead>
<tr>
<th>Organ</th>
<th>Defect</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage/Bone</td>
<td>Mechanical</td>
<td>Resists compression</td>
</tr>
<tr>
<td>Liver</td>
<td>Metabolic</td>
<td>Nitrogen metabolism</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Synthetic</td>
<td>Insulin production</td>
</tr>
<tr>
<td>Nerve</td>
<td>Communication</td>
<td>Coordination</td>
</tr>
<tr>
<td>Skin</td>
<td>Combination</td>
<td>Prevents $H_2O$ loss, immunologic barrier, vitamin metabolism</td>
</tr>
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Primary Cell Culture

- Adult
- Embryo
- Egg

1. Dissection
2. Enzyme digestion
3. Finely chopped
4. Further dissection if necessary
5. Cell culture
6. Primary explants
7. Organ culture
Cell Senescence- Hayflick Limit
Embryonic and Adult Stem Cells

THE SUPPLY CHAIN
Embryonic and adult stem cells as a source of new tissue.

Egg → Zygote → Blastocyst → Gastrula → Embryonic stem cells → Self renewal → Differentiation signals → Endoderm, Mesoderm, Ectoderm

Sperm

Ectoderm, Mesoderm, Endoderm

Embryonic stem cells

Self renewal

Somatic stem cells

Differentiation signals

Cell types restricted to organ source

Any cell type?
Patient-Specific Pluripotent Stem Cells

Designing an Engineered Tissue

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      • Natural/ECM vs. Synthetic scaffolds
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Synthetic Biomaterial Scaffolds

PEG-DA polymer + photo-initiator + cells \rightarrow cellular hydrogel

- PLGA, PCL
- PEG
- ePTFE
- Glycans
- Titanium

S. Bhatia
Designing an Engineered Tissue

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Scaffold Architecture-3D Fabrication

- Stereolithography

**Figure 16.12** Building parts with light. Stereolithography is an example of a solid free-form fabrication technique. A layer of liquid polymer is turned into a solid by a pattern of light. The stage is then lowered so that the next layer of the structure can be solidified. Through repetition of this process, complex three-dimensional structures can be formed.

Hydroxyapatite structure formed using stereolithography

3D Fabrication

3D Printing

Artificial Trachea

University of Michigan
Scaffolds from Decellularized Organs: Heart

Ott et al, Nat Medicine, 2008
Scaffolds from Decellularized Organs: Heart

http://www.nature.com/news/tissue-engineering-how-to-build-a-heart-1.13327
Hierarchical Structure of Tissues

Cellular/Subcellular Scale
- 1-10μm
- Adhesion Receptor (e.g. integrin)
- Growth Factor Chemokine Hormone
- ECM
- Mechanical

Multicellular Scale
- 10-100μm
- Homotypic
- Heterotypic

Tissue Scale
- 100-1000μm
Course Overview

• Assignments and Dates
  – Homeworks/reading assignments
  – In-class quizzes/exercises
  – Midterm #1 Tues 10/10
  – Midterm #2 Thurs 11/16
  – Project group presentations
    12/5, 12/7, 12/12
  – Project group papers due 12/20

Online Syllabus
http://courses.engr.illinois.edu/bioe476/
Course Overview

• Grading
  – Homeworks/In-class exercises: 24%
  – In-class quizzes: 5%
  – Midterm #1: 24%
  – Midterm #2: 24%
  – Project presentation: 10%
  – Project paper: 13%

Grade Reporting- Gradebook
https://my.bioen.illinois.edu/gradebook
Course Overview

• Please do not disturb others during lecture
  – If you must use laptops in class, make sure they are for note taking only
• No cheating, copying, plagiarism, etc.
  – I take academic integrity very seriously
  – All group members will be held responsible for any plagiarism in the project work that is turned in
• Please let me know if you have any questions, concerns, problems, etc.