Tissue Engineering and Regenerative Medicine

NIH Center for Engineering Complex Tissues (CECT)
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Regenerative Medicine

- Process of creating living, functional tissues to repair or replace tissue or organ function
- Translational research for bench-to-bedside therapies
- Relatively long history
  - Transplants: Bone Marrow, Kidney in the 1950s.
  - Autografts, Allografts, Xenografts

Addressing a biomedical need

- Large tissue defects
- Scar tissue formation
- Limited innate healing capacity
- Other pathologies that limit desired regeneration
Tissue Engineering

- **1988**
  - “Tissue Engineering” is the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue function. – Skalak R, Fox CF, eds., Tissue Engineering, 1988

- **1993**
  - Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function. – Langer R, Vavanti JP, "Tissue Engineering", Science 1993 May 14;260:920-6.

Tissue Engineering

- Transplantation of chondrocytes into a biodegradable, ear-shaped mold, followed by implantation under the skin of a mouse (subcutaneous)

[Image of Chondrocyte transplantation]
Tissue Engineering

- Regeneration
  - Replacement of lost tissue with the tissue itself
  - Initiate regeneration where it is not normally observed
  - Cartilage defects
  - Large (critical size) bone defects

- Repair
  - Replacement of lost tissue with a functional substitute
  - Enhance the rate of repair where it is seen
  - Nearly any tissue defect

- Replacement
  - Replacement of a missing cell population
  - Red blood cells in a blood transfusion
  - Bone marrow cells in marrow replacement

Tissue Engineering Challenge

- Capturing native heterogeneity and complexity

- Importance of the Biomaterial
  - Biocompatible, Biodegradable
  - Natural vs. Synthetic
  - Chemical, Biomechanical, Structural similarity

- Engineering large constructs
  - Critical size defects
  - Vascularization

- Biomanufacturing limitations

Tissue Engineering ‘Triad’
Cells

- Cell types
  - Adult cells
  - Embryonic stem cells
  - Induced pluripotent stem cells
  - Embryonic stem cells
- Primary cells
  - Adult cells
  - Embryonic cells
  - Stem cells
  - Undifferentiated
  - Self-renewal
  - Source may be a challenge

Extracellular Matrix (ECM)

- Composed of various proteins (collagen, fibronectin, laminin etc.) and proteoglycans
- Scaffold material that provides support for cell growth and function
  - Growth, differentiation, bioactivity
- Deliver appropriate biomolecular and biomechanical cues
**Scaffold Properties**

- Bulk properties that correlate to the native tissue
  - Mechanical
  - Architectural
  - Chemistry

- Microstructural properties that dictate cell response
  - Pore size
  - Cell infiltration and surface mechanics
  - Porosity
  - Dictates mechanical properties, transport phenomenon
  - Fiber orientation
  - Dictates cell migration and growth

**Hydrogels**

- Polymeric chain network dispersed in an aqueous medium
  - Retains a high fraction of water compared to the polymer

- Individual polymer chains can be cross-linked to assemble and form a network
  - Thermal
  - pH
  - Chemical
  - Photo-sensitive

**Scaffold examples**

<table>
<thead>
<tr>
<th>Natural</th>
<th>Synthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen</td>
<td>Polyethylene glycol (PEG) and derivatives</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Polycaprolactone (PCL)</td>
</tr>
<tr>
<td>Alginate</td>
<td>Polylactic acid and derivatives</td>
</tr>
<tr>
<td>Fibrin</td>
<td>Poly (propylene fumarate)</td>
</tr>
<tr>
<td>Hyaluronic Acid</td>
<td>Polycrylamide</td>
</tr>
<tr>
<td>Decellularized ECM</td>
<td></td>
</tr>
</tbody>
</table>
Biomolecules

- Communication and molecular signaling conduit
- Cytokines
- Growth Factors and Receptors
- Cell adhesion molecules

Biomolecules: Function-specific

<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Tissue treated</th>
<th>Representative function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang-1</td>
<td>blood vessel, heart, muscle</td>
<td>blood vessel maturation and stability</td>
</tr>
<tr>
<td>Ang-2</td>
<td>blood vessel</td>
<td>destabilize, regress and disassociate endothelial cells from surrounding tissue</td>
</tr>
<tr>
<td>FGF-2</td>
<td>blood vessel, bone, cartilage, skin, nerve, muscle</td>
<td>migration, proliferation and survival of endothelial cells, inhibition of differentiation of erectile tissue cells</td>
</tr>
<tr>
<td>BMP-2</td>
<td>bone, cartilage, skin, nerve, muscle</td>
<td>differentiation and migration of osteoblasts, renal development</td>
</tr>
<tr>
<td>BMP-7</td>
<td>bone, cartilage, skin, nerve, muscle</td>
<td>differentiation and migration of osteoblasts, renal development</td>
</tr>
<tr>
<td>EGF</td>
<td>skin, nerve</td>
<td>regulation of epithelial cell growth, proliferation and differentiation</td>
</tr>
<tr>
<td>IGF-1</td>
<td>muscle, bone, cartilage, liver, lung, kidney, nerve, skin</td>
<td>cell proliferation and inhibition of cell apoptosis</td>
</tr>
<tr>
<td>NGF</td>
<td>nerve, spinal nerve, brain</td>
<td>survival and proliferation of neural cells</td>
</tr>
<tr>
<td>PDGF-AB (or BB)</td>
<td>blood vessel, muscle, bone, cartilage, skin</td>
<td>embryonic development, proliferation, migration, growth of endothelial cells</td>
</tr>
<tr>
<td>TGF-α</td>
<td>brain, skin</td>
<td>proliferation of basal cells or neural cells</td>
</tr>
<tr>
<td>TGF-β</td>
<td>bone, cartilage</td>
<td>proliferation and differentiation of bone-forming cells, anti-proliferative factor for epithelial cells</td>
</tr>
<tr>
<td>VEGF</td>
<td>blood vessel</td>
<td>migration, proliferation and survival of endothelial cells</td>
</tr>
</tbody>
</table>

Adapted from Biofabrication Workshop, Rice University

Other factors

- Time
  - Matrix degradation, remodeling

- Physicochemical
  - Shear forces, mechanical stresses, cyclic tension

- Topography
  - Curvature, roughness
Applications of TERM

• Promising in vitro platform to interrogate in vivo biology
  • Wealth of research exploiting TE capabilities

• Several clinical applications to date

Applications of TERM

• Dermal regeneration

<table>
<thead>
<tr>
<th>Brand</th>
<th>Scaffold material</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermagraft® (Advanced Biomedics)</td>
<td>PGA, PLA, Silicon</td>
<td>Fibroblasts</td>
</tr>
<tr>
<td>Apligraf® (Organogenesis)</td>
<td>Collagen</td>
<td>Keratinocytes, Fibroblasts</td>
</tr>
<tr>
<td>Dermgraft® (Cutter Inc.)</td>
<td>Collagen sponge</td>
<td>Keratinocytes, Fibroblasts</td>
</tr>
<tr>
<td>Leukoplast® Hydalograft® (Vitrella, Beapharm)</td>
<td>Hyaluronic acid</td>
<td>Keratinocytes, Fibroblasts</td>
</tr>
</tbody>
</table>

Applications of TERM

• Various bone/cartilage products
  • Efforts to combine the right cellular, molecular and structural cues

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<tr>
<th>Brand</th>
<th>Scaffold material</th>
<th>Application</th>
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<tbody>
<tr>
<td>Collagraft® (Nuance Inc.)</td>
<td>Collagen, HA, TCP</td>
<td>Subchondral support</td>
</tr>
<tr>
<td>ChondroMimetic® (Tigersen Inc.)</td>
<td>Cartilage, calcium phosphate</td>
<td>Osteochondral</td>
</tr>
<tr>
<td>Gel-De® (Zimmer-Biomet)</td>
<td>Hyaluronic acid</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>TruGraft® (Osteobiologics)</td>
<td>PGA granulate</td>
<td>Bone void filler</td>
</tr>
</tbody>
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Brand Apligraf: bone graft cement (hydroxyapatite and collagen)
Applications of TERM

- Pioneering work by WIRM on Bladder tissue engineering (2006)
  - Cells seeded on a biodegradable bladder-shaped scaffold made of collagen/PGA composite

- Tissue Engineered Tracheal replacement (2012)
  - Donor tracheal scaffold with multiple cell/biomolecule stimulations

- Ongoing work with various other organs: cornea, blood vessels, liver etc.

- In a lot of cases, despite initial success, there was no long-term improvement

Takeaways

- Important components of Tissue Engineering
  - Cells, Biomolecules, Scaffolds

- Several parameters that are known to influence final outcome

- Right balance between perfectly mimicked *in vivo* system vs. key elements that answer important questions