Tissue Engineering and Regenerative Medicine

NIH Center for Engineering Complex Tissues (CECT)
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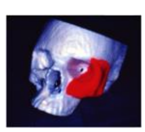
Bhushan Mahadik, Ph.D.
Assistant Director, CECT
University of Maryland

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*

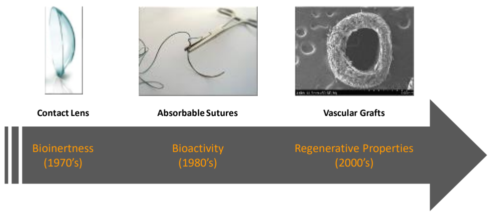
Addressing a biomedical need

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



(Photo: Ann Surg Treat Res. 2014 Nov; 87(5):253-259)

Biomaterials in Medicine



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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, Vacanti JP, "Tissue Engineering", *Science* 1993 May 14;260:920-6.**

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Tissue Engineering

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

C. A. Vacanti et al., 1997

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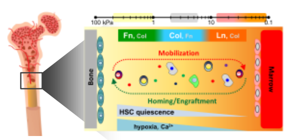
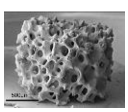
Tissue Engineering

- **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

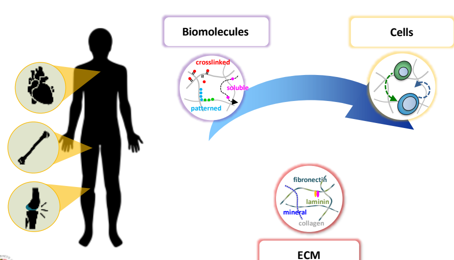
- Capturing native heterogeneity and complexity
- Importance of the Biomaterial
  - Biocompatible, Biodegradable
  - Natural vs. Synthetic
  - Chemical, Biomechanical, Structural similarity
- Engineering large constructs
  - Critical size defects
  - Vascularization
- Biomanufacturing limitations



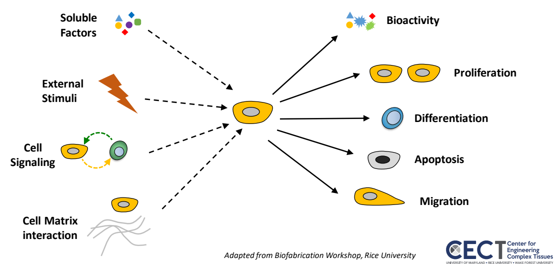


Hui et al., Composites Part B: Engineering 2017

Tissue Engineering 'Triad'



Cells



Adapted from Biofabrication Workshop, Rice University

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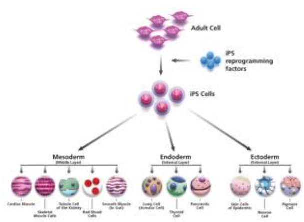
Cells

- Cell types
  - Mature cells
  - Adult stem cells or somatic stem cells
  - Induced pluripotent stem cells
  - Embryonic stem cells
  - Totipotent stem cells
- Primary cells
  - Potential harvest challenges
  - Cells may be differentiated from patients
  - Age-related challenges
- Passaged cells
  - Serially expanded primary cells
  - May lose function or de-differentiate over passages
- Stem cells
  - Undifferentiated
  - Self-renewal
  - Source may be a challenge



Adapted from Biofabrication Workshop, Rice University

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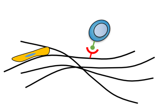
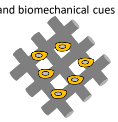
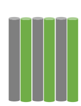
Extracellular Matrix (ECM)

- 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







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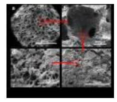
Scaffold Properties

- 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



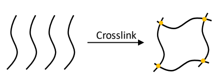
Above: porous hydroxyapatite/starch scaffold
Below: Human adult bone sample

Xu, et al. *World Biomaterials Congress*. 2016 and Paul Hansma Research Group, 2018

Adapted from Biofabrication Workshop, Rice University

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

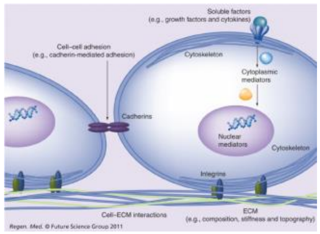


Scaffold examples

Natural	Synthetic
Collagen	Polyethylene glycol (PEG) and derivatives
Gelatin	Polycaprolactone (PCL)
Alginate	Polylactic acid and derivatives
Fibrin	Poly (propylene fumarate)
Hyaluronic Acid	Polyacrylamide
Decellularized ECM	

Biomolecules

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



Li et al., Regen Med. 2011 Mar;6(2):229-40

Biomolecules: Function-specific

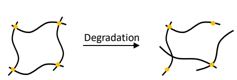
Abbreviation	Tissues treated	Representative function
Ang-1	blood vessel, heart, muscle	blood vessel maturation and stability
Ang-2	blood vessel	destabilize, regress and disassociate endothelial cells from surrounding tissues
FGF-2	blood vessel, bone, skin, nerve, spine, muscle	migration, proliferation and survival of endothelial cells, inhibition of differentiation of embryonic stem cells
BMP-2	bone, cartilage	differentiation and migration of osteoblasts
BMP-7	bone, cartilage, kidney	differentiation and migration of osteoblasts, renal development
EGF	skin, nerve	regulation of epithelial cell growth, proliferation and differentiation
EPO	nerve, spine, wound healing	promoting the survival of red blood cells and development of precursors to red blood cells.
HGF	bone, liver, muscle	proliferation, migration, differentiation of mesenchymal stem cells
IGF-1	muscle, bone, cartilage, bone liver, lung, kidney, nerve, skin	cell proliferation and inhibition of cell apoptosis
NGF	nerve, spine, brain	survival and proliferation of neural cells
PDGF-AB (or -BB)	blood vessel, muscle, bone, cartilage, skin	embryonic development, proliferation, migration, growth of endothelial cells
TGF-α	brain, skin	proliferation of basal cells or neural cells
TGF-β	bone, cartilage	proliferation and differentiation of bone-forming cells, anti-proliferative factor for epithelial cells
VEGF	blood vessel	migration, proliferation and survival of endothelial cells.

Adapted from Biofabrication Workshop, Rice University

Lee, et al. *J R Soc Interface*. 2011

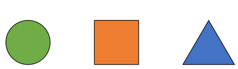
Other factors

- **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

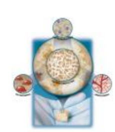
Integra ® Skin grafts

Brand	Scaffold material	Cells
Dermgraft® (Advanced Biohealing)	PGA, PLA, Silicon	Fibroblasts
Apligraf® (Organogenesis)	Collagen	Keratinocytes, Fibroblasts
Orcel® (Ortec Inc.)	Collagen sponge	Keratinocytes, Fibroblasts
Laserkin®, Hyalograft® (Fidia Adv. Bioploymers)	Hyaluronic acid	Keratinocytes, Fibroblasts

Applications of TERM

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

Brand	Scaffold material	Application
Collagraft ® (Nuecoll Inc.)	Collagen, HA, B-TCP	Subchondral support
ChondroMimetic™ (TiGenix NV)	Collagen, calcium phosphate	Osteochondral
Gel-One® (Zimmer Biomet)	Hyaluronic acid	Osteoarthritis
TruGraft™ (Osteobiologics)	PLGA granulate	Bone void filler



Osiris Therapeutics Bio4® bone matrix

Bond Apatite: bone graft cement (biphasic calcium sulfate and HA)

Applications of TERM

- Pioneering work by WFIRM on Bladder tissue engineering (2006)
  - Cells seeded on a biodegradable bladder-shaped scaffold made of collagen/PGA composite
- Tissue Engineered Tracheal replacement (2012)
  - Donor trachaeal scaffold with multiple cell/biomolecule stimulations
- On-going work with various other organs: cornea, blood vessels, liver etc.
- In a lot of cases, despite initial success, there was no long-term improvement

Atala et al., Lancet., 367 (9518) (2006), pp. 1241-1246

Elliott et al., Lancet, 380 (9846) (2012), pp 994-1000

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