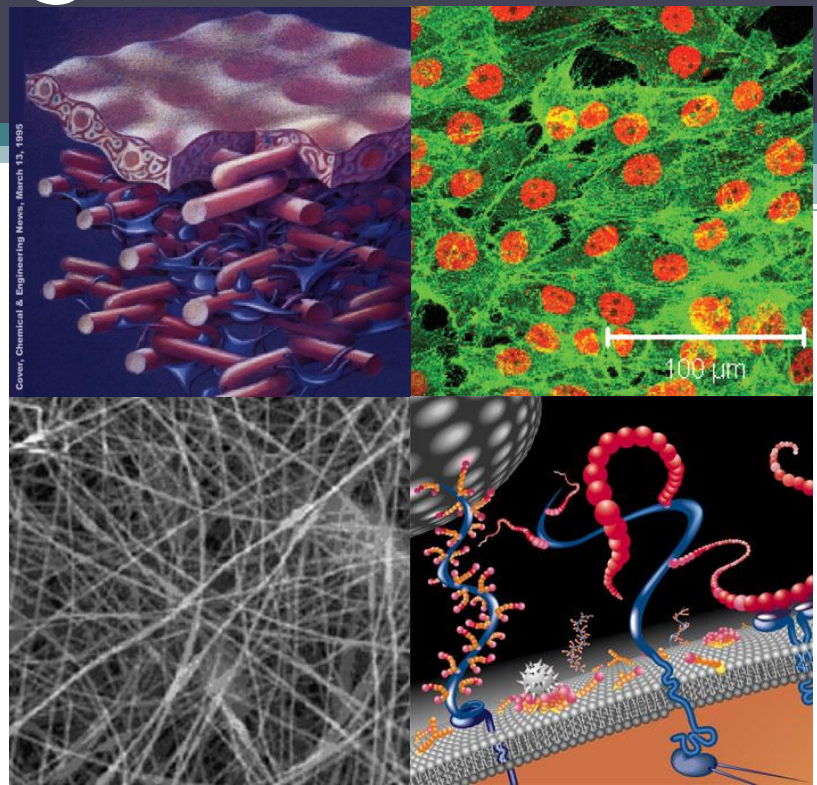
ECM dynamics in regenerative medicine



Cell and Tissue Engineering
2011/2012

- Jorge Santos, nº63428
- Lisa Deckert, nº 72255

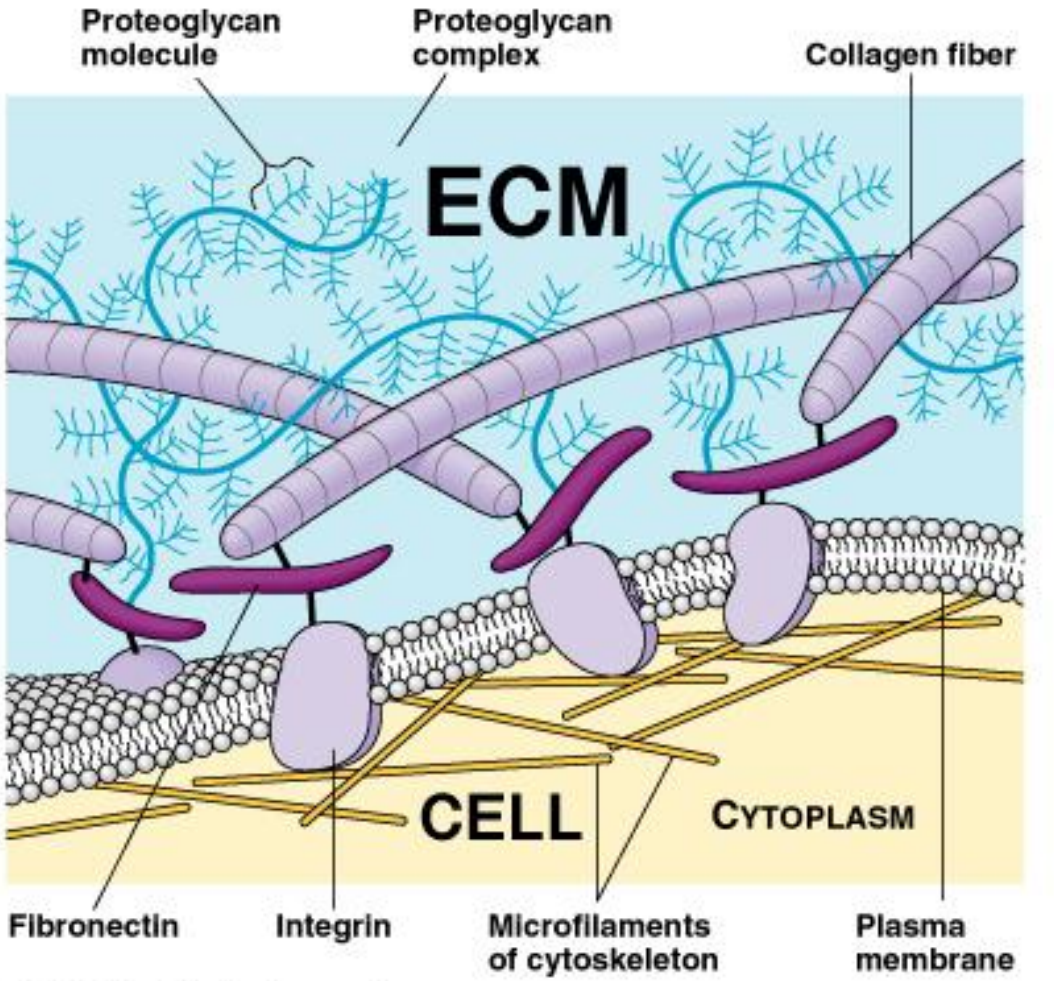
EXTRACELLULAR MATRIX

- Function:
  - Spatial patterning
  - Rigidity
  - Chemical signaling
  - Depot of growth factors
    - Change in conditions triggers protease that release the depots

EXTRACELLULAR MATRIX COMPOSITION

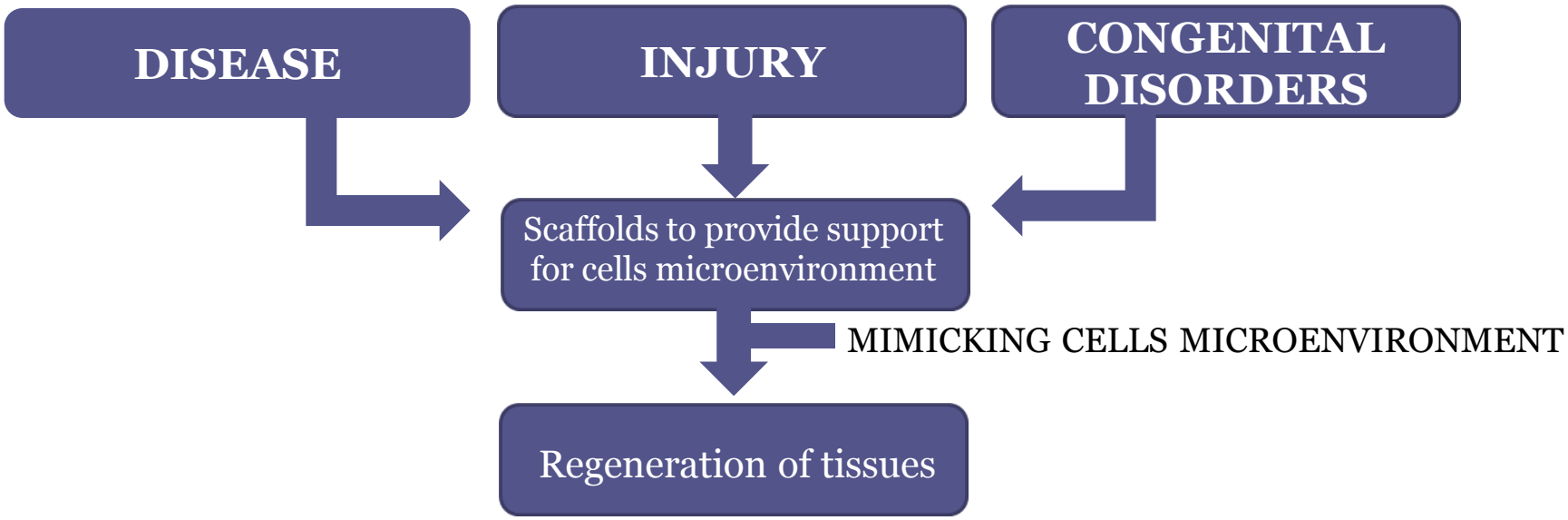
- Fibrous structural proteins (Collagen and Elastin)
- Proteoglycans (ex: Aggrecan)
  - Bind cations, water, growth factors, …
  - Have negative charge
- Glycosaminoglycans (ex: Hyaluronic acid)
  - Absorb water and swell, resist compression
  - Environmental cue that regulates cell behavior
- Specialized proteins
  - Fibronectin
    - Binds integrins and promotes cell movement and signaling
  - Laminin
    - resist tensile forces and assist in cell adhesion

EXTRACELLULAR MATRIX COMPOSITION



Regenerative Medicine

Regenerative medicine is the process of replacing or regenerating human cells, tissues or organs to restore or establish normal function



Regenerative Medicine

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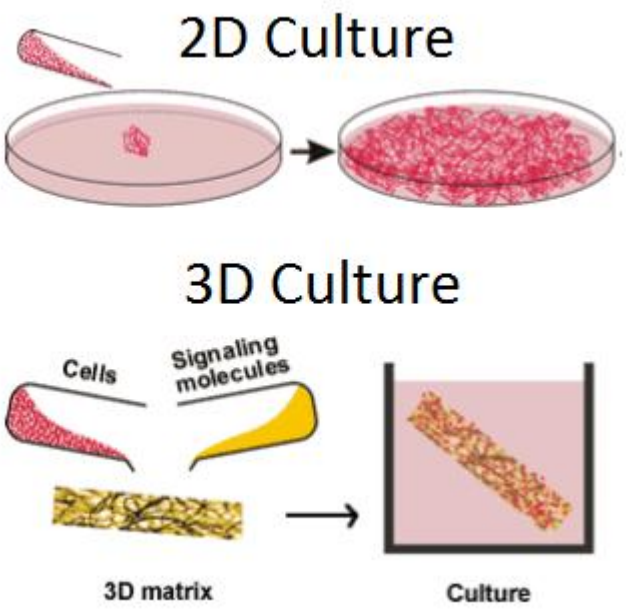

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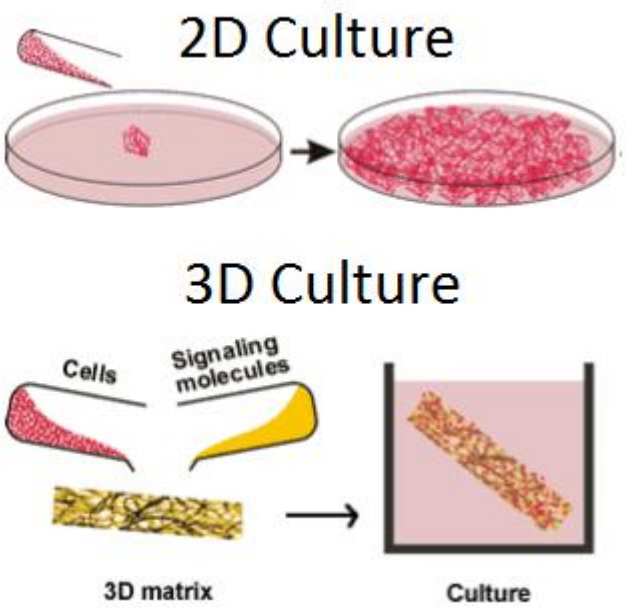

Differentiation of cells is influenced by chemical, physical and structural properties of in vivo environment provided by ECM

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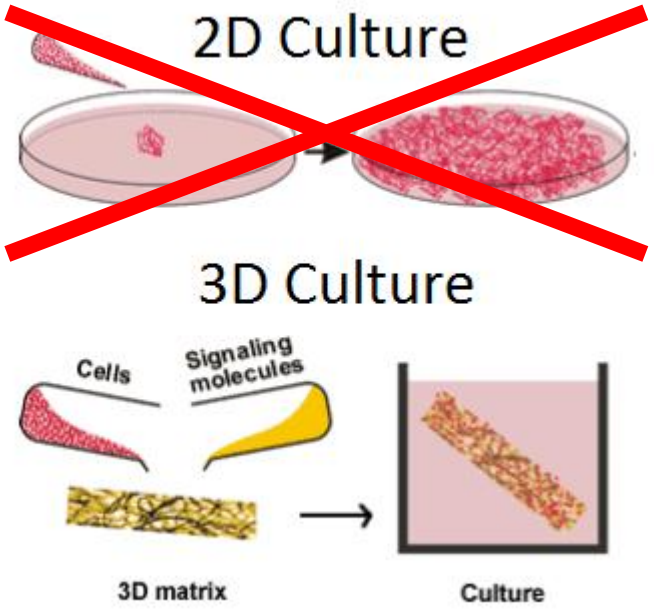

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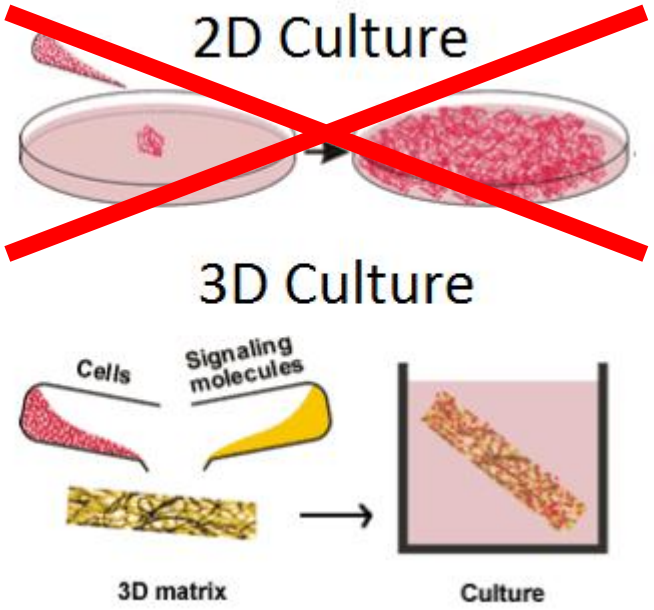

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3D SCAFFOLD HAS TO MIMICK THE ECM

ECM Mimicking

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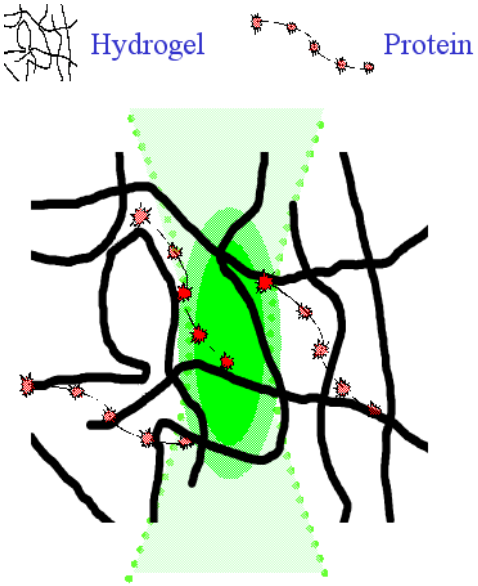

ECM Mimicking

- To create a 3D scaffold we can use:
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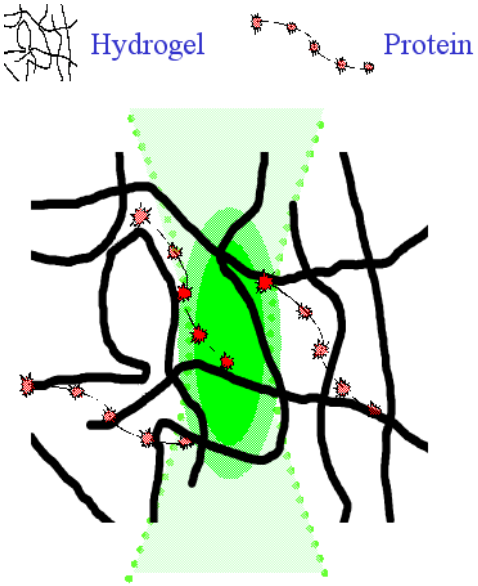

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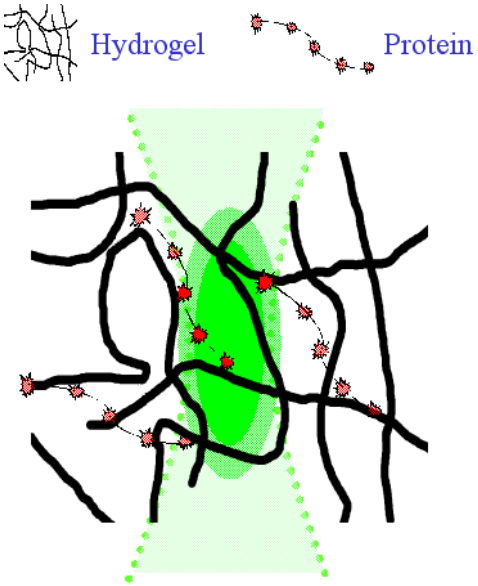

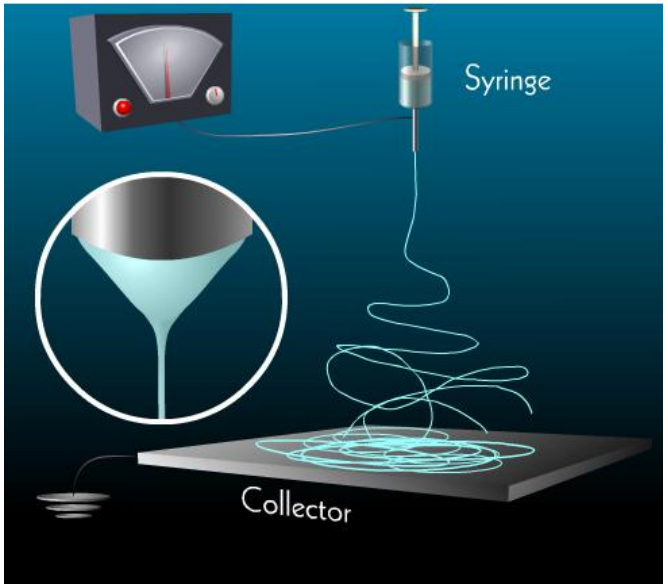

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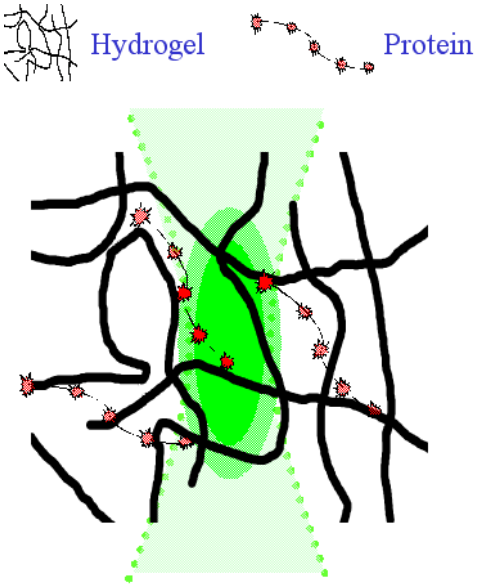
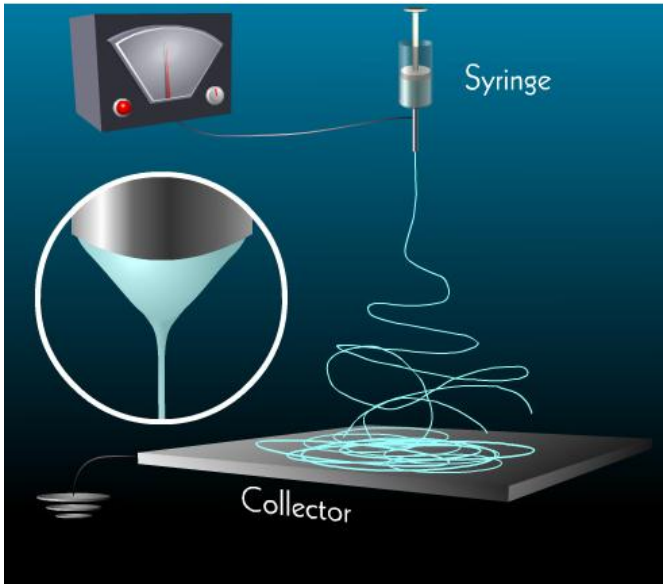
Materials used to create the structure must have similar properties to natural ECM components





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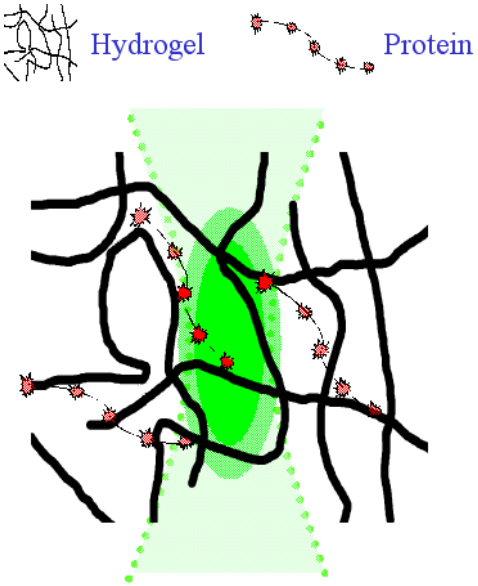

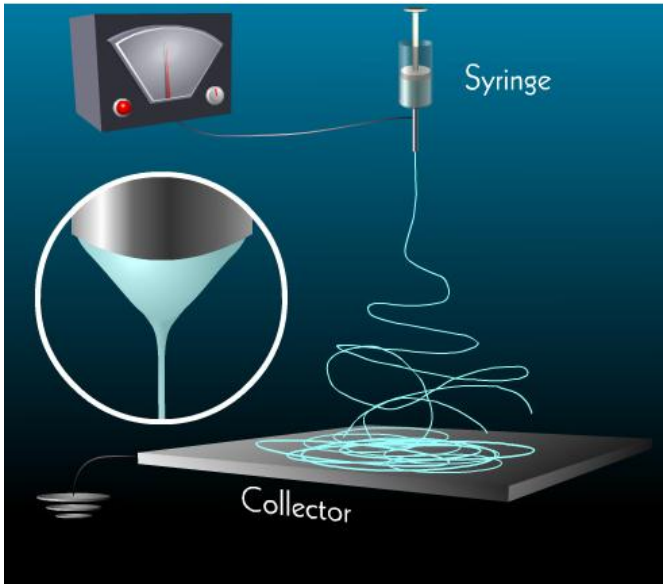

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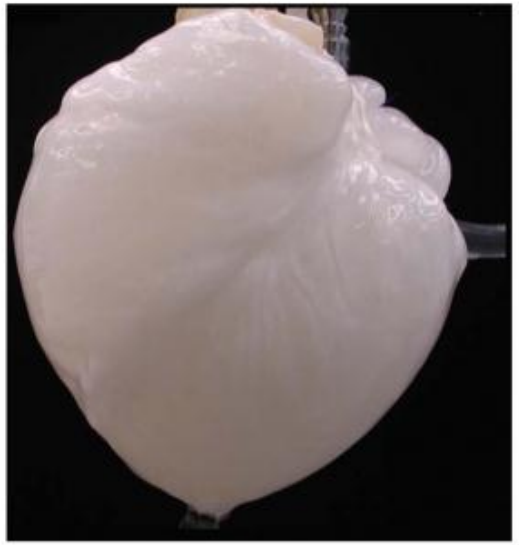
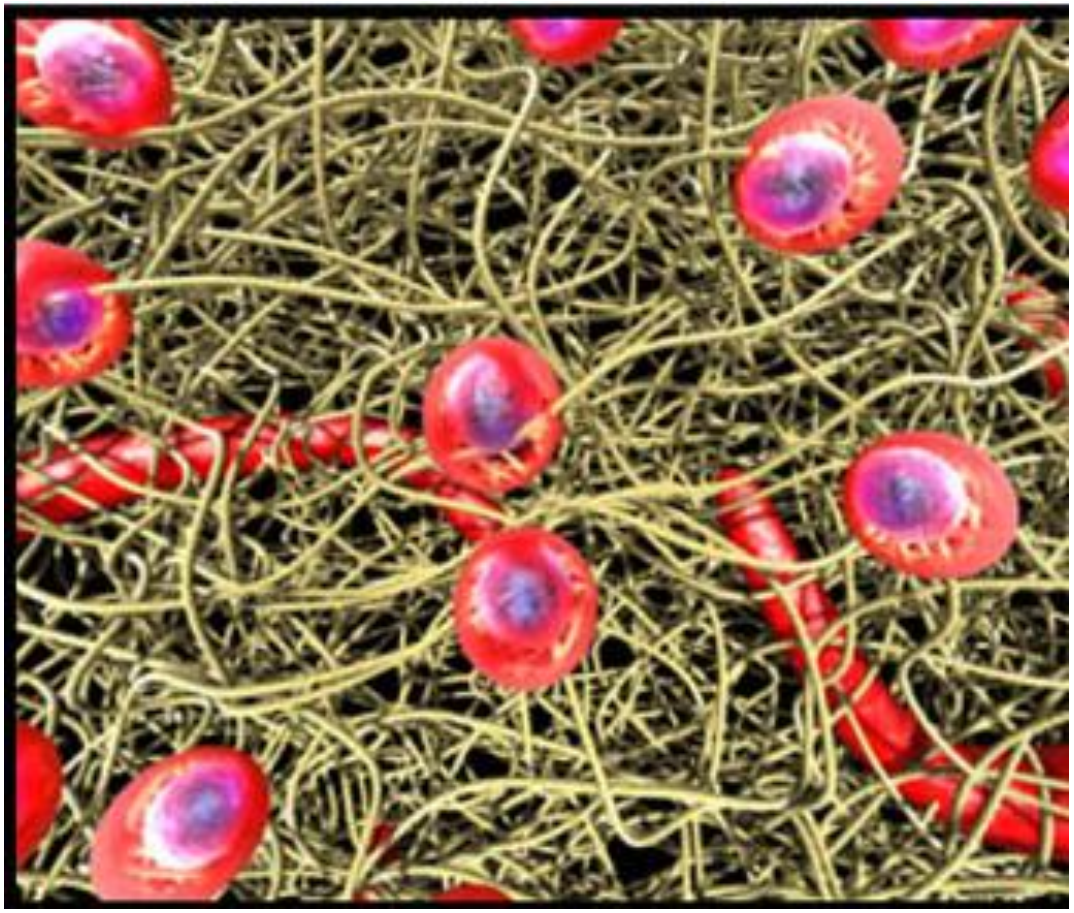
Day 0

8 Hours



Day 2

Recellularization of ECM



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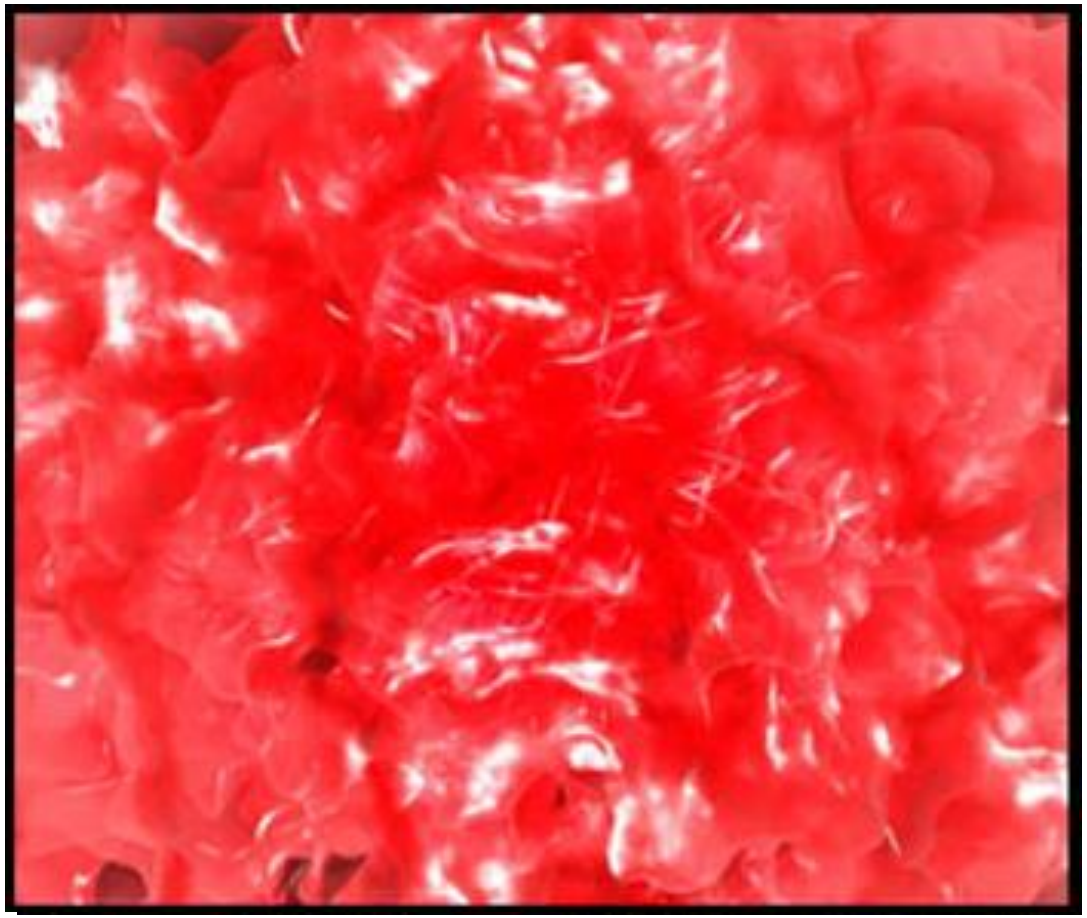

ECM Mimicking

- Decellularization of natural tissues produces results faster and better than synthetic scaffolds
  - For now we can't make a perfect copy of the biological scaffolds

- EXAMPLE:
  - PGA scaffold vs ECM scaffold (reference 8):

    - White cartilage-like tissue after 1 week of culture in ECM scaffold and 4 weeks in PGA scaffold

    - ECM molecules, growth factors, cytokines, etc fill uniformly ECM scaffold, but remain only in periphery in PGA scaffold

ECM Mimicking

- Beside similar physical and structural properties in the scaffold, we need similar chemical properties:
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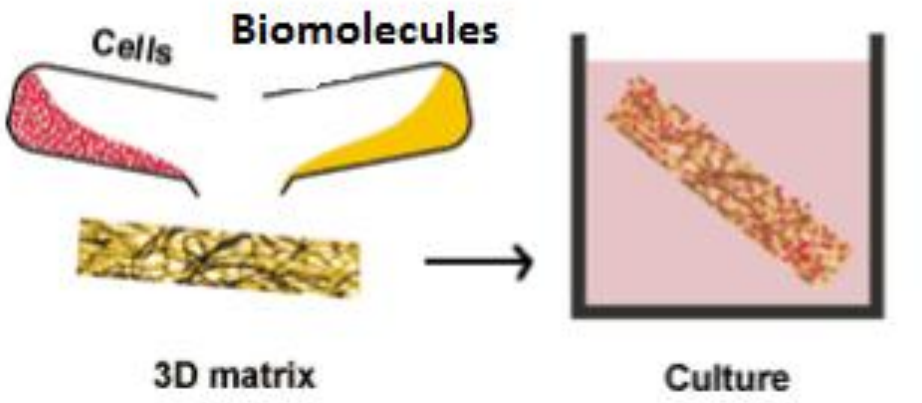

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    - Create a scaffold utilizing a cross-linked combination or a mixture of ECM macromolecules

ECM Mimicking

- Mimicking in vivo microenvironment allow us to control cell differentiation and morphogenesis:
  - Biomolecule in the scaffold can direct the cellular processes:
    - Differentiation
    - Growth
    - Adhesion
    - Etc.
    - Depends on release ratio and spatial distribution

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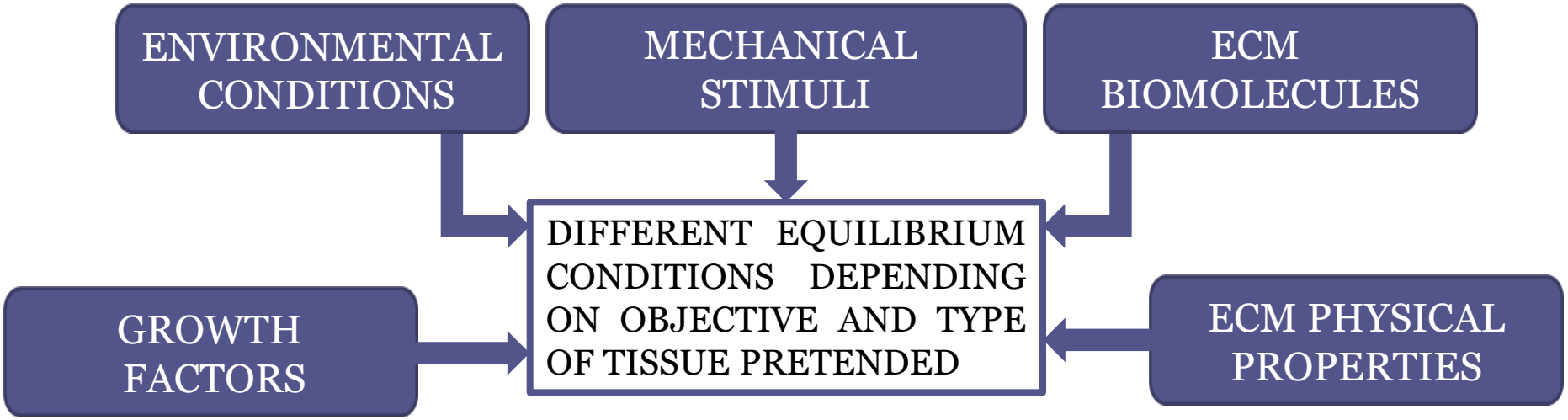

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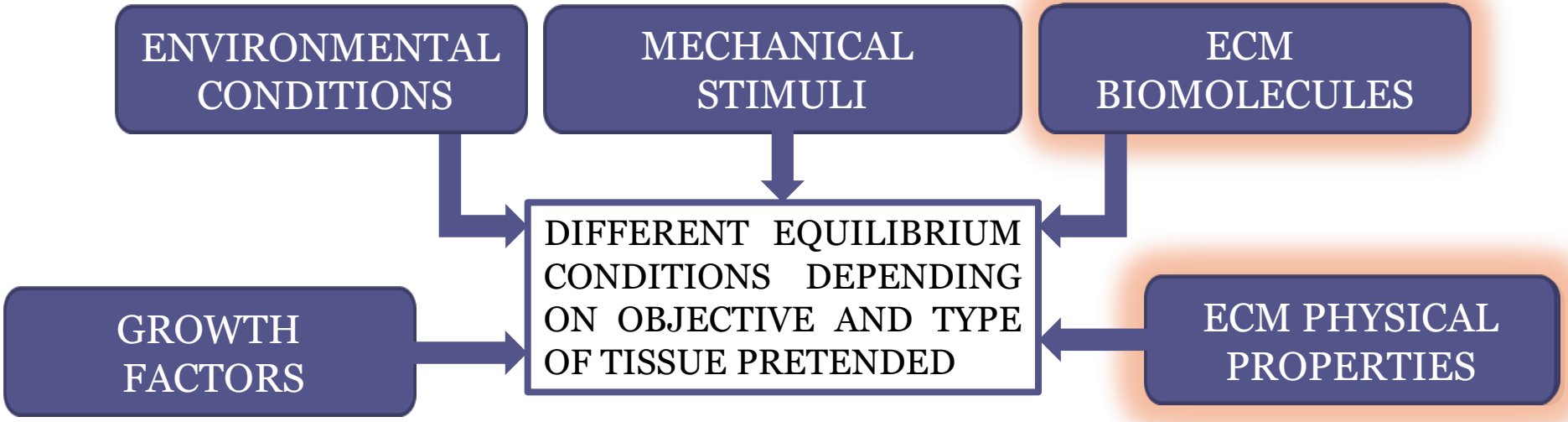
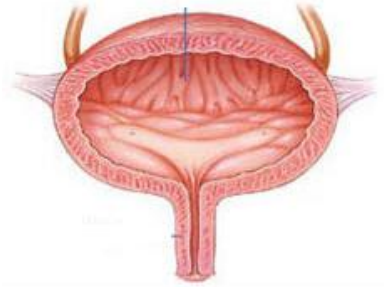
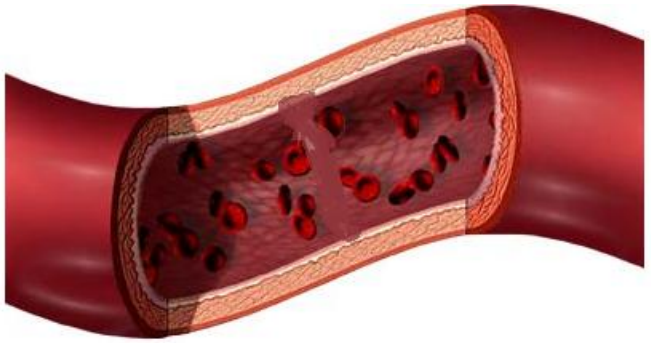
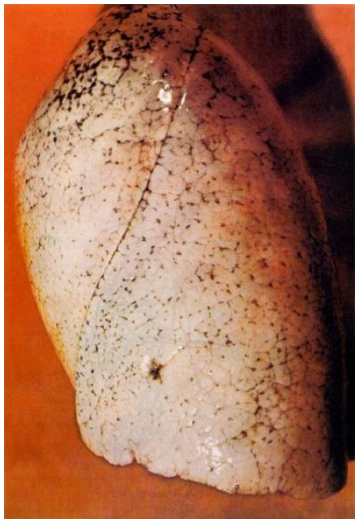


THERAPY APPLICATIONS

- Bladder
- Blood vessels
- Bone
- Lungs
- Skin
- Cartilage







EXAMPLES

- HSC
  - Travelling through bloodstream
  - Lodge in bone marrow or other niches

Depend on interactions between the cells and the ECM proteins of the various microenvironments

  - Adhesion to osteoblasts maintain HSC quiescent
    - Osteopontin interacts with integrins to form receptors to proteins that suppress HSC expansion
  - MMP9 enzyme triggers the breakdown of ECM, which releases the cells in the bloodstream

EXAMPLES

- MSC
  - Laminin-332 in ECM triggers osteogenic differentiation of human MSC through interaction with cell integrins
- ESC
  - Less ESC attached to ECM -> More aggregation, better differentiation in cardiomyocetes
    - Less cell attachment force in ECM leads cells to aggregate
      - Aggregation is better for differentiation
    - Physical factors are more important than chemical factors
- Pore sizes in engineered trabecular bone depend on the initial scaffold geometry and pore radius

Conclusion

- ECM acts as structural guidance for cell growth and tissue morphogenesis
- ECM Enhance cell attachment and metabolism

→ understand how this is done to produce biomimetic scaffolds

- Composition, stiffness and geometry of substrate, cell attachment strength, matrix compliance and chemical environment influence stem cell fate
- Nanotechnology has made possible to produce biomimetic synthetic nanofibers, the diameters of which are within the sub-micrometer range
- ECM remodeling involved in the release of stem cells from their niche, migration and differentiation
  - Signals regulating these events are only beginning to be understood

FUTURE PROSPECTS

- Understand:
  - The role of spatial patterning, rigidity and other physical properties of ECM
  - Cell-ECM interactions
    - Improvement in methods for imaging individual cells within 3D aggregates
  - Regulation signals of ECM

- Ensure biomolecules diffusion within synthetic scaffolds without harming its mechanical properties

- Discover new biomaterials that mimic the ECM physical properties

- Discover ways to store and release growth factors and other biomolecules in the scaffold
  - Like ECM does

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