Massachusetts Institute of Technology
Harvard Medical School
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BIOMATERIALS-TISSUE INTERACTIONS:

"Tools" for Understanding the Molecular, Cellular, and Physiological, Bases of the Tissue Response to Implants

M. Spector, Ph.D. and I.V. Yannas, Ph.D.

BIOMATERIALS-TISSUE INTERACTIONS

Tissue* + Biomaterial**

Cell + Matrix**

* Structure comprising cells of the same type
** Solid surface

CELL-MATRIX INTERACTIONS

In Tissue

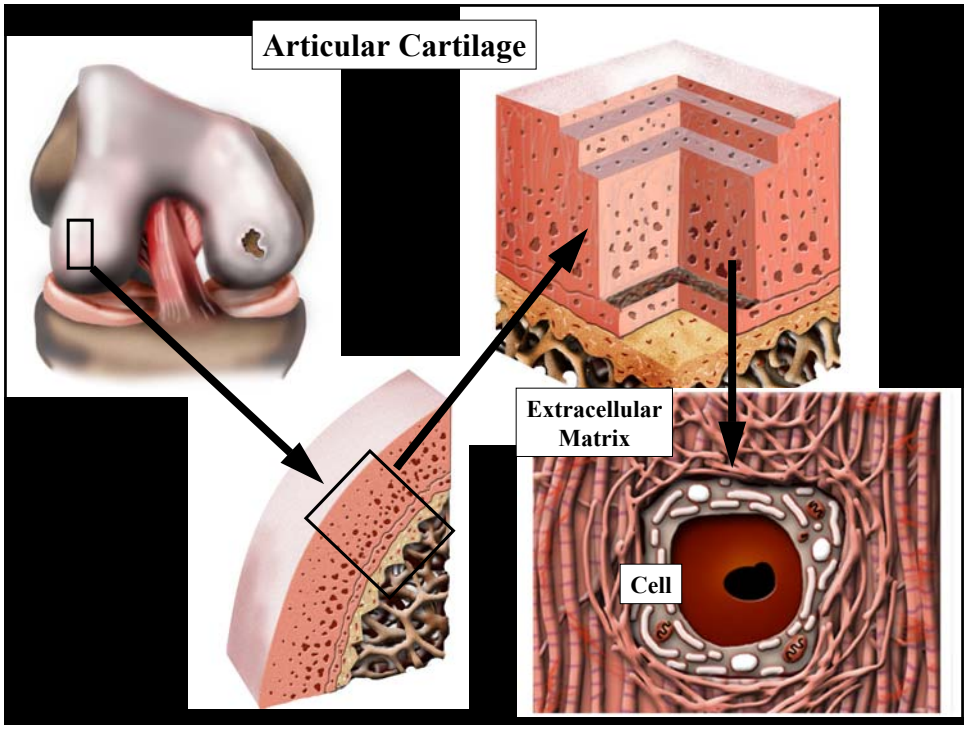
Cell + Extracellular Matrix

In Tissue Engineering Scaffolds

Cell + Biomaterial Scaffold

CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

- **Control Volume**
- **Unit Cell Processes**
- **Types of Tissues**
- **Tissue Formation and Remodeling *In Vitro***
- **Wound Healing *In Vivo***



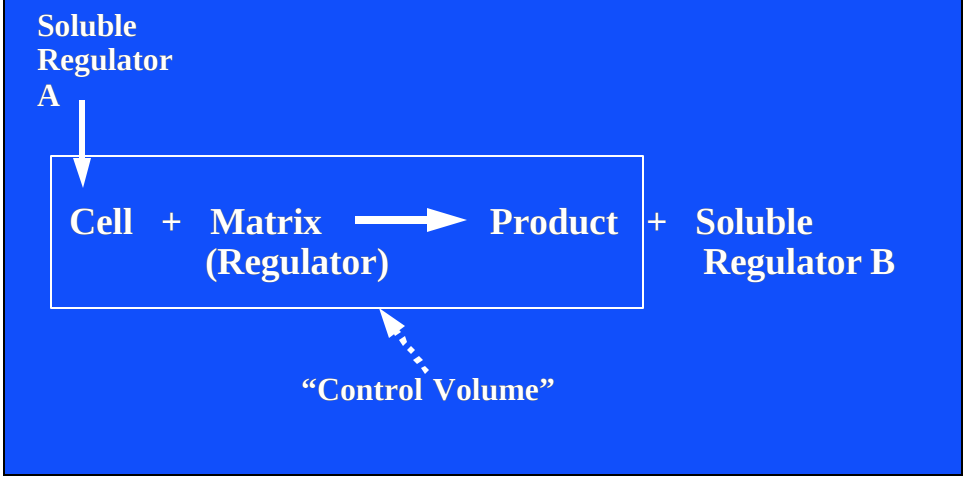
Chondrocytes (P2 Canine) in a Type I Collagen-GAG Scaffold

Image removed due to copyright considerations.

"Control Volume"

Source: B. Kinner

UNIT CELL PROCESSES
Concept of a "Control Volume" around a Cell



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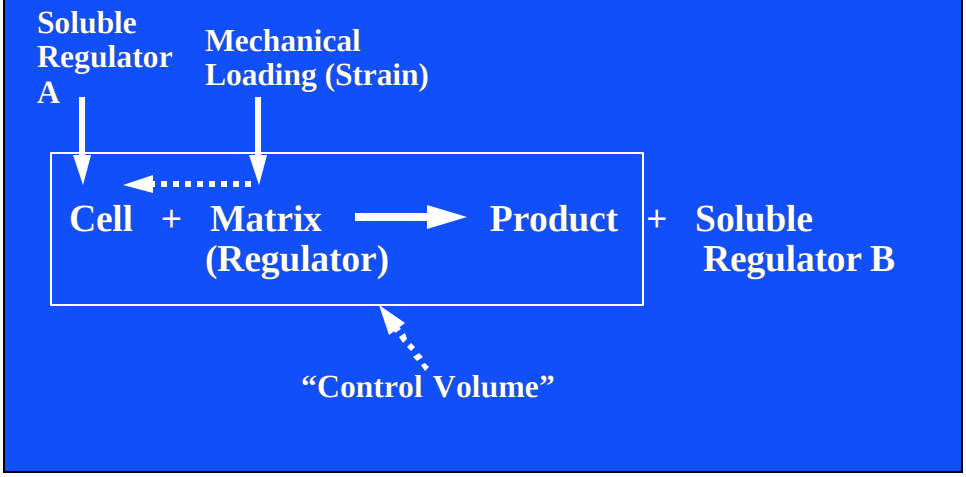


CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

- Control Volume
- Unit Cell Processes
- Types of Tissues
- Tissue Formation and Remodeling *In Vitro*
- Wound Healing *In Vivo*

UNIT CELL PROCESSES

- Mitosis
- Migration
- Synthesis
- Contraction
- Endocytosis
- Exocytosis

COLLAGEN-GAG MATRICES: MODEL BIOMATERIALS (ANALOGS OF EXTRACELLULAR MATRIX)

Investigation of cell interactions (UCPs) *in vitro*

- **Type I (bovine and porcine)**
- **Type II (porcine)**
- **Chondroitin 6-sulfate**

Image removed due to copyright considerations.

Image removed due to copyright considerations.

1mm

- **Freeze-dried**
- **Dehydrothermally cross-linked**
- **Additional cross-linking**

500㎛

IV Yannas, *et al*. PNAS, 1989

CELL –MATRIX INTERACTIONS WITH COLLAGEN-GAG MATRICES *IN VITRO*

- **Can provide insights into interrelationships among cell processes.**
  - **How do mitosis and synthesis interrelate?**
  - **How do mitosis and synthesis relate to contraction?**
  - **How does migration relate to contraction?**
- **Can provide insights into cell behavior *in vivo.***
- **Can provide insights into scaffold composition and structure for improved performance in regenerative medicine.**

Chondrocytes (Passage 2 Canine) in a Type I Collagen-GAG Matrix

Live cell imaging for a period of 5 hours.

Image removed due to copyright considerations.

J. Cheng

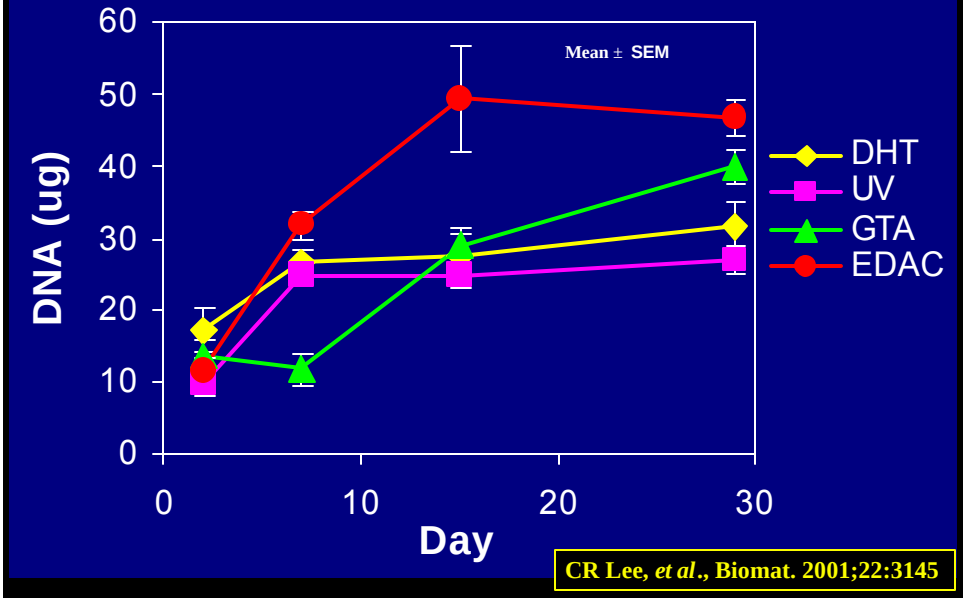
CELL –MATRIX INTERACTIONS

- **Mitosis**
- **Migration**
- **Synthesis**
- **Contraction**

Chondrocyte (P2 Canine) in a Type I Collagen-GAG Matrix: Mitosis

J. Cheng

Effects of Cross-Linking on Chondrocyte Proliferation in Collagen-GAG Matrices



CR Lee, *et al*., Biomat. 2001;22:3145

CELL –MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction

40min

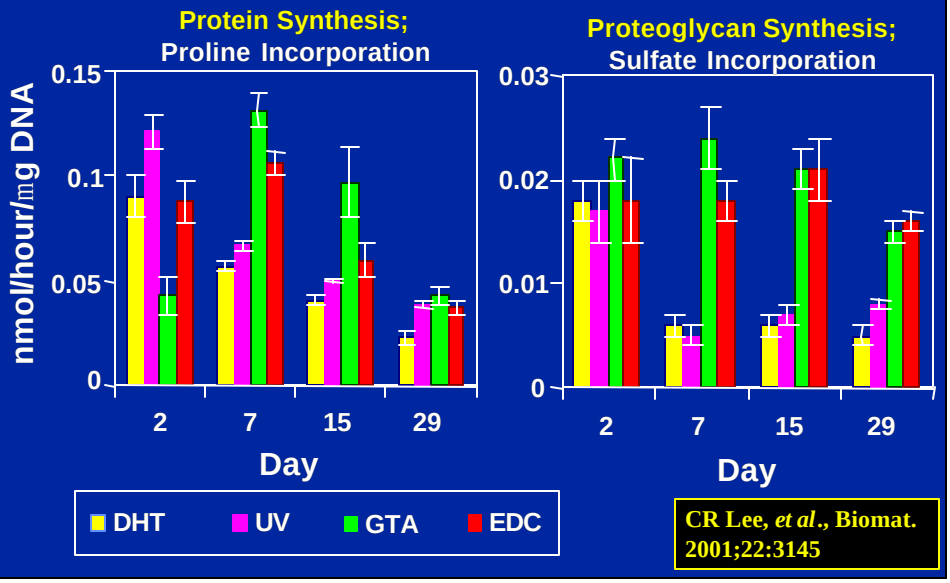
Chondrocytes (P2 Canine) in a Type I Collagen-GAG Matrix: Migration and Contraction

B. Kinner

CELL –MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction

Effects of Cross-Linking on Chondrocyte Biosynthesis in Collagen-GAG Matrices



CR Lee, *et al*., Biomat. 2001;22:3145

CELL –MATRIX INTERACTIONS

- Mitosis
- Migration
- Synthesis
- Contraction

Chondrocytes (P2 Canine) in a Type I Collagen-GAG Matrix: Contraction

Image removed due to copyright considerations.

40 min

B Kinner

Non-Seeded: 8 days

Cell-Seeded: 8 days

Image removed due to copyright considerations.

Image removed due to copyright considerations.

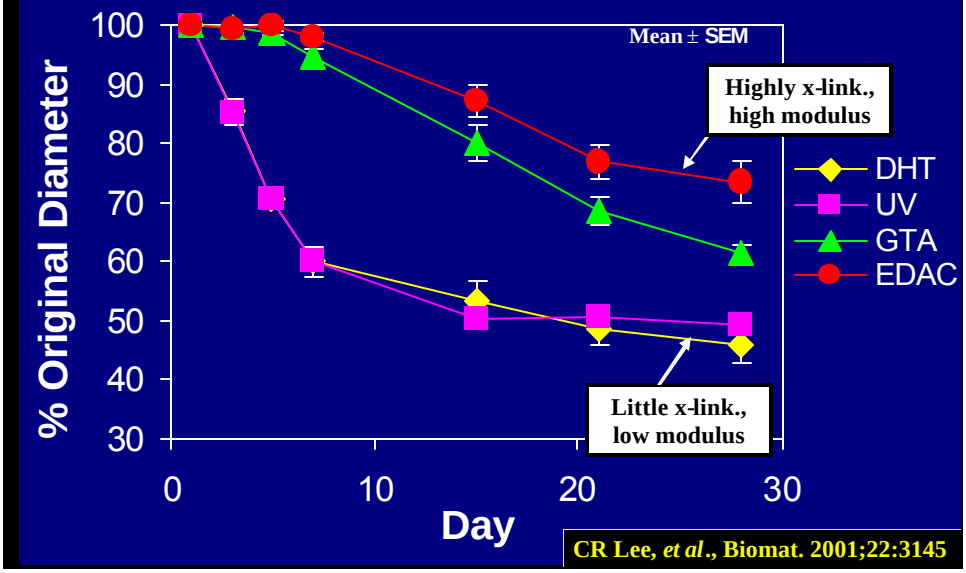
Non-Seeded and Cell-Seeded Collagen-GAG Scaffolds

Image removed due to copyright considerations.

21 days

S. Vickers

Adult canine articular chondrocytes (passage 3) contract a type I collagen-GAG matrix, reflected in the decrease in diameter



CR Lee, *et al*., Biomat. 2001;22:3145

Human Articular Chondrocytes in Monolayer Culture

IH - Green: a -smooth muscle actin; Orange: type II collagen

Image removed due to copyright considerations.

Chondrocytes express the gene for a -smooth muscle actin and this enables them to contract

B. Kinner, *et al*. JOR 2001;19:233

a -Smooth Muscle Actin Immunohistochemistry of Human Articular Cartilage

Image removed due to copyright considerations.

Kim and Spector, JOR 2000;18:749

MUSCULOSKELETAL CELLS THAT CAN EXPRESS a-SMOOTH MUSCLE ACTIN AND CAN CONTRACT

- Articular chondrocyte
- Osteoblast
- Meniscus fibroblast and fibrochondrocyte
- Intervertebral disc fibroblast and fibrochondrocyte
- Ligament fibroblast
- Tendon fibroblast
- Synovial cell
- Mesenchymal stem cell

M. Spector, Wound Repair Regen. 9:11-18 (2001)

POSSIBLE ROLES FOR a-SMOOTH MUSCLE ACTIN-ENABLED CONTRACTION

Musculoskeletal Connective Tissue Cells

• Tissue engineering	Contracture of scaffolds
• Healing	Closure of wounds (skin wounds and bone fractures)
• Disease processes	Contracture (Dupuytren's)
• Tissue formation and remodeling	Modeling of ECM architecture (*e.g.*, crimp in ligament/tendon?)

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TYPES OF TISSUES
Which Tissues Can Regenerate Spontaneously?

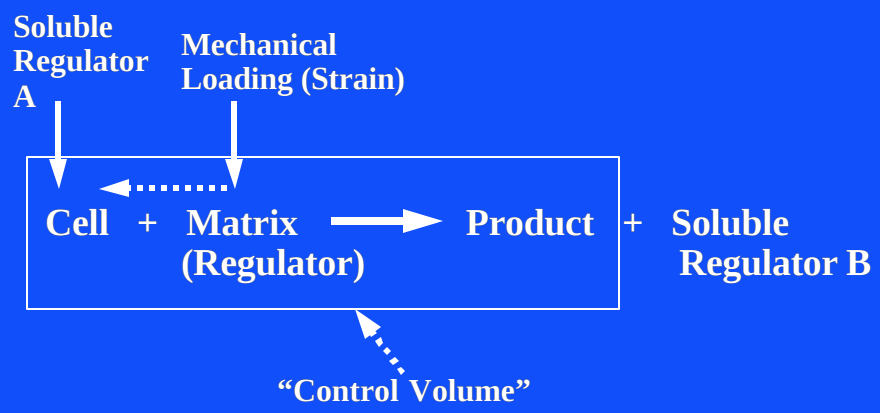
	Yes	No
Connective Tissues		
• Bone	v	
• Articular Cartilage, Ligament, Intervertebral Disc, Others		v
Epithelia (e.g., epidermis)	v	
Muscle		
• Cardiac, Skeletal		v
• Smooth	v	
Nerve		v

BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

Connective Tissue
Epithelia
Muscle
Nerve

UNIT CELL PROCESSES
Concept of a "Control Volume" around a Cell



BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

Connective Tissue	Adhesion Protein
Epithelia	Collagen
Muscle	Biomaterial
Nerve	

BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

Connective Tissue	Adhesion Protein
Epithelia	Collagen
Muscle	Biomaterial
Nerve	

Integrin

"UNIT CELL PROCESSES"

Cell + Matrix —UCP→

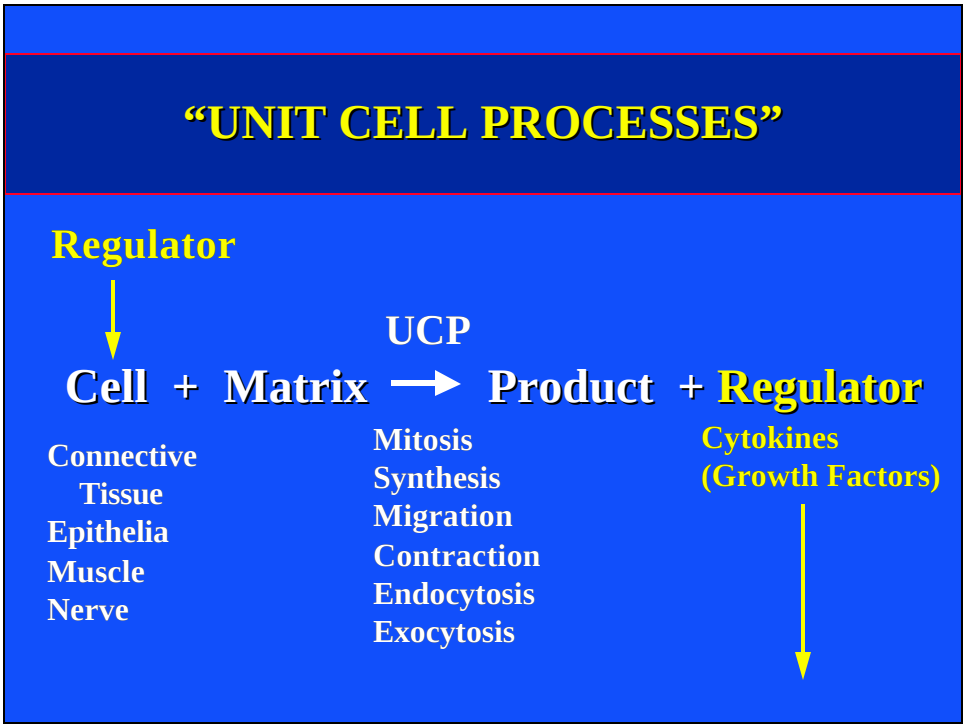
Connective Tissue
Epithelia
Muscle
Nerve

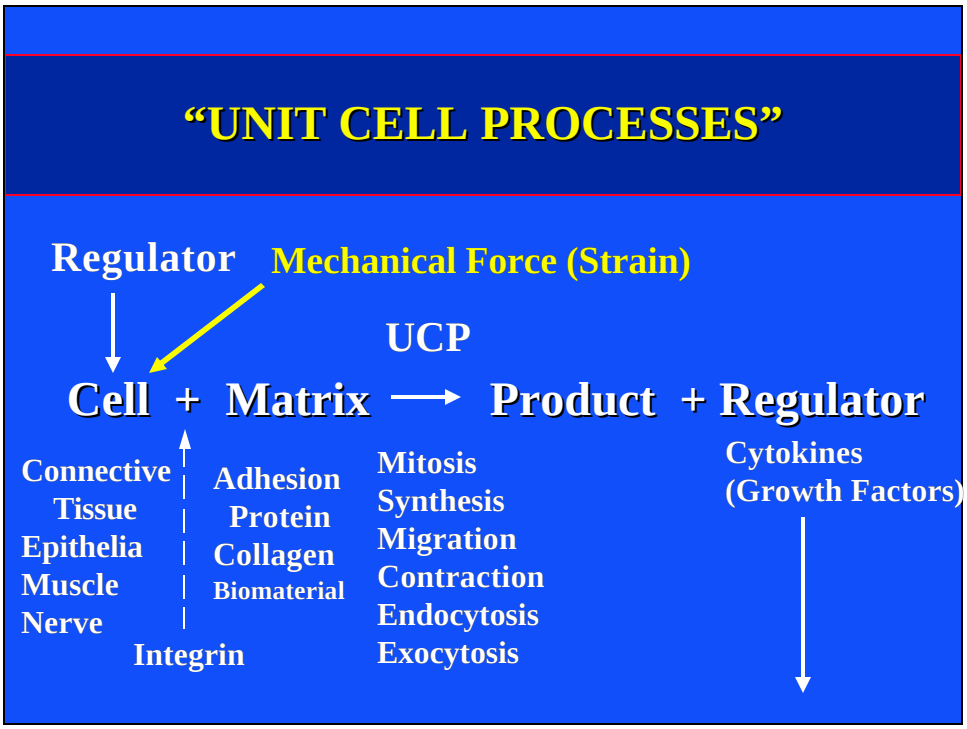
Mitosis
Synthesis
Migration
Contraction
Endocytosis
Exocytosis

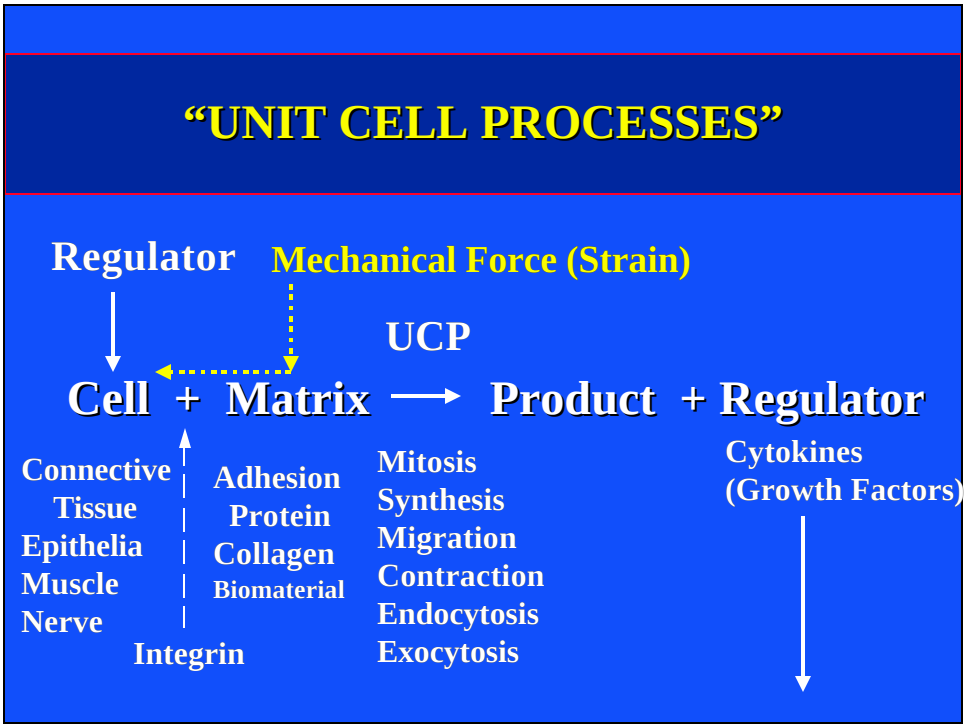
"UNIT CELL PROCESSES"

Cell + Matrix —UCP→ Product

Connective Tissue Epithelia Muscle Nerve	
Mitosis	Cell proliferation
Synthesis	Matrix molecules, enzymes, cytokines
Migration	Translocation
Contraction	Strain
Endocytosis	Solubilized fragments
Exocytosis	Regulators


"UNIT CELL PROCESSES"
Regulator
UCP
Cell + Matrix → Product + Regulator
Connective Tissue
Epithelia
Muscle
Nerve
Mitosis
Synthesis
Migration
Contraction
Endocytosis
Exocytosis
Cytokines
(Growth Factors)


"UNIT CELL PROCESSES"
Regulator
Mechanical Force (Strain)
UCP
Cell + Matrix → Product + Regulator
Connective Tissue
Epithelia
Muscle
Nerve
Integrin
Adhesion Protein
Collagen
Biomaterial
Mitosis
Synthesis
Migration
Contraction
Endocytosis
Exocytosis
Cytokines
(Growth Factors)


"UNIT CELL PROCESSES"
Regulator
Mechanical Force (Strain)
UCP
Cell + Matrix
Product + Regulator
Connective Tissue
Epithelia
Muscle
Nerve
Integrin
Adhesion Protein
Collagen
Biomaterial
Mitosis
Synthesis
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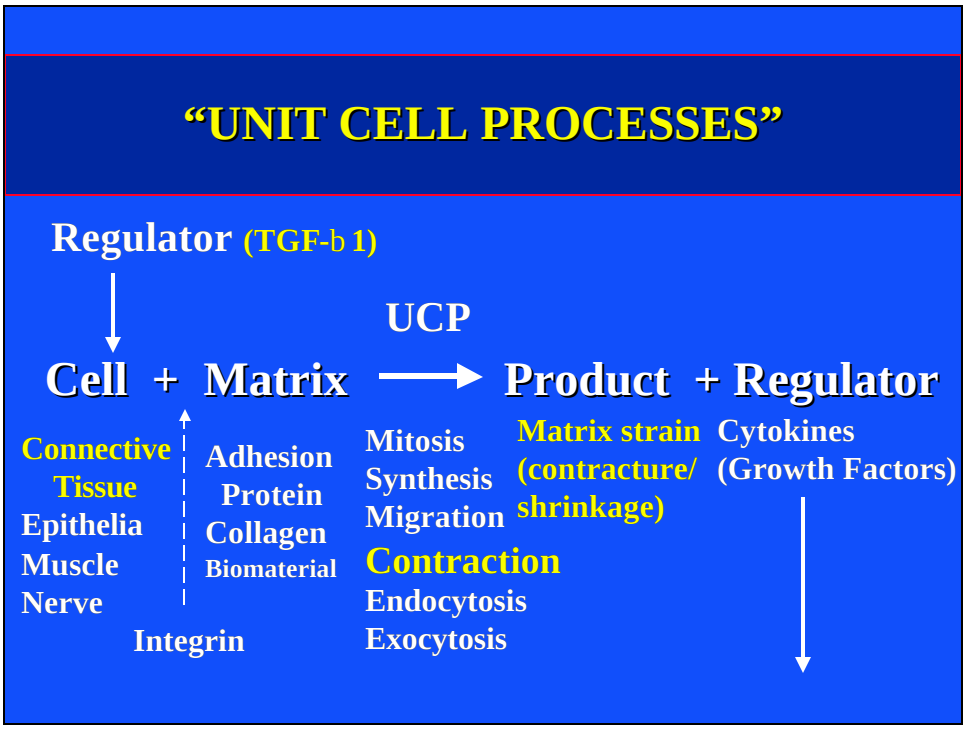
Cytokines
(Growth Factors)


"UNIT CELL PROCESSES"
Regulator (TGF-b 1)
UCP
Cell + Matrix
Product + Regulator
Connective Tissue
Epithelia
Muscle
Nerve
Integrin
Adhesion Protein
Collagen
Biomaterial
Mitosis
Synthesis
Migration
Contraction
Endocytosis
Exocytosis
Matrix strain (contracture/ shrinkage)
Cytokines
(Growth Factors)

"UNIT CELL PROCESSES"

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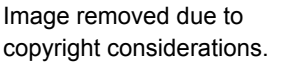
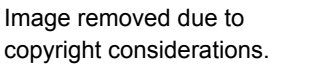
TISSUE FORMATION AND REMODELING *IN VITRO*

-FGF-2



+FGF-2



Canine chondrocytes grown in a type II collagen-GAG scaffold for 2 weeks. (Safranin O stain for GAGs)

N. Veilleux

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WOUND HEALING
Roots of Tissue Engineering

Injury

↓

Inflammation
(Vascularized tissue)

↓

Reparative
Process

Regeneration*	Repair (Scar)
CT: bone	CT: cartilage
Ep: epidermis	Nerve
Muscle: smooth	Muscle: cardiac, skel.

*spontaneous

4 Tissue Categories
Connective Tissue
Epithelium
Nerve
Muscle

RESPONSE TO IMPLANTS:
WOUND HEALING

Surgical Implantation

↓

Vascular Response
Clotting
Phagocytosis
Neovascularization
New Collagen Synthesis

Acute Inflammation

Granulation Tissue

Tissue of Labile and Stable Cells

Tissue of Permanent Cells

Implant Movement

Framework Intact → Regen. (incorp. of implant)

Framework Destroyed → Scarring (fibrous encapsulation; synovium)
Chronic Inflammation

Scarring (fibrous encapsulation; synovium)
Chronic Inflammation