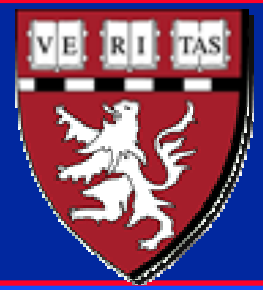
Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



2.785j/3.97J/BEH.411/HST523J

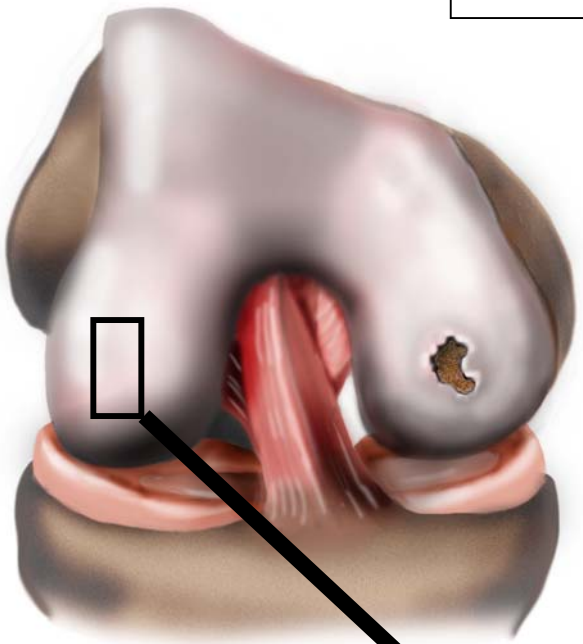
"UNIT CELL PROCESSES"
Tools for Understanding the Molecular, Cellular, and Physiological, Bases of the Tissue Response to Implants

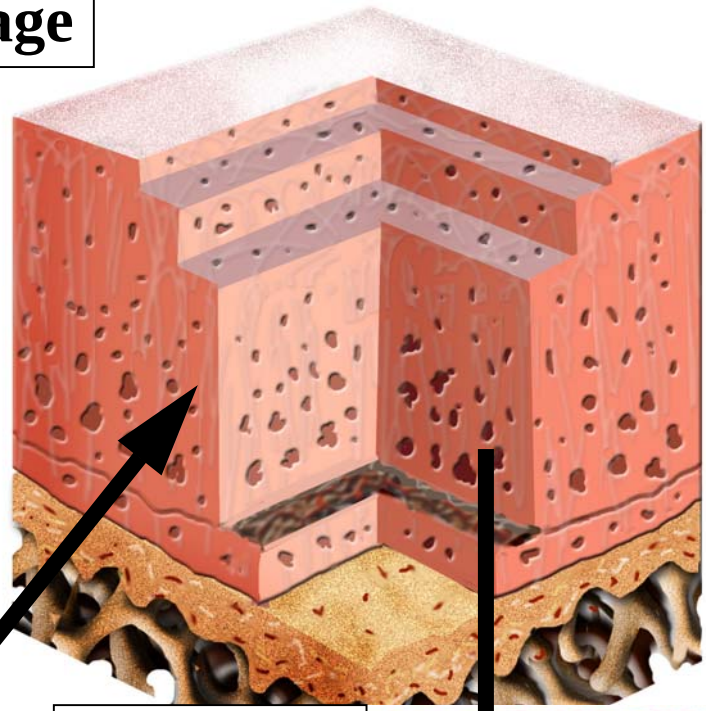
M. Spector, Ph.D. and I.V. Yannas, Ph.D.

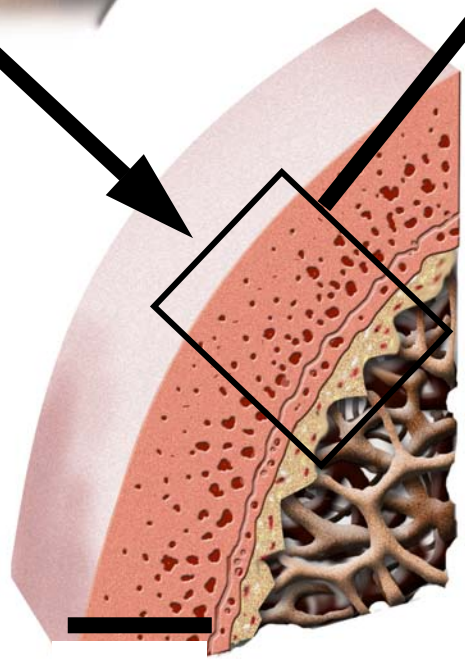
CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

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

Articular Cartilage

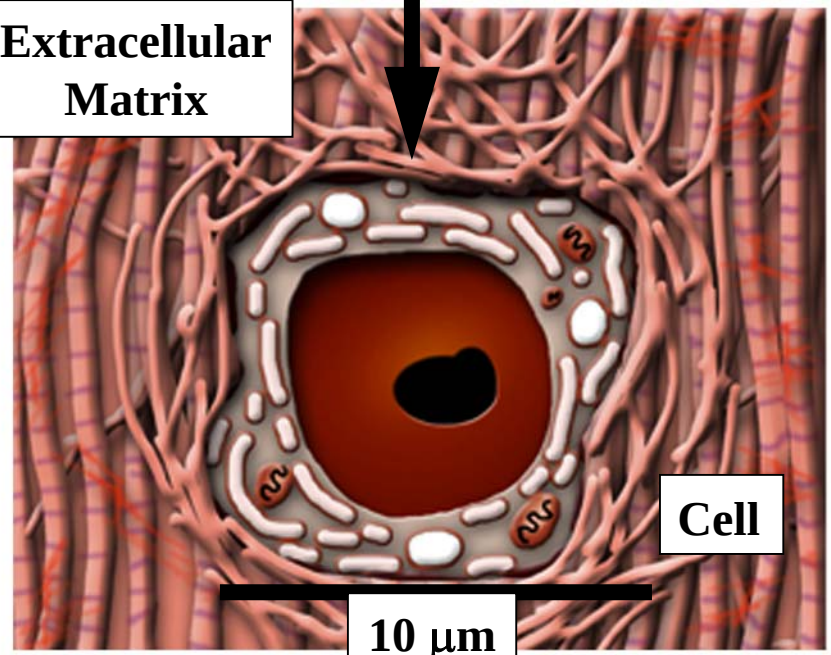






4 mm

Extracellular Matrix



Cell

10 μm

Figures by MIT OCW.

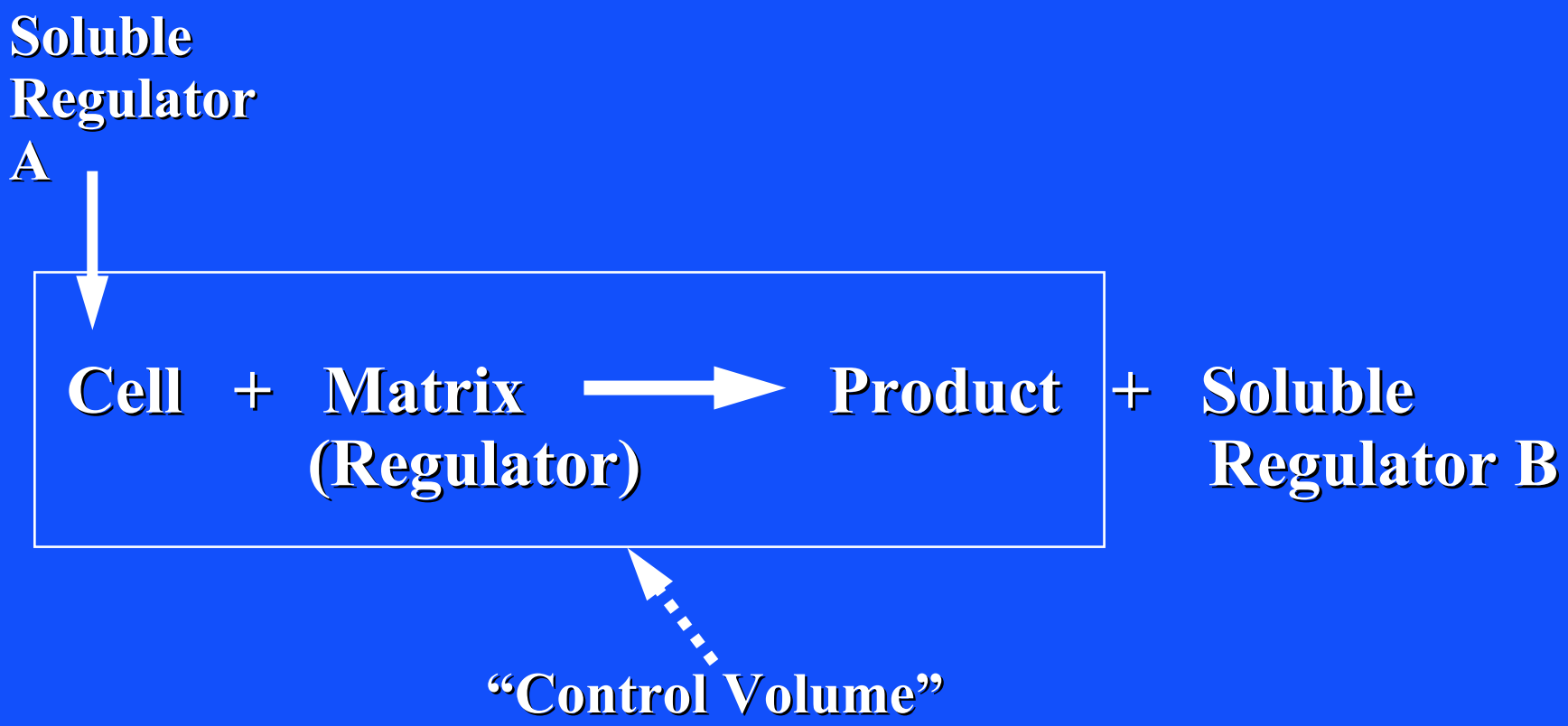
Chondrocytes (P2 Canine) in a Type I Collagen-GAG Scaffold

Photo removed for copyright reasons.

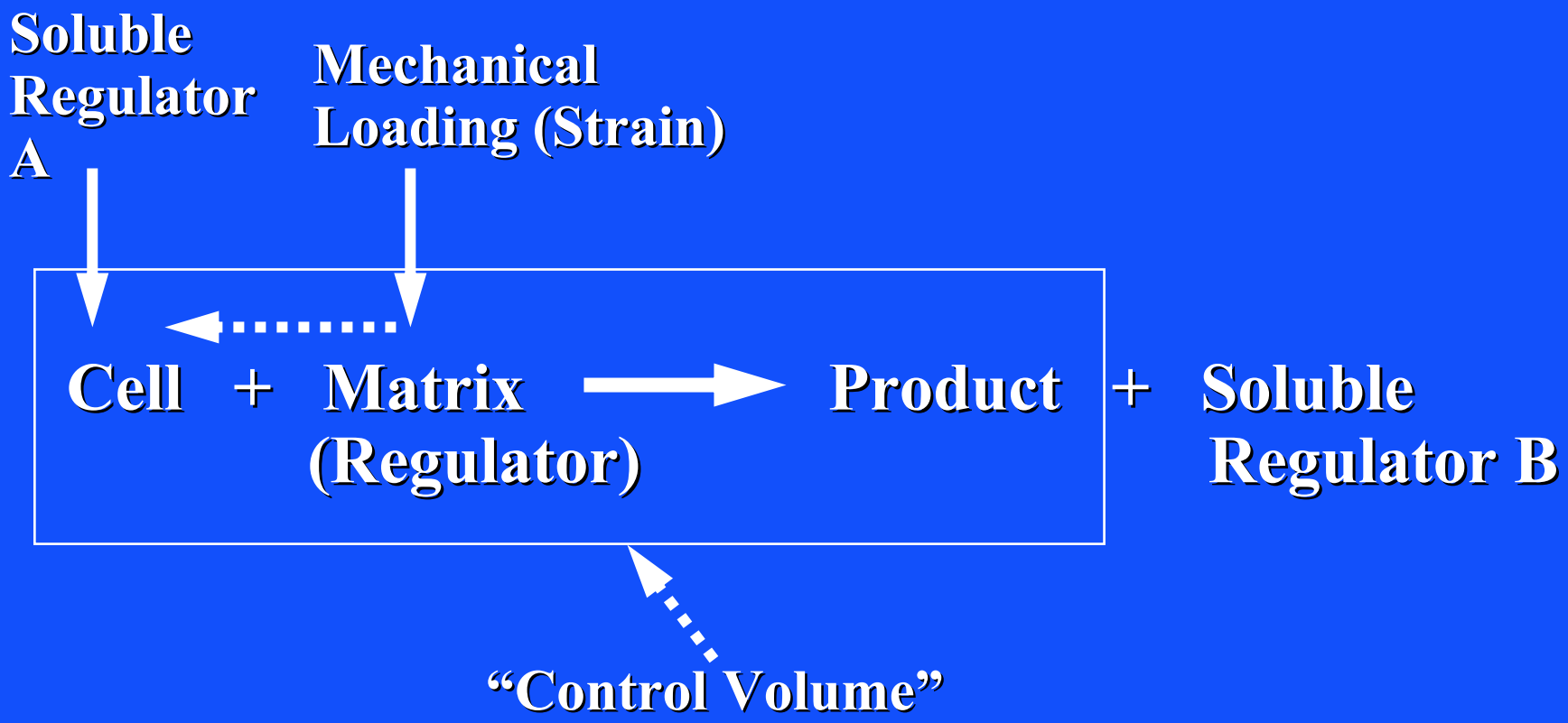
“Control Volume”

Source: B. Kinner

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



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



CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

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

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

Photo removed for copyright reasons.

1mm

Photo removed for copyright reasons.

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

500μm

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 serve as a model in which to investigate the effects of exogenous forces on cells and the contractile behavior of cells (*i.e.*, generating endogenous force).**

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

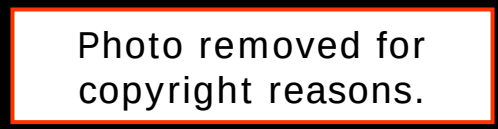
Photo removed for copyright reasons.

J. Cheng

UNIT CELL PROCESSES

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

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



J. Cheng

UNIT CELL PROCESSES

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

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

Photo removed for copyright reasons.

B. Kinner, in *JM Zaleskas Biomat.* 2004;25:1299

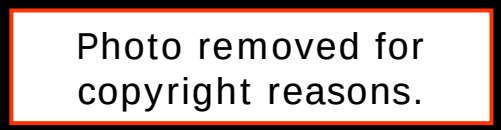
Image removed for copyright reasons.
See Figure 6 in Mitchison and Cramer. “Actin-Based Cell Motility and Cell Locomotion.” *Cell* 84:371 (1996)

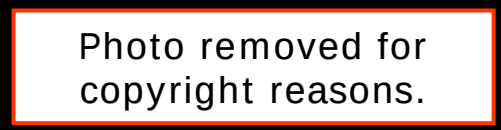
Two Models for Generation of Traction Force Using Myosin II Activity
In the contraction model (A), myosin pulling on filaments of opposite polarity creates a cortical tension that pulls the cell equally in all directions. This contraction can be converted into movement by combining it with preferential assembly of the cortex at the front of the cell and disassembly at the back, and/or by regulating the relative strength of adhesive contacts to the substratum at the front and back. In the transport model (B), myosin activity pulls the body of the cell over an oriented track of actin filaments attached to the substratum.

UNIT CELL PROCESSES

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

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





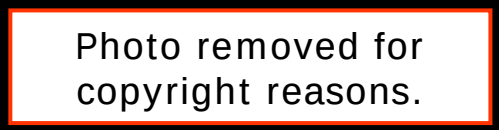
40 min

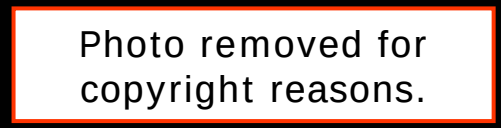
300 min

B. Kinner, in *JM Zaleskas*
Biomat. 2004;25:1299

Non-Seeded: 8 days

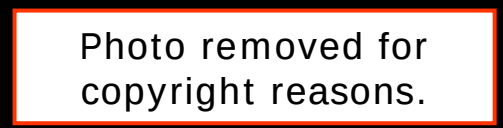
Cell-Seeded: 8 days





21 days

Non-Seeded and Cell-Seeded Collagen-GAG Scaffolds



S. Vickers

Human Articular Chondrocytes in Monolayer Culture

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

Photo removed for copyright reasons.

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

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

α-Smooth Muscle Actin Immunohistochemistry of Human Articular Cartilage

Photo removed for copyright reasons.

Kim and Spector, *JOR* 2000;18:749

MUSCULOSKELETAL CELLS THAT CAN EXPRESS α-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 α-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?)

CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

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

TYPES OF TISSUES
Which Tissues Can Regenerate Spontaneously?

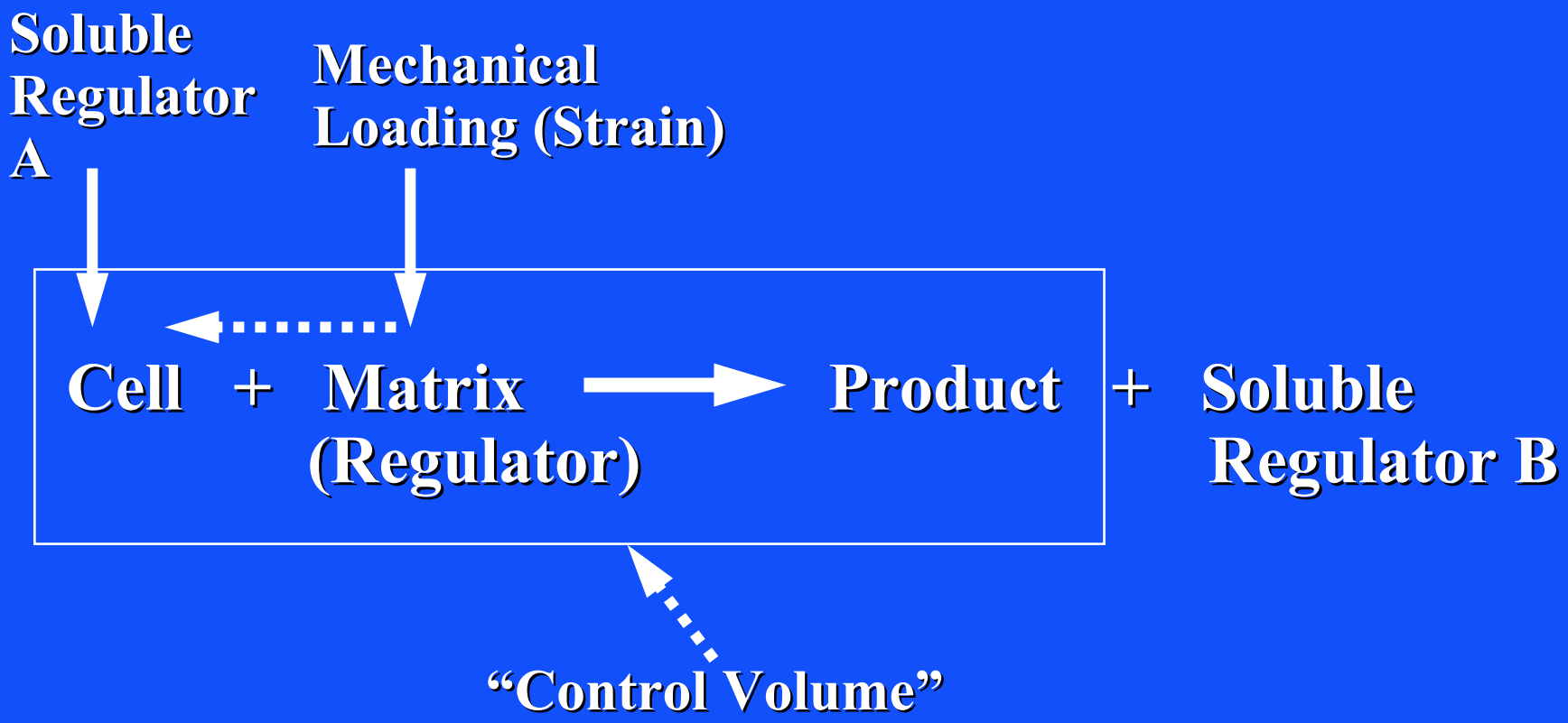
	Yes	No
Connective Tissues		
• Bone	√	
• Articular Cartilage, Ligament, Intervertebral Disc, Others		√
Epithelia (e.g., epidermis)	√	
Muscle		
• Cardiac, Skeletal		√
• Smooth	√	
Nerve		√

BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

- Connective Tissue
- Epithelia
- Muscle
- Nerve

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



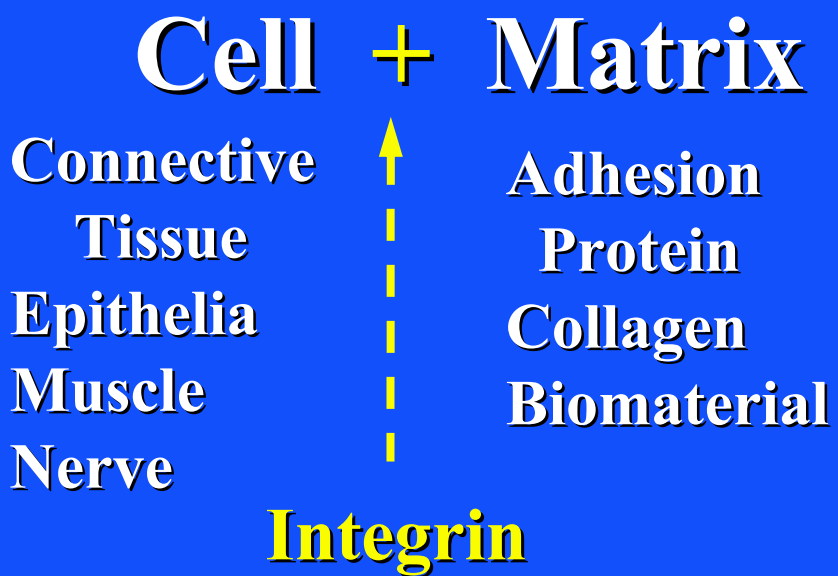
BIOMATERIALS-TISSUE INTERACTIONS

Cell + Matrix

Connective Tissue
Epithelia
Muscle
Nerve

Adhesion Protein
Collagen
Biomaterial

BIOMATERIALS-TISSUE INTERACTIONS



"UNIT CELL PROCESSES"

Cell + Matrix —**UCP**→

Connective Tissue
Epithelia
Muscle
Nerve

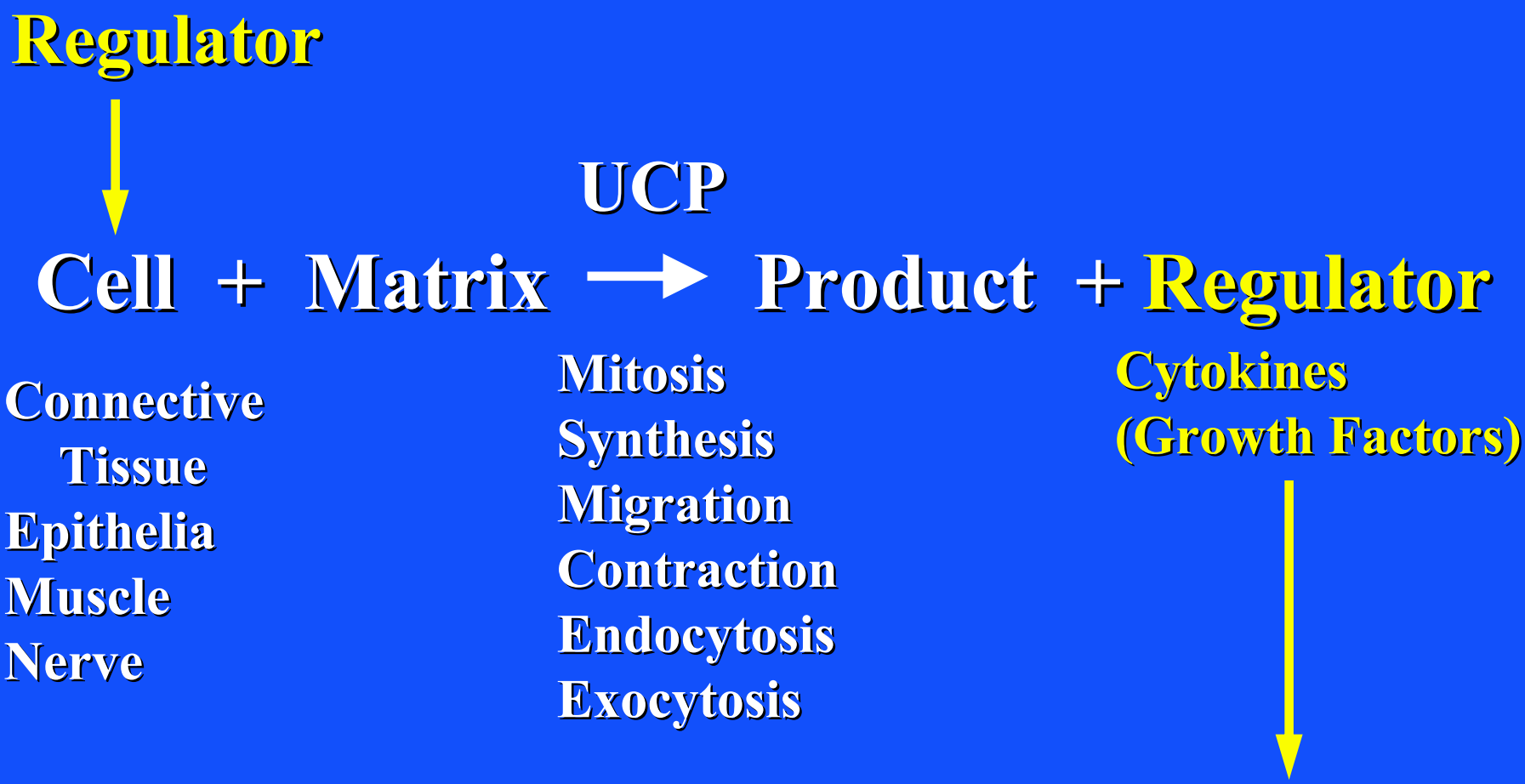
Mitosis
Synthesis
Migration
Contraction
Endocytosis
Exocytosis

"UNIT CELL PROCESSES"

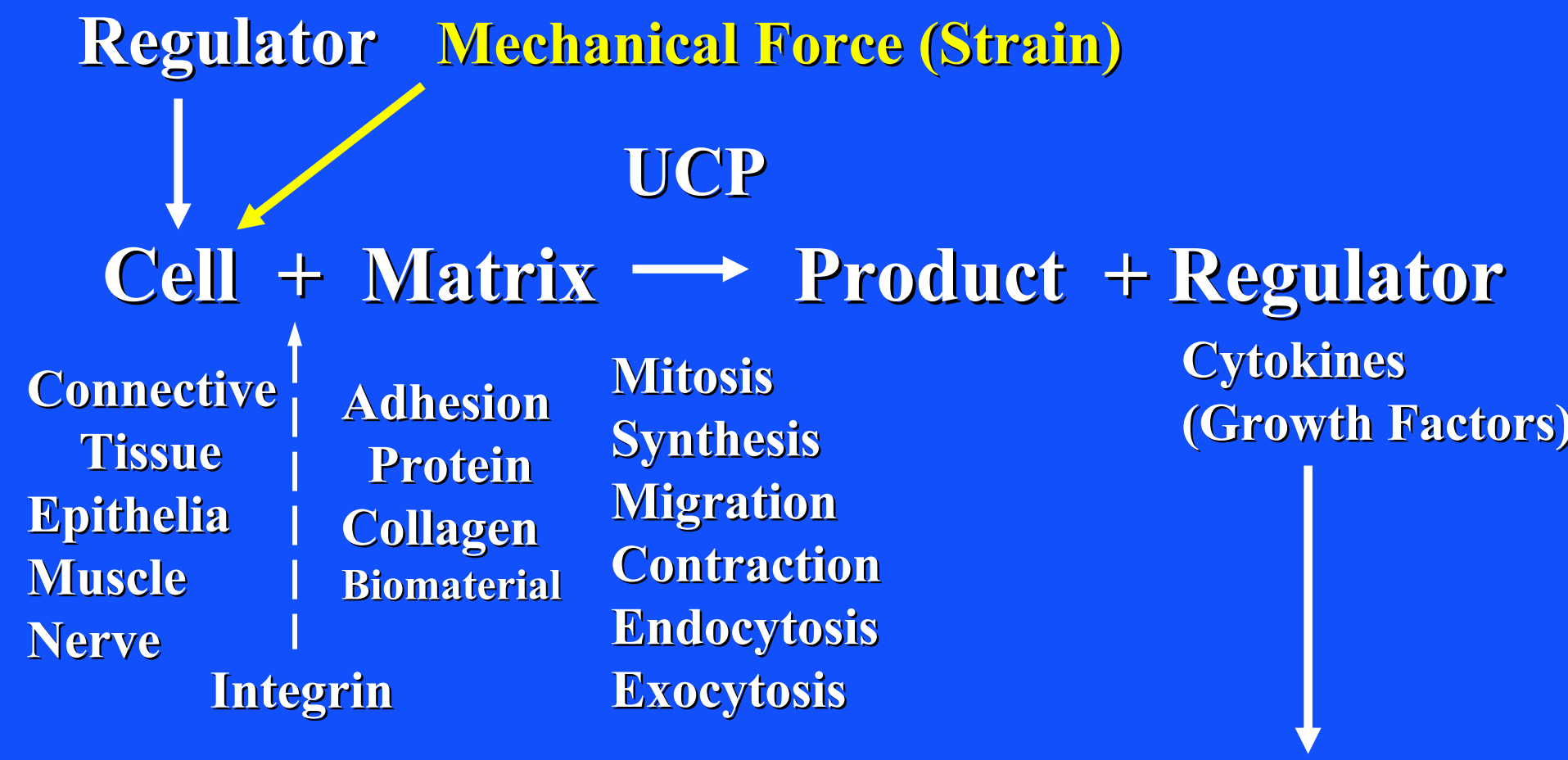
Cell + Matrix —UCP→ **Product**

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

"UNIT CELL PROCESSES"



"UNIT CELL PROCESSES"



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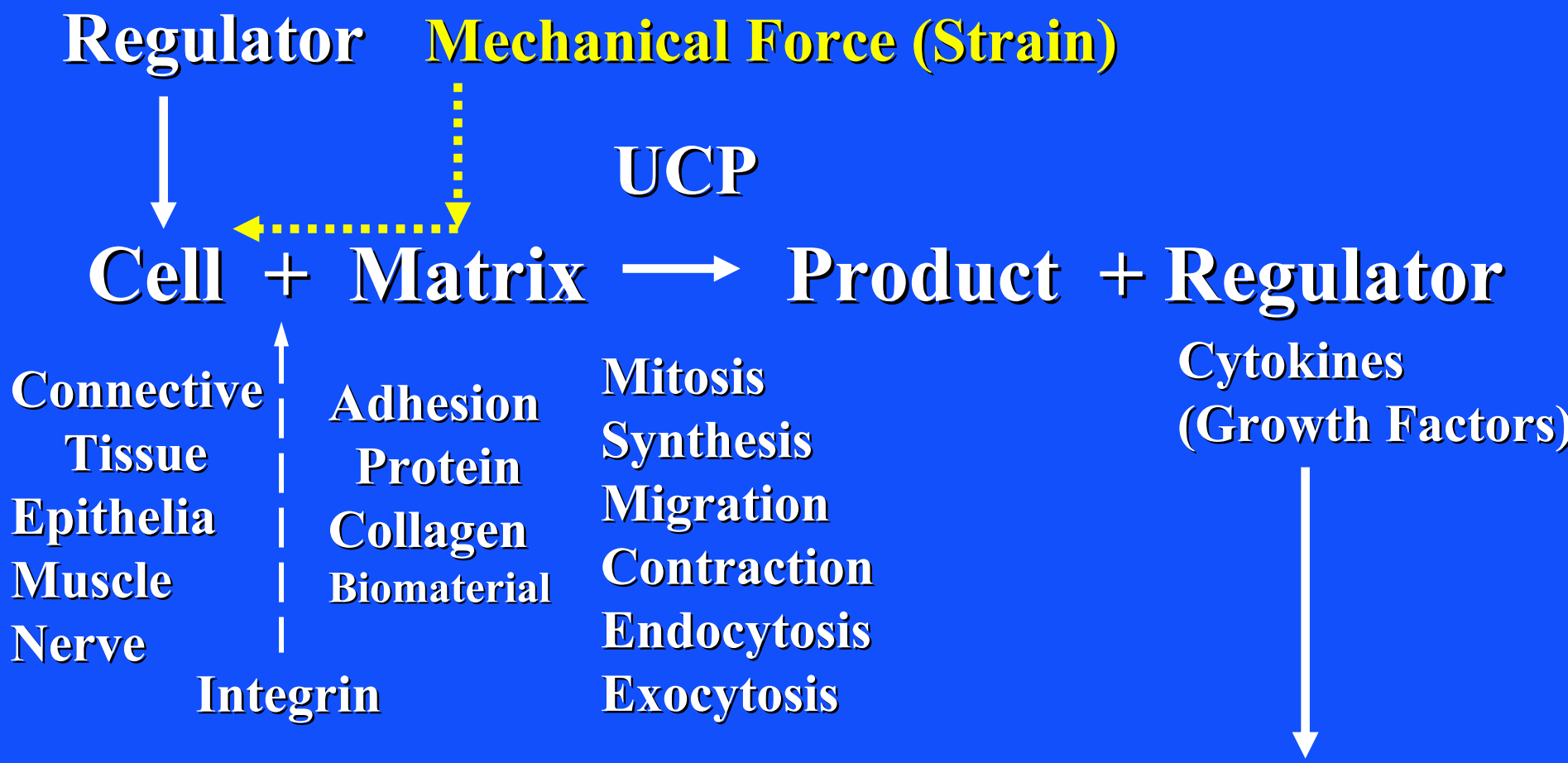

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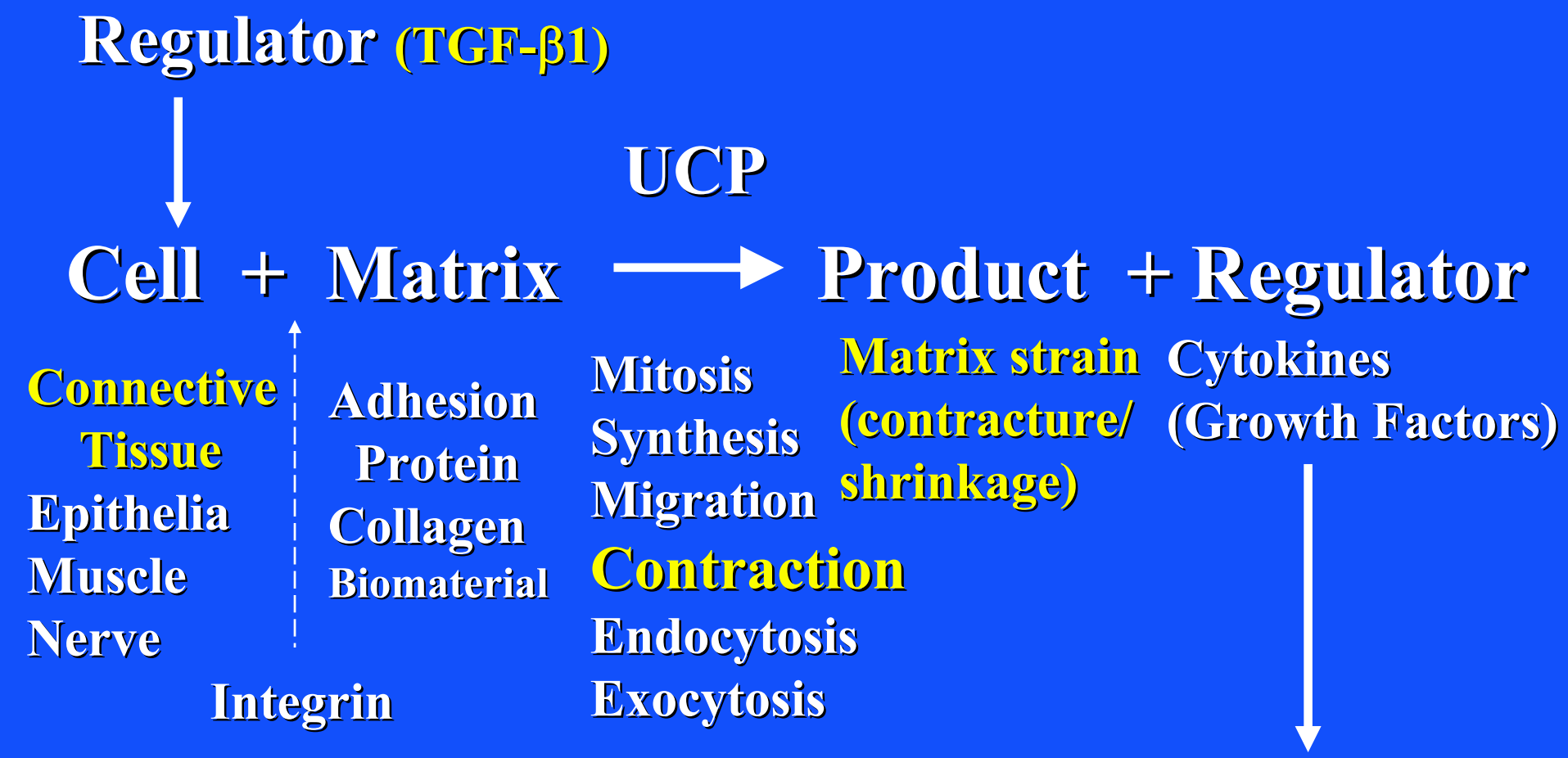

"UNIT CELL PROCESSES"

TGF-β1

↓

Contraction

Fibroblast + Collagen ⟶ Contracture + Reg.

CONCEPTS FOR UNDERSTANDING BIOMATERIALS-TISSUE INTERACTIONS

- Control Volume
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- Wound Healing *In Vivo*

-FGF-2

TISSUE FORMATION AND REMODELING *IN VITRO*

Photo removed for copyright reasons.

+FGF-2

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

Photo removed for copyright reasons.

N. Veilleux

UNIT CELL PROCESSES
BONE REMODELING

Degradation

Synthesis: collagenase, H^+

Osteoclast + ECM ⟶ Sol. ECM + Reg.

Formation

Synthesis: collagen

Osteoblast + ECM ⟶ New ECM + Reg.

UNIT CELL PROCESSES
BONE REMODELING

Reg.

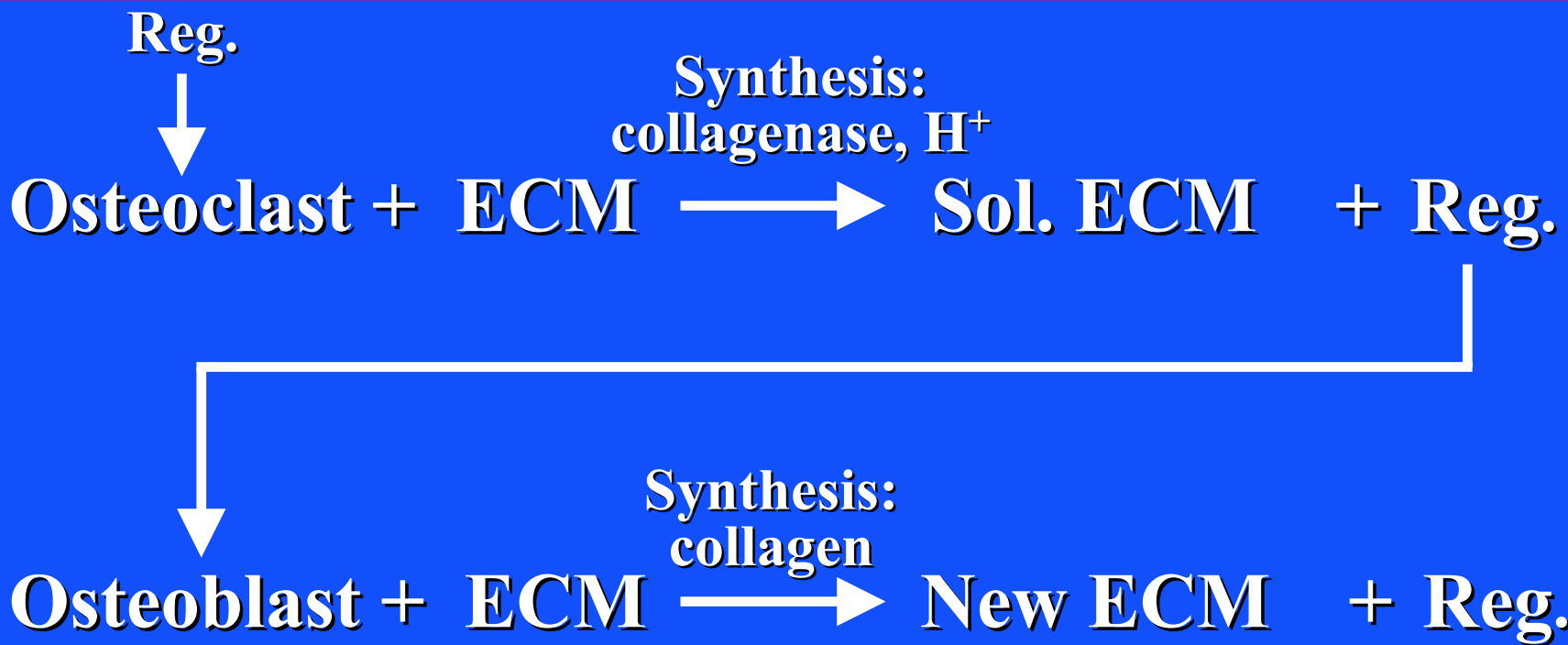
Synthesis:
collagenase, H^+

Osteoclast + ECM → Sol. ECM + Reg.

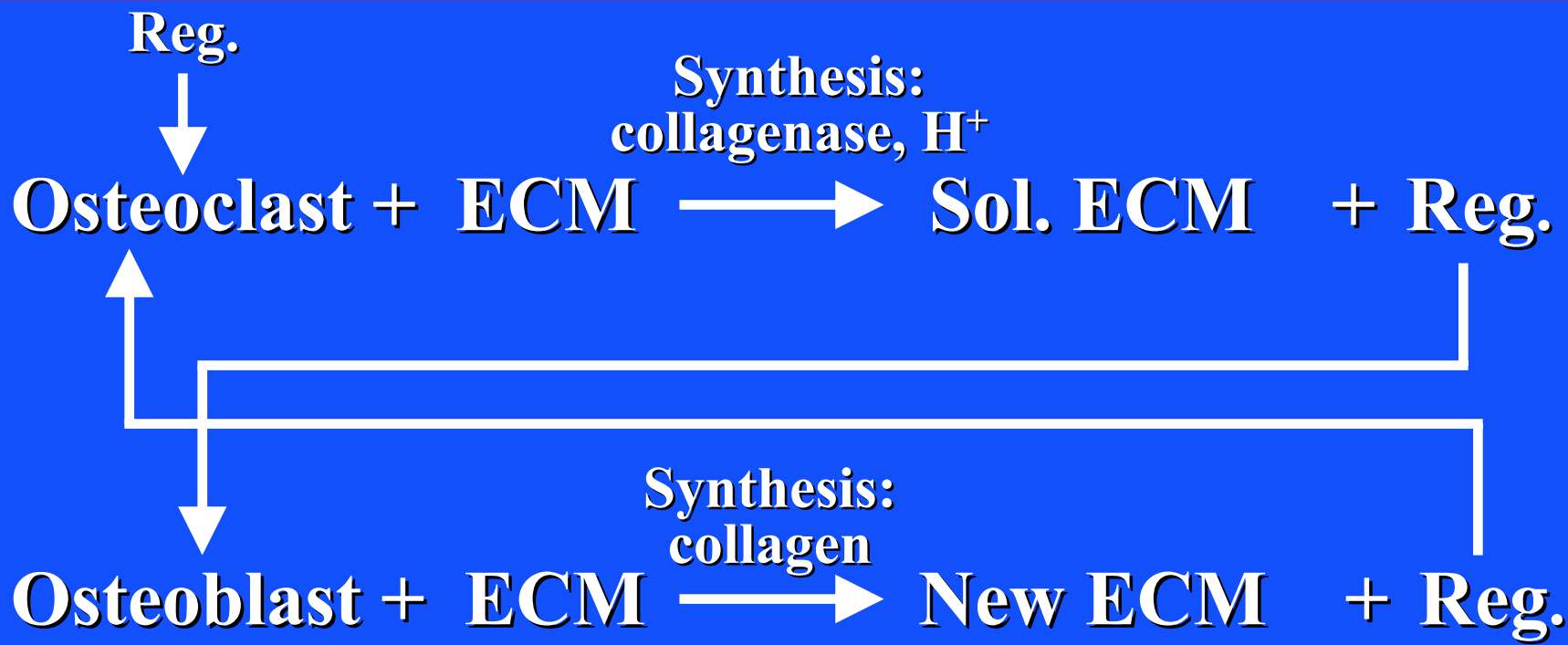
Synthesis:
collagen

Osteoblast + ECM → New ECM + Reg.

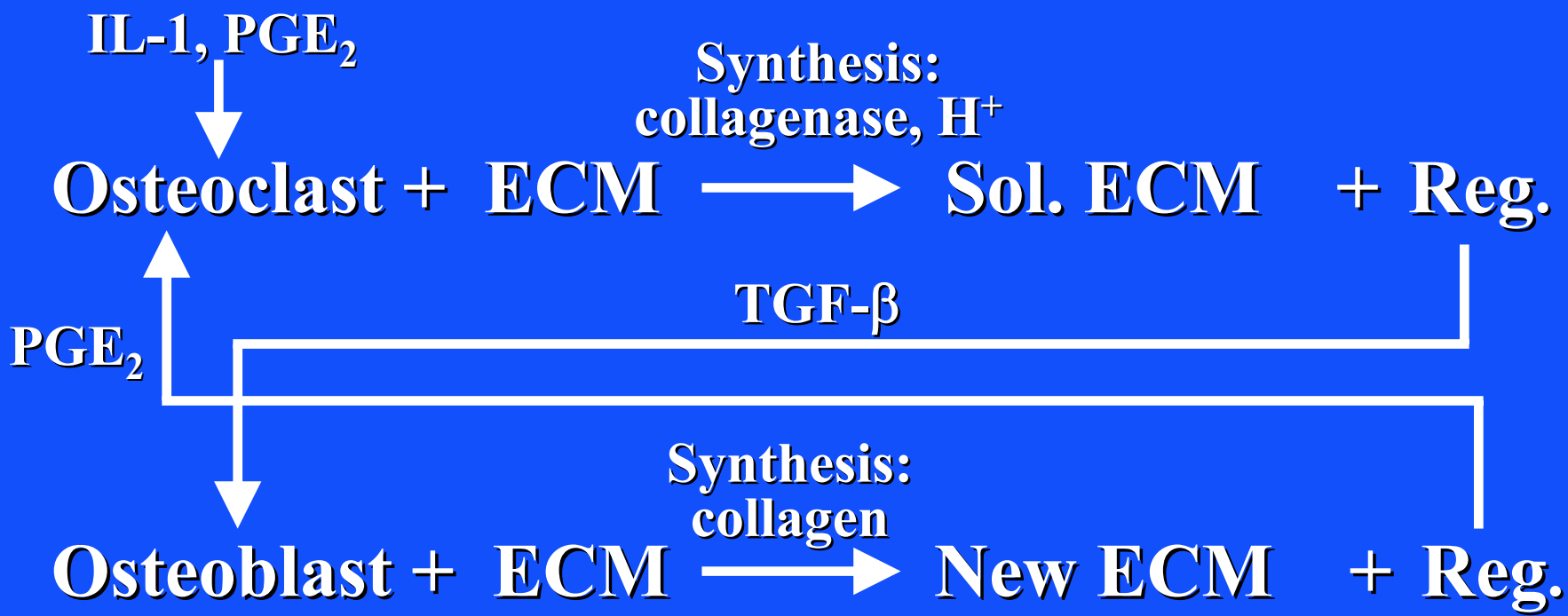
UNIT CELL PROCESSES
BONE REMODELING



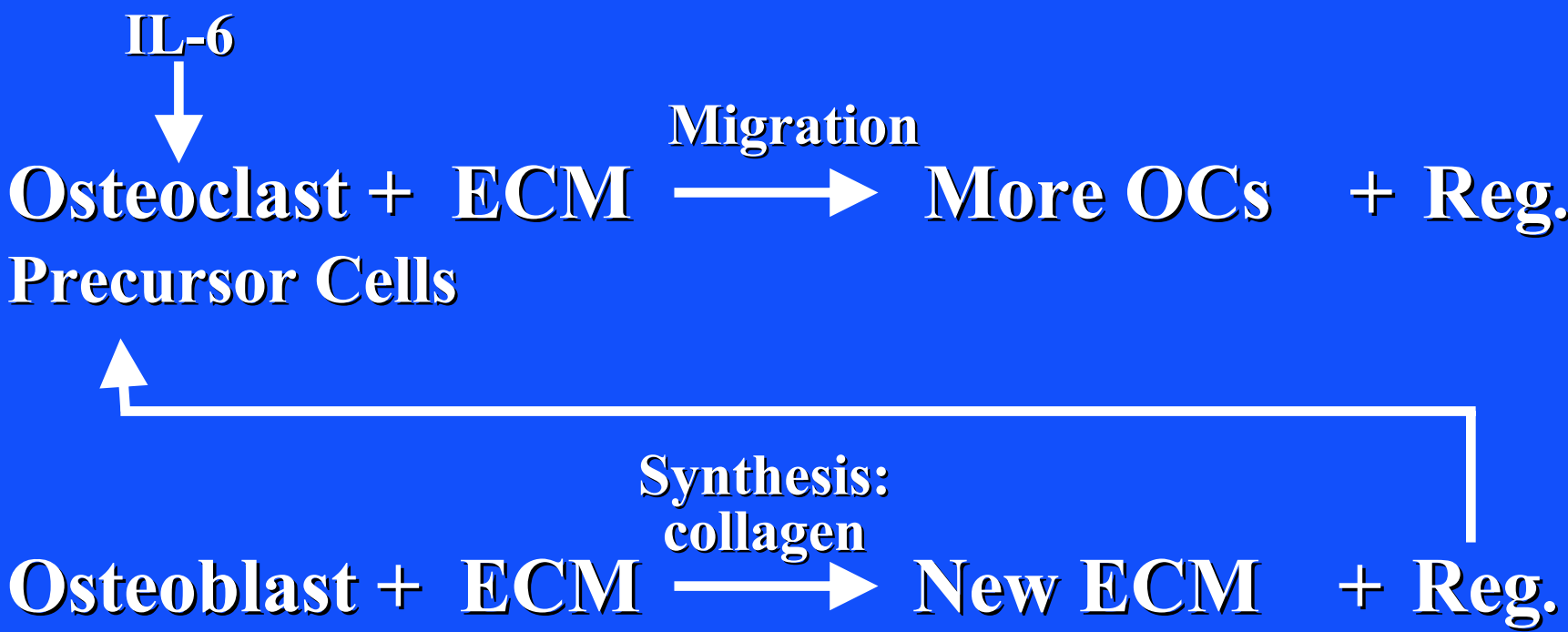
UNIT CELL PROCESSES
BONE REMODELING



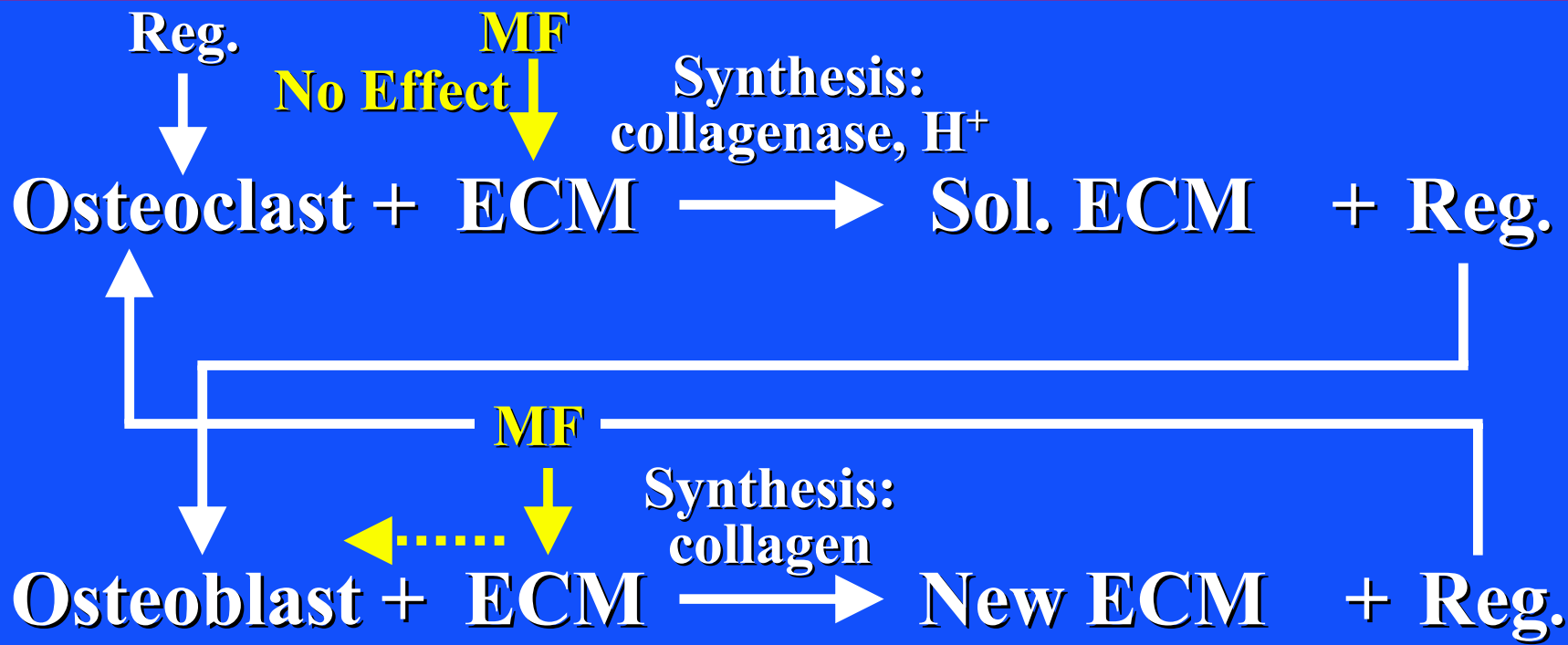
UNIT CELL PROCESSES
BONE REMODELING



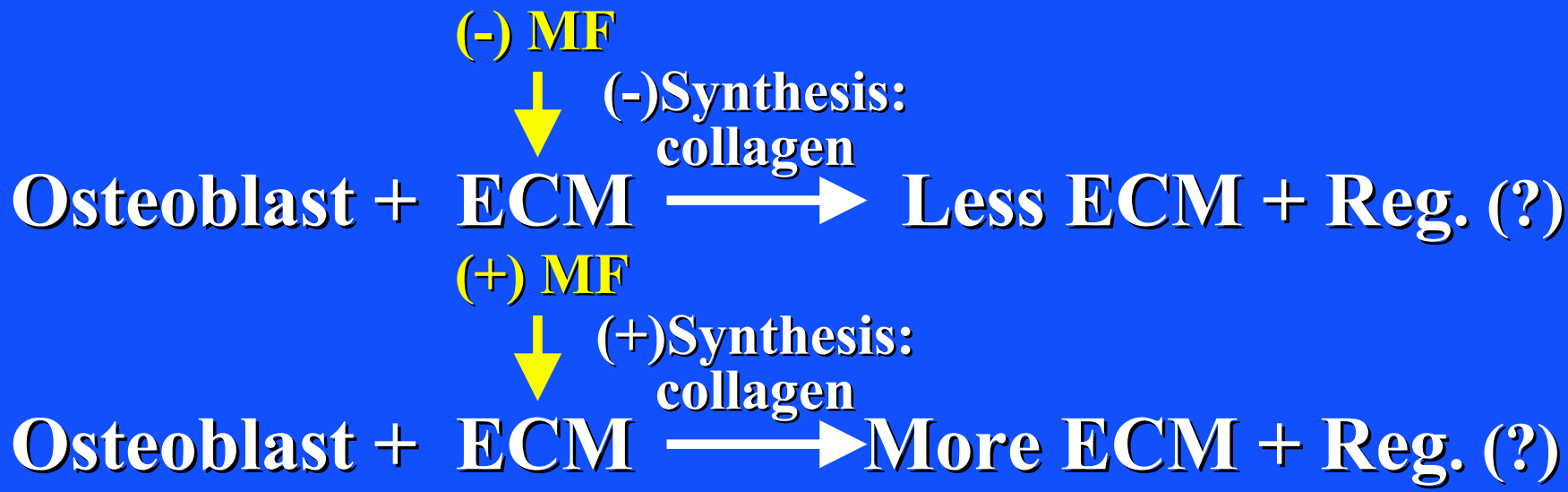
UNIT CELL PROCESSES
BONE REMODELING



UNIT CELL PROCESSES
BONE REMODELING



UNIT CELL PROCESSES
BONE REMODELING



UNIT CELL PROCESSES
BONE REMODELING

Degradation

MF

Synthesis: collagenase

Fibroblast + ECM → Sol. ECM + Reg.

Formation

MF

Synthesis: collagen

Fibroblast + ECM → New ECM + Reg.