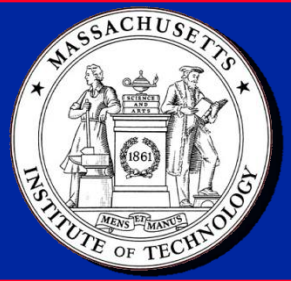
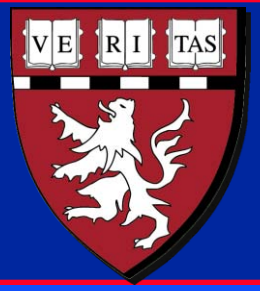


Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



2.79J/3.96J/20.441/HST522J

BIOMATERIALS-TISSUE INTERACTIONS
Introduction

M. Spector, Ph.D.

2.79J/3.96J/20.441/HST522J
BIOMATERIALS-TISSUE INTERACTIONS

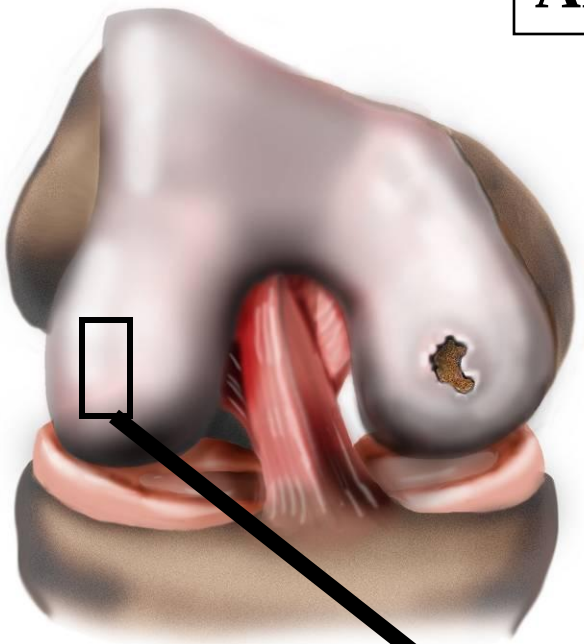
Course Characteristics

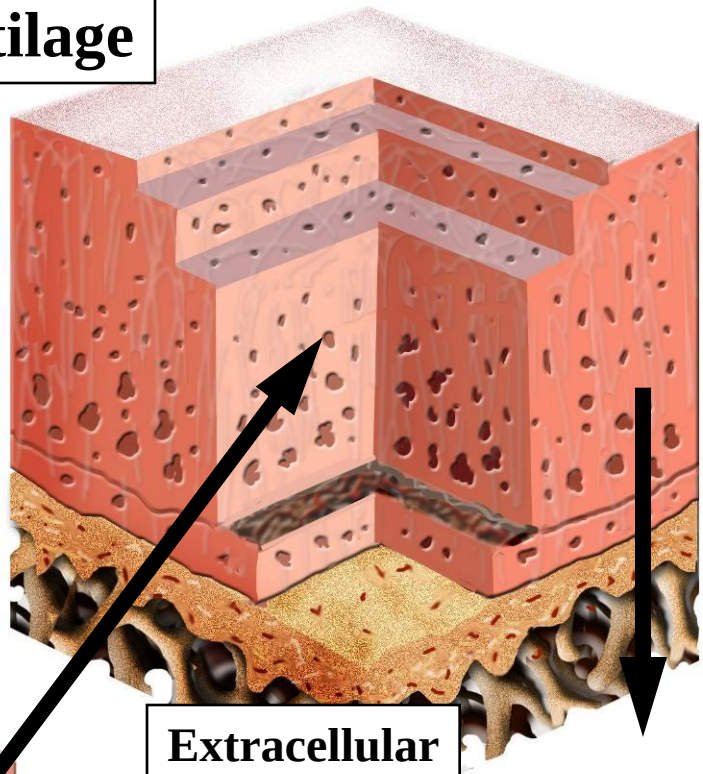
- Codification of the behavior of cells in the context of their interaction with biomaterials
  - "Unit Cell Processes"
- Emphasis on wound healing
- Emphasis on the molecular and cellular interaction with materials

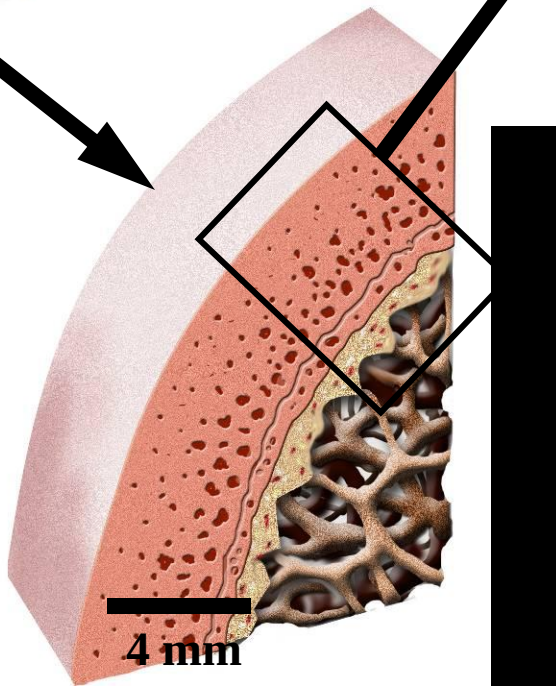
BIOMATERIALS-TISSUE INTERACTIONS

- **Tissue** is a biological structure made up of cells of the same type.
  - Cells of the same phenotype (*i.e.*, same genes expressed).
  - An aggregation of morphologically similar cells and associated extracellular matrix acting together to perform one or more specific functions in the body.
  - There are four basic types of tissue: **muscle, nerve, epithelia, and connective.**
  - An **organ** is a structure made up of 2 or more tissues.

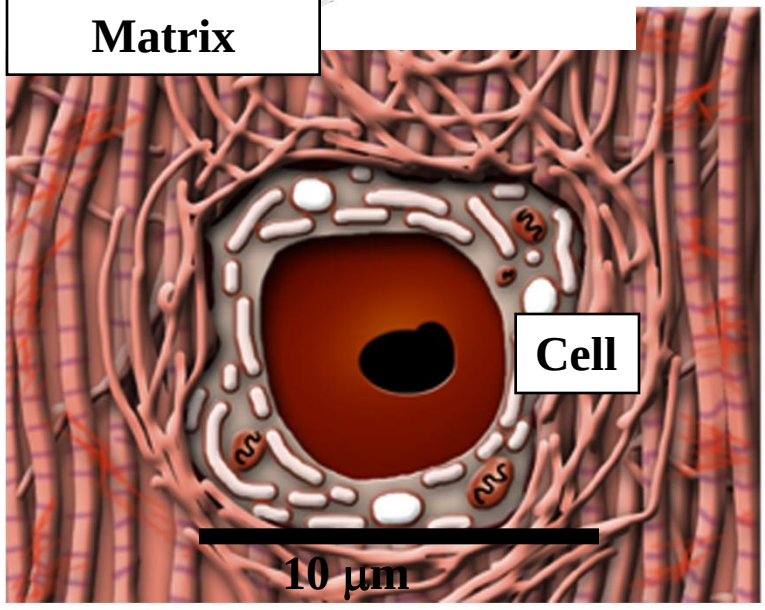
Articular Cartilage







Extracellular Matrix



BIOMATERIALS-TISSUE INTERACTIONS

Permanent versus Absorbable Biomaterials

- Roles of permanent biomaterials for the production of permanent implants versus the roles as absorbable scaffolds for tissue engineering

BIOMATERIALS IN ORTHOPAEDIC SURGERY

1920-50	Era of stainless steel	Fixation of tissue
1950-	Introduction of cobalt chromium alloy and silicone	Replacement of tissue
1960-	Introduction of polymethyl methacrylate and polyethylene	
1970-	Titanium alloy	
1980-	Porous metals; hydroxyapatite	
2000	Porous, absorbable materials for tissue engineering	Regeneration of tissue
2010	Biomaterials for gene therapy	

Biomaterial used for Tissue Regeneration

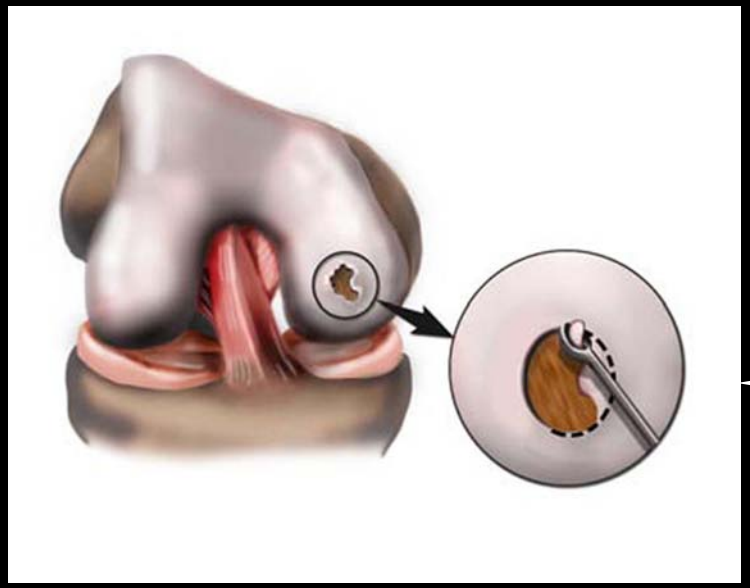
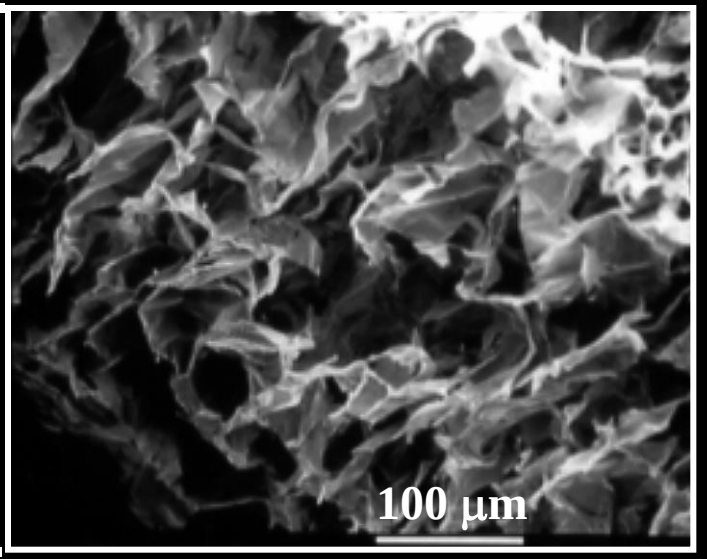


Figure by MIT OpenCourseWare.

Medical illustration of scaffold implantation removed due to copyright restrictions.

Cell-Seeded Scaffold



Scaffold Alone

BIOMATERIALS-TISSUE INTERACTIONS

Effects of Biomaterials on Tissue

- In Bulk Form (Nonporous or Porous)
  - Accommodates tissue attachment
  - Promotes tissue formation
  - Affects tissue remodeling (degradation followed by formation); *e.g.*, by altering the mechanical environment
- In Particle (Molecular) Form
  - Tissue degradation

BIOMATERIALS-TISSUE INTERACTIONS

Effects of Biomaterials on Cells

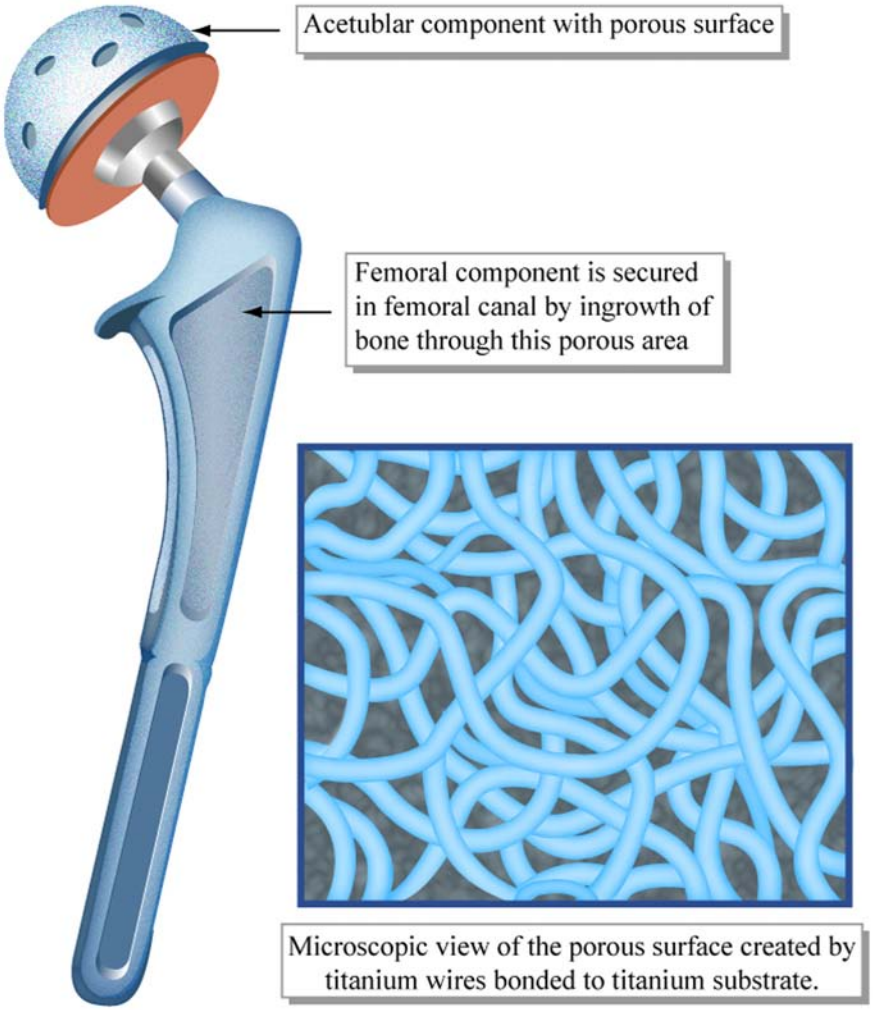
- In Bulk Form
  - Cell attachment
  - Cell proliferation (mitosis)
  - Production of matrix molecules and enzymes (synthesis)
  - Migration
  - Contraction
  - Release of pre-packaged reactive molecules (exocytosis)
- In Particle (Molecular) Form
  - Ingestion of particles (endocytosis)

BIOMATERIALS-TISSUE INTERACTIONS

Permanent Biomaterials

- Favorable Response
  - Tissue attachment
- Adverse Responses
  - Contraction
  - Reaction to particles; tissue destruction
- Passive Response

Total Hip and Knee Replacement Prostheses

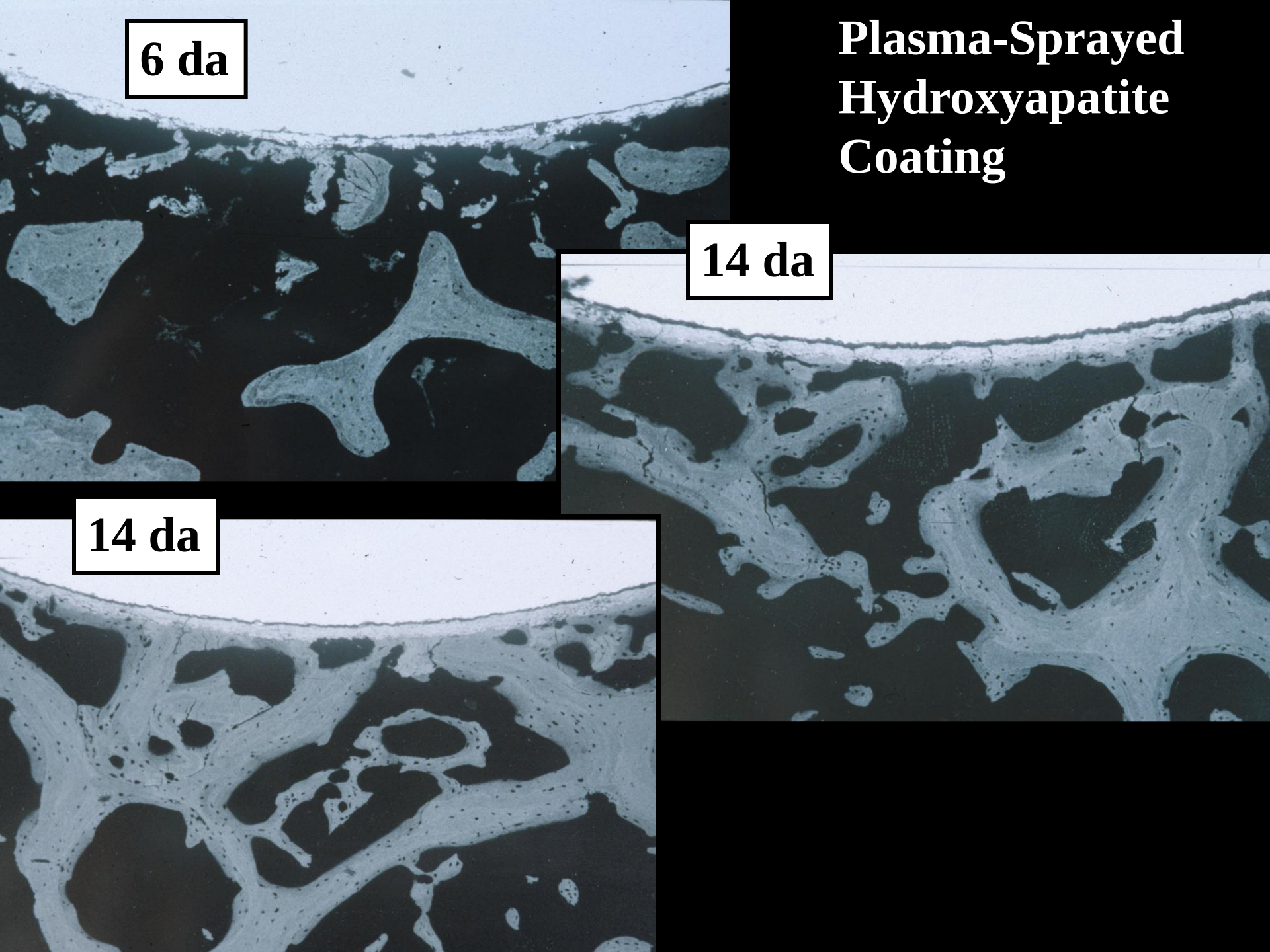


Photos of knee replacement prostheses removed due to copyright restrictions.

Figure by MIT OpenCousreWare.

Hydroxyapatite-Coated Implants

Photos of implants removed
due to copyright restrictions.


6 da
Plasma-Sprayed
Hydroxyapatite
Coating
14 da
14 da

BIOMATERIALS-TISSUE INTERACTIONS

Permanent Biomaterials

- Favorable Response
  - Tissue attachment
- Adverse Responses
  - Contraction
  - Reaction to particles; tissue destruction
- Passive Response

Breast Implant Position and “Capsular Contraction”

Images removed due to copyright restrictions.

Contracted Fibrous Tissue Capsule

Boston Globe, July 22, 1991

Food and Drug Administration
Breast Implant Complications

Photographs of
Breast Implant Complications
http://www.fda.gov/cdrh/breastimplants/breast_implants_photos.html

FDA has developed this website for displaying photographs and/or illustrations of breast implant complications.

This website is not intended to be photographic representation of all breast implant complications. FDA will continue to add photographs and/or illustrations of complications associated with saline-filled and silicone gel-filled implants as they become available.

You should refer to the breast implant consumer handbook, which is available on the FDA breast implant website at http://www.fda.gov/cdrh/breastimplants/ for a description of potential breast implant complications.

http://www.fda.gov/cdrh/breastimplants/breast_implants_photos.html

BREAST IMPLANTS
Capsular Contracture

Capsular contracture occurs when the scar tissue or capsule that normally forms around the implant tightens and squeezes the implant. It may be more common following infection, hematoma (collection of blood), and seroma (collection of watery portion of blood). There are four grades of capsular contracture.

The Baker grading is as follows:

I the breast is normally soft and looks natural

II the breast is a little firm but looks normal

III the breast is firm and looks abnormal (visible distortion

IV the breast is hard, painful, and looks abnormal (greater distortion)

Additional surgery may be needed to correct the capsular contracture. This surgery ranges from removal of the implant capsule tissue to removal (and possibly replacement) of the implant itself. Capsular contracture may happen again after this additional surgery.

BREAST IMPLANTS
Capsular Contracture

Photo removed due to copyright restrictions.

Capsular contraction

Photograph shows Grade IV capsular contracture in the right breast of a 29-year-old woman seven years after subglandular (on top of the muscle and under the breast glands) placement of 560cc silicone gel-filled breast implants.

BREAST IMPLANTS Capsular Contracture

Removed implant: viewing the outside of the fibrous capsule

Implant

Capsule

Inside of the fibrous capsule

Implant

Photos removed due to copyright restrictions.
See http://www.implantforum.com/capsular-contracture/

http://www.implantforum.com/capsular-contracture/

BREAST IMPLANTS
Capsular Contracture

What is Capsular Contracture?

Scar tissue that forms around the implant which causes the breasts to harden (similar to what a contracted muscle feels like) as the naturally forming scar tissue around the implant tightens and squeezes it. While capsular contracture is an unpredictable complication, it is also the most common complication of breast augmentation.

How can Capsular Contracture be prevented?

Textured implants help deter contracture because of their rough surface which is intended to discourage a hard capsule from forming.

Under the muscle (sub-pectoral or 'partial sub-muscular') placement of the implant reduces risk of capsular contracture by an average of 8 - 10%. Whereas over the muscle (in front of the muscle or 'sub-mammary') has 10 - 25% or more chance of capsule contracture.

CAUSE OF CAPSULAR CONTRACTION

Myofibroblasts, and the regulatory protein TGF-β, were found in the contracted capsules around silicone breast implants but not in non-contracted capsules. Mature skin scar tissue did not contain TGF-β or myofibroblasts.

Lossing C, and Hansson HA,
Plast Reconstr Surg 91:1277 (1993)

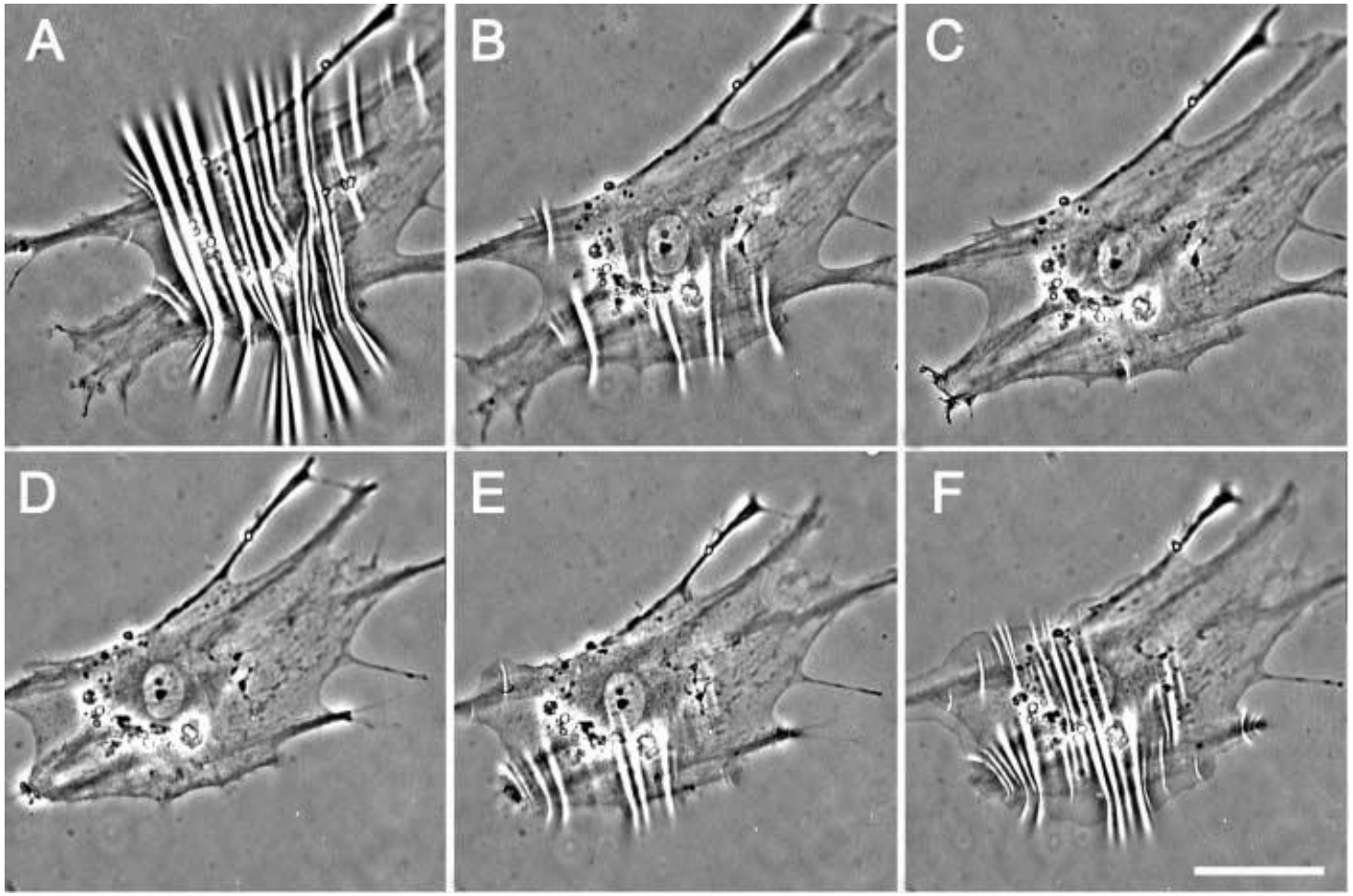
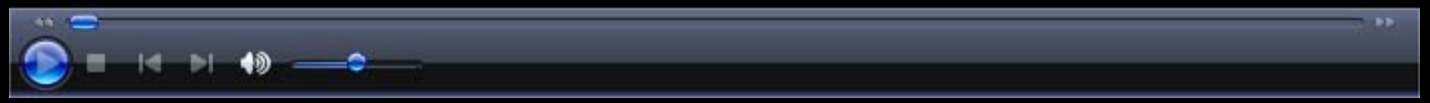


Figure 3. **SMA-FP inhibits the tension exerted by LFs on silicone substrates.** (A) Untreated LFs produce wrinkles on deformable silicone substrates during 60 min recording. (B) Wrinkles decrease in number already 15 min after treatment with SMA-FP and completely disappear after 30 min (C). (D) 10 min after removal of the SMA-FP by repeated washing, LFs contract again followed by gradual wrinkle reformation after 30 (E) and 60 min (F). Bar, 50 μm. Also see the video available at http://www.jcb.org/cgi/content/full/jcb.200201049/DC1.

Hinz B, *et al.*, J Cell Biol 157:657 (2002)

α-smooth muscle actin-fusion peptide (SMA-FP) inhibits the tension exerted by lung fibroblasts on silicone substrates. After washing our of the FP, cells contract again.

Video: See http://jcb.rupress.org/content/suppl/2002/05/03/jcb.200201049.DC1/1.html



Hinz B, *et al.*, J Cell Biol 157:657 (2002)

The Journal of Cell Biology, Volume 157, Number 4, May 13, 2002 657–663

The NH_2-terminal peptide of α–smooth muscle actin inhibits force generation by the myofibroblast in vitro and in vivo

Boris Hinz, Giulio Gabbiani, and Christine Chaponnier
Department of Pathology, Centre Médical Universitaire, University of Geneva, 1211 Geneva 4, Switzerland

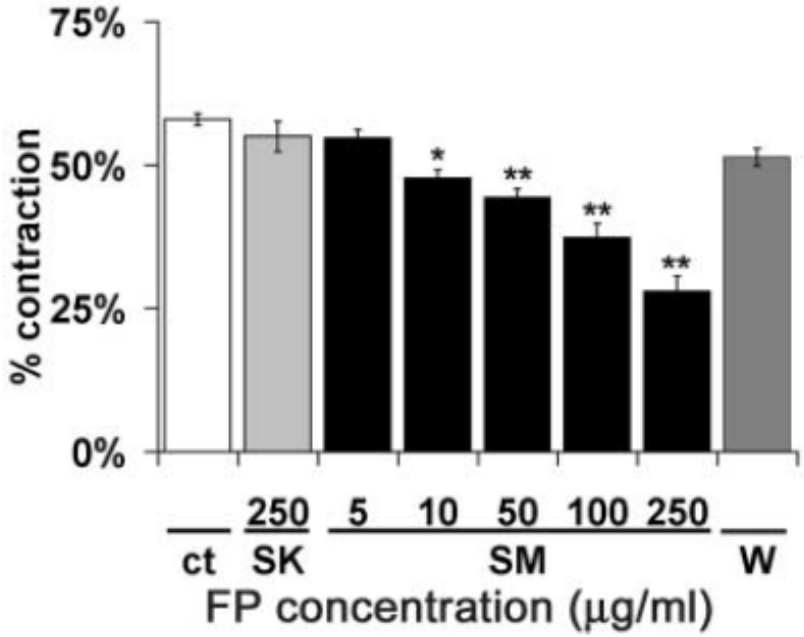
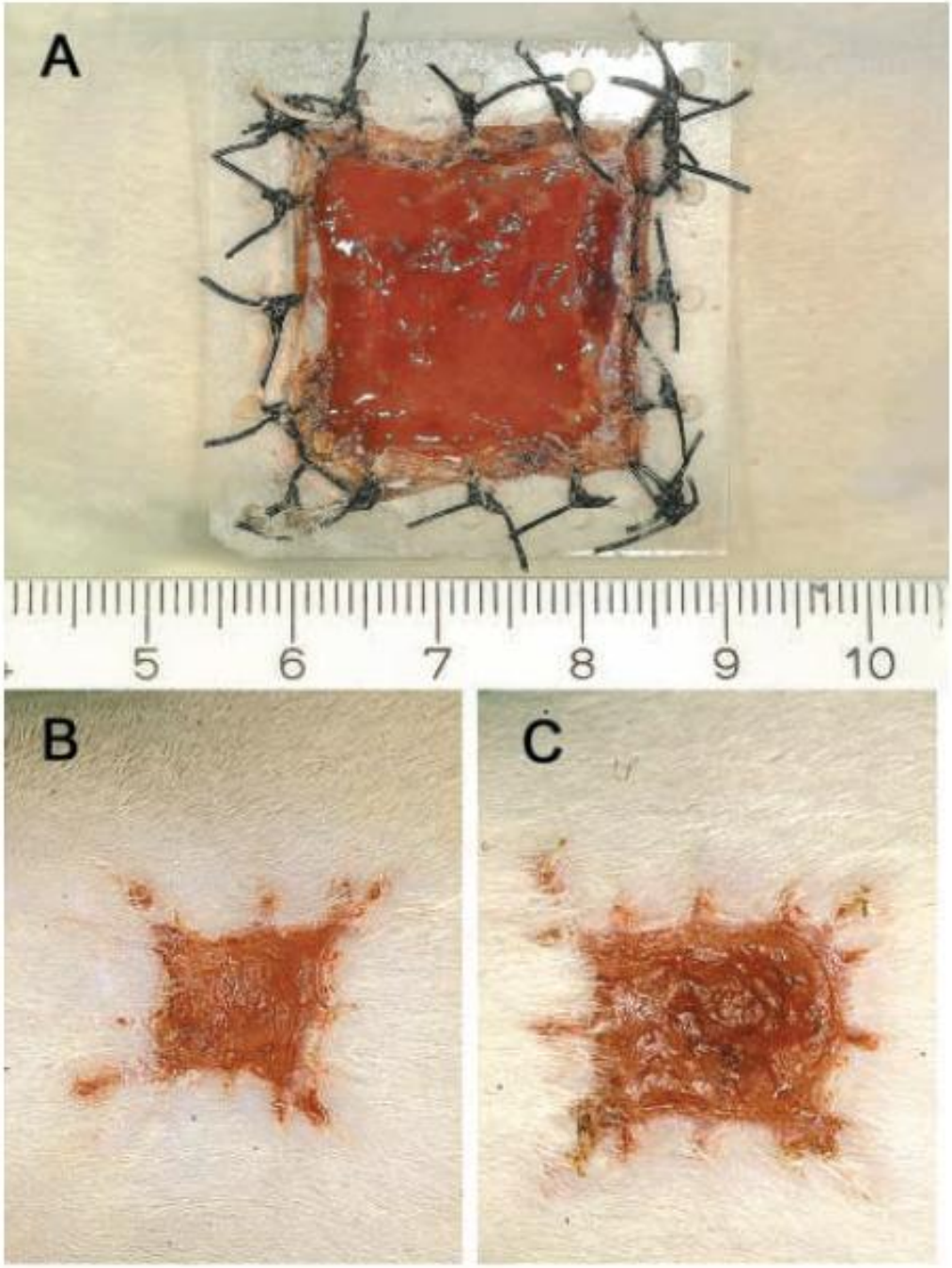


Figure 4. **SMA-FP inhibits LF-mediated contraction of collagen lattices.** Attached collagen lattices were treated with FPs for 30 min and released; their diameter, measured after another 30 min, was normalized to the diameter before release (equals % contraction). Compared with untreated control lattices, (ct) SKA-FP (SK) has no effect on lattice contraction, whereas SMA-FP (SM) reduces contraction dose dependently; washing out SMA-FP before release (W) reverses this effect. $^{*}p \leq 0.01$ and $^{**}p \leq 0.001$ compared with control.



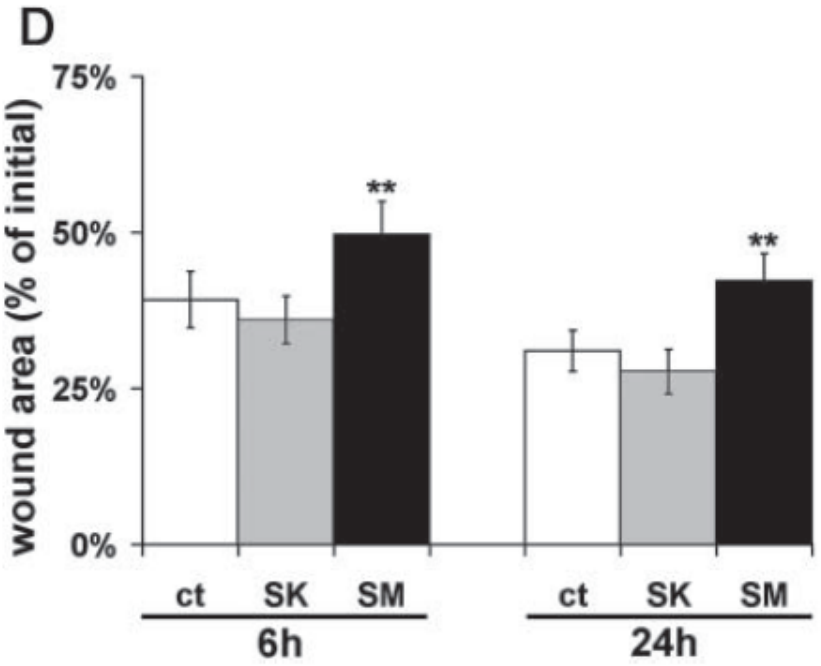


Figure 8. **SMA-FP reduces in vivo wound contraction.** (A) A representative full thickness wound on the rat dorsal region was subjected to mechanical tension by splinting; the frame was left in place for 10 d. The scab was removed 8 d after wounding, and wound tissue was treated with FPs in carrier gel or with carrier gel only. Treatment was repeated on the ninth and tenth day after wounding. (B) 24 h after splint removal, the wound treated with SKA-FP exhibits an important surface reduction comparable to that of untreated controls. (C) The wound treated with SMA-FP exhibits a significantly less important reduction. (D) Wound area was measured 6 and 24 h after splint removal and normalized to the initial wound area. Mean values were calculated using 20 animals per experimental condition. ct, carrier gel only; SK, SKA-FP; SM, SMA-FP. $^{**}p \leq 0.001$ compared with control.

Formation and Function of the Myofibroblast during Tissue Repair

Journal of Investigative Dermatology (2007), Volume 127

Boris Hinz[1]

Image removed due to copyright restrictions.
Figure 1, regulation of α-SMA transcription in myofibroblasts.
http://dx.doi.org/doi:10.1038/sj.jid.5700613

BREAST IMPLANTS
Capsular Contracture

How can Capsular Contracture be prevented?

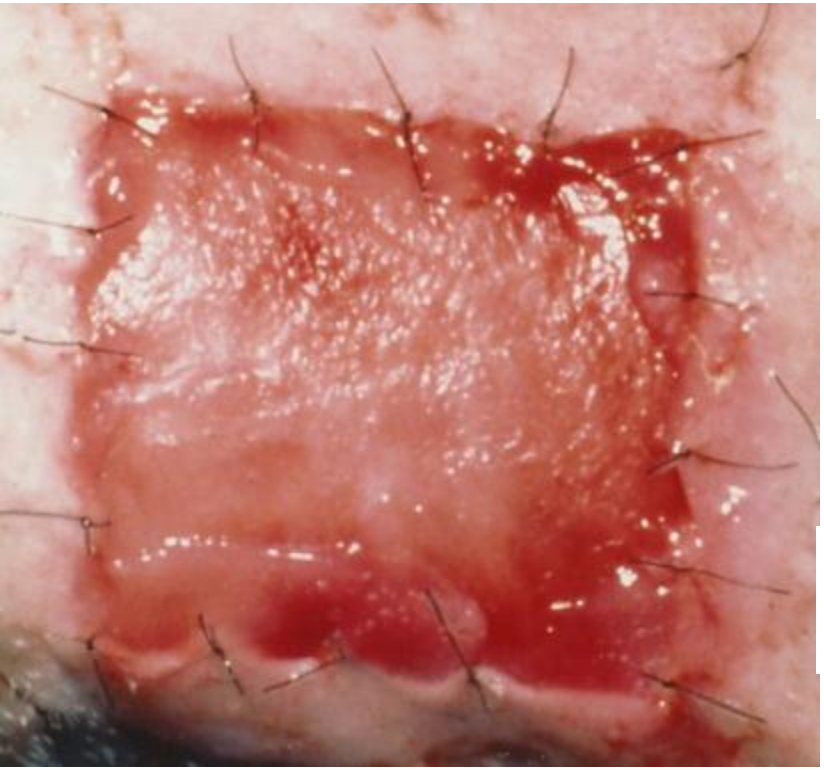
Massage and or compression. This is usually only done with smooth implants and may be suggested for a period between a few weeks to as long as you have your implants. Do not massage bruises!

The "no-touch" technique. This method includes meticulously rewashing surgical gloves before handling any instrument and implants. Only the head surgeon touches the implant, using a unique Teflon cutting board and immediately inserting the implant underneath the muscle. All of these measures help ensure that no foreign substance attach themselves to the implant, which could inflame the surrounding tissue and cause complications such as capsular contracture.

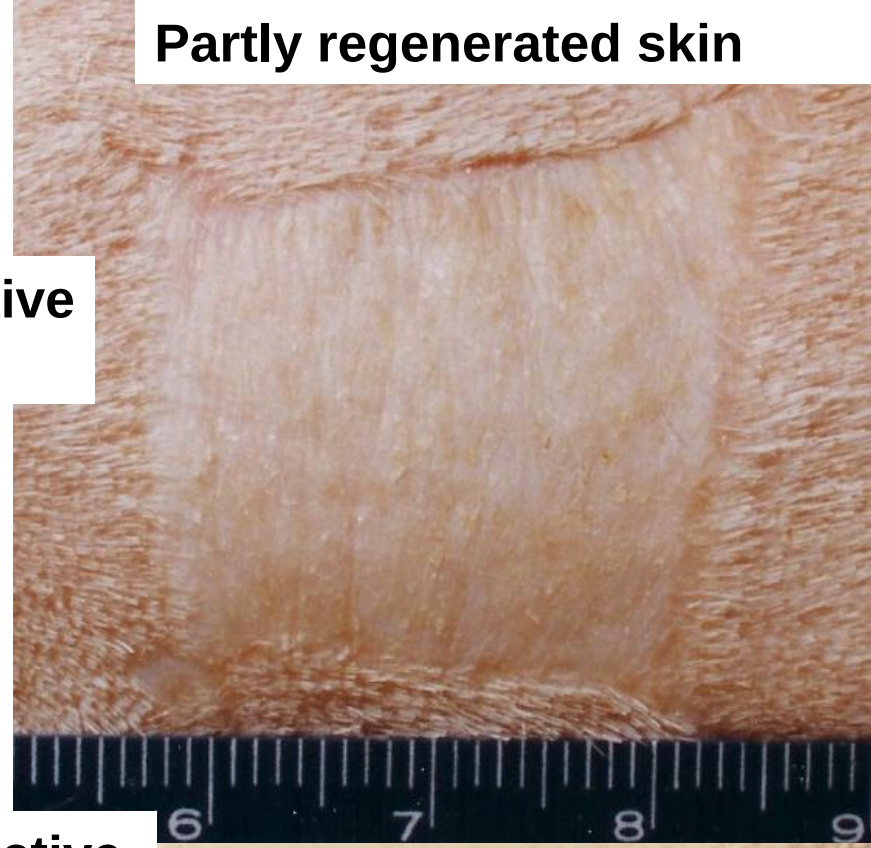
Burn patient has closed severe skin wounds in neck partly by contraction and partly by scar formation

Image removed due to copyright restrictions.

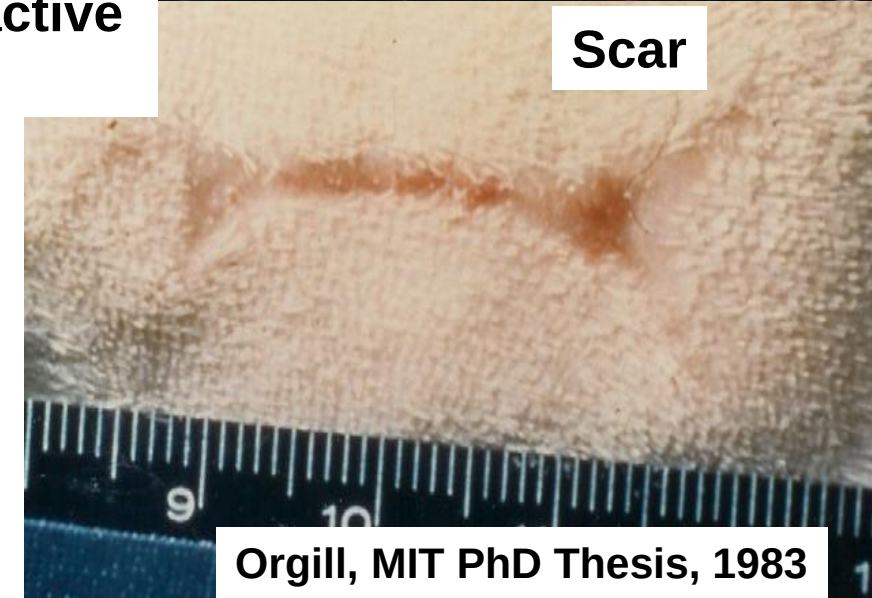
Spontaneous contraction and scar formation in burn victim



KC + active scaffold



KC + inactive scaffold

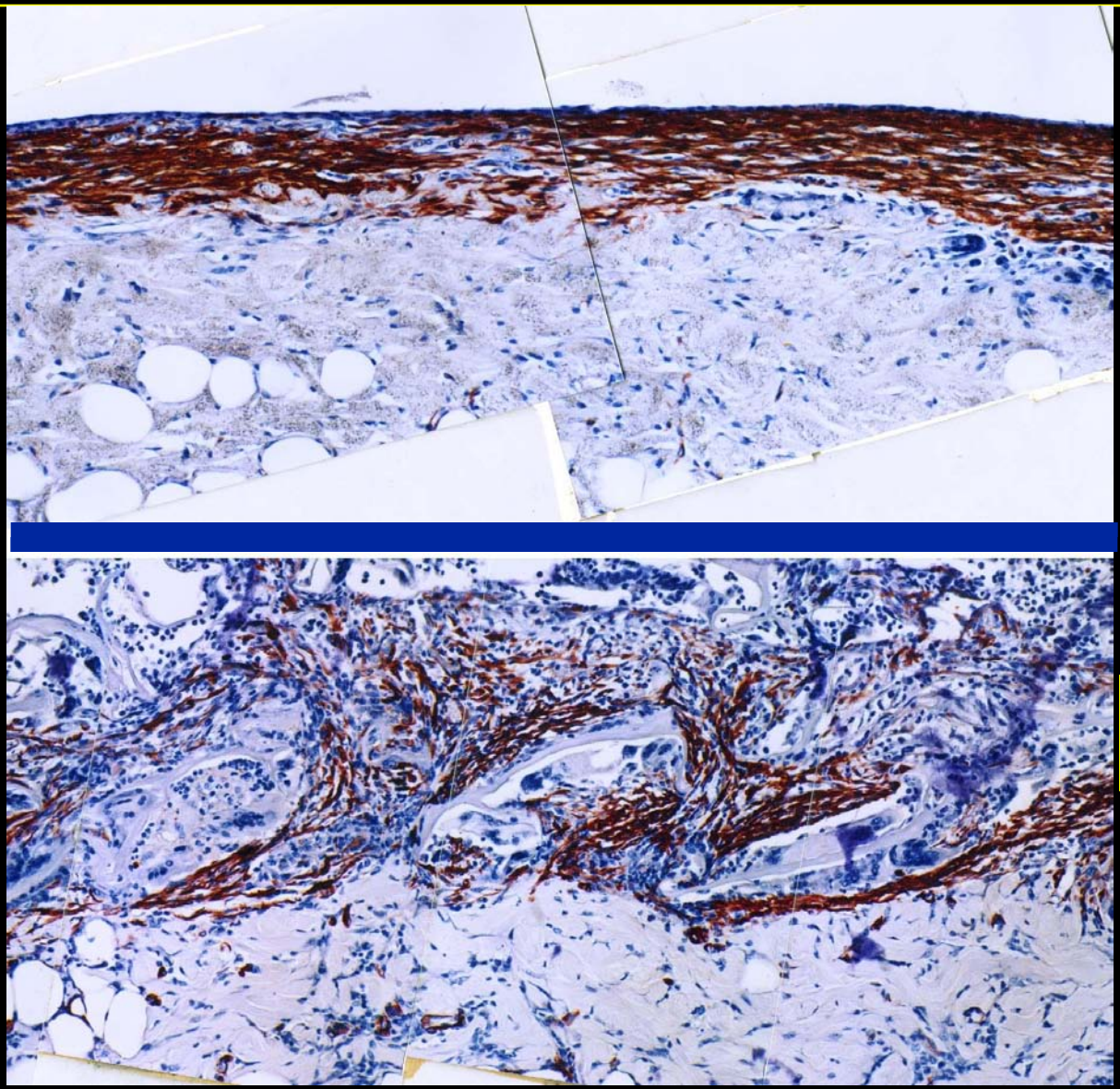


Full-thickness skin wound (guinea pig) grafted with keratinocytes (KC) seeded in an active or inactive scaffold

Collagen-GAG Regeneration Templates

Images removed due to copyright restrictions.
Cover and photo from article: “Unmasking Skin,” National Geographic, Nov. 2002.

α-Smooth Muscle Actin-Containing Fibroblasts Myofibroblasts (day 10)

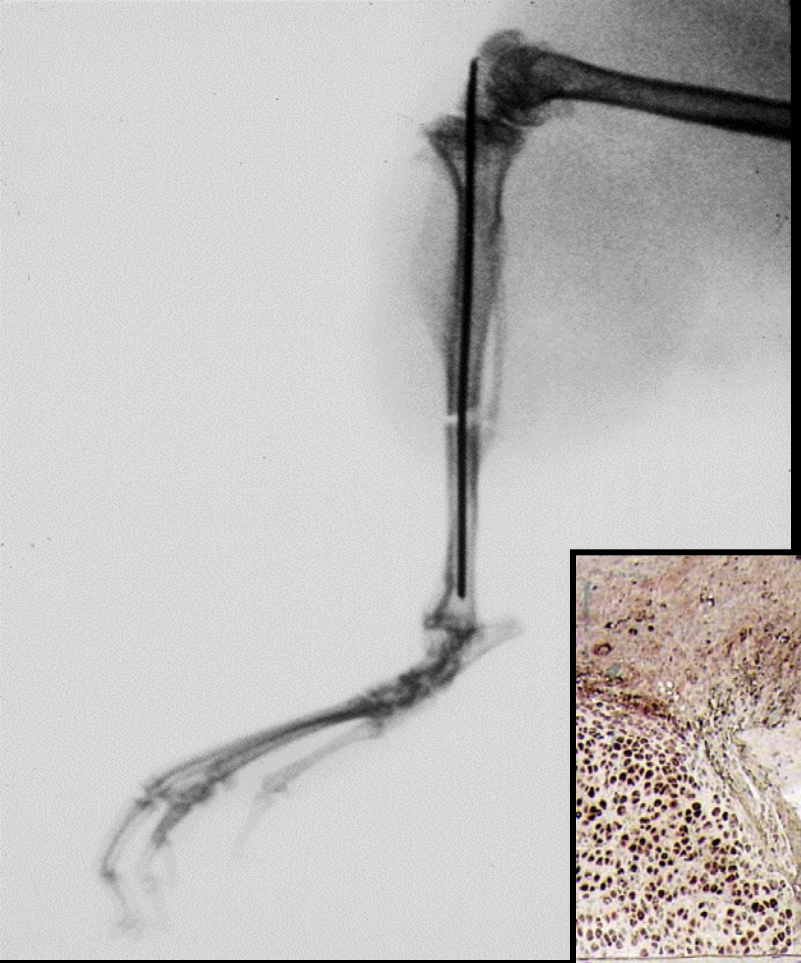


Ungrafted

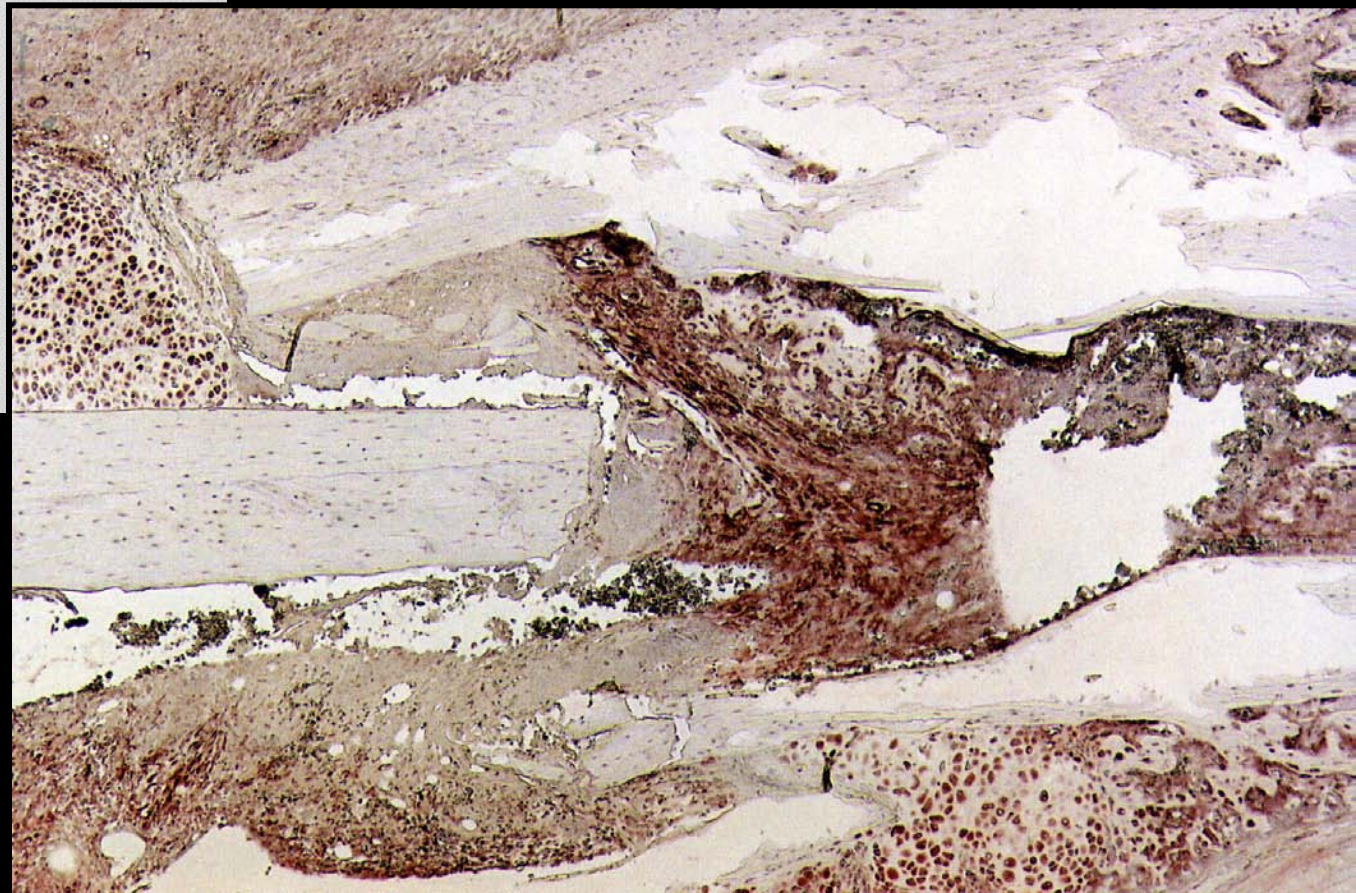
Grafted

IV Yannas, *et al.*

Mouse Tibia (Closed) Fracture Model

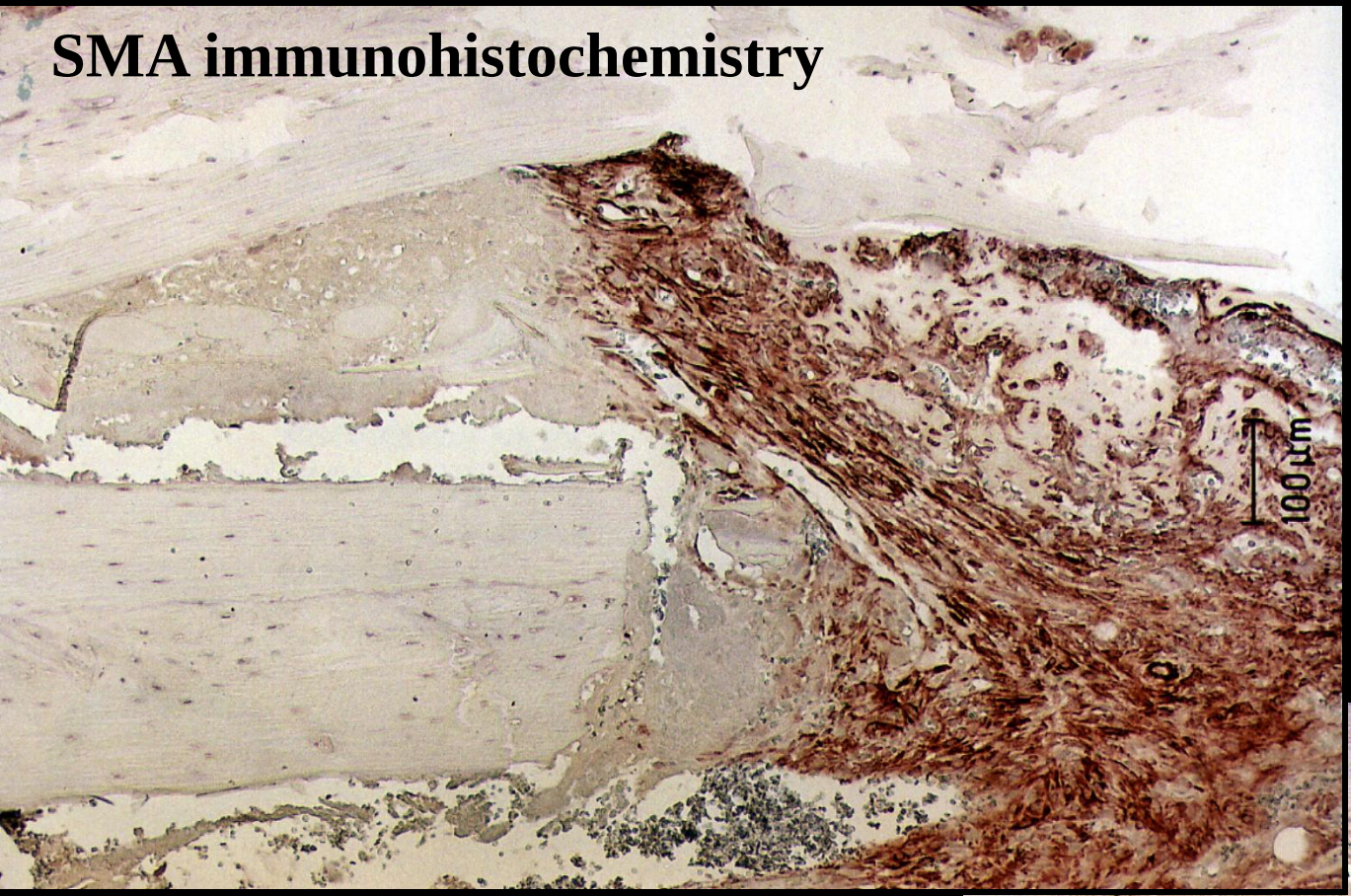


B. Kinner, *et al*., Bone 2002;30:738

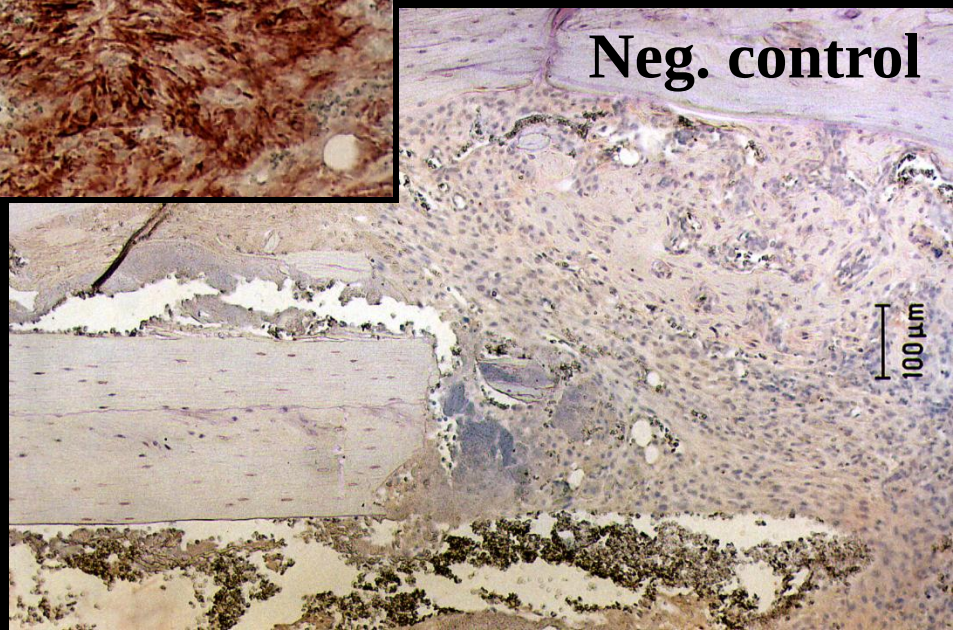


3 weeks post-fracture

Mouse Tibia (Closed) Fracture Model

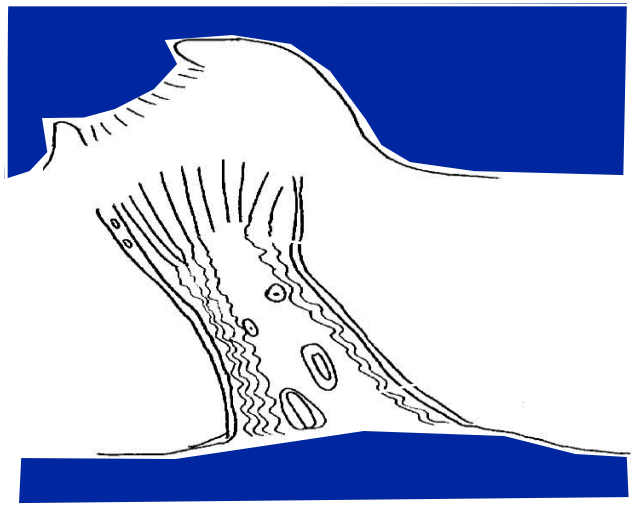


3 weeks post-fracture

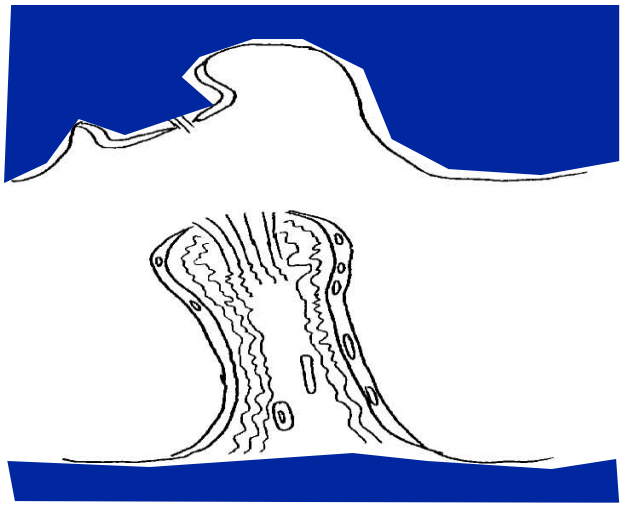


B. Kinner, *et al*., Bone 2002;30:738

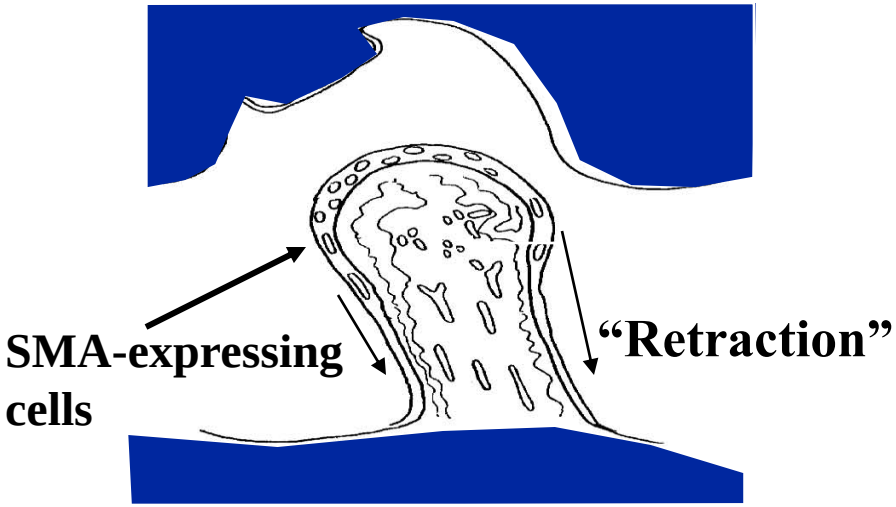
Histologic Changes in the Human ACL after Rupture



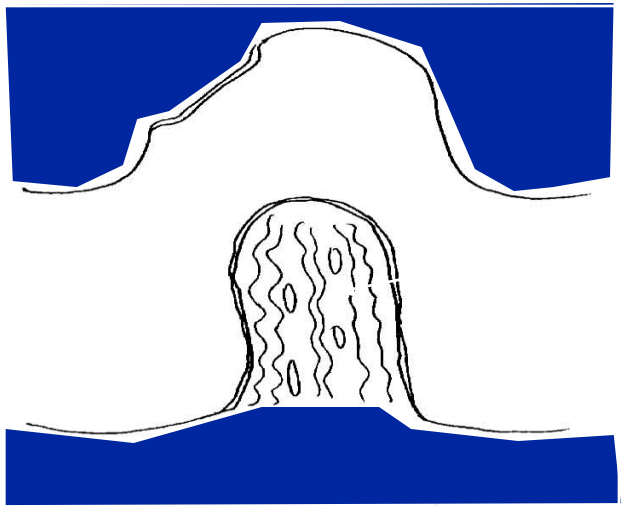
A. Inflammation



B. Epiligamentous Regeneration



C. Proliferation



D. Remodeling

See Murray, M., S. Martin, T. Martin, and M. Spector. *J. Bone Jt. Surg*., 2000;82-A:1387

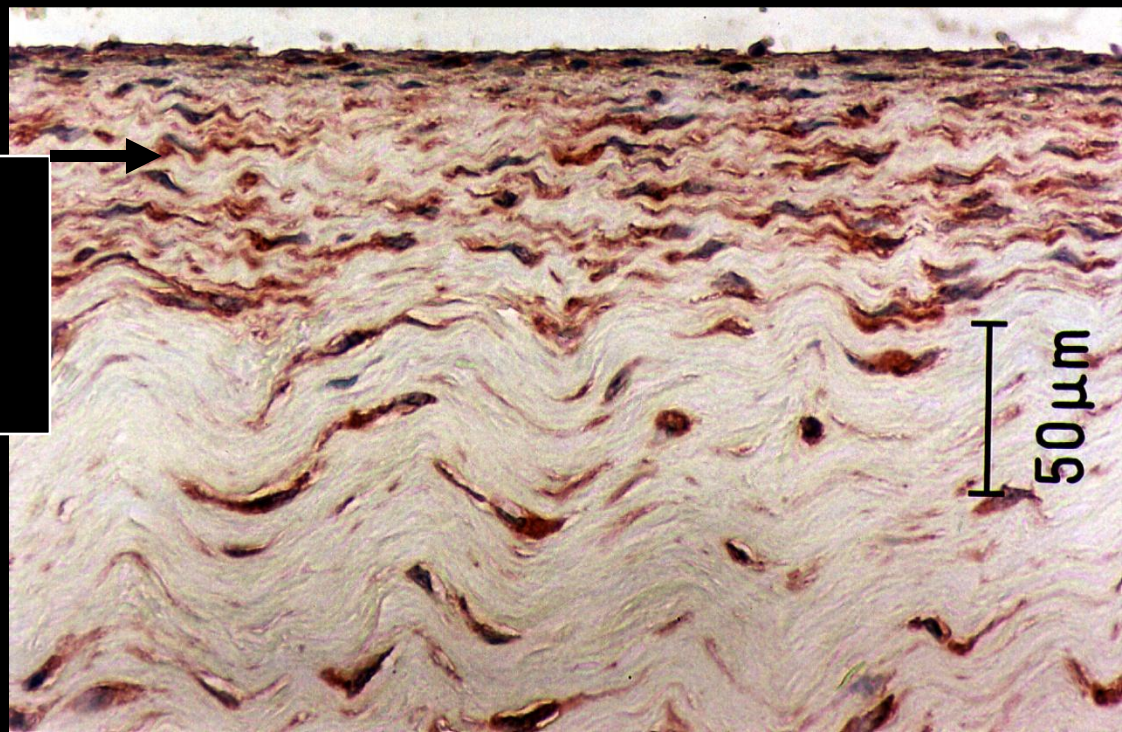
Ruptured Human Anterior Cruciate Ligaments

← **Blood Vessel**

Image removed due to copyright restrictions.
See Fig 5 in Murray, M., S. Martin, T. Martin,
and M. Spector. *J Bone Jt Surg* 82-A (2000): 1387.

Evidence supporting the hypothesis that SMA-enabled contraction is responsible for retraction of the ruptured ends.

Crimped morphology of SMA-containing (red) cells consistent with contraction. Imparting crimp to matrix?

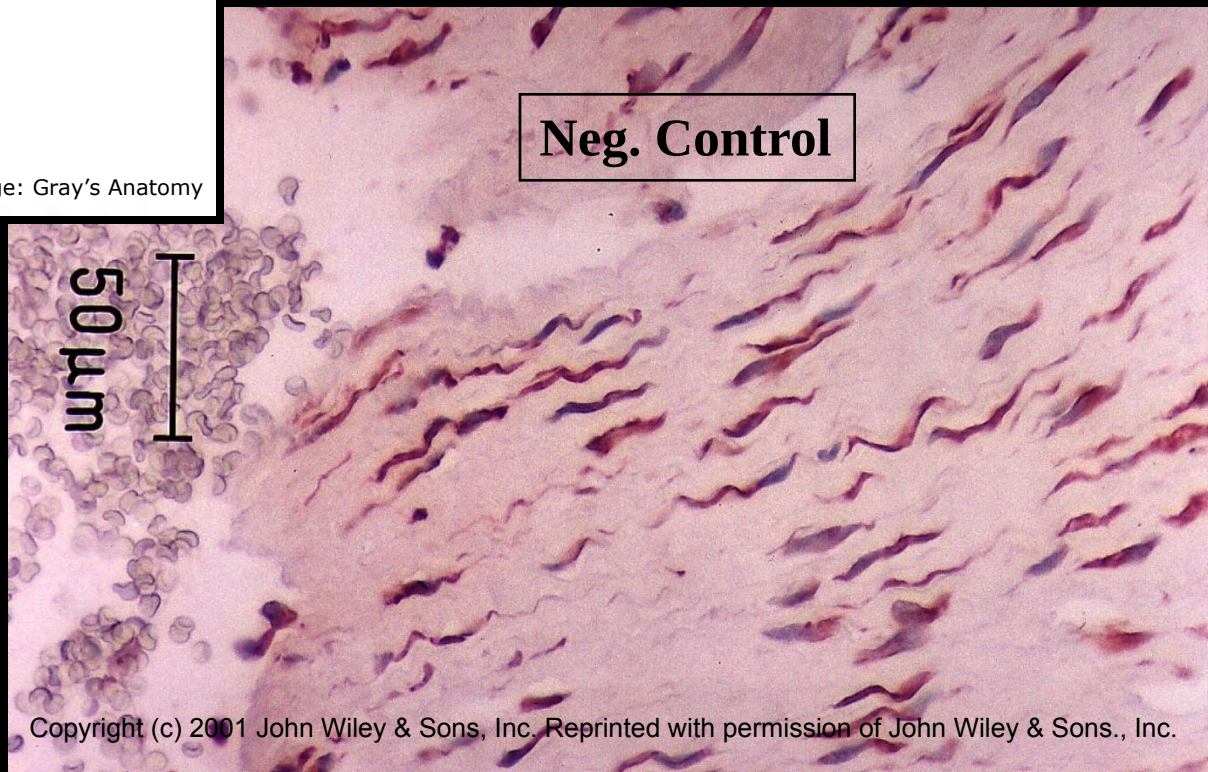


Murray, M., S. Martin, T. Martin, and M. Spector. *J. Bone Jt. Surg.*, 2000;82-A:1387

Ruptured Human Rotator Cuff

Image: Gray's Anatomy

Is SMA-enabled contraction responsible for retraction of the ruptured ends?

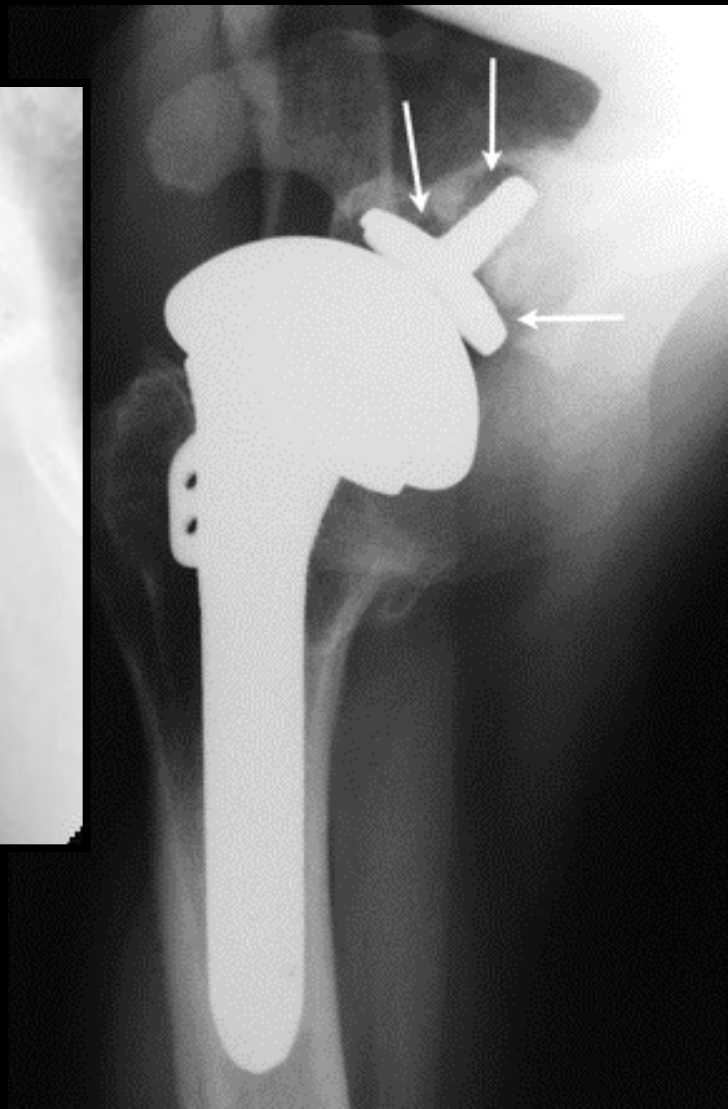


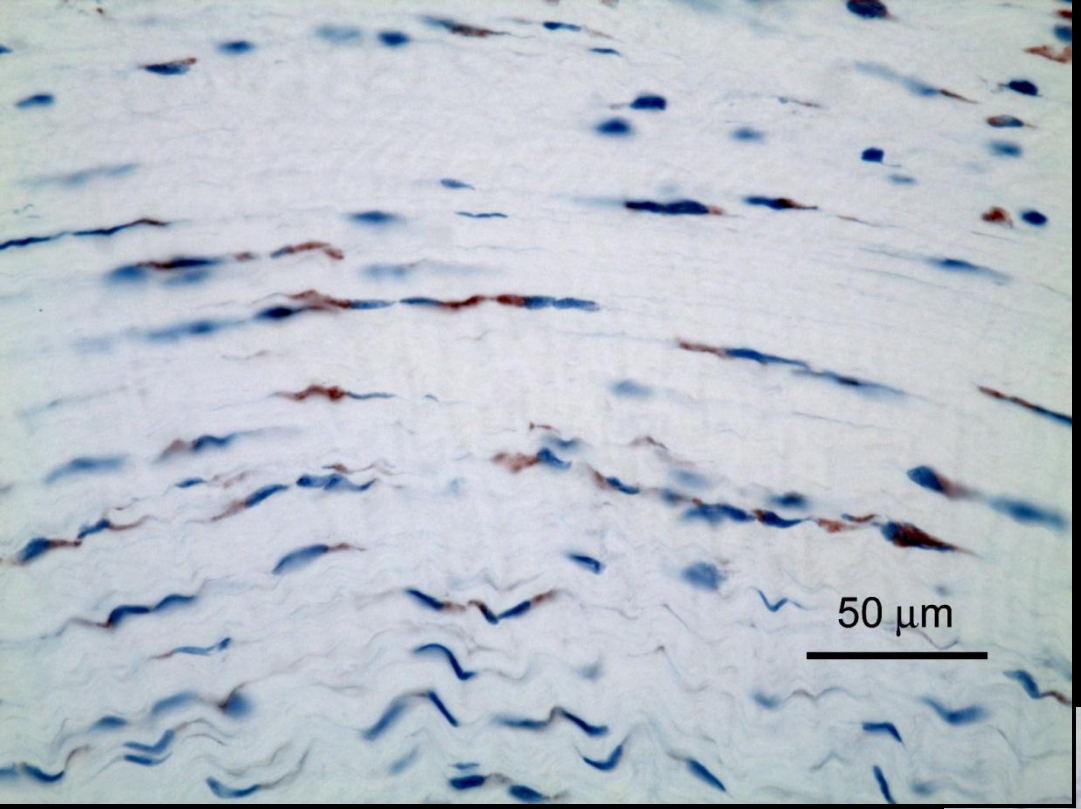
J. Premdas, *et al.*
JOR, 2001;19:221-228

Tissue was resected during revision of symptomatic, non-cemented, glenoid components of Kirschner-IIc total shoulder arthroplasty

Medical illustration of shoulder joint removed due to copyright restrictions.

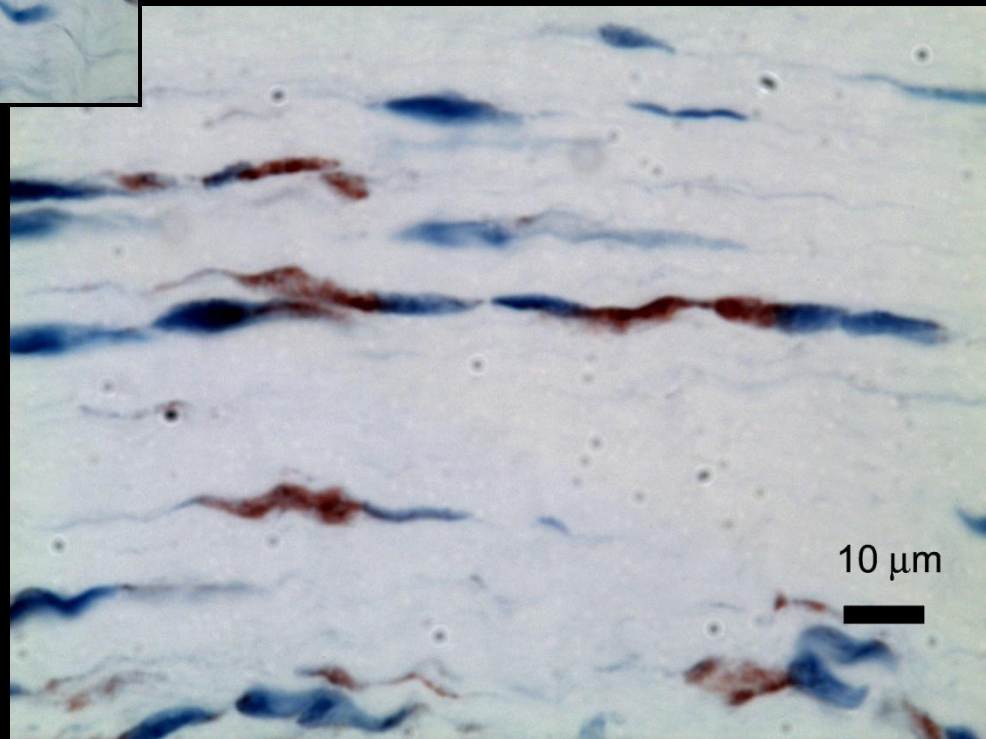
Shoulder





- **Scar-like fibrous tissue around a loose shoulder prosthesis.**
- **Many of the fibroblasts contain α-smooth muscle actin (red) indicating that they are myofibroblasts.**

T. Funakoshi

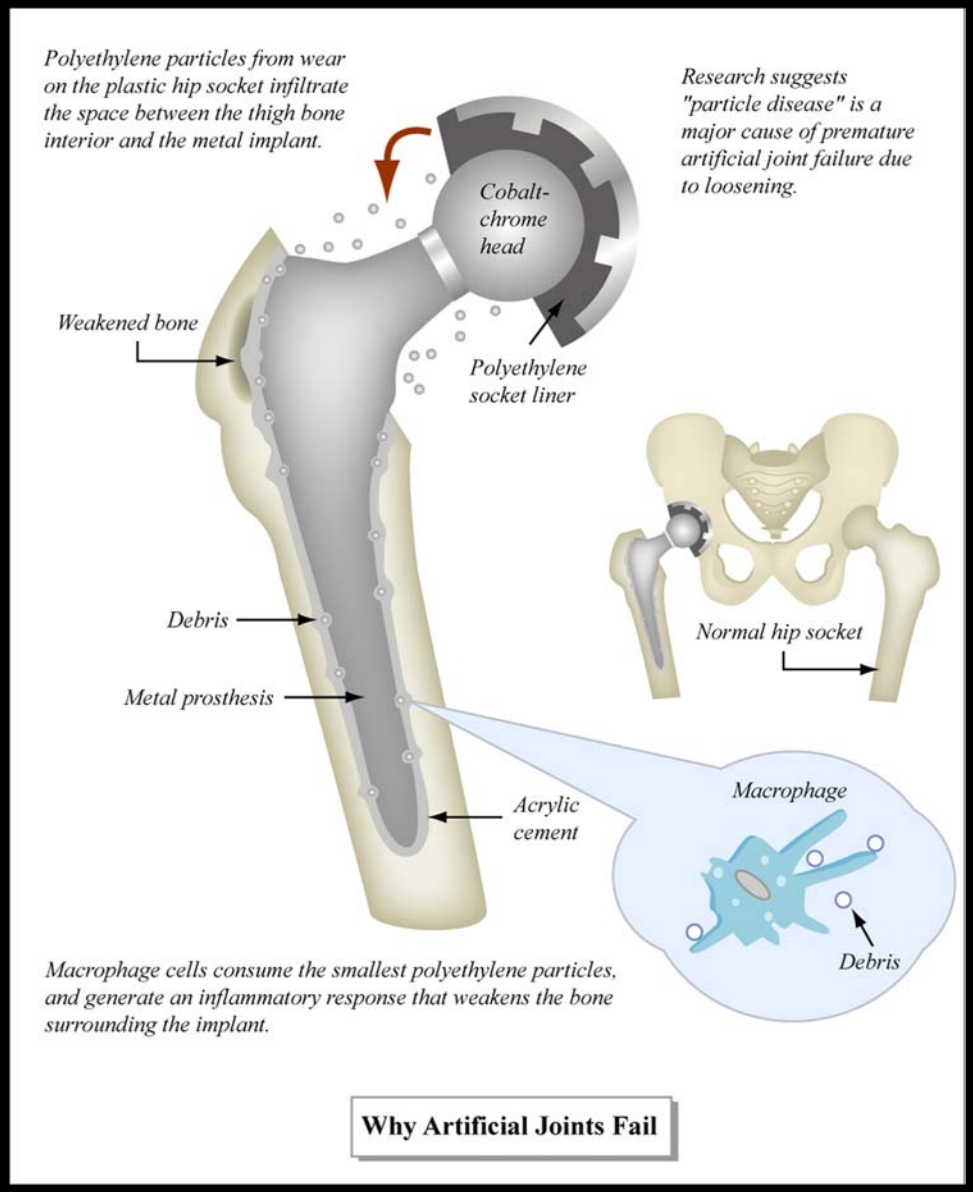


BIOMATERIALS-TISSUE INTERACTIONS

Permanent Biomaterials

- Favorable Response
  - Tissue attachment
- Adverse Responses
  - Contraction
  - Reaction to particles; tissue destruction
- Passive Response

"Small Particle Disease"
Particles Released From Implants



Images removed due to copyright restrictions.

- Article about risks of silicone breast implants: *Newsweek*, April 29 1991.
- Image of jaw implant.
- Article: "Small particles Add Up to Big Disease Risk." *Science* 295 (2002): 1994.

Figure by MIT OpenCourseWare. Sources: University of Pittsburgh and Pittsburgh Post Gazette.

EXAMPLES OF THE USE OF BIOMATERIALS FOR TREATING SPINE PROBLEMS

- Treating a collapsed vertebra: Kyphoplasty
  - Use of self-curing polymethyl methacrylate (PMMA) for restoring vertebral height
  - http://www.spine-health.com/dir/kyph.html
- Spine fusion: Posterior approach with laminectomy
  - http://www.spine-health.com/dir/bonefusion.html
- Treating a degenerative intervertebral disc: Anterior lumbar interbody fusion (ALIF)
  - http://www.spine-health.com/dir/alif.html
- ALIF with a bone growth factor: "Hybrid" approach employing regenerative medicine and permanent replace approaches
- Prosthesis to replace the bone-disc-bone "joint": spinal arthoplasty

Images of INFUSE® Bone Graft (recombinant human bone morphogenetic protein (rhBMP-2) in an absorbable collagen sponge) removed due to copyright restrictions.

BIOMATERIAL-TISSUE INTERACTIONS

- With what tissue is the biomaterial interacting? How do the structure and functions of the tissues differ? (Unit Cell Processes)
  - Connective Tissue
  - Epithelia
  - Muscle
  - Nerve
- What is the normal process of healing ?

WOUND HEALING
Roots of Tissue Engineering

Injury

↓

Inflammation
(Vascularized tissue)

↓

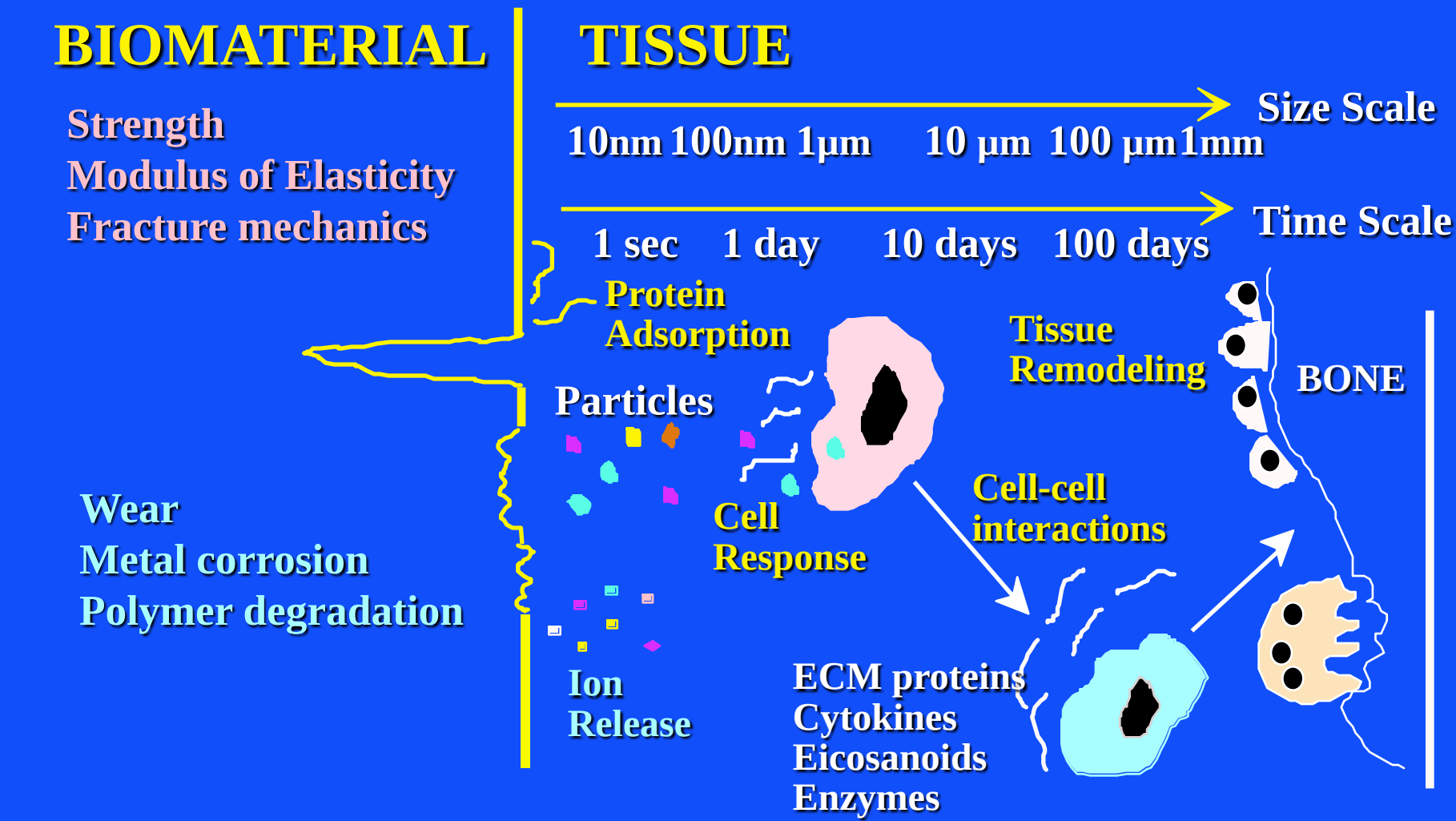
Reparative Process

4 Tissue Categories
Connective Tissue
Epithelium
Nerve
Muscle

Regeneration*
CT: bone
Ep: epidermis
Muscle: smooth
*spontaneous

Repair (Scar)
CT: cartilage
Nerve
Muscle: cardiac, skel.

BIOMATERIALS-TISSUE INTERACTIONS



20.441J / 2.79J / 3.96J / HST.522J Biomaterials-Tissue Interactions

Fall 2009