2.79J/3.96J/20.441J/HST522J
Biomaterials-Tissue Interactions

Prof. Myron Spector

Harvard Medical School

Director, Orthopedics Research Laboratory

Brigham and Women's Hospital

Prof. Ioannis Yannas

MIT

Departments of Mechanical and Biological Engineering

Fibers and Polymers Laboratory

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INTRODUCTION

- How are biomaterials used?
- Today's brief survey: from organs to cells.

How are biomaterials used?

Today's brief survey: from organ to cell

outline of survey

A. Five Therapies for the Missing Organ

- **Examples of permanent implants**
- **Examples of regenerated organs**

B. Tissue and organ regeneration viewed as processes of chemical synthesis.

C. What is the mechanism of organ regeneration?

D. Cell-matrix interactions.

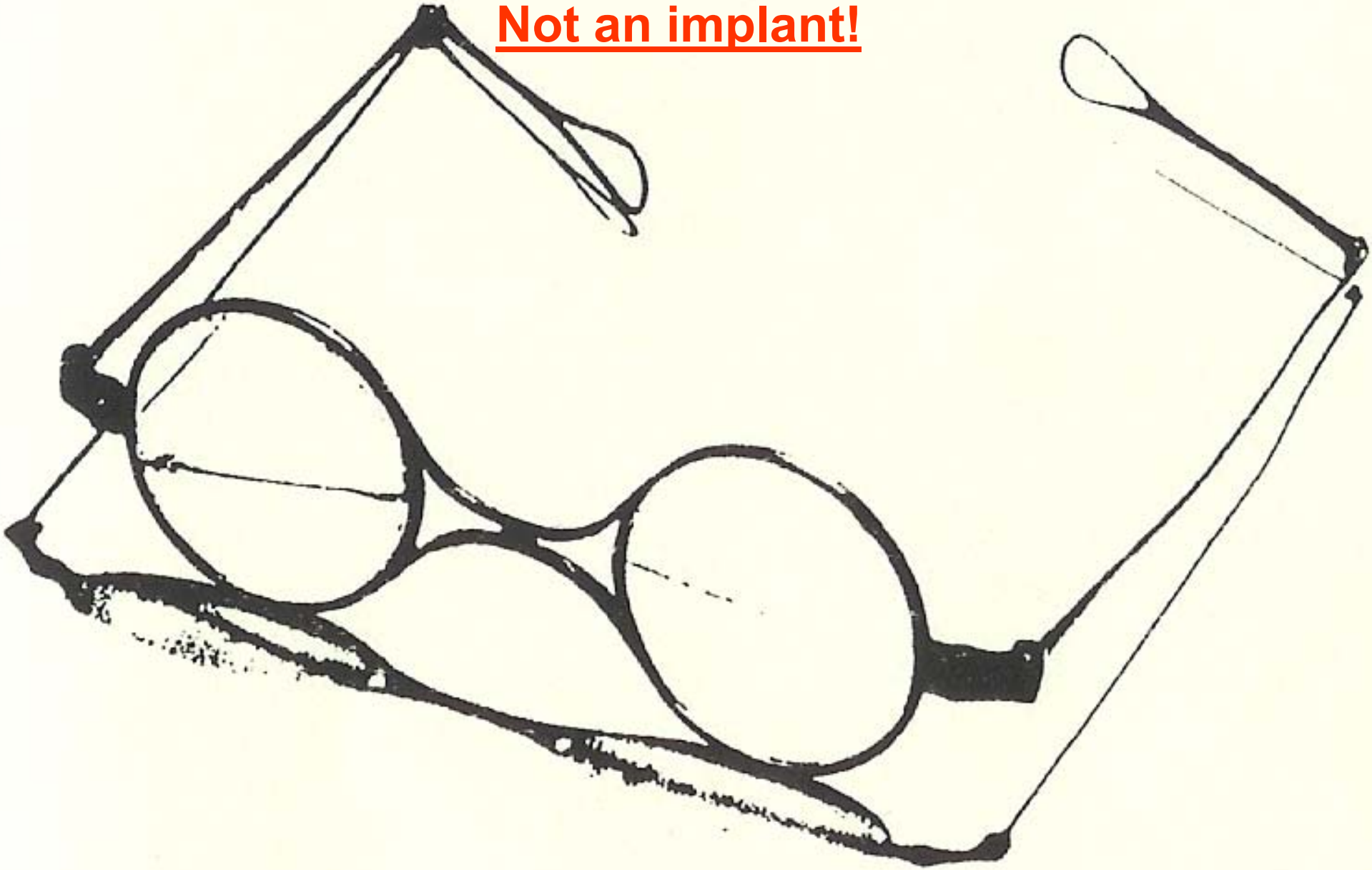
E. The unit cell process.

A. Five Therapies for the Missing Organ

1. Transplantation (e.g., kidney transplant, heart transplant, liver transplant)
2. Autografting (e.g., heart bypass, skin grafting).
3. Permanent implants (e.g., hip prosthesis, pacemaker, breast implant)
4. In vitro synthesis (e.g., epidermis)
5. In vivo synthesis or regeneration (e.g., skin, nerves, conjunctiva). ”Regenerative medicine”.

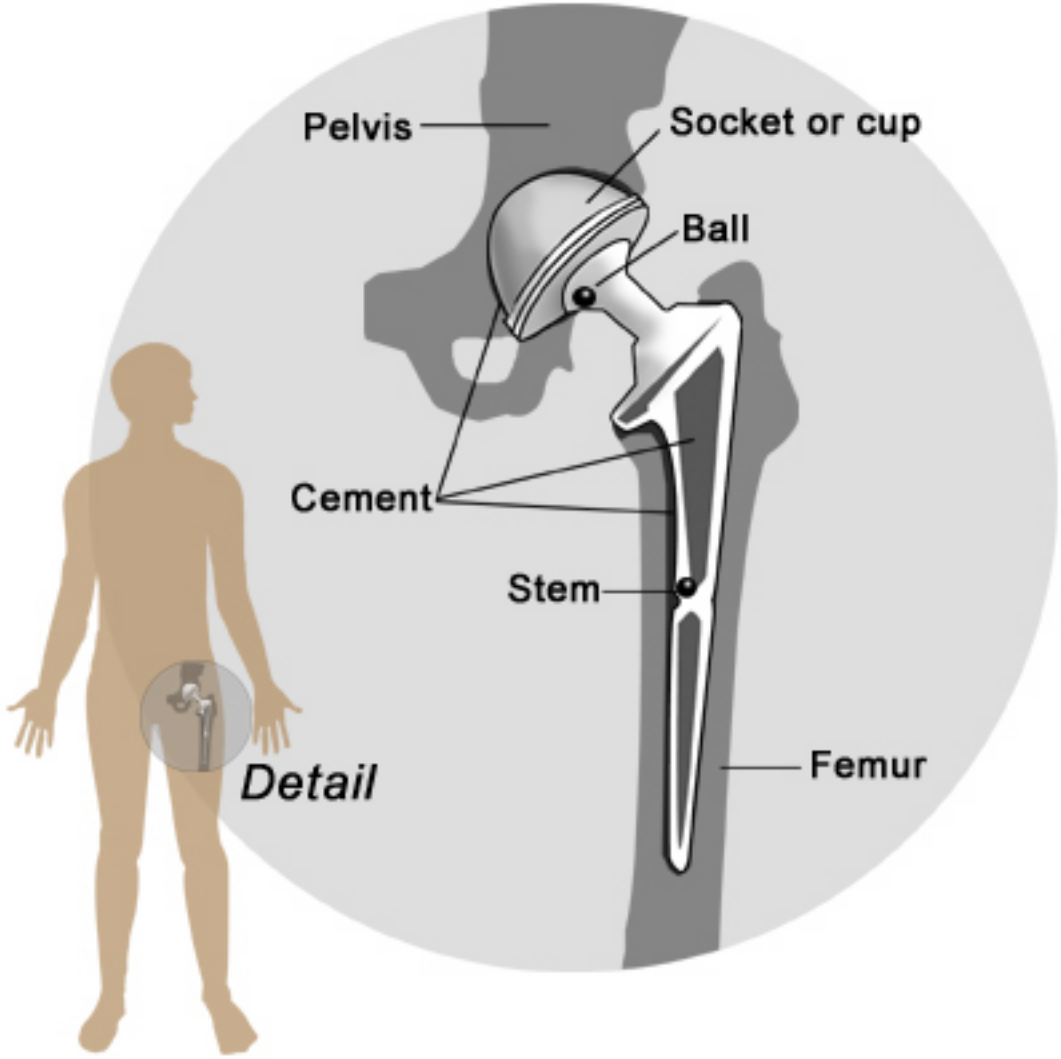
Remarks: Biomaterials are used in therapies #3, 4 and 5.
Tissue engineering includes therapies #4 and 5.

Not an implant!



Schubert's Glasses

Organ Replacement Therapy Class 3 : Example of permanent implant



In total hip replacement, surgeons remove the head of the thigh-bone (femur), and insert in its place a metal ball on a stem, anchored in the femur's marrow cavity. The ball pivots in a hard plastic cup inserted in the old socket in the pelvis.

Figure by MIT OpenCourseWare.

Organ Replacement Therapy Class 3 : Another example of permanent implant

Image removed due to copyright restrictions.
Boston Globe newspaper graphic about FDA approval for the AbioCor artificial heart.

Image removed due to copyright restrictions.
Photo of severe burn victim.

Organ Replacement Therapy Class 5: Examples of regeneration of the injured skin organ

Severely burned victim heals injury by contraction and scar formation

Study of skin regeneration

A device that regenerates skin in burned patients, patients undergoing plastic surgery and treats chronic skin wound patients is currently used clinically

Visualization of device.
Bilayer device to regenerate skin

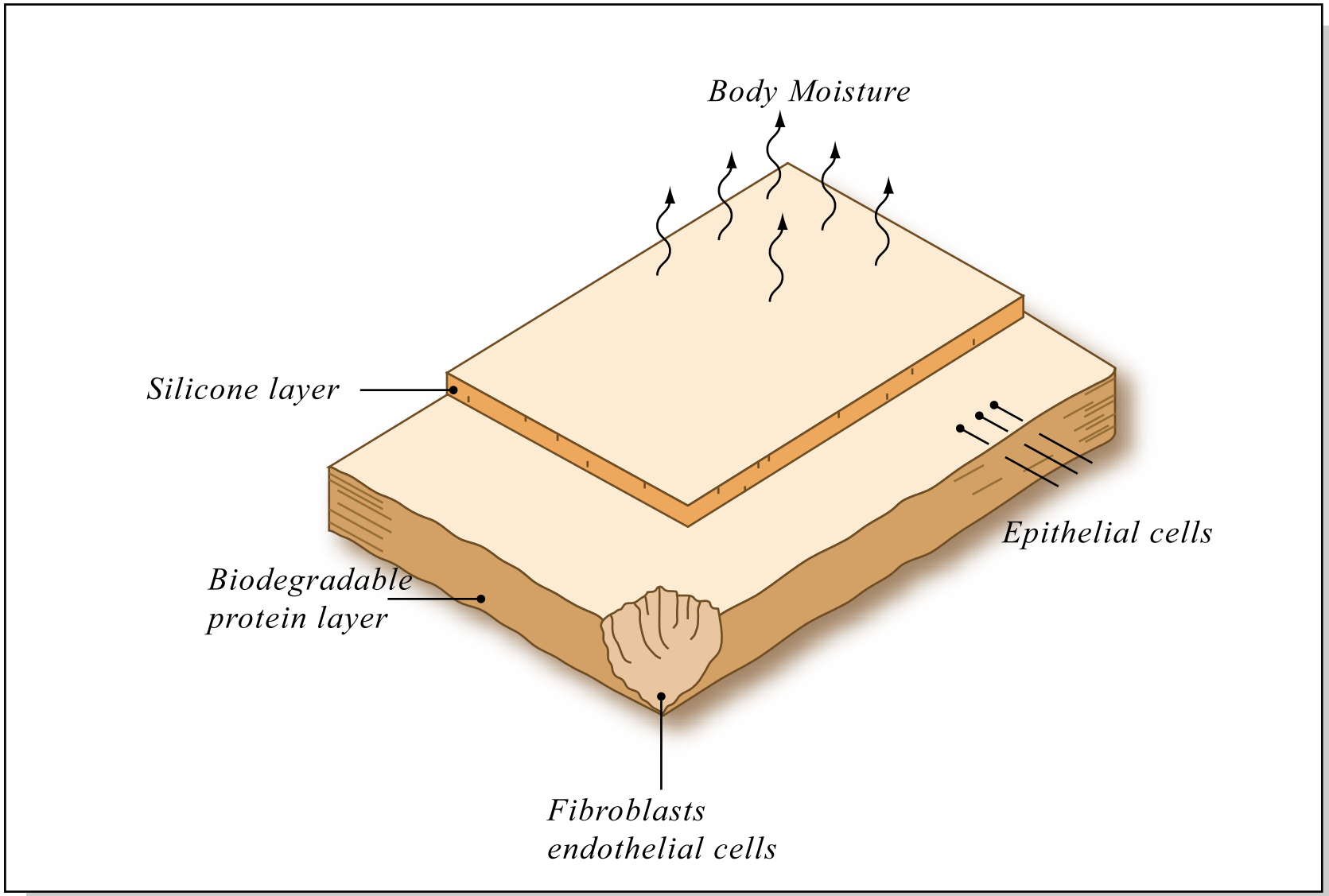


Figure by MIT OpenCourseWare.

Top layer protects wounded site while bottom layer induces regeneration of dermis

Yannas et al., Science, 1982

A case of skin regeneration studied by Dr. Andrew Byrd, Bristol, UK

Burn victim, a female teenager, was treated by 1) excision of burn scar, 2) grafting of a biologically active scaffold (template) and 3) regeneration of skin in place of burn scar

(Several subsequent slides removed due to copyright restrictions.)

Several subsequent slides removed due to copyright restrictions.

1. Left breast failed to develop due to mechanical stresses of scar on it.

2. Surgeon has excised the entire scar around breast generating a deep skin wound

3. Wounds have been grafted with the bilayer device (silicone layer outside; scaffold inside). Side view shows that left breast has now erupted.

4. Top view emphasizes the shiny silicone layer outside.

5. New vascularized skin has grown two weeks after grafting of scaffold. Two-stage procedure: (1) Graft scaffold to regenerate dermis; (2) Graft an epidermal autograft on top of new dermis. “Alligator” pattern disappears later.

Two cases of massively burnt patients (treated by Dr JF Burke, MGH)

1. Six-year-old boy burned massively was treated in upper abdomen with own skin (meshed autograft) and in lower abdomen with template.
2. Middle-aged man burned in industrial fire, lost skin in right side of face was treated with template.

KINETICS OF SKIN SYNTHESIS II.

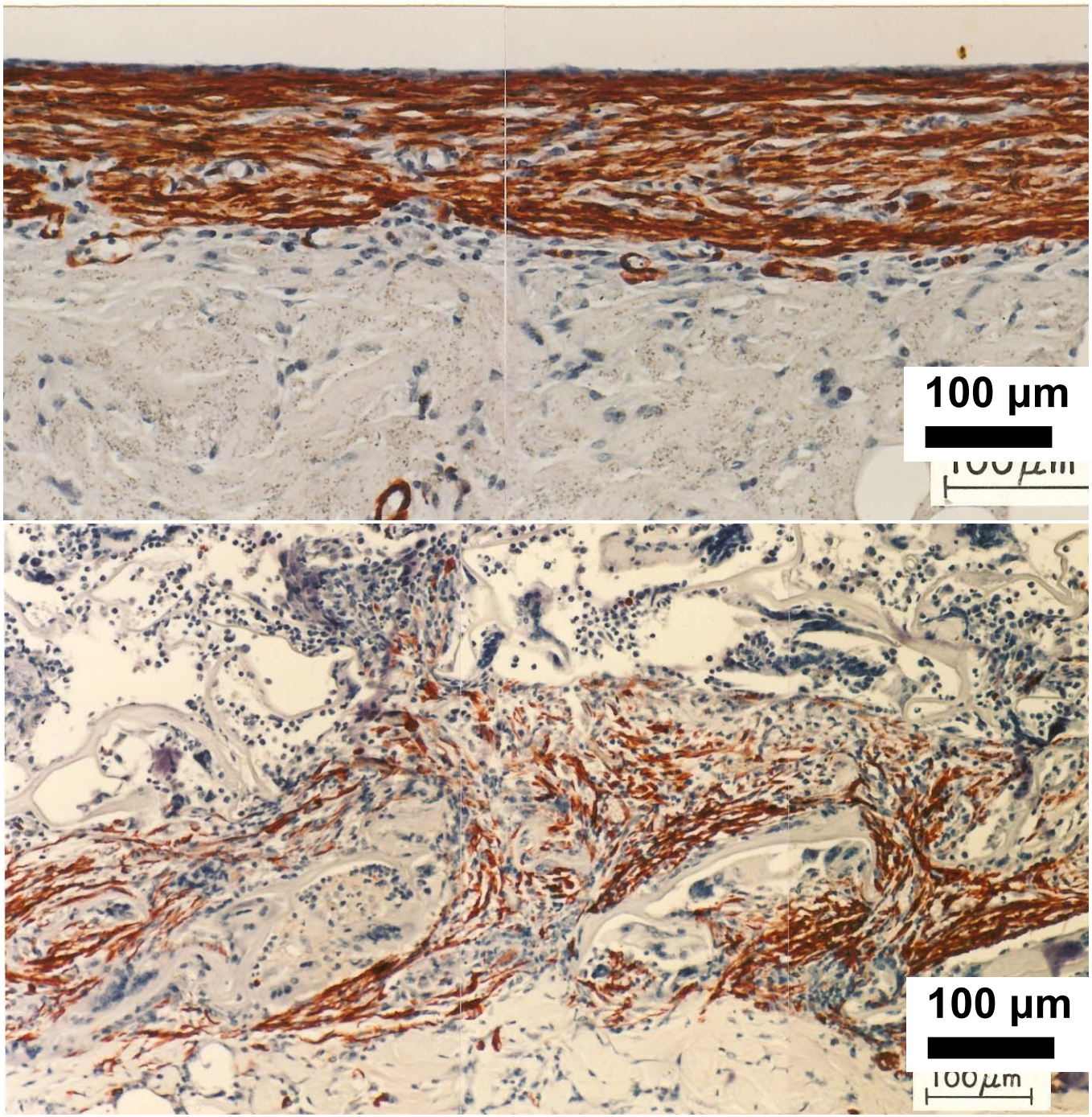
Images removed due to copyright restrictions.

Scaffold degraded; diffuses away

Butler et al., 1998

No scaffold
This wound is contracting vigorously

Scaffold
This wound is not contracting



Contraction blocked by active scaffold.

Troxel, MIT Thesis, 1994

Study of peripheral nerve regeneration

A device that treats nerve paralysis in human limbs by regenerating the injured nerve is currently used in clinics

Regeneration of peripheral nerves in patients with limb paralysis

Rat model for study of nerve regeneration following complete transection of sciatis nerve

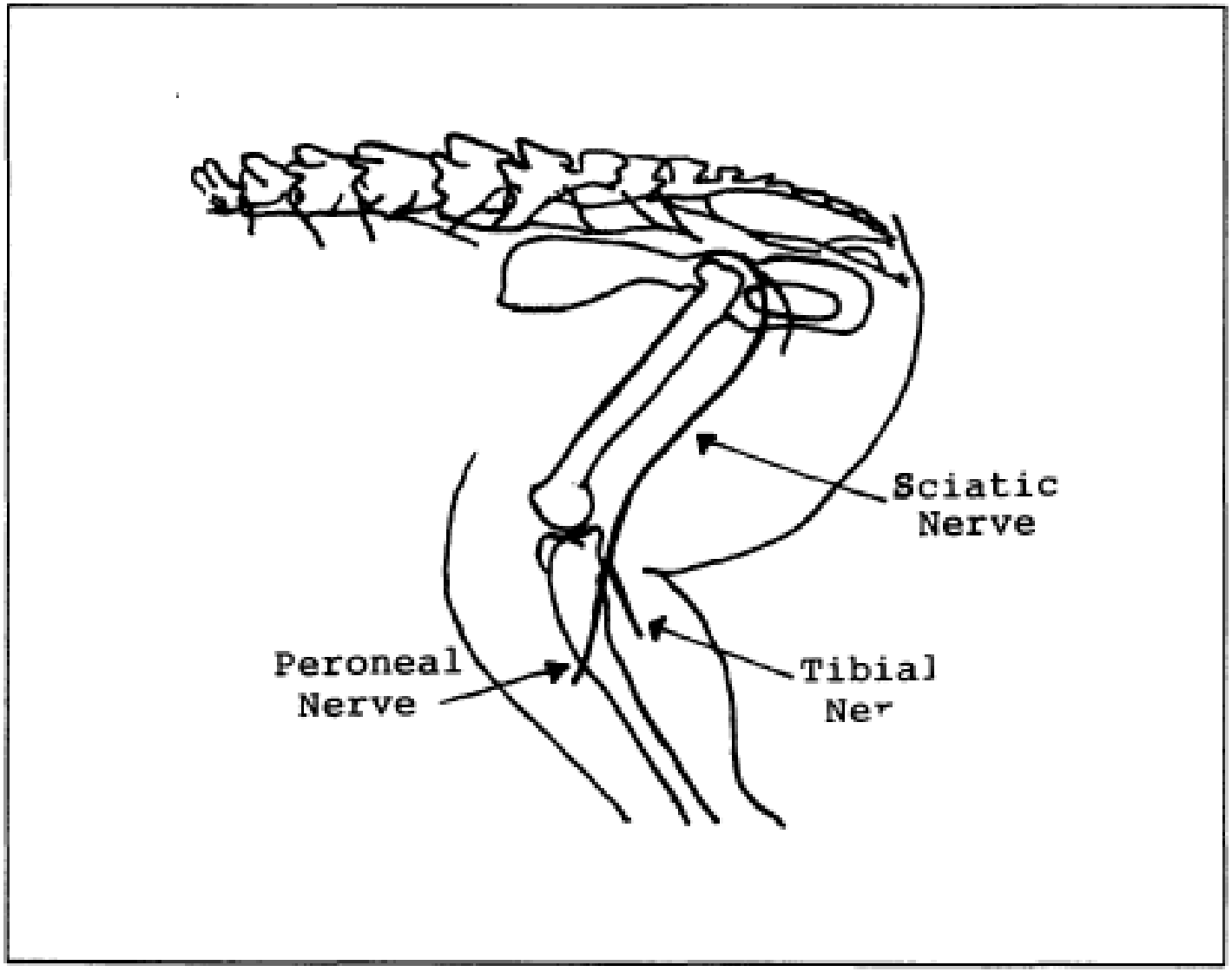


Figure 2-1: Rat hindquarter, showing location of sciatic nerve.

Landstrom, Aria. "Nerve Regeneration Induced by Collagen-GAG Matrix in Collagen Tubes." MS Thesis, MIT, 1994.

Nerve chamber filled with scaffold used to reconnect cut nerves

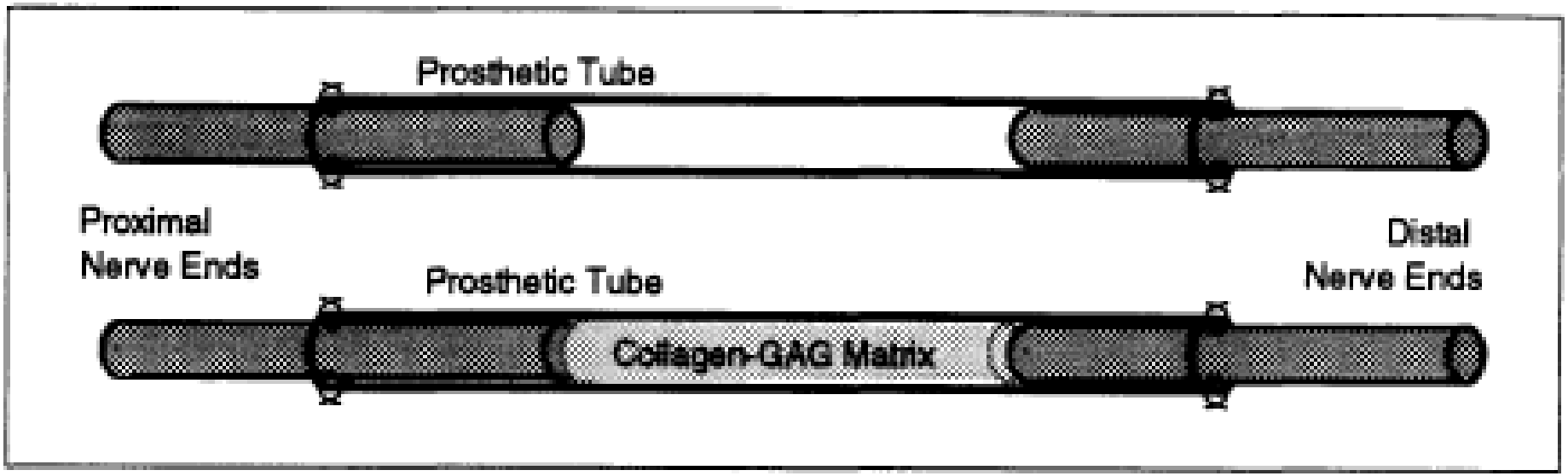


Figure 2-2: Arrangement of prosthesis and nerve, the top figure shows an empty tube and the bottom includes the CG matrix..

Landstrom, Aria. "Nerve Regeneration Induced by Collagen-GAG Matrix in Collagen Tubes." MS Thesis, MIT, 1994.

Example of good nerve regeneration

axons

Photo removed due to copyright restrictions.

scaffold inside nerve chamber degraded optimally
leading to regeneration of new nerve throughout cross section

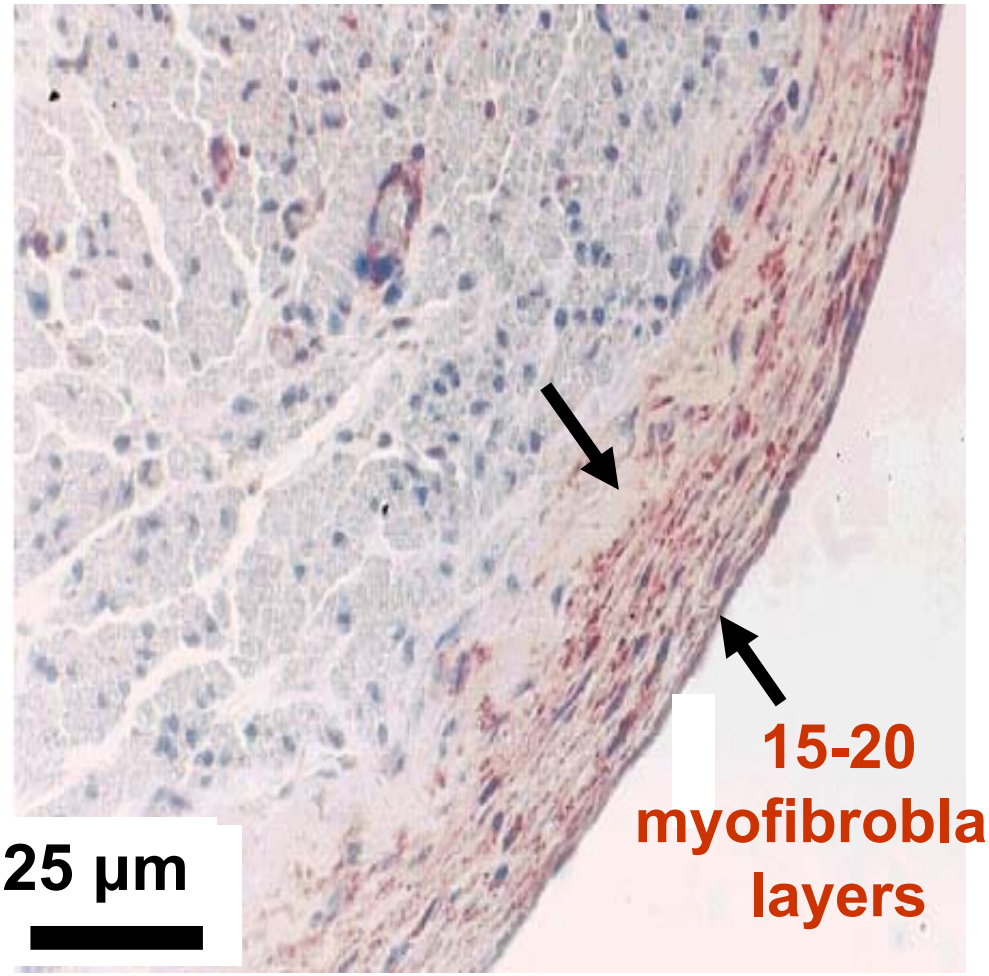
Example of poor nerve regeneration

axons

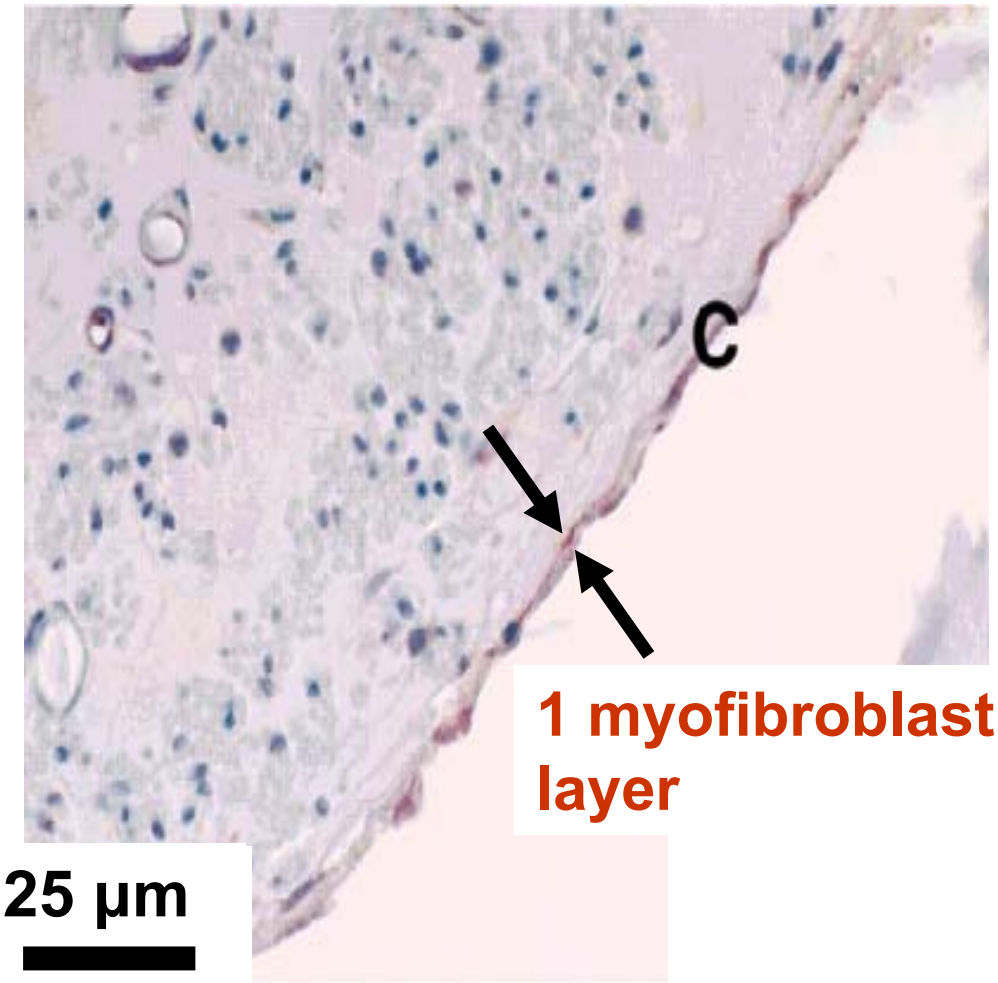
Photo removed due to copyright restrictions.

undegraded scaffold in the center of the new nerve blocks regeneration of axons

Poorly regenerated nerve



Well-regenerated nerve



A poorly regenerated nerve is surrounded by a thick layer of contractile cells.

Chamberlain et al., 2000

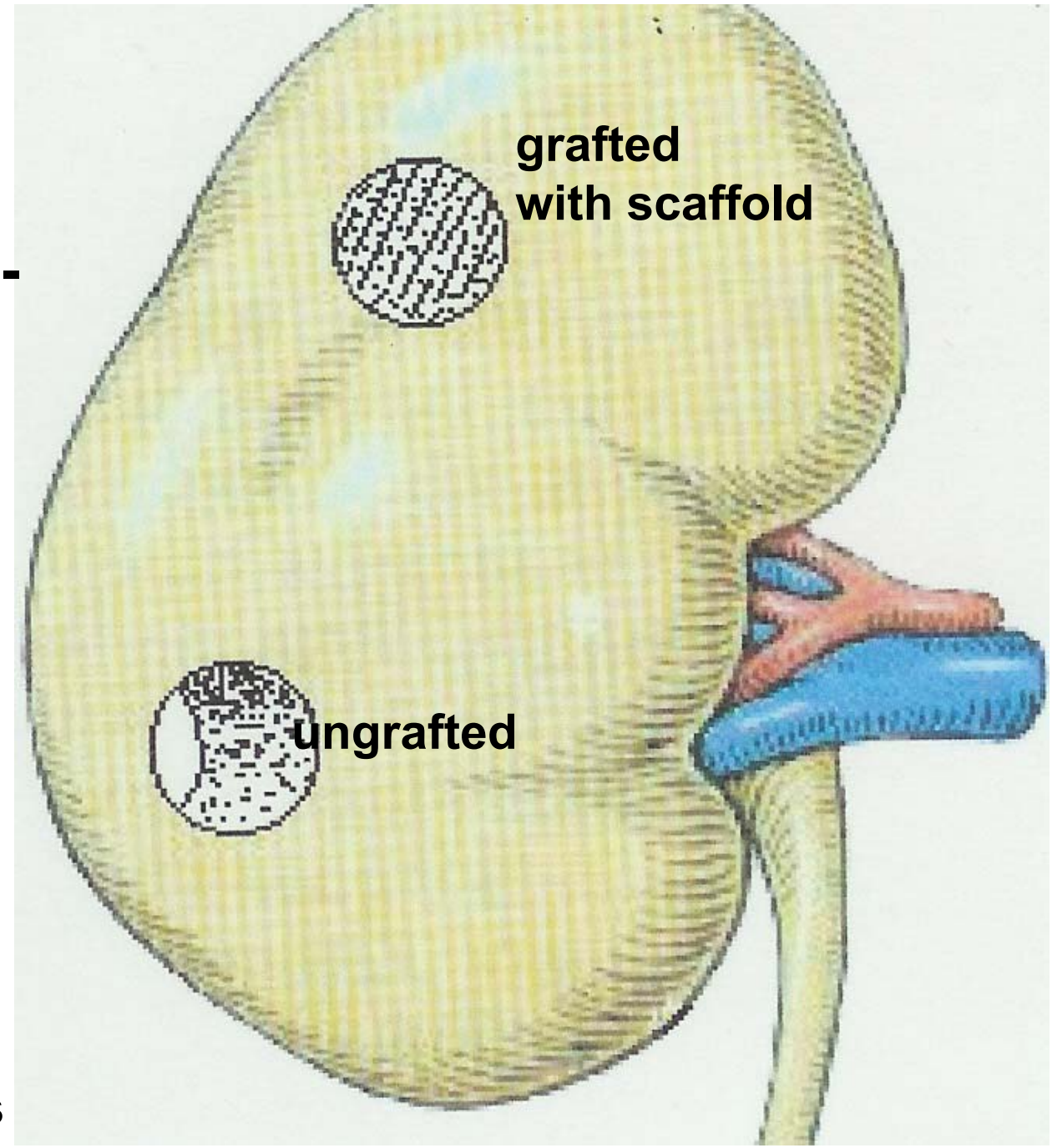
Study of kidney regeneration

Preliminary data with rat kidney .

Blocking of wound contraction and scar inhibition in adult rat kidney

EXPERIMENTAL ARRANGEMENT FOR STUDY OF SCAR INHIBITION IN KIDNEY

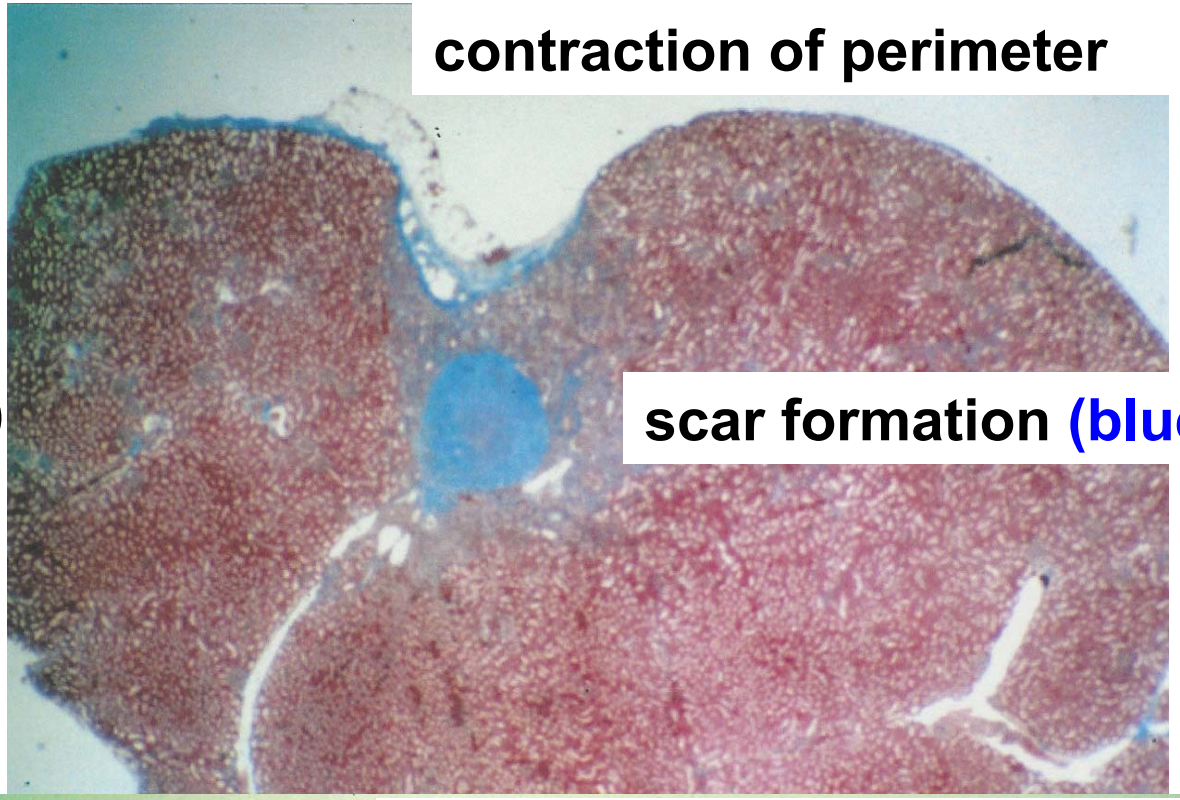
rat kidney wound model--- 3-mm diam. perforations



Hill et al., 2003
MIT Masters Thesis

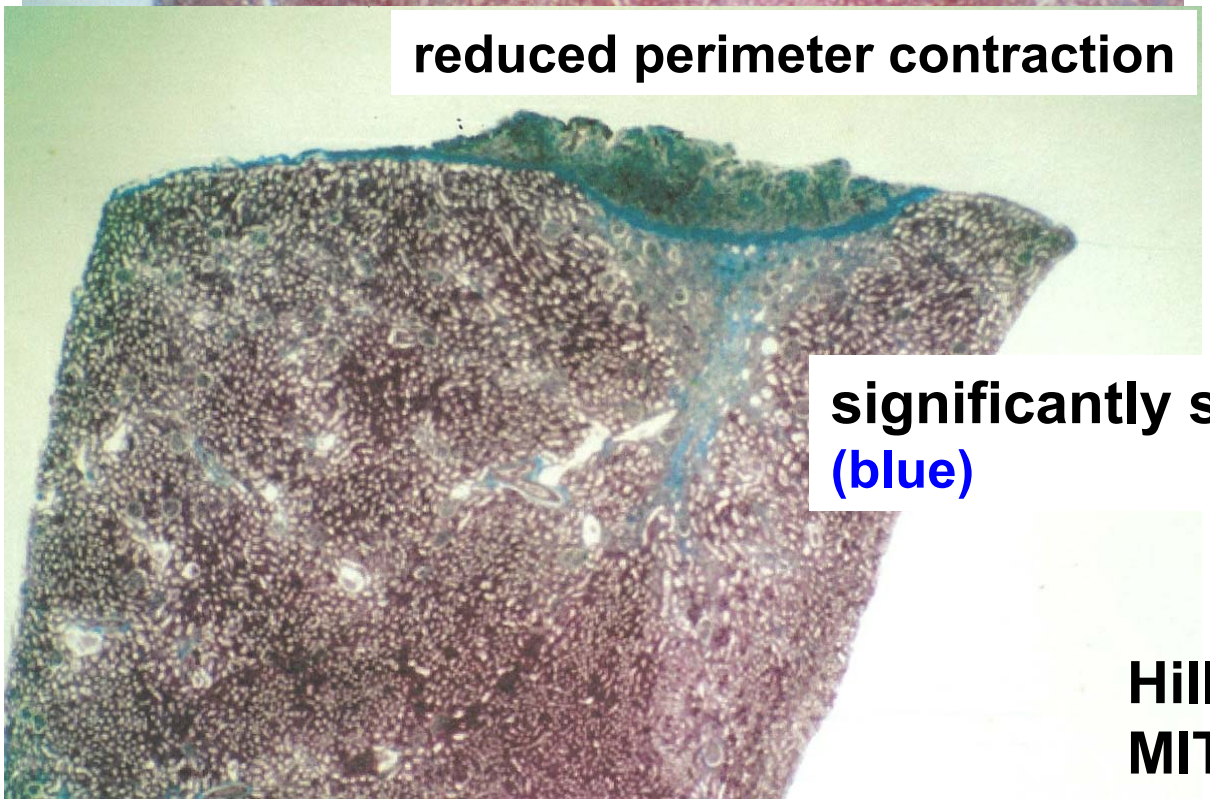
Rat kidney

UNTREATED



fibrotic tissue stains blue

TREATED WITH SCAFFOLD



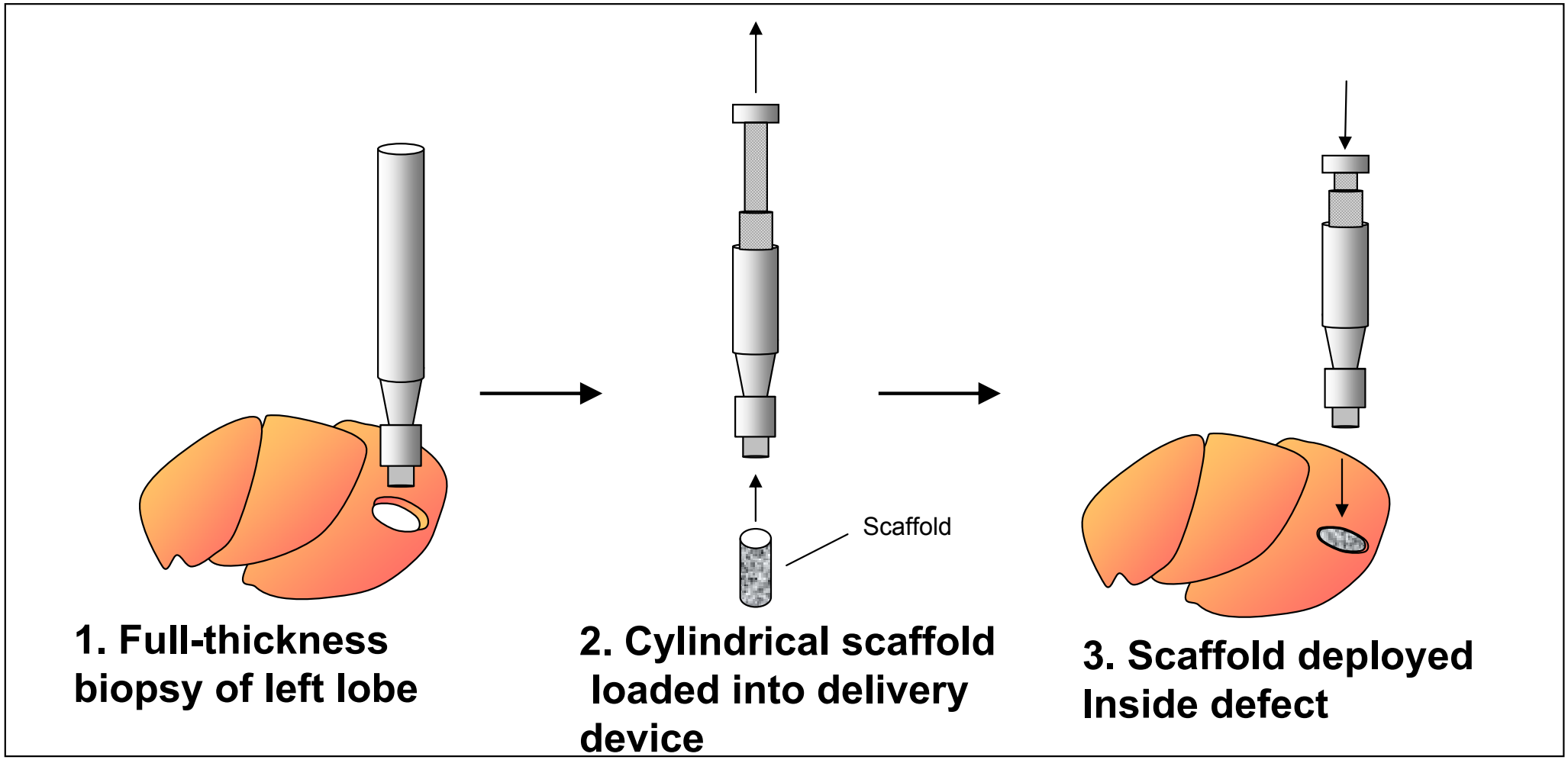
Hill et al., 2003
MIT Masters Thesis

Study of liver regeneration

Preliminary data with rat kidney .

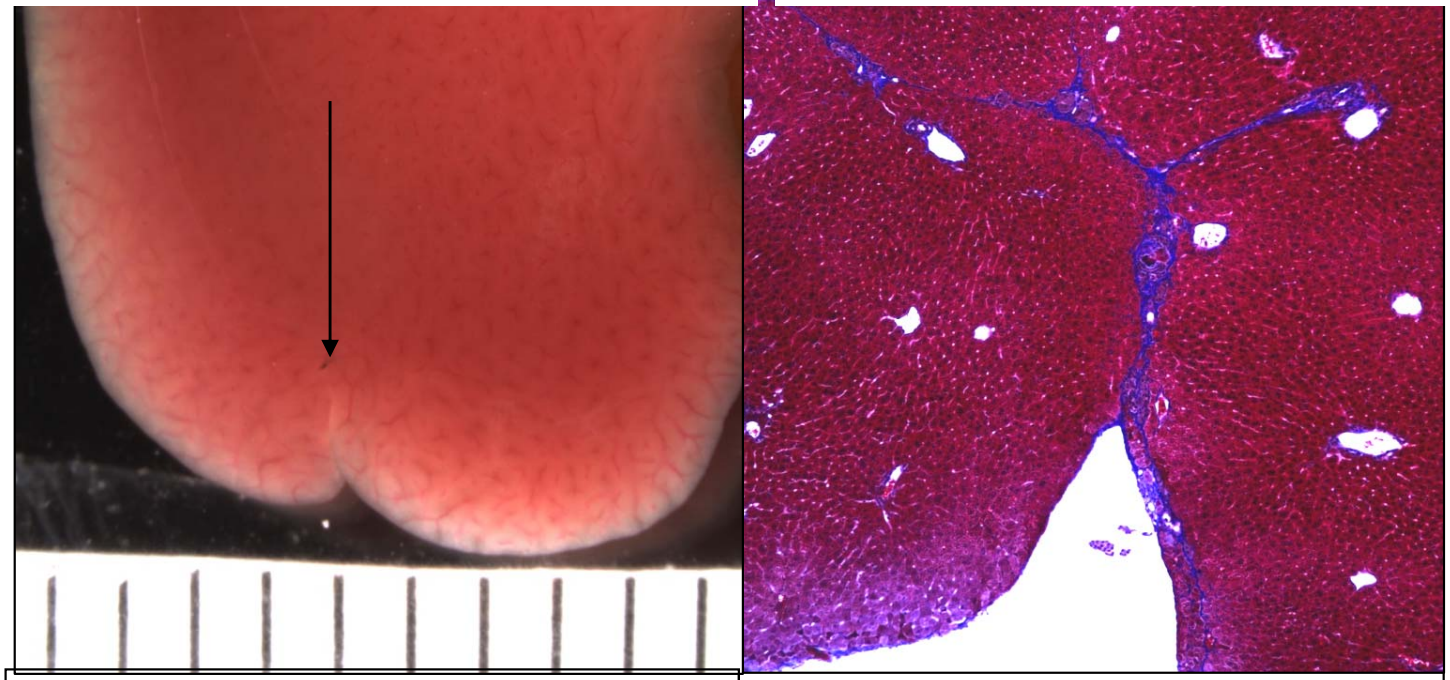
Blocking of wound contraction and scar inhibition in adult rat kidney

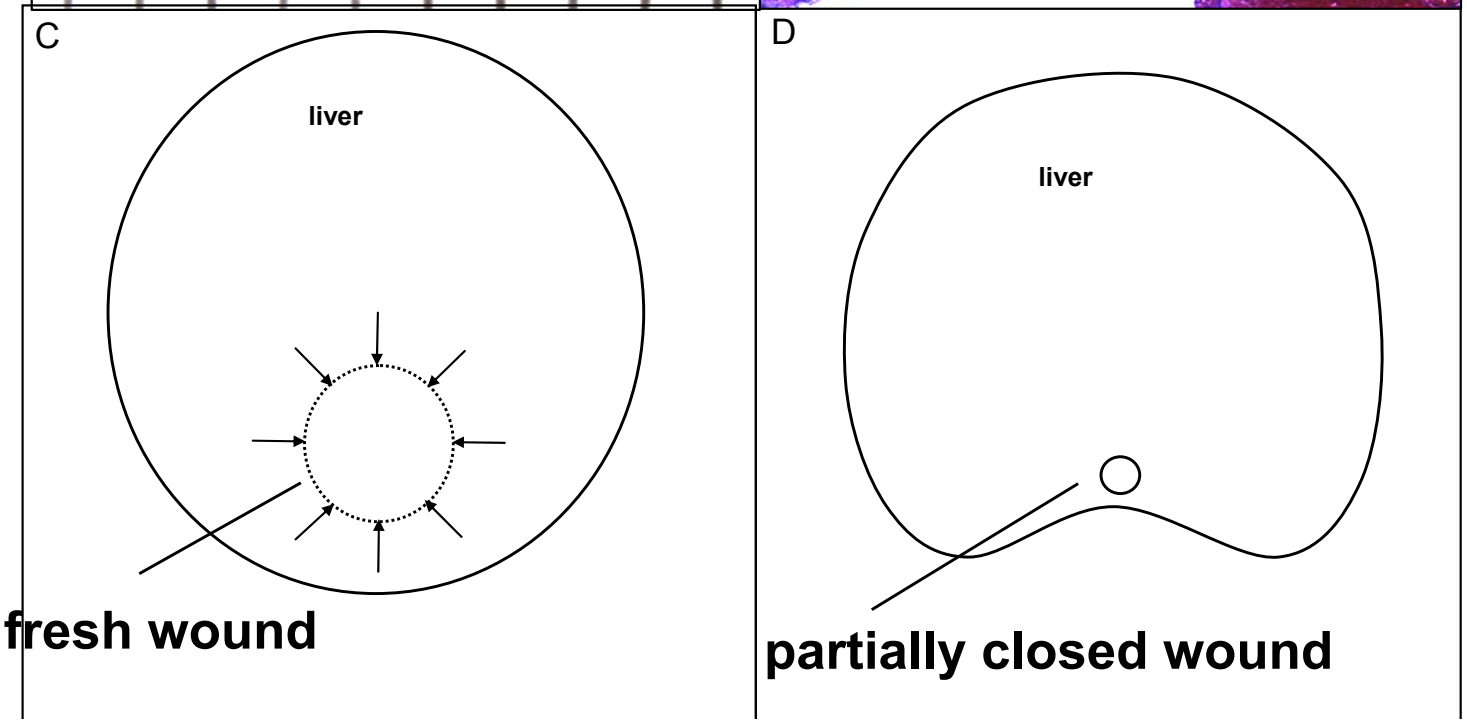
Schematic of Wound Model in Adult Mouse Liver



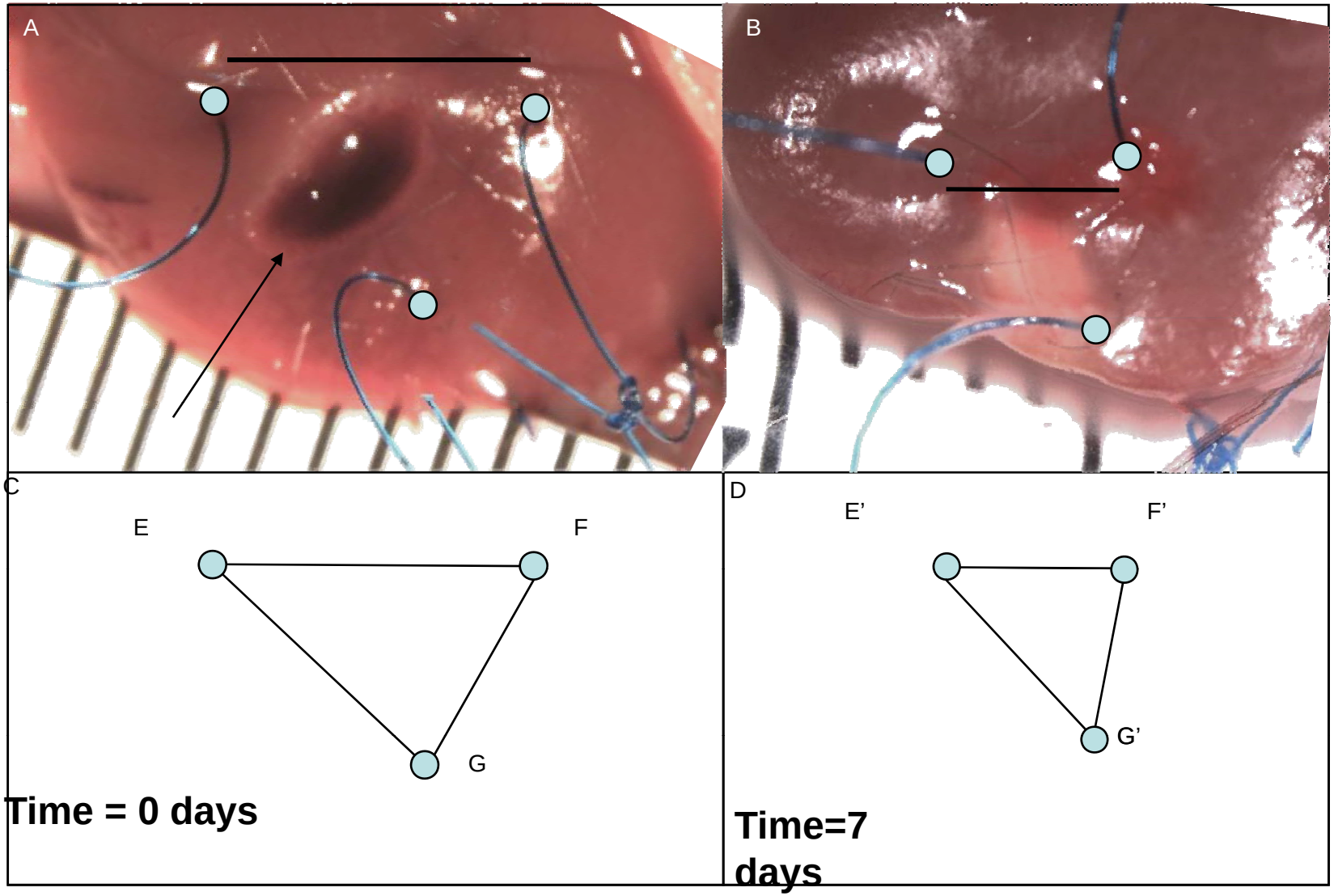
Spontaneously healed mouse liver 4 weeks following dissection of lobe. Gross view.

Histology (trichrome stain) shows fibrotic tissue (blue) lining edges of closed wound.

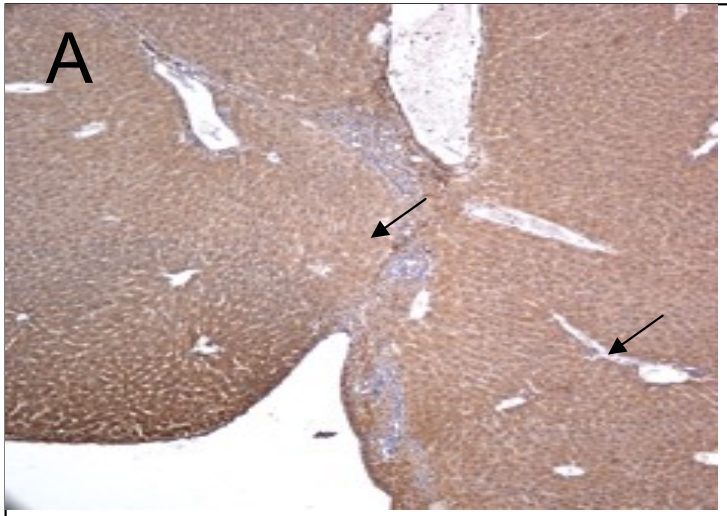


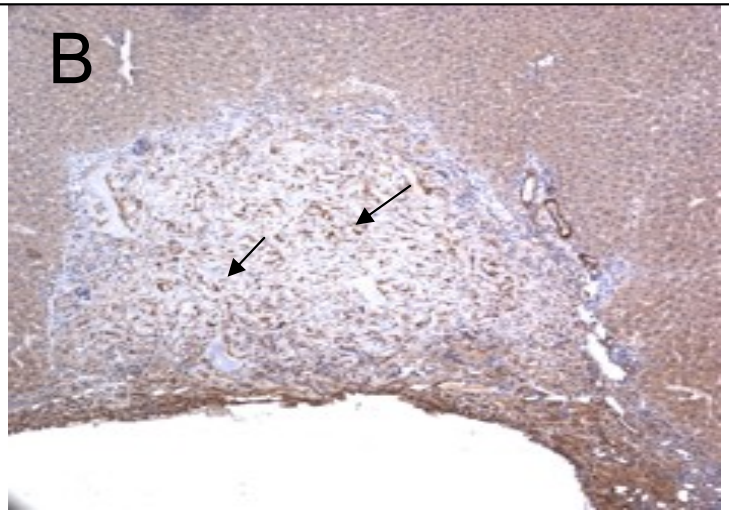


Sutures are used to monitor wound contraction in adult mouse liver



Contraction of wounded adult mouse liver is blocked following grafting of scaffold (4 weeks' data). Scaffold is extremely compliant; does not act as a mechanical splint.





In the absence of the scaffold the wounded liver heals by contraction and scar formation (blue)

In the presence of the scaffold the wounded liver heals with little contraction and no scar (blue absent)

B. Tissue and organ regeneration viewed as as processes of chemical synthesis.

Ammonia synthesis (F. Haber)

$$3H_2 + N_2 \xrightarrow{T,\ P} 2NH_3$$

Reactants → Products

NOTE: stoichiometry of chemical equation expresses conservation of mass (Lavoisier)

Apply chemical symbolism and terminology to organ regeneration. Use "reaction diagram" to identify the simplest protocol for organ regeneration

- **Example of reaction diagram (NOT a chemical equation!):**

$$KC + DRT \rightarrow E \bullet BM \bullet RR \bullet D$$

- **Reactants: cells, regulators, matrices**
- **Reactors: in vitro cell culture; in vivo (anatomical site)**
- **Products: either scar or regenerated tissue (or intermediate cases)**

Note: Conservation of mass is not implied by reaction diagram!

Abbreviations: KC, keratinocytes. DRT, dermis regeneration template. E, epidermis. BM, basement membrane. RR, rete ridges. D, dermis.

Abbreviation for tissues in skin structure

E•BM•RR•D

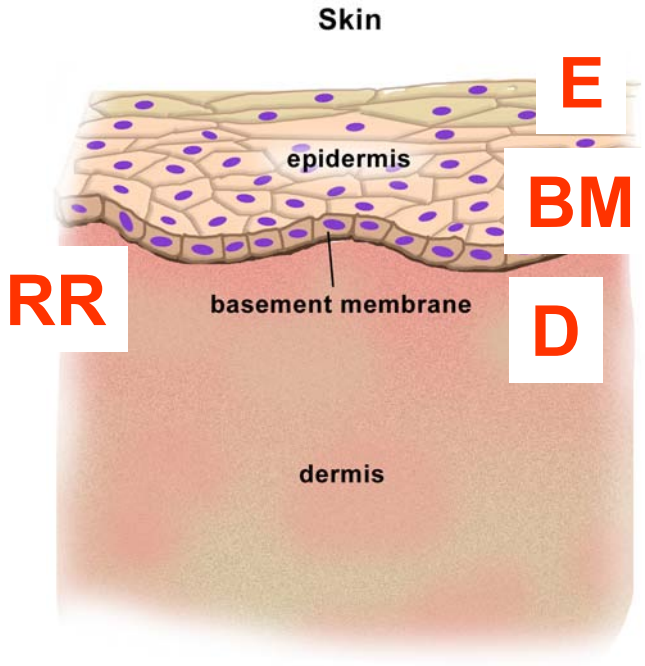
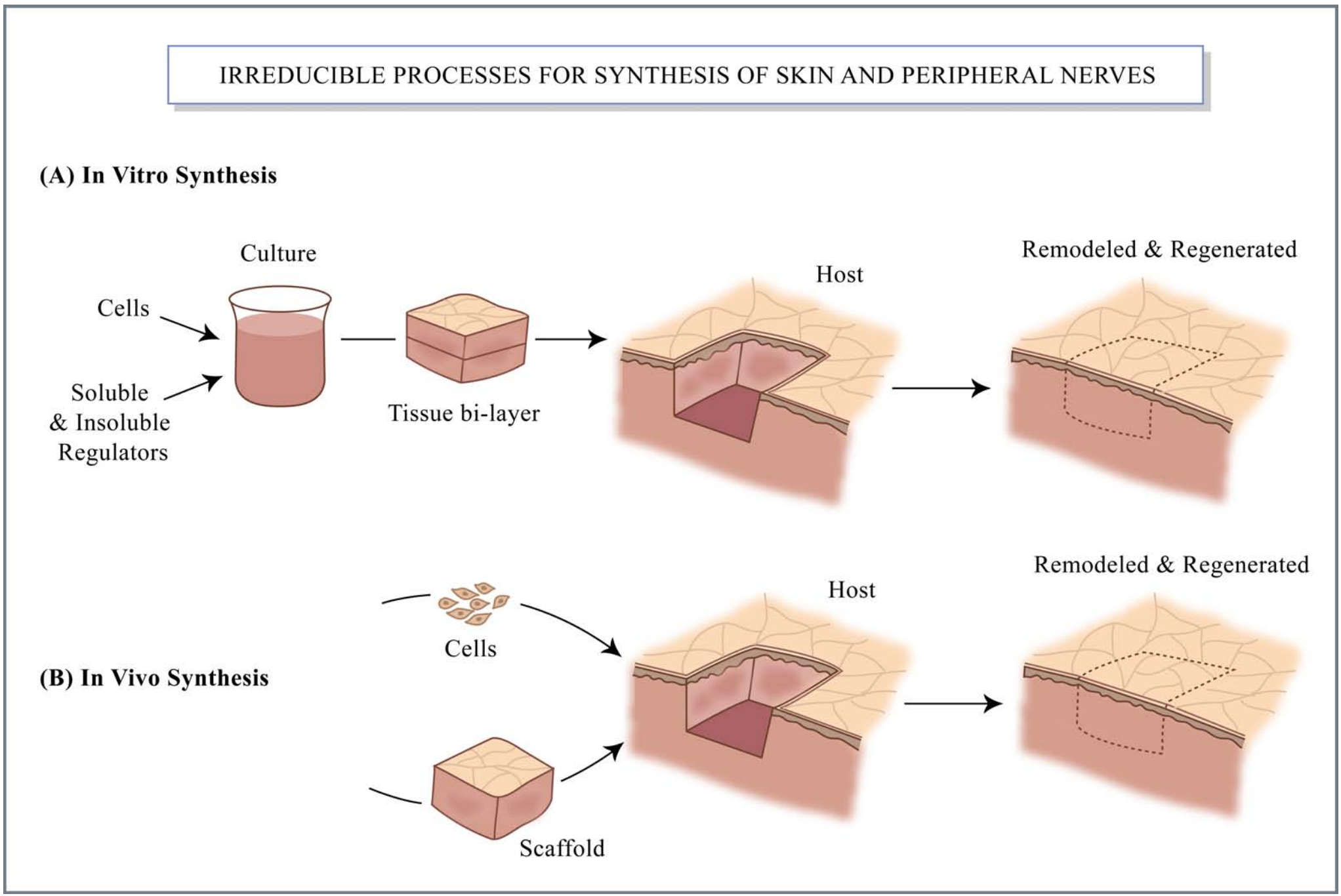
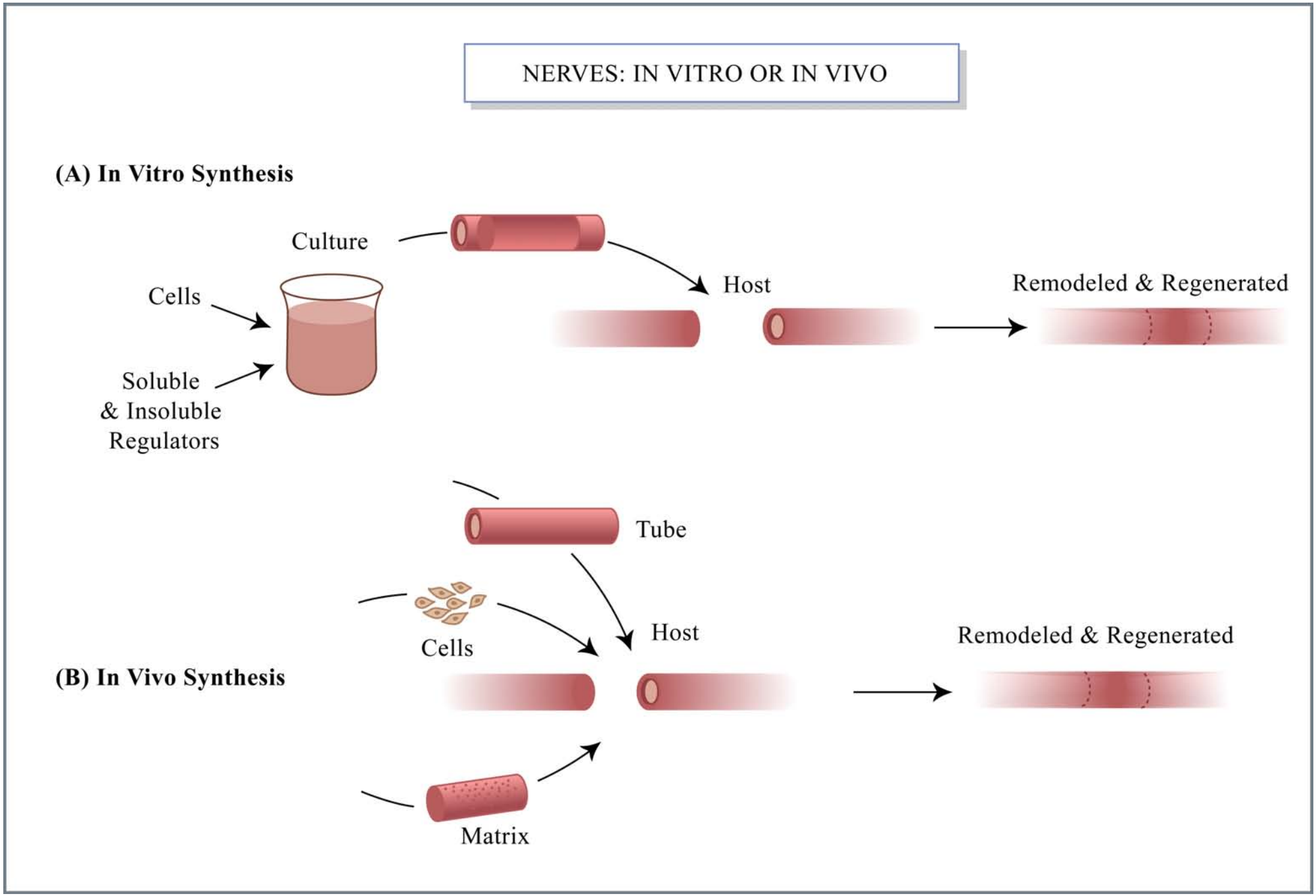


Figure by MIT OpenCourseWare.

Skin: In vitro or in vivo synthesis?



Peripheral nerves: In vitro or in vivo synthesis?



Why study the healing process?

1. In vitro or in vivo method → implant
2. Implant → **injured anatomical site undergoing healing**
3. Implant + healing → organ synthesis

<u>Conclusion</u>. Either way, in vitro or in vivo, something has to be eventually implanted inside a wound. The implant interacts with the wound. This interaction determines whether a new organ will form or not at that anatomical site.

C. What is the mechanism of organ regeneration?

1. Fact: There is an antagonistic relation between contraction of a wounded site and regeneration at that site.
2. Fact: Blocking of contraction process is required (but is not sufficient) for regeneration.
3. Theory: Induced regeneration = contraction blocking + tissue synthesis.
4. Fact: Contraction is mediated by cell-matrix interactions. Regeneration templates block these interactions.

Two adult healing modes

Spontaneous healing in adults

injury → contraction + scar formation

Healing by regeneration in adults

injury → implant an active cell-seeded scaffold → MECHANISM? → organ synthesis

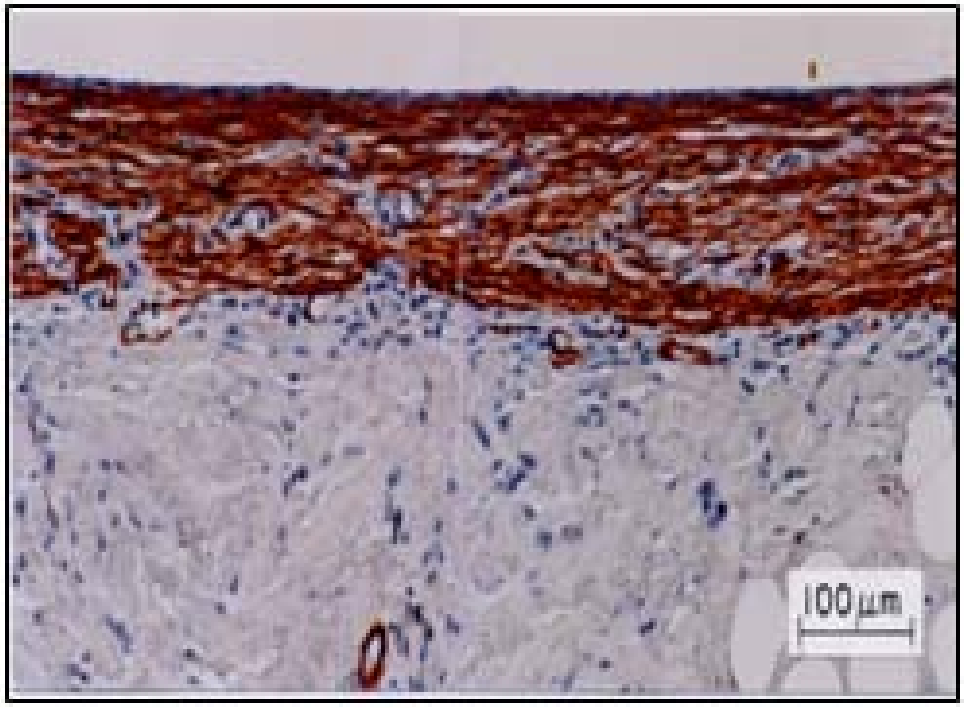
Irreversible injury in adult mammal

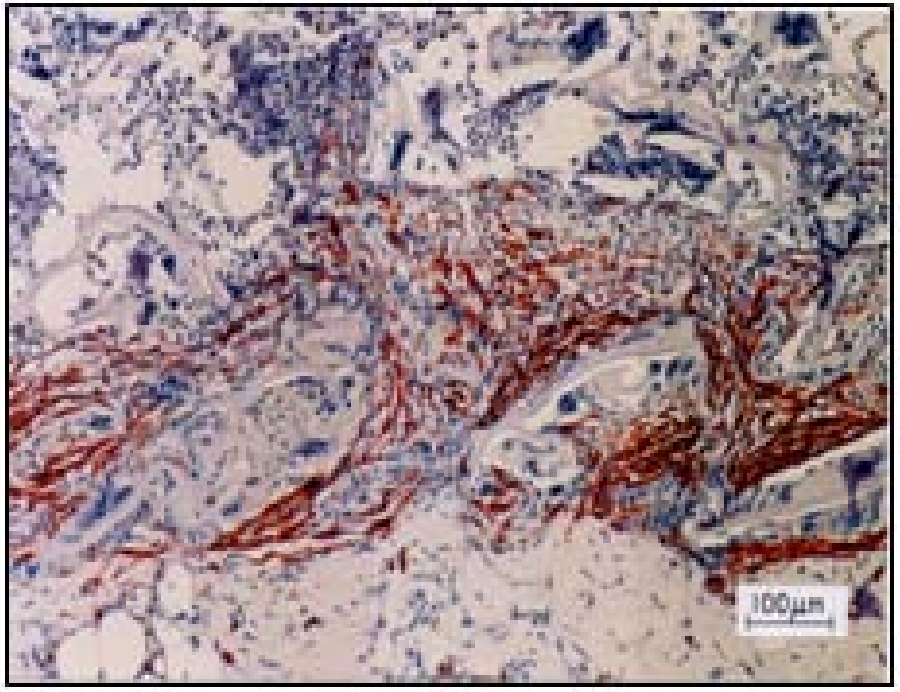
Photo removed due to copyright restrictions.

Burn victim suffering from severe contraction and scar formation

Tomasek et al., 2000

How does a scaffold with regenerative activity work?





No scaffold. Spontaneous healing of deep skin wound (guinea pig). Contractile fibroblasts (red brown) form thick layer that pulls wound edges together, inducing contraction and closing wound

Scaffold grafted. No contraction. Contractile fibroblasts are fewer and are also disorganbized, leading to cancellation of mechanical forces for contraction

Troxel, MIT Thesis, 1994

D. Cell-matrix interactions

A typified cell

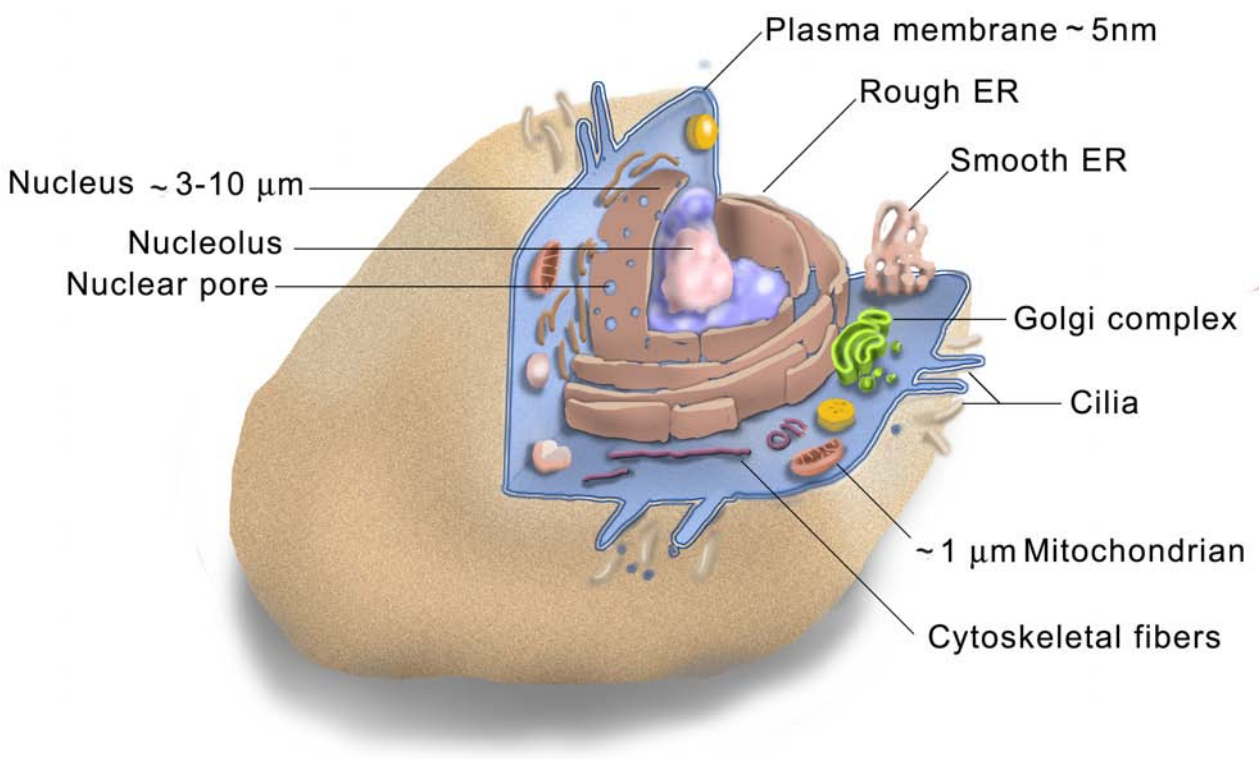
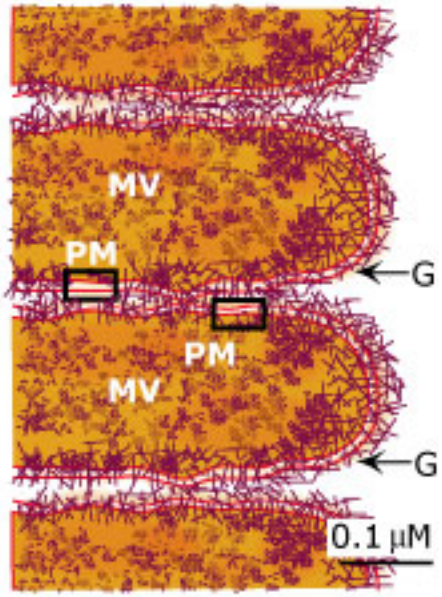
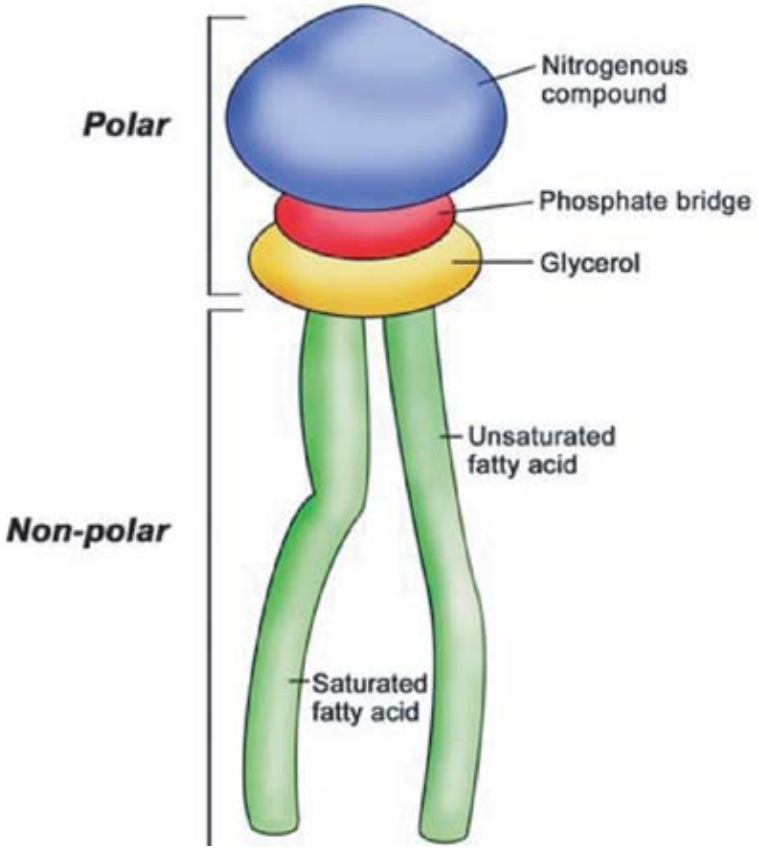
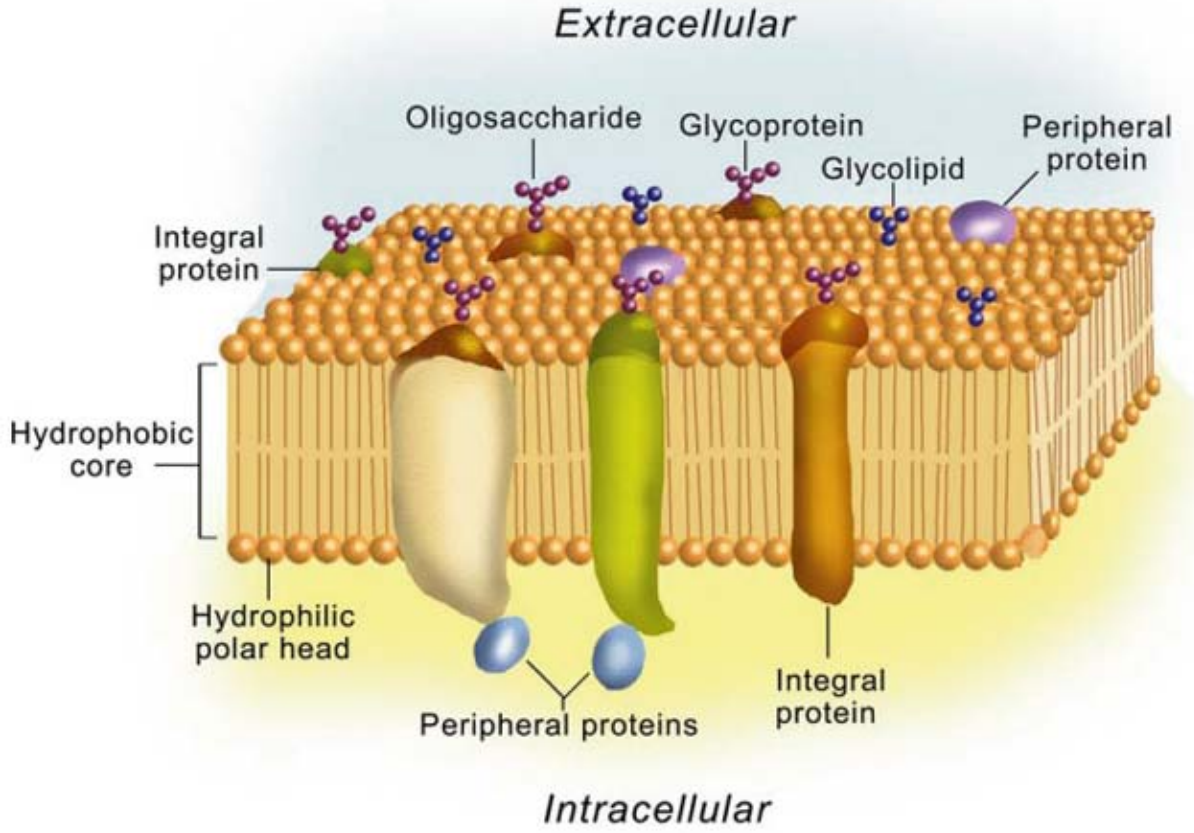


Figure by MIT OpenCourseWare.

Cell membrane







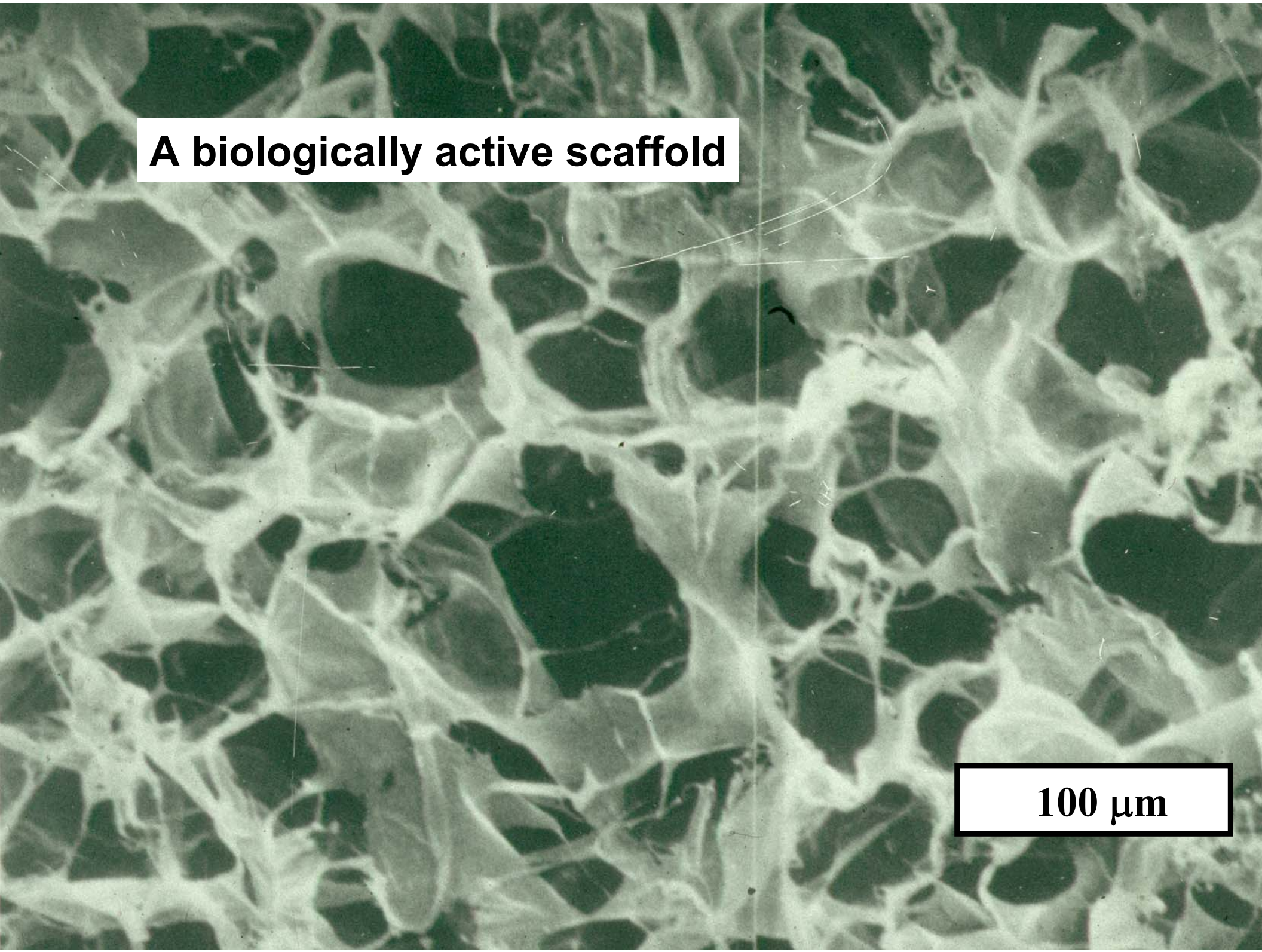
Figures by MIT OpenCourseWare.

Burkitt et al.

Cytoplasm

Photo removed due to copyright restrictions.

Cells contract thin silicone substrate


A biologically active scaffold
100 μm

Cell-matrix interaction through integrins and ligands

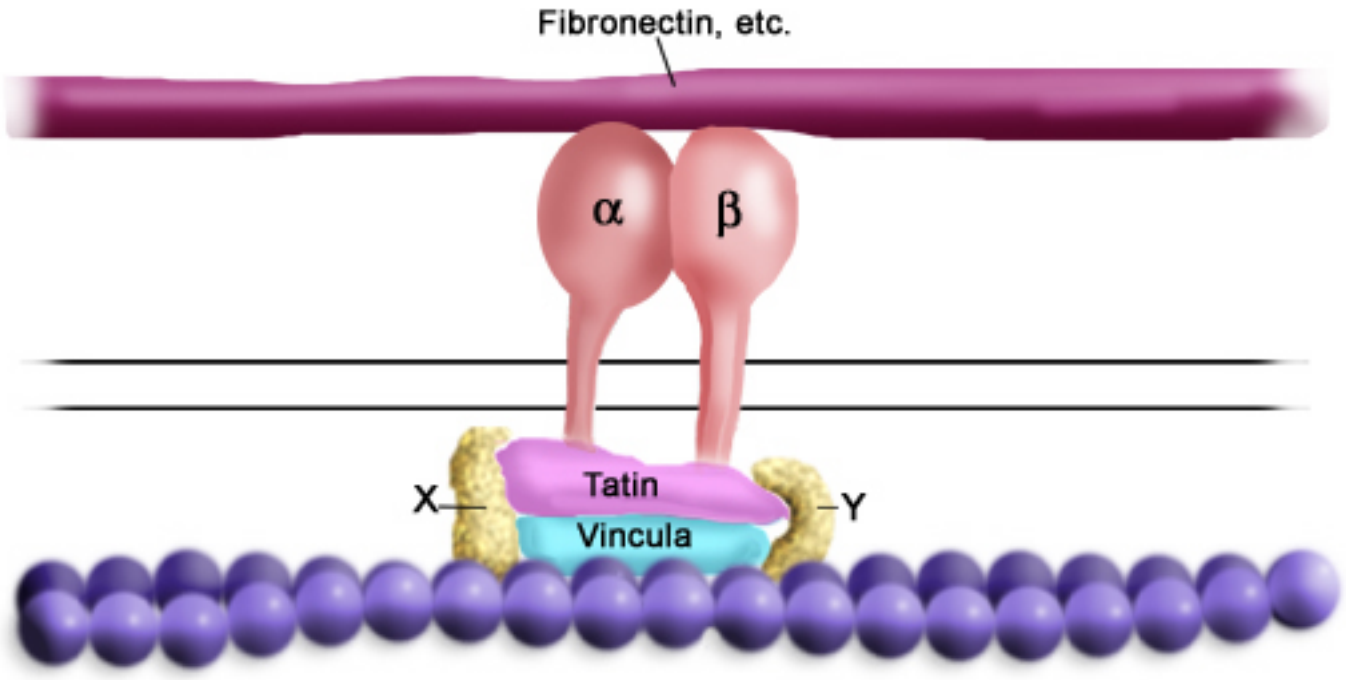
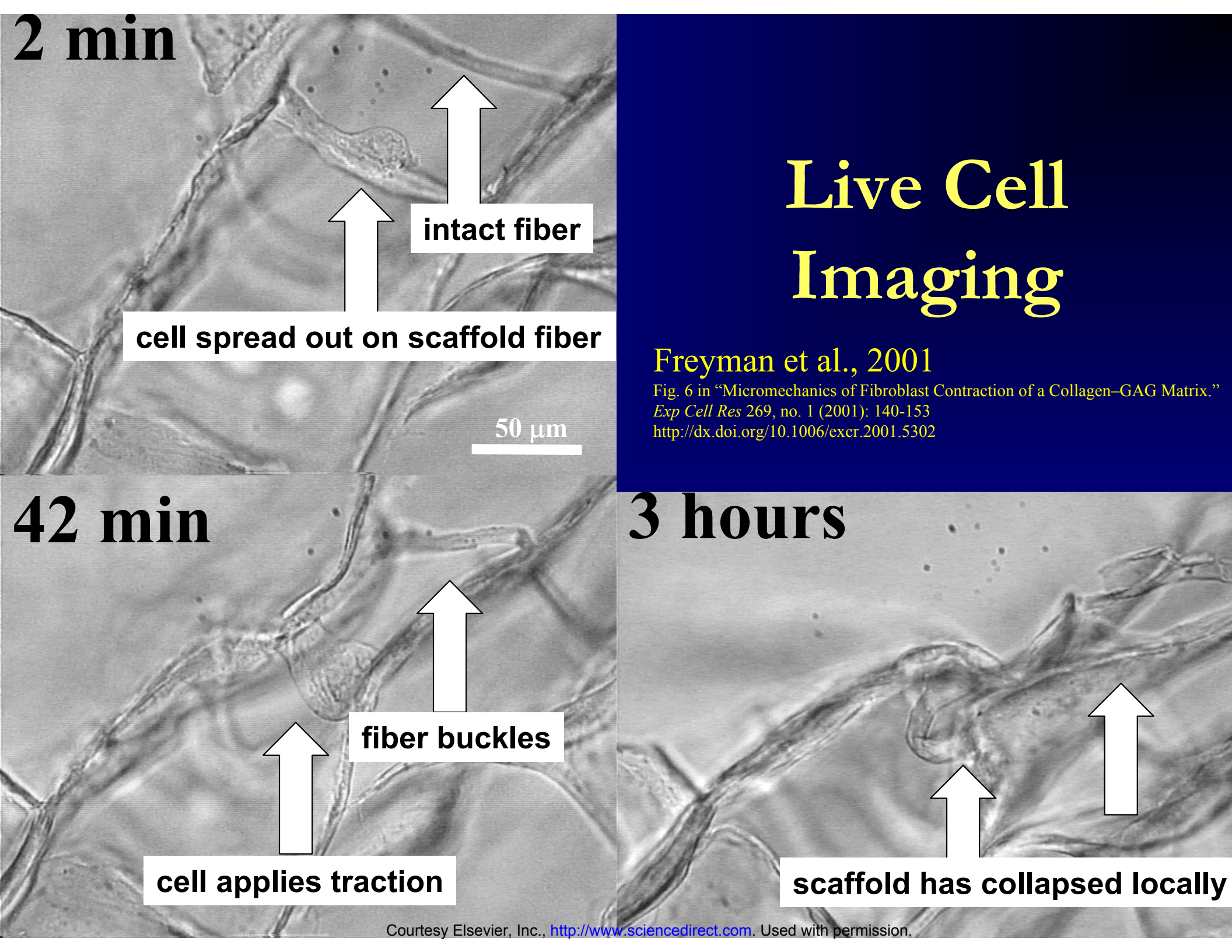


Figure by MIT OpenCourseWare.

Hynes, 1990



Live Cell Imaging

Freyman et al., 2001

Fig. 6 in "Micromechanics of Fibroblast Contraction of a Collagen–GAG Matrix."
Exp Cell Res 269, no. 1 (2001): 140-153
http://dx.doi.org/10.1006/excr.2001.5302

Modified cell force monitor

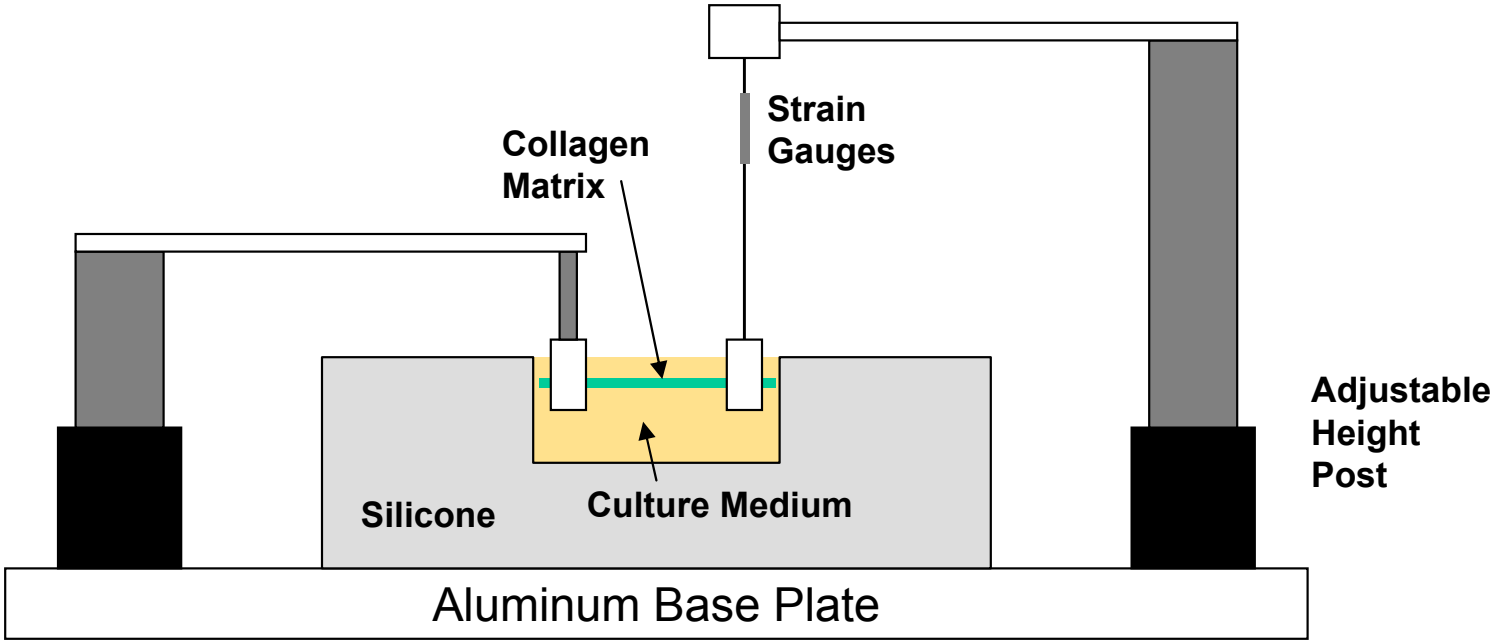


Figure by MIT OpenCourseWare.

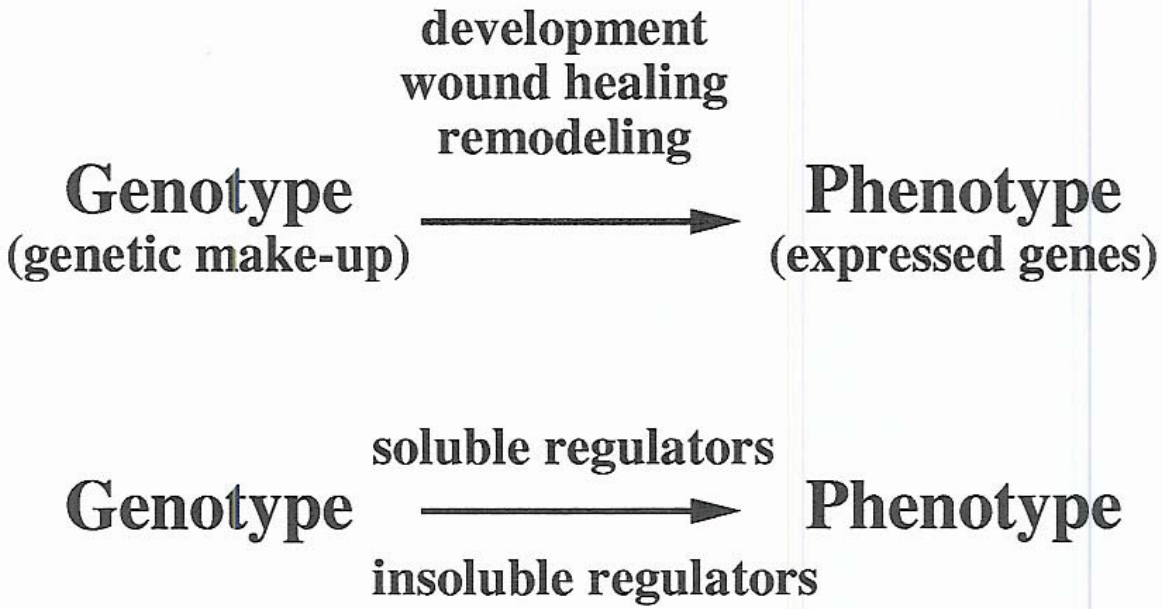
Use to study unit cell processes quantitatively

See Freyman et al., 2001

E. The unit cell process

- **Study cell function as if it comprises each of several distinct processes.**
- **Identify the critical unit cell process.**
- **Focus attention on controlling the critical unit cell process.**

Conditions for gene expression



Classic data: Cell-matrix interaction affects cell shape

Epithelial cell + collagen → Rounded cell

(Cytoplasmic structures, which control shape, are modulated by insoluble substrate.)

2. Endothelial cells + plastic → multilayered structures

Endothelial cells + plastic + FGF → confluent monolayer

Endothelial cells + plastic + FGF → ECM

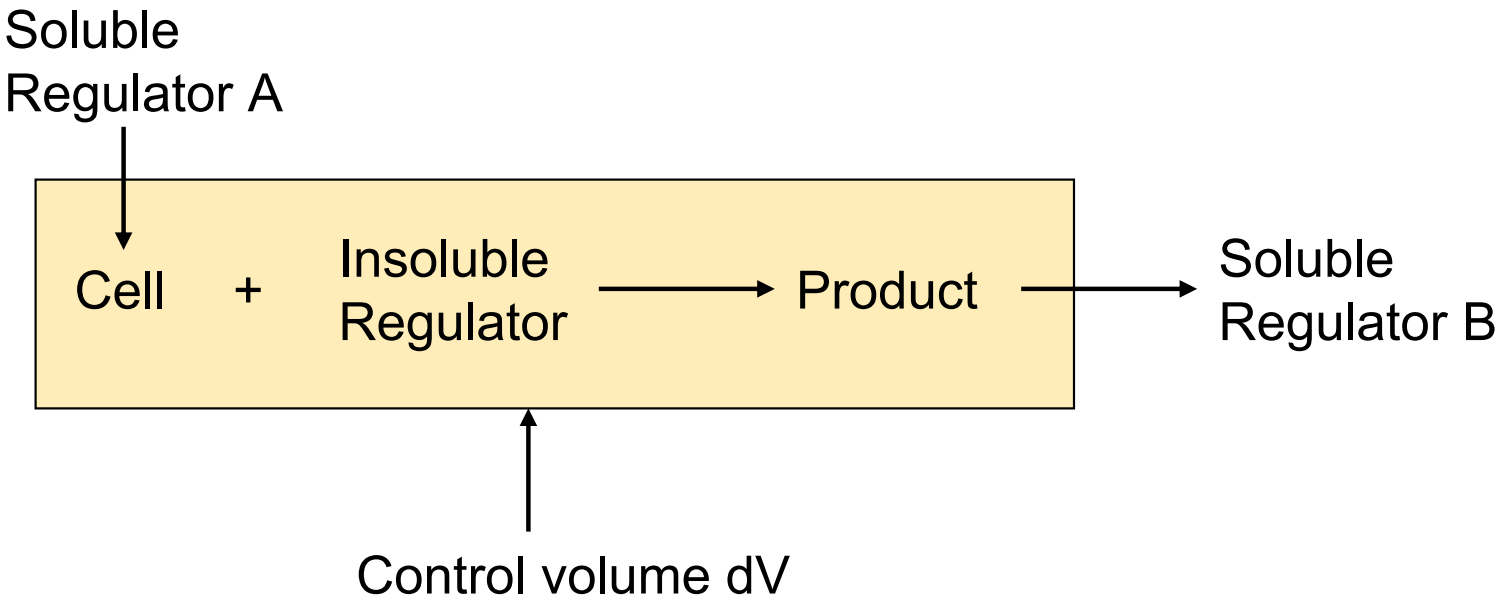
Endothelial cells + ECM → confluent monolayer

Endothelial cells + ECM → new ECM

(Loss of normal phenotypic properties in absence of regulator or in absence of ECM.)

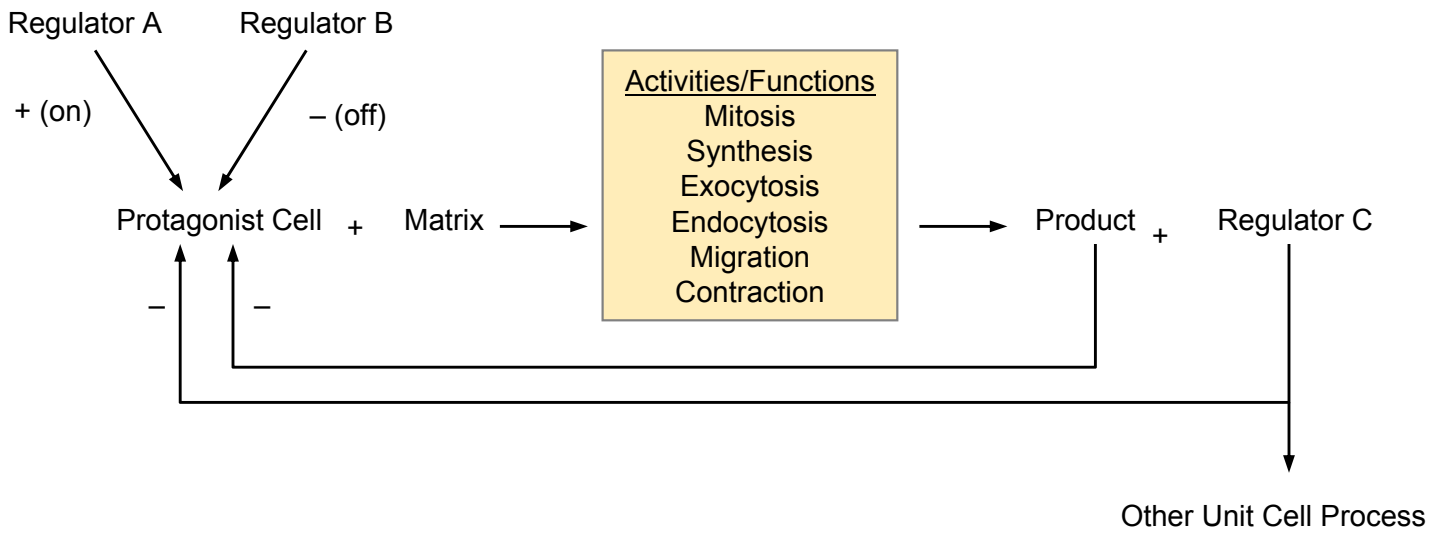
D. Gospodarowiez et al, *Cancer Res.* **38**:4155 (1978).
S.C.G. Tseng et al, *J. Cell Biol.* **97**:803 (1983).

Definition of unit cell process

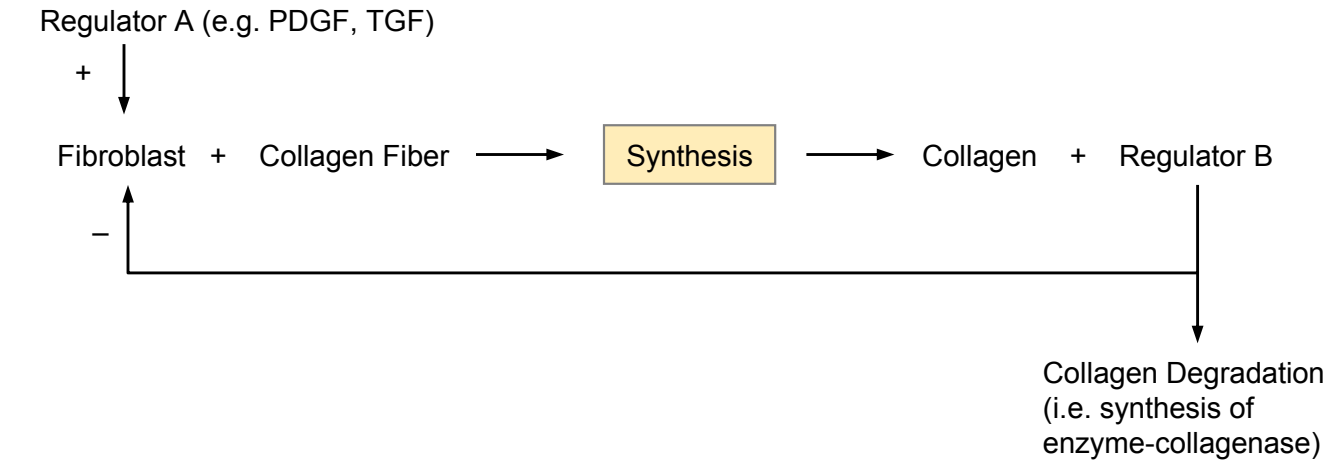


Unit cell process confined conceptually in a control volume dV

Various unit cell processes



Example: Collagen Synthesis



Properties of a unit cell process

1.3 THE WOR ING PARADIGM: THE UNIT CELL PROCESS

a) Describes a specific **cell-matrix interaction**. Usually it describes the induction of a specific phenotype of the **protagonist cell** by an insoluble **substrate**.

b) Confined conceptually in a **control volume** dV (Fig. 1.2).
Order of magnitude: 10x10x10 μm.

c) **Regulated by diffusible substances** which enter into and exit from control volume. These substances regulate the cell-matrix interaction. Also regulated by **mechanical forces** which act by deforming the matrix, thereby modulating the cell-matrix interaction.

d) The cell-matrix interaction is a highly specific process: the **cooperative configurational interaction** between ligand and receptor. Usually both ligand and receptor are macromolecules, each with a highly specific configuration.

e) Can be **reproducibly** demonstrated (or rejected) *in vitro*. **Falsifiability** of each model of cell-matrix interaction.

f) **Scale**: small enough to be reproduced *in vitro* and large enough to have significant physiological content.

g) Forms a conceptual bridge between ***in vitro and in vivo*** phenomena.

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