The problem of the missing organ

1. Irreversible injury (acute and chronic) destroys organ function.
2. Five basic therapies for the missing organ.
3. Examples of widespread clinical problems that have not been solved adequately.

<u>**Additional reading**</u>**:** [TORA] ***Tissue and Organ Regeneration in Adults (TORA)*****, by I.V.Yannas, New York, Springer, 2001. Chap. 1.**

1. Irreversible injury (acute and chronic) destroys organ function.

Various Medical Problems

- The aggressive bacterium (virus)
- The missing enzyme
- The defective gene
- The missing organ

Irreversible organ injury

- The mammalian <u>fetus</u> regenerates lost organs spontaneously.
- <u>Adult</u> mammals do not regenerate damaged or diseased organs.
- The adult response to trauma or chronic disease includes wound closure by contraction and formation of scar (repair).

Amphibian (newt) limbs regenerate spontaneously

Figure 1.1. Montage of individual newt limbs amputated across the lower or upper arms, photographed at indicated times and regenerating spontaneously. (From Goss, 1992.)

All Organs Can Be Irreversibly Injured

Liver: compensatory hypertrophy, not "real" regeneration of two lobes

Figure removed due to copyright restrictions.
See Figure 1.2 in [TORA].

FIGURE 1.2. Liver does not regenerate at the anatomical site of injury. When the median and left lateral lobes of a rat liver are removed (broken line shows shape of intact organ), only the caudate and right lateral lobes remain, representing about one-third of the intact organ. After three weeks, these lobes enlarge to a mass equivalent to the initial size of the liver. The shape of the intact liver is not restored. (From Goss, 1992.)

Example of adult healing response. Severe burn causes skin loss. Wound closes by contraction and scar synthesis

Photo removed due to copyright restrictions.

Figure removed due to copyright restrictions.

See Chapter 1 in [TORA] - examples of injury healing in various tissue types.

Poor organ function leads to unpleasant choices

--- scarred heart muscle: poor pumping action; congestive heart failure; drugs, heart transplant

--- scarred kidney: poor filtration; use kidney dialysis machine

--- scarred heart valve: inefficient pumping due to leaky valve; congestive heart failure

--- scarred liver: cirrhosis; poor function; liver transplant

--- scarred eye: loss of vision

2. Five therapies for the missing organ.

Five Approaches to the Problem of the Missing Organ

Approach	Example
Transplantation	Kidney
Autografting	Coronary bypass
Passive implant	Hip prosthesis
(Stem cells	Not available)
In vitro synthesis	Epidermis
In vivo synthesis	Skin

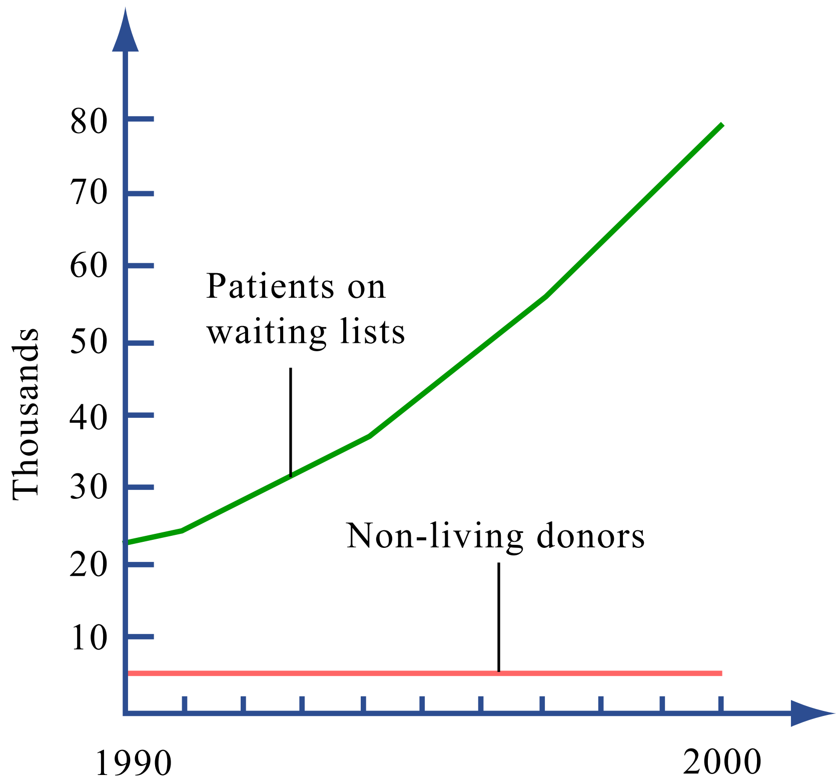
A. Transplantation (e.g., kidney transplant, heart transplant)

donor organ

donor $\Rightarrow \Rightarrow \Rightarrow \Rightarrow$ host $\Rightarrow$rejection? $\Rightarrow$

$\Rightarrow$ treatment impairs immune system

Also, demand for organ transplants greatly outstrips supply



Demand for organs is growing, while the supply stays constant.

Figure by MIT OCW.

Data from United Network for Organ Sharing.

B. Autografting (e.g., heart bypass, skin grafting)

Donor = recipient

Example: In heart bypass surgery, a length of leg vein is removed and used to shunt clotted coronary artery

part host organ

Host $\Rightarrow \Rightarrow \Rightarrow \Rightarrow \Rightarrow$ host $\Rightarrow$ host trauma? sufficient recovery of function?

Third-degree burn: complete skin loss

Figure removed due to copyright restrictions.

6-yr-old burn victim – total skin loss on upper and lower abdomen

patient of Dr. John Burke

Figure removed due to copyright restrictions.

C. Passive Implant (e.g., hip prosthesis, pacemaker)

metallics/polymers/ceramics $\Rightarrow$ device fabrication $\Rightarrow$ host $\Rightarrow$ long-term function?

<u>materials used</u>: stainless steel, Ti alloys, CoCr alloys, polylactic acid, polyglycolic acid, nylon; dacron (PET) vascular graft; polyurethane heart chamber

C. Passive Implant (cont.)

Problem #1: host attacks implant

migration of hip prosthesis

abrasion of polyethylene 'cup'

tissue fluid attacks pacemaker electronics

Problem #2: implant attacks host

hip prosthesis causes bone loss (stress shielding)

heart valve causes blood cell rupture

vascular graft causes blood clotting

Several slides on different implants removed due to copyright restrictions.

Cementing artificial hip with PMMA
Silicone gel breast implant
Heart pacemaker
Balloon catheter
Left ventricular assist device: responds to changes in workload by adjusting its beats per minute
Liver assist machine: passes blood through culture of human cells, provides 20% normal liver function
Artificial lung device inserted into large vein in chest, enables body to absorb oxygen
Hearing aid

D. In vitro synthesis

1. Synthesize a construct resembling the desired organ (organoid) in vitro in the presence of cells of one or more types, solutions of cytokines and one or more scaffolds.
2. Implant the organoid at the correct anatomical site.
3. If successfully synthesized, the organoid becomes incorporated in the organism and functions physiologically.

<u>Problem</u>: Physiological cytokine field unknown, cannot be replicated in vitro.

Several slides removed due to copyright restrictions.

Design strategy

Analyze problem of irreversible injured organ by identifying tissues in organs that regenerate spontaneously (regenerative) and those that do not (nonregenerative).

Rather than planning a device that can synthesize the entire organ, the designer's task is made simpler if the design focuses on synthesis of just those tissue(s) that do not regenerate by themselves. Which are they?

Identify nonregenerative tissues

1. **Every organ is different, but….**
2. **Generalize by focusing on individual <u>tissues</u> that comprise organ.**

3. Most organs are made up of three basic tissues (“tissue triad”): epithelia, basement membrane, and stroma.

3. Epithelia and basement membrane are spontaneously regenerative; the stroma is not.

4. Therefore, the central problem in biomaterials selection for organ replacement by regeneration is synthesis of the stroma.

Members of the tissue triad

- **EPITHELIA**

  100% cells. No matrix. No blood vessels.

- **BASEMENT MEMBRANE**

  No cells. 100% matrix. No blood vessels.

- **STROMA (CONNECTIVE TISSUE)**

  Cells. Matrix. Blood vessels.

The tissue triad in skin and nerves

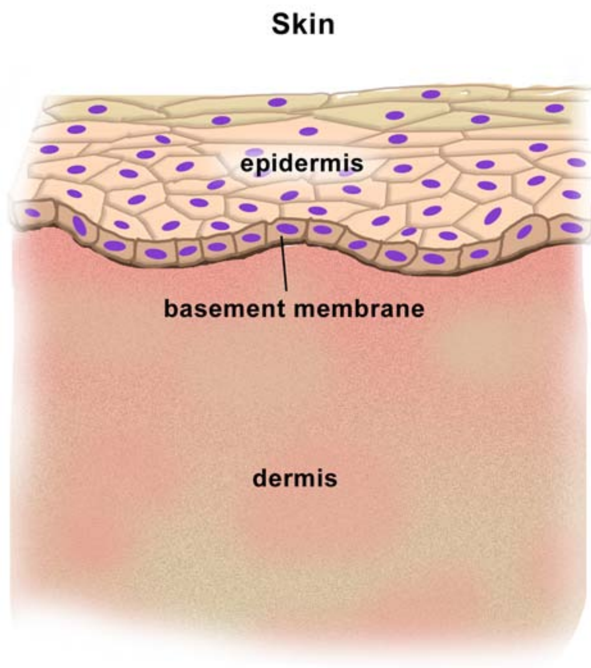


Figure by MIT OCW.

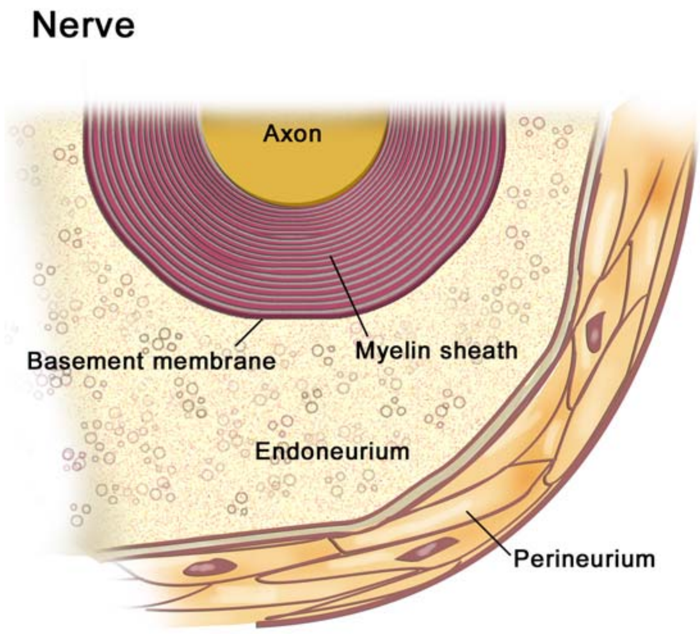


Figure by MIT OCW.

Skin

Nerve

The tissue triad in the organism

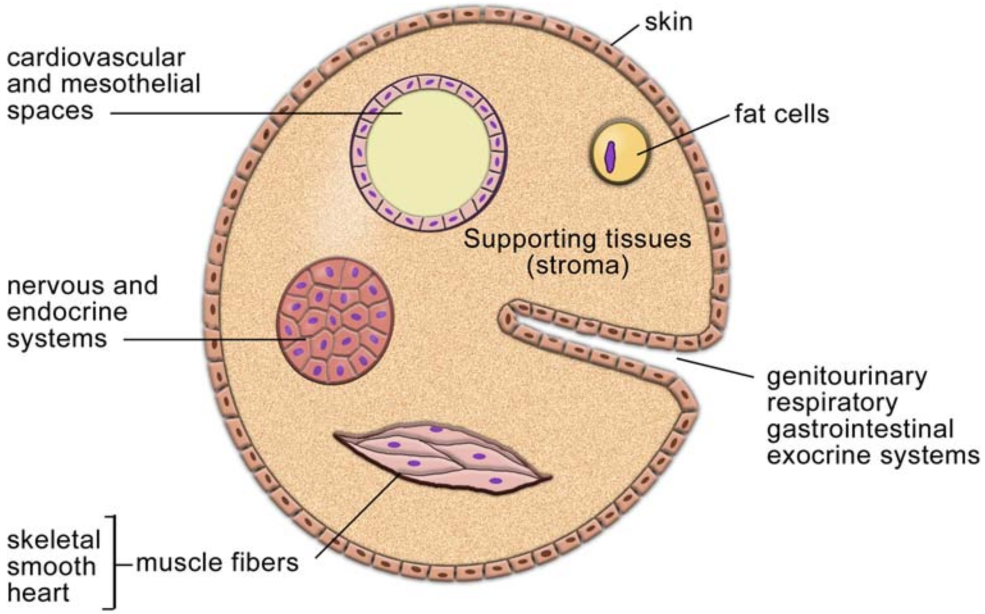


Figure by MIT OCW.

The epidermis is regenerative

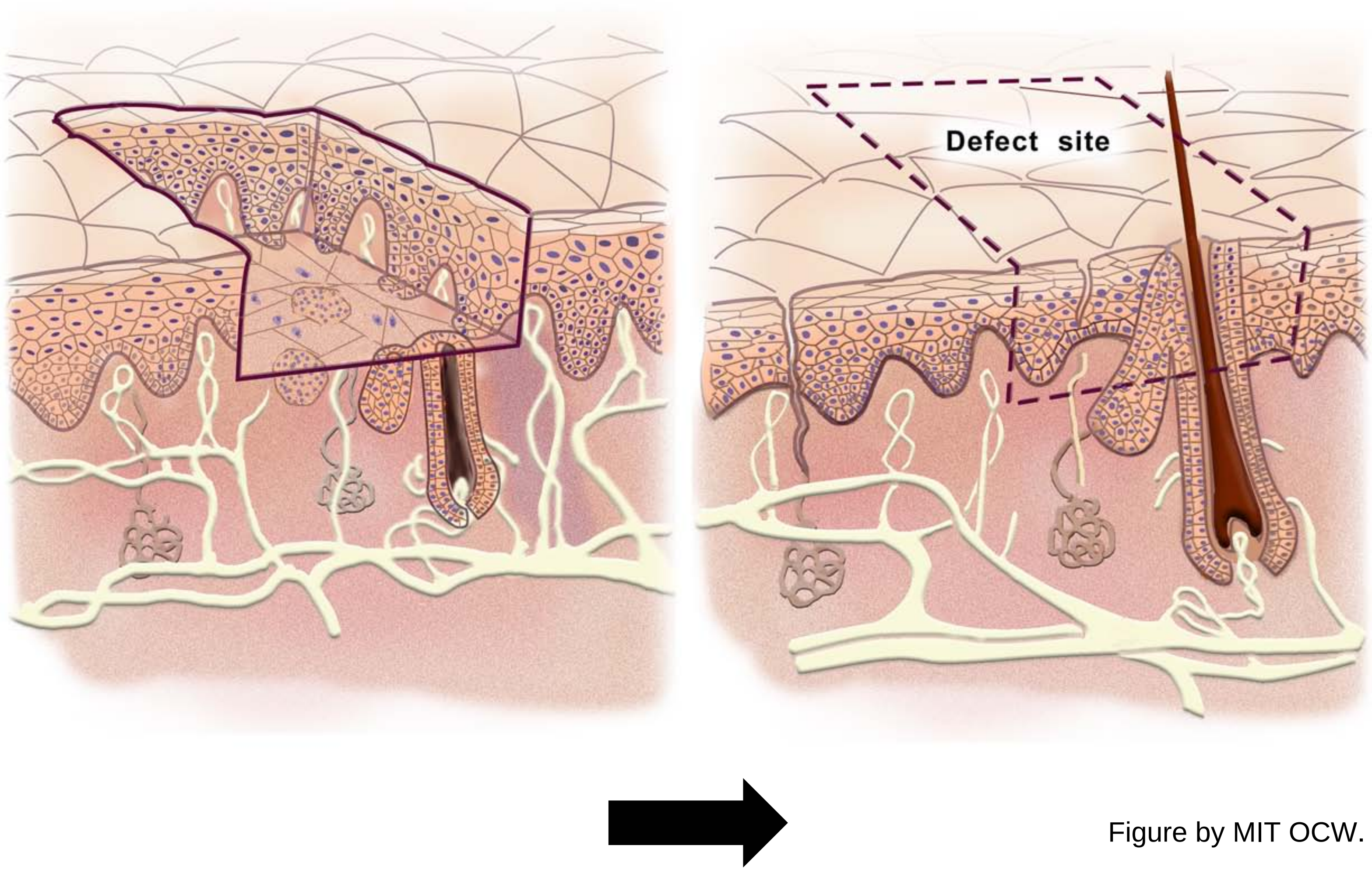


Figure by MIT OCW.

Spontaneous regeneration of excised epidermis

Left: a controlled injury (e.g. stripping or blistering) which leaves the dermis intact. Right: the epidermis recovers completely at the defect site. Hair follicles are lined with epidermal tissue and also regenerate.

The dermis is nonregenerative

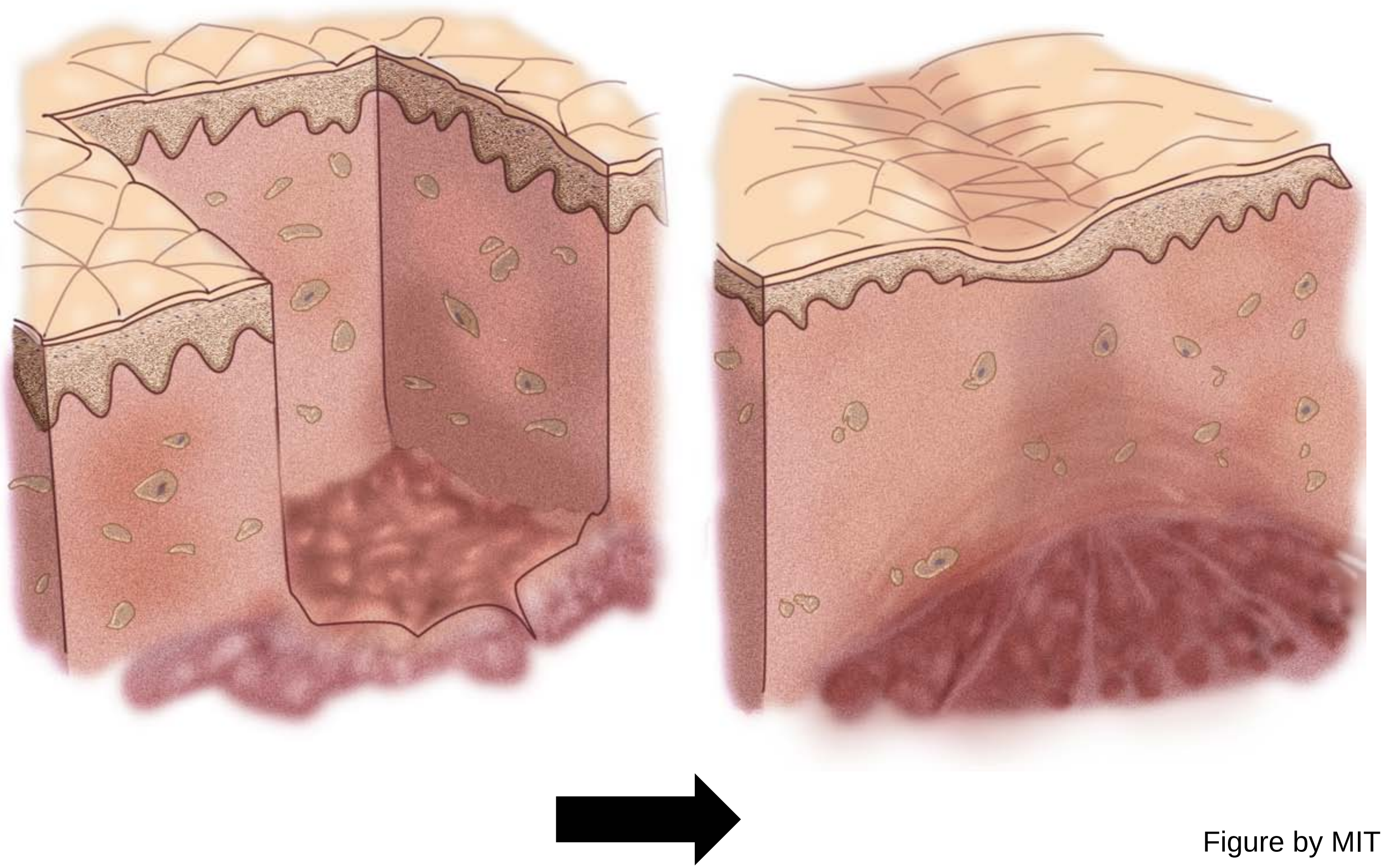


Figure by MIT OCW.

Spontaneous healing of skin excised to full thickness by contraction and scar formation. The dermis does not regenerate.

Left: Excision of the epidermis and dermis to its full thickness. Right: Wound edges contract and close, while scar tissue forms simultaneously in place of a physiological dermis. The epidermis that forms over the scar is thinner and lacks undulations (rete ridge).

injury mode (blister)

Evidence that epidermis and basement membrane in skin are regenerative

through epidermis: reversible healing

Image removed due to copyright restrictions.
See Figure 2.6 in [TORA].

between epidermis and dermis: reversible healing

through dermis: irreversible healing

crushed nerve heals spontaneously by regeneration

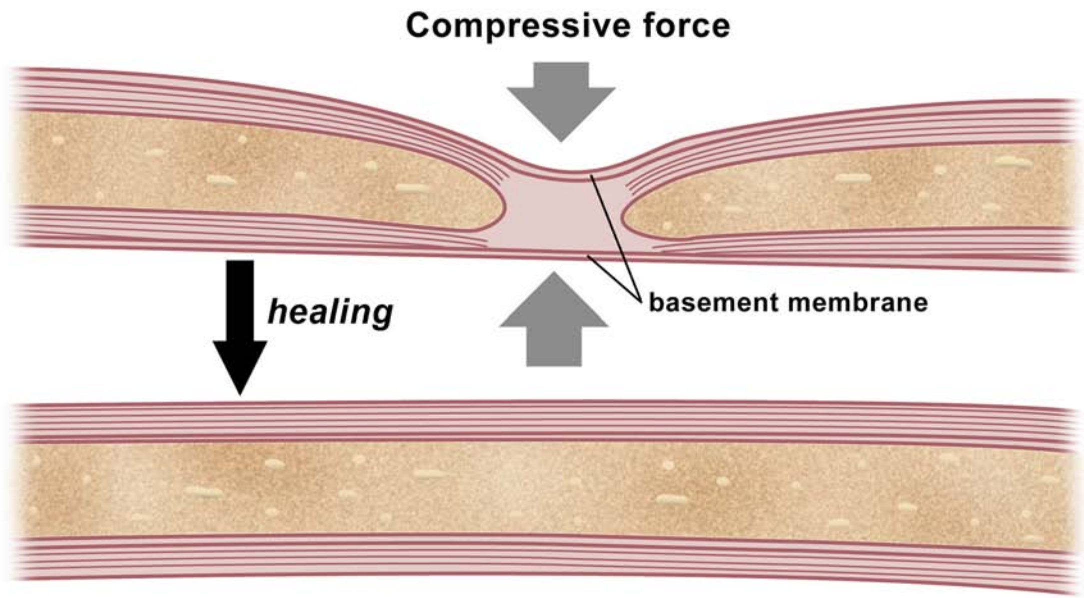


Figure by MIT OCW.

Within the nerve fiber, axons and their myelin sheath are regenerative. Top: Following mild crushing injury, the axoplasm separates and the myelin sheath degenerates at the point of injury. However, the basement membrane stays intact. Bottom: The nerve fiber regenerates after a few weeks.

The endoneurium (= stroma) is nonregenerative

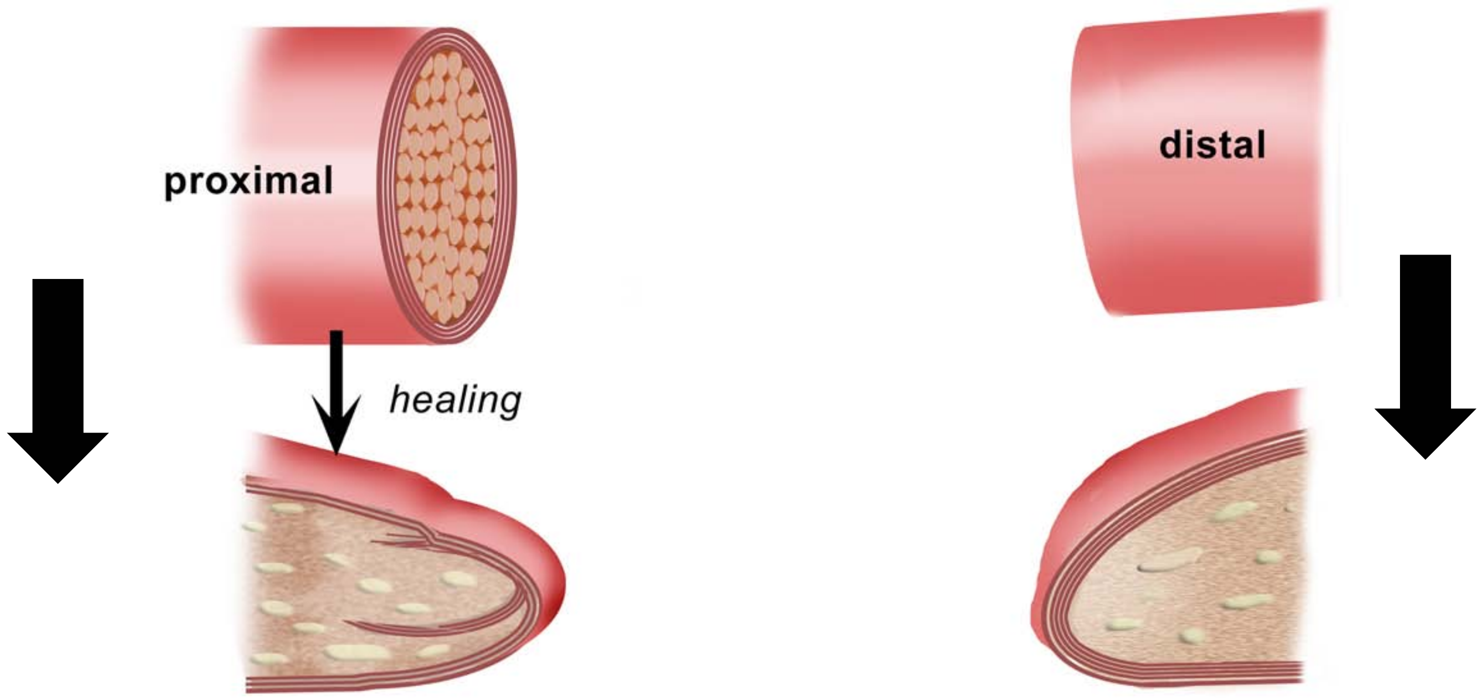


Figure by MIT OCW.

Transected nerve heals spontaneously by contraction and neuroma (neural scar) formation. No reconnection of stumps.

Most supporting tissues (stroma) that surround nerve fibers are not regenerative. Thus, while nerve fibers can regenerate following a transection, the other tissues in the nerve trunk cannot regenerate. After transection, the nerve trunk stumps become neuromas - clumps of scarred tissue that close largely by contraction.

intact nerve with myelinated (M) axon (A) and Schwann cell (S)

A completely transected nerve fiber is nonregenerative

Photos removed due to copyright restrictions.

spontaneously healed nerve (following transection) is filled with collagen fibers (scar) but has no myelinated axon or Schwann cell

	Skin	Peripheral Nerves
1. Regenerative tissues	Epidermis Basement membrane	Myelin sheath basement membrane (perineurium, in part only)
2. Nonregenerative tissues	Dermis	Endoneurial stroma

Regeneratively similar tissues in skin and peripheral nerves.

Figure by MIT OCW.
See [TORA] Chapter 2.

The central question is…

- <u>Epithelia</u> and <u>basement membrane</u> (BM) are synthesized from remaining epithelial cells.
- The <u>stroma</u> is not synthesized from remaining stromal cells. Instead these cells induce closure of the injury by contraction and synthesis of scar.
- Therefore, the key process is synthesis of the stroma.
- Once the stroma has been synthesized, epithelial cells can synthesize both epithelia and BM over it ("sequential" synthesis).
- Also, consider "simultaneous" synthesis.

Skin: In vitro or in vivo synthesis?

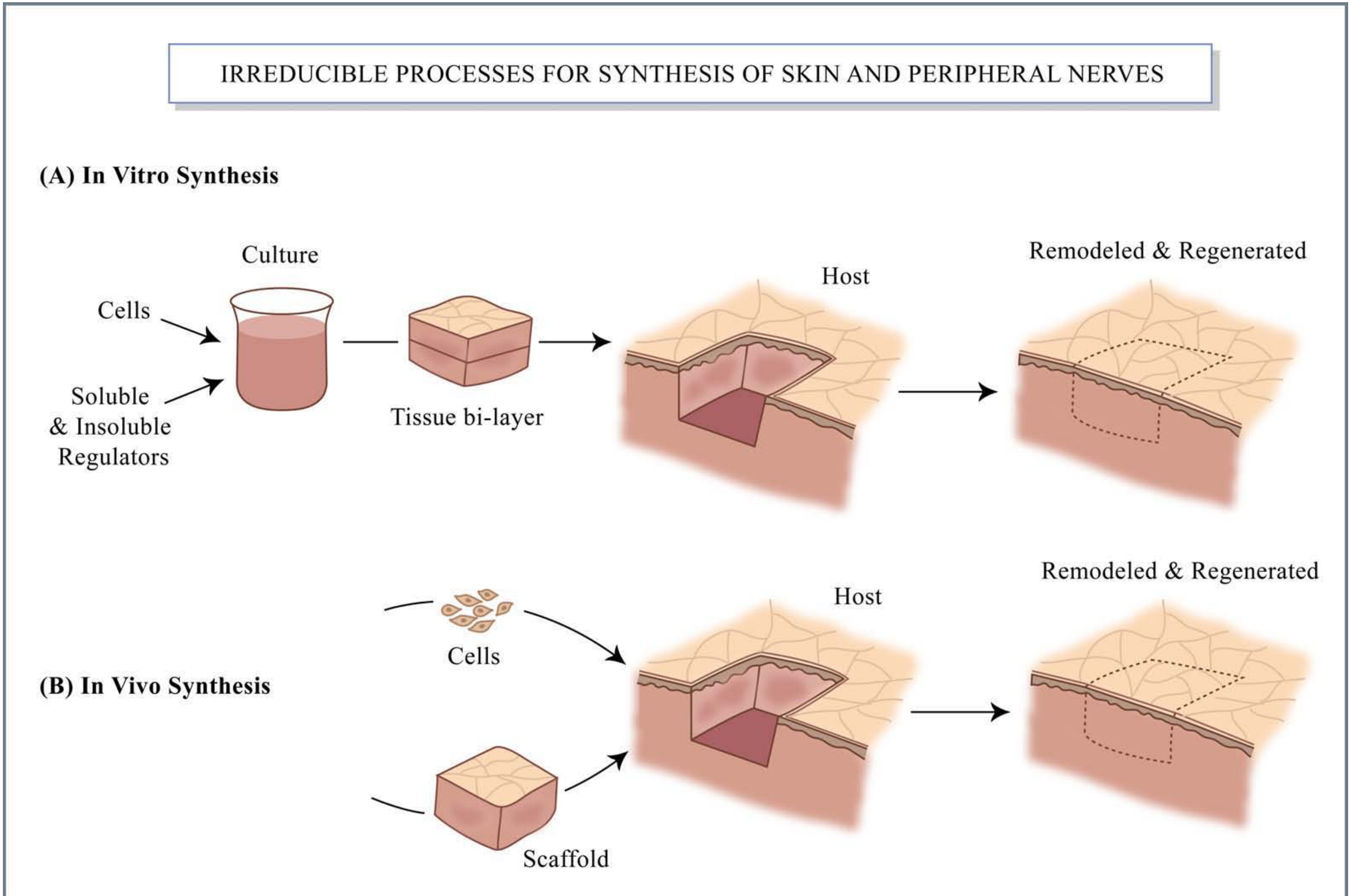


Figure by MIT OCW.

Peripheral nerves: In vitro or in vivo synthesis?

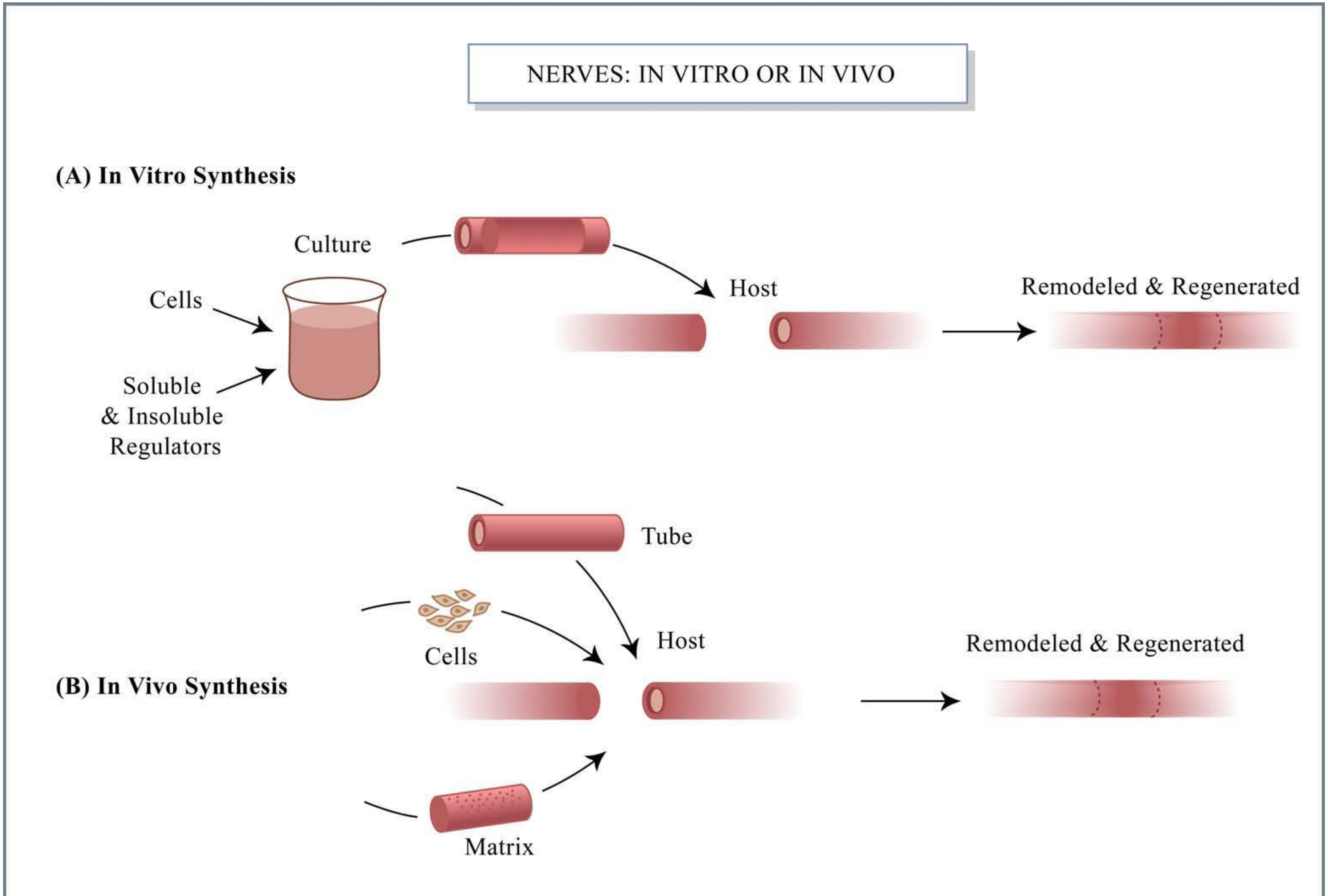
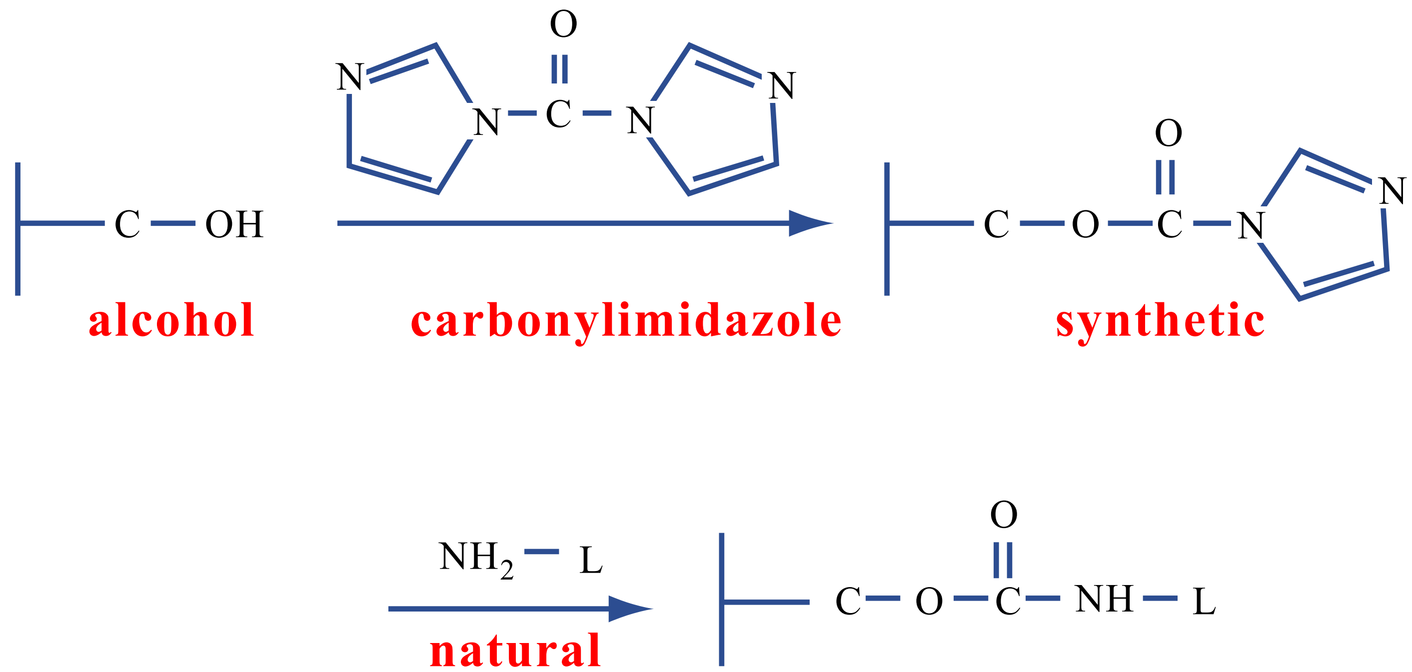


Figure by MIT OCW.

Example of scaffold studied for possible use with in vitro synthesis: synthetic and natural polymers used together



Alcohols react readily with carbonyldiimidazole to produce reactive imidazole-N-carboxylates for coupling to amine-containing ligands.

Figure by MIT OCW.

3. Examples of widespread clinical problems that have not been solved adequately

Arthritis

Several slides describing unsolved clinical problems removed due to copyright restrictions. These slides described:

Arthritis
Alzheimer's Disease
Cataracts
Glaucoma
Digestive system disorders
Obesity
Back pain
Ischemic and hemorrhagic strokes
Prostate problems
Impaired lung function and lung diseases
Heart arrhythmias
Heart attack