Tissue Engineering
(조직공학)

Changes of paradigm for organ damage treatment

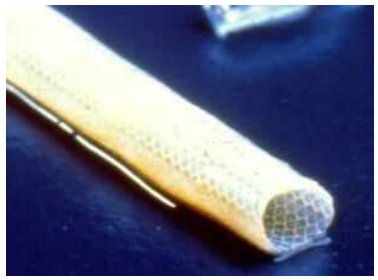
미래의학 = 재생의학
(再生醫學)
Regenerative medicine

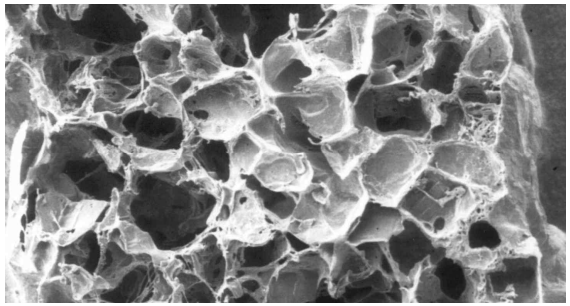
Tissue Engineering

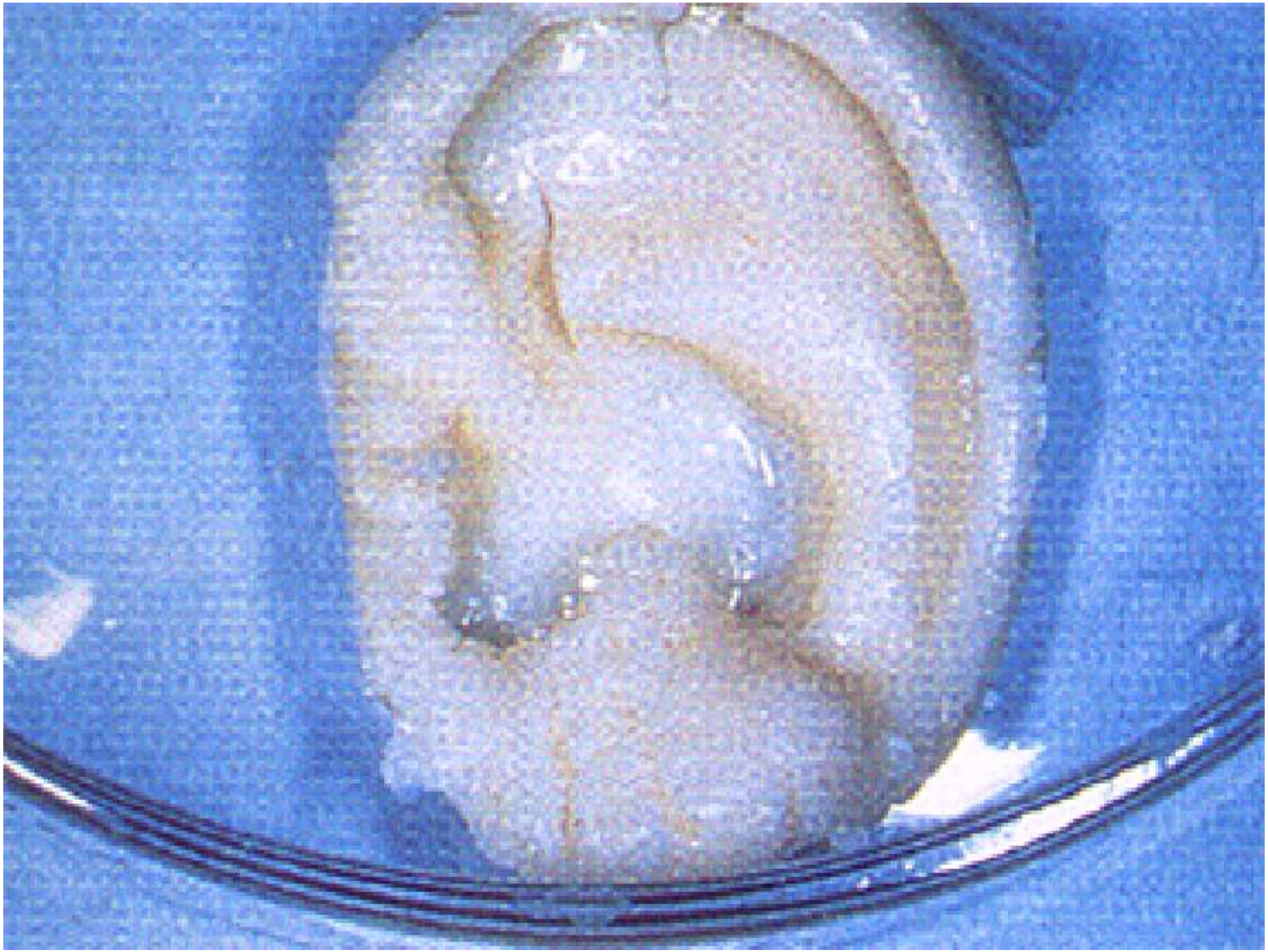
Tissue Engineering is the *in vitro* development of tissues or organs to replace or support the function of defective or injured body parts, or the directed management of the repair of tissues within the body.

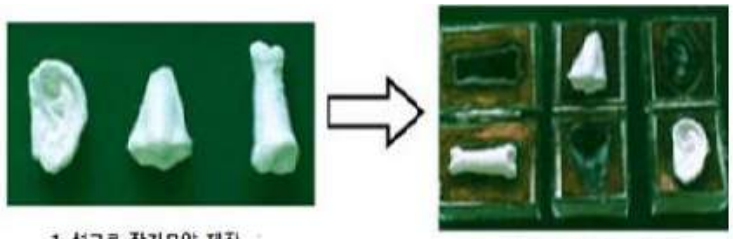
Research is presently being conducted on several different types of tissues and organs, including:

- *Skin*
- *Cartilage*
- *Blood Vessels*
- *Bone*
- *Muscle*
- *Nerves*
- *Liver*
- *Kidney*
- *etc. etc. etc.*









1. 석고로 장기모양 제작

Plaster cast

2 등판과 실리콘을 이용한 장기 형틀 제조

Mold

3. 생분해성 고분자를 이용한 코와 귀의 틀 제조 과정

Biodegradable polymer

4. 귀와 코 모양의 완성된 생분해성 고분자 틀

Scaffolds with ear or nose shape

5. 토끼의 귀에서 연골 채취

Isolation of chondrocytes from rabbit ear

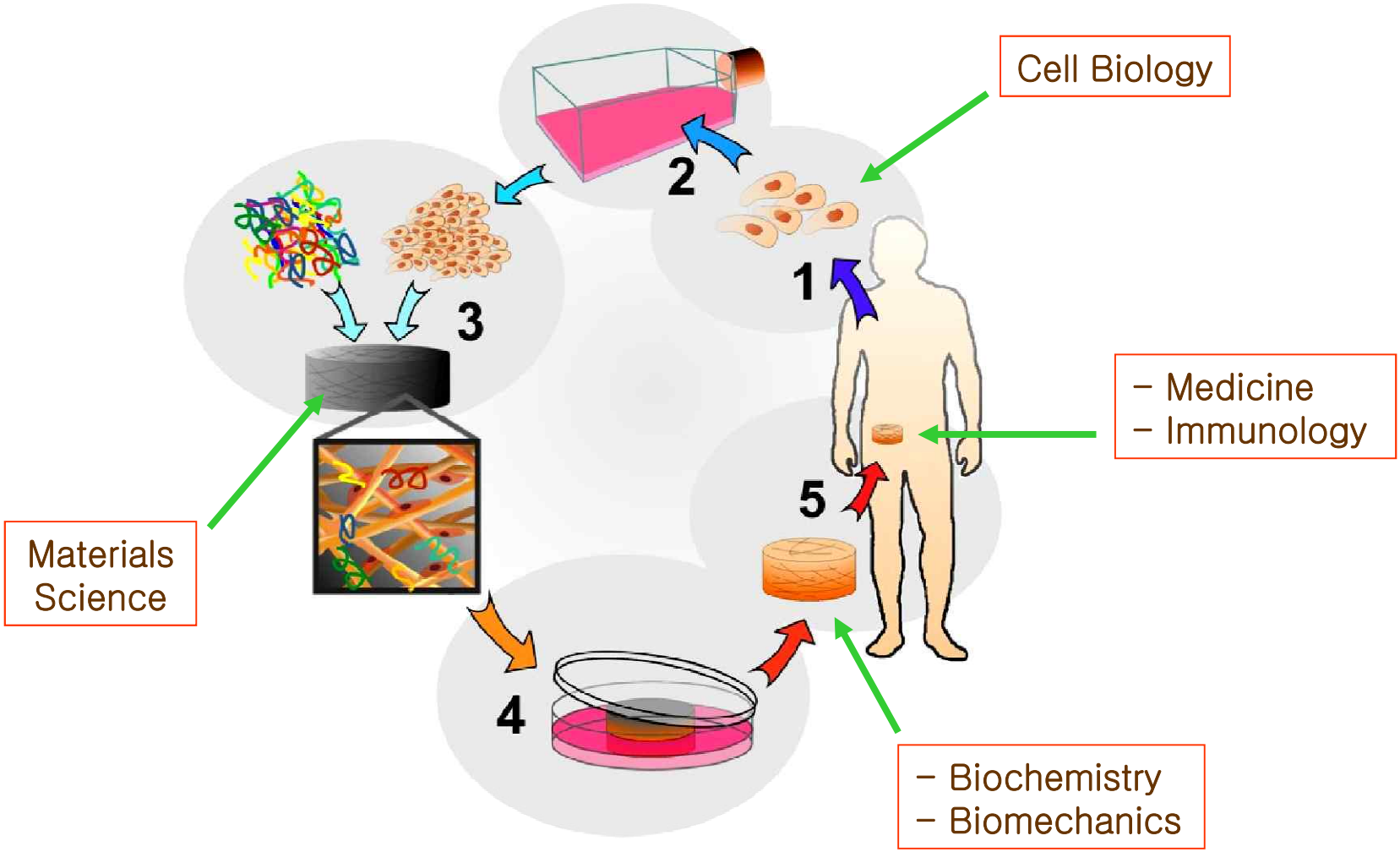
6. 생분해성 틀에 연골세포의 파종

Seeding chondrocytes on scaffold

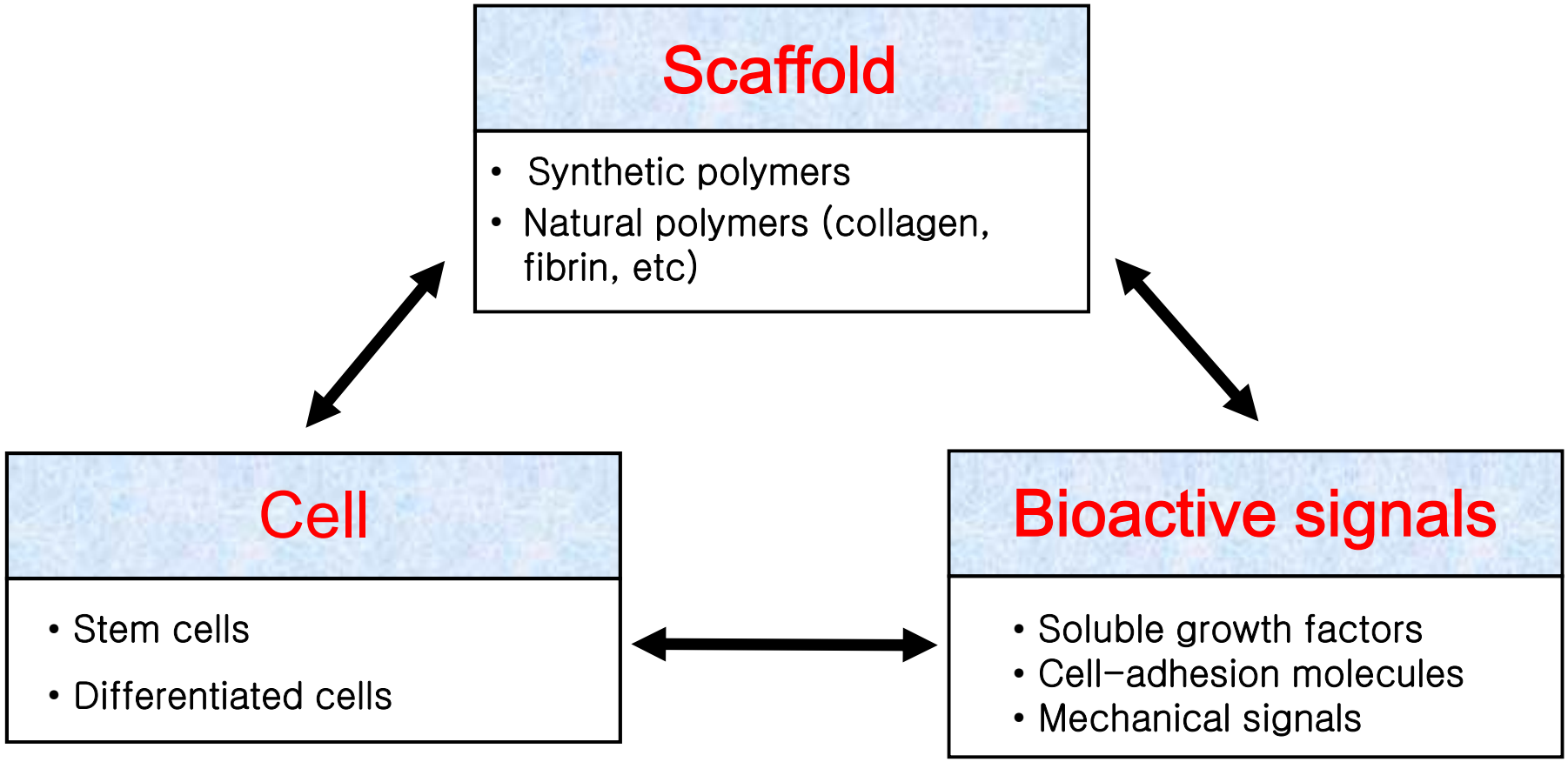
7. 코 및 귀 모양으로 제조된 인공 연골을 동물에 이식

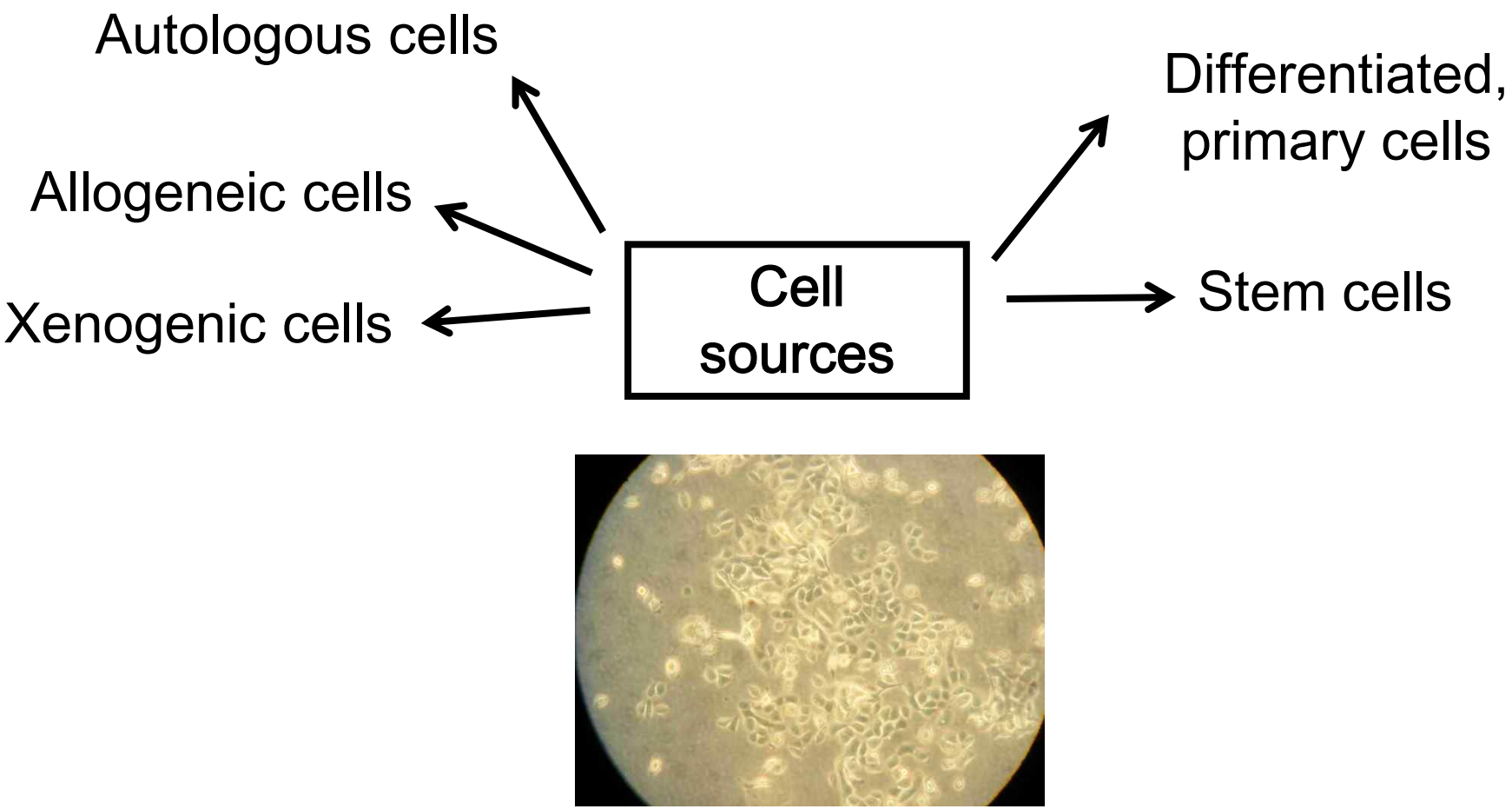
Implantation

Interdisciplinary nature of tissue engineering



Three Elements for Tissue Engineering




Autologous cells
Allogeneic cells
Xenogenic cells
Cell sources
Differentiated, primary cells
Stem cells

Soluble Signals

Three categories of soluble signals:

- Autocrine factors:

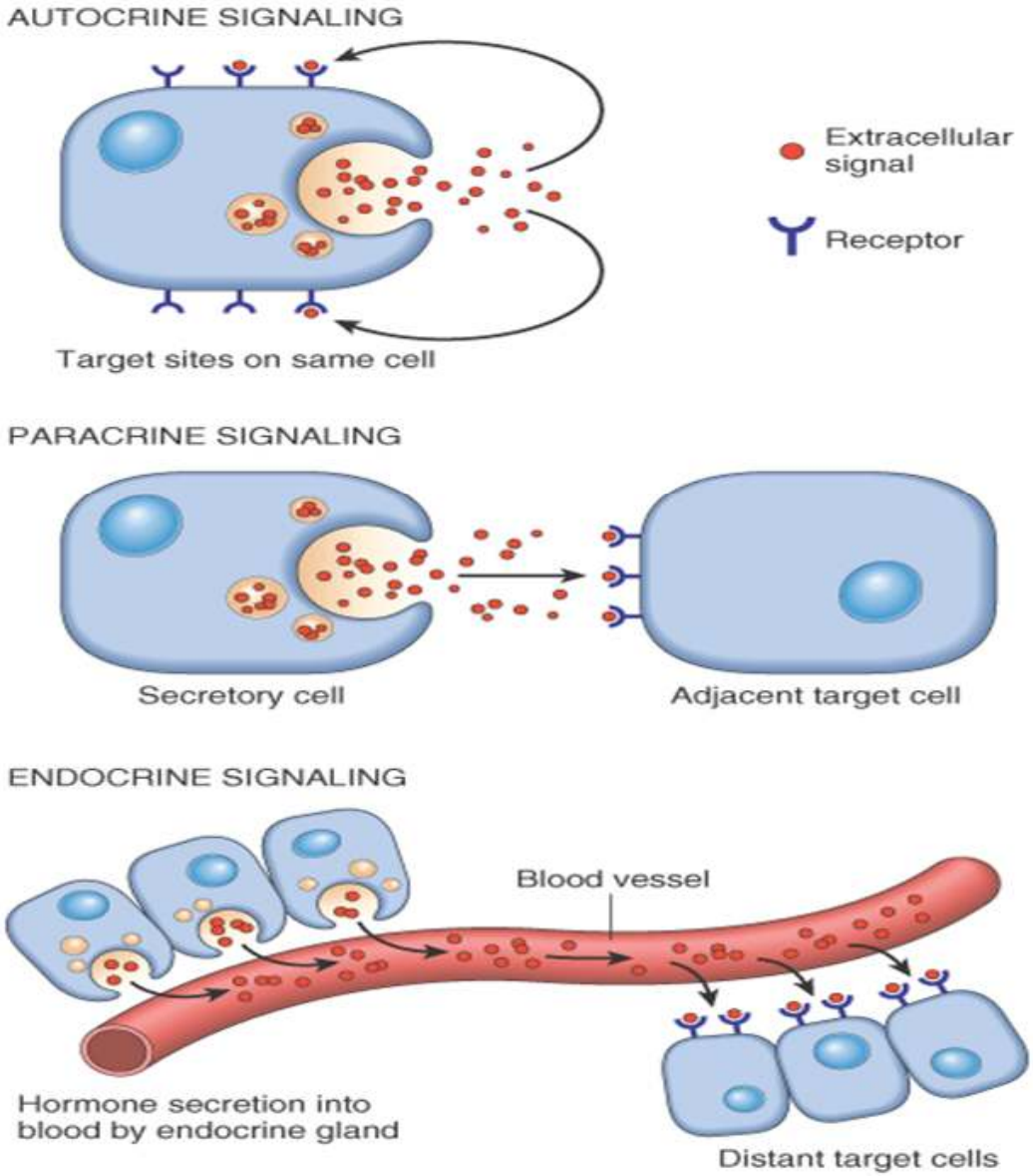
  Factors produced by cells and active on the same cell

- Paracrine factors:

  Factors produced by cells and active on their neighbors

- Endocrine factors:

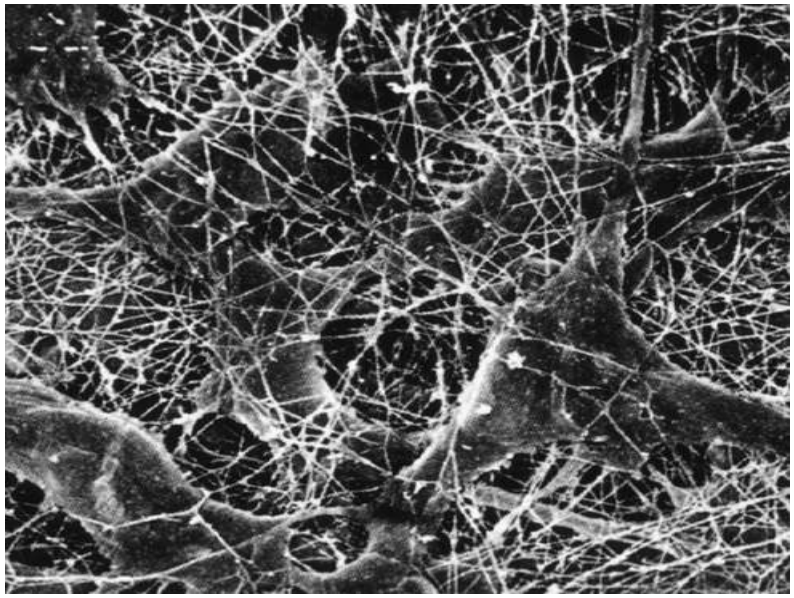
  Factors produced by cells at a distance from the target cells and carried through the blood or lymphatic fluid to the target cells



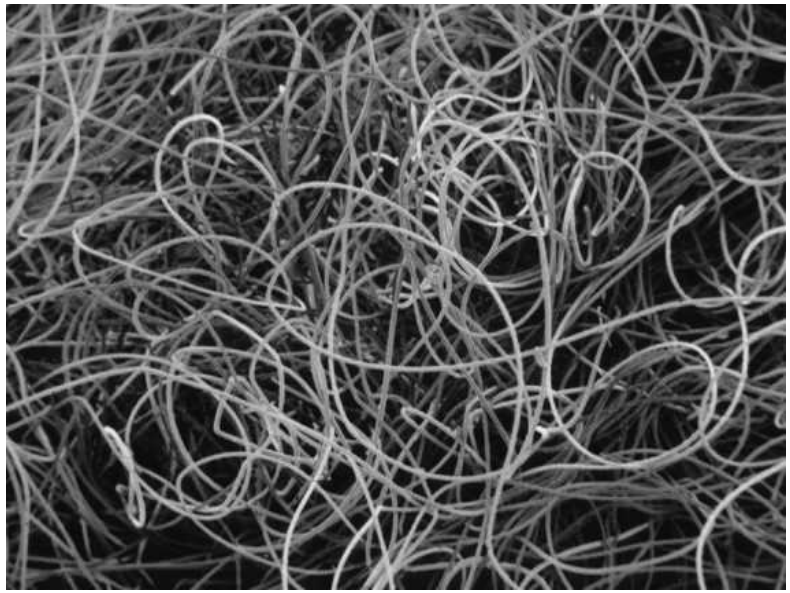
Extracellular Matrix

- play an entirely mechanical role, binding together cells in specific arrays
- major signaling system
  - direct signaling to cells in the form of chronic or persistent signaling
  - Indirectly, the components also facilitate signaling by:

  1. Stabilizing cells in appropriate configurations of ion channels, receptors, antigens, etc.
  2. Influencing intracellular pathways
  3. Inducing appropriate cell shapes (flattened or three-dimensional)

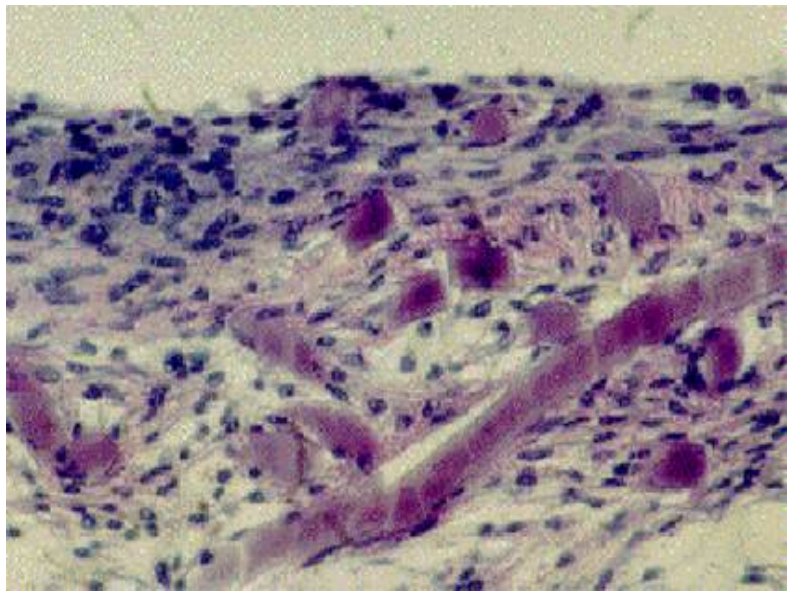


Connective tissue



Polymer scaffold

Cell-seeded polymer scaffold



Engineered tissue

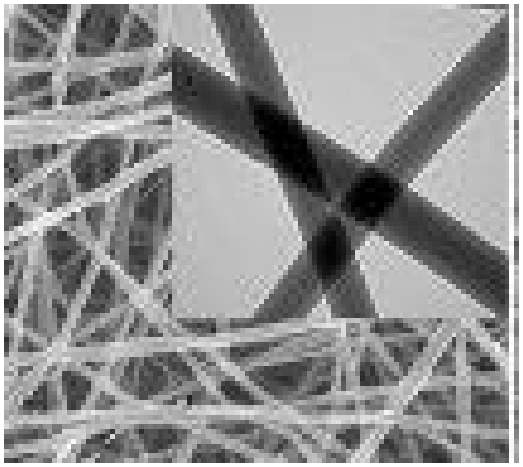
The Roles of Scaffold in Tissue Engineering

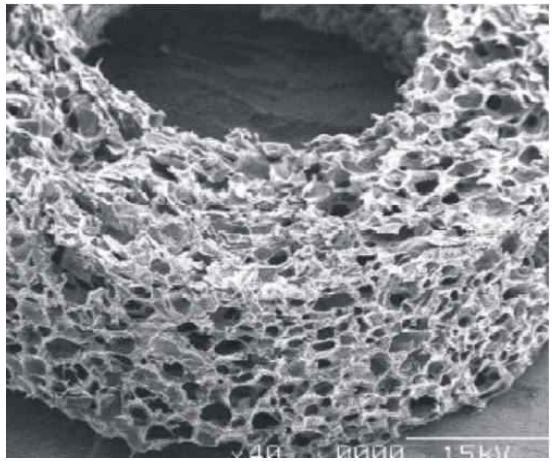
- Provide surface for cell adhesion
- Induce differentiation of cells on scaffold
- Provide space for tissue formation
- Determine 3D structure of engineered tissue
- Provide mechanical support
- Act as a delivery vehicle for cells and bioactive molecules

PRASAD SHASTRI AND IVAN MARTIN Massachusetts Institute of Technology

Synthetic biomaterials

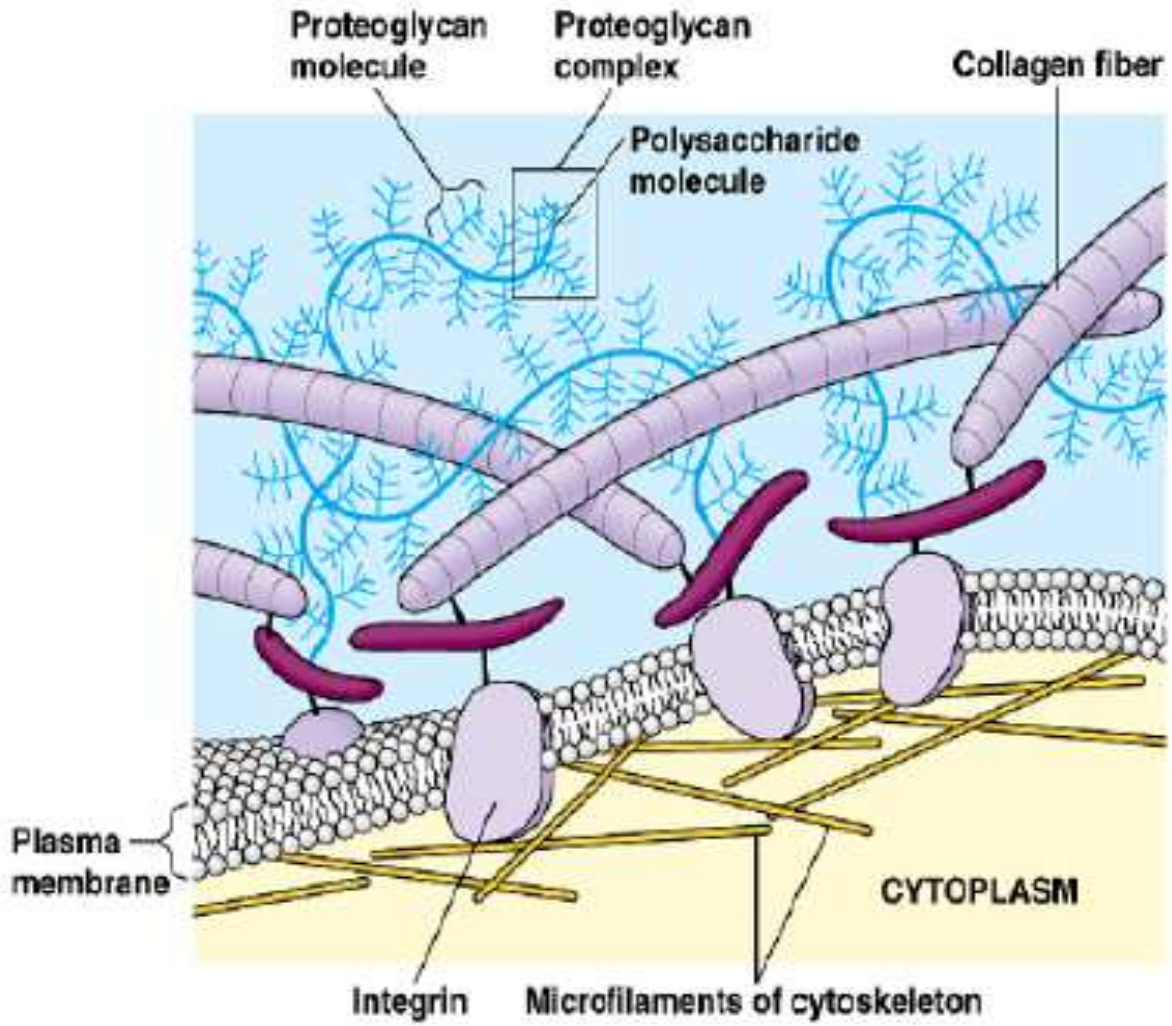
- Polylactic acid (PLA)
- Polyglycolic acid (PGA)
- Poly-e-caprolactone (PCL)





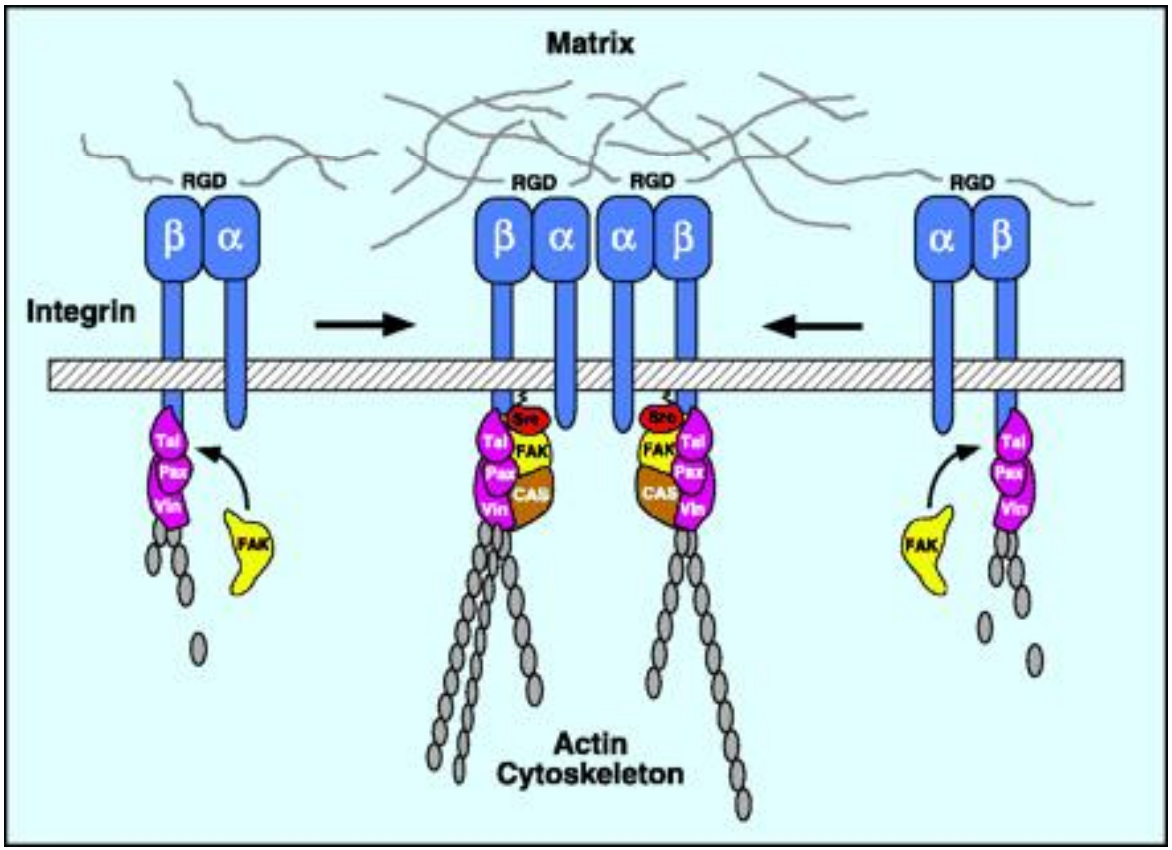
Natural biomaterials

- Collagen
- Fibrin
- Hyaluronic acid

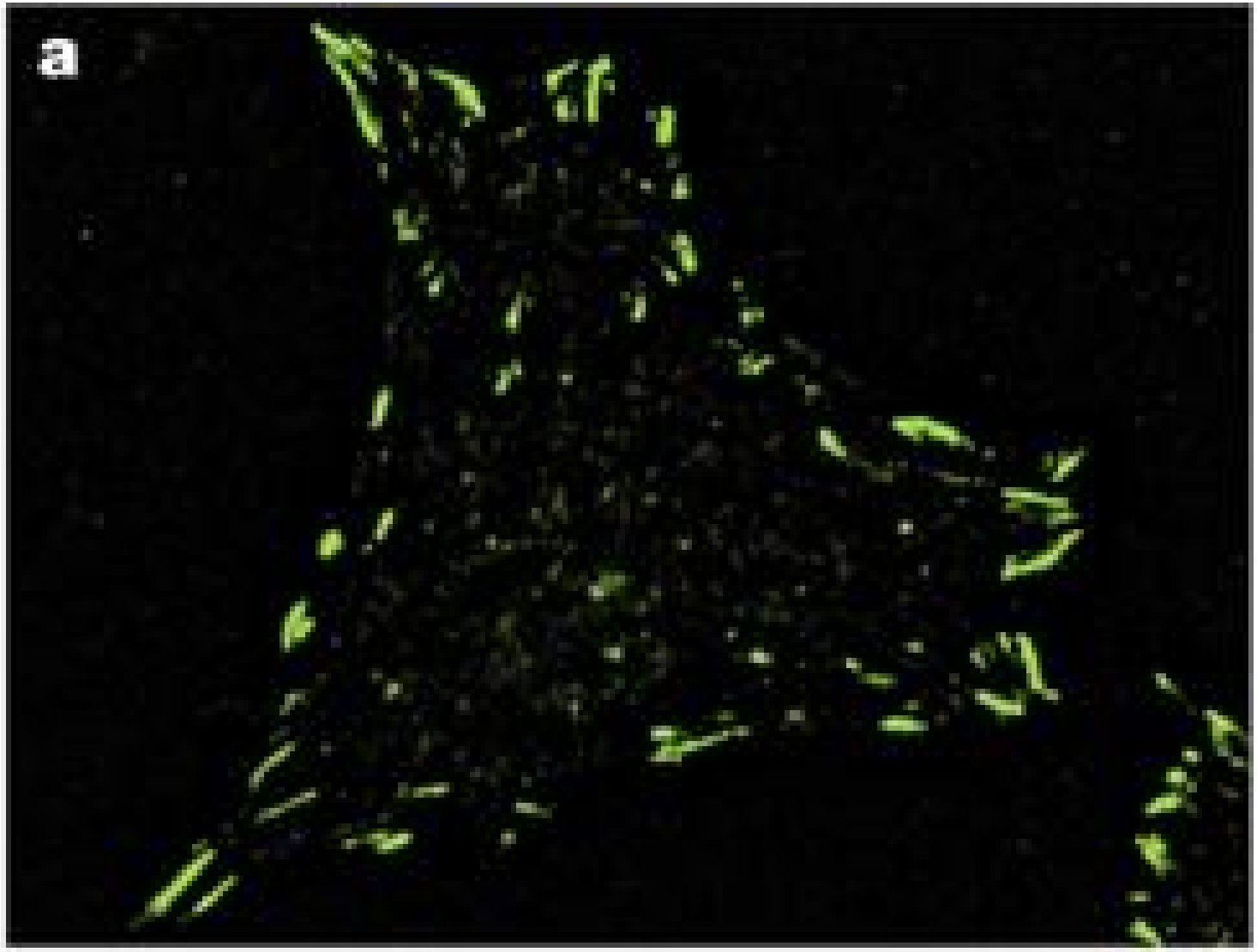


Cell adhesion process

- integrin binding
- association with actin cytoskeleton
- integrin clustering
- focal adhesion assembly



Focal adhesion



Advantages of Tissue Engineering

- Unlimited supply
- No immunosuppression therapy necessary when autologous cells are used
- Replacement of complete tissue functions
- Ability to repair and grow
- Durable

THE NEW ERA OF REGENERATIVE MEDICINE

Dozens of biotech companies and university labs are developing ways to replace or regenerate failed body parts. Here are a few of the projects:

BONE

Bone-growth factors or stem cells are inserted into a porous material cut to a specific shape, creating new jaws or limbs. A product that creates shinbones is in clinical trials.

COMPANIES: Creative Biomolecules, Orquest, Sulzer Orthopedics Biologics, Genetics Institute, Osiris Therapeutics, Regeneron.

SKIN

Organogenesis' Apligraf, a human-skin equivalent, is the first engineered body part to win FDA approval, initially for leg ulcers. Other skins are in the works for foot ulcers and burns.

COMPANIES: Organogenesis, Ad-vanced Tissue Sciences, Integra LifeSciences, LifeCell, Ortec International.

PANCREAS

Insulin-manufacturing cells are harvested from pigs, encapsulated in membranes, and injected into the abdomen. The method has been tested in animals and could be in human trials in two years.

COMPANIES: BioHybrid Technologies, Neocrin, Circe Biomedical

HEART VALVES, ARTERIES, AND VEINS

A 10-year initiative to build a heart has just started. Genetically engineered proteins have been successfully used to regrow blood vessels.

COMPANIES: Organogenesis, Advanced Tissue Sciences, Genetech, LifeCell, Reprogenesis.

DATA: BUSINESS WEEK, DRUG & MARKET DEVELOPMENT REPORTS

SALIVA GLANDS

Proteins called aquaporins that allow cells to secrete water are used to recreate saliva glands damaged by disease or radiation. Glands are also being engineered to secrete healing drugs. The technique has proven successful in mice.

COMPANIES: None yet.

URINARY TRACT

Cartilage cells are taken from the patient, packed into a tiny matrix, and injected into the weakened ureter, where they bulk up the tissue walls to prevent urinary backup and incontinence. The method is in late-phase clinical trials.

COMPANIES: Reprogenesis, Integra LifeSciences.

BLADDER

Doctors at Children's Hospital in Boston have grown bladders from skin cells and implanted them in sheep. They are about to try the same process on a patient

COMPANIES: Reprogenesis.

CARTILAGE

A product is already on the market that regrows knee cartilage. A chest has been grown for a boy and a human ear on a mouse.

COMPANIES: Genzyme Tissue, Biomatrix, Integra LifeSciences, Advanced Tissue Sciences, ReGen Biologics, Osiris Therapeutics

TEETH

Enamel matrix proteins are used to fill cavities. It works in dogs; human trials are a few years away.

COMPANIES: Biora, Atrix Laboratories, Creative BioMolecules.

BREAST

In preclinical studies, several companies have been able to create a cosmetic nipple by inserting a ball of cartilage. Researchers are now trying to grow a whole cosmetic breast.

COMPANIES: Reprogenesis, Integra LifeSciences.

LIVER

A spongy membrane is built up and then seeded with liver cells. Organs the size of a dime have been grown, but a full-size liver could take 10 years due to its complexity.

COMPANIES: Advanced Tissue Sciences, Human Organ Sciences, Organogenesis.

SPINAL CORD NERVES

Scientists are in-vestigating nerve-growth factors, injecting them at the site of damage to encourage regeneration or seeding them along biodegradable filaments and implanting them. Rats have been made to walk again.

COMPANIES: Acorda, Regeneron, CytoTherapeutics, Guilford Pharmaceuticals.

Tissue-engineered Skin

- Skin
  - Two layers : dermis, epidermis
  - Grows very well in *ex vivo* cultivation
  - Transplanted dermal fibroblasts are nonimmunogenic
  - Transplantation for burns and diabetic ulcers

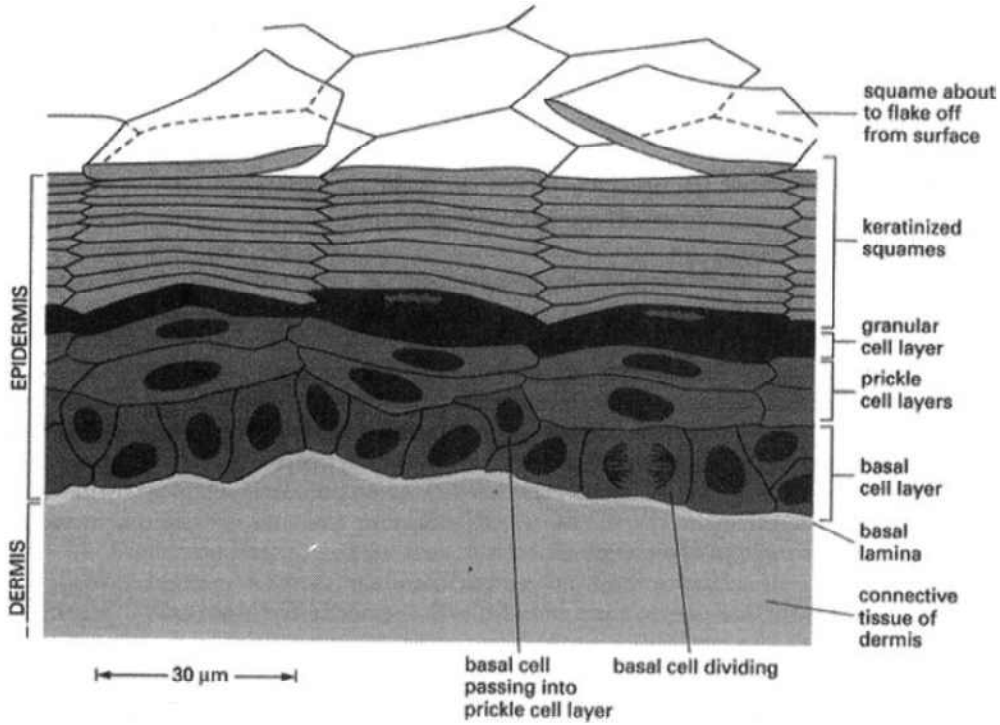


Figure 7.4 The cellular arrangement and differentiation in skin. The cross section of skin and the cellular arrangement in the epidermis and the differentiation stages that the cells undergo (from Alberts et al., 1994).

Strategies of Tissue Engineered Skin

Ortec International

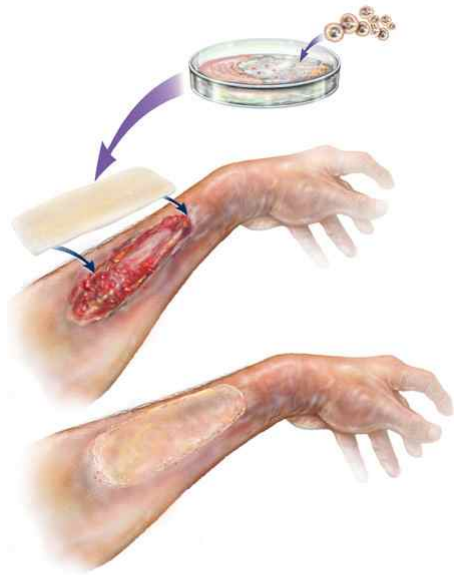
ATS
(Smith & Nephew)

Two
-layered

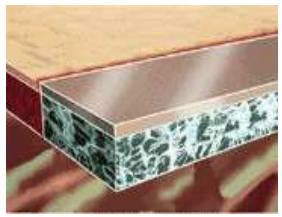
Uni-layered

Without cells

Organogenesis
(Norvatis)

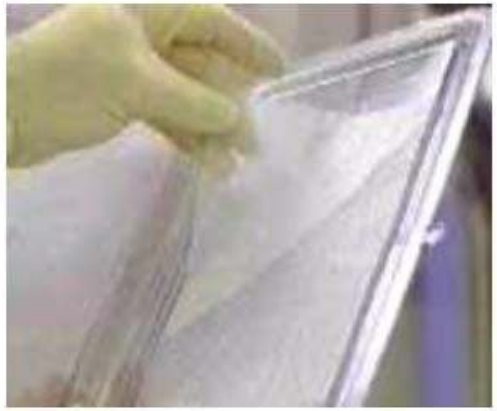


Integra LifeSci.

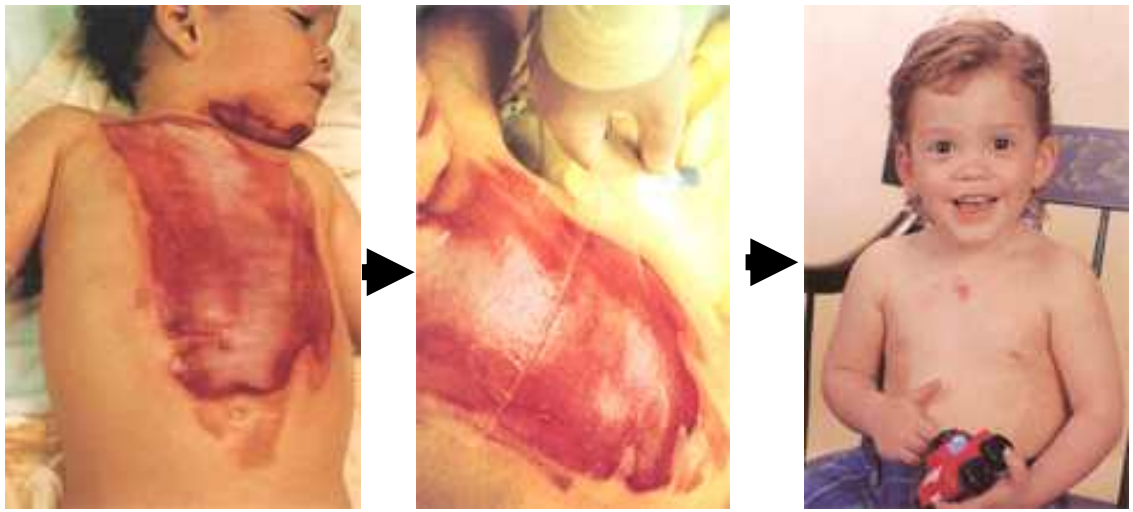


Skin : The first TE product

(Dermagraft™)



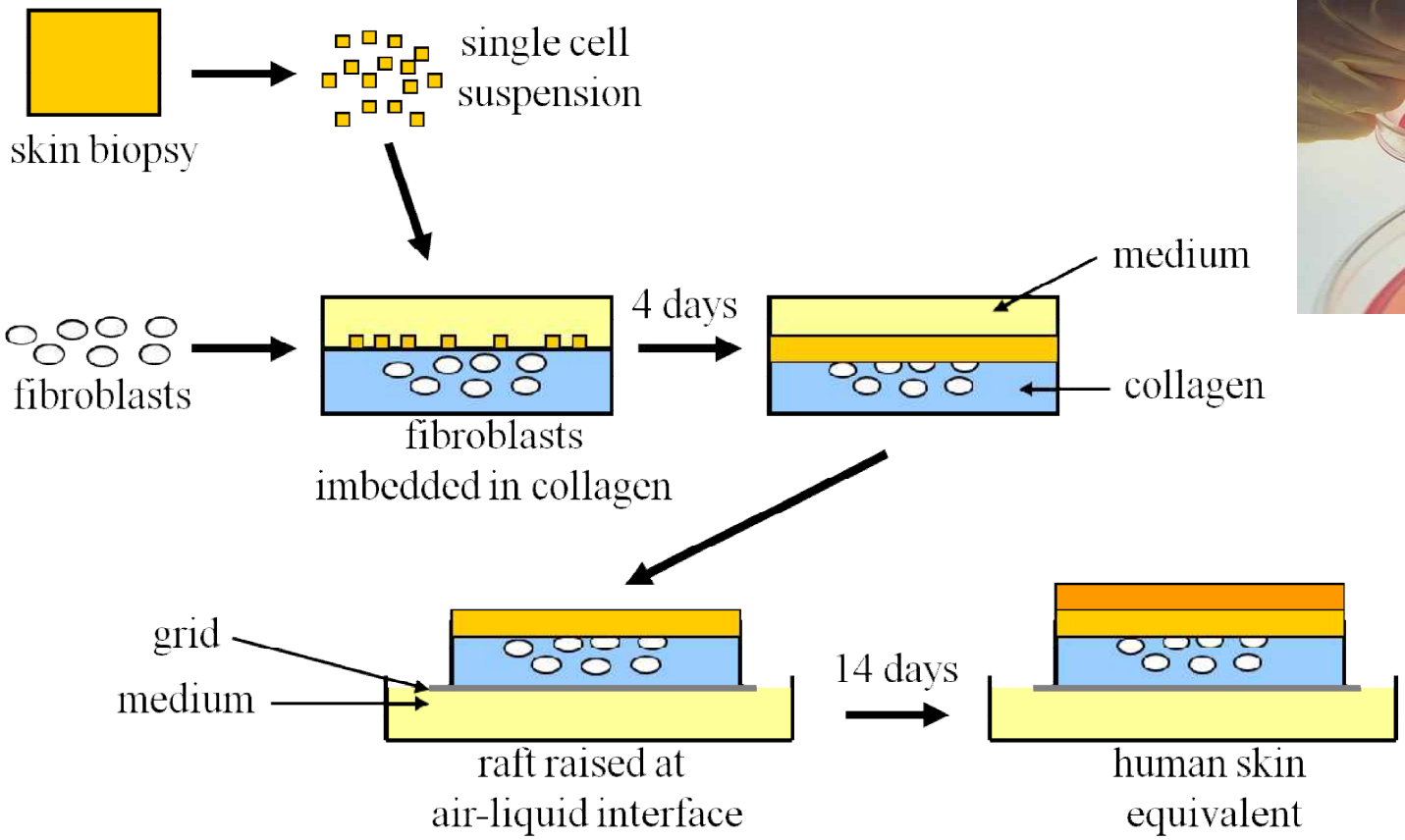
Fibroblasts isolated from baby foreskin collected from circumcison and seeded on synthetic polymer scaffold (Advanced Tissue Sciences)



Burn

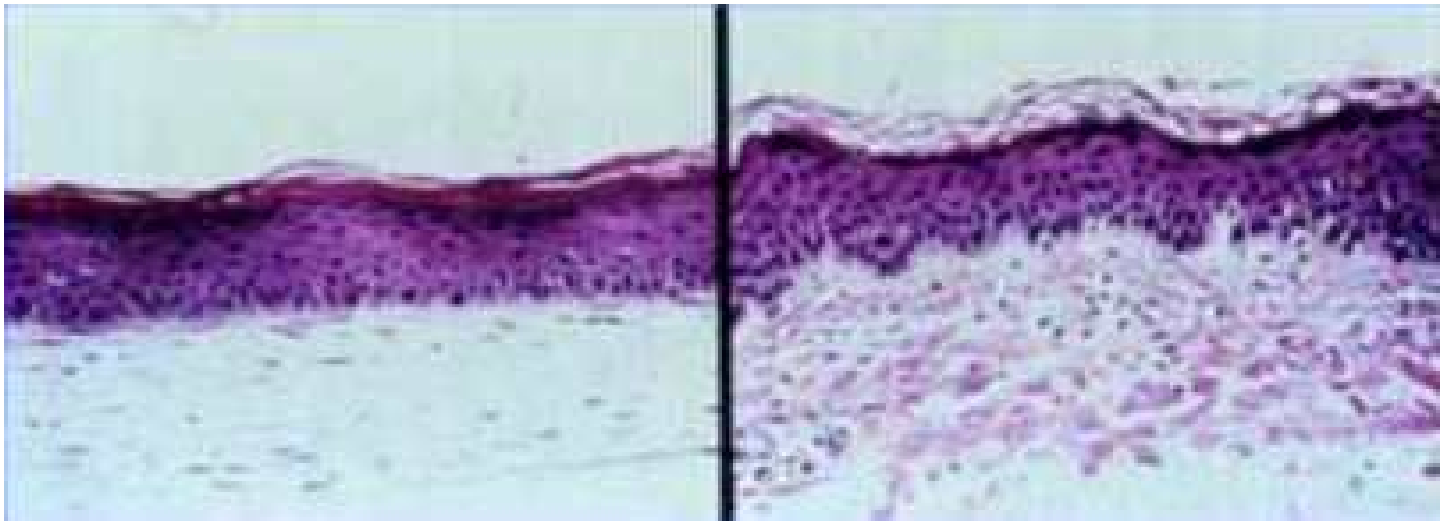
Ulcer

Fabrication method of Apligraf



Apligraf

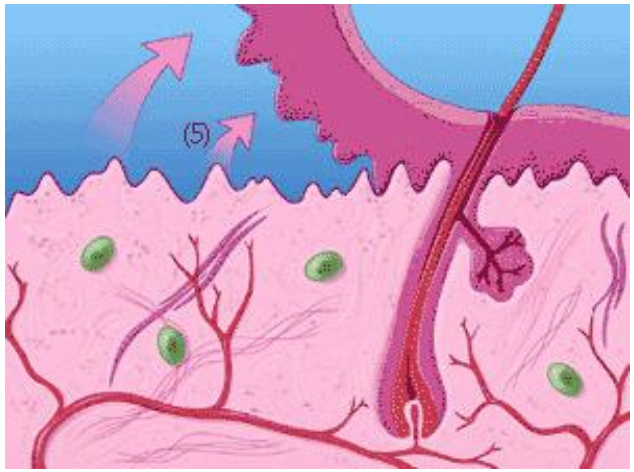
Human skin

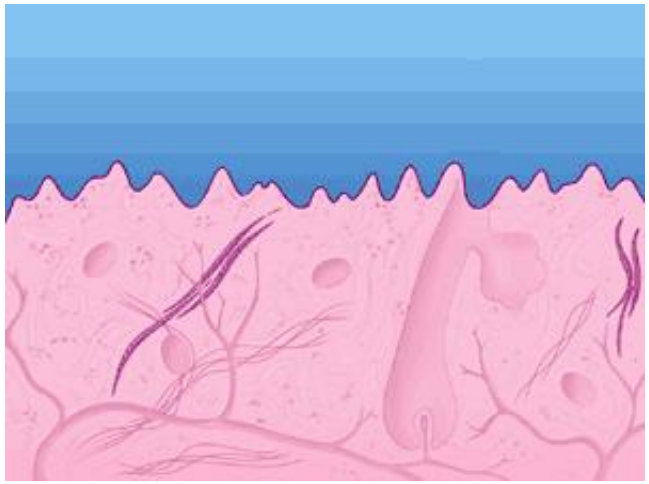


Pre application

Day 21

Day 28





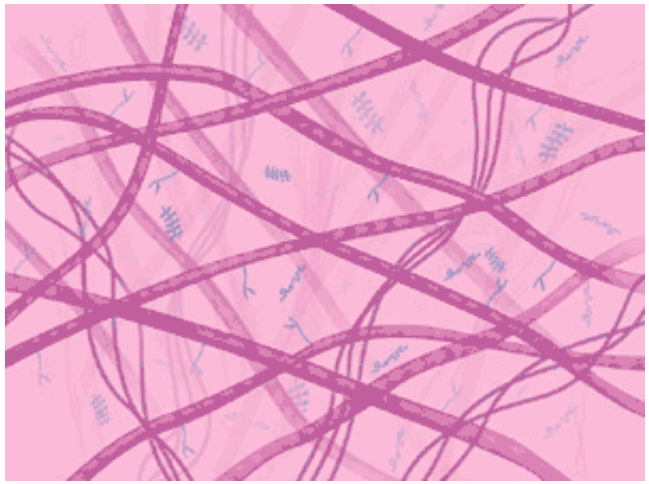
LifeCELL

AlloDerm®;

Dry-preserved allogaft

Cell removed by NaCl

and SDS, freeze-dried.



Bioland

Nature, Science & Life

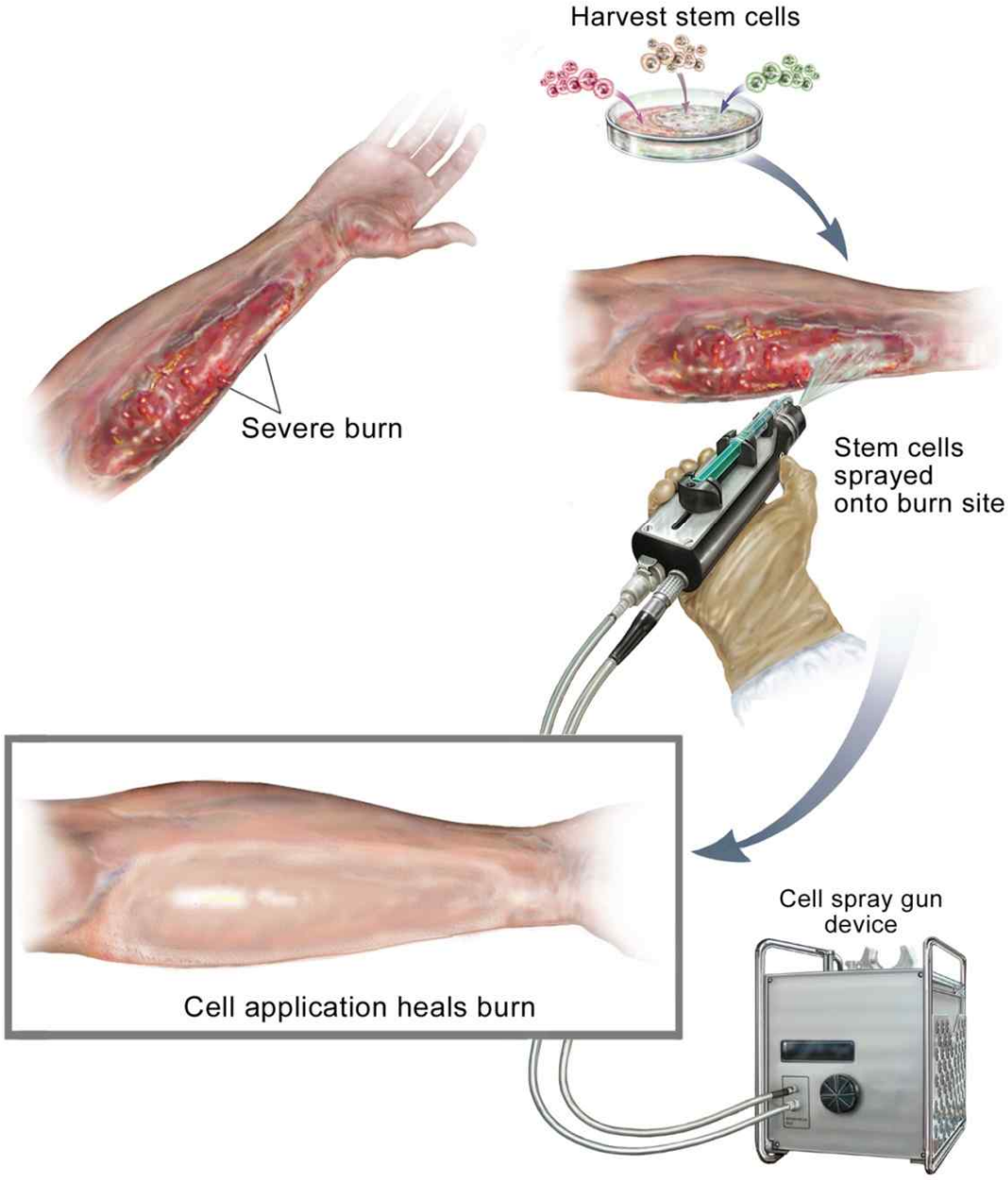
Artificial Skin
Integra®
Dermal Regeneration Template®

INTEGRA® Artificial Skin

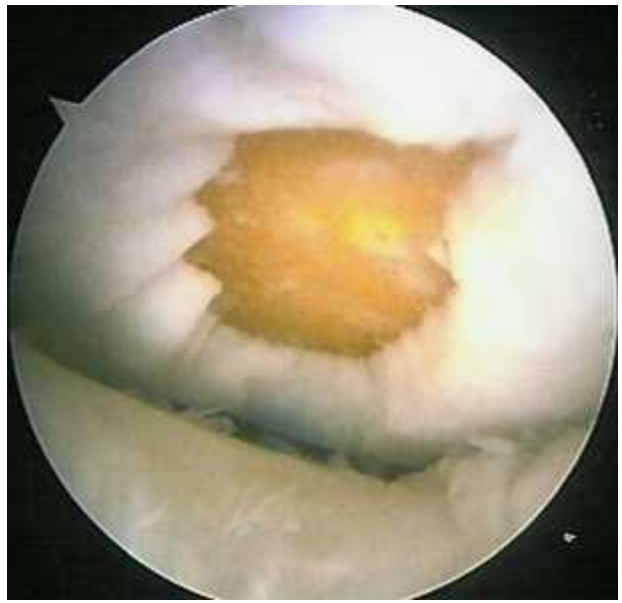
Skin The dermal replacement layer is made of a porous matrix of fibers of cross-linked ***bovine tendon collagen and a glycosaminoglycan (chondroitin-6-sulfate)*** that is manufactured with a controlled porosity and defined degradation rate.

Skin Cell Spray-Transplantation Device

(Phase II) - Cell application



Cartilage injury



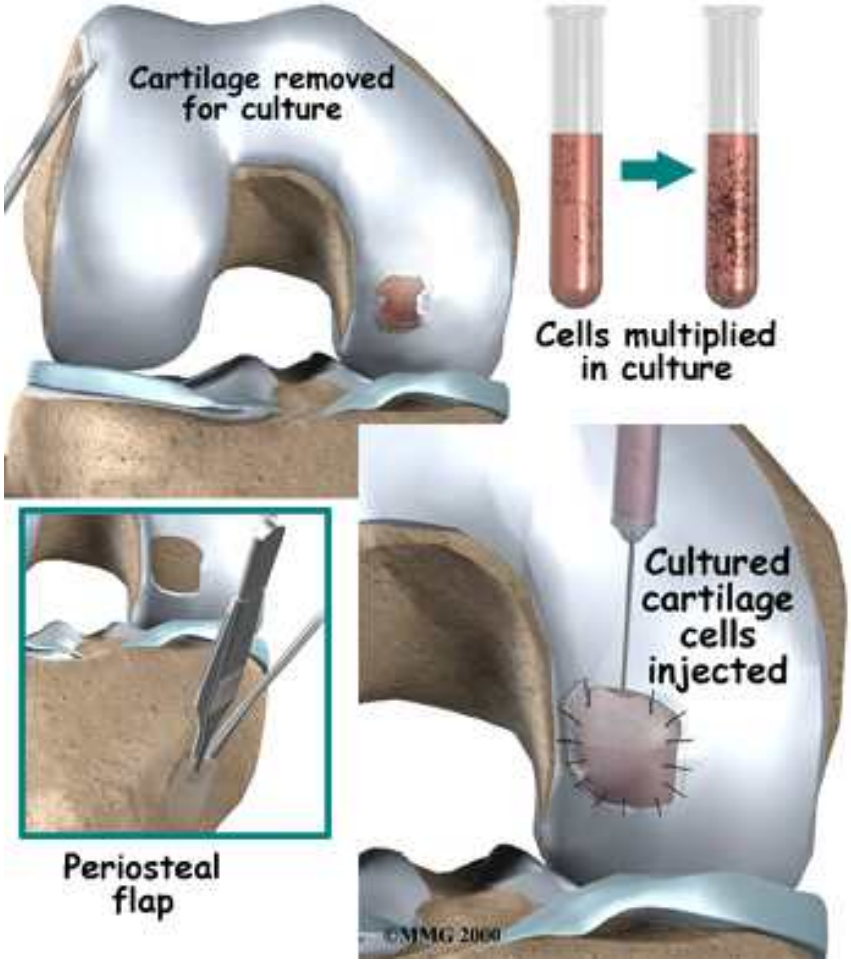
www.yorkshirekneeclinic.com

- Articular cartilage has limited self-healing potential. Since articular cartilage has neither vascular supply nor easy access to stem cells, repair is often unsuccessful.
- Approximately 10% of total population suffers from cartilage injury.

Current therapies for cartilage repair :

1. Autologous chondrocyte implantation (ACI)

㈜세원셀론텍

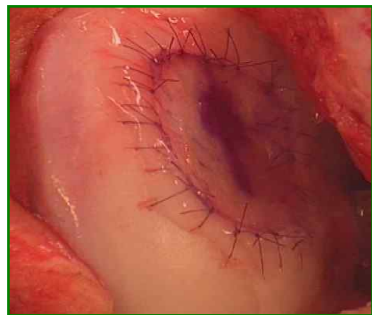


Strengths

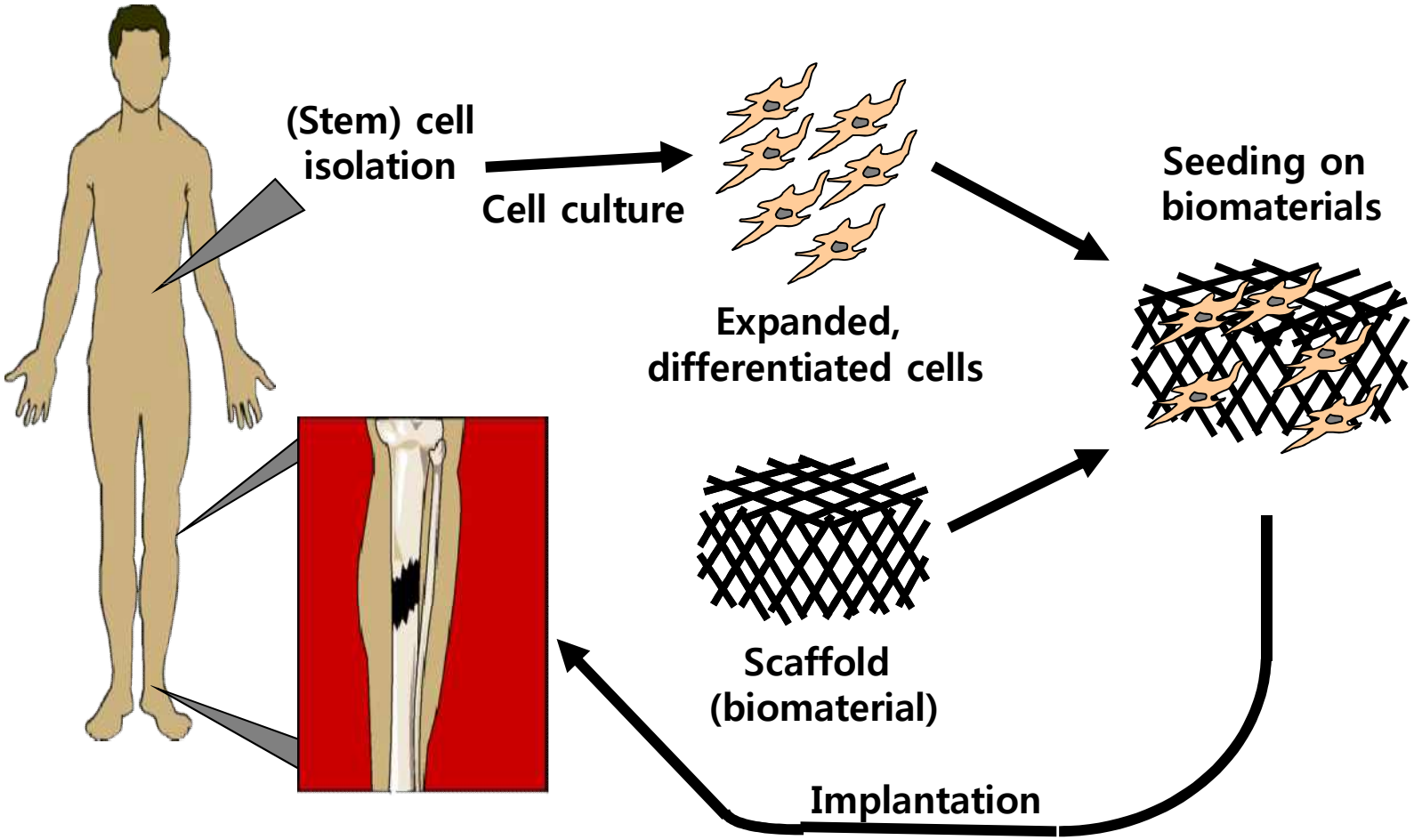
- Regeneration of hyaline-like cartilage
- Not limited by defect size

Limitations

- Multiple surgery procedures
- Open/More invasive procedure
- Expensive cost due to in vitro cell expansion step
- Patients' waiting during the in vitro cell expansion period
- Longer recovery period



Bone Regeneration: Convergence of tissue engineering, stem cells, and biomaterials

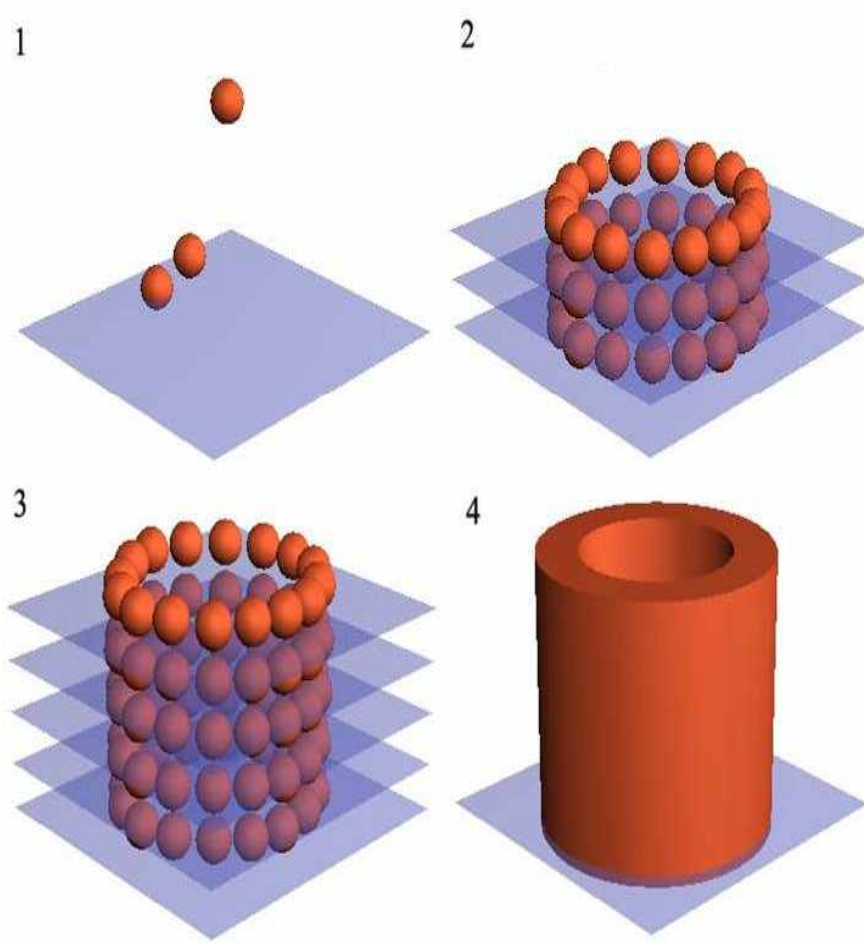


Organ Printing Technology

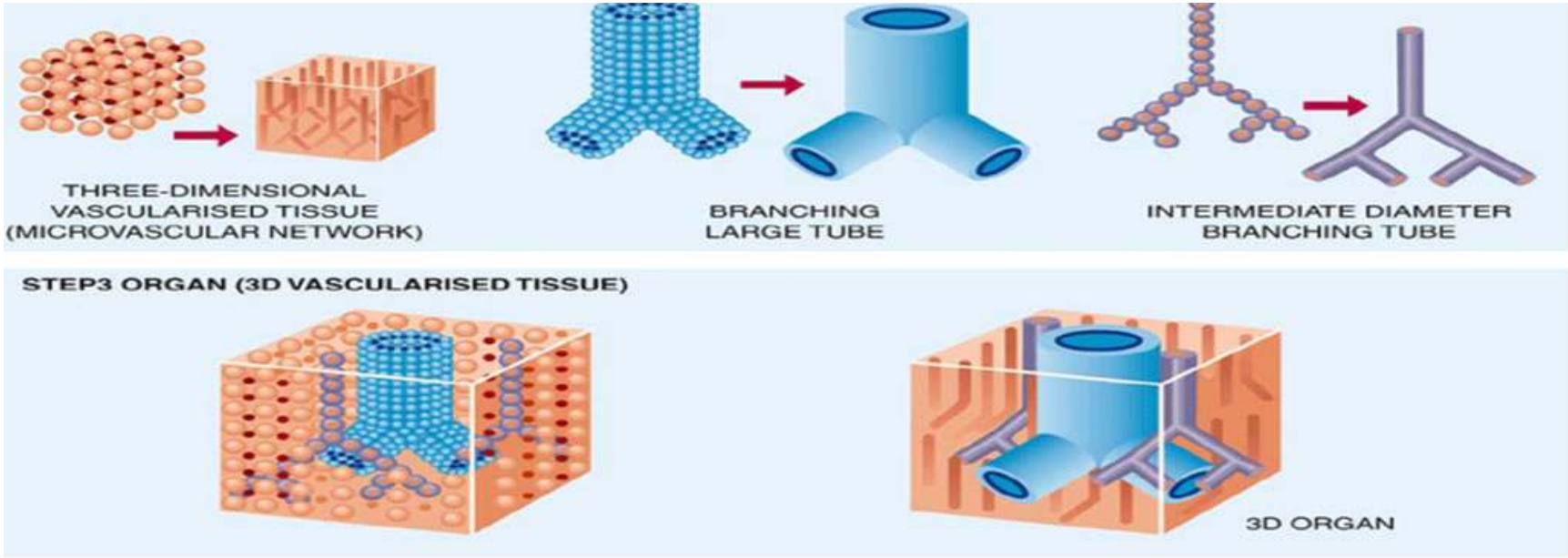
- Nanoscaled spheres are fused with cell sheet tissues to form vessels or cardiac tissues
- Advantage

  - Reduces undesirable cell differentiation that can be activated by nanoparticles

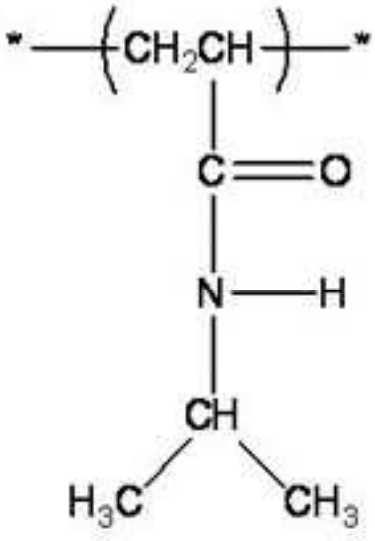
  – Precision controlled robotic bio-fabrication of organs and vessels



Designing a 3-D Organ



Cell sheet engineering



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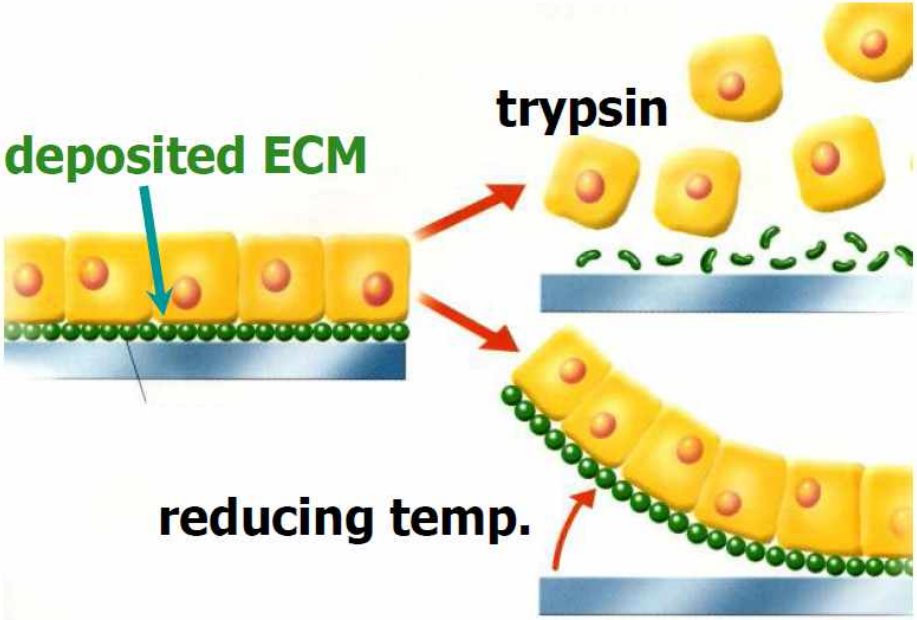
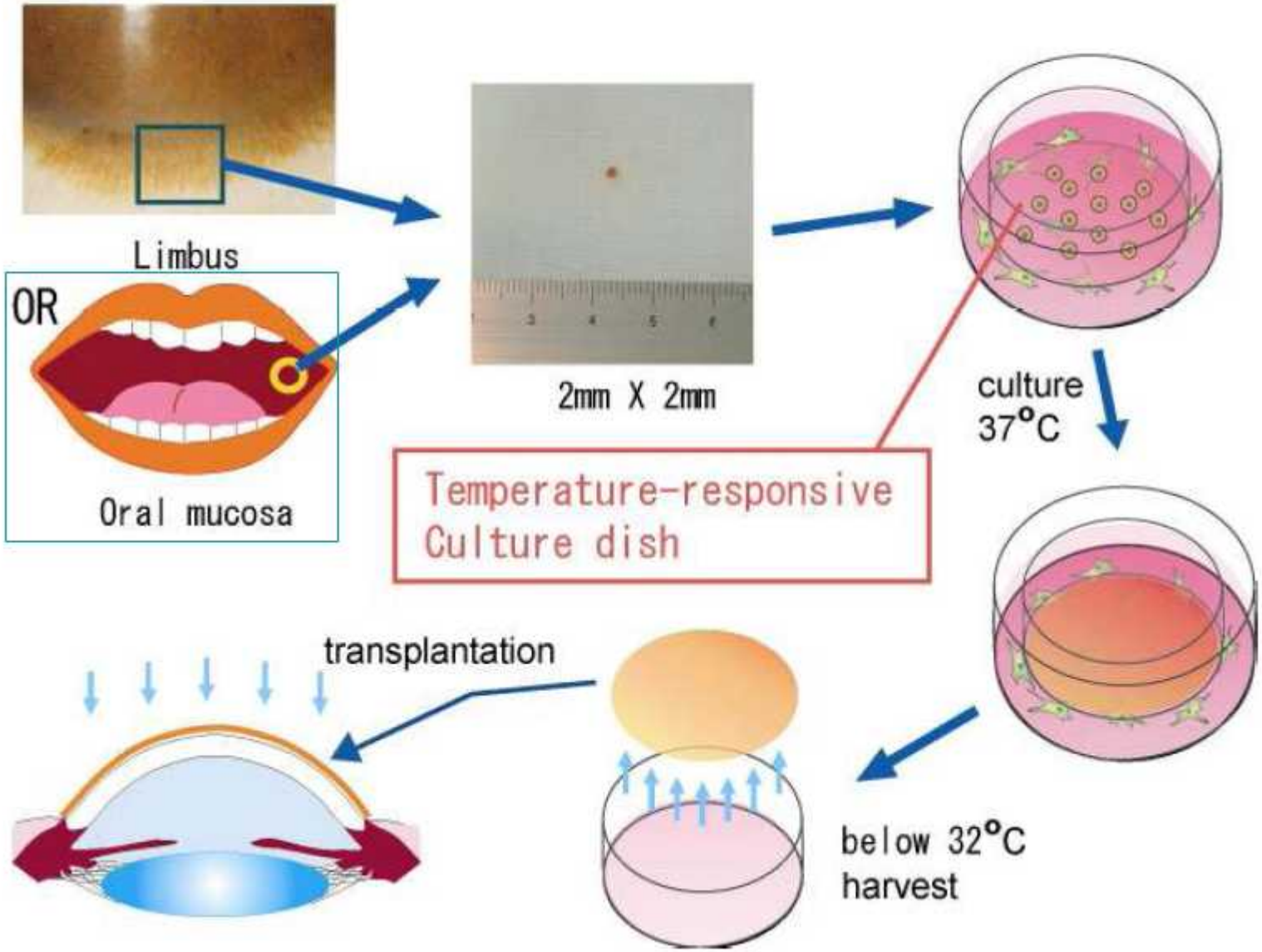
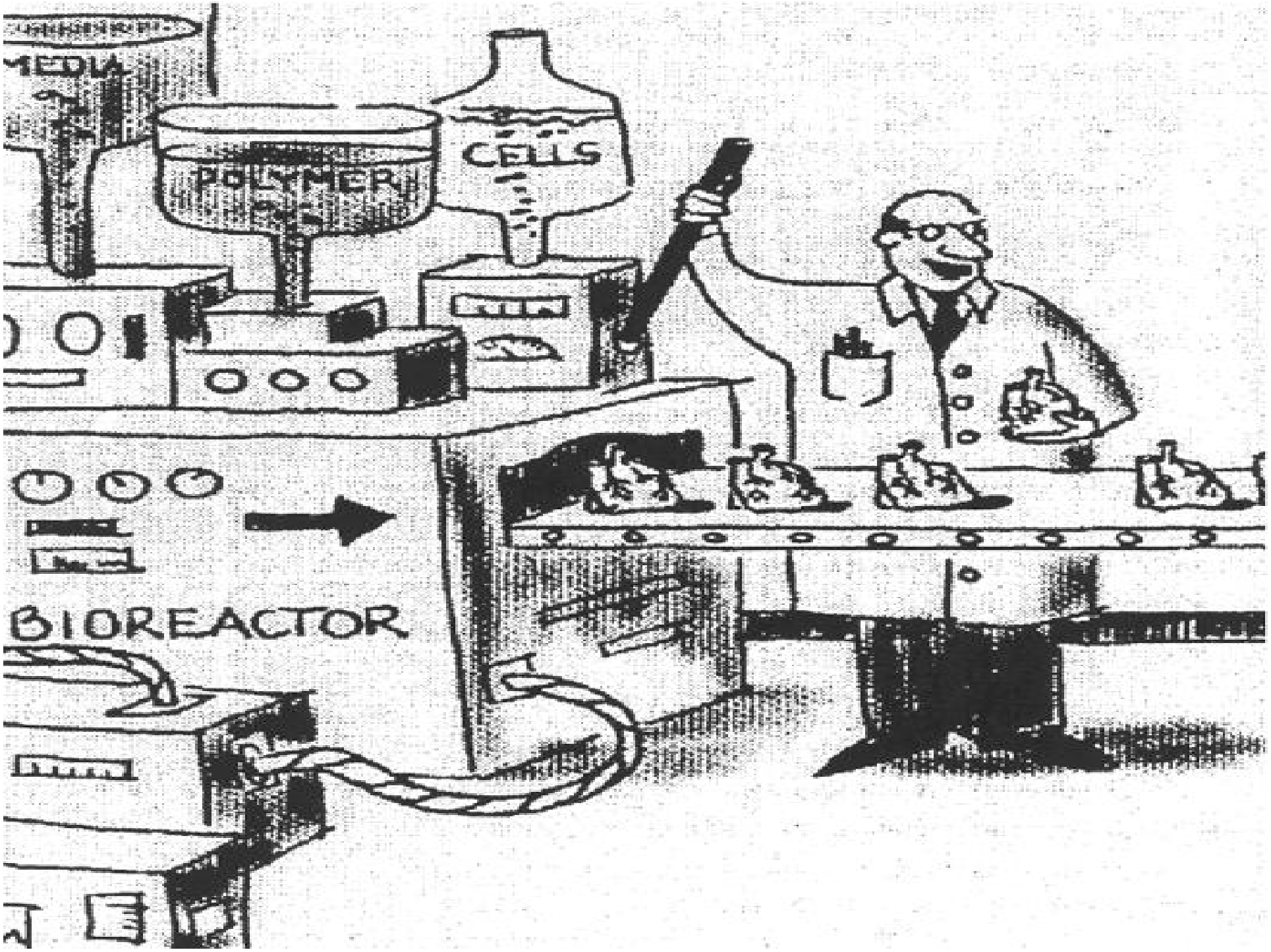
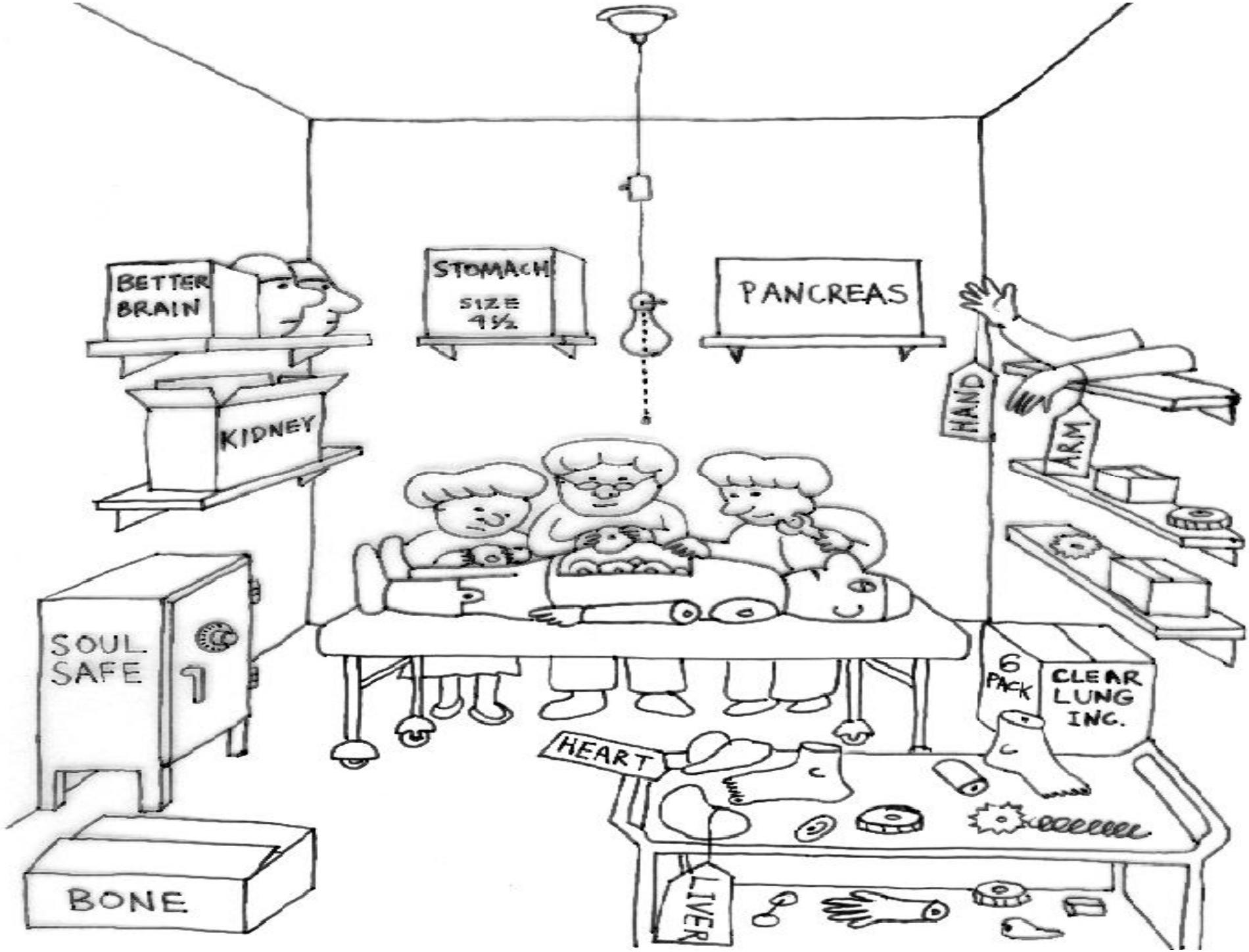


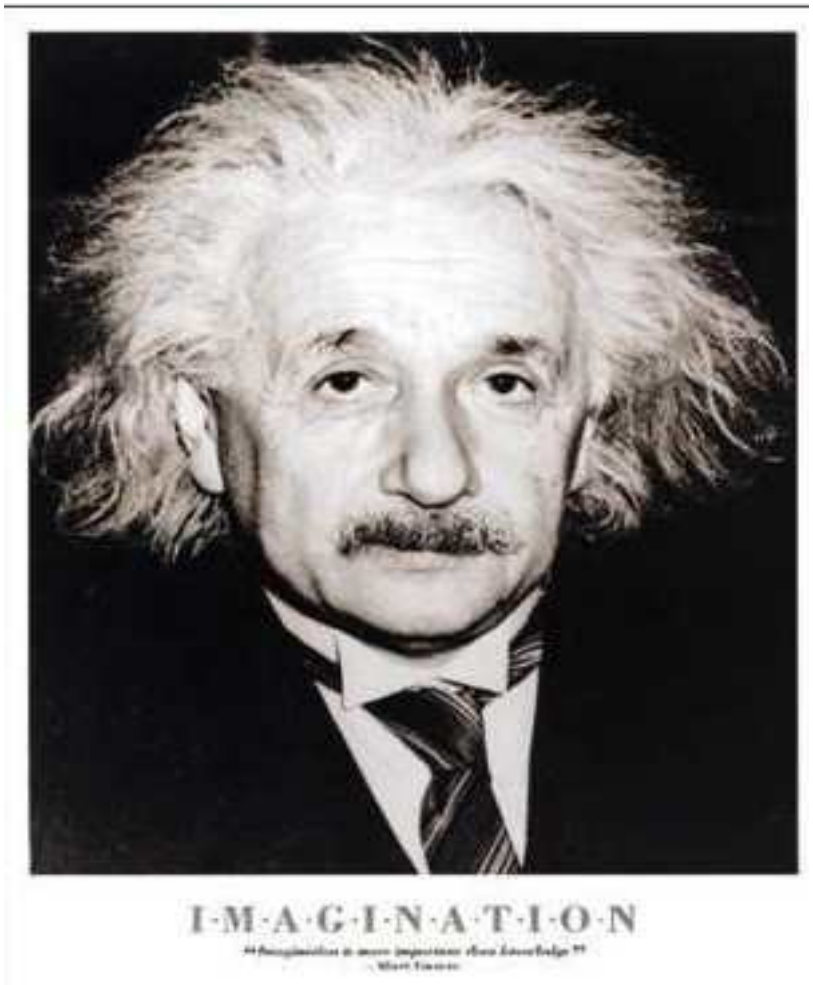
Deposited ECM is recovered together with Cell Sheets.

Transplantation of carrier-free tissue-engineered epithelial cell sheet




MEDIA
POLYMER
CELLS
BIOREACTOR


BETTER BRAIN
KIDNEY
STOMACH SIZE 9½
PANCREAS
HAND
ARM
SOUL SAFE
6 PACK
CLEAR LUNG INC.
HEART
BONE
LIVER



Imagination
is more important
than
knowledge.