Polymers in Tissue Engineering

Organs and Tissues

- Loss
  - Accidents
  - Birth defects
  - Hereditary disorders
  - Diseases
- Current treatments
  - Transplantation of organs
  - Surgical reconstruction
  - Mechanical devices
  - Metabolic supplements

National Waiting List

As of April 2002

51,544	Kidney transplant
17,641	Liver transplant
1,253	Pancreas transplant
276	Pancreas islet cell transplant
2,530	Kidney–pancreas transplant
179	Intestine transplant
4,136	Heart transplant
208	Heart–lung transplant
3,824	Lung transplant
79,226	Total*

Median waiting times for liver transplants from 1998 to 1999, all status groups. [From (5), courtesy of the National Academy Press]

UNOS unites the transplant community to save lives through organ transplantation. More >

Transplant Trends

Waiting list candidates as of today 1:21pm	108,481
Transplants January - June 2010	14,148
Donors January - June 2010	7,136

As of September 2010

Transplant Drawbacks

- Shortage
- Tissue mismatch
- Lifelong immunosuppression
- Graft rejection
- Drug therapy cost
- Cancer
- Cost

Are Animal Organs Safe for People?

Critics of transplants fear that viruses could jump from other species to humans and trigger deadly epidemics

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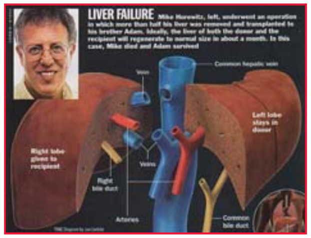
The Ultimate Sacrifice

A healthy man gives his brother half his liver—and dies. Should this kind of transplant be allowed?



LIVER FAILURE Mike Horowitz, left, underwent an operation in which more than half his liver was removed and transplanted to his brother Adam. Ideally, the liver of both the donor and the recipient will regenerate to normal size in about a month. In this case, Mike died and Adam survived

---

Nasty Infections

As the government cracks down on tissue banks, patients worry about safety and consider their options

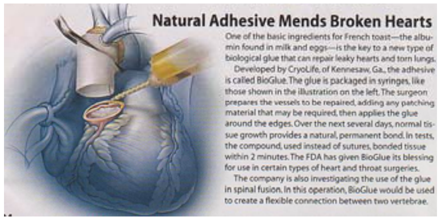
FDA site inspection

Pharmaceutical companies:
Excellent history

Tissue banks: no history

A cure worse than the disease

When FDA oversight falters, tissue implants can do more harm than good



Natural Adhesive Mends Broken Hearts

One of the basic ingredients for French toast—the albumin found in milk and eggs—is the key to a new type of biological glue that can repair leaky hearts and torn lungs.

Developed by CryoLife, of Kennesaw, Ga., the adhesive is called BioGlue. The glue is packaged in syringes, like those shown in the illustration on the left. The surgeon prepares the vessels to be repaired, adding any patching material that may be required, then applies the glue around the edges. Over the next several days, normal tissue growth provides a natural, permanent bond. In tests, the compound, used instead of sutures, bonded tissue within 2 minutes. The FDA has given BioGlue its blessing for use in certain types of heart and throat surgeries.

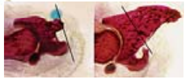
The company is also investigating the use of the glue in spinal fusion. In this operation, BioGlue would be used to create a flexible connection between two vertebrae.

Recipes For Limb Renewal

Salamanders and other creatures that regrow lost body parts provide clues for ways to regenerate human limbs (Sophie L. Rovner)

BODY ELECTRIC By inducing expression of a particular potassium ion channel in this tadpole, Levin's team altered its bioelectrical signaling, enabling it to grow multiple arms.

REGENERATION CHAMPION Salamanders, including this Notophthalmus viridescens specimen, can regrow lost limbs multiple times.



REGENERATION FERTILIZER A mouse can regrow an amputated digit tip, but if enough of the digit is removed—as shown in the image at left, in which the black bar indicates the line of amputation—the digit won't grow back. However, Muneoka found that treating such an amputation site with bone morphogenetic proteins enables a mouse to grow a replacement tip (right). In these images, captured with a dissecting microscope, bones are stained red and surrounding tissue appears clear. The triangular bone on the right is 1–2 mm long.

http://pubs.acs.org/cen/science/88/8831sci1.html

Newt Knowhow

Salamanders can regrow legs, tails, jaws, spines—even parts of their eyes

Over 10 weeks, cells at an amputation site revert to a biological blank slate, with the potential to become skin, bone, or cartilage. Then they proliferate, form a cone, specialize, and grow into a limb.

Thalidomide's horrifying effects on newborns became known in 1962. Distribution of two million tablets by Merrell for investigational use.

Frances Kelsey: Medical officer at FDA Refusal to allow NDA of thalidomide based on insufficient safety data.

- **Shortage of natural organs:**
- **Partial solutions**

- **Building bionic parts based on biomaterials**

- **Building natural organs based on body cells (tissue engineering)**

21 IDEAS FOR A CHANGING WORLD

Minimal Medicine

HEALTH 21

Doing the Least Damage

TISSUE ENGINEERING

Application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and development of biological substitutes to restore, maintain, or improve function. (Skalak 1988)

Body by Science

Time, May 22, 2000

what will be the 10 hottest jobs?

5 DATA MINERS

... and what jobs will disappear?

1 STOCKBROKERS, AUTO DEALERS, MAIL CARRIERS, INSURANCE AND REAL ESTATE AGENTS

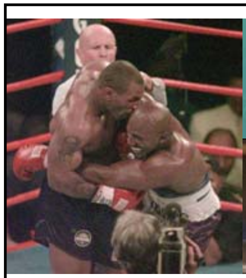
7 PRISON GUARDS

10 FATHERS

Allograft (also known as homograft) (Organs, tissues, and cells)
Tissue from one species transplanted to another animal of the same species (e.g., dog to dog or human to human).

Organ allografts (kidneys, liver, lung, heart, etc.) all require immediate surgical revascularization for their metabolic requirements, thereby requiring reattachment by surgical anastomosis of the major arteries and veins.
Tissues and cells do not require revascularization and can be implanted without immediately establishing a direct blood supply (heart valves, blood vessels, orthopedic tissues, skin, cornea, etc.).

Xenograft
Tissue transplanted from one species to another (e.g., pig to monkey or pig to human).
Autograft
Tissue reimplanted into the donor (e.g., use of a patient's own veins or arteries in heart bypass grafting).



Mike Tyson bites into the ear of Evander Holyfield in the third round of their WBA Heavyweight match Saturday, June 28, 1997, at the MGM Grand in Las Vegas. (AP Photo/Jack Smith)

REBUILDING THE TROOPS

For wounded soldiers, the military's Institute of Regenerative Medicine offers dramatic new ways to heal

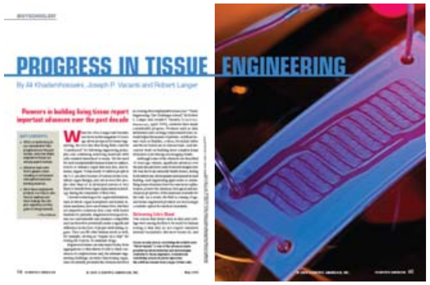
JULY 2008 POPULAR SCIENCE

THE ULTIMATE BABY BOTTLE

In The Year 2525

Are artificial wombs in our future? Was Aldous Huxley right? By Tabitha M. Powledge

Eventually a woman who **wants a uterus** could place her order, donate her cells and **take delivery** of her **custom-made womb** in just six weeks.



PROGRESS IN TISSUE ENGINEERING

By Ali Khademhosseini, Joseph P. Vacanti and Robert Langer

Pioneers in building living tissue report important advances over the past decade

The difficulty of providing a blood supply has always limited the size of engineered tissues.

Building Blood Vessels

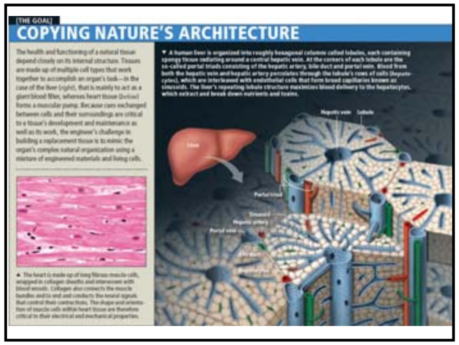
Living tissues quickly starve without the oxygen and nutrients delivered to cells by blood, so an engineered tissue construct that is more than a few cells thick usually requires an

MICROFABRICATION

To control the vasculature pattern within an implantable liver-assisting device, tissue engineers etch the desired blood vessel arrangement into a silicon mold (1). A biocompatible polymer scaffold cast from the silicon template (2) is then seeded with endothelial cells to coat the artificial vessel walls. Liver cells are cultured in the channels of similar scaffolds (3). Alternating layers of scaffolds containing "blood vessels" or liver cell cultures are stacked, with a nanoporous membrane between each layer, so that the liver cells are always close to the blood supply (4). The resulting hybrid tissue device, which has been tested in animals, is intended to serve as a bridge for patients awaiting a liver transplant.

NANOPATTERNED SURFACE

Cells respond to chemical signals from their neighbor
around them, but cells also respond to mechanical cu
on which they are growing. Grooves 600 nanometers
natural matrix topography of certain tissues and prov
that affect the cells' shape and rate of migration and
patterned surface for six days, the cells multiply and a
(2) and form a network of capillarylike tubes (3).



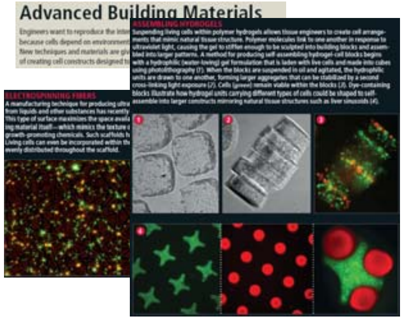
[THE GOAL]

COPYING NATURE'S ARCHITECTURE

The health and functioning of a natural tissue depend closely on its internal structure. Tissues are made up of multiple cell types that work together to accomplish an organ's task—in the case of the liver (right), that is mainly to act as a giant blood filter, whereas heart tissue (below) forms a muscular pump. Because cues exchanged between cells and their surroundings are critical to a tissue's development and maintenance as well as its work, the engineer's challenge in building a replacement tissue is to mimic the organ's complex natural organization using a mixture of engineered materials and living cells.

▲ The heart is made up of long fibrous muscle cells, wrapped in collagen sheaths and interwoven with blood vessels. Collagen also connects the muscle bundles end to end and conducts the neural signals that control their contractions. The shape and orientation of muscle cells within heart tissue are therefore critical to their electrical and mechanical properties.

▼ A human liver is organized into roughly hexagonal columns called lobules, each containing spongy tissue radiating around a central hepatic vein. At the corners of each lobule are the so-called portal triads consisting of the hepatic artery, bile duct and portal vein. Blood from both the hepatic vein and hepatic artery percolates through the lobule's rows of cells (hepatocytes), which are interleaved with endothelial cells that form broad capillaries known as sinusoids. The liver's repeating lobule structure maximizes blood delivery to the hepatocytes, which extract and break down nutrients and toxins.



Advanced Building Materials

Engineers want to reproduce the inter
because cells depend on environment
New techeiques and materials are giv
of creating cell constructs designed to

ASSEMBLING HYDROGELS

Suspending living cells within polymer hydrogels allows tissue engineers to create cell arrangements that mimic natural tissue structure. Polymer molecules link to one another in response to ultraviolet light, causing the gel to stiffen enough to be sculpted into building blocks and assembled into larger patterns. A method for producing self-assembling hydrogel-cell blocks begins with a hydrophilic (water-loving) gel formulation that is laden with live cells and made into cubes using photolithography (1). When the blocks are suspended in oil and agitated, the hydrophilic units are drawn to one another, forming larger aggregates that can be stabilized by a second cross-linking light exposure (2). Cells (green) remain viable within the blocks (3). Dye-containing blocks illustrate how hydrogel units carrying different types of cells could be shaped to self-assemble into larger constructs mirroring natural tissue structures such as liver sinusoids (4).

ELECTROSPINNING FIBERS

A manufacturing technique for producing ultra
from liquids and other substances has recently
This type of surface maximizes the space availa
ing material itself—which mimics the texture o
growth-promoting chemicals. Such scaffolds h
Living cells can even be incorporated within the
evenly distributed throughout the scaffold.

Naturally derived materials-based cell and drug delivery systems in skin regeneration

Sha Huang, Xiaobing Fu

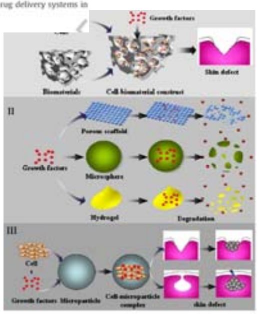


Fig. 1. The fundamental technologies or methodologies with naturally derived materials in tissue engineering.

The extracellular matrix (ECM)

Biological tissues and organs consist of cells surrounded by a complex molecular framework that is known as ECM.

ECM is a complex mixture of different macromolecules, such as collagens, proteoglycans, glycoproteins, and elastin and one of its important roles is to provide tissues with the appropriate structural integrity.

Tissue Regeneration

Organization of cells into higher ordered structures

Cell-cell interactions
Cell-extracellular matrix (ECM) interactions
Cell-polymer surface interactions
Cell adhesion, growth and differentiation
Angiogenesis (vascularization) growth factors
Environmental factors

Template/scaffold

1. Materials

   Biocompatible materials, biodegradable

2. Fabrication

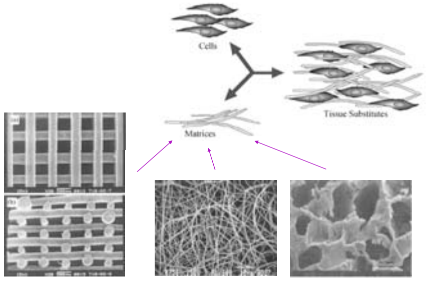
   Shape and size

   (nonwoven) fiber mesh, porous matrix

3. Surface modification

   Cell adhesive proteins

   Drug delivery



Components necessary for tissue engineering (Auger & Germain)

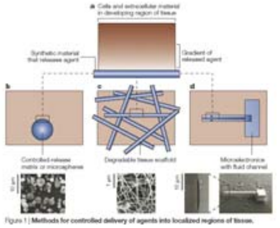
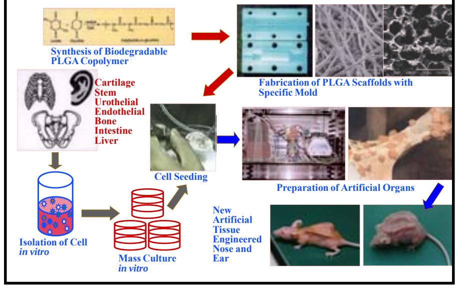


Figure 1 | Methods for controlled delivery of agents into localized regions of tissue.

a | The general situation, in which an agent (indicated by white) is released from a synthetic material into the tissue (indicated by dark brown), and produces a gradient of the agent in the tissue that surrounds the material. This general situation can occur when an agent is released from different materials, as illustrated in **b–d**. **b** | Controlled-release technology can provide continuous agent release from a solid material. The inset shows a scanning electron micrograph of poly(lactide-coglycolide) microspheres that release nerve growth factor. **c** | Agent delivery by release from a degradable porous scaffold, which is composed of either synthetic polymers or natural polymers, such as collagen (shown in the inset) or fibrin. **d** | Agent delivery from a system with microfluidic channels. The microelectronic probe (shown in the right inset; the shank of the probe is 2 mm in length and 100 μm in width) has an internal microchannel (shown at higher magnification in the left inset), which is indicated by the dark blue shaded region in the schematic illustration. The photograph in part **b** is reprinted by permission from *Nature Biotechnology* (REF. 10)

Development of Tissue Engineered Artificial Organs



Synthesis of Biodegradable PLGA Copolymer

Fabrication of PLGA Scaffolds with Specific Mold

Cartilage
Stem
Urothelial
Endothelial
Bone
Intestine
Liver

Cell Seeding

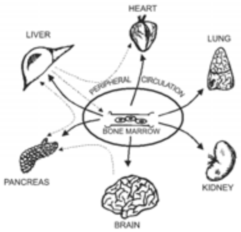
Preparation of Artificial Organs

Isolation of Cell *in vitro*

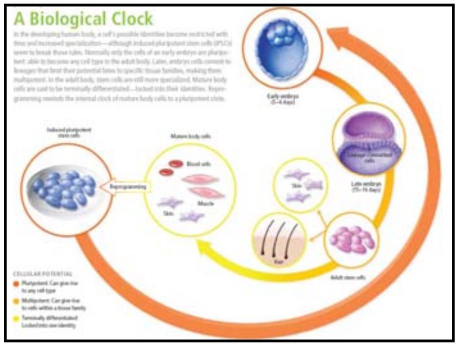
Mass Culture *in vitro*

New Artificial Tissue Engineered Nose and Ear

Advanced Tissue Sciences is one company developing spare parts for hearts, including vascular grafts (shown above) and replacement heart valves.



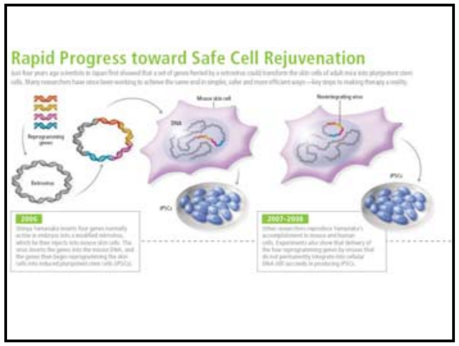
The interchangeable stem cell hypothesis. Primitive stem cells may exist within the bone marrow that are capable of homing to tissues that need repair or regeneration (solid lines). Likewise, progenitor cells from an adult organ, such as liver, may act as a source of reneration-competent cells for another tissue, including the bone marrow (dotted lines).



A Biological Clock

In the developing human body, a cell's possible identities become restricted with time and increased specialization—although induced pluripotent stem cells (iPSCs) seem to break those rules. Normally only the cells of an early embryo are pluripotent: able to become any cell type in the adult body. Later, embryo cells commit to lineages that limit their potential fates to specific tissue families, making them multipotent. In the adult body, stem cells are still more specialized. Mature body cells are said to be terminally differentiated—locked into their identities. Reprogramming rewinds the internal clock of mature body cells to a pluripotent state.

CELLULAR POTENTIAL
- Pluripotent: Can give rise to any cell type
- Multipotent: Can give rise to cells within a tissue family
- Terminally differentiated: Locked into one identity

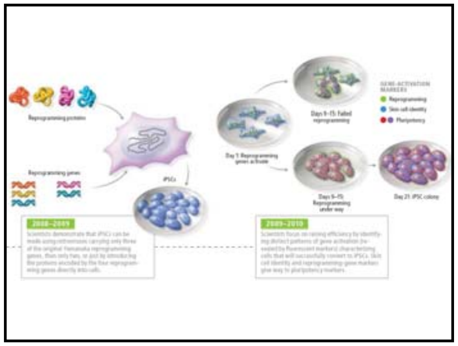


Rapid Progress toward Safe Cell Rejuvenation

Just four years ago scientists in Japan first showed that a set of genes ferried by a retrovirus could transform the skin cells of adult mice into pluripotent stem cells. Many researchers have since been working to achieve the same end in simpler, safer and more efficient ways—key steps to making therapy a reality.

2006
Shinya Yamanaka inserts four genes normally active in embryos into a modified retrovirus, which he then injects into mouse skin cells. The virus inserts the genes into the mouse DNA, and the genes then begin reprogramming the skin cells into induced pluripotent stem cells (iPSCs).

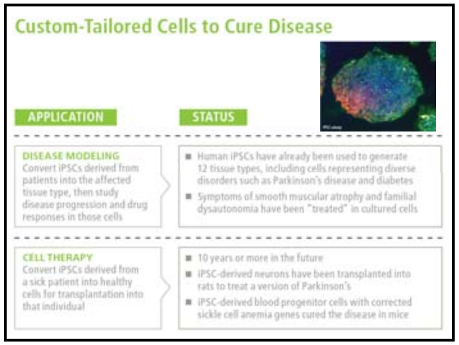
2007–2008
Other researchers reproduce Yamanaka's accomplishment in mouse and human cells. Experiments also show that delivery of the four reprogramming genes by viruses that do not permanently integrate into cellular DNA still succeeds in producing iPSCs.



GENE-ACTIVATION MARKERS
- 🟩 Reprogramming
- 🟦 Skin cell identity
- 🟥 🟪 Pluripotency

2008–2009
Scientists demonstrate that iPSCs can be made using retroviruses carrying only three of the original Yamanaka reprogramming genes, then only two, or just by introducing the proteins encoded by the four reprogramming genes directly into cells.

2009–2010
Scientists focus on raising efficiency by identifying distinct patterns of gene activation (revealed by fluorescent markers) characterizing cells that will successfully convert to iPSCs. Skin cell identity and reprogramming gene markers give way to pluripotency markers.



Custom-Tailored Cells to Cure Disease

iPSC colony

APPLICATION	STATUS
DISEASE MODELING Convert iPSCs derived from patients into the affected tissue type, then study disease progression and drug responses in those cells	■ Human iPSCs have already been used to generate 12 tissue types, including cells representing diverse disorders such as Parkinson's disease and diabetes ■ Symptoms of smooth muscular atrophy and familial dysautonomia have been "treated" in cultured cells
CELL THERAPY Convert iPSCs derived from a sick patient into healthy cells for transplantation into that individual	■ 10 years or more in the future ■ iPSC-derived neurons have been transplanted into rats to treat a version of Parkinson's ■ iPSC-derived blood progenitor cells with corrected sickle cell anemia genes cured the disease in mice

cloning of a human

The process is extremely difficult, but it also seems inevitable *By Charles Q. Choi*

Ever since the birth of Dolly the sheep in 1996, human cloning for reproductive purposes has seemed inevitable. Notwithstanding past dubious claims of such an achievement—including one by a company backed by a UFO cult—no human clones have been made, other than those born naturally as identical twins. Despite success with other mammals, the process has proved much more difficult in humans—which may strike some people as comforting and others as disappointing.

Scientists generate clones by replacing the nucleus of an egg cell with that from another individual. They have cloned human embryos, but none has yet successfully grown past the early stage where they are solid balls of cells known as morulas—the act of transferring the nucleus may disrupt the ability of chromosomes to align properly during cell division. "Whenever you clone a new species, there's a learning curve, and with humans it's a serious challenge getting enough good-quality egg cells to learn with," says Robert Lanza of Advanced Cell Technology in Worcester, Mass., who made headlines in 2001 for first cloning human embryos. Especially tricky steps include discovering the correct timing and mix of chemicals to properly reprogram the cell.

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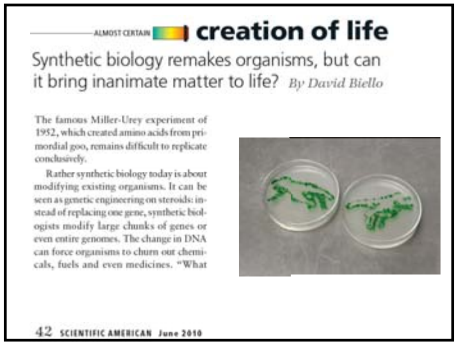

creation of life

Synthetic biology remakes organisms, but can it bring inanimate matter to life? *By David Biello*

The famous Miller-Urey experiment of 1952, which created amino acids from primordial goo, remains difficult to replicate conclusively.

Rather synthetic biology today is about modifying existing organisms. It can be seen as genetic engineering on steroids: instead of replacing one gene, synthetic biologists modify large chunks of genes or even entire genomes. The change in DNA can force organisms to churn out chemicals, fuels and even medicines. "What

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Cloning History

- February 1997—the first cloning of a mammal, Dolly the sheep, from an adult body cell is announced.
- March 1997—President Clinton bans federal funding of human-cloning research.
- 1998–2000—Researchers clone mice, calves, goats, and pigs. A bull is "recloned" from a cloned bull.
- April 2000—Scientists find that cloning can restore body cells to a youthful state.
- October 2001—The first cloned human embryos are created at Advanced Cell Technology Lab in Worcester, MA

Cloning for Medicine

MEGAN AND MORAG (above) were the first mammals cloned from cultured cells. That basic technique has allowed the creation of cloned sheep carrying human genes. Such animals produce milk that can be collected and processed (left) to yield therapeutic human proteins.

EDITOR'S PAGE

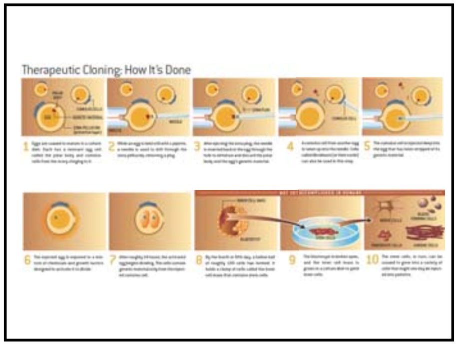
No Chemistry, No Physics

LETTERS

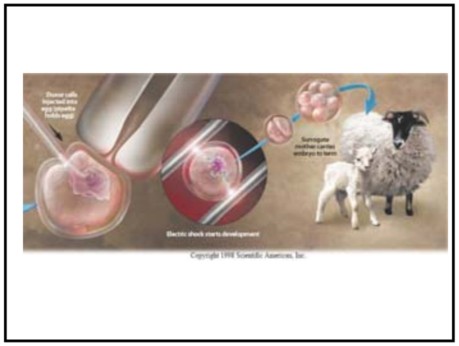
America's Best: Science & Medicine

"Here are the people our society needs to idolize, not the sports stars who are all too often put on pedestals undeservedly."

Straddling Two Tracks



Therapeutic Cloning: How It's Done



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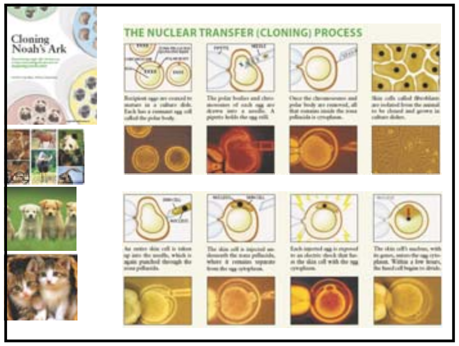
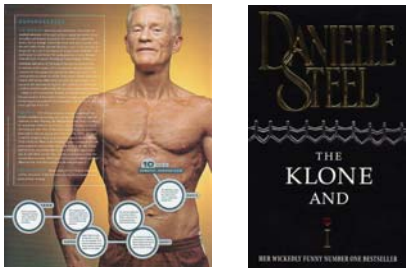


Human Cloning



Beckman Coulter 2010
Science & Technology Symposium

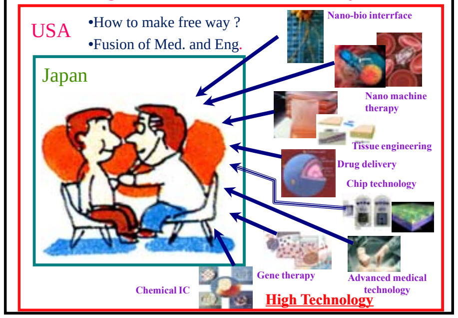
Cell Sheet Tissue Engineering and Organ Repair

Teruo Okano, Ph.D
Director and Professor
Institute of Advanced Biomedical
Engineering and Science, TWIns
TWMU

Drug Therapy

	Small Molecules
1980s	Proteins and Peptides Cell Eng. and Genetic Eng.
1990s	DNA, RNA and Cells
2000s	Tissues and Organs Tissue Eng. and Stem Cell Eng.

Building of Advanced Medical Society

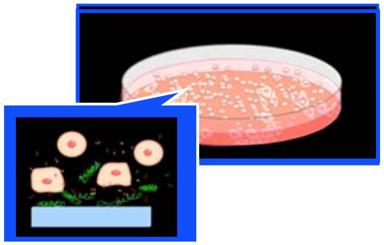


USA
- How to make free way ?
- Fusion of Med. and Eng.

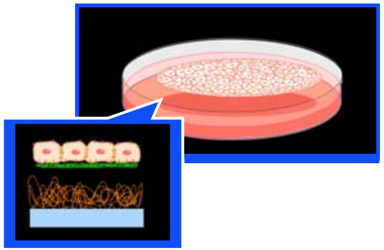
Japan

High Technology

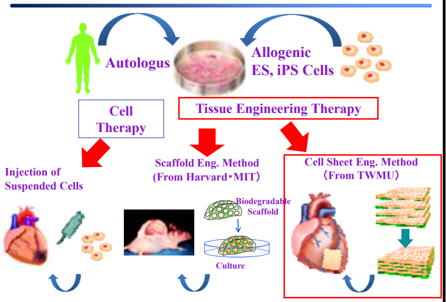
Conventional Cell Harvest with Proteolytic Enzymes

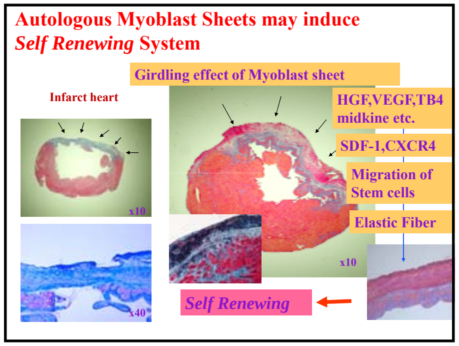


Non-Invasive Cell Sheet Harvest by Reducing Temperature

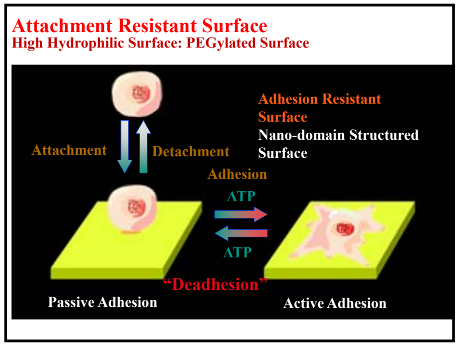


Cell Therapy / Tissue Eng. Therapy



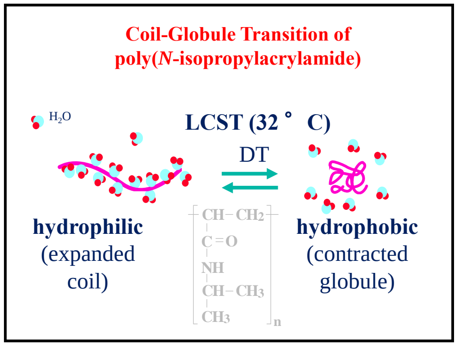


Autologous Myoblast Sheets may induce *Self Renewing* System

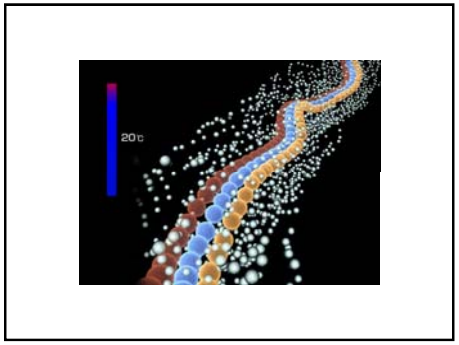


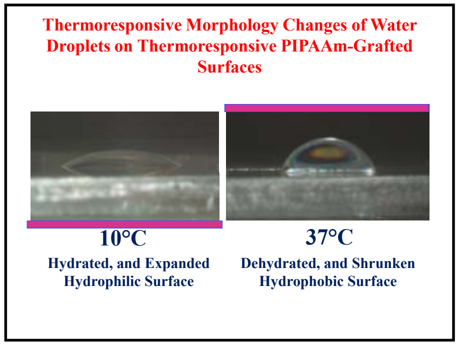
Attachment Resistant Surface

High Hydrophilic Surface: PEGylated Surface

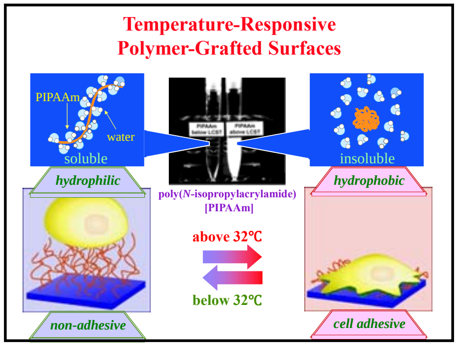


Coil-Globule Transition of poly(*N*-isopropylacrylamide)

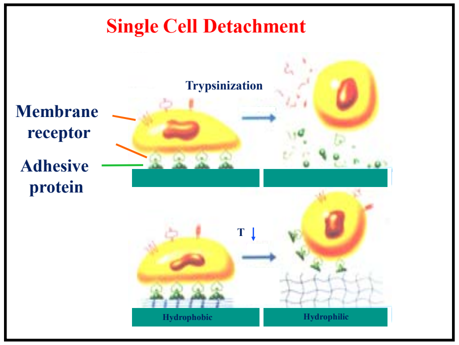




Thermoresponsive Morphology Changes of Water Droplets on Thermoresponsive PIPAAm-Grafted Surfaces

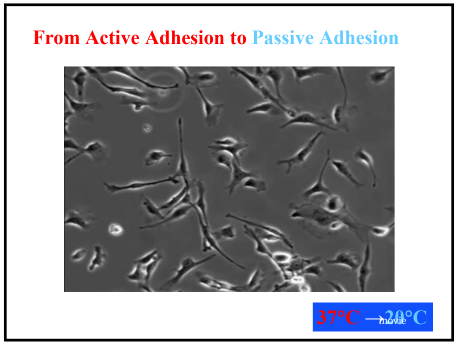


Temperature-Responsive Polymer-Grafted Surfaces



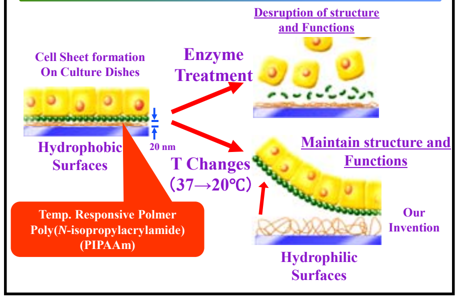
Single Cell Detachment

From Passive Adhesion to Active Adhesion



From Active Adhesion to Passive Adhesion

Cell Sheet Manipulation by Temperature Change


Desruption of structure and Functions

Cell Sheet formation On Culture Dishes

Enzyme Treatment

Hydrophobic Surfaces

20 nm

T Changes (37→20℃)

Maintain structure and Functions

Our Invention

Temp. Responsive Polmer Poly(*N*-isopropylacrylamide) (PIPAAm)

Hydrophilic Surfaces

Cell Sheet Engineering

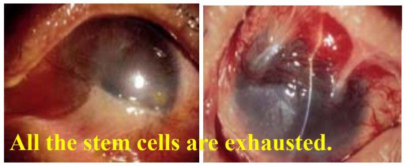
Corneal Epithelium Stem Cell Deficient Disease by Oral Mucosal Cell Sheet
(Clinical Study in Japan, 2003-
and Clinical Trial in France, 2007-, Cell Seed, Inc)

Esophageal Cancer ESD Surgery by Oral Mucosal Cell Sheet
(Clinical Study in Japan, 2008-)

Cardio-myopathy by Myoblast Cell Sheet
(Clinical Study in Japan, 2007-)

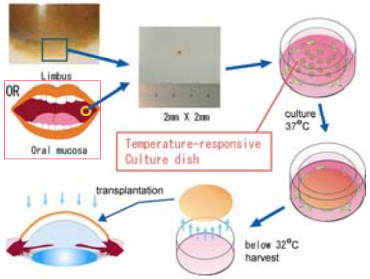
Organ/Tissue Transplantation → Tissue Engineering

Limited donor
Rejection

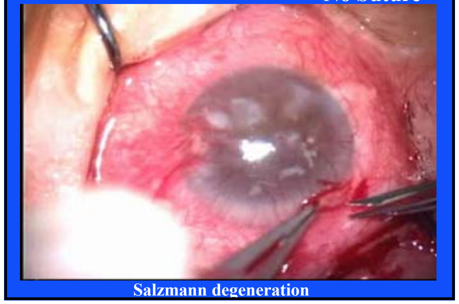

All the stem cells are exhausted.

alkali injury Stevens-Johnson syndrome

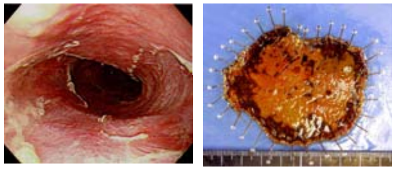
Transplantation of carrier-free tissue-engineered epithelial cell sheet



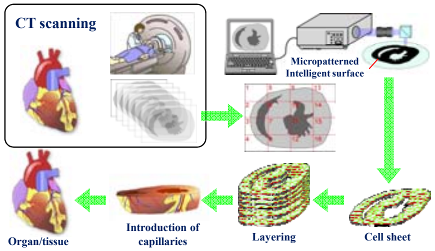
Human Patient No Suture


Salzmann degeneration

Removal of Early Esophageal Cancer by Endoscopic Submucosal Dissection


Inoue,H. Stomach and Intestine 39:53-56,2004

Ultimate Method for Fabrication of Tissue-Mimicking Structured Cell Sheets


CT scanning

Micropatterned Intelligent surface

Organ/tissue

Introduction of capillaries

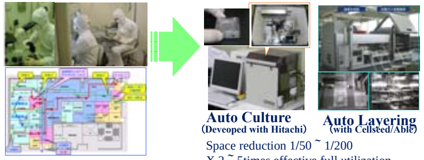
Layering

Cell sheet

FIRST: Automatic Tissue Factory & Thick Tissue Evaluation System Development

Cell Processing Center (GMP)

Automated Cell Culture System


Auto Culture
(Deveoped with Hitachi)

Auto Layering
(with Cellseed/Able)

2U・CPC requires 280 m^2
Maximum 48 sheets/year・2U・CPC
Huge HR and related cost to cover GMP manual process and human error

Space reduction 1/50 ~ 1/200
X 2 ~ 5times effective full utilization
→ 100 ~ 1000times production capability

And avoid human error by process standardization

CSTEC package to accelerate clinical transfer to world patients

Natural Polymers for Scaffolds

Collagen

Hyaluronic acid

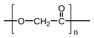
Gelatin

Chitosan

Porous structure by freeze-drying, porosigen, foaming
Chemical cross-linking
Weak mechanical properties
Potential immunogenicity (proteins)

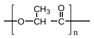
Biodegradable Polymers for Scaffolds

Polyglycolide



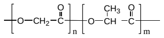
$$\left[O-CH_2-\overset{\overset{\displaystyle O}{\|}}{C} \right]_n$$

Polylactide [poly(D,L-lactide), poly(L-lactide)]



$$\left[O-\overset{\overset{\displaystyle CH_3}{|}}{CH}-\overset{\overset{\displaystyle O}{\|}}{C} \right]_n$$

Poly(lactide-co-glycolide)



$$\left[O-CH_2-\overset{\overset{\displaystyle O}{\|}}{C} \right]_n \left[O-\overset{\overset{\displaystyle CH_3}{|}}{CH}-\overset{\overset{\displaystyle O}{\|}}{C} \right]_m$$

Polymeric Scaffold

Degradation rate and degradation products (toxic?)

Biocompatibility (benefit/risk ratio)

Physical properties

Surface properties

Porosity

- Pore size (Cell ingrowth)
- Pore structure and connectivity

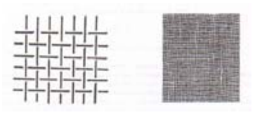
Cell Interactions (adhesion, growth, differentiation)

Processibility

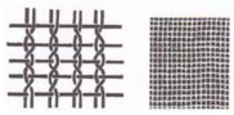
Shape dimension

Polymer Scaffold Processing

- **Scaffold structures**
  - **PGA non-woven**
  - **PGA fiber bonding: thermal treatment, polymer coating**
  - **Membrane lamination**
- **Scaffold preparation**
  - **Solution casting**
  - **Spray casting**
  - **Melt molding: compressing molding**
- **Porous structure**
  - **Emulsion freeze-drying: lyophilization**
  - **Particulate leaching**
  - **Gas saturation (high pressure)**
  - **Phase separation**
- **Polymers for scaffolds**
  - **Polymer blending (*e.g.*, PLGA+PEG)**
  - **Polymer/ceramic composite**

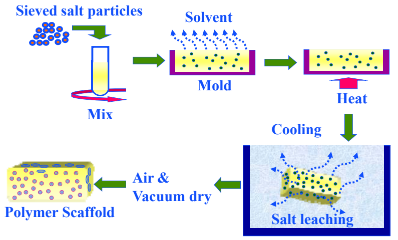


Plain Weave



Leno Weave

Solvent-casting/Particulate leaching Technique



Sieved salt particles

Mix

Solvent

Mold

Heat

Cooling

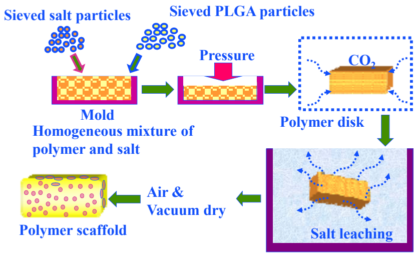
Salt leaching

Air & Vacuum dry

Polymer Scaffold

Percentage of salts to make interconnected pores?

High Pressure Gas Expansion



Sieved salt particles

Sieved PLGA particles

Mold

Homogeneous mixture of polymer and salt

Pressure

CO_2

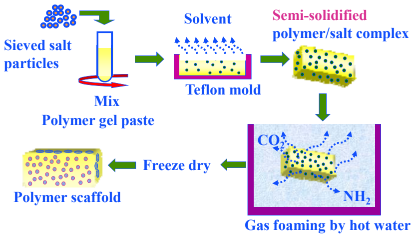
Polymer disk

Salt leaching

Air & Vacuum dry

Polymer scaffold

Gas Foaming /Salt Leaching



Sieved salt particles

Mix

Polymer gel paste

Solvent

Teflon mold

Semi-solidified polymer/salt complex

CO_2

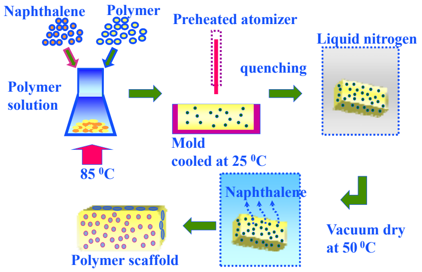
NH_3

Gas foaming by hot water

Freeze dry

Polymer scaffold

Phase Separation



Naphthalene

Polymer

Polymer solution

85 ^{0}C

Preheated atomizer

quenching

Mold cooled at 25 ^{0}C

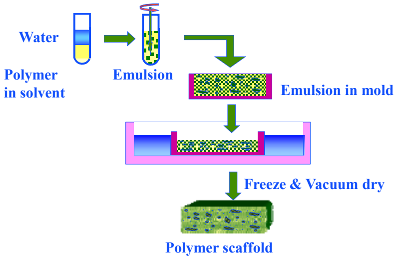
Liquid nitrogen

Vacuum dry at 50 ^{0}C

Naphthalene

Polymer scaffold

Emulsion Freeze-drying



Water

Polymer in solvent

Emulsion

Emulsion in mold

Freeze & Vacuum dry

Polymer scaffold

Surface Modification

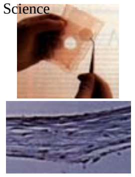
Plasma treatment
Chemical (acid/base) treatment
Grafting of cell adhesive motifs

Cell Adhesion Sequences Derived From ECM Proteins

RGD	fibronectin, collagen, fibrinogen, laminin, vitronectin
YIGSR	laminin
IKVAG	laminin
LRE	laminin
REDV	fibronectin
DGEA	collagen
VTXG	thrombospondin
VGVAPG	elastin

FDA-Approved and Commercialized Tissue-Engineered Products

Skin		Cartilage
Aprigraf®	Dermagraft®	Carticel®
Organogenesis	Advanced Tissue Science	Genzyme


Artificial Skin

- **Collagen matrix**
- **Cell-adhesive proteins in matrix**
- **Morphogenic proteins**
- **Nutrients**
- **Oxygen**
- **Waste**


Among the first products of regenerative medicine are living skin substitutes such as Organogenesis' Apligraf (left) and Vitrix (right).

Health for Life

New Secrets for Youthful Skin

Blame sun and smoking for early wrinkles. What will erase these marks of time?

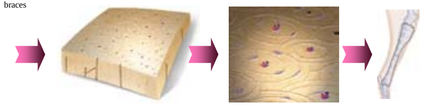
Hair Apparent

Development of Artificial Bone by Tissue Engineering

A rabbit femur bone with a missing section is held in place with braces

Inserted polymer scaffold with dimineralized bone particle (DBP)

The scaffold is slowly infiltrated by new bone



The scaffold ultimately gets completely replaced

The cells have their own blood supply (red and blue vessels).

The femur bone has healed