

## Recent Advances in Biomaterials

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*Biomaterials for medical use have been developed in accordance with progress of the fields of medicine, biochemistry, material science, and pharmaceuticals. Advances in the medicine have changed the concept of surgery from the deletion of damaged tissue for the preservation of the remaining healthy tissue to the reconstruction or replacement of damaged tissue by promoting regeneration of the natural tissue. All the materials used in medicine should be biocompatible. Conventional materials such as metals, ceramics, and synthetic polymers are usually bioinert and support the structural defects. But recently introduced biomaterials are designed to provide biological functions as much as possible by mimicking natural tissue structures.*

**Key Words:** Biomaterials, metal implants, bioceramics, biopolymers, biocompatibility

### Brief history of biomaterials

Developing an medical material is a typical multi-disciplinary subject that cannot be achieved without close cooperation between basic researchers and clinicians

Orthopedic surgeons who have an interest in looking for the more efficient tools to support the skeletal system were pioneers in the history of the biomaterials. Contemporary artificial implantable material has been widely introduced since Dr. Lane's report of using a metal plate and screw to immobilize a bone fracture in 1890.

Stainless steel and cobalt-chrome alloys are representative of metallic materials which have been developed and used in skeletal systems since the early 1920s. In the 1960s, ceramics gained intensive consideration as implantable materials because they produce less immune reaction after implantation. One example is the synthetic hydroxyapatite, which is a

typical bone reconstructive material widely used in clinics (Park and Lakes, 1992).

In general, materials used in medicine which are classified Class I materials are those that do not directly contact bodily tissues; Class II materials are those that contact intermittently or instantly to tissues; and Class III materials are those that are constantly contacting tissues as implants. These days, it is the Class III materials which are called biomaterials or biomedical materials. These Class III materials are divided into 3 categories according to their biological interactions with surrounding tissues. Bioinert materials do not produce any immunological host reactions but retain their structure in the body after implantation. Bioactive materials demonstrate biological functions mimicking the tissue, and finally, biodegradable materials are dissolved in body and replaced by regenerated natural tissues (Williams, 1987) (Table 1).

Polymeric materials have greatly contributed to the development of bioactive and biodegradable materials. In 1937, the first synthetic polymer, a polymethylmethacrylate (PMMA) as a denture base, was introduced for medical use. Plastic's ease of manipulation has led to broad applications in surgery. In 1952, Dr. Voorhees experimented with an artificial arterial graft made of parachute cloth

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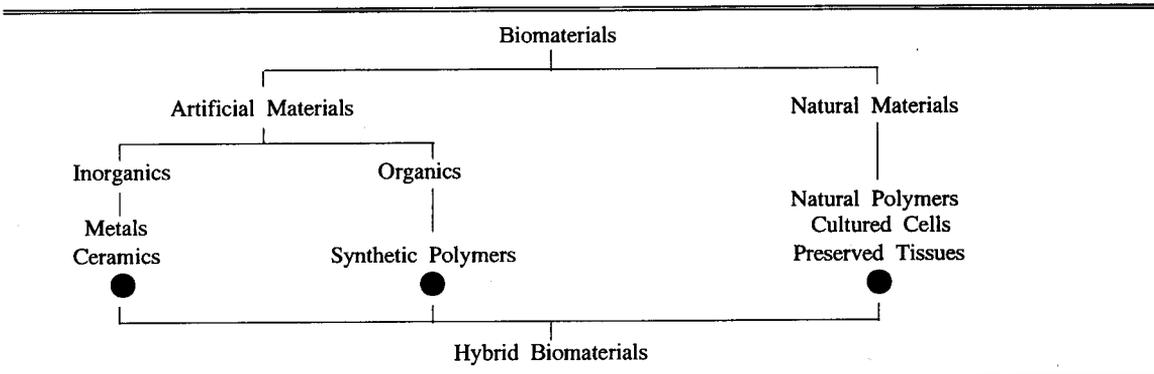
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**Table 1. Classification of materials in medical use**

Class I	do not directly contact bodily tissues		
Class II	contact intermittently or instantly to tissues		
Class III	constantly contacting tissues		
	Biomaterials	Bioinert	no immunological host reactions but remaining structures in body
		Bioactive	biological functions mimicking natural tissue
		Biodegradable	absorption in body and replacement by tissue regeneration

**Table 2. The biomaterials for tissue restoration**



(Dacron), and that opened a new era of using anti-thrombogenic biomaterial in cardiovascular surgery. Dr. Charnley replaced a total hip joint in 1962; femoral condylar head and stem was made of stainless steel that was immobilized in bone by acrylic cement(PMMA), and the acetabular fossa was replaced by a polyethylene(PE). The birth of biodegradable polymeric materials such as polylactic acid(PLA) has generated the development of implantable materials that are gradually dissolved in the body by hydrolysis, and then replaces the lesion with regenerated natural tissue. On the other hand, the advancement of biotechnology has accelerated development of biomaterials mimicking natural tissue. Recently, many researchers have been engaged in the hybridization of cells on a bioinert polymer surface to obtain a favorable environment for providing biological functions onto synthetic polymers. As well, peptide synthesis has made it possible to initiate host tissue regeneration by supplying tissue growth factors conjugated with biodegradable polymers into the tissue defects (Silver, 1994) (Table 2).

**Biocompatibility**

The primary requirement to use an implantable material in medicine is that the material should be biologically adaptable to the bodily system. This biological adaptation consists of biological stability and compatibility to the tissue. Generally, biostability is defined, in relation to host immune reactions, as any biomaterial not having pyrogenic, inflammatory, cytotoxic, antigenic, and oncogenic characteristics after implantation, while biocompatibility is defined as the need for any biomaterial to be mechanically, volumetrically and biochemically harmonized with the nearby tissue (Table 3).

Anatomically, the size and shape of an implanted material should be accurately suitable to the lesion that is to be reconstructed, and the mechanical properties such as Young's modulus also have to be similar to those of the lost tissue to avoid mechanical deterioration or fatigue. The continuously accumulated physical stress in the implanted material is not only directly related to the its durability, but it

Table 3. Biological adaptation of biomaterials

Biadaptability	Biostability	no host immune reactions after implantation (ex.) pyrogen, inflammation, cytotoxicity, antigen, oncogen	
	Biocompatibility	material's mechanical and biochemical harmonization with tissue.	
		Mechanical Biocompatibility	size shape mechanical properties (ex.1) deterioration, fatigue. (ex.2) tissue resorption, hypertrophy.
		Interfacial Biocompatibility	ingredient release tissue disturbance organ dysfunctions

Table 4. Mechanical properties of metallic biomaterials

Material	Young's modulus (GPa)	Yield strength (MPa)	Tensile strength (MPa)
Cortical bone	20	150~190	50~150
316L SUS	190	220~1210	480~1350
Co-Cr alloy	210	448~1600	650~1900
Ti	110	485~1030	760~1100

also induces tissue resorption or, in reverse, hypertrophy.

Every biomaterial has the potential to induce biological dysfunctions in the surrounding tissues after implantation. The interface between the material and tissue is the key area where the biological disturbance is initiated. To restore a tissue defect caused by an artificial material, the *in vitro* and *in vivo* investigations of the released substance from the material surface are indispensable in determining the biochemical characteristics of the material. The implanted material should not inhibit the biological function of the host with having an acceptable biocompatibility (Williams, 1987).

### Metallic biomaterials

Biomaterials for skeletal systems have mainly been made of metals. Stainless steel (SUS 316 series) was the first metallic implant material that was widely used for bone fixation wire, pins, screws, and plates, since 1926 due to its less corrosive characteristics. Cobalt chrome alloy has less

corrosive and less abrasive properties, and has been used as a load-bearing implant in hip and knee-joint heads. But these metals are not "never corrosive" material and the released substances reduce biological compatibility. The elastic coefficients of these materials are at least 10 times greater than natural bone, 200 GPa to 20 GPa, which reveals mechanical compatibility-related problems such as atrophy or hyperplasia after implantation (Table 4).

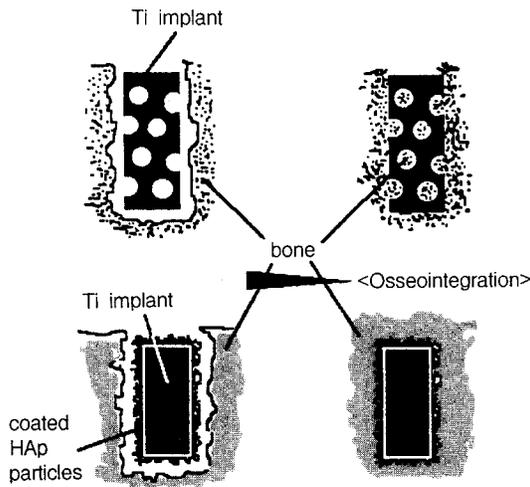
These days, titanium (Ti) and its alloys is the biocompatible metal of choice among many surgeons. It has been reported that, at least, the implanted Ti binds directly to bony tissue without demonstrating host immune reactions. An artificially produced oxidized layer on the Ti surface, which is generated by passivation, actively prevents corrosion caused by body fluid and metallic ions releasing toward the surrounding tissues.

Osseointegration is a recently introduced term that indicates a direct biochemical bond between a non-natural substance and a bony tissue (Fig. 1).

After implantation, the oxygen atoms in the body fluid naturally react with Ti atoms and form the

oxidized layer of titanium oxide(TiO<sub>2</sub>), and the newly formed and fully mineralized bone is deposited directly upon the metal surface without any interposition. But there's no method of binding tissue completely to metal by any artificial tool.

The elastic coefficient of Ti is less than half that of stainless steel and cobalt chrome alloys. Therefore, an implanted Ti demonstrates reduced biomechanical tissue problems, and the fatigue fracture rate following continuous physiological load-bearing is also far lower than it is with other known metals.



**Fig. 1.** Schematic diagram of the osseointegration of a titanium implant. Osteoblasts proliferate into the implant's pores and the matured bone fixes the implant by directly binding to the titanium surface. The hydroxyapatite (a calcium phosphate ceramic) particles spray-coated on the metal implant surface are chemically bound to the bone.

(Cochran *et al.* 1998).

The disadvantages of Ti for medical use are the relatively low shear strength, the weakness against abrasion, the difficulty in casting due to its active atomic movements, and the destruction of the surface oxidized layer caused by the ion release from the metal that stimulates foreign body reaction, though this possibility is much lower than with other metals.

**Ceramic biomaterials**

Ceramics are defined as materials with regularly-aligned mineral crystal molecules. This is quite an important consideration in using ceramics as implant material, for the regular atomic lattice is strongly related to its biological compatibility without the ionic release that usually induces host immune reactions, as well as its biomechanical compatibility with extremely high strength and hardness. But this lattice structure also has limited use in a physiologically load-bearing area, because the regular molecular alignment can easily be destructed by just a small external force. As we think of a china bowl or a glass, the most important physical characteristic of ceramic materials is their extreme brittleness. To increase the resistance against brittleness, a rearrangement of the lattice or monocrystallization is recommended (Table 5).

Progress in the production of fine ceramics has improved their prospects for medical use. In the 1960s, alumina(Al<sub>2</sub>O<sub>3</sub>) was first introduced as a "bioceramic". Naturally, it was highly compressive but had low tensile strength and high brittleness.

**Table 5. Ceramics in medical use**

Types	Ceramics	Formula
Bioinert	Alumina Zirconia	Al <sub>2</sub> O <sub>3</sub> ZrO <sub>2</sub>
Bioactive	Bioglass Hydroxyapatite (high temperature sintered)	Na <sub>2</sub> O-CaO-P <sub>2</sub> O <sub>5</sub> -SiO Ca <sub>10</sub> (PO <sub>4</sub> ) <sub>6</sub> (OH) <sub>2</sub>
Biodegradable	Carbonateapatite Hydroxyapatite (low temperature sintered) Tricalcium phosphate Soluble calcium aluminate	Ca <sub>10</sub> (PO <sub>4</sub> ) <sub>6</sub> CO <sub>3</sub> Ca <sub>10</sub> (PO <sub>4</sub> ) <sub>6</sub> (OH) <sub>2</sub> Ca <sub>3</sub> (PO <sub>4</sub> ) <sub>2</sub> CaO-Al <sub>2</sub> O <sub>3</sub>

However, a monocrystallized version demonstrated increased tensile strength and reduced brittleness. The surface of an implanted alumina is covered by a thin water layer due to its high hydrophilicity. This layer is related to the biocompatibility toward the surrounding tissue, and also provides lubricating characteristics. However, brittleness still remains a problem (Hench and Wilson, 1993).

Hydroxyapatite [ $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ] is a representative implantable ceramic material widely used in clinics. It is well known that the most abundant mineral ingredients in the hard tissue are apatite crystals made of calcium and phosphates. Since the 1970s, various kinds of artificially-synthesized hydroxyapatite have been commercially available. An implanted hydroxyapatite surface binds to the natural bone apatites via body fluid, and this chemical bonding promotes the bone-implant monosystem. Though hydroxyapatite has less strength than alumina and is difficult to produce in monocrystal structure, its excellent biological compatibility is close to natural bone.

And the mechanical property of hydroxyapatite can be controlled by synthesizing and sintering temperature in the process. The hydroxyapatite is usually sintered to increase its strength, but the one synthesized under  $100^\circ\text{C}$  and sintered under  $800^\circ\text{C}$  demonstrates less strength but gradual degradation after implantation (Bloebaum *et al.* 1998).

These days, hydroxyapatite is used as a bone defect filler, or fabricated as an artificial bone replacement which is free from the physiological loads, such as an ossicle or nasal septal bone. As well, some artificial metallic joints are covered by hydroxyapatite to promote osseointegration.

### Polymeric biomaterials

Almost all bodily organs except the skeletal system consist of soft tissues, and provide physiological and biochemical functions. But there is no artificial biomaterial that has the same biological functions of the natural tissues, therefore, the search for materials which can provide a favorable environment for regenerating tissue or mimicking tissue structure has been undertaken with a focus on the development of synthetic polymers. In the fabrication of synthetic polymers, the chemical and mechanical properties of

the base polymer can be easily modified to adjust to the characteristics which the material should possess.

Homopolymers are composed of a single type of monomer, and there are many homopolymeric biomaterials. Polymethyl methacrylate (PMMA) has hydrophobicity, good transparency, toughness, and a glassy texture at the room temperature. It is also practical in the manufacture of intraocular lenses and hard contact lenses. Soft contact lenses are made from the 2-hydroxyethyl methacrylate (HEMA), which is a modified PMMA by adding a methylene-hydroxide ( $-\text{CH}_2\text{OH}$ ) group to the MMA side group. The PolyHEMA is cross-linked by ethylene glycol dimethylacrylate (EGDM) to prevent the polymer from dissolving when it is hydrated.

Polyethylene (PE) has acceptable toughness, and resistance to lipids as biomaterials. Because the PE with low density would lose its shape at the sterilization temperature, high molecular weight PE is used as a biomaterials in catheters and drainage tubes (Chinn and Sauter, 1998). And ultra high molecular weight PE (UHMWPE) has been used as the acetabular component in artificial hip joints.

Polytetrafluoroethylene (PTFE), commonly known as teflon, is a PE but the hydrogen in the molecule is replaced by fluorine. PTFE has a very stable thermal and chemical structure. The very excellent hydrophobicity and lubricity of PTFE is the main reason for using it as a vascular graft material and its microporous form is called Gore-tex (Bujan and Garcia-Honduvilla, 1998).

Polyvinylchloride (PVC) is also used in medical tubing. The pure PVC has hard and brittle mechanical properties, but can be treated to be soft and flexible by adding plasticizers. The tubes for blood transfusions, feeding and dialysis are typical PVC applications. Though the additive plasticizer has low toxicity, the release of a plasticizer from a long-term applied material occurs, and this phenomenon deteriorates the mechanical property of the PVC, causing it to lose the flexibility.

Polydimethylsiloxane (PDMS) is a very versatile polymeric biomaterial. Its silicon-oxygen ( $-\text{SiO}_2-$ ) backbone labels it as a silicone. The mechanical property of the silicone varies according to the molecular weight, from grease phase to rubber or resin phase. It is used in catheters, drainage tubing, insula-

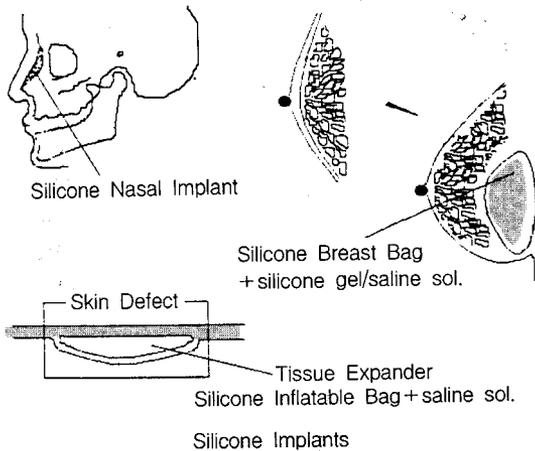


Fig. 2. Silicone uses in medicine.

tion for a pace-maker lead, and in vascular graft at high blood stream area. It has high oxygen permeability and is used in membrane oxygenators. Its exceptional flexibility and stability has been applied to produce finger joints, heart valves, breast implants, tissue expanders, chin and nasal implants, outer ear prostheses, etc. (Fig. 2).

Copolymers consist of different monomers and this is very useful in producing a polymer that has concentrated advantages from each monomer. Polyglycol lactide (PGL) is a random copolymer made by a ring-opening reaction of a glycolide, and is gradually degraded after implantation by hydrolysis that occurs at the ester linkages in the polymer backbone. These days, PGL is used in absorbable suture thread and polylactide (PLA) is applied to biodegradable bone screw, that is gradually degraded after fixing the fractured bone during reunion generation.

Polyurethane (PU) is a block copolymer containing typical phase segregational characteristics composed of hard and soft blocks. The hard block consists of diisocyanate and a chain extender, has a glass transitional temperature above room temperature and acts as a glassy or semicrystalline reinforcement. The soft block is comprised of polyether polyols that have lower glass transitional temperatures than room temperature, which provides a rubbery property to PU. The hard block reveals hydrophilicity and the soft block demonstrates hydrophobicity. This phenomenon is closely related to protein adhesion onto the PU surface, for it is recognized that proteins tend

to adhere to a hydrophobic, but escape from a hydrophilic surface. PU is a tough elastomer and it has favorable uses in continuous pulsative blood flowing arterial vascular reconstruction with its phase segregative surface that prevents the blood cell adhesion on the surface and thrombus formation (Kim and Park, 1997).

### Tissue engineering

The concepts of biomaterials have been changing recently as replacements for damaged tissue by viable or at least tissue regenerative materials instead of the conventional non-vital materials. Recent advances in molecular biology have provided highly applicable information for developing materials closer to natural tissues (Urist, 1965).

To provide biological functions to non-vital conventional metals, ceramics, and synthetic polymeric biomaterials, the development biochemically functional artificial tissues has been concerned with those consisting of cells. The study of reconstructing the lost tissue by artificially-treated natural tissue, cell culture and tissue ingredients has been undertaken in accordance with progress in the fields of cytology, molecular biology and protein engineering, and it has been called tissue engineering.

The purpose of tissue engineering is to provide a biocompatible environment for non-vital materials by supplying biological functions, or to produce an artificial living tissue.

Cells obtained from the necessary tissue are cultured, extracellular matrices (ECM) are extracted and reassembled as the natural polymers, those natural materials are hybridized with the non vital biomaterials to provide biological functions and total organs are preserved for transplantation.

Obtaining suitable cells is the key to tissue restoration by this method. Using normal host cells is the best, but in general, cells are obtained from other sources when there is no sufficient resource in the host organ in spite of immune problems. The *in vitro* culture methods for cells separated from living organ while maintaining viability are already relatively well established, and those methods are effective for increasing cell numbers to obtain the optimal amount of tissue cells for engineering. Adding specific growth factor during a specific cell

culture would induce rapid cell growth.

On the other hand, a culture produced by continuously proliferating cells while maintaining the tissue structure of the original organ and reconstructing the organ is called the organ culture. The recent research methods for *in vitro* reconstruction of tissue include the reaggregation of different cells, the culture of the homogeneous cell to high concentration by multicellular spheroids, the cell culture forming multilayer on the surface of ceramics or synthetic polymers, and cells cultured on the tissue structural collagen matrix. But the adjustment of the culture condition is still difficult due to the biological dynamics of the cell, and the *in vitro* cellular interactions do not reappear in the *in vivo* condition (Jauregui, 1997).

Extracellular matrix and proteins are the typical natural polymers used in biomaterials, while collagen, fibronectin, and vitronectin are widely considered for use as biomaterials, respectively. The specific cell adhesive peptide Arginine(R)–Glycine(G)–Aspartic acid(D) sequences are contained in the collagen and fibronectin molecules. The RGD peptides artificially aligned on a biomaterials surface would provide an environment favorable to induce the surrounding tissue cell's adhesion on the material surface, and the natural tissue could be imitated on the material-tissue interface (Zhao and Ivic, 1998).

On the premise that the ideal replacement for damaged tissue is by the regenerated host tissue, supplying an adequate amount of extracellular matrix to the damaged tissue would promote the host cell induction. Growth collagen exists in all mammalian tissue as the structural component and matrix for supporting cell adhesion and for proliferation to construct tissues and organs, and as a result, the artificially reassembled collagen could act as a structural scaffold and supplementary extracellular matrix for cell adhesion (Nimni, 1988).

For biomaterials usage, collagen is extracted from the tissue, purified and manufactured as hemostatic agents, skin wound dressings, transparent corneal dressings, etc. Another method is fabricating natural organs without destructing the collagen structures in the tissue, as in porcine tissue heart valves and crosslinked amnion for tissue patches, etc.

The first commercially available hemostatic agent

made of purified collagen from calf skin appeared in 1974, while spongy membrane type was developed later. Collagen conducts platelet aggregation, which results in thrombus formation and blood cell aggregation. Wound dressing is another important material in preventing infection and loss of body fluid following skin denudation following burns or other skin damage. Porous collagen membrane with sufficient thickness has been used for lesions to conduct dermal cellular regeneration. The corneal dressing is used as a biodegradable postoperative bandage in the eye clinics. Extremely transparent collagen is necessary to provide the light transmission.

Collagen is also widely used in cell culture as an additive to maintain homeostasis of the culture, for the material balance of cell differentiation and cytolysis. At high collagen fiber concentration, cellular DNA synthesis decreases and activates collagenase synthesis, which results in cytolysis function, but under normal conditions, collagen continuously stimulates stable cell differentiation to maintain homeostasis in cell numbers. Adhesive growth cells like fibroblasts demonstrate this growth with flat morphology in the general culture media, but in the presence of collagen, cells grow rapidly with abundant cellular spindles. The addition of collagen to the media results in transglutaminase which is activated during keratinocyte culture and albumin synthesis which is stimulated during hepatocyte culture. Therefore, in using collagen as a biomaterial, rapid growth of the surrounding cells can be induced by reducing collagen fiber density or by prohibiting fiber formation to promote cell differentiation and to decrease cytolysis.

Type I collagen is the most abundant one in mammals, especially in skin, bone and tendons, and it is widely used in biomaterials applications (Table 6).

To improve biocompatibility of collagen materials with tissues, the surface of collagen materials are modified by succinylation, esterization, branching of hydroxycarbon radicals to control electric charge, degradation rate, and interactions with blood or cells. And to produce a biofunctional material, enzymes such as protamine or heparin are also used in combination.

Succinylation of amines in the collagen molecule changes the molecule to obtain an abundant negative

Table 6. Collagen resources and uses

Resource	Treatment method	Fabricated shape	Usage
epithelium	pepsin treatment telopeptide removal	atelocollagen low immunogenicity	translucent solution, gel, membrane, hollow fiber, microsphere, sponge, rod, lens, etc.
tendon	dispersion	fibrous collagen high platelet coagulation	hemostatic agent, wound dressing, etc.
blood vessel, heart valve, pericardium, etc.	blood removal, cross linking	maintain natural collagen	natural tissue material for xenograft

charge, and the collagen becomes soluble in the neutral pH regions. Then, a uniformly dispersed collagen solution is produced. The succinylated collagen surface also demonstrates the antithrombogenicity by preventing platelet adhesion and aggregation. Esterization of the collagen by reacting ethanols to the carboxyls of the molecule produces an abundant positive charge in collagen, which is also soluble in the neutral condition with highly thrombogenic characteristics. Blanching of the hydrocarbons to the collagen increases the hydrophobicity by which the surfactant potential appears. Therefore, modification of the collagen molecular side chains by chemical treatment is a useful method in providing a specific function to collagen. Succinylation is a good tool to fabricate an artificial vessel, while esterization is acceptable for hemostatic agents (Suh *et al.* 1994).

The heparin grafted collagen surface provides a highly acceptable antithrombogenic property by the gradually released heparins. The immobilized heparin would be released gradually and prevent the platelet aggregation, and the proliferating endothelial cells would recover the heparin detached region, and finally, a biomimic artificial vessel could be produced. The protamine-only grafted collagen, which expresses a high positive charge, can also be used as a hemostatic agent, for the negative charged platelets would covalently bind to the protamines (Jeong and Schwartz, 1997).

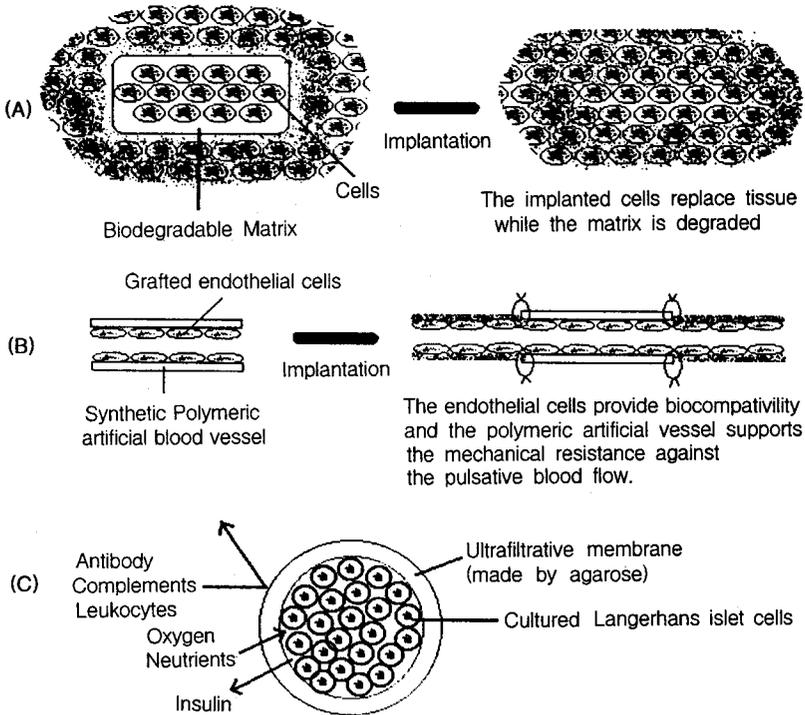
The implanted collagen is degraded by collagenase, and this property is applied to use collagen as a carrier for the drug delivery system. The controlled release of a drug with an adequate amount of collagen for a adequate period in the body helps to minimize the side effects and to maximize the drug's efficiency. The implanted drugs chemically-

integrated with collagen would be released as the collagen carrier was gradually degraded by collagenase. The lymphocaines such as interferon are considered to be encapsulated by a collagen carrier (Woznet, 1988).

The hybridization is an effective tool for expanding applications of the conventional metallic, ceramic or polymeric biomaterials by adding cellular biological functions to their outstanding physical properties as structural scaffolds in artificial tissues. The successfully-grown *in vitro* cells do not guarantee a successful *in vivo* cell life after implantation, for the living environment is quite different from the other. Therefore, hybrid biomaterials should be designed to maintain the cellular functions with the opposite non-vital material component that has to provide an adequate living environment for cells (Suh and Lee, 1995).

There are various types of hybrid biomaterials according to the physical characteristics of the scaffolds that are usually made of synthetic polymers. The cells collected from the normal portion of the damaged tissue are cultured in a biodegradable polymer scaffold to make a hybrid material. The implanted cells are growing and regenerating the tissue while the structural scaffold is degrading. Collagens, lactic acids and synthetic polymers such as aliphatic polyesters are commonly applied to the degradable structural components (Fig. 3).

By contrast, some implanted material should not be degraded. In the case of an artificial blood vessel, the lumen needs to be covered by endothelium, for the surface is continuously in contact with flowing blood that would create the blood coagulation if it causes direct contact with a foreign body, including the synthetic biomaterials. The endothelial cell culture on the inner surface of the artificial vessel



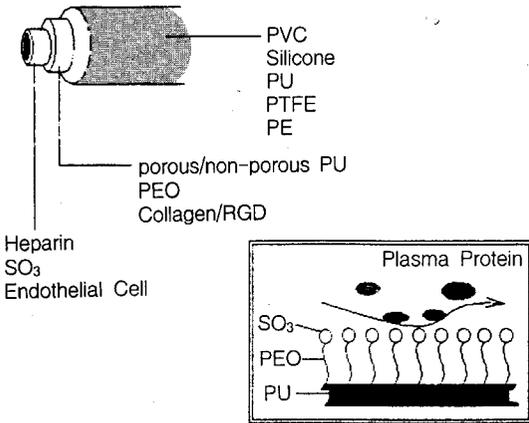
**Fig. 3.** Types of hybridized biomaterials. (A) Delivered cells induce tissue regeneration, replacing the implanted matrix which is gradually resolved. (B) Hybridized cells provide biochemical necessity of the implanted material that supports the biomechanical structure. (C) Protection of the viability of implanted cells from immunologically-adverse reactions.

is an acceptable tool in providing an antithrombogenic property. However, the artificial vessel itself should maintain sufficient fluid mechanical characteristics to uphold the continuously pulsative blood flow without losing any biomechanical deterioration. Therefore, the biodegradable scaffold is not suitable to use as a scaffold. Synthetic polymers with sufficient biomechanical strengths, with less deterioration, and blood compatible properties such as polyethylenes, polytetrafluoroethylenes, and polyurethanes are the best candidates as vessel structures where endothelial cells are cultured on the surface (Lanza *et al.* 1997) (Fig. 4).

Highly advanced organic tissues like a liver are almost impossible to be reconstructed by any recent engineering technologies, but a bioreactor is in intermittent clinical use for patients who can be helped in recovery by temporary detoxification for up to 2 weeks. The bioreactor is designed to detoxify the blood by passing through the hollow fibers made by

the porous membranes, those which are surrounded by cultured hepatocytes. The pores are providing the toxic substance transmission toward the hybridized hepatocytes during blood passage (Davis and Vacanti, 1996).

Using heterogeneous cells raises immunological problems after implantation, so, the encapsulation of cells by membranes which provide substances necessary for cellular viability, except the immunological matters, is being deeply considered these days. For the treatment of insulin dependent diabetes mellitus patients, implantation of insulin-releasing Langerhans islet cells has been studied. The basic idea is that the heterogeneous Langerhans islet cells are encapsulated by a semipermeable synthetic membrane that permits the insulin release but protects the direct binding of the host antibody to the foreign body, the implanted cells. In May, 1997, an American laboratory announced that erythrocytes encapsulated by polyethyleneglycol avoiding the



Designs of the Artificial Vessels

**Fig. 4.** To prevent blood coagulation, the lumen of an artificial vessel made of polyurethane (PU) is grafted by sulphonate (SO<sub>3</sub>) through polyethyleneoxide (PEO), anticoagulatory enzyme (heparin), or the cultured endothelial cell to avoid blood plasma protein adhesion onto the PU surface.

transfusion-rejection had been developed. This marks the opening of the free-cross transfusion era without concern for blood types.

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