Perspective

Biomaterials: Status, Challenges, and Perspectives

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Biomaterials are substrates other than foods or drugs contained in therapeutic or diagnostic systems that are in contact with tissue or biological fluids. Nearly every individual utilizes biomaterials whether they are in the form of dental fillings, as coatings for tablets or capsules, or in medical devices such as contact lenses, kidney dialyzers, vascular grafts, or cardiac pacemakers. Annual sales of medical systems using biomaterials in the U.S. currently exceeds $100 billion (Peppas and Langer, 1994; Langer, 1998), and the potential markets for such systems as discoveries are made in such new growth areas as tissue engineering are far greater (Langer and Vacanti, 1993).

Chemical engineers have been contributing significantly to biomaterials science. Starting in the 1960s and 1970s, these contributions include understanding what factors affect biocompatibility of a material when it is in contact with blood (Merrill et al., 1966), examining mass transfer in clinical blood filtration devices and defining mass transport properties of hemodialysis membranes (Colton et al., 1975), the design of transdermal drug delivery systems (Michaels, 1976), and developing the foundation for controlled release systems for macromolecules (Langer and Folkman, 1976). In spite of these advances, however, there is much to learn about how materials interact with the human body and a great need to create new biomaterials and medical devices to address unsolved medical problems.

Development of new biomaterials

The choice as to what materials are currently utilized in the human body has generally not been made by chemists or chemical engineers, but by clinicians. Their strategy was often to replace an organ or tissue with an off-the-shelf material that in some manner resembled the tissue they were trying to fix (Peppas and Langer, 1994). For example, materials used in the artificial heart, such as polyetherurethanes, were originally derived from ladies' girdles because of their good flexural properties. One of the materials chosen for use in breast implants was used in mattress stuffings.

While this approach enabled progress to be made in biomedical device development, it also created problems. For example, while artificial hearts have been used successfully for short time periods, there are problems associated with blood compatibility, which can lead to clot formation and strokes (Peppas and Langer, 1994).

One important area of study is to create better biomaterials. We and others have suggested that, rather than using off-the-shelf materials, the desired material could be chemically synthesized from first principles to possess precisely the correct engineering, chemical and biological properties for the intended medical application. One example can be found in the area of synthetic degradable polymers that are potentially useful for drug delivery. Currently, most polymers dissolve by a process known as bulk erosion, in which a polymer matrix becomes spongy over time and eventually falls apart. Thus, if a drug were originally distributed uniformly throughout the matrix, the drug could potentially "dump" out as the matrix erodes. From an engineering standpoint, it would be far more desirable to have polymers that degrade by surface erosion, analogous to the way a bar of soap dissolves. To achieve this goal, we approached this as an engineering design problem and asked the following questions:

1. What should cause the degradation of the polymer—enzymes or water? Water was chosen because there may be differences in enzyme levels between individuals, and the cellular response (cells contain different enzymes) surrounding a material will change over time. However, everyone has excess water.

2. What should be the nature of the monomers? To achieve surface erosion the monomers should be hydrophobic to keep water out of the polymer matrix interior.

3. What should the chemical bonds connecting the monomers be? Here it is important that the bonds be hydrolytically labile. The anhydride bond was found to serve that purpose.

4. What should be the precise chemical structure of the monomers connecting the anhydride bonds? This was examined from both toxicological and polymer chemistry standpoints; several monomers such as carboxyphenoxypropane and sebacic acid were selected on this basis. The polymers were then synthesized, formed into microspheres or discs, and drugs could be placed inside them (Tamada and Langer, 1992).

These polymers have already led to new ways of delivering chemotherapy to brain cancer patients. For example, drugs such as carmustine (BCNU) can be mixed with these polymers and the polymers formed into wafers that can be placed into the brain at the time of surgery. There, they locally deliver drug to the tumor and increase patient survival about fivefold (after two years) compared to patients receiving conventional treatments. Furthermore, by delivering the drug locally rather than systemically, the side effects of conventional chemotherapy are reduced.

Another important area of biomaterials is tissue engineering. Over half of the nation's health care costs can be attributed to tissue loss or organ failure. Several approaches have been explored involving biomaterials for tissue engineering (Figure 1). One utilizes semipermeable polymer membranes that encapsulate cells in such a way that allows nutrients and wastes to pass through and yet keep larger molecules such as antibodies or immune cells away, thereby preventing immune rejection. In a second approach, poly-

mers act as scaffolds onto which seeded cells can multiply and form new tissue structures. The cells are placed on a polymer scaffold, which is then placed in a reactor vessel containing the media required for cell growth; over time the tissue will form and can then be placed in the body. By synthesizing polymers that are adhesive for the appropriate cells and then designing polymer scaffolds in the desired geometry for the engineered tissue, the appropriate cells [which could be a specific cell type such as a cartilage cell (chondrocyte) or skin cell (dermal fibroblast), or an undifferentiated cell (a cell that has yet to become a specific cell type) such as a stem cell] in the presence of the correct growth media and reactor conditions (e.g. type of mixing) will produce extracellular matrix and form a tissue. This approach has already led to the formation of skin that can be used for treating burn victims. Other engineered tissues such as urological structures and systems for treating liver disease are in clinical trials (Vacanti and Langer, 1999).

Surgery and dentistry have been very important areas for biomaterials development. Some of the more classic endeavors have included the development of sutures and, subsequently, staples. More recently, the possibility of creating sealants has been explored. One such sealant involves new biomaterials where polyethylene glycol is copolymerized with degradable blocks of lactic acid oligomers with acrylate groups placed at the ends of the polymer chains. The acrylate groups enable the polymer to be photopolymerized (Sawhney et al., 1993). For example, a liquid can be placed on leaks in the lung at the time of surgery, and when a light is shone on this area a gel forms sealing the leaks. In the dental area, materials ranging from fillings to bondings to slow release systems (releasing antibodies) for treating periodontal disease are being explored.

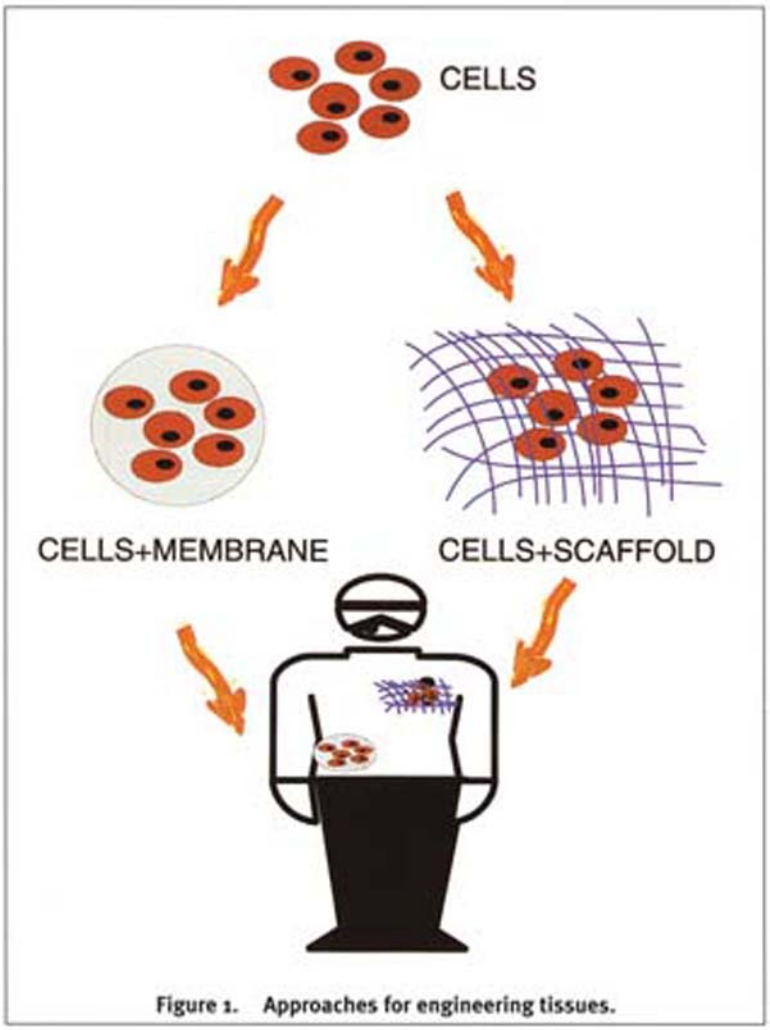

Figure 1. Approaches for engineering tissues.

Another area involves the development of contrast agents for imaging. Currently, it is extremely difficult to image many parts of the body such as the blood vessels perfusing the heart using noninvasive, cost-effective approaches such as ultrasound. One way to address this issue is to develop contrast agents such as microcapsules containing gases that have a high echogenicity when exposed to ultrasound. The microspheres should also be able to travel through the circulatory system for long time periods so that useful images can be created. One approach to creating contrast agents involves using alginates that can be gelled in aqueous media to encapsulate gas (Wheatley et al., 1990).

Challenges

There are enormous challenges that are important for the future of biomaterials development. One of these involves the design of materials that will enable noninvasive delivery of complex drugs such as proteins to the body (Figure 2). Another challenge relates to gene therapy. One of the greatest problems in gene therapy today is the design of nonviral delivery systems that are both safe and highly efficient in delivering genes to the appropriate cells. To succeed in this area it would be important to have safe materials, with the following properties:

- Condense or "package" DNA to small sizes so that DNA can be taken up by cells.
- Enable DNA to be stable before and after cellular uptake.
- Bypass or escape the cell's endocytic pathways.
- Enable the DNA to travel to the cell's nucleus.
- "Unpackage" DNA by releasing it in active form (Luo and Saltzman, 2000).

One of the strategies being explored is the design of charged polymeric cyclodextrins that bind to DNA (Gonzalez et al., 1999). Another approach involves the synthesis of "proton sponge" polymers. Such materials, if they are positively charged, might be able to condense DNA, which is negatively charged, and subsequently enter the cell and its endosomes. If they have a pK range between 4.5–6.5, they may be able to subsequently lyse endosomes by attracting protons, thereby causing osmotic rupture. Other chemical features such as nuclear localization sequences might be incorporated into such polymers.

The synthesis of new materials for tissue engineering and for examining cell-surface interactions is also important. For example, polymers that conduct electricity are being explored for nerve regen-

eration. When small voltages (e.g., 100 mV) are applied to such polymers, nerve like cells growing on them form neurities that are much longer compared to when no voltage is applied and orders of magnitude greater compared to conventional polymer, such as polylactic acid surfaces (Schmidt et al., 1997). Another area involves the synthesis of polymers that contain specific ligands (often these are specific amino acid oligomers) attached to them that can control cell behavior (Peppas and Langer, 1994). Such materials may be useful not only in creating new tissues but also as tools for basic research in molecular cell biology.

Polymers that can be photopolymerized, for potential use in minimally invasive surgery, represent another area of research. Such polymers might lead to minimally invasive ways of treating such problems as adhesions (tissues adhering together creating blockage) (Hill-West et al., 1994a), restenosis (the resulting narrowing of a blood vessel that has previously been opened physically for patients with cardiovascular disease) (Hill-West et al., 1994b), or even to create new tissues. Placing a polymer liquid (with a drug or cells mixed in, if desired) in the appropriate place in the body and photoactivating that liquid with external light enables the creation of a photopolymerized gel that can become a tissue such as cartilage (if cartilage cells were originally placed in the liquid, for example) or release a drug (if a drug is placed in the liquid) (Elisseeff et al., 1999).

One interesting area involves the convergence of nanotechnology and medicine. An example has been the creation of microchips housing nanosized reservoirs (containing drugs) that might be able to deliver these drugs for prolonged time periods and in a controlled predictable manner (Santini et al., 1999). By placing a microprocessor, power source, and perhaps a biosensor on such a chip, an implantable system that can deliver drugs in response to specific regulatory *in vivo* molecules might someday be designed. Still another area of importance is the design of materials that are "smart" and can response to external stimuli such as pH, temperature, ions, or specific affinity ligands (Peppas, 1997). Such materials might be designed to deliver drugs in response to specific physiological changes in the body for example.

Another challenge is to create approaches for manufacturing complex tissue structures. One interesting approach has been the application of three-dimensional printing (Park et al., 1998) to make complex structures like vascular beds in a tissue-engineered liver. Finally, it is important to develop new analytical techniques to study materials and their surfaces and interactions with proteins, DNA, and cells *in vitro* and *in vivo*.

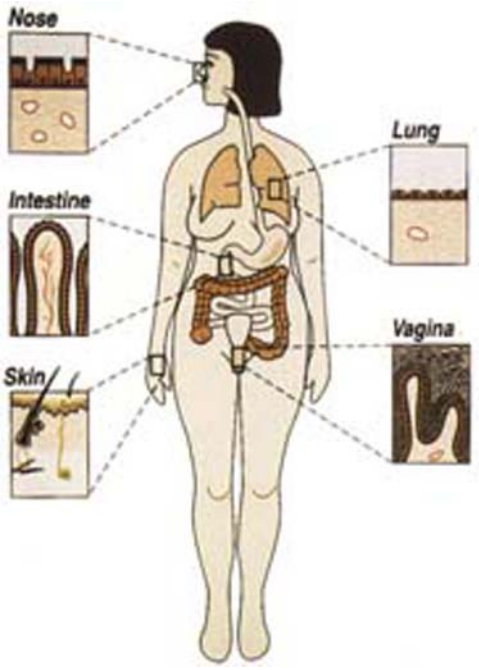

Figure 2. Drug delivery through different body sites. Both the macroscopic and microscopic anatomy must be considered. In such cases as skin, vagina, and nose, it is easy to physically target the macroscopic site that the drug must reach to access the systemic circulation. On the other hand, the cellular barriers at those sites may be a significant barrier to transport. For lung, it is difficult to physically target the drug to the desired part of the organ (deep lung). However, if one is able to do that successfully, the cellular barrier to transport may be less (note the thinness of lung epithelial cells). The microscopic sections are derived from hematoxylin and eosin stained sections of actual tissues. Epithelial cells are dark pink, basement membrane is purple, and blood vessels appear red.

In Summary

In the new millennium, the interface between two of the most exciting areas of chemical engineering—bioengineering and materials science—presents important challenges for our discipline. Undoubtedly, the opportunities that biomaterials have already created and will continue to create in medicine will profoundly affect human health in the years to come. Chemical engineering can play an increasingly important role in this endeavor.

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