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The future of biomedical materials

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Abstract The purpose of this communication is to present the author's perspectives on the future of biomedical materials that were presented at the Larry L. Hench Retirement Symposium held at Imperial College, London, in late September 2005. The author has taken a broad view of the future of biomedical materials and has presented key ideas, concepts, and perspectives necessary for the future research and development of biomedical polymers and their future role as an enabling technology for the continuing progress of tissue engineering, regenerative medicine, prostheses, and medical devices. This communication, based on the oral presentation, is meant to be provocative and generate discussion. In addition, it is targeted for students and young scientists who will play an ever-increasing role in the future of biomedical materials.

Introduction

Over the past decade, research and development of new biomedical materials has turned from "passive" materials to materials that actively interact and integrate with their biological environment. Unfortunately, this paradigm shift has not been matched by a requisite enhancement of our knowledge of the mechanisms of interaction between the materials and proteins, cells, and other materials within the biological environment. Given the unique nature of tissues and organs, we lack biological design criteria for the development of new materials and devices constructed from these materials. Additional constraints in our developing biological design criteria and structure/biological property relationships are our dependence on *in vitro* studies and non-human models in the development process.

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The history of biomaterials

As has been stated by many authors in many different ways, if we do not understand and appreciate the past, we are doomed to repeat it in the future. Table 1 presents the author's perspective on the history of biomaterials. As exemplified by the change in font size of the word "biomaterials", the first quarter century, 1950 to 1975, of biomaterials development was dominated by the characteristics of the materials intended for prostheses and medical devices. Important in the early days was the long-term integrity of the biomaterial as well as its non-toxic nature. Biological interactions that were considered included the non-toxic nature of the biomaterial as well as its normal inflammatory and wound healing responses when implanted. Many materials were described as being inert, but this was a confusing descriptor as it did not adequately and appropriately describe material changes following implantation or cell and tissue responses to the implanted biomaterial. It eventually became clear that materials could change without adversely affecting the function and interaction of the biomaterial, prosthesis, or medical device. Likewise, modulation of the inflammatory and wound healing responses could occur without altering the function of the biomaterial, prosthesis, or medical device. From a biological perspective, no material is inert.

From 1975 to 2000, biological interactions with biomaterials began to be more extensively investigated. Advances in our knowledge of biological mechanisms, for example, the coagulation, thrombosis, and complement pathways, led to a

Table 1 History of biomaterials

1950–1975	bioMATERIALS
1975–2000	BIOMATERIALS
2000–	BIOmaterials

better understanding of biological interactions with biomaterial surfaces. In the 1980's, the revolution in techniques for the study of cell and molecular biology led to their application to the investigation of interactions occurring at biomaterial interfaces. More recently, with the advent of the areas of tissue engineering and regenerative medicine, heavy emphasis has been placed on biological interactions with biomaterials. In some cases, this has led to an undesirable decrease in the appreciation of material properties and their role in these new scientific areas. An example of these types of problems is presented with biodegradable polymer scaffolds for tissue engineering and their ultimate disposition including changes in form and integrity with resultant changes in the inflammatory and foreign body reactions over the implantation time period.

Medical implant design

In approaching the research and development of new biomedical materials for prostheses and medical devices as well as an enabling technology for tissue engineering and regenerative medicine, a comprehensive, virtually all-inclusive perspective is initially necessary to begin to appreciate design criteria. Table 2, Medical Implant Design, illustrates this in a simple manner. The development of design criteria begins with the identification of patient needs. We must remember that our overall goal is to provide biomedical materials, prostheses, medical devices, and other constructs that will enhance the health and welfare of patients. With the identification of patient needs, concepts are then developed based on known anatomical and physiological processes and their alteration by disease processes that are integrated to begin the design process. Following from this, configuration, prototype, manufacture and assembly, test/use, reliability, and clinical trials follow from the original design criteria. It is important to note that the last factor in medical implant design is implant retrieval and evaluation. Implant retrieval and evaluation permits the identification of modes and mechanisms of failure or success that ultimately in turn provide feedback information for further development of the concept based on additional design criteria obtained from implant retrieval and evaluation. The author acknowledges the significant contribution of Dr. John Watson, Department of Bioengineering, University of California-San Diego, La Jolla, CA, who originally developed this construct of medical implant design during his tenure at the National Heart, Lung, and Blood Institute in Bethesda, MD.

Table 2 Medical implant design

1.	PATIENT NEEDS
2.	CONCEPT
3.	CONFIGURATION
4.	PROTOTYPE
5.	MANUFACTURE AND ASSEMBLY
6.	TEST/USE
7.	RELIABILITY
8.	CLINICAL TRIALS
9.	IMPLANT RETRIEVAL

Biomedical materials and devices

Over the past decade, new constructs bringing together synthetic and biological components have been developed and described as being biomimetic, biohybrid, or combination products. It should be noted that combination products are not necessarily new. For example, collagen coated vascular grafts were developed in the 1980's. The use of biodegradable polymers to deliver drugs was also developed in the 1980's. Both of these types of combination products have found extensive clinical use for the treatment of various diseases. A more current example of a combination product that has proven successful is the development of the drug eluting stent for the treatment of atherosclerotic, occlusive coronary artery disease. The complex, interactive nature of drug eluting stents is illustrated in Fig. 1. In approaching design criteria for drug eluting stents, the stent, polymer matrix, drug, and interactive vascular tissue must be considered in the development of design criteria. These obviously then speak to important contributions from materials engineering, polymer chemistry, pharmacology, and vascular biology. Integrating these into design criteria and the important issues involved in the development of a drug eluting stent are further identified in Fig. 1.

The author appreciates the use of this figure through the efforts of Dr. Lothar Kleiner and Dr. Syed Hossainy of the Guidant Corporation, Santa Clara, CA.

Challenges and barriers

In the future use of biomedical materials as an enabling technology and the development of new biomaterials and tissue engineering constructs, numerous challenges and barriers are present. Table 3 presents a limited and biased perspective on some of the major challenges and barriers to the successful development of new biomedical materials and tissue-engineered constructs. Rarely is the architecture of the tissue and organs taken into consideration as a design criterion. All

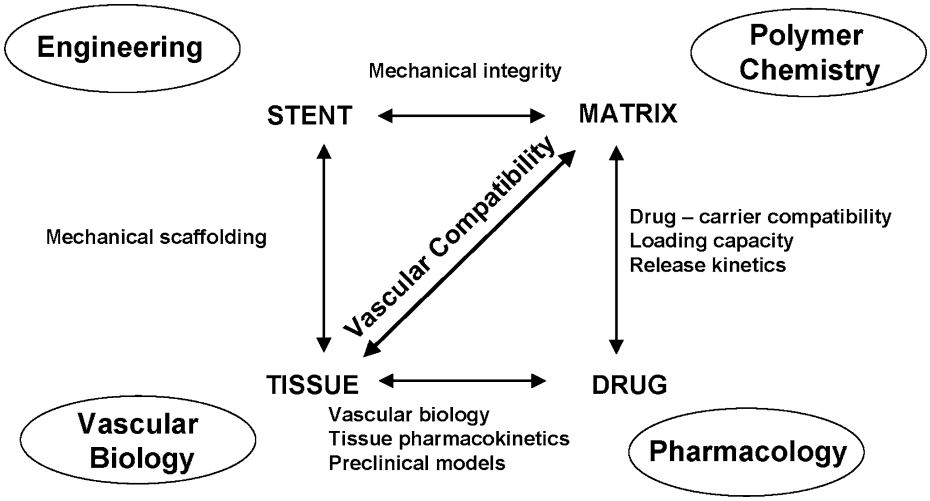

Fig. 1 An interdisciplinary approach to drug-eluting stent development

Table 3 Challenges and barriers

Perspective of Tissues and Organs
Tissue Skeleton: Arteries, Veins, Lymphatics, and Nerves
Biomaterials (2D) and Matrices/Scaffolds (3D)
Micro- and Nano-scaled Systems
Species Similarities and Differences
Cell Culture Systems and Tissue Reactors
Stem Cells, Bone Marrow Cells, Progenitor Cells
Functional Overlap: Inflammation, Immune Response, Wound Healing, and Developmental Biology
Vascularity: Angiogenesis and Vasculogenesis
Over Engineering, Under Engineering, and No Engineering

vascularized organs and tissues have a tissue skeleton that is basically arteries, veins, lymphatics, and nerves, which are contained within an extracellular matrix, composed mainly of collagen. Most certainly, veins, lymphatics, and nerves generally are not considered in the development of tissue-engineered constructs. From a biomaterials perspective, little is known that relates the two-dimensional *in vitro* behavior of cells with their behavior in three-dimensional matrices and scaffolds. Studies relating these dimensional aspects are necessary to provide guidance for further studies as well as interpretation of results obtained from studies in these systems. In addition, cells are large, micron-dimensional structures when compared to nano-scale structures such as receptors or even macromolecules, and an appreciation of the dimensional scale in cell/material interactions is needed. A major void in knowledge exists in appreciating the similarities and differences in species that may be used to test new biomedical materials and tissue-engineered constructs. An appreciation of the similarities and differences is necessary. Little is known regarding the similarities and differences in the cellular behavior between species. An excellent example here is the relatively rapid endothelialization of vascular graft materials in a wide variety of mammals when compared to the virtual non-endothelialization of vascular grafts in humans. Further knowledge is necessary regarding stem cells, bone marrow cells, and other cell types that would be used in cell culture systems and tissue reactors for constructing products to be used in tissue engineering or regenerative medicine. From a biological perspective, inflammation, immune responses, wound healing, and developmental biology share many interacting and overlapping pathways. Knowledge here is scant and thus limits the appreciation of these processes and their ultimate usefulness. Emphasis in tissue-engineered constructs is generally placed on providing vascularity to these constructs for the maintenance of cell life; however, the venous return of the deoxygenated blood has not been appreciated in tissue-engineered constructs. This area offers additional opportunity for significant contributions. Finally, the literature contains numerous examples of devices that have not fully appreciated the appropriate design criteria and thus are either over-engineered, under-engineered, or have virtually no engineering.

These challenges and barriers are presented to students and young scientists as areas for significant advancement and areas in which these individuals can make significant contributions.

Conclusion

The future of new biomedical materials is dependent upon the development of an enhanced knowledge base of molecular, cellular, and tissue interactions with materials. Our focus for the future must be on understanding mechanisms of interaction between the new biomedical materials and their *in vivo* environment. This focus on broadening our mechanistic understanding of tissue/material interactions will permit development of design criteria from a biological perspective.