Fundamental considerations for biomaterial selection

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BEFORE THE LATE 1950S, BIOMECHANICAL sciences and engineering were in a slump. Prostheses were rudimentary and unimaginative, and biomaterials science simply did not exist. Until this point, according to *The Cultural Body*, wooden peg-legs and gold teeth were the only clinically and socially accepted prosthetic devices; the only accepted transplantation procedure was blood transfusion. Three major events helped propel biomechanics out of the dark ages and create the field of biomaterial science as a requisite for the production of functional medical devices.

The first major event was the race to the moon. Starting in the late 1950s, massive government spending provided the motivation and resources needed to answer a rather daunting question: how would the human body react to the stress induced during space travel and extended periods of time spent in microgravity?

The second major event was the improved technological capability of the digital computer, which was first developed around 1945, that allowed researchers new computational freedom and computational power in the highly complex and nonlinear world of biomechanics.

The final event was the birth of modern biology, which provided a sound scientific basis for biomechanics at the microscopic level. In 1951, Linus Pauling began to uncover the basic structure of protein, and in 1953, Watson and Crick revealed the double helical structure of DNA.

These three events provided the motivation and technology that led to a proliferation of advancements in biomedical instrumentation. Within a decade, an explosion of new clinical applications had been realized. Most notably, the artificial hip joint, the artificial kidney and heart, the lung machine, the cardiac pacemaker, and the prosthetic cardiac valve were all produced during that time period. This article will provide a glimpse into a fundamental part of the process that was developed over the past six decades to create those devices: the materials out of which they are made.

A widely accepted and useful definition of a biomaterial offered by Williams is "a nonviable material used in a medical device that is intended to interact with biological systems for the purpose of improving health." A more recent consensus definition of a biomaterial excludes the word "nonviable" due to the development of tissue-engineered scaffolds and hybrid prosthetics in which living cells are combined with nonorganic material. Today, there are a relatively limited number of different biomaterials being used in the clinical setting. Standard polymers, metals, and ceramics encompass the bulk of functional biomaterials. One may wonder why so few biomaterials are accepted clinically. The answer to this lies in the fact that the positive effect a material has on the mechanical soundness of a device often is negated by its incompatibility with the tissue with which it will be in contact. This problem, referred to as biocompatibility, is the first issue, in addition to a basic material utility analysis, that an engineer must consider for a candidate biomaterial when improving an existing device or creating a new one.

BIOCOMPATIBILITY

Biocompatibility is defined by Williams as the ability of a material to perform with an appropriate host response in a specific application. This means that the material must elicit the correct reaction, or lack of reaction, from any tissue with which it is in direct or indirect contact for a particular treatment. Identification of a material with good biocompatibility requires a host of different tests. These tests fall into two general categories: in vitro and in vivo. In vitro testing is used to determine the overall tradeoff between performance and biocompatibility that can be reached with a certain material. In vivo testing tackles questions relating to the performance of a biomaterial in a clinical situation.

The distinction between in vitro testing versus in vivo testing is that in vitro testing occurs in an artificial environment, whereas in vivo testing takes place within a living system. Generally, in vitro tests identify cytotoxicity, cell activation, cell adhesion, or necrosis due to a particular biomaterial using cell cultures. In vitro testing employs three main types of assays to determine basic information about the material in question: direct contact, agar diffusion, and extract dilution.

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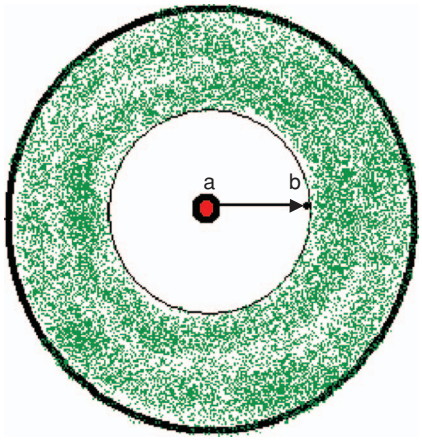

Fig. 1 Agar diffusion occurs from the well at position (a) outward, creating a concentration gradient of the substance being tested. Because the zone of inhibition has a radius that ends at position (b), it can be stated that the concentration at that distance from the well is the lowest at which the bacteria is inhibited successfully.

A direct contact assay is the most general and simple test for biocompatibility and usually is used to identify possible candidate biomaterials for a new application. The material under investigation is placed in direct physical contact with cells that it will encounter while in use and can identify any adverse reaction that the cells may have to the foreign material. This type of test has a distinct advantage in that it can be used to see the effects of a potential biomaterial on a single type of cell in isolation without secondary interactions that would occur in a living organism. Cells needed for these tests can usually be acquired from different cell lines that are widely available though various cell repositories.

An agar-diffusion assay is used to quantify the susceptibility or resistance of a bacterial strain to a potential biomaterial (see Fig. 1). First, a bacterial suspension is spread on the surface of an agar gel assay. Then, the material in question is placed in different wells cut into the gel. A zone of inhibition will form around the material where no bacteria grow because of the material's inhibitive effect. The area of this zone can be used to determine a material's potential susceptibility to bacterial infection when placed in a living system. If there appears to be no zone of inhibition around the material, then the bacteria on the agar assay is deemed resistant to that material.

Extract dilution assays are used to determine if extracts of a biomaterial (a submaterial within a biomaterial) may be cytotoxic in any way. Both hydrophilic and hydrophobic solvents are used to extract low-molecular-weight materials from a candidate biomaterial at varying concentrations. Each of these extracts is tested for cytotoxicity or any other harmful reaction in a cell culture.

When considering in vivo testing, there are two important purposes for testing on living biological systems. The first is to screen for a new biomaterial by incorporating it into a living system and observing any obvious complications or abnormalities. The complex nature of a living system is impossible to create in a cell culture. Before a researcher burdens him or herself with extensive in vitro testing, it is a good idea to see whether this endeavor is worth pursuing rather than being surprised by an interaction in the living system that causes the biomaterial to be incompatible. The second purpose for in vivo testing is verification of the biocompatibility of the final, or "as used" product. A final product must pass a multitude of different in vivo tests before it will be accepted clinically. Recently, there have been extensive efforts put forth by the U.S. Food and Drug Administration (FDA) and its regulatory agencies to standardize and regulate in vivo testing requirements for biomaterials to reach the clinical level.

Medical devices are categorized by the tissue that the instrument will contact and the duration of that contact. Table 1 displays a standard categorization scheme for medical devices based on principles and guidelines that have been used in the past to create safe and functional medical equipment. To decide what in vivo testing protocols are appropriate, the instrument under investigation must be characterized using this scheme.

Ultimately, "end use" in vivo testing will determine an instrument's biocompatibility. For a new biomaterial, extra precautions must be made to ensure biocompatibility. If an instrument being tested does not fit easily into the categories presented in Table 1, then in vivo tests associated with more than one category may be necessary. On the other hand, when designing a new device with biomaterials that have been tested exhaustively in vivo, some in vivo tests are not necessary to gain regulatory authorization. Some common in vivo tests are listed in Table 2.

BIOLOGICAL FUNCTION

The degree of a biomaterial's biocompatibility is clearly not a designer's only concern. Steps must be taken to ensure that the biomaterial will be fully compatible with its environment as well as biologically functional. The functionality of a material is determined by its performance in a specific application. For example, the material used to create an artificial hip joint must have high sheer strength, be durable enough to last many years without any major degradation, and have good ductility making it difficult to fracture. The leads of a pacemaker must be highly resistant to degradation and must be impervious to the build up of organic insulating substances around electrical contacts. A bone-void filler must degrade at a rate

Table 1. Classification of devices by tissue contact and duration of contact.

Tissue Contact
- 1) Surface Instruments
  - • Epidermal
  - • Mucosal membranes
  - • Compromised surfaces
- 2) External Communicating Devices
  - • Blood path, indirect
  - • Tissue, bone, or dentin linking
  - • Circulating blood
- 3) Implant Devices
  - • Soft tissue or bone
  - • Blood

Duration of Contact
- 1) Limited: less than 24 hours
- 2) Extended: more than 24 hours, less than 30 days
- 3) Permanent: more than 30 days

Adapted from: Anderson, James M., "Fundamental biological requirements of a biomaterial," in *An Introduction to Biomaterials*, Scott A. Guelcher and Jeffery O. Hollinger, Eds. Boca Raton, FL: CRC Press, 2006, pg. 7.

Table 2. In vivo testing classes for biocompatibility.

Sensitization
Irritation
Intradermal Reactivity
Acute Toxicity (less than 24 hours of exposure)
Subacute Toxicity (14–28 days of exposure)
Chronic Toxicity (24 hrs-10% of lifespan of animal of exposure)
Genotoxicity
Implantation (pathological effects on living tissue)
Hemocompatibiltiy
Carcinogenicity
Reproductive and Developmental Toxicity
Biodegradation
Immune system response

Adapted from: Anderson, James M., "Fundamental biological requirements of a biomaterial," in *An Introduction to Biomaterials*, Scott A. Guelcher and Jeffery O. Hollinger, Eds. Boca Raton, FL: CRC Press, 2006, pg. 8.

constant to that of new bone growth so none of the material is present by the time the bone has fully healed. In this aspect of a biomaterial, there exists a delicate trade-off between functionality and compatibility to produce a high-quality device. The scale of this trade-off can be adjusted depending on the application. For instance, in a device that will only come into contact with the body for a short period of time, slightly toxic, inflammatory, or immune-system responses can be excepted if the performance of the material far exceeds its more biocompatible counterparts.

Some of the design and testing to determine the biological functionality of a biomaterial is carried out by materials scientists, chemists, and biomechanical engineers long before it is ever subjected to any in vitro or in vivo testing. However, testing for biological function and biocompatibility is generally carried out in parallel. This way, general problems can be identified early, and tests become more specific and rigorous as candidate biomaterials prove their capability. As a general rule, the design of a clinical instrument must be based strictly in terms of function and not true biological structure. The end product may look nothing like the body part it is designed to replace, and this is most often the case. This is exemplified in the modern devices for transtibial (below the knee) prostheses as in Fig. 2 and the artificial cardiac valve as seen in Fig. 3.

Another factor used to define a material's functionality is ease of use in a professional setting. Complex storage, sterilization, or handling procedures for a biomaterial are a great hindrance in a clinical situation. An engineer designing a biomaterial, or the device in which it will be used, must take into consideration the inherent difficulty that will arise while trying to incorporate the device into the human body. For example, during surgery to replace a cardiac valve, time is precious, and the artificial valve must be simple and easy to install. Sterilization is a key issue in this regard that needs to be dealt with carefully. It is possible that autoclaving, radiation sterilization, or ethylene oxide sterilization may lead to unwanted alterations of the biomaterial that could elicit problems with biocompatibility or biological function.

REGULATORY ISSUES

Before a medical device can be used clinically, it must prove both its functionality and biocompatibility according to a series of standards provided by the Center for Devices and Radiological Health, a regulatory body of the FDA. Regulatory control of biomaterials focuses on their end use rather than the materials themselves. Therefore, the guidelines set forth, specifically the International Organization for Standardization (ISO) 10,993 standard: "Biological Evaluation of Medical Devices, in Presenting a Systematic Approach to In Vivo Assessment of Tissue Compatibility of Medical Devices," concentrate heavily on in vivo testing. However, this should not understate the importance of in vitro testing. In vitro testing allows verification of new biomaterials that is needed before they can be incorporated into medical instruments and tested in vivo. Table 3 displays a list of the 18 ISO 10993 standards issued to date by the ISO's Technical Committee 194.

ISO 10993 *Biological Evaluation of Medical Devices* provides an excellent overview of the testing needed to prove a biomaterial's safety and biocompatibility for use in a clinical instrument. It places emphasis on the importance of sound experimental methods and covers safety issues such as leachables, extractables, and temporal degradation, which may not be obvious to a designer but are essential when considering the safety of a biomaterial. However, as can be recognized from the list of tests in Table 3, the ISO 10993 standards are solely concerned with biocompatibility and safety. The functionality of the device and the appropriateness of the material in question for a certain purpose is left up to the designer to determine.

BIOMATERIALS IN THE CLINIC

A clinically applicable biomaterial is the product of an extensive and diverse set of experimental analyses. Biomaterials have been implemented clinically in almost every type of medicine, from dental work, to organ replacement, to prosthetics, to drug delivery systems. Some of the most commonly used biomaterials being employed clinically appear in Table 4. It is surprising how many of these materials are now commonplace in modern medicine, considering that less than 40 years ago, almost none of these biomaterials were used.

Fig. 2 The Flex Foot Cheetah, a transtibial prosthetic device. Used with permission of Ossur Americas.

Fig. 3 An artificial cardiac valve <http://ninsight.at/bioSamplesHeartValve.shtml.> Used with permission.

CONCLUSIONS

The human body is the result of millions of years of evolution during which countless variations and trials driven by a commanding environment occurred. The result is a magnificent display of efficiency, robustness, and complexity. Trying to introduce incredibly simple instruments into such a complex structure is challenging. Because of the complex nature of the human body, specific problems with biomaterial biocompatibility and function are almost impossible to predict without extensive testing in cell cultures as well as in living systems. Because of the extensive nature of these tests, strict regulatory protocols are required to ensure that reliable products are produced. The considerations for the selection of biomaterials presented in this article are fundamental. Before proceeding to the advanced stages of instrument design and implementation, it is imperative that a biomaterial prove itself in regard to these primary issues. As the field of biomechanical engineering progresses and new biomaterials are needed for exciting new designs, these fundamental considerations for biomaterials selection may change. However, the basic principals guiding them will remain paramount to any person wishing to design a functional instrument.

READ MORE ABOUT IT

- "The Cultural Body: The History of Prostheses," University of Iowa Medical Museum Online, (2006). University of Iowa, [Online]. Available: http://www.uihealthcare.com/depts/medmuseum.
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Table 3. ISO 10993 standards.

10993-1: "Guidance on Selection of Tests"
10993-2: "Animal Welfare Requirements"
10993-3: "Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity"
10993-4: "Selection of Tests for Interactions with Blood"
10993-5: "Tests for Cytotoxicity-In Vitro Methods"
10993-6: "Tests for Local Effects After Implantation"
10993-7: "Ethylene Oxide Sterilization Residuals"
10993-8: "Selection and Qualification of Reference Materials for Biological Tests"
10993-9: "Framework for Identification and Quantification of Potential Degradation Products"
10993-10: "Tests for Irritation and Delayed-Type Hypersensitivity"
10993-11: "Tests for Systemic Toxicity"
10993-12: "Sample Preparation and Reference Materials"
10993-13: "Identification and Qualification of Degradation Products from Polymeric Medical Devices"
10993-14: "Identification and Qualification of Degradation Products from Ceramics"
10993-15: "Identification and Qualification of Degradation Products from Metals and Alloys"
10993-16: "Toxicokinetic Study Design for Degradation Products and Leachables"
10993-17: "Establishment of Allowable Limits for Leachable Substances"
10993-18: "Chemical Characterization of Materials"

Adapted from: http://www.devicelink.com/mddi/archive/98/01/023.html

Table 4. Common biomaterials and their uses.

Metals and Alloys	
316L stainless steel	Fracture repair, stents, surgical instruments
CP-Ti, Ti-Al-V, Ti-Al-Nb	Bone replacement, joint replacement, facture repair, dental implants, pacemaker capsules
Co-Cr-Mo, Cr-Ni-Cr-Mo	Bone replacement, joint replacement, dental restoration, heart valves
Ni-Ti	Bone plates, stents, orthodontic wires
Gold Alloys	Dental restoration
Silver	Antibacterial Agents
Platinum, Pt-Ir	Electric leads
Hg-Ag-Sn amalgam	Dental restoration
Ceramics and Glasses	
Alumina	Joint replacement, dental implants
Zirconica	Joint replacement
Calcium phosphates	Bone repair, metal surface coatings
Bioactive glasses	Bone replacement
Porcelain	Dental restoration
Carbons	Heart valves, percutaneous devices, dental implants
Polymers	
Polyethylene	Joint replacement
Polypropylene	Sutures
PET	Vascular prostheses, sutures
PTFE	Soft tissue augmentation, vascular prostheses
Polyesters	Vascular prostheses, drug-delivery
Polyurethanes	Blood contact devices
Silicones	Soft tissue replacement, ophthalmology
Hydrogels	Ophthalmology, drug-delivery
Composites	
PMMA-glass fillers	Dental cements
BIS-GMA-quartz/silica filler	Dental restoration

Adapted from: "Overview of biomaterials and their use in medical devices," *Handbook for Materials for Medical Devices*, J.R. Davis, Ed. ASM International, 2003.