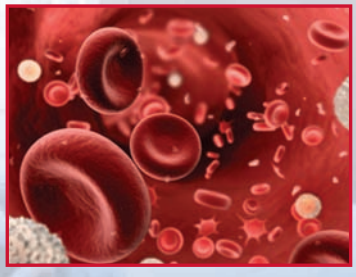
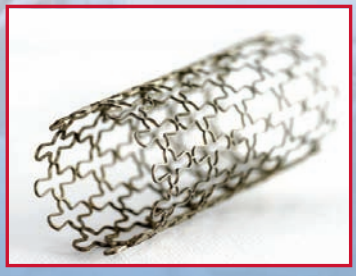
BIOMATERIALS SCIENCE

An Integrated Clinical *and* Engineering Approach





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Contents

Foreword

Biomaterials science is a multi-disciplinary field. The book offers a good overview of biomaterials as medical devices, drug delivery and tissue engineering systems. The emphasis is on integrating clinical and engineering approaches. In particular, the book covers various applications of biomaterials in unmet clinical needs in a variety of fields which include tissue engineering of musculoskeletal and cardiovascular tissues, neurosurgery, hemocompatibility, Micro-Electro Mechanical Systems (MEMS), nanoparticle based drug delivery, dental implants, and obstetrics/gynecology. It also covers areas such as regulatory challenges and commercialization issues.

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Summary

This book provides a comprehensive list of applications summarized as follows:

- **Hemocompatibility.** Overview of clinical and engineering integration and its role and importance; examples of stents and their challenges. This chapter discusses examples of special clinical states such as hypercoagulability in pregnancy and patient individual differences.
- **Nanoparticles.** This chapter provides a review of drug delivery methods, challenges, and complications. These include various nanoparticle-based systems and their functionalization with targeting molecules for various applications.
- **Neurosurgery/Neurology.** This chapter provides a review of examples of devices and their integration barriers and complications. The challenges from a clinician point of view are discussed.
- **Dental.** Odontological – Engineering Integration. This chapter provides an insightful review on the need to combine clinical and materials engineering to design new materials for dental applcations. Various materials are described with their impact.

- **BioMEMS.** Biological Micro-Electro-Mechanical-Systems. This chapter provides a technological review of devices. A number of examples are described, as well as microdevices, materials, and integration challenges.
- **Tissue Engineering.** Musculoskeletal description. This chapter provides methodologies for scaffolding in this area. Hydrogels are described for this purpose as well as the use of designated stem cells. Also, the use of electrospun nanofibers and supercritical CO_2 are described.
- **Tissue Engineering.** Cardiovascular application. This chapter provides methodologies for scaffolding. Hydrogels, polymeric porous scaffolding, biomaterial free tissue engineering and various stem cells are described.
- **Obstetrics and Gynecology.** Clinical integration. This chapter provides a comprehensive insight related to a number of issues in this field, including: fetal toxicity; understanding the histological, physiological aspects; design of new materials and devices. A number of cases are described, including an example of clinical and engineering integration with a copper intrauterine device releases copper ions into the endometrium.
- **FDA.** Regulation/Ethic. This chapter provides an overview of clinical trials and regulation. The differences between various regulation administrations in the world are described. Radiological applications are also discussed. Excellent case studies are used.
- **Commercialization.** Transition. This chapter provides an understanding of market needs and transitioning into the market. Diagrams are used to describe a useful process to achieve market endpoints.
- **Appendix.** FDA references. This appendix provides relevant references related to the regulatory processes.

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Noel Elman, PhD, is currently a research scientist at the Institute for Soldier Nanotechnologies at the Massachusetts Institute of Technology (MIT). He leads a research group focused on biomedical technologies based on nano- and microtechnologies for both diagnostics and therapeutics. He received his BS and Master's degrees in Electrical Engineering from Cornell University, where he focused on the development of micro-opto-electro-mechanical systems (MOEMS). He received his PhD degree in Physical Electronics from the Department of Electrical Engineering at Tel Aviv University in 2006. His PhD thesis focused on the development of a new family of biosensors based on the unique integration of living whole cells with semiconductor, MOEMS, and nanotechnologies. His postdoctoral studies at the Department of Materials and Engineering at MIT focused on the development of biomedical microdevices based on MEMS and nanotechnologies for both therapeutics and diagnostics. He is also the

founder of high-tech startups in the field of micro- and nanotechnologies. His current interests relate to translational research for biomedical and biotechnological applications. He is the author of publications in the fields of biomedical technologies, MEMS, materials science and engineering, and micro- and nanotechnologies.

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1

Introduction

Yitzhak Rosen, Noel Elman, Emanuel Horowitz

Biomaterials science is a multi-disciplinary field. There are numerous fields involved in assisting in the research and development (R&D) of biomaterials. These fields include, but are not limited to, materials engineering, clinical medicine, mechanical engineering, biomedical engineering, molecular cell biology, histology, bioethics, regulatory affairs, business administration, and commercialization transition.

These fields require an interactive approach, as one can contribute to the others, and vice versa. For example, an unmet clinical need will be an important driving force for the engineering approach. However, the implementation of biomaterials must impact important clinical parameters, which include mortality, morbidity, and quality of life. These parameters need to be used to question the indications for the use of the biomaterial; furthermore, these parameters can be used with additional biological and physiological data to improve the biomaterial or inspire research in the development of more innovative and relevant biomaterials. This is applicable as well for the implementation of biomaterials in biomedical devices and drug delivery systems.

We must take these possibilities into account as best as we can. For example, a biomaterial used in a biomedical device may be implemented in a woman who eventually becomes pregnant. Pregnancy is a hypercoagulable state with possibly a variety of mechanisms in place that may affect the hemocompatibility of that biomaterial and its implementation overall [1]. By understanding the physiological mechanisms of such special states as pregnancy, we may be able to develop better biomaterials that may be applicable to a wider patient population. The integrated approach may be simplified if we continually ask two critical questions:

- While listening to and understanding the patient, what is the patient telling us?
- Will the biomaterial and its implementation truly impact the morbidity, mortality, and quality of life of the patient?

The process involved in the clinical and engineering integration approach is a double-edged sword in terms of its complexity. It is complex, as patients can be quite different from one another. There are numerous diseases that have complex pathophysiological processes, and each patient may react differently to these diseases. Each patient may also react differently to a biomaterial itself as well as to the implementation of a biomaterial in various clinical states. However, there is also a simplicity, which can be viewed as the certain overlap across many patients and disciplines. Listening to and understanding the patient is critical and will assist in elaborating this overlap. Therefore, a critical focus should be our patient.

There are already many books on biomaterials science. This book differs from existing books in that it emphasizes the need for the integrated clinical and engineering approach, an integration that often is lacking. To achieve this objective, the book includes a variety of contributors from many fields, including tissue engineering of musculoskeletal and cardiovascular tissues, neurosurgery, hemocompatibility, regulation, commercialization transition, micro-electro-mechanical systems (MEMS), nanoparticle-based drug delivery, dental implants, and obstetrics/gynecology. Some contributors are engineers, while others are clinicians. Furthermore, the areas of regulation and clinical trials have also been discussed, as these play a pivotal role in biomaterials science. In addition, commercialization transition has been addressed, as it plays an important role in how market needs, as defined by the aforementioned clinical parameters, assist in the research and development of new biomaterials and their implementations. While it is beyond the scope of the book to encompass all fields of biomaterials, the book includes important examples dispersed throughout its chapters that emphasize the need for a clinical and engineering integration approach.

Based on our experiences, without this integration many critical R&D components may be missed. Moreover, R&D resources may become squandered in addressing unnecessary issues. We may miss out on the possibilities of developing biomaterials that may fit a wider patient population needing them. This approach continuously focuses on the patient and always attempts to answer these two critical questions, described herein, from the idea stage all the way to many years thereafter.

In Memory

This book is being dedicated to Professor Moshe Rosen, Ph.D., (RIP), father of Dr. Yitzhak Rosen. Professor Rosen was a Holocaust Survivor of a concentration camp, previous chair of the Department of Materials Science and Engineering at Johns Hopkins University, previous Rector

of Ben-Gurion University, loving husband of 45 years to wife Lea and father to three sons. By being exemplary to Dr. Yitzhak Rosen and many people, he has truly taught what it means to be a mensch (the Yiddish equivalent of being a man of noble character having social conscience, honor and integrity) and to do good deeds for the world at large, for all people [2,3].

Disclaimer: The material in this book, whether related to medicine or any other topic, should be verified as to its accuracy, currency, and preciseness by the reader. It should in no way replace any advice given by a medical professional or any other professional. None of the information provided here should be a substitute for additional reading, advice, experience, or other relevant information in any topic discussed in this book.

References

1. James AH, Grotegut CA, Brancazio LR, Brown H. 2007. Thromboembolism in pregnancy: Recurrence and its prevention. *Semin Perinatol.* June 31(3): 167–75.
2. Leo Rosten (author), Lawrence Bush (editor). 2003. *The New Joys of Yiddish*. Completely Updated. Various Pagings. Three Rivers Press.
3. http://www.merriam-webster.com/dictionary/mensch.

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2

Principles of Clinical and Engineering Integration in Hemocompatibility

Yitzhak Rosen, Noel Elman

CONTENTS

Overview

Hemocompatibility, compatibility when coming into contact with blood, is an important component of biocompatibility [1, 2]. It is also a great example where clinical and engineering integration is critical. Many life-saving devices come into contact with blood, whether permanently

or temporarily [1–3]. Therefore, in these types of devices, the hemocompatibility component can significantly influence the failure or success of a medical procedure. Any foreign material introduced into the body will impact the behavior of blood in some way; however, the ultimate objective is to minimize the incidence of thrombogenesis [1, 2, 60–62]. It has been suggested that an ultimate design of a biomaterial would be its ability to orchestrate desirable biological effects and then degrade without leaving undesirable metabolites [4]. As far as hemocompatibility is concerned, much effort in biomaterials science has been done towards designing inert materials having a minimized reaction with platelets and coagulation factors [1, 61, 62].

In order to understand hemocompatibility, it is as important to define what is incompatible. A suggested definition of *incompatibility* is a material that induces an unacceptable adverse reaction when placed in contact with blood for a specified time [1, 60–62]. The adverse reactions include the formation of a thrombus, also referred to as a local blood clot, and a possible shedding of this clot, which will undesirably travel elsewhere as an embolus and have devastating effects, such as stroke [1–3]. It should be noted that any foreign material will cause some kind of reaction, whether local and/or systemic, that may or may not be controllable [1, 2].

So why has a whole chapter in this book been dedicated to hemocompatibility? The answers included the following:

1. Many devices, particularly life-saving ones, come into contact with blood. They include catheters for blood access and manipulation, extracorporeal pump oxygenators, hemodialyzers, heart-assist devices, stents, heart valves, and vascular grafts [1–3].
2. The future prospects of permanently implanted artificial organs will have to deal with this important subject [1].
3. The future prospects of biodegradable implants, such as stents, that will come into contact with blood [26, 27, 60].
4. The clinical indications of these devices are being modified by a more comprehensive research and development of improved hemocompatible devices [1, 2, 27].
5. It has been realized that the use of the database of biological knowledge from clinical medicine may result in the modification biomaterials, particularly in the area of surface modification, in order to make them more hemocompatible [1, 9, 30–32].
6. There are synergistic effects from other venues, such as inflammation, that can affect hemocompatibility [1, 5–7]
7. The need for a more comprehensive standard in both design and testing [1].

8. The need for careful examination of the contribution of adjunct therapies, such as oral systemic therapy, to the success and failure of the biomaterial and its implementation in a particular medical technology [2, 3, 8].
9. The need for assessing the degree of contribution, or lack of contribution, of factors such as individual genetic polymorphism and other individual specifications to the success or failure of the biomaterial [5, 6, 8].
10. The need for long-term implanted devices and tissue-engineered products [1, 2, 60].
11. The issue of contact time with blood may be a particularly important factor to consider regarding various biomaterials and their respective medical technologies [1, 2].

Interestingly, there is still a lack of consensus on testing standardization with respect to hemocompatibility. One reason for this is the need for a more comprehensive understanding of the physiological mechanisms leading to materials failure; furthermore, blood interactions have a complex, dynamic, and unpredictable behavior. There are a multitude of biomaterial–blood interactions, many of them not fully understood. Therefore, evaluation of these interactions in order to achieve a complete regulatory consensus cannot be easily performed [1, 2, 60–62].

As with testing, the engineering process of surface modification of biomaterials also lacks consensus. This ultimately has clinical implications in choosing a specific approach for surface modification versus conservative treatments. Moreover, discussions about short- and long-term morbidity and mortality related to hemocompatibilities are taking place, questioning the indications for the minimally invasive implantations of medical devices, such as stents, having direct contact with blood, as well as weighing advantages of stents versus a complete surgical coronary bypass procedure, for example [1, 2, 60–62, 64, 70].

It is beyond the scope of this chapter to encompass the many facets of hemocompatibility. Instead of focusing on a myriad of details that can be found in other references, we have focused on particular principles and considerations that should be taken into account when discussing biomaterials and hemocompatibility, albeit with a strong clinical focus. A key underlying principle is to understand the patient's needs. That is, by listening to the patient, we can ultimately create biomaterials that will have better hemocompatibility with superior indications for their implantation [2, 4]. In this chapter, we have chosen to focus specifically on cardiac stents as a reference point, as they represent an excellent multi-disciplinary example of clinical and engineering venues coming together, with several clinical trials. An important goal of this book is also to stimulate readers to suggest additional questions relevant in the field of biomaterials that integrate clinical and engineering approaches.

Questions That Should Be Addressed

The integration of the clinical and engineering approaches also involves addressing important questions concerning hemocompatibility. Below is a short list that we suggest readers use throughout this chapter. It is recommended, however, to expand on this list when reading this book and to think how the principles of integration can be implemented for each question.

1. What relevant database of knowledge in clinical medicine do we need in order to improve the biomaterial, particularly for surface modification purposes? [8, 27]
2. What are the risk-management issues, that is, benefit versus risk, involved? [1, 2, 7, 8, 27]
3. What systems are involved where clinical and engineering integration is needed to improve the biomaterial (inflammatory, blood, etc.)? [1, 8, 19, 16, 27]
4. How long does the biomaterial need to be in contact with blood? [1]
5. What can we learn by listening to and understanding the patient? [2]
6. What is the patient saying to us about him- or herself, the biomaterials, and their implementation? [1]
7. Can the biomaterial orchestrate desirable biological functions and then degrade into desirable metabolites? [3, 60]
8. How do we address the limiting conditions of keeping the biomaterial and its relevant medical technology in the body? [1, 4–6, 9, 16, 27, 53, 60]
9. What concomitant complicating conditions, also known as "special clinical states," need to be addressed? [3, 10–15, 33–46]
10. How do we deal with the change of influences by the body once the system is implanted? [1, 3]
11. Can the system be modified during its presence in the body when these special states or any other changes arise? [1, 4–6, 9, 16, 26, 27, 30, 53, 54, 56]
12. While integrating the engineering and clinical approaches, how do we advance towards a better standardization testing methodology? [1]
13. What are the short-term and long-term morbidity and mortality issues involved? [1]
14. What can we learn from the end-points of clinical trials to improve the biomaterial? [27, 57–59]

The Patient

The patient's needs represent the most important aspect when addressing hemocompatibility and biomaterials. Ultimately, the patient determines the

validity of the biomaterial. It is therefore critical that when designing biomaterials, we take into account various considerations that focus on the patient [1, 27, 60]. There are enormous individual differences, yet we can attempt to better characterize and classify certain similarities among patients that may explain the successes and failures of a biomaterial once implanted into a patient [1, 3, 9, 17–23].

Stratifying patients can allow us to achieve several important objectives with respect to the biomaterial being implemented in a particular medical technology. First, better patient selection, according to relevant risk factors inherent to the patients, can allow a higher success rate in a targeted patient population in terms of the hemocompatibility of the biomaterial. Such factors can include predispositions to thrombogenesis due to inherent biological factors such as polymorphisms of inflammatory factors and genetic resistance to anticoagulation adjunct therapy [2, 22–24]. Second, by distinguishing the factors that do or do not contribute to the success of the biomaterial, we can achieve additional targets for future surface modification of the biomaterial. This would allow us to enlarge the targeted patient population. Yet we must be aware that while the attempts must continue to better stratify patients, individual patient differences can still occur [2].

Genetic Polymorphism and Individual Variability: Focus on Cardiac Stents

Genetic polymorphism has a critical influence on the development of thrombosis as well as on the specific treatment response, in that it affects the efficacy and safety of drugs used in the treatment and prevention of thrombosis. Genetic polymorphism may impact the systemic and local response to the surface modification of a biomaterial [2, 6, 22–24]. Cardiac stents are an example where the impact of genetic polymorphism and individual variability can be seen [4, 6, 22–24]. The characterization of inflammation as an important factor of stent restenosis has assisted in identifying several culprit genes that may impact thrombosis [4, 6]. Much effort is continuously being allocated to preventing thrombosis by minimizing local inflammation and, the proliferation of particular cells, such as smooth cells, by the use of drug-eluting stents that carry agents that prevent smooth-cell proliferation. At the same time, a confluent layer of endothelial cells is needed within the lumen of the stent to prevent thrombosis [1, 6, 8, 16–21, 27, 50, 60]. In this section, we will discuss the multiple targets of genetic polymorphisms that have demonstrated predisposition to thrombosis with respect to cardiac stents.

CardioGene Study

A large study called the CardioGene Study was created under the auspices of the National Heart, Lung and Blood Institute to further understand the factors involved in in-stent restenosis (ISR) in bare mental stents (BMS) for the treatment of coronary artery disease. The overall goal of the study was to understand the genetic determinants of the responses to vascular injury that result in the development of restenosis in some patients but not in others. In this study, global-gene and protein-expression profiling were used to define the molecular phenotypes of patients. Well-defined clinical phenotypes were paired with genomic data to define analyses in order to determine blood gene and protein expression in patients with ISR, investigate the genetic basis of ISR, develop a predictive gene and protein biomarkers database, and identify new targets for treatment. Interestingly, the implications of such a study for biomaterials science can include the following:

- Identifying which patients would less likely benefit from treatment despite a relatively inert biomaterial.
- Identifying new targets to be used for surface modification.
- Providing alternative solutions that emphasize thrombogenic properties of predisposed patients carrying polymorphisms—which may also be helpful for patients without these types of polymorphisms.

Such databases can have enormous potential for improving surface modification of biomaterials in a variety of settings [8].

One potential application of genetic polymorphism testing has been found in the use of drug-eluting stents (DES). DESs, while reducing in-stent restenosis after percutaneous coronary intervention (PCI), have been associated with late stent thrombosis. No accurate method of predicting in-stent restenosis has been found; it should be noted that several risk factors for atherosclerosis do overlap with those for in-stent restenosis. In addition, atherosclerosis candidate genes have been investigated for their possible association with in-stent restenosis [2, 16–24].

Polymorphisms in Inflammation and Proliferation Effects on In-Stent Stenosis

Polymorphisms related to proliferation and inflammation may contribute to in-stent stenosis. Inflammatory activities as well as proliferation of particular cells such as smooth muscle cells can contribute to in-stent stenosis. These effects are related to vascular remodeling after procedures, such as percutaneous coronary stent implantation, that frequently lead to stenosis. One particular enzyme, heme oxygenase 1 (HO-1), is involved in the generation of the endogenous antioxidant bilirubin and carbon monoxide, both of which have anti-inflammatory and antiproliferative effects. Gulesserian et al. showed

that the long allele of the HO-1 gene promoter polymorphism, which leads to low HO-1 inducibility, may represent an independent prognostic marker for restenosis after PCI and stent implantation. Interestingly, the effect of this particular allele, with more than 29 repeats, is attenuated in smokers, who have chronic exogenous carbon monoxide exposure [4].

Interleukin (IL)-10 is an important component in the inflammatory response. The Genetic Determinants of Restenosis (GENDER) study by Monraats, which included 3,105 patients treated with percutaneous intervention stent deployment, has indicated that genetic variants in IL-10 may predispose to the risk of restenosis. The primary end-point of this study was target-vessel revascularization. Genotyping of the –2849G/A, –1082G/A, –592C/A, and +4259A/G polymorphisms of the IL-10 gene was assessed along with adjustment for clinical variables. It was demonstrated that three polymorphisms significantly increased the risk of restenosis. The results of this study also indicated that the association of the IL-10 gene with restenosis was independent of flanking genes. Monraats et al. concluded that IL-10 is associated with restenosis; furthermore, Monraats et al. suggest that anti-inflammatory genes also may be involved in developing restenosis. Finally, the authors suggest that a new targeting gene may be used to improve drug-eluting stents [22].

Monraats et al. in another study examined the polymorphisms of genes for caspase-1, interleukin-1-receptor, and protein tyrosine phosphatase nonreceptor type 22, which are important mediators in the inflammatory response. Caspase-1 is also important in *apoptosis*, programmed cell death. Patients with the 5352AA genotype in the caspase-1 gene showed an increased risk of developing restenosis of stents. Monraats et al. suggest that the possibility of screening patients for this genotype may lead to better risk stratification and provide indications for improving individual treatment in addition to providing a new target for drug-eluting stents [6].

Shah et al. identified 46 consecutive cases of PCI with bare-metal stents where the patients subsequently developed symptomatic in-stent restenosis of the target lesion (>/= 75% luminal narrowing) within 6 months. Moreover, 46 matched controls with respect to age, race, vessel-diameter, and gender without in-stent restenosis after PCI with bare-metal stents were also identified. Single-nucleotide polymorphisms from 39 candidate atherosclerosis genes were genotyped for this study. Interestingly, ALOX5AP, a gene within the inflammatory pathway involving chemical inflammatory mediators called leukotrienes and linked to coronary atherosclerosis, has been shown to be associated with in-stent restenosis [9].

Polymorphisms that may contribute to thrombotic events may not always predict an increased rate of these same kinds of events with biomaterials. For example, polymorphisms of receptors involved in platelet adhesion and aggregation-modulating platelet thrombogenicity and found to predispose to premature arterial thromboses in individuals at risk are not necessarily correlated with acute stent thrombosis. Sucker

et al., comparing the genotype prevalence of respective polymorphisms in patients with acute coronary stent thrombosis and healthy control subjects, did not find an increased risk of carriers of prothrombotic variants of platelet receptors for this complication [5]. However, being aware of the existence of such variations and delving into the exact causes of in-stent stenosis can ultimately assist in creating enhanced stents with minimized in-stent stenosis [2, 5, 8, 9].

Platelet Receptor Genes

It has been suggested by Rudez et al. that a common variation in the platelet receptor gene P2Y12 may serve as a useful marker for risk stratification for developing restenosis after percutaneous coronary interventions (PCI). Common variations in the P2Y12 gene were assessed by genotyping five haplotype-tagging single-nucleotide polymorphisms (ht-SNPs). These were assessed in 2,062 PCI-treated patients who received a stent. These patients participated in the Genetic Determinants of Restenosis (GENDER) Study. Target vessel revascularization (TVR) was assessed here, too. The study demonstrated that common variation in the P2Y12 gene can predict restenosis in PCI-treated patients [23].

Adjunct Therapy Resistance Stratification

Clopidogrel is a P2Y12 receptor blocker agent used to reduce the risks of acute coronary syndromes and considered an important adjunct therapy for stent deployment together with aspirin, yet clopidogrel-resistance genotypes may occur. It is important to realize that adjunct therapy resistance may be an important contributor to biomaterial failure in selected patients. This should also be taken as a consideration when assessing novel biomaterials and their applications [2, 7, 23, 24, 63].

Common variation in the P2RY12 gene has been demonstrated to be a significant determinant of the inter-individual variability in residual on-clopidogrel platelet reactivity in patients with coronary artery disease. This was corroborated in a study by Rudez et al. of 1,031 consecutive patients with coronary artery disease scheduled for elective percutaneous coronary interventions [23].

Clopidogrel is mentioned here since it plays an important role in adjunct systemic therapy together with aspirin for the success of stent deployment [2, 67, 68]. However, it should be noted that there are individual differences when clopidogrel is used that may influence the failure or success of a stent deployment. Price et al. have shown that platelet reactivity in clopidogrel therapy, as measured by a point-of-care platelet function P2Y12 assay, is associated with thrombotic events after percutaneous coronary intervention (PCI) with drug-eluting stents (DES). Moreover, high post-treatment platelet reactivity measured with a point-of-care platelet function assay has been

associated with post-discharge events after PCI with DES, including stent thrombosis. The authors suggest that the investigation of alternative clopidogrel dosing regimens to reduce ischemic events in high-risk patients identified by this assay is warranted [67, 68].

The example of clopidogrel was presented for several reasons. Since clopidogrel is used as an adjunct systemic therapy after stent deployment, its individual variability, which may be assessed by platelet receptor polymorphism, may influence the risk of thrombotic events [8, 24]. Furthermore, this assessment may further assist in deciding whether resistance to adjunct therapy rather than the biomaterial alone may play a role in the risk for thrombosis [2, 24, 67, 68].

Endothelial Cell Trafficking Stratification

Identifying which patients may benefit from the biomaterial and its relevant medical technologies is critical. In fact, careful patient selection with exclusion and inclusion criteria for a particular intervention is often done in clinical medicine. An important reason for such patient selection is to address risk versus benefit [1, 2]. The example below underlines how patient selection according to progenitor endothelial cells capabilities can be influential in the success or failure of implanting a cardiac stent. Endothelial cells, which line the vasculature as a monolayer, play a critical role in the implementation of cardiac stents. They express and excrete a variety of molecules that regulate vascular tone, permeability, inflammation, thrombosis, and fibrinolysis, all of which are important components in hemocompatibility. They are also involved in wound repair. The expression levels of these molecules change according to interactions with the surrounding extracellular matrix and a variety of peripheral cells. They are also a target for pharmacological agents. Interestingly, a failure to re-endothelialize and form a confluent layer on the lumen of the stent is thought to be responsible late (>30 days) thrombosis of cardiac stents.

A clinical study performed by Georges et al. [69] suggests that the characteristics and numbers of circulating endothelial progenitor cells have a potentially important impact on stent restenosis. Patients with angiographically demonstrated in-stent restenosis were compared with patients with a similar clinical presentation that exhibited patent stents. Both groups of patients had similar medication administration that could potentially influence endothelial progenitor numbers. Their characteristics were determined by the colony-forming unit assay, endothelial-cell markers, and adhesiveness. Interestingly, patients with in-stent restenosis and with patent stents displayed a similar number of these cells. However, fibronectin-binding was compromised in patients with in-stent restenosis compared with their controls having patent stents. Furthermore, patients with diffuse in-stent restenosis exhibited reduced numbers of cells in comparison with subjects with focal in-stent lesions. The authors conclude that an intact endothelialization machinery is important for vessel healing after stent placement

and as a means of preventing restenosis; moreover, their ability to traffic to damaged vasculature is an important characteristic that could affect stent restenosis. Interestingly, the authors point out a potential, future-risk stratification using such markers and related characteristics of these cells for the likelihood of patients developing in-stent restenosis. Furthermore, this study emphasizes the need for a careful selection of patients for whom such a biomimicry should take place.

These preliminary results can lead to the following:

1. Identification of markers to carefully select patients as candidates for successful stent deployment, as George et al. suggest
2. Identification of cell markers, such as surface ligands, that are needed for adhesion of endothelial cells
3. Immobilization of these markers and/or their relevant counterparts on stents for both patients with their deficiencies as well as for patients with no deficiencies to enhance adhesion

In summary, the work by George et al. corroborates the importance in the success of stent deployment of creating a careful pre-selection of patients by predefined criteria that can be measured by assays [69].

Special Clinical States

There are several clinical states where hemocompatibility may be modified. It is important to be aware of these states, as many patients may be facing them at some point in time. This section will focus on some of the common ones, such as pregnancy, cancer, and autoimmune states. It should be noted, however, that hypercoagulability can be inherent and be acquired in many other ways. Understanding these special clinical states will aid in further optimizing hemocompatibility designs [34–46].

Pregnancy

Pregnancy is considered to be a hypercoagulable state and a risk factor for deep venous thrombosis (DVT). The risk for DVT is further increased when personal or family history of thrombosis or thrombophilia exists. Venous thromboembolism, a phenomenon which includes both deep venous thrombosis (DVT) and pulmonary embolism (PE), complicates an estimated 0.5 to 3.0 pregnancies per 1,000. Thromboembolism is a leading cause of maternal death in the United States, and therefore this risk requires careful evaluation [2, 33, 35, 36, 38–41].

Hypercoagulability of pregnancy is caused by modifications in the plasma levels of many clotting factors. Fibrinogen can be increased up to 3 times the normal value while protein S, a physiological anticoagulant, decreases. Thrombin also increases. Protein C and antithrombin III are not predisposed to change. An impairment in fibrinolysis due to an increase in plasminogen activator inhibitor-1 (PAI-1) and the placenta-synthesized PAI-2 is observed. These changes have been suggested to be a preparation for the prevention of bleeding during labor [33, 35, 36, 38–41].

Other etiologies for hypercoagulability of pregnancy have also been pointed out. Venous stasis can be a culprit, and may occur at the end of the first trimester, from enhanced distensibility of the vessel walls by hormonal effect as well as prolonged bed rest. Acquired etiologies include antiphospholipid antibodies, as in systemic lupus erythematosis, which can exist before pregnancy. Congenital etiologies that can cause hypercoagulability in pregnancy and in the general population include factor V Leiden mutation, prothrombin mutation, protein C and S deficiencies, and antithrombin III deficiency [2, 33–41].

Pregnant women with prosthetic valves have an increased incidence of thromboembolic complications. An important consideration is adequate and effective antithrombotic therapy. Among other important consideration to take into account here is the ability of a therapeutic agent to cross the placenta and cause harm to the fetus. Warfarin, for example, is known to cross the placenta. Since warfarin use in the first trimester of pregnancy is associated with a substantial risk of embryopathy and fetal death, warfarin is typically stopped when a patient is trying to become pregnant or when pregnancy is detected. Typically, heparin, particularly low-molecular-weight heparin, is used alternatively and does not typically cross the placenta. This treatment may be continued until delivery [33–41].

When assessing biomaterials, it is important to take into consideration such hypercoagulable states and their underlying physiological mechanisms, as many patients can have these concomitant conditions. Suggestions would include using models with these coagulation changes to assess these conditions, especially where a specific need for a particular medical device during this condition should arise. Furthermore, altering the coagulation concentrations in order to define a pregnancy-related model may introduce interesting and insightful information as a whole for innovative surface modifications of biomaterials [1, 2, 33–41].

Autoimmune States

There are many autoimmune states in which the body produces antibodies against a variety of antigens. One of the problems that may be faced in these states is hypercoagulability. One particularly noteworthy state is the antiphospholipid syndrome (APS), which is the most common acquired thrombophilia, characterized by venous and arterial thrombosis, recurrent

pregnancy loss, and various other clinical manifestations in the presence of antiphospholipid antibodies (aPL) [2, 13, 14]. This syndrome can also perturb the function of endothelial cells, which are important in forming a confluent layer within the lumen of the stent in order to minimize in-stent stenosis. Similar to other autoimmune diseases, the etiology of APS has been suggested to occur from a combination of genetic and environmental factors [2, 13, 14, 42–46].

One important interaction related to thrombosis is that of aPL with endothelial cells (EC). It has been demonstrated that aPL antibodies active endothelial cells in vitro as an enhanced expression of adhesion molecules on human umbilical vein endothelial cells along with enhanced monocyte adherence to ECs in vitro. The adhesion molecules that have been demonstrated to show increased expression include intercellular cell-adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and (E-selectin) [14, 42–45].

The perturbance of ECs in APS has been demonstrated in a clinical study by Cugno et al. This study assessed the plasma levels of soluble adhesion molecules (s-ICAM-1, s-VCAM-1, s-E-selectin), soluble thrombomodulin (sTM), von Willebrand factor (vWF), and tissue plasminogen activator (tPA) using solid-phase assays in 40 selected APS patients as well as 40 healthy subjects matched accordingly by age and sex. Circulating endothelial cells by flow cytometry and brachial artery flow-mediated vasodilation were also evaluated. Their results indicated no noteworthy difference in plasma levels of sTM, s-E-selectin, and s-VCAM-1 between the APS group and controls differ. However, a significant increase in s-ICAM-1 ($P = 0.029$), t-PA ($P = 0.003$), and vWF titres ($P = 0.002$) was observed along with significantly higher levels of circulating mature endothelial cells in patients ($P = 0.05$), which were decreased when vitamin K antagonists and antiplatelet treatments were administered to the APS patients group. In addition, it was demonstrated that mean brachial artery flow-mediated vasodilation responses were significantly impaired compared with those of healthy subjects ($P = 0.0001$) [42].

It is evident that the function of ECs can be impaired in APS. Much can be learned about ECs in the APS milieu [14, 42, 43]. Enhanced characterization of ECs in a variety of clinical settings may lead to a better understanding of their role and variability in these settings. This knowledge may be re-applied to attempt to improve surface modification in biomaterials, particularly in cardiac stents, in order to better assist ECs to form a confluent layer within cardiac stents to minimize in-stent thrombosis [1]. That is, more potential targets may be identified for enhanced surface modification of biomaterials [1,8]. That may assist in developing a biomaterial accessible for a larger patient population that would otherwise not be able benefit from biomaterials implanted in their bodies [1].

Since autoimmune states may develop at different ages, it is important to know of their existence and the hypercoagulability potential that may occur in autoimmunity such as APS. For example, a patient with APS implanted with a biomedical device with a specific biomaterial may be

more prone to thromboembolic phenomena [1, 43–46]. A variety of modifications in the coagulation system may affect the blood–biomaterial interactions and should be considered. Therefore, an enhanced characterization of the blood–biomaterial interactions in autoimmune models may ultimately lead to the development of an enhanced surface modification of the biomaterial [1].

Cancer

Cancer can lead to an acquired thrombophilic condition associated with a significant risk of thrombosis. Both venous and arterial thromboembolism are common complications for patients with cancer, who also present with a hypercoagulable state. The hypercoagulability, also referred to as the prothrombotic state, of malignancy is due to the ability of tumor cells to activate the coagulation system and cause a variety of associated clinical symptoms [2, 10–12].

There are multifactorial pathogenesis mechanisms for thrombosis in cancer. An important one is attributed to the tumor cells' capacity to interact with and activate the host hemostatic system cells, which can produce and secrete substances that have procoagulant substances and inflammatory cytokines. Tumor cells can allow physical interactions between themselves and a variety of other cells, which can include monocytes, platelets, neutrophils, and vascular cells. The generation of acute-phase reactants, abnormal protein metabolism, hemodynamic compromise, and necrosis can also promote thrombus formation. Anticancer therapies such as surgery, chemotherapy, and hormonal therapy can also assist in inducing procoagulant release, endothelial damage, and stimulation of tissue factor production by host cells [2, 10–12, 15].

One interesting example of hypercoagulability of malignancy was shown with non-small cell lung cancer (NSCLC), which comprises of 75% of all lung cancers. Here, it was shown that human full-length tissue factor (flHTF), the physiological initiator of blood coagulation, is aberrantly expressed in certain solid tumors. Furthermore, flHTF and its soluble isoform, alternatively spliced human tissue factor (asHTF), have been shown to contribute to thrombogenicity of the blood of healthy individuals [15]. It would be interesting to see what the variability of the expression of this factor in blood-biomaterial interaction and assess its role in biomaterial hemocompatibility failure at different timelines of contact with blood [1, 15].

Cancer is quite prevalent in society and thus should be used as a model to assess the thrombogenicity of a biomaterial. As in the case of antiphospholipid antibodies, a more thorough investigation is needed in order to better understand how cancer cells interaction with the various coagulation factors and assess biomaterial–blood interactions [1, 2, 10–13, 15]. Interestingly, existing evidence does not suggest a mortality benefit from oral anticoagulation in patients with cancer, because of the increased risk of bleeding. The

potential complications of thrombosis after having a biomaterial implanted are, however, evident [1, 2, 10–12, 15].

Biodegradable and Bioabsorbable Cardiac Stents

It is important to distinguish between biodegradable and bioabsorbable cardiac stents. When using cardiac stents as a reference point, biodegradable stents can refer to polymer-based stents that can degrade and have their by-products assimilate into the body [25, 27, 60]. There are exceptions, where a polymer such as polylactic acid undergoes a degradation of the polymeric chemical backbone, which is controlled mainly by simple hydrolysis and is independent of a biological mediation [1, 25, 27, 28, 60]. Corrodible metallic stents have been considered bioabsorbable, as they directly assimilate into tissues rather than truly degrade [27, 47–49, 51–53, 55, 60].

A variety of biomaterials exist for these stents. Two metals proposed for bioabsorbable stents include Mg-based and Fe-based alloys [50–52, 54–56, 60]. Additional suggested materials involved in clinical evaluation have included poly-L-lactic acid (PLLA), polyglycolic acid (PGA), poly (D, L-lactide/glycolide) copolymer (PDLA), and polycaprolactone (PCL) [51–60].

The potential advantages are enormous in terms of hemocompatibility, assuming that there are minimal initial thrombogenic events and the material can produce its desired mechanical results for the necessary period of time. It is evident that fully biodegradable/bioabsorbable platforms are attracting both clinical and research interest. As mentioned previously, a biomaterial can be designated to orchestrate a necessary event and then degrade into absorbable constituents. The main question is whether these events can be achieved as intended. For example, for stents, it has been questioned how material parameters such as the elastic modulus, yield strength level, and material hardening all influence stent recoil and collapse. Yet biodegradability has shown its success in various animal studies, showing that these stents suggested less neointimal thickening, thrombosis, and inflammation while retaining an adequate radial force [60, 64–66].

A fully biodegradable or bioabsorbable stent, particularly in a drug-eluting stent scenario, would need several important features. A controlled, sustained drug release is required when using drug elution. Sufficient mechanical strength and structural functionality must be maintained in order to prevent negative vessel remodeling, as well as to avoid stent deformity and potential strut fractures. Compatibility with non-invasive coronary angiography is needed in order to maintain

follow-ups. No residual stent prosthesis in the area should be present once biodegradability is completed. No potential adverse reactions with the coronary artery should take place. Vasomotion restoration of the artery is necessary [1, 27, 51–62].

Should Cardiac Stents Be Biodegradable/Bioabsorbable?

Overview

The injured vessel, after percutaneous coronary intervention, can necessitate scaffolding. There has not been a consensus about the necessary time for such a scaffolding. Current DESs have demonstrated their capacity in providing scaffolding for injured vessels and limiting in-stent restenosis. Typical permanent polymers used in sirolimus- and paclitaxel-eluting stents include poly(ethylene-co-vinyl acetate), poly(n-butyl-methacrylate), and poly(styrene-b-isobutylene-b-styrene) [17–21, 60, 65].

There have been long-term safety concerns about the permanent nature of the stent material and polymers. Several noteworthy adverse effects that occur with DES include delayed healing, endothelial dysfunction, chronic arterial-wall inflammation, impaired neointimal formation, and late-acquired stent malapposition [9–15, 64]. In addition, particularly serious concerns are late and very late stent thrombosis, which appear long after stent deployment. These can lead to severe clinical outcomes, including death [2, 47, 48, 50–60, 64, 65].

The durable polymers used in DES have been shown to provoke an inflammatory response in animals, such as giant cell infiltration around the stent struts, and progressive granulomatous and eosinophilic reactions. These reactions can increase beyond the first year. Chronic inflammation may decrease efficacy [60, 64–66]. Reports of increased rate of endothelial dysfunction after DES implantation compared with bare-metal stent (BMS) implantation have given impetus to considering biodegradable and bioabsorbable options for cardiac stents [2, 16–21, 57–60].

Moreover, these effects can increase the incidence of very late stent thrombosis, a rare event, after DES implantation [16–21]. In addition, delayed loss of anti-restenotic efficacy has also been observed with the early DES technologies [22, 23]. Chronic arterial-wall inflammation and endothelial dysfunction may be associated with the increased rate of target vessel revascularization at a late stage, which has been found particularly in patients with complex lesions, including those with diabetes [24, 25].

Among the biodegradable polymers implemented, polylactic acid, polyglycolide, and poly(D,L-lactic-co-glycolic acid) are particularly common. These can be completely metabolized as they break into monomers, water, and carbon dioxide. Stents with these biodegradable polymers have antiproliferative agents as eluting agents, which include sirolimus, tacrolimus, biolimus, and paclitaxel [27, 51–60].