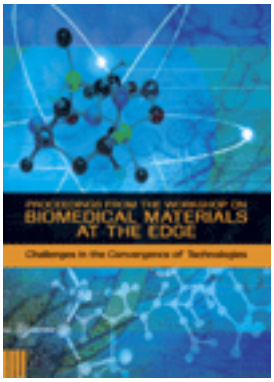

Proceedings from the Workshop on Biomedical Materials at the Edge: Challenges in the Convergence of Technologies

Crystal M. Cunanan and Bonnie A. Scarborough, Editors, Roundtable on Biomedical Engineering Materials and Applications, National Research Council

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PROCEEDINGS FROM THE WORKSHOP ON BIOMEDICAL MATERIALS AT THE EDGE

Challenges in the Convergence of Technologies

Presentation to the
Roundtable on Biomedical Engineering Materials and Applications

Crystal M. Cunanan, ReVision Optics
Bonnie A. Scarborough, National Research Council

National Materials Advisory Board

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Preface

Recent advances in biomedical materials technology, such as the use of stem cells as biomaterials, the development of biomolecular materials composites, and supramolecular/nanoscale biomaterials engineering and design, hold the promise of a revolution in clinical medicine. Potential applications of these technologies include treatments for cancer, AIDS, congenital diseases, orthopedic problems, and cardiovascular disease. Despite their promise for clinical applications, however, there are many barriers to the development, manufacture, regulatory approval, and commercialization of these materials.

ROUNDTABLE ON BIOMEDICAL ENGINEERING MATERIALS AND APPLICATIONS

The Roundtable on Biomedical Engineering Materials and Applications (BEMA) is an activity of the National Research Council (NRC) convened with the objective of bringing together government officials, industry representatives, academics, and others to discuss research, development, applications, and regulation of biomedical materials and devices. BEMA provides a forum for participants to identify opportunities for applying engineering principles to create and improve the clinical performance of medically useful materials and devices. In addition, the roundtable discusses strategies for overcoming the technical, legal, and cultural obstacles that impede the transition of new materials and devices to clinical application. BEMA achieves these objectives by three means:

- Providing a neutral setting for the exchange of information about issues related to biomaterials science, research, and practice;
- Identifying and discussing priority issues in the general area of biomaterials and their application in the development, manufacture, and use of medical devices; and
- Conducting problem-solving and issue-identification activities such as workshops that address these issues in greater depth.

WORKSHOP ON BIOMEDICAL MATERIALS AT THE EDGE

A workshop entitled “Biomedical Materials at the Edge: Challenges in the

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Convergence of Technologies" was held on September 30 and October 1, 2004, at the National Academies in Washington, D.C. (the theme was identified in BEMA meetings held earlier that year). The purpose of the workshop was to discuss breakthrough biomedical materials technologies that could be used in the development of future treatments and the manufacture of future medical devices. To facilitate discussion, the workshop was organized into sessions on three emerging technologies: stem cells as biomaterials of the future, biomolecular materials composites, and supramolecular/nanoscale biomaterials engineering and design. Each session, and the resulting discussion, is summarized in this report, and abstracts of the individual presentations are offered. The agenda for the workshop is included as Appendix A and biographical sketches of the speakers are given in Appendix B. The viewgraphs presented by the speakers are reproduced, as originally supplied, on the accompanying CD-ROM.

NRC roundtables are established solely to provide open forums for discussion of emerging issues. They are prohibited by NRC policy from producing conclusions and recommendations or from offering advice to government agencies. As such, the primary purpose of this workshop was to educate the individuals who attended so that they might take this information back to their organizations and use it in their daily planning and decision making. This proceedings therefore serves primarily as a guide for those participants to remembering the content of the discussions. The abstracts of the workshop presentations and the unedited viewgraphs represent the viewpoints of the presenters only.

ACKNOWLEDGMENTS

The BEMA roundtable has no head and no foot. While prohibited from providing advice or recommendations, the BEMA roundtable was formed so that its members might learn, analyze, freely exchange ideas, identify challenges, suggest the need for more formal NRC meetings and publications, and publish workshop proceedings such as these. On behalf of BEMA, I would like to thank the speakers for their informative presentations, the session chairs for keeping the discussions focused and on time, and the workshop participants for taking the time to join with BEMA members for a day and a half of lively discussion.

I would also like to thank the BEMA members who volunteered their time to organize this workshop, especially Jim Burns, Alan Goldstein, Josh Jacobs, and Sohi Rastegar. Crystal Cunanan deserves special recognition for her role as program chair. She and Bonnie Scarborough did a terrific job of putting together the workshop summary. In addition, I would like to thank

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Thanks are extended to the following individuals, who reviewed the contents of this proceedings volume: Ray A. Gsell, Zimmer, Inc.; Jack E. Lemons, University of Alabama; Martha S. Lundberg, National Heart, Lung, and Blood Institute; and Scott G. McNamee, U.S. Food and Drug Administration. The review of this proceedings was overseen by Howard Freese, Allvac Incorporated. Appointed by the National Research Council, he was responsible for making certain that an independent examination of this proceedings volume was carried out in accordance with institutional procedures and that all review comments were carefully considered. The individual presenters and the summary authors are responsible for the substance of this proceedings.

Buddy D. Ratner, *Chair*
Roundtable on Biomedical Engineering
Materials and Applications

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WORKSHOP SUMMARY

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Workshop Summary

Crystal M. Cunanan
ReVision Optics

Bonnie A. Scarborough
National Research Council

INTRODUCTION

Rapid developments in biomedical materials are being enabled by continuous advances in other areas of science, such as genomics and proteomics, cell-processing techniques, supramolecular chemistry, permutational chemistry, bioinformatics, and information technology. The need for interdisciplinary research in biomedical materials is therefore increasing, with the most exciting potential for new therapies lying at the point where a number of research disciplines converge. For example, promising new therapies can be created through combination products, miniaturization of biosensors, gene-based therapies, and the generation of engineered tissues to restore functional organs. Emerging biomedical materials hold out the promise of new therapies for the treatment of many currently untreatable medical conditions.

However, this convergence of technologies, while presenting new opportunities, also presents new challenges. Although scientific discoveries are being achieved at an ever faster pace in the life and physical sciences, these advances are not being translated as rapidly into medical innovation. Improved medical technologies are therefore not reaching patients at a rate that matches the rate of scientific advances. Because these scientific advances create an awareness of the tremendous complexity of the systems being studied, it can be argued that they may be slowing technology transfer by raising questions that are difficult, if not impossible, to answer. The emerging field of systems biology promises to synthesize this basic science into more usable formats. However, it will be many years before this promise can be fulfilled.

To explore the opportunities and challenges being created in the development and application of new biomedical materials and to discuss possible pathways to overcoming the challenges, the workshop "Biomedical Materials at the Edge: Challenges in the Convergence of Technologies" was held by the National Research Council's Roundtable on Biomedical Engineering Materials and Applications (BEMA) on September 30 and October 1,

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2004, in Washington, D.C. The workshop consisted of four sessions: setting the context for new biomedical materials; stem cells as biomaterials of the future; biomolecular materials composites; and supramolecular biomaterials engineering and design (nanotechnology) (see Appendix A for the agenda).

CONTEXT FOR NEW BIOMEDICAL MATERIALS

To understand the context in which new biomedical materials are evolving and the challenges and opportunities faced in creating innovative medical therapies from these emerging materials, it is important to understand current policy, regulatory, and economic conditions. In this session, presentations were given by Susan Bartlett Foote, Division of Health Services Research and Policy, University of Minnesota; Larry G. Kessler, Center for Devices and Radiological Health, U.S. Food and Drug Administration (FDA); Annabelle R. Hett, Swiss Re; and Stephen N. Oesterle, Medtronic, Inc.

Susan Foote presented her views on the role of public policy in medical technology innovation. Current public policy does not match the innovative advances occurring in science and technology. This is largely because the process of creating public policy is reactive rather than adaptive. Policy is constrained to develop within the limits of authorizing legislation, and while the law provides the authority to regulate, it also limits the extent to which that regulation can change. Instead of considering the overall landscape, the policy-making process normally focuses on making individual distinctions and incremental decisions with regard to smaller issues. Strategies for public policy could be developed, however, that would enable the design of more flexible and adaptable systems. The disciplines that will most likely have a substantial impact on the medical community include the biological sciences, information technology, and materials science. Out of these disciplines, new technology fields are being created: telemedicine, bioinformatics, microelectromechanical systems, tissue engineering, nanotechnology, and gene therapy, to name a few. In addition, the combination of biological materials with medical devices to repair, replace, restore, and regenerate tissues and organs promises to be an important new area of medicine.

When considering the role of public policy in medical technology innovation, it is difficult to generalize, because different device technologies will face different hurdles for development and commercialization. In addition, not all hurdles are policy-related. Markets, territory, costs, alternative technologies, and other intangibles also create barriers to the development of innovative technologies. For example, to understand the impact of the medical marketplace, one must consider the variety of customers, including providers, hospitals, physicians, and government and private

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payers. Other factors that affect the development process are intellectual property, public perception, costs, and liability. Ms. Foote ended by saying that public policy is often in a state of flux, affected by the politics of the current environment, and this makes it difficult for policy to be as flexible and innovative as the basic sciences and technology can be.

Larry Kessler presented data showing that while advances in basic research have generated exciting new discoveries in, for example, genomics and nanotechnology, there has been a steady decline in the number of applications to the FDA for the approval of new drugs and biologics. In contrast, there has been an increase in applications for approval of new medical devices over the past 10 years. These medical devices are increasingly complex and are designed to address more serious diseases. FDA recognizes that it plays a key role in regulating the translation of medical discoveries into new therapies, especially in the final stages of clinical testing and market release. FDA does not want to be a barrier to that flow of new products, yet it recognizes that it may not have the organizational structure to assess these new technology submissions.

To avoid roadblocks in the translation of new ideas into new products, the U.S. Department of Health and Human Services (HHS), which oversees the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the FDA, and the National Institutes of Health (NIH), has developed a number of center-specific initiatives to keep these organizations abreast of scientific advances. NIH spearheaded this effort with its Roadmap Initiative,[1] which has three main themes: new pathways to discovery, research teams of the future, and reengineering the clinical research enterprise. FDA launched its Critical Path Initiative[2] to ensure that breakthroughs in medical science are demonstrated to be safe and effective for patients as quickly and inexpensively as possible. In addition, programs to advance clinical research are supported by the Agency for Healthcare Research and Quality (AHRQ) with the Translating Research into Practice (TRIP-II) Initiative.[3] This effort focuses on the techniques and factors associated with successfully translating original research into routine clinical practice. Also at AHRQ, the Centers for Research on Therapeutics[4] (CERTs) conduct research and provide education to advance the optimal use of drugs, medical devices, and biological products. Taken together, these programs and the Medicare Modernization Act of 2003 are examples of government efforts to ensure that systems keep pace with technology advances.

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[1]For more information, see http://nihroadmap.nih.gov.
[2]For more information, see http://www.fda.gov/oc/initiatives/criticalpath.
[3]For more information, see http://www.ahrq.gov/research/trip2fac.htm.
[4]For more information, see http://www.certs.hhs.gov.

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In May 2004, HHS formed an internal task force to encourage innovation in health care and to speed the development of effective new medical technologies, such as drug and biological products and medical devices. The Medical Innovation Task Force involved the CDC, CMS, FDA, and NIH. In recognition of the fact that a new technology must often clear hurdles in different parts of HHS before it can reach consumers, the task force was asked to make recommendations on how this process can be better coordinated across HHS. Dr. Kessler invited workshop participants to submit suggestions to the HHS task force. The task force submitted a report to the Secretary of HHS in January 2005 outlining opportunities for synergy and collaboration both within and between HHS and other government and private organizations.[5]

The successful development of an innovative medical technology will depend on economic as well as policy and regulatory conditions. Annabelle Hett explained that an emerging biomedical material may face additional economic hurdles because it is difficult to define the risks associated with it. If the risks cannot be defined, then global reinsurance companies cannot underwrite the companies seeking to develop applications for that technology. This can delay the introduction of new biomedical products into the marketplace for medical therapies.

Global reinsurance companies such as Swiss Re are the foundation that allows investment in emerging technologies. They identify, evaluate, underwrite, and diversify risk in order to minimize the total capital cost of carrying such risk. The ability to insure a risk depends on a number of factors, including the ability to assess and quantify the risk and its true randomness of occurrence. In addition, the exposed parties must be willing to join together to build a risk community to share and diversify risk, and it must be economically feasible to charge a premium commensurate with the risk. Finally, it must be possible to prove a causal relationship between an action or omission and the resulting damage or loss to cover liability costs associated with a newly developed product. Without these key elements, the industry cannot insure risk.

Underwriting for new products that use emerging technologies poses special difficulties. For example, nanotechnology is an area where the insurance industry does not have a clear risk profile. One reason is that although nanomaterials are expected to be ubiquitous in industrial production, their effects on living organisms are largely unknown. Because nanoparticles are relatively new, little is known about how they interact with living organisms, whether or not they are biodegradable, and how they behave. Nanomaterials exhibit properties different from their bulk properties.

[5]To read the final report online, see http://www.hhs.gov/reference/medicalinnovations.shtml.

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In addition, it is difficult to assess the environmental impacts of nanotechnologies. Federal regulatory agencies do not have an adequate framework to assess whether a material's properties on the nanoscale are different from that material's properties on the macroscale or whether any such differences might affect public health. Finally, public perception is an unknown variable in evaluating technology risk. In summary, more accurate terminology, an improved ability to assess risk and severity, and improved regulatory guidelines are needed for insurance companies to develop appropriate models to support new technologies such as nanotechnology. To move forward with these technologies, Dr. Hett recommends starting a risk dialogue among regulators, businesses, scientific institutions, the insurance industry, and the general public.

New biomedical materials create challenges for traditional medical device companies as well. Stephen Oesterle described a new business model created by two health-care companies, Medtronic, Inc., and Genzyme Corporation, to address these challenges and take advantage of emerging opportunities. Medtronic partnered with Genzyme in the formation of MG Biotherapeutics, which is exploring, among other things, clinical applications of skeletal myocyte transplantation into the diseased hearts of congestive heart failure patients. The financial investments, technology contributions, and skilled expertise across a variety of disciplines associated with addressing this medical condition were estimated to be more than any one company could support. By partnering with Genzyme, Medtronic lowered its investment risk and thereby increased its probability of developing successful cell-based treatments. An interdisciplinary organization was created with skills in both traditional medical device technologies, which are essential for delivery of the new therapy, and autologous cell manufacturing techniques, a unique core competency of Genzyme. MG Biotherapeutics represents a new business model for the convergence of new technologies to make products with high potential; it combines contributions in basic research, development, engineering, intellectual property, regulatory affairs, clinical research, quality control, and marketing. MG Biotherapeutics plans to create a pipeline of new products to treat serious medical conditions such as neurodegenerative diseases, diabetes, and cardiovascular disease.

STEM CELLS AS BIOMATERIALS OF THE FUTURE

The first technical session of the workshop focused on stem cells as biomaterials of the future. Speakers were Philip H. Schwartz, director of the National Human Neural Stem Cell Resource at the Children's Hospital of Orange County

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(CHOC); Steven L. Stice, University of Georgia; Michael A. Laflamme, University of Washington; and Mark F. Pittenger, Osiris Therapeutics.

Many challenges are involved in using stem cells as a biomaterial, including funding issues,[6] ethical considerations, and cell quality. In addition, stem cells are difficult to work with because they can spontaneously differentiate into different lineages. The precise culturing conditions needed to control cellular differentiation are poorly understood. Despite the belief that stem cells are immune-privileged, we know that stem cells from pooled sources or cell lines present safety concerns due to issues of immunogenicity and tumorgenicity. Nevertheless, interest in using stem cells as biomaterials or in combination with biomaterials remains high because they could allow the treatment of currently untreatable diseases. NIH has developed centers such as those at CHOC and the University of Georgia to train scientists and technicians in the specialized techniques required to properly isolate, propagate, and maintain these cells.

While embryos are one source of stem cells, the hematopoietic system is another source that is free of many of the ethical issues surrounding embryonic stem cells. Human mesenchymal stem cells also have differentiation capabilities, although they are more limited than those of embryonic stem cells. Because these cells present the potential for autologous therapies, numerous companies, including Osiris Therapeutics, are performing clinical trials of a variety of applications, including treatments for congestive heart failure. An emerging issue with hematopoietic stem cells is that, although they can be injected into healthy heart tissue, they do not appear to do as well when injected into diseased heart tissue. Thus the environment plays a role in influencing stem cell differentiation even in vivo.

BIOMOLECULAR MATERIALS COMPOSITES

The second technical session of the workshop focused on biomolecular materials composites, or the ability to manipulate biological molecules to create novel materials. Nadrian C. Seeman, New York University; Virgil Percec, University of Pennsylvania; and James L. Harden, the Johns Hopkins University, presented information on their research in this area.

[6]At the time of the workshop, NIH funding was restricted to work using stem cell lines established prior to August 9, 2001. In the November 2004 election, California voters passed a state resolution providing funds to support stem cell research in California. This resolution is currently being challenged in court.

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Nadrian Seeman has used the unique repeating structure of deoxyribonucleic acid (DNA) to create materials that can be used for the design of various objects, lattices, and devices. Specifically, he has exploited the base pairing capabilities of DNA that allow structures to self-assemble in specific and reproducible ways. His research group has successfully created nanoelectronic components, polyhedral catenanes, and crystalline arrays with the intent of combining these biomolecular structures to create the desired nanomechanical devices. The inherent properties of DNA make it uniquely well suited to meet the requirements of lattice design components, which include predictable local product structure interactions and structural integrity.

Using self-assembled monolayers (SAMs), Virgil Percec has been able to create supramolecular structures that mimic porous transmembrane proteins. Modeling of these proteins has important therapeutic applications because transmembrane proteins are an important means of introducing molecules into cells. These proteins can be either selective or nonselective, and Dr. Percec focuses on the selective proteins as a means to control the introduction of molecules into cells. By taking advantage of the inherent properties of selective membrane proteins, his research group is trying to determine how to assemble the correct structure in order to create the desired function. Reversing chirality is one way to make a protein that can be both selective and permeable, and Dr. Percec's group exploits solvent differences to create supramolecular helical hollow columns that self-assemble. One example of the group's work is dendritic, dipeptide, hydrophobic, pore-protein transport molecules. Solvents such as cyclohexanes enable the use of phospholipids to create the supramolecular structures.

James Harden engineers proteins for specific biomaterials applications using modular protein polymers, much like synthetic block copolymers, for biomimetic designs. Proteins make a suitable starting point for such bioengineered materials because of their tremendous sequence diversity as polymers. In addition, the ability to modify and create artificial amino acids provides a wide variety of basic building blocks. For example, design-directed protein synthesis can be used to control important molecular properties such as sequence length and molecular weight, secondary and tertiary structure, and inter- and intramolecular attractions. This, in turn, allows one to create self-assembled reversible hydrogels with specific structural and mechanical properties that mimic functional motifs from a variety of natural structural materials such as collagen, elastic, and silk. By mimicking these designs, Dr. Harden is able to create structures that have great biomechanical strength but no enzymatic degradation cleavage sites. These qualities make the materials both strong and biostable, giving them potential applications in the creation of vascular grafts, for example, where each layer of the trilaminate construct could be specifically designed to have

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the properties desired (e.g., strength, elasticity, cell binding matrix). Currently, protein-based biomolecular materials tend to be either soft hydrogels or somewhat glassy brittle materials. The biocompatibility of these materials must be better understood, however, as proteins can trigger rejection when recognized as foreign by the immune system.

SUPRAMOLECULAR BIOMATERIALS ENGINEERING AND DESIGN

The final technical session of the workshop focused on the creation of new biomaterials using nanotechnology—in other words, supramolecular biomaterials engineering and design. Three speakers addressed the context in which nanotechnologies are developing in the United States today: James Murday, Naval Research Laboratories; Edward K. Moran, Deloitte & Touche; and Nik Rokop, Chicago Microtechnology and Nanotechnology Community. Three other speakers described potential environmental and public health issues related to nanotechnology and described research focused on manufacturing nanostructures for biological and medical applications: Vicki L. Colvin, Rice University; Charles R. Martin, University of Florida; and Jennifer L. West, Rice University.

To understand the context in which nanotechnology is developing in the United States, James Murday described the National Nanotechnology Initiative (NNI),[7] an innovative federal program created by Congress that committed over $1 billion in 2005 toward the development of nanotechnology capabilities in the United States. Many believe that nanotechnology is tremendously important to the future of materials and that nanomaterials will someday be as ubiquitous as polymers are today. The goals of the NNI are therefore to strengthen and maintain U.S. leadership in nanotechnology.

The NNI represents a new paradigm in federally funded research, with the activities of a number of federal agencies and laboratories being coordinated across agency lines in order to build on the expertise of each group. Federal agencies involved in the NNI include NIH, NSF, FDA, the U.S. Environmental Protection Agency, the National Aeronautics and Space Administration, the Department of Defense, the Department of Energy, and the National Institute of Standards and Technology. These agencies would not normally have the opportunity to participate in the early stage development of such a technology. By involving so many agencies early on, however, each agency may begin to develop competency in nanotechnology,

[7]For more information, see http://www.nano.gov.

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thereby promoting an understanding of the impact of this technology on its mission. In addition, NNI provides research funding for many universities and small businesses focused on understanding the basic chemistry and physics of nanostructures; developing methods for earlier detection and treatment of diseases; improving implants; and enabling better delivery of therapeutic agents through nanostructures that have enhanced solubility properties, that contain specific targeting mechanisms, and that can provide localized delivery without systemic side effects.

While early signs of success do exist for some nanotechnologies, Edward Moran said, nanotechnology is still too new for most venture capital firms to invest in nanotechnology companies. Venture capitalists are reluctant to invest in a high-technology field that they do not understand well, perhaps as a result of their experiences with dot com and biotechnology companies. When venture capitalists consider an investment strategy, they evaluate technical risk, market risk, and team risk. Technical risk includes the probability that the technology will work, that intellectual property positions can be secured and maintained, and that regulatory agencies will approve the product. Market risk includes customer acceptance, potential revenue streams, the impact of competition and competitive technologies, and technology roadmaps for continuous evolution of the base technology. Team risk includes an evaluation of the management and technical team members, including their track record and prior associations, which determines whether or not the team will be able to deliver on its promises.

Today's business environment is a new world, and partnering often makes sense when bringing capital-intensive new technologies to market. Venture capitalists do not fund science for the sake of science, and there is a high failure rate among early-stage companies that are unable to cross the chasm from concept to commercial reality. In addition, the complexity of competition has increased across several dimensions, including competition from other nations that may have advantages over the United States because of concerted support from their governments or a cheap labor force and other economic factors. Some environmental issues—potential liability and regulatory constraints—can constrain technology development. Because of the small proportion of nanotechnology funding from venture capitalists, federal funding remains important for the early support and development of this technology.

To support and educate the growing nanotechnology business community, the Chicago Microtechnology and Nanotechnology Community trade organization holds public educational seminars and special events. The organization serves as a convergence point for midwestern micro- and nanotechnology companies seeking knowledge and resources and participates in an international technology exchange that showcases technologies from organizations around the world. Nik Rokop brought the first part of this

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session to a close by stating that one should not look at nanotechnology in the United States alone but should consider it instead in a global sense and promote the growth of nanotechnology research and companies internationally as well as domestically.

Having a better understanding of nanostructures is important, as it is increasingly apparent that these materials have unique properties as a result of their size. Nanocrystals, for example, are highly crystalline with large surface areas and therefore offer potential for surface interactions in a biological system. Vicki Colvin, director of the Center for Biological and Environmental Nanotechnology at Rice University, presented her research on issues of biocompatibility for nanostructures.

In the past, incidental exposures to nanomaterials such as asbestos caused significant harm to public health. There is currently some negative public perception of nanotechnology materials as having potentially adverse environmental and health impacts. Dr. Colvin is working to understand the interactions of a variety of engineered nanomaterials with cells and biological systems. She hopes that by working proactively, it will be possible to understand potential safety issues early in the development of the technology. Dr. Colvin is exploring the risk to humans from direct exposure to nanomaterials and is characterizing the environmental impact of nanoparticles, which could indirectly affect human health.

While there are unknowns surrounding supramolecular materials in terms of public health and environmental safety, these materials clearly offer significant promise in the treatment of human diseases as well as protection against bioterrorism. Charles Martin and Jennifer West presented their research on the diagnostic and therapeutic applications of nanotechnology. Through proper design and functionalization, carbon nanotubes, for example, could be capable of detecting single molecules. They could therefore be used as ultrasensitive sensors, with applications in the detection of biological weapons.

Nanotechnology has also enabled an important new advance in cancer treatment that could one day be used therapeutically. Metal nanospheres can be fabricated that absorb energy at specific levels due to their metallic composition. When such nanospheres are functionalized with antibodies that target cancer cells, they bind specifically to the cancer cells and become internalized through the normal mechanisms of endophagocytosis. If the tumor area is then irradiated with energy specifically absorbed by the nanoshell, the heat absorbed by the nanosphere is enough to kill the cancer cells, thereby providing an effective, nonsurgical means of destroying the tumor in a specific and targeted way.

Another potential application of nanoshells is their use as optical imaging contrast agents for early detection of tumors. When nanoshells are targeted to breast carcinoma cells using conjugated antibodies, tumor

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detection improves twofold compared to imaging without the nanoshells. Within this context, it may be possible to combine the imaging capability of nanoshells with the therapeutic capability of the nanospheres, thereby advancing the state of cancer therapy.

KEY QUESTIONS

The workshop presentations and discussions raised six new and important questions for further consideration:

- What is the best business model for developing complex new biomedical materials, such as cell-based therapies?
- Is new policy necessary to ensure that the U.S. regulatory process can match the pace of science and technology innovation and development?
- What role will public perception play in the adoption of radically new technologies? How will it affect the further development and use of these technologies?
- Can new technologies ever be safe enough for widespread use when we don't know what we don't know yet? Should the development of new technologies be slowed in order to try to better understand their real risks?
- How does the convergence of new technologies affect the education system? Can we teach interdisciplinary teamwork in today's academic system, which is typically structured around individual departments?
- How can the process from good idea to actual product be strengthened, particularly to narrow the gap between academia, where many good ideas originate, and product commercialization?

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ABSTRACTS

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Context for New Biomedical Materials

CAN PUBLIC POLICY BE AS INNOVATIVE AS SCIENCE AND TECHNOLOGY?

Susan B. Foote
Division of Health Services Research and Policy
University of Minnesota

The process of making public policy can be characterized as follows: it classifies products, evolves over time, reflects political trends and opportunities, and works incrementally, not globally, to design appropriate regulations. The history of the U.S. Food and Drug Administration (FDA) is characterized by the use of distinctions—for example, drugs, devices, biologics, and procedures. The different centers within FDA have been set up based on these distinctions. For example, combination products are named to reflect the combination of FDA units under whose jurisdiction they fall. New medical technologies do not fall into neat categories, however. As a matter of fact, it is difficult to generalize about technologies. Not all device technologies face the same hurdles, not all hurdles are policy-driven, and the success or failure of a medical technology can be impacted by market factors, turf, costs, the existence of alternatives, or other intangibles. To succeed with a medical technology, it can help to understand the medical marketplace, including the role of intellectual property and public perception. Additional factors to consider are that although public policy should be as innovative as technology, policy values are often in flux, and politics is now an important factor in medical technology.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES' MEDICAL INNOVATION TASK FORCE

Larry G. Kessler
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Although both government spending and industry spending on biomedical research increased steadily over the past decade, the number of major drug and biological product submissions to the FDA has been decreasing. In May 2004, U.S. Department of Health and Human Services (HHS) Secretary Tommy G. Thompson formed an internal task force to identify steps that HHS could take to speed the development and availability of innovative medical technologies. The task force was asked to weigh new ideas and promote new ways to encourage innovation in health care and speed the development of effective new medical technologies, such as drug and biological products and medical devices. The task force was chaired by the FDA commissioner and included the heads of the CDC, the NIH, the National Cancer Institute, the AHCRQ, and the CMS. The task force issued a report in January 2005; it can be read online at http://www.hhs.gov/reference/medicalinnovations.shtml.

DIALOGUE ON INNOVATION AND RISK

Annabelle R. Hett
Swiss Re

The core business of the insurance industry is the transfer of risk. Thus the insurance business identifies, evaluates, underwrites, and diversifies risk in order to minimize the total capital cost of carrying it. A risk is insurable if the following conditions are met: the probability and severity of losses can be quantified to calculate the premium; the time of the insured event must be unpredictable and its occurrence independent of the will of the insured; the exposed parties are able to join together to form a risk community in which the risk is shared and diversified; insurers and reinsurers are able to charge a premium that is commensurate with the risk; and, in liability insurance, there is a causal relationship between the action or omission of the insured and the resulting damage/injury/financial loss. As one of the major risk takers, the reinsurance business must have a clear picture of the risk landscape in order

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to avoid cumulative and serial loss exposures that exceed the capacity of the private insurance industry.

Nanotechnology challenges the insurance industry because there is great uncertainty about the potential for nanotoxicity or nanopollution, the ubiquity of nanoproducts in the near future, and the long-term possibility of latent, unforeseen claims. The insurance industry is concerned because there are few scientific evaluations of the potential risks for human health and the environment, and the existing evaluations remain inconclusive. Regulatory guidelines that adequately address potential risks are lacking. It is therefore essential to start a risk dialogue among regulators, businesses, scientific institutions, the insurance industry, and the general public. Whether the public accepts the new technology and sees in it advantages for itself, or whether it rejects it, will largely depend on how well informed the public is and to what degree it is able to make objective judgments. The assessment of risks associated with nanotechnology should concern all involved stakeholders. The only way to prevent a polarized debate about nanotechnology, which could slow down future research and economic growth in this field, is to develop a common approach to lessen uncertainty and to answer some questions about potential nanotoxicity and nanopollution.

CONVERGENT CALLING: MG BIOTHERAPEUTICS, A RATIONAL JOINT VENTURE BETWEEN THE DEVICE AND BIOTECHNOLOGY WORLDS

Stephen N. Oesterle
Medtronic, Inc.

Patients with chronic degenerative diseases are responsible for more than 75 percent of U.S. health care expenditures. According to demographic projections, the number of people over age 65 will increase by 20 percent to 50 percent over the next two decades. The implications for health care spending are clear and daunting. Some of the most challenging medical problems associated with chronic degenerative diseases include heart failure, arteriosclerosis, spine disease, and degenerative neurological disorders. Thus far, medical device companies have focused on electromechanical solutions to many of these problems. For the most part, these solutions have been palliative; few are restorative and virtually none are curative.

Biological products, or biologics, are of interest as treatments because they offer the potential for restoration or cures. The term biologics can be broadly viewed as including proteins, cells, small interfering RNA, and

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genes. In order to realize their therapeutic potential, most biologics will require controlled local delivery. This type of delivery can be facilitated by catheter-based systems, implantable pumps, and navigational tools to target diseased organs. The device industry and biotechnology companies can collaborate to create products that incorporate both biologics and delivery systems; such products are known as combination products. Examples of currently approved combination products include the use of recombinant human bone morphogenetic protein (Medtronic's INFUSE™) with spinal cages and continuous insulin delivery by a wearable pump (Medtronic's Paradigm®).

Early feasibility studies suggest that cell therapy may enhance cardiac performance in patients suffering from ischemic cardiomyopathies. Seminal work by Genzyme Corporation led to an ongoing trial in Europe of the use of autologous skeletal myoblasts given by injection at the time of bypass surgery. Recently, Genzyme entered into a joint venture, MG Biotherapeutics, with Medtronic. It will explore the use of less invasive catheter-based systems for cell delivery to the heart. This joint venture was propelled by the belief that each of the two companies brings unique and synergistic research and development capabilities to the table. Initially, MG Biotherapeutics will direct its activities toward autologous cell therapy for heart failure. This organizational structure is expected to serve as a model for how biotechnology companies can pair with device companies to effectively deliver biotherapies to targeted areas. Such experience will be particularly important for brain therapies where device tools will be essential for effective delivery across the blood-brain barrier.

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Stem Cells as Biomaterials of the Future

STEM CELLS AS BIOMATERIALS OF THE FUTURE: AN OVERVIEW OF SOME STEM CELL ISSUES

Philip H. Schwartz
National Human Neural Stem Cell Resource
Children's Hospital of Orange County

Few advances in science have generated as much controversy as the recent discovery that human embryonic stem cells (hESCs) can be harvested from the preimplantation embryo. The potential of hESCs to replace dead or damaged cells in any tissue of the body may herald the advent of a new field of medicine that can deliver cures for diseases now thought to be incurable. In addition, hESCs offer a new model system for studies of basic mechanisms in normal and abnormal developmental biology as well as for drug discovery studies. These remarkable cells have captured the imagination of scientists and clinicians alike and given a new sense of hope to patients. Although the public controversy surrounding the use of hESCs arises primarily from the technique required to harvest these cells—destruction of the human embryo—logistical, technical, and legislative hurdles to the use of hESCs also exist. In this overview presentation, issues surrounding basic cell culture techniques, implantation safety, funding sources, legislation, stem cell sources, and transplantation are discussed.

PROPAGATING AND DIFFERENTIATING HUMAN EMBRYONIC STEM CELLS

Steven L. Stice
University of Georgia

The Stice research group at the University of Georgia derived three of the hESC lines (BG01, BG02, and BG03) that have been approved by the NIH using mechanical dissection of the original colonies. Mechanical passaging entails the selection of specific areas of hESCs, followed by separation of

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these areas from the colony using a fine-drawn pipette and subsequent placement of these cells on a new mouse embryonic fibroblast feeder layer. The group has determined that mechanically passaged hESCs have normal karyotypes at passages 41, 50, 62, 74, 100, and 105 under identical cell culture conditions. However, this method is labor-intensive and requires specialized training. Other materials and methods for passaging hESCs have therefore been developed for more general use of these cells in the scientific community. This presentation discusses these techniques and the need for new materials and methods for propagating hESCs, as well as the Stice research group's recent advances in directing in vitro differentiation of hESCs to neural fates.

CARDIAC REGENERATIVE STRATEGIES USING HEMATOPOIETIC AND HUMAN EMBRYONIC STEM CELLS

Michael A. Laflamme
University of Washington

Because the adult human heart has little regenerative capacity, irreversible injury to the myocardium, such as by infarction, typically results in the formation of a noncontractile scar and often initiates progressive heart failure. Because of the limited number of suitable donor hearts for transplantation, there has been much recent interest in cellular approaches to cardiac repair—that is, cell transplantation. A number of cell types have been considered for this application, including skeletal muscle precursors, adult stem cells, and cardiomyocytes derived from hESCs. The Murry Laboratory at the University of Washington has explored the capacity of marrow-derived hematopoietic stem cells to regenerate the infarcted heart. Researchers found that, after direct injection into the infarct, none of these adult stem cells transdifferentiated into cardiomyocytes. Because hESCs have an unquestioned capacity to differentiate into cardiomyocytes in vitro, the Murry Laboratory has focused on examining the potential of hESC-derived cardiomyocytes to form new human myocardium in the hearts of immunodeficient rats. In experiments involving transplantation into the uninjured hearts of athymic rats, researchers found that hESC-derived cardiomyocytes indeed formed substantial, highly proliferative, and, at least at later time points, exclusively cardiac grafts within the rat heart. While ongoing studies have demonstrated the successful formation of similar human cardiac implants within experimentally infarcted hearts, this preclinical work has also highlighted important but perhaps surmountable challenges for such cell-based

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therapies, including the need for improved strategies to achieve a homogeneous cardiac preparation and enhanced cell survival after implantation.

NEW TISSUES FROM HUMAN MESENCHYMAL STEM CELLS

Mark F. Pittenger
Osiris Therapeutics, Inc.

Mesenchymal stem cells (MSCs) can be isolated from many tissues; bone marrow provides a convenient and renewable source. Human mesenchymal stem cells (hMSCs) can be grown in culture, resulting in the production of billions of these multipotential cells, which can then be formulated for various tissue repair and regeneration purposes. Osiris Therapeutics has experience with formulating therapies for orthopedic applications—bone, meniscus, and cartilage—as well as therapies for aiding bone marrow transplantation and cardiac therapies following infarction. Much of this work has been described in peer-reviewed publications.

Over the past several years, Osiris Therapeutics has evaluated the ability of MSCs to engraft in recipients without immunological matching. This use of allogeneic stem cells for tissue repair in unrelated recipients has exciting implications for the ready availability of adult stem cell therapies in the clinic. Previous methods for the application of autologous stem cells have required harvesting the patient's own tissue, followed by isolation and expansion of the patient's autologous MSCs over a three- to four-week period. This presentation will review the evidence for the multilineage potential of hMSCs and their ability to avoid rejection when implanted in the allogeneic host. The mechanism by which allogeneic MSCs interact with different isolated immune cells is presented, along with several tissue repair models.

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Biomolecular Materials Composites

NOT MERELY THE SECRET OF LIFE: DNA AND NANOTECHNOLOGY

Nadrian C. Seeman
New York University

Structural DNA nanotechnology uses the concept of reciprocal exchange between DNA double helices (hairpins) to produce branched DNA motifs, such as Holliday junctions, or related structures, such as double crossover (DX), triple crossover (TX), paranemic crossover (PX), and DNA parallelogram motifs. At the Seeman Laboratory at New York University, DNA motifs are combined to produce specific structures by means of sticky-ended cohesion or by other interactions, such as PX cohesion. The key strength of sticky-ended cohesion is that it produces predictable adhesion combined with known structure. From branched junctions, researchers at the Seeman Laboratory have constructed DNA stick-polyhedra, whose edges are double helices and whose vertices are the branch points of DNA branched junctions. They have also begun to template the topology of industrial polymers, such as nylon, with DNA-like scaffolds. That living systems have nanoscale structural components proves that autonomous systems can build up and function on this scale; such systems are capable of energy transduction and replication. The overall challenge that biology presents to the physical sciences is to move from biokleptic to biomimetic to abiological systems that perform in this same manner. To move in the direction of nanorobotics, Seeman Laboratory researchers have used two DX molecules to construct a DNA nanomechanical device by linking them with a segment that can be switched between left-handed Z-DNA and right-handed B-DNA. PX DNA has been used to produce a robust sequence-dependent device that changes states by varied hybridization topology. The sequence-dependent nature of this device means that a variety of such devices attached to a motif can all be addressed individually. Two such devices have been coupled to create a prototype of a translational machine, logically equivalent to a ribosome. Researchers have used sequence control to build a bipedal walker that moves on a sidewalk. They have also constructed a protein-activated device that can be used to measure the ability of the protein to do work.

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HELICAL POROUS PROTEIN MIMICS

Virgil Percec
University of Pennsylvania

The fluid mosaic model of a cell membrane can be used as a model for the design of multifunctional, porous, supramolecular systems. It is possible to understand the functioning of molecules by looking at their structure. Porous transmembrane proteins can be either nonselective or selective, with all selective protein channels being hydrophobic. The Percec group is working to develop synthetic supramolecular porous structures. The group has developed a library of synthetic building blocks that includes combinations of macrocyclic, dendritic, and other primary sequences that are able to fold into well-defined conformations and also contain all the information required to control and self-repair their secondary, tertiary, and quaternary structure at the same level of precision as in biological molecules. Synthetic peptides can self-assemble to form porous and nonporous protein mimics, enabling the design of helical porous protein mimics. Protein translocation can be achieved through dendritic dipeptide hydrophobic pores.

ENGINEERING PROTEINS FOR BIOMATERIALS APPLICATIONS: PROSPECTS AND CHALLENGES

James L. Harden
Johns Hopkins University

In recent years, genetically engineered proteins have emerged as novel and potentially useful components for biomaterials. Engineered proteins are particularly attractive as building blocks for biomaterials because they are natural constituents of the body. Their tremendous potential derives from the sequence diversity possible in polypeptide systems and researchers' ability to use the tools of molecular biology and biochemistry to design and produce engineered proteins with a precisely controlled sequence. Precise control of sequence allows for control of the secondary and tertiary structure of these proteins, inclusion and presentation of bioactive polypeptides (such as ligands for cell surface receptors), and the directed assembly of these proteins at interfaces or into three-dimensional structures. In this presentation, several case studies of proteins engineered for biomaterials applications are described. These case studies are then used to highlight the strengths and challenges of the protein engineering approach and the potential for these systems in hybrid biomaterials platforms.

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Supramolecular Biomaterials Engineering and Design

NATIONAL NANOTECHNOLOGY INITIATIVE

James S. Murday
Office of Naval Research

The prospects for significant scientific discoveries and economic gain have caused investment in the development of nanometer-scale structures to grow significantly around the world. The National Nanotechnology Initiative (NNI) is a U.S. federal research and development (R&D) program established to coordinate multiagency efforts in nanoscale science, engineering, and technology. Of the 23 participating federal agencies, 11 have budgets for nanotechnology R&D. The NNI is managed within the framework of the National Science and Technology Council (NSTC), whose members, appointed by the President, are leaders in industry, academia, and government. The Nanoscale Science, Engineering, and Technology Subcommittee of the NSTC, composed of representatives of the agencies participating in the NNI, coordinates planning, budgeting, program implementation, and review to ensure a balanced and comprehensive initiative.

The goals of the NNI are to (1) maintain a world-class research and development program aimed at realizing the full potential of nanotechnology; (2) facilitate the transfer of new technologies into products for economic growth, jobs, and other public benefit; (3) develop educational resources, a skilled workforce, and the supporting infrastructure and tools to advance nanotechnology; and (4) support the responsible development of nanotechnology. As the NNI enters its fifth year, rapid progress is being made within nanotechnology and evidence is growing that nanostructures can play significant roles in medicine. This presentation provides an overview of the NNI, with specific attention to its medicine and health components, selected examples of exciting nanostructure work in medicine, and a status report on the evolving NNI strategic plan.

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NANOTECHNOLOGY AND BIOMATERIALS: VENTURE CAPITAL INVESTMENT AND EMERGING BUSINESS ISSUES

Edward K. Moran
Deloitte & Touche

Although the profile of nanotechnology is being raised by the attention it is receiving from several well-known venture capitalists and financial institutions, most venture capitalists are still not very knowledgeable about nanotechnology. Many states don't have trade associations or initiatives in nanotechnology, and setbacks for individual companies can be interpreted as proof that nanotechnology is overhyped and underperforming. However, over $40 billion in uninvested venture capital is driving the search for the next big thing, and investment in nanotechnology increased from an estimated 5 deals worth less than $20 million in venture capital funding in 1998 to an estimated 34 deals worth $300 million in 2003.[1] Between the beginning of 2001 and the end of 2003, the percentage of total venture capital funding being spent on expansion and later-stage activities as opposed to start-up/seed and early-stage activities steadily increased from less than 20 percent to over 70 percent.[2]

Biomaterials still account for less than half of nanotechnology investment, with one source estimating that only about 30 percent of venture capital investments in nanotechnology are in biomaterials companies. The idea of a blockbuster drug, device, or material has a tremendous allure for investors, but the costs and risks of investing in such technologies are also high. Emerging biomaterials companies face a variety of business issues. First, because of the novelty of these technologies, it makes sense to partner. Second, although venture capitalists are comfortable with the biotechnology model, many early-stage biomaterials companies fail when trying to move from concept to commercialization. In addition, the competition has become more complex over two dimensions: geography and industry. Other issues that affect investment include environmental concerns, competition with other countries, technology transfer, clustering best practices, and the need for a model for dealing with the export of potentially problematic technologies.

[1] *Small Times*, March 2004.
[2] Ibid.

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GLOBALIZATION: CHALLENGES FOR TRADE ORGANIZATIONS

Nik Rokop
Chicago Microtechnology and Nanotechnology Community

Nanotechnology is broad in scope, even when applied to a limited field such as biomedical materials. The success of any nanotechnology venture will be a function of the ability to interact with those in complementary fields. Researchers, companies, and trade organizations can no longer ignore the work being done in the rest of the world. Competition for resources is particularly strong in the sciences, but the benefits of collaboration outweigh its costs. This presentation provides several examples of regional efforts to facilitate international collaboration.

ENGINEERING BIOCOMPATIBLE NANOSTRUCTURES

Vicki L. Colvin
Rice University

Traditionally, nanotechnology has been driven by the growing importance of very small (diameter less than 50 nm) computational and optical elements in diverse technologies. However, this length scale is also an important and powerful one for living systems. Researchers at Rice University believe that the interface between the "dry" side of inorganic nanostructures and the "wet" side of biology offers enormous opportunities for medicine and environmental technologies, as well as entirely new types of nanomaterials. As part of their work on potential biological applications of nanomaterials, they also consider the unintended environmental implications of water-soluble forms of these materials. Given the breadth of nanomaterial systems, Rice University researchers use a carefully selected group of model nanoparticles in their studies and focus on the natural processes that occur in aqueous systems. They characterize the size- and surface-dependent transport and fate of these engineered nanomaterials and their facilitated contaminant transport. In some cases, models from larger colloidal particles can be extended to the nanometer size regime, while in others entirely new phenomena present themselves. Rice University researchers also consider the biological interactions of nanoparticles and specifically address the interactions of a classic nanomaterial, C_{60}, with cellular systems.

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BIOCONJUGATED NANOTUBES FOR BIOSENSING AND BIOSEPARATIONS

Charles R. Martin
University of Florida

Starting in the 1980s, the Martin research group pioneered a versatile method for preparing nanomaterials called template synthesis. This method entails synthesizing nanoscopic particles of the desired materials within the pores of a nanopore membrane or other solid. The Martin research group has been especially interested in template-prepared nanotubes. These nanotubes are model systems for naturally occurring protein channels (e.g., ion channels). In addition, they are developing nanotube-containing membranes for bioseparations and biosensors. The work involves the biofunctionalization of nanotubes with, for example, enzymes, antibodies, and DNA. The group is especially interested in nanotube membranes for DNA and chiral separations and in nanotube-based biosensors for proteins such as immunoglobulins and the bioterror agent ricin.

METAL NANOSHELLS: DIAGNOSTIC AND THERAPEUTIC APPLICATIONS OF NANOTECHNOLOGY

Jennifer L. West
Rice University

Nanoshells are a new type of nanoparticle with tunable optical properties. They consist of a non-conducting core (e.g., silica) and a metal shell (e.g., gold) of a desired thickness. The particle is optically tuned by varying the thickness of the shell and the size of the core. Nanoshell fabrication consists of the following steps: (1) growth of silica cores using the Stöber method; (2) coating of the core with amino propyl triethoxysilane to terminate the surface of the nanoparticle with amine groups; (3) immersion of amine-coated silica particles in a bath of small gold colloid; and (4) reduction of more gold onto the seed particles until the particles coalesce into a complete shell.

For medical applications, these particles can be designed to strongly absorb or scatter light in the near infrared, where tissue and blood are relatively transparent. In a cancer therapy application, nanoshells are designed to absorb near-infrared light and convert the energy to heat in order to destroy the cancerous cells to which they are bound. This binding is accomplished by conjugating antibodies or peptides to the nanoshell

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surfaces and results in specific and localized destruction of the tumor. A photothermally modulated drug delivery system, optically controlled valves for microfluidics devices, and a rapid whole blood immunoassay are also under development using nanoshells.

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APPENDIXES

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APPENDIX A
WORKSHOP AGENDA

Thursday, September 30, 2004

7:30 AM	Continental Breakfast
8:00 AM	Welcome and Introduction *Buddy D. Ratner, BEMA Chair*
8:30 AM	Convergent Calling: MG Biotherapeutics, a Rational Joint Venture Between the Device and Biotechnology Worlds *Stephen N. Oesterle, Medtronic, Inc.*
9:00 AM	U.S. Department of Health and Human Services' Medical Innovation Task Force *Larry G. Kessler, U.S. Food and Drug Administration*
9:30 AM	Discussion *All*
10:00 AM	Break
10:15 AM	Can Public Policy Be as Innovative as Science and Technology? Policy Challenges for Breakthrough Technologies *Susan B. Foote, Medical Technology Leadership Forum*
10:45 AM	Dialogue on Innovation and Risk *Annabelle R. Hett, Swiss Re*
11:15 AM	Discussion *All*
11:45 AM	Lunch
12:45 PM	Introduction to the Panel on Stem Cells as Biomaterials of the Future *Sohi Rastegar, National Science Foundation*

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12:50 PM	Stem Cells as Biomaterials of the Future: An Overview of Some Stem Cell Issues *Philip H. Schwartz, National Human Neural Stem Cell Resource*
1:35 PM	Propagating and Differentiating Human Embryonic Stem Cells *Steven L. Stice, University of Georgia*
2:00 PM	Cardiac Regenerative Strategies Using Hematopoietic and Human Embryonic Stem Cells *Michael A. Laflamme, University of Washington*
2:25 PM	New Tissues from Human Mesenchymal Stem Cells *Mark F. Pittenger, Osiris Therapeutics*
2:50 PM	Discussion *All*
3:20 PM	Break
3:35 PM	Introduction to the Panel on Biomolecular Materials Composites *Buddy D. Ratner, BEMA Chair*
3:40 PM	Not Merely the Secret of Life: DNA and Nanotechnology *Nadrian C. Seeman, New York University*
4:05 PM	Helical Porous Protein Mimics *Virgil Percec, University of Pennsylvania*
4:30 PM	Engineering Proteins for Biomaterials Applications: Prospects and Challenges *James L. Harden, Johns Hopkins University*
4:55 PM	Discussion *All*
5:25 PM	Engineering Biocompatible Nanostructures *Vicki L. Colvin, Rice University*

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5:45 PM	Discussion *All*
5:55 PM	Plenary Discussion *All*
6:30 PM	Adjourn to Reception

Friday, October 1, 2004

7:30 AM	Continental Breakfast
8:00 AM	Review of Day One *Buddy D. Ratner, BEMA Chair*
8:15 AM	Introduction to the Panel on Supramolecular Biomaterials Engineering and Design *Joshua J. Jacobs, American Academy of Orthopaedic Surgeons*
8:20 AM	Bioconjugated Nanotubes for Biosensing and Bioseparations *Charles R. Martin, University of Florida*
8:45 AM	Metal Nanoshells: Diagnostic and Therapeutic Applications of Nanotechnology *Jennifer L. West, Rice University*
9:10 AM	National Nanotechnology Initiative *James S. Murday, Office of Naval Research*
9:35 AM	Discussion *All*
10:05 AM	Break
10:20 AM	Nanotechnology and Biomaterials: Venture Capital Investment and Emerging Business Issues *Edward K. Moran, Deloitte & Touche*
10:45 AM	Globalization: Challenges for Trade Organizations *Nik Rokop, Chicago Microtechnology and Nanotechnology Community*

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11:10 AM	Discussion *All*
11:35 AM	Working Lunch
11:50 AM	Summary: Stem Cells as Future Biomaterials *Sohi Rastegar, National Science Foundation* *James W. Burns, Genzyme Corporation*
NOON	Summary: Biomolecular Materials Composites *Buddy D. Ratner, BEMA Chair* *Crystal M. Cunanan, BEMA Vice Chair*
12:10 PM	Summary: Supramolecular Biomaterials Engineering and Design *Sohi Rastegar, National Science Foundation* *Joshua J. Jacobs, American Academy of Orthopaedic Surgeons*
12:20 PM	Plenary Discussion *Panel of All Speakers*
1:15 PM	Concluding Remarks *Buddy D. Ratner, BEMA Chair*
1:30 PM	Adjourn

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APPENDIX B
BIOGRAPHICAL SKETCHES OF SPEAKERS AND SUMMARY AUTHORS

Vicki L. Colvin is professor of chemistry and chemical engineering at Rice University, where she has taught since 1996. In addition, she is director of the university's Center for Biological and Environmental Nanotechnology, a nanoscience and engineering center funded by the National Science Foundation. Previously, she completed postdoctoral work at AT&T Bell Laboratories. Dr. Colvin is the recipient of numerous awards for both teaching and research, including Phi Beta Kappa's Teaching Prize (1998-1999); the Camille Dreyfus Teacher Scholar Award (2002); an Alfred P. Sloan fellowship; and the Victor K. LaMer Award from the American Chemical Society for her work in colloid and surface chemistry. In 2002, she was named one of *Discover* magazine's Top 20 Scientists to Watch. Dr. Colvin is a frequent contributor to many peer-reviewed journals, including *Advanced Materials* and *Physical Review Letters*, and holds four U.S. patents.

Crystal M. Cunanan is vice president for development and operations at ReVision Optics, where her responsibilities include the development of novel biomaterials for intracorneal refractive procedures. She also provides technical input into the company's strategy, its intellectual portfolio, and its clinical and regulatory activities. Concurrently, she serves as scientific advisor to a start-up company, Arbor Surgical Technologies, where she was previously the director of operations with responsibility for establishing the manufacturing process for the company's bioprosthetic heart valve. Prior to her work at Arbor Surgical Technologies, she spent 6 years at Edwards Lifesciences and 11 years at Allergan. At Edwards, she served as chief technical expert in tissue products, processes, and materials and was responsible for developing new analytical test methods and animal implant models as well as writing U.S. and European regulatory submissions and patent applications. At Allergan, she served as project leader on numerous refractive projects in the surgical division, developed and qualified new material platforms, conducted testing required to commercialize products, and designed and executed animal toxicology studies to demonstrate product safety. Ms. Cunanan is the author of 14 U.S. patents and 13 published patent applications. She is the author or coauthor of over 20 published abstracts, articles, and book chapters. She has been active in numerous professional societies, including the Association for Research in Vision and Ophthalmology, the Surfaces in Biomaterials Foundation, the American Chemical Society, and the American Society for Artificial Internal Organs and has chaired the Industry Advisory

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Board for the Washington Engineered Biomaterials Engineering Research Center. She is a member of the NRC Committee to Review the National Nanotechnology Initiative.

Susan B. Foote is associate professor and head of the Health Services Research and Policy Division at the School of Public Health, University of Minnesota. She is the policy director of the Medical Technology Leadership Forum, a nonprofit think tank on medical technology issues, and serves on its board. In addition, she is on the board of directors of two medical technology companies. From 1990 to 1995, Ms. Foote served as a Robert Wood Johnson Health Policy Fellow and senior health policy advisor to U.S. Senator David Durenberger (R-Minn.). She has published widely in the field of medical technology and health policy and has served as an advisor to many national organizations, including the neurological devices panel of the U.S. Food and Drug Administration, the Office of Technology Assessment, the General Medicine Institute of the National Institutes of Health, the Medicare Coverage Advisory Committee of the Centers for Medicare and Medicaid Services, and to numerous projects and committees of the Institute of Medicine, the National Academy of Engineering, and the National Academy of Sciences.

James L. Harden is assistant professor in the Department of Chemical and Biomolecular Engineering at Johns Hopkins University, where he has worked since 1997. His research interests include engineered artificial proteins for biomaterials applications, the multiscale modeling of the role of the glycocalyx in microcirculation physiology and mechanical signal transduction, and the structural and rheological properties of soft materials and complex fluids. Currently, his work involves a combination of materials design, experiment, theory, and simulation. Since joining the faculty at Hopkins, he has developed programs in biomaterials, protein engineering, biophysical aspects of microcirculation physiology, and soft glassy materials. Prior to joining Hopkins, he completed postdoctoral work at Nagoya University in Japan, at the Ecole Supérieure de Physique et de Chimie Industrielles in Paris, and at Cambridge University. He is the author or coauthor of numerous publications and presentations and is associate editor of *Soft Materials*. He is active in several professional societies, including the Society of Rheology and the American Institute of Chemical Engineers.

Annabelle R. Hett is a risk expert in the Risk Engineering Services Division of Swiss Re, a global reinsurance company, where she has worked since 2002. She is in charge of Swiss Re's risk perception system, SONAR, and is involved in projects related to the identification, assessment, and communication of risk. After obtaining a degree in veterinary medicine with a thesis in

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radiology and nuclear medicine, Dr. Hett worked as a veterinarian in an equine clinic. She then joined the division for epidemiology at the Swiss Federal Veterinary Office, where she focused on bovine spongiform encephalopathy and conducted research projects in collaboration with the Swiss Reference Laboratory for Spongiform Encephalopathies in Animals. She attended further training in risk communication before joining Swiss Re.

Larry G. Kessler is director of the Office of Science and Engineering Laboratories (OSEL) at the FDA's Center for Devices and Radiological Health (CDRH). OSEL plays a crucial role in identifying key scientific questions and solutions concerning device safety and effectiveness. Since taking over as director of OSEL in 2002, when it was still the Office of Science and Technology, Dr. Kessler has overseen the efforts of the CDRH laboratories and the Standards Coordination Program. From 2001 to 2002, he was a visiting scientist at the Fred Hutchinson Cancer Research Center, working on research projects involving prostate cancer trends, the National Emphysema Treatment Trial, and studies of colorectal and lung cancer. Dr. Kessler originally joined CDRH in 1995, as director of the Office of Surveillance and Biometrics. Under his leadership, the office implemented the medical device reporting regulation for user reporting, developed a program for reducing the burden on industry caused by repetitive reporting, and completed a pilot program to develop a sentinel system for user facility reporting of adverse events. From 1996 to 2001, he served as chair of Study Group 2 of the Global Harmonization Task Force, concentrating on postmarket vigilance and surveillance. Prior to joining CDRH, Dr. Kessler served for 9 years as chief of the Applied Research Branch at the National Cancer Institute. His research has concentrated on applications of quantitative methods and health services research to problems in surveillance and public health. He has published more than 100 peer-reviewed journal articles as well as numerous book chapters and government reports.

Michael A. Laflamme is acting instructor in the Department of Pathology at the University of Washington (UW) and physician with the UW Medical Center. His current research focuses on the regenerative potential of cardiomyocytes derived from human embryonic stem cells (hESCs) in a rodent model of myocardial infarction. Dr. Laflamme completed the Medical Scientist (MD/PhD) Training Program at Emory University School of Medicine in 1999, with graduate work examining the role of b-adrenergic signal transduction and homeostasis in ventricular myocytes. He completed his residency training in anatomic pathology at UW in Seattle, with subsequent training in diagnostic cardiovascular pathology. He completed postdoctoral work in the UW Department of Pathology, investigating the potential of both endogenous and exogenous stem cells in cardiac repair. In December 2005,

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Dr. Laflamme became a principal investigator in the new UW Center for Cardiovascular and Regenerative Medicine. In addition to continuing to examine the potential of hESC-derived cardiomyocytes in rodent preclinical models of cardiac injury, his laboratory will address the electrophysiological properties of hESC-derived cardiomyocytes as well as strategies to derive specialized pacemaking and cardiac conduction system cells from hESC cultures.

Charles R. Martin is Colonel Allen R. and Margaret G. Crow Professor of Chemistry, professor of anesthesiology, and director of the Center for Research at the Bio/Nano Interface at the University of Florida. His research interests are in nanomaterials, the bio/nano interface, and bioanalytical chemistry. His research group pioneered a novel approach for preparing nanomaterials—called the template method —that is now practiced in laboratories throughout the world. He has published over 250 papers on these topics and is one of the most highly cited authors in nanotechnology. Dr. Martin was the winner of the 1999 Carl Wagner Memorial Award of the Electrochemical Society and serves on the editorial advisory boards of *Advanced Materials, Electrochimica Acta,* and *Small Times*.

Edward K. Moran is director of the tristate innovation practice of the Technology, Media, and Telecommunications Group at the New York office of Deloitte & Touche. In addition, he heads up the nanotech industry practice and is a leader of the tristate venture-capital-backed company practice. He provides clients with consultative assistance in securing financing, strategic planning, product innovation, market segmentation, competitive positioning, and industry analysis. As part of the product innovation process, he also assists clients with the identification of strategic partners and consults on the management of these relationships. Prior to joining Deloitte & Touche, Mr. Moran was managing partner of a Manhattan law firm serving technology and entertainment clients. He also cofounded a multidisciplinary consultancy that targeted high-tech and entertainment companies and was a managing director of a Manhattan investment and advisory company that specializes in technology and media investments. Mr. Moran speaks widely on the topics of product innovation, business strategy, nanotechnology, technology transfer, and the financing of technology companies. He is executive director and serves on the board of directors of the New York State NanoBusiness Alliance, the first industry association founded to advance the emerging business of nanotechnology and microsystems. He is the author or coauthor of several publications on the impact of nanotechnology.

James S. Murday is chief scientist at the Office of Naval Research and executive secretary to the U.S. National Science and Technology Council's

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Subcommittee on Nanometer Science Engineering and Technology. He joined the Naval Research Laboratory (NRL) in 1970, led the surface chemistry effort from 1975 to 1987, and has been superintendent of the Chemistry Division since 1988. From May to August 1997 he served as acting director of research for the Department of Defense, Research, and Engineering. Dr. Murday is a member of the American Physical Society, the American Chemical Society, and the Materials Research Society, as well as a fellow of the American Vacuum Society (AVS) and the Institute of Physics in the United Kingdom. For the AVS, he has served as trustee (1981 to 1984), director (1986 to 1988), representative to the American Institute of Physics' governing board (1986 to 1992), president (1991 to 1993), and representative to the Federation of Materials Societies (1998 to present). His research interest in nanoscience began in 1983 as an Office of Naval Research program officer and continues through the NRL Nanoscience Institute. He has organized numerous conferences and conference proceedings on scanning tunneling microscopy and nanoscience. Under his direction, both the AVS and the International Union for Vacuum Science, Technology, and Applications created a nanometer science/technology division.

Stephen N. Oesterle is senior vice president for medicine and technology at Medtronic, Inc., where he provides executive leadership for scientific research, formation of technological strategies, and continued development of strong cooperative relationships with the world's medical communities. Prior to joining Medtronic in 2002, he served as associate professor of medicine at the Harvard University Medical School and director of invasive cardiology services at Massachusetts General Hospital, Boston. Dr. Oesterle has been an advisor and consultant to medical device companies, financial institutions, and Internet service providers. He has international experience in clinical research and has trained many physicians in interventional cardiology, traveling widely to teach and demonstrate modern techniques in Europe and Asia. He has made more than 200 invited presentations to regional, national, or international medical symposia and workshops. Dr. Oesterle received his medical doctorate from Yale University, completed his internship and residency years at Massachusetts General Hospital, and completed a fellowship in interventional cardiology at Stanford University.

Virgil Percec is P. Roy Vagelos Chair and professor of chemistry at the University of Pennsylvania. His research experience has been directed to a wide range of fundamental issues of polymer synthesis and modification, particularly the development of new polymerization reactions and understanding reaction mechanisms. He has applied Williamson and Wittig phase-transfer catalyzed reactions to the preparation of new classes of functional polymers and sequential copolymers, as well as novel alternating block

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copolymers and liquid crystalline polyethers. His research interests include living metathesis polymerization on acetylenic monomers; a novel method for the synthesis of thermally stable polyethersulfones and polyetherketones; cyclic, hyperbranched, and dendrimeric liquid crystalline polymers; and a living radical polymerization process initiated by arenesulfonyl chlorides and metal catalysts. Most recently, his work has focused on the design of molecular-recognition-directed, self-assembled supramolecular systems and other aspects of supramolecular chemistry. He is editor of the *Journal of Polymer Science: Part A: Polymer Chemistry* and serves on the editorial boards of 11 journals.

Mark F. Pittenger is vice president for research at Osiris Therapeutics, where he has worked since 1994. Dr. Pittenger has 20 years of research experience in cellular and molecular biology and has spent the past decade leading research activities in the isolation and characterization of adult mesenchymal stem cells (MSCs). His research group has studied the differentiation of MSCs to many lineages, including cartilage, bone, fat, marrow stroma, and cardiomyocytes. The results of this research have been published in leading scientific journals and have become benchmarks in stem cell research. Dr. Pittenger served as the principal investigator for several grant awards from the National Institute of Standards and Technology and the Defense Advanced Research Projects Agency. Prior to joining Osiris Therapeutics, Dr. Pittenger was a staff associate with Cold Spring Harbor Laboratories. He completed postdoctoral work at Yale University after receiving his Ph.D. from the Johns Hopkins University School of Medicine.

Nik Rokop is president and chief executive officer of nLake Technology Partners, a management, business development, and technology commercialization group specializing in nanotechnology. In addition, he is president and a founding member of the Chicago Microtechnology and Nanotechnology Community. He has 25 years of entrepreneurial experience in engineering, manufacturing, sales, marketing, and international operations, with experience in the iron and steel industries, manufacturing, and the Internet. Mr. Rokop has lectured widely on the impact of nanotechnology and was named one of *i-Street Magazine*'s Top 100 in Technology and Economic Development in 2002. He is a founding member of the BIG Idea Forum and was the project executive on the U.S.-Israel NanoBiotechnology seminar series in 2004.

Bonnie A. Scarborough is a program officer with the National Materials Advisory Board and the Board on Manufacturing and Engineering Design of the National Research Council (NRC), where she has worked since 1995. Her responsibilities include developing and directing policy studies in

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biomedical engineering, materials science, and manufacturing. She is the project director for the Roundtable on Biomedical Engineering Materials and Applications (BEMA) and was editor of the first BEMA workshop proceedings, *Science-Based Assessment: Accelerating Product Development of Combination Medical Devices* (2004). She has served as study director for a number of NRC publications, including *Decreasing Energy Efficiency in Manufacturing* (2005), *Use of Lightweight Materials in 21st Century Army Trucks* (2003), *Defense Manufacturing in 2010 and Beyond* (1999), and *Separation Technologies for the Industries of the Future* (1998), and has contributed to many others. Previously, she worked for the Board on Environmental Studies and Toxicology at the NRC and for Hampshire Research Associates, an environmental consulting firm specializing in industrial process analysis.

Philip H. Schwartz is director of the National Human Neural Stem Cell Resource at Children's Hospital of Orange County, as well as associate research biologist at the Developmental Biology Center of the University of California at Irvine, and visiting associate professor in the Stem Cells and Regeneration Program of the Burnham Institute. Dr. Schwartz's early research included studies of models of energy-failure-induced brain damage and preclinical and clinical studies of pharmacologic agents aimed at maintaining cerebral perfusion and/or neuroprotection. For the past 8 years, he has been involved in the harvesting of human brains from patients with neurogenetic diseases, and his current research is directed at understanding the factors influencing the behavior of human central nervous system (CNS) stem cells and multipotent CNS progenitor populations in the normal and neurogenetically diseased brain. He is also interested in novel ways to derive human embryonic stem cell lines and has established neural stem cell lines from transgenic pigs and cats. Dr. Schwartz's recent manuscripts on human stem cells include techniques for the harvest and characterization of postmortem cerebrocortical neural stem cells, studies of asymmetric cell division in neural stem cells, and techniques for the harvest and characterization of postmortem neural retina stem cells. In addition, he has been involved in studies of stem cells taken from patients with the fragile X tremor ataxia syndrome, Rett syndrome, and mitochondrial disease. As principal investigator for a T15 human embryonic stem cell culture training course funded by the National Institutes of Health, Dr. Schwartz trains scientists from all over the world in current embryonic and neural stem cell techniques.

Nadrian C. Seeman holds the Margaret and Herman Sokol Chair and is professor in the Department of Chemistry at New York University, where he has taught for 16 years. His research laboratory is investigating unusual DNA molecules in model systems that use synthetic molecules. A major effort is

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devoted to DNA nanotechnology. The attachment of specific sticky ends to a DNA branched junction enables the construction of sticky figures, whose edges are double-stranded DNA. This approach has been used to assemble a cube, a truncated octahedron, nanomechanical devices, and two-dimensional crystals from DNA. Potential applications include the assembly of a biochip computer, nanorobotics, and the rational synthesis of periodic matter. Previously, Dr. Seeman worked at the State University of New York at Albany and completed postdoctoral training at Columbia University and the Massachusetts Institute of Technology. He is the recipient of numerous awards, including the Science and Technology Award from *Popular Science* (1993); the Feynman Prize in Nanotechnology (1995); the Emerging Technology Award from *Discover* (1997); and the Tulip Award in DNA-Based Computing (2004). He is a fellow of the American Association for the Advancement of Science and founding president of the International Society for Nanoscale Science, Computation, and Engineering.

Steven L. Stice holds a Georgia Research Alliance Eminent Scholar endowed chair and is professor in the Animal and Diary Science Program at the University of Georgia. In addition, he is director of the university's Regenerative Bioscience Center. He has over 16 years' experience in biotechnology research and development with a focus on developing innovative stem cell technologies for curing diseases. Dr. Stice produced the first cloned rabbit in 1987 and the first cloned transgenic calves (George and Charlie) in 1998. In 1997 his group produced the first genetically modified embryonic-stem-cell-derived pigs and cattle. This research led to publications in *Science* and *Nature*, national news coverage, and the first U.S. patents on cloning animals and cattle embryonic stem cells. In 2001, Dr. Stice announced a breakthrough in the cloning process and the first animal cloned from an animal that had been dead for 48 hours. Dr. Stice is a cofounder of five biotechnology companies, including CytoGenesis, Inc., later purchased by BresaGen. He helped BresaGen develop four of the human embryonic stem cell lines approved for National Institutes of Health funding. Dr. Stice was also a cofounder and chief scientific officer at Advanced Cell Technology, a company developing cloning and stem cell technology. He was named one of the top 40 entrepreneurs under 40 years old in Georgia (2000) and was named one of the 100 Most Influential Georgians in 2002 by *Georgia Trend*. Throughout his career he has published and lectured on cloning and stem cell technologies.

Jennifer L. West is Isabel C. Cameron Professor of Bioengineering and professor in the Chemical and Biomolecular Engineering Department at Rice University. Her research in biomaterials and tissue engineering focuses on the synthesis and development of novel biofunctional materials and on the

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use of biomaterials and engineering approaches to the study of biological problems. Her current research includes work on tissue-engineered vascular grafts, nitric-oxide-releasing polymers, and mechanisms of restenosis. She is the author or coauthor of over 60 publications and has made more than 25 presentations in the field.

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