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PRINCIPAL INVESTIGATOR: Joachim Kohn, Ph.D.
Carole Kantor
David Devore, Ph.D.

CONTRACTING ORGANIZATION: Rutgers-The State University of New Jersey
New Brunswick, NJ 08901-8559

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Joachim Kohn, Ph.D.
Carole Kantor
David Devore, Ph.D.

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Rutgers-The State University of New Jersey
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14. ABSTRACT

In order to develop a requirements document detailing the medical product needs of the military that could be enabled by biomaterials technologies, we conducted a planning conference on February 2-4, 2004 in Iselin, New Jersey. About 80 people representing the military medical enterprise, biomedical companies and academic researchers engaged in a workshop structured around the key topics of wound care, drug delivery, tissue engineering/restoration and sensors and diagnostics. The National Research Council's National Materials Advisory Board facilitated the process, and subsequently applied the highest level of scholarly and technological expertise to producing the "roadmap report" that appears in the appendix of this document. This report will provide the guidance necessary for the programs of the new Center for Military Biomaterials Research, a program of the New Jersey Center for Biomaterials.

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- CV – *David Devore, Ph.D.*
- Report – *Capturing the Full Power of Biomaterials for Military Medical Needs*

Introduction

The goal of the conference/workshop " Building a Roadmap for Biomaterials Science and Technology to Serve Military Needs" was to design a comprehensive approach to bringing new biomaterials technologies into service to fulfill the Army's medical care needs as early as possible. The conference program involved scientific, clinical and business leaders from the field of medical biomaterials as knowledge sources and guides who interacted with Army scientists, clinicians and program planners. The leading role played by the National Research Council's National Materials Advisory Board ensured a productive agenda during the workshop and a well-constructed final report. The focus areas of the report are Far Forward Wound Care, Tissue Engineering, Drug Delivery, Physiological Sensors and Diagnostics, and Technology Integration. The roadmap report, and its future updates, will guide the Army and other services in developing interactions with technology-rich companies and basic researchers in order to accelerate acquisition of biomaterials-enabled products. The roadmap report will be the fundamental guidance document for the new Center for Military Biomaterials Research.

Body

This project had a single task: to plan, conduct, and report on the workshop "Building a Roadmap for Biomaterials Science and Technology to Serve Military Needs."

Key Research Accomplishments

The key accomplishment of this project is the creation of a human and organizational nucleus for communication and planning focused on new and emerging biomaterials technologies to fulfill military medical needs. That linkage among military, academic and industrial participants offers a channel for continually verifying and updating the project plans that the workshop produced. The operation and enhancement of this organizational nucleus is the key role of the Center for Military Biomaterials Research, CeMBR, a network of academia, industry and the military that provides rapid and effective pathways for identification, development and utilization of biomaterial-based technologies and products for the military's health care needs. CeMBR has recently received its first year of funding from USAMRAA and is now embarking on the implementation of the "roadmap's" high priority projects. Rutgers has hired Dr. David Devore to be the Chief Operating Officer of CeMBR (see appendix for CV).

Reportable Outcomes

The workshop produced a National Research Council document "Capturing the Full Power of Biomaterials for Military Medical Needs." This is provided in the appendix and it includes a full agenda of the workshop and list of participants on pages 38-42.

Conclusions

This project was a necessary precursor to the creation of CeMBR by providing a broad consensus document to guide research and development of a variety of key biomaterial-based products for the military. Now that CeMBR is established, it will include in its programs annual

reviews of the "biomaterials roadmap" to ensure maximal correspondence between the military's changing needs and projects supported by CeMBR.

References

See Appendix.

DAVID I. DEVORE, Ph.D.
Department of Chemistry and Biological Chemistry
Rutgers, the State University of New Jersey
610 Taylor Rd., Piscataway, NJ 08854
devore@rutchem.rutgers.edu

RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY 2003- present
Associate Research Professor, Dept. of Chemistry, and Associate Director, NJ Center for Biomaterials

- Leadership of the newly created Center for Military Biomaterials Research
- Research on biodegradable block copolymers: self-assembly; tissue engineering scaffolds
- Technology transfer licensing negotiations and patent applications

CIBA SPECIALTY CHEMICALS 1998-2003
Vice President, Coating Effects Research, Tarrytown, NY, and Newport, DE (2001-2003)
Head, Innovation & Technology, Imaging & Coatings, Basel, Switzerland (2000-2001)
Director, Additives Division Research & Development, Tarrytown, NY (1998-2000)

HENKEL CORPORATION, Ambler, PA 1990 – 1998
Director, Organic Chemicals Research: coatings, surfactants, paper chemicals

BETZ LABORATORIES, Trevose, PA 1980 – 1989
Group Leader: Polymers for water treatment and paper chemicals

EXXON RESEARCH & ENGINEERING, Linden, NJ 1978 - 1980
Research Chemist: surface science, tribology, and polymer synthesis

HONORS, SOCIETIES, COMMITTEES

1999-2000	Chair, Ciba Additives Division Leadership Conference Organizing Committee
1998-2000	Chair, ACS Colloid & Surface Science Symposium Committee
1995	Henkel President's Award, for Value Added Service Team
1994	Founder and Chair, Henkel Polymer Technology Council
1989-94	Founder and chair, ACS – Henkel Graduate Fellowship in Colloid and Surface Chemistry
1989	Ben Franklin Partnership Grant, Betz Labs and Drexel U.
1986-89	Vice President, Cationic Flocculant Producers Assoc., SOCMA

EDUCATION

Postdoctoral Fellow and Lecturer, Dept Chemistry, U. California, Berkeley, 1976-1977
Postdoctoral Fellow, Dept. Physiology, Columbia U., NY, 1973-1976
Ph.D, Physical Chemistry, Rutgers U., New Brunswick, NJ, 1968-1973
B.S., Biological Sciences, Rutgers U., New Brunswick, NJ, 1964-1968

SELECTED PATENTS AND PUBLICATIONS

- J. McNamara, A. Gupta, D.I. Devore, "Hyperbranched Amphiphilic Polymeric Additives and Polymer Compositons with Increased Surface Energy," (Ciba) U.S. 6,444,758, Sept. 3, 2002
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Capturing the Full Power of Biomaterials for Military Medicine

Report of a Workshop

Committee on Capturing the Full Power of Biomaterials for Military Medical Needs
Board on Manufacturing and Engineering Design
National Materials Advisory Board
Division on Engineering and Physical Sciences

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500 Fifth Street, N.W.
Washington, DC 20001
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JOHN B. HOLCOMB, U.S. Army Institute for Surgical Research, Ft. Sam Houston, Texas
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ARUNA NATHAN, Ethicon, Inc., Somerville, New Jersey
JAQUES REIFMAN, U.S. Army Medical Research and Materiel Command, Ft. Detrick, Maryland
JAMES SCHEIRER, Robert Wood Johnson Medical School, New Brunswick, New Jersey
PETER P. TOLIAS, Ortho-Clinical Diagnostics, a Johnson and Johnson company, Raritan, New Jersey
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Staff

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MARTA VORNBROCK, Research Assistant

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T.S. SUDARSHAN, Materials Modification, Inc., Fairfax, Virginia
JULIA WEERTMAN, Northwestern University, Evanston, Illinois

Staff

TONI MARECHAUX, Director

Preface

This document is the result of a technology planning process undertaken by the new Center for Military Biomaterials Research and the National Academies to begin closing the gap between available biomaterials-related technologies and the military's needs. The critical first step in this process was the organization of a workshop, held in Iselin, New Jersey, on February 2-4, 2004. To ensure that the directions taken would be aligned with the military's needs, participants included 15 senior U.S. Army officers and scientists who are experts in the health care needs of warfighters. Participants also included 27 industrial scientists and business leaders who provided the state of the art in commercial biomaterial product developments. The third constituency was the 40 academicians who presented the most recent basic and applied research concepts in the field.

The principal goal of the workshop was to explore a comprehensive approach to bringing new biomaterials technologies into service to fulfill the military's medical needs as early as possible. The workshop was intended to involve scientific, clinical, and business leaders from the field of medical biomaterials as knowledge sources and guides interacting with military scientists, clinicians, and program planners. The content was intended to address both the science contributing to biomaterials-based products and the corporate culture of technology companies working in biomaterials areas.

The technology development roadmap that is detailed here is the first step for enabling the military to modify and enhance its existing research and development programs in order to take best advantage of academic-based and corporate advances in biomaterials technology. A near-term benefit of implementing this roadmap will be advances in combat casualty care through focused attention on targeted modification of emerging industrial products to increase their suitability for use on the battlefield. Through the implementation of the technology development plan articulated in this roadmap, the Army's interests will be connected with a comprehensive network of scientific leaders, core competency laboratories, and innovative companies.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's (NRC's) Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

The authors wish to thank the following individuals for their participation in the review of this report:

Pat Black, Picatinny Arsenal, U.S. Army
Gary Fischman, consultant to the biomaterials industry
Michael Helmus, Boston Scientific Corporation
Joshua Jacobs, Rush Medical College
Julie Swain, consultant to the Food and Drug Administration
Ranji Vaidyanathan, Advanced Ceramics Research, Inc.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the views expressed, nor did they see the final draft of the report before its release. The review of this report was overseen by Robert Frosch of Harvard University. Appointed by the NRC, Dr. Frosch was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee also acknowledges the invaluable contributions of Pablo Whaley, Michele Iacoletti, and Shara Williams, interns at the National Academies, in the preparation of this report. Barbara M. Boyan also greatly assisted the work of the committee through her participation in many of the committee's activities as liaison to the National Materials Advisory Board.

James M. Anderson, *Chair*
Committee on Capturing the Full Power of Biomaterials for Military Medical Needs

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Summary

Advances in biomaterials research and development offer exceptional opportunity for utilization in military medicine and biotechnology. The workshop "Capturing the Full Power of Biomaterials for Military Medical Needs" was held on February 2-4, 2004, to explore this potential. This report of the workshop provides significant information and in-depth perspectives of the presenters and participants with the overall goal of capturing the full power of biomaterials for military medical needs. This summary is intended as a guidance document for the identification of biomaterials with relevance to military medicine, the assessment of current biomaterials technology, and the enabling of new biomaterials development for unique military medical needs.

This summary document identifies many of the specialized needs of military medicine: for example, care of massive and acute trauma and the development of functional devices to aid in rehabilitation. Although not a focus of the report, it is important to understand that all of these technologies will eventually be transferred to civilian treatment of related medical problems. Thus, the development of new biomaterials technology and products will find application and utilization in both the military and the civilian marketplace.

In identifying biomaterials and their potential importance to military medicine, workshop participants considered both needs-driven and technology-driven product development perspectives. Whereas the development of biomaterials and medical devices in the past has focused on passive and noninteractive materials and devices, the future development of biomaterials and medical devices requires the development of active, interactive, and functional components. In addition to this new complexity, these new materials and devices will most likely require a systems integration approach to combine multiple functions to achieve their intended goal of better health and well-being of the soldier.

Although workshop participants were encouraged to look up to 10 years in the future, the report has as its primary focus the practical and useful near-term and mid-term applications of biomaterials in military medicine. Four areas in which enhancement of biomaterials technology and development of new biomaterials will have a major impact on acute, chronic, and rehabilitation care in military medicine are (1) wound care, (2) tissue engineering, (3) drug delivery, and (4) physiological sensors and diagnostics. The discussion and analysis of each of these areas resulted in the identification of specific needs, a vision for the future of the identified biomaterial or product, and a plan for product development that achieves the vision. The ultimate goals of each area discussed are (1) the ability of military personnel to complete their mission, (2) the ability to resolve chronic medical problems, and (3) the ultimate rehabilitation of injured military personnel.

In wound care, the discussion of new biomaterials and products focuses on injuries of warfighters at the far-forward position on the battlefield and emphasizes control of bleeding, pain, and infectious contamination. For tissue engineering, the discussion included here identifies significant biomedical areas in which repair of bone, blood vessels, and nerves are required. The vision of these advances and the requirements for such products are presented chronologically, and the report cites important milestones that can be achieved through the application of bioactive materials and tissue engineering concepts.

Drug delivery technologies crosscut all areas of the report—in wound care and tissue engineering as well as vaccine delivery against infectious diseases and functional barriers for environmental factors. Specific topics are presented with a vision of their usefulness across all of these areas. Finally, in the discussion of physiological sensors and diagnostics, an array of information is included that can be learned via sensors and other assessment tools. The real-time assessment of a soldier's physical and mental state is significant, and this knowledge may enable improved tactics and strategies to permit a soldier to complete his mission. The development of reliable physiological sensors and diagnostic products is important to ultimately accomplish the military mission.

To enable biomaterials development, new materials and processes will be required to transition ideas into products. In addition, evaluation protocols must be appropriate and adequate to allow testing of products under real-time and true environmental conditions. Because the military follows federal regulatory guidelines, many products developed for military medicine will easily find usefulness in the civilian sector. The report highlights the need to include regulatory concerns early in the planning process.

Participants in the workshop listed several outcomes anticipated as a result of capturing the full power of biomaterials for military medicine:

- Improving soldier health and well-being
- Preserving fighting strength
- Improving the benefit of medical spending
- Transfer of cutting-edge technologies into civilian medical practice
- Strengthening the biomedical technology industry
- Improving troop morale and public perception

1

Biomaterials and Their Importance to Military Medicine

Modern medicine is beginning to understand, realize, and utilize the benefits of biotechnology in health care and casualty care. Practical knowledge of the causes of human disease, biological targets for new drugs, genetic markers, and sophisticated diagnostic tests will all increase the effectiveness of medical professionals and the health and healing of everyone. Because of the highly specialized needs of military medicine,[1] it may provide unique opportunities to absorb these advances at a rapid rate. The impacts of this may be profound, as observed by the Military Health Services System 2020 study:[2]

> The study group's overall assessment is that likely developments in biotechnology will transform every aspect of military medicine over the next ten to twenty years. These developments will significantly enhance our capabilities in warzone medicine. Beneficiary care will experience a paradigm change—a fundamental change in assumptions about how to go about the process of providing health care. And enormous new capabilities will emerge for carrying out health operations other than war.

A key contributor to this revolution has been and will continue to be biomaterials. Biomaterials have been essential to such major medical breakthroughs as kidney dialysis, prosthetic heart valves, hip replacement implants, and cardiac pacemakers.[3]

A biomaterial is generally defined as any material that is used to replace or restore function to a body tissue and is continuously or intermittently in contact with body fluids.[4] Medical applications of biomaterials fall into three broad categories: (1) extracorporeal uses, such as catheters, tubing, and fluid lines; dialysis membranes/artificial kidneys; ocular devices; and wound dressings and artificial skin; (2) permanently implanted devices, such as sensory devices; cardiovascular devices; orthopaedic devices, and dental devices; and (3) temporary implants, such as degradable sutures, implantable drug delivery systems, scaffolds for cell or tissue transplants, temporary vascular grafts and arterial stents, and temporary small bone fixation devices.[5]

Biomaterials have been used since the first bark bandage was pressed onto a wound. Today, physicians worldwide implant more than 200,000 pacemakers; 100,000 heart valves; 1 million orthopaedic devices; and 5 million intraocular lenses each year. The tremendous increase in medical

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[1] National Association of Emergency Medical Technicians. 2005. Basic and Advanced Prehospital Trauma Life Support, Military Version. 5th ed. Philadelphia, Pa.: Elsevier Health Sciences Division. Prepublication data available at *http://www.phtls.net/datafiles/military5th2003sept04.pdf.* Accessed July 2004.

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[5] S. Dumitriu, ed. 2002. Polymeric Biomaterials, 2nd ed. New York, N.Y.: Marcel Dekker.

applications means the demand for new biomaterials grows by 5 to 15 percent each year.[6] The general categories of materials are as follows:

- Ceramic biomaterials, generally used for their hardness and wear-resistance in applications such as articulating surfaces in joints and in teeth as well as bonding bone surfaces in implants. They also show great promise for bone scaffolding with controlled degradation rates. Bioceramics are based on simple oxides, hydroxyapatite, calcium salts, silicate ceramics, silicate glasses, and glass ceramics, and also include ceramic-matrix composites.
- Metallic biomaterials, used for load-bearing applications, must have sufficient fatigue strength to endure the rigors of such daily activity as walking and chewing. The metals used in biological applications today are primarily titanium and stainless steel alloys for pins, plates, and bone stems.
- Polymeric materials, usually selected for their flexibility and stability, and also used for low-friction articulating surfaces. A range of synthetic biodegradable polymers has been developed, including polylactide, polyglycolide, poly(lactide-co-glycolide), poly(e-caprolactone), polydioxanone, polyanhydride, trimethylene carbonate, poly(ß-hydroxybutyrate), poly(g-ethyl glutamate), poly(DTH iminocarbonate), poly(bisphenol A iminocarbonate), poly(ortho ester), polycyanoacrylate, and polyphosphazene. A number of biodegradable polymers can be derived from natural sources such as modified polysaccharides (cellulose, chitin, dextran) or modified proteins (fibrin, casein).

Limitations to the use of biomaterials generally center on materials-body interactions such as immune response, inflammation, wound healing, blood-materials interactions, implant-associated infections, and tumor generation. More typical materials issues are also limiting factors. They include implant and tissue compatibility, biochemical and biophysical degradation, and calcification. Body chemistry remains a highly corrosive environment, and many parts of the human body undergo tens of thousands of loading and unloading cycles every day. Because of this unique array of challenges, the full potential of biomaterials has yet to be realized.

To discuss strategies to capture the full power of biomaterials for military medical needs, a key workshop was held on February 2-4, 2004. During this time, representatives from academia, government, and industry engaged in intense and far-ranging discussions. The goal of the more than 70 attendees was to plan a way forward for the applications of biomaterials to military medicine. This report is intended to find ways to leapfrog current materials development and implementation processes. If these goals are targeted by the military and scientific communities, it is anticipated that time lines to implementation will be shortened dramatically.

THE PROCESS OF BIOTECHNOLOGY ADAPTATION TO MILITARY NEEDS

Advances in biomaterials technologies today are driven by the federally funded research of university faculty and by the commercial interests of biomedical companies.[7] Although many of the discoveries and products emerging from these endeavors have some potential for military use, military needs are not typically a factor in research and development processes at an early enough stage to influence them. In particular, a large proportion of medical product research and development in the civilian sector is directed toward chronic diseases, whereas much of the military's unmet needs relates to trauma and acute diseases. Workshop attendees noted that in spite of the extremely large civilian biomaterials

[6] Glacier Valley Medical Education. 2002. History of Medical Discovery. Available at *http://www.glaciermedicaled.com/history/hxmed01c.html.* Accessed July 2004.
[7] H. Kelly. 2001. DARPA's beachhead in biomedical research. Academic Medicine 76(12):1178-1180.

research and development budget, the military's biomaterials needs have not been met in an optimum fashion.

Recognizing that biotechnology advances would be as important in the twenty-first century as information technology advances were in the twentieth century, the Army commissioned the National Research Council (NRC) to help it plan in taking the fullest possible advantage of biotechnology developments. In 2001, the NRC issued the report *Opportunities in Biotechnology for Future Army Applications.*[8] This report provided specific recommendations relating to biomaterials for tissue engineering and for therapeutics, including drug delivery systems. In addition, the report stated that the area of medical biomaterials had not been covered adequately there and that further assessment would be required to determine its importance to the military.

That earlier report identified weaknesses in the Army's research approach to providing biomaterial solutions to improve soldier well-being and made the following key recommendations:

- The Army should adopt new approaches toward commercial developers to accommodate cultural differences between the government and the biotechnology industry.
- The Army should develop a cadre of science and technology professionals capable of translating advances in the biosciences into engineering practice.
- The Army should conduct a study focusing on future biomedical applications, including biological implants, biocompatibility, and medical biomaterials and their implications for future military operations.

Attendees at this workshop noted that current military support of biomaterials-related research is distributed over a variety of projects ranging from organic and inorganic prostheses to tissue banking. Within this decentralized structure, the rapidly expanding portfolio of military biomaterials-related projects may be missing important opportunities for interdisciplinary collaborations and industry-academia interactions. The military could therefore benefit from a coordinated vision for advancing its needs emerging biomaterials technologies.

Tissue engineering technology is critical to combat casualty care and injuries suffered in terror attacks. Drug and vaccine delivery systems are also important for preventive care and soldier well-being. The design and development of such products for the military requires a full range of scientific expertise, clinical input, and technological capability. Specifically, the following research areas are centrally important and represent a starting point for the development of a comprehensive, coordinated resource: polymer science, biomaterials science, biocompatibility, self-assembly of materials, molecular recognition, extracellular matrix biology, cell biology, and developmental biology. In addition, the military must access a number of core competencies to successfully develop and deploy these new products. They include biomaterials design; advanced methods of synthesis, characterization, processing, and fabrication; drug delivery technologies; cell and stem cell technologies; and in vitro and in vivo model development for preclinical performance evaluations.

THE STATUS OF BIOMATERIALS RESEARCH AND DEVELOPMENT

Ongoing advances in our understanding of cell biology and wound healing are creating opportunities for the use of degradable, biocompatible materials in unprecedented ways. The biomedical research community is creating a paradigm shift in the treatment of trauma and aging-related tissue loss. Instead of using permanently implanted prostheses to replace damaged tissue, surgeons in the future may implant a regenerative, temporary scaffold that enables the body to heal itself.

[8] National Research Council. 2001. Opportunities in Biotechnology for Future Army Applications. Washington, D.C.: National Academy Press.

The selection of biomaterials is fundamental to the design and development of regenerative medicine and drug delivery therapies. Whereas the classical selection criterion for a safe, stable implant dictated choosing a passive, inert material, it is now understood that any such device will elicit a cellular response. Therefore, it is now widely accepted that a biomaterial must interact with tissue rather than act simply as a static implant. Thus, the principal criterion for biomaterials performance becomes a desirable, controlled cellular response. Consequently, a major focus of research on biomaterials centers on the control of cellular interactions with artificial material and the surrounding living tissue.

The imagination of biomedical engineers and clinicians and advances in biology have outpaced the ability of materials scientists to provide the new generation of biomaterials that is critically needed for full clinical implementation of the tissue engineering approach. While biomedical engineers speak about resorbable polymer scaffolds that promote a variety of regenerative therapies, simple copolymers of lactic and glycolic acids remain the most commonly used scaffolding material in all tissue engineering research. Reviews of tissue engineering advocate the use of increasingly complex monomers, monomer combinations, polymer structures, and polymer blends that are meant to facilitate the design, synthesis, and fabrication of novel materials with properties tailored to specific biological needs and clinical applications. In reality, the widely used glycolic and lactic acids are the simplest of all hydroxy acids, there are very few polymers under consideration that have complex monomer structures, and current approaches to tailor the properties of polymers to specific applications are based mostly on trial and error.

Similar challenges exist for the fabrication of bioceramics. Novel gelforming processing has the potential for rapid and cost-effective fabrication of net shape ceramics and ceramic microcomponents. Automated rapid fabrication of net shape ceramics via green machining shows promise, and the potential has also been proposed for desktop fabrication of bioceramics for orthopaedic and dental implants. Additional challenges for small-scale forming of materials include micropatterning and assembly of colloids and thin films, low temperature growth of one-dimensional oriented nanoscale arrays, development of nanofibers for structural and functional applications, and vapor deposition of bioactive coatings for metals and ceramics.

Discussion of science related to biopolymers dominated the workshop discussion at times, because many attendees felt that the newest advances in polymers offer great promise for major advances in military medicine. The reasons for the slow progress toward an appropriate pool of candidate polymers are the scientific community's limited abilities to (1) characterize and quantify the properties of structurally complex bio-relevant materials, (2) control cell-material interactions, and (3) fabricate in a cost-efficient way graded scaffolds with truly engineered and reproducible pore architecture and surface properties.

While the application of biomaterials to military medical needs poses a number of similar technical challenges, the nontechnical aspects, especially regulatory requirements, of biomaterials may be more difficult to overcome. The 1976 medical device amendments to the Federal Food, Drug, and Cosmetic Act[9] require that all new biomaterials used in applications (or existing biomaterials used in new applications) that are life-sustaining or involve significant risks to patients must undergo premarket approval to establish their safety and effectiveness. Materials must be biocompatible within the environment in which they are used, and a material must perform its intended function safely and effectively in that environment. Clinical trials involving both animals and humans are also part of the approval process.[10] Clinical trials are costly and time-consuming, and are generally frustrating to materials scientists who have come to rely on accelerated testing and other science-based methods. While regulation has a clear role in ensuring patient safety, these regulatory and legal constraints are understood by many to inhibit innovation in biomaterials and medical devices. Many at the workshop observed the importance of optimizing the regulatory process so that an appropriate balance is achieved between innovations to improve patient health and avoiding risks to patient safety.

However, progress has been slow. Although it is important for the biomedical community to have a wide range of biomaterials options available, over the last 40 years only five fundamentally new,

[9] U.S. Code, Title 21, Chapter 9. Available at *http://www.access.gpo.gov/uscode/title21/chapter9_.html*. Accessed July 2004.
[10] H.R. Piehler. 2000. The future of medicine: Biomaterials. Materials Research Society Bulletin (August):67-70.

TABLE 1.1 Synthetic Degradable Polymers in Clinical Use

Date of First Routine Clinical Use	Polymer	Chemical Structure of Polymer Backbone
1969	Poly(glycolic acid)	Ester
1971	Lactide-glycolide copolymers	Ester
1982	Polydioxanone	Ester
1996	Polyanhydride	Anhydride
1998	Acrylate-terminated poly(lactide)-poly(ethlene glycol)	Ester

synthetic, degradable polymers have reached wide clinical use in the United States. As shown in Table 1.1, the rate of entry of new, synthetic polymers into clinical use has historically been about one per decade. In fact, the data illustrate that development efforts for biomaterials in the past were not only too slow but also did not result in a sufficient diversity of chemical structures. A 1995 National Institutes of Health (NIH) workshop[11] concluded that the slow rate of biomaterials development may be a bottleneck in the clinical implementation of (1) support devices for new tissue growth; (2) prevention of cellular activity (where tissue growth, such as in surgically induced adhesions, is undesirable); (3) guided tissue response (enhancing a particular cellular response while inhibiting others); (4) enhancement of cell attachment and subsequent cellular activation (e.g., fibroblast attachment, proliferation, and production of extracellular matrix for dermis repair); (5) inhibition of cellular attachment and/or activation (e.g., platelet attachment to a vascular graft); and (6) prevention of a biological response (e.g., blocking antibodies against homograft or xenograft cells used in organ replacement therapies). Several workshop presentations focused on the need for a more coordinated path for new technology development and application in this field.

SCIENCE AND TECHNOLOGY ROADMAPS—PRECEDENTS

Technology roadmaps provide an effective framework for focused product development by highlighting technology gaps that limit the translation of product concepts to market reality. The classic example of such a roadmapping effort is that used by the semiconductor industry to direct technical activities for the past 25 years. Roadmaps in this field have focused research and development efforts in the chip industry to stay on the predicted information density curve, allowing the computer hardware and software industries to develop products in anticipation of a technology's becoming available. The rapid growth of the computer industry over the past two decades bears witness to the utility of roadmaps.

This strategy has demonstrated that the coupling of product vision to technical reality can be an effective tool to drive market development. Technology roadmaps can direct the application of technical resources to achieve defined market goals, providing a critical path time line to translate the current technological state of the art to needed future products. Over the past decade, many other industries have embraced the technology roadmap concept, leading to a proliferation of roadmap models available for study. Examples include the electricity technology roadmap,[12] the national electronics manufacturing series of roadmaps,[13] and the many technology roadmaps for energy-intensive industries developed under the auspices of the Department of Energy Office of Industrial Technology.[14] The organization of its technology roadmap for the petroleum industry, published in 2000, is a particularly useful model for the construction of a technology roadmap for a complex, multiproduct industry.

[11] National Institutes of Health. 1995. Workshop on biomaterials and medical implant science: Present and future perspectives. October 16-17. Available at *http://odp.od.nih.gov/biomaterials/report.html*. Accessed July 2004.

[12] The Electric Power Research Institute sponsored this effort beginning in 1999; available at *http://www.epri.com/corporate/discover_epri/roadmap/*. Accessed July 2004.

[13] The National Electronics Manufacturing Initiative roadmapping overview is available at *http://www.nemi.org/roadmapping/index.html*. Accessed July 2004.

[14] Several industry roadmaps developed by the Department of Energy Industrial Technologies Program are available at *http://www.eere.energy.gov/industry/technologies/industries.html*. Accessed July 2004.

The production of a useful technology roadmap requires an understanding of a range of technical and nontechnical issues, including the current science and technology; future performance targets; technical, institutional, and market barriers; and research and development needs.

FINDING A PATH FORWARD

This document is intended to aid the technology planning process undertaken by the new Center for Military Biomaterials Research and the National Research Council to begin closing the gap between available biomaterials-related technologies and the military's needs. The technology development roadmap elements detailed in Figure 1.1 describe the first step in enabling the military to modify and enhance its existing research and development programs in order to take best advantage of academic-based and corporate advances in biomaterials technology.

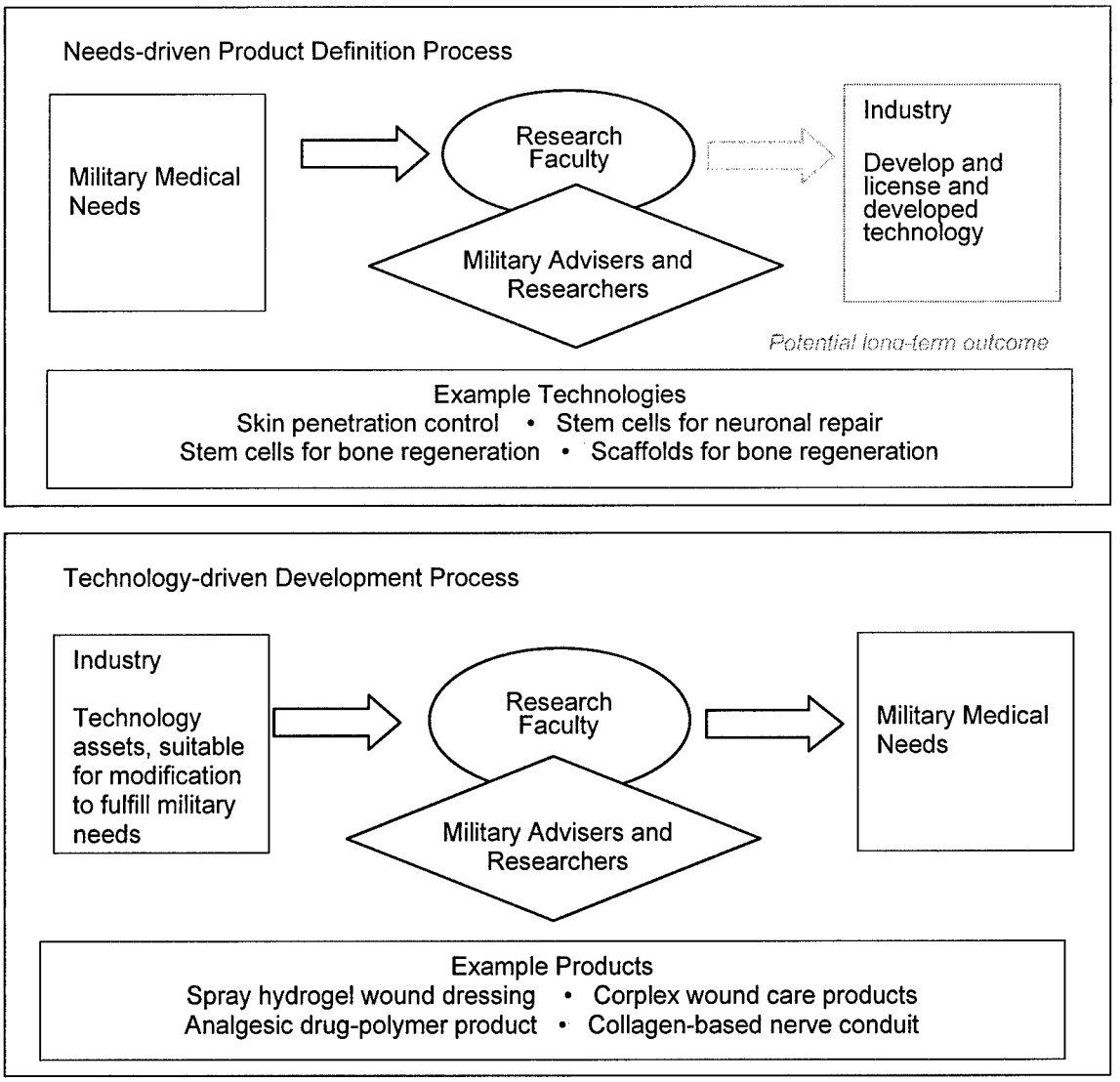

FIGURE 1.1 Schematic of the differences between a needs-driven process and a technology-driven process.

A critical first step in this process was the workshop, held in Iselin, New Jersey, on February 2-4, 2004. To ensure that the directions taken would be aligned with the military's needs, participants included 15 senior U.S. Army officers and scientists who are experts in the health care needs of the warfighter. Participants also included 27 industrial scientists and business leaders who provided knowledge of the state of the art in commercial biomaterial product developments. The third constituency was the 40 academicians who presented the most recent basic and applied research concepts in the field.

A near-term benefit of implementing this roadmap will be advances in combat casualty care through focused attention on targeted modification of emerging industrial products to increase their suitability for use on the battlefield. Application areas addressed by workshop participants included wound care, hemostasis, and healing agents; prophylaxis for exposure to chemical and biological warfare agents; tissue regeneration applications in orthopaedic, vascular, and neural systems; agent and vaccine delivery; sensors; and diagnostics.

All speakers at the workshop were in the plenary sessions and those are referenced throughout the report. Much of the focused discussion took place in the breakout sessions, which are referenced in their respective sections of Chapter 2. Each of the breakout sessions commented on its specific topic, but all also noted specific materials development issues. These had many commonalities and are described in Chapter 3. For the research area directorates (RADs) within the Army's Medical Research and Materiel Command, the roadmap will be:

- Highly relevant to many efforts of the Combat Casualty Care Research Program (RAD2) in terms of delivery of immediate far-forward and en route care for soldiers; implants to address musculoskeletal and cardiovascular injuries; and techniques or technologies to improve the acquisition and availability of blood products;
- Relevant to the Military Infectious Diseases Research Program (RAD1) in terms of delivery systems for vaccines and drugs; and
- Relevant to the Medical Chemical and Biological Defense Research Program[15] in terms of products to enhance a medical defensive posture, such as protective clothing or sprayable films based on biomaterials and delivery systems for vaccines and drugs against biological threat weapons.

[15] Formerly RAD4, now overseen by the Defense Threat Reduction Agency.

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Biomaterials Technology Assessment and Roadmapping

The workshop began with a number of presentations on both the military needs and the state of the art in biomaterials research, development, and application. Workshop attendees then separated into groups to address the various aspects of biomaterials development. They looked at outcomes and goals and assessed the development steps needed to accomplish them. Finally, each group discussed barriers to success. The following sections summarize their discussions.

FAR-FORWARD WOUND CARE

As the size of the U.S. armed forces decreases,[1] it becomes more important to allow wounded soldiers to remain functional on the battlefield and, if that is not possible, to treat wounded soldiers and return them to duty as quickly as possible. Products that will allow a soldier to complete his mission before the need for evacuation are becoming extremely important to today's fighting force.

A variety of wounds are incurred in battle, and they can be categorized as follows: Abrasions are generally caused by scraping of the skin's outer layers; incisions are cuts commonly caused by knives, metal edges, or other sharp objects; lacerations are jagged, irregular cuts or tears of the skin; punctures are caused by an object piercing the skin layers, creating a small hole; and burns cause damage to skin cells that may vary greatly in depth, size, and severity. Many wounds in the field include all of these forms of trauma, and many are severe to the point that tissue is torn away from the body or entire limbs are amputated.

Wounds have also been categorized by their severity, depth, and chronicity, and each category has its own standards of care. However, the principles of cleanliness, wound covering, tissue apposition, and protection from physical trauma while tissues return to their normal physiological state apply to all wounds.

Even minor wounds have the potential to incapacitate a soldier in battlefield conditions. Products for far-forward wound care have as their principal goal the rapid stabilization and return to function of wounded soldiers, thus enabling them to complete their mission. Members of the breakout session listed the characteristics of an ideal wound care product as follows:

- Can be self-administered or be easily applied by a medic or colleague;
- Can be rapidly applied;
- Acts rapidly and is functional from the moment of wound or tissue contact;
- Reduces blood loss;
- Reduces infection;
- Inhibits or reduces contamination;

[1] Edward F. Bruner. 2004. Military forces: What is the appropriate size for the United States? Congressional Research Service Report No. RS21754. Available at *http://www.fas.org/man/crs/RS21754.pdf.* Accessed July 2004.

- Provides pain control at the wound site only with no systemic effects; and
- Has minimum mass (load) and volume.

Ideal products would be multifunctional, in that they could simultaneously control bleeding, protect against bacterial infection or contamination, control pain at the wound site, and provide for adequate wound sealing or closure. Reducing the cube, or the volume of the product in the soldier's pack or in a shipping container, is also very important, meaning that spray- or paint-on products that can control and stop bleeding would be highly desirable. Finally, workshop participants added that the ideal product would be packaged in a durable, nonbreakable, sealed package or container that would permit easy access and application.

Bleeding Control and Wound Closure

Current bandages are made of gauze and are often applied in conjunction with an elastic bandage. They allow the wound to breathe but are not good barriers to subsequent contamination. They also do not have any antimicrobial properties and cannot stop serious bleeding. New bandages have been developed recently made of natural chitosan and fibrin materials. Several presentations at the workshop discussed the benefits of these bandages in the field. Although both types of bandage are clearly more effective, they are relatively expensive, with the fibrin costing as much as $1,000 per bandage.[2] Members of this breakout session expressed the need for an improved bandage that is antimicrobial, is resistant to subsequent infection and contamination, and can stop massive hemorrhage. In addition, a bandage that can protect large surface area wounds from subsequent contamination and at the same time reduce pain and infection would be of great value. The aim of this product would be to allow soldiers to complete their mission before they have to be evacuated for further treatment.

Superficial wounds currently are closed primarily with sutures. Suturing requires a moderate level of training by the health care provider as well as suturing instruments, sutures, and local anesthesia. A way to glue these injuries closed such that sutures and anesthesia would not be required would be of great value. Workshop attendees pointed out that cyanoacrylate glues have received regulatory approval for limited use but are not used routinely for external wound closure.

Fracture Care

Fracture care at the far-forward position offers unique challenges given the incapacitation of the wounded soldier. Currently if a limb is fractured, wooden splints are applied with cravats or aluminum splints are applied with elastic bandages. Neither technology leaves much functionality in the fractured limb, and often the soldier is not able to complete the mission. This is especially the case for leg fractures where the soldier not only is incapacitated but also becomes an evacuation burden to the unit. A limb stabilization system is needed that would allow a soldier to complete a mission or, at a minimum, reduce the impact of the injury on the unit's mission. To accomplish this, some workshop attendees suggested that the system should incorporate ultralightweight and strong materials and that an ideal product would weigh less than a pound and be able to be applied very quickly by a medic.

Pain Control

Currently, severe pain is controlled by morphine. Use of this drug results in complete incapacitation of the patient, which means that the patient is no longer able to help with his or her own care or defense. Morphine also depresses respiration and heart rate, which can be dangerous with some injuries and lethal if it is not administered properly. Breakout session members indicated the need for a safe, effective replacement for morphine that can both be easily and quickly applied and have immediate effect. It is

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[2] J. Whittle. 2003. Medics armed with new technology. Air Force Link. Available at *http://www.af.mil/news/story.asp?storyID=31003821*. Accessed July 2004.

important that this drug have minimal psychoactive effects so that patients can continue to assist in their own care, evacuation, and defense. Preferably, this drug would act only at the wound site and not systemically.

Measures of Success

Many synthetic and natural materials have been investigated for treating wounds.[3] Such materials include biodegradable polymers or modified materials that slowly release such potentially beneficial medicines as blood-clotting agents, growth factors,[4] or agents that induce blood vessel creation. Although there has certainly been progress, wound healing remains difficult for a number of reasons. This is especially true in the field, where conditions include dirt and other contaminants, sweat and other bodily fluids, and severe time constraints that may necessitate moving the injured soldier prior to stabilizing the wound. All of these things mean that traditional bandages are generally less than effective.

New materials are needed that can arrest blood loss, impede infection, counteract shock, and foster biological regeneration. Such materials will have to be multifunctional, providing structural support for large wounds, pressure on wounds that require compression, and the ability to carry medicines where and when they are needed.

A number of metrics were suggested by the wound care breakout session members, including the following:

- A wound care system that combines wound cleaning, wound closure, infection control, and pain management;
- Effective and cheap bandages that cost 10 percent of the cost of advanced bandages in current use; and
- Ultralightweight splints that weigh less than a pound and can be applied in less than a minute.

TISSUE ENGINEERING

When a wound is very severe, much more than battlefield medicine is required. A critical need exists in the military for effective methods to repair injuries to muscle and bone structure. Army personnel at the workshop who had only recently returned from the field stated that more than 70 percent of combat-inflicted injuries damage muscles and bones in the limbs, head, or face. This heightened percentage was partially attributed to the efficacy of new ceramic body armor that prevented many immediately life-ending injuries.[5-8]

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[3] L. Germain and F.A. Auger. 1995. Tissue engineered biomaterials: Biological and mechanical characteristics. Pp. 699-723 in Encyclopedic Handbook of Biomaterials and Bioengineering, Part B: Applications, Vol. 1, D.L. Wise, ed. New York: Marcel Dekker.

[4] There is an inevitable gap between in vitro phenomena that occur under carefully controlled conditions, such as ideal concentrations of growth factors that have predictable effects on selected cell lines, and practical situations that involve the complex of mammalian systems and a plethora of different growth factors (both stimulatory and inhibitory) in environments complicated by infection, tissue necrosis, and external extremes. Although several angiogenic growth factors have been identified, controlling their activity in vivo remains elusive, probably because we lack understanding of the extracellular milieu of growth factors in vivo. Although the sources of growth factors have been identified (e.g., endothelial cells, macrophages, fibroblasts), the mechanisms that stimulate their controlled release and the three-dimensional ultrastructure in which they naturally reside are not well understood. It should therefore not be surprising that growth factors attached to synthetic polymers such as polylactic acid and Marlex mesh are not particularly effective. Similarly, bioartificial membranes comprised of selected molecules, such as hyaluronic acid or purified Type I collagen laced with a variety of growth factors, usually fail to produce the desired effect in clinical situations. As discussed in National Research Council. 2003. Materials Research for 21st Century Defense Needs. Washington, D.C.: The National Academies Press, pp. 201-204.

[5] J.M. Uhorchak and W. Rodkey. 1992. Casualty Data Assessment Team Operation Desert Storm. San Francisco, Calif: Letterman Army Institute of Research Report No. 121.

[6] R.F. Bellamy, P.A. Maningas, and J.S. Vayer. 1986. Epidemiology of trauma: Military experience. Ann. Emerg. Med. 15:1384-1388.

Severe trauma may be only a small percentage of medical care dispensed in the United States, but it is typical of wounds encountered on the battlefield, and both present unique challenges to the medical community. To address the dual need to treat muscle and bone injuries, workshop participants cited the need for suitable biomaterials to replace the damaged tissue and bone, to restore structure and load-bearing capacity, and to facilitate healing. Breakout group members concluded that if the military can provide effective treatment for these potentially debilitating types of injuries, injured combat personnel will benefit from higher morale, will be able to return to duty more rapidly, and will retain greater physical function.

Although there are civilian applications for many types of medical biomaterials, the military has a particular interest in developing solutions to the problems posed by battlefield-induced trauma. This level of interest cannot exist in an entirely commercial or academic environment. The military makes excellent, civilian-quality health care facilities available to the injured warfighter, but to have treatment programs that match the military's needs outside the civilian sector, some workshop attendees believed that the military must take an active role in their development. Tailoring treatment for injuries to the needs of a military environment means that newly developed technologies must address either the need to perform some operations in challenging conditions outside a sterile operating room or the need to treat the types of injuries military personnel, as opposed to civilian personnel, tend to encounter.

Currently, military medical personnel are skillfully transferring existing civilian technologies to therapies suitable for battlefield conditions. Breakout group participants cited a number of treatment methods including repairing skeletal structure by grafting pieces of living bone removed from other locations onto the patient (autografts) or by grafting dead bone from cadavers (allografts). Surgeons have also used bone substitutes such as various calcium phosphate materials, calcium sulfate, collagen, hyaluronan, chitosan, chondroitin sulfate, synthetic polymers (polylactides, polyglycolides, polyethylene glycol, etc.), and metal prostheses.

Both inside and outside the military, a common problem exists in the choice of the best treatment technology. That is, doctors have difficulty obtaining independent and objective advice about how to select the best materials for a particular medical procedure. Participants in the workshop recommend that a clearinghouse be quickly established to independently evaluate the merits and potential problems associated with each existing or proposed material and technology in the context of its likely applications. They suggested that the results of these evaluations, along with grades for each material in relevant applications, be published and available to surgeons. There exists a wide variety of materials that can be used to replace or repair bone in the body, and independent advice from such a clearinghouse can greatly aid surgeons in comparing the relative merits of available state-of-the-art technologies.

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[7] R.L. Mabry, J.B. Holcomb, A.M. Baker, C.C. Cloonan, J.M. Uhorchak, D.E. Perkins, A.J. Canfield, and J.H. Hagmann. 2000. United States Army Rangers in Somalia: An analysis of combat casualties on an urban battlefield. Journal of Trauma—Injury Infection and Critical Care 49(3):515-528; discussion 528-529. Reproduced in J. Spec. Op. Med. 2001; 1(3):24-40. This study was undertaken to determine the differences in injury patterns between soldiers equipped with modern body armor in an urban environment compared with soldiers in the Vietnam War. *Methods*: From July 1998 to March 1999, data were collected for a retrospective analysis on all combat casualties sustained by United States military forces in Mogadishu, Somalia, on October 3, 1993. This was the largest and most recent urban battle involving United States ground forces since the Vietnam War. *Results*: There were 125 combat casualties. Casualty distribution was similar to that of Vietnam; 11 percent died on the battlefield, 3 percent died after reaching a medical facility, 47 percent were evacuated, and 39 percent returned to duty. The incidence of bullet wounds in Somalia was higher than in Vietnam (55 percent vs. 30 percent), whereas there were fewer fragment injuries (31 percent vs. 48 percent). Blunt injury (12 percent) and burns (2 percent) caused the remaining injuries in Somalia. Fatal penetrating injuries in Somalia compared with Vietnam included wounds to the head and face (36 percent vs. 35 percent), neck (7 percent vs. 8 percent), thorax (14 percent vs. 39 percent), abdomen (14 percent vs. 7 percent), thoracoabdominal area (7 percent vs. 2 percent), pelvis (14 percent vs. 2 percent), and extremities (17 percent vs. 7 percent). No missiles penetrated the solid armor plate protecting combatants' anterior chests and upper abdomens. Most fatal penetrating injuries were caused by missiles entering areas not protected by body armor, such as the face, neck, pelvis, and groin. Three patients with penetrating abdominal wounds died from exsanguination, and two of these three died after damage control procedures. *Conclusions*: The incidence of fatal head wounds was similar to that in Vietnam despite modern Kevlar helmets. Body armor reduced the number of fatal penetrating chest injuries. Penetrating wounds to the unprotected face, groin, and pelvis caused significant mortality. These data may be used to design improved body armor.

[8] J. McBride, Jr., and M. Hunt. 1991. Report and Medical Analyses of Personnel Injury from Operation "Just Cause." San Francisco, Calif.: Letterman Army Institute of Research Report No. 86.

Desired Future Vision

To provide an overview of possible future directions for biomaterials in tissue engineering, it is useful to consider three time frames:[9]

1. The past: removal of tissues
2. The present: replacement of tissues
3. The future: regeneration of tissues

Some workshop participants believed that the ultimate goal for military applications of tissue engineering is to have the capacity to routinely regenerate functional limbs, organs, and tissue that have been damaged by injuries sustained on the battlefield. The critical need for tissue, limb, and organ replacement technologies is illustrated by the fact that 71 percent of battlefield injuries cause damage to the muscular and skeletal systems and 13 percent cause damage to the head and face.[10] The capacity to heal these types of injuries would improve the long-term quality of life for those warfighters who are injured and could better enable their return to duty. Current efforts have made some incremental steps toward providing the injured with prostheses that have some useful functions, but the present state of technology does not restore the former capacity of the body for physical performance or provide the appearance or structure of the natural limb or tissue.[11]

Aside from the goal of developing techniques for the actual regeneration of damaged tissue, organs, or limbs, another goal would be to develop a way to attach or implant a rudimentary replacement structure at the location of the injury. The rudimentary structure could serve as scaffolding that would then gradually be modified or replaced by the body itself so the new tissue could take on its natural structure and function.[12] For example, a development of this proposed technique could include further progress on the use of resorbable materials that can degrade over time and be replaced with natural tissues. Workshop attendees pointed out that in practice, it would be desirable to ensure that the rate at which the body degrades this artificial material would match the rate at which the body manufactures its natural replacement.

Another approach mentioned was the use of biological self-replicating materials. These systems could quickly integrate living cells into synthetic scaffolds for generation of tissue (skin or muscle) at the wound site.[13] A further alternative would be to develop permanent artificial replacements for injured limbs, organs, or tissue that, unlike current technologies, restore full function and integrate fully with existing bone, structure, and tissue.

There was agreement among breakout session members that achieving any or all of these solutions for the repair of severe tissue injuries will require the development and understanding of new biomaterials. It will also require better control of the properties of interfaces between natural and artificial materials. The success of a treatment method will depend on its ability to balance its interface requirements with surrounding material with its needs for structural function.

Although repair of large-scale injuries, even in the presence of complicating infections, is potentially the most significant, long-term goal for progress in this field, there is also a need to develop of treatments for smaller-scale, less devastating injuries. Finding effective treatment methods for small injuries will be an independently useful and incrementally necessary step. Development of small-scale treatments is a practical near-term problem. Breakout session members pointed out that understanding how to make

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[9] L.L. Hench. 1998. Biomaterials: A forecast for the future. Biomaterials 19:1419.

[10] R.F. Bellamy, P.A. Maningas, and J.S. Vayer. 1986. Epidemiology of trauma: Military experience. Ann. Emerg. Med. 15:1384-1388.

[11] E. Bell. 2000. Tissue engineering in perspective. Pp. xxxv-xl in Principles of Tissue Engineering, 2nd ed., R.P. Lanza, R. Langer, and J. Vacanti, eds. San Diego, Calif.: Academic Press.

[12] G.D. Gentzkow, S.D. Iwasaki, K.S. Hershon, M. Mengel, J.J. Prendergast, J.J. Ricotta, D.P. Steed, and S. Lipkin. 1996. Use of Dermgraft, a cultured human dermis, to treat diabetic root ulcers. Diabetes Care 19(4):350-354.

[13] S.G. Zhang. 2002. Emerging biological materials through molecular self-assembly. Biotechnology Advances 20(5-6):321-339.

repairs on a small scale will improve our overall ability to repair larger areas of fractured bone, heal larger burns, and prevent scarring.

To achieve progress in biomedical materials for the military, members of the scientific and medical community will have to collaborate in a multidisciplinary environment. This was clear from a quick assessment of the backgrounds of breakout session members as well. Applying any new technologies and developing usable products will also require ongoing, active cooperation between members of commercial, academic, regulatory, and military organizations. Interactions with field surgeons and physicians will also be critical to success. Workshop participants expected that the example of the diverse organizations they represent would establish a precedent for future interorganizational collaborations in this field.

In addition to interorganizational collaboration, the process of developing the necessary technology to heal and repair battlefield injuries will require the participation of members of diverse scientific disciplines. Materials scientists; developmental and microbiologists; biochemists; and trauma, neural, vascular, and orthopaedic specialists can all contribute fundamental understanding to the task of improving existing technology and discovering new materials and methods. Some workshop attendees believed that only a team approach could realize the full potential of new technology for the warfighter.

Certain areas of potential development were identified by participants as crosscutting and enabling technologies. These technologies have applications in any of several possible solutions to the general problem of healing and repairing injuries, regardless of the ultimate choice of injury repair technology, whether it is regeneration, resorption and replacement, or an artificial prosthetic. Examples cited included wound-healing enhancement, scar mitigation, infection control and its elimination, and high-throughput assays. Even general methods and techniques for facilitating seamless interactions among academics, corporate developers, and clinical personnel were considered by some attendees to be a necessary enabling technology.

Several participants indicated that the end result of implementing this vision for the future must be the design and development of an effective and practical treatment method useful to military surgeons. The availability of a practical and functional suite of products could have a revolutionary impact on the care of injured warfighters, allowing military personnel to benefit from enhanced recovery, decreased infections, rapid return to duty, restoration of form and function, active participation in work and society, and an enhanced sense of well-being and confidence.

Goals for Achieving the Vision

The tissue engineering group identified three necessary pathways for biomaterials technology development: neuronal, vascular, and orthopaedic. Each of these pathways has some goals in common with other pathways, along with some unique technological demands. The goal of the group's discussion was ultimately to integrate progress in all three of these pathways with progress in other enabling technologies to lead to the production of fully functional replacement tissue, limbs, or organs.

At the workshop, breakout group participants laid out a time line that recognizes the existing technological challenges, the current rapid rate of progress in this field, and the critical need of the military for improved treatment plans.

Bone and Muscle Repair

Discussion at the workshop on the topic of bone and muscle repair benefited from the presence of a large depth of experience in this field. The description by several presenters of the prevalence of combat-induced injuries that affect the bone and muscle system and the resulting need for orthopaedic treatment was also an important driving force behind the significant focus on this topic in the roadmap.

Workshop participants believed that there was potential for near-term success in the development of bone void-fillers. These are materials that can be injected into existing voids to replace bone structure, catalyze regeneration of missing bone, or deliver therapeutics to promote healing or prevent infection.

Participants viewed these types of treatment as relevant and practical to develop immediately, and early versions are likely to be available in the very near term, perhaps in less than a year.

In the next phase, workshop participants anticipated the development of a bone replacement material that has greater functional capabilities and load-bearing capacity in addition to being compatible with the surrounding bone and tissue environment. The breakout group anticipated that ensuring load-bearing capacity might be difficult for replacements not made of metal or a high-density ceramic. Up to this time, advances in materials technology have not resulted in materials that provide function in addition to biocompatibility. As a result, some members of the group cautioned it would probably take 7 to 10 years before a biomaterial that was both weight-bearing and biologically compatible could be developed to address the injuries that most commonly occur in combat.

A realistic near-term, biomaterials-based limb replacement therapy could separate the provisions for bone wound healing acceleration and infection control from the provisions for function. Compartmentalizing these technology challenges could enable the use of traditional metallic devices to restore function while adjoining, biologically compatible surfaces provide a suitable interface to the surrounding tissue and bone. Workshop participants observed that a strong interface between the different materials would be critical to the success of such a strategy.

The breakout group recognized the potential in 3 to 5 years for further development of bioactive materials that promote bone healing and decrease the incidence of nonunions. Nonunions arise when replacement material fails to bond properly with existing tissue and also can arise when adjacent tissues fail to generate an adequate healing response (atrophic nonunion) or attempt to heal in a mechanically unstable setting (hypertrophic nonunion). Tailoring the material to better facilitate recognition by bone could help prevent nonunions. Also, during this mid-term period, participants believed that bioactive biomaterials will be able to enhance the development of new blood vessels, promoting better healing and preventing infections during bone and muscle repair.

Workshop participants were aware of the long-term potential of cell therapies. They did not, however, see a near-term potential for simple applications of cell therapies on the battlefield or in hospitals near the battlefield. Instead, military applications of biomaterials containing bioactives (such as antibiotics or tailored reactive groups) will likely be significantly more practical and realistic. Further, even within the civilian sector, the technology for cell-based orthopaedic therapeutics has not yet matured, so participants anticipate a significant wait for military-ready versions.

A bone void-filler is one candidate for near-term (1 to 3 years) use in repairing the skeletal system. Discussion among workshop participants resulted in the following list of desired properties in a bone void-filler:

- Ease of use—for example, a paste-like consistency may be desirable because it could be introduced through an injection and would not be displaced by bleeding. If such a material were properly designed, it could surround the point of fracture outside the periosteum and then harden quickly in place without heating the surrounding area.
- Controlled X-ray imaging properties—the ability to see the bone void-filling material using X-ray imaging is desirable for many applications. However, participants also envisioned some applications in which transparency to X-rays was adequate or even preferable.
- Biodegradability—an ideal hardened bone filler material would degrade at a rate equal to the rate of bone healing and replacement in the body.
- Bioactivity—a bone filler material that could release wound-healing accelerant or an antibiotic in a controlled manner over a period of 1 to 3 weeks would be very desirable. A release that is timed to the biological action of therapeutics and the availability of responding cell populations would result in very rapid acceptance and healing.
- Regulatory approval—it is very important that such a product be designed for speedy regulatory approval so as to transition to the field quickly.

Depending on the outcome of bone void-filler therapies, their applications could be extended to ablative bone wounds and fractures. Goals for the 3- to 5-year period would include availability of biomaterials that decrease the incidence of fracture nonunions and accelerate the regeneration of destroyed bone. Biomaterial-based therapeutic goals for 5 years and beyond would include materials that enhance generation of new capillaries or blood vessels and have functional and weight-bearing capabilities consistent with complete replacement limb function.

Blood Vessel Repair

All tissue is necessarily linked, so that it is impossible to repair bone and muscle without also repairing blood flow and, ultimately, neural function. However, the specific expertise of workshop participants limited the group's ability to address the significance and involvement of both circulatory and nervous system components of this task. The make up of the committee and the workshop attendees was chosen in part because of the perception that biomaterials will be more important in the near term to tissue and bone reconstruction than to blood vessel and nerve regeneration.

Some of the identified development goals in the field of repair and restoration of blood vessels included the following:

- Materials for artificial blood flow conduits;
- Methods to increase vessel patency;
- Capacity to extend, regenerate, and enhance circulatory structures; and
- Ways to prevent materials-induced blood clotting and adverse tissue responses.

For the near term (1 to 3 years), workshop participants emphasized that an increased knowledge of the healing process for inner surfaces of vessels or grafts by endothelial cells would guide therapy design. Specific requirements for blood vessel treatment methods during this period may include bioactives in implanted artificial blood vessels or in devices designed to help blood circulation and the development of extracellular matrix-derived materials that enhance vessel development.

For the mid-term (3 to 5 years), workshop participants anticipated readiness for the task of developing implantable small- and large-caliber blood vessels.

For the longer-term (5 years and beyond), workshop participants emphasized such tasks as improving blood flow through vessels by increasing patency, developing artificial blood vessels made of resorbable materials that are replaced over time by functional natural blood vessels, and making artificial blood vessels that do not induce blood clotting.

Nerve Repair

Breakout session members made a number of observations about nerve repair and regeneration, although there was general agreement that much of this progress is a long-term goal. Improving treatment of nerve damage will include making replacement conduits that are antifibrogenic, neuronal regeneration enhancers that promote proper joining of nerves to muscle fibers. Injury recovery will also improve with the introduction of seamless attachment of the nerve replacements to existing nerve and muscle structures that allow appropriate conduction properties.

Requirements for the development of better nerve repair methods would center on, in the near term, the development of artificial nerve conduits. In addition, new biomaterials that work as biomimetic extracellular matrices could be developed to promote nerve regeneration.

Mid-term goals (3 to 5 years) may include the improvement of nerve conduits to make them antifibrogenic and prevent the formation of scar tissue that might interfere with nerve regeneration. Long-term goals (5 years and beyond) include the development of biomaterial-based therapeutics for neuronal devices that are functional and can carry action potential signal. Finally, workshop participants identified technologies necessary to induce merging of cells between host and regenerated nerve areas.

Measures of Success

Workshop attendees described the demanding constraints of military applications and emphasized that the design and development of biomaterials-based treatments must be responsive to them. There was also good agreement that simplicity of use is a virtue for any proposed treatment plan. Finally, participants added that therapeutics that successfully control infection would be particularly helpful.

The group chose not to list precise requirements either for the treatment of small injuries, such as the repair of fractures and localized wounds, or for the treatment of massive injuries requiring limb salvage.

A number of metrics were suggested by the tissue engineering breakout group members, including

- Implementation of bone void-fillers within 1 year;
- Incorporation of bioactives into implanted artificial blood vessels within 3 years;
- Development of load-bearing, biocompatible polymers and composites within 5 years; and
- Development of anti-fibrogenic nerve conduits within 7 years.

DRUG DELIVERY

Workshop attendees assigned to assess drug delivery needs first focused on the current state of therapeutic areas and enabling biomaterial technologies that could enhance casualty prevention and management. Discussion ensued on the research and development possible within the next 3 to 7 years for three target areas: prophylaxis, infection control, and pain management. Prophylaxis was targeted at both vaccines against infectious diseases and attack from chemical or biological weapons. Target areas have unmet needs that, if satisfied, would benefit military medicine with respect to improved outcomes, cost-effectiveness, and better delivery of medicine and care for warfighters. Medical products with improved therapeutic delivery would be deployed to battlefield, field hospital, and recovery facilities. At the workshop, breakout group participants laid out a time line to give direction to the development of products within therapeutic and enabling biomaterials technology areas.

The Current State

Challenges related to the prevention of endemic infectious diseases, control of infections, and management of pain in the hospital setting are magnified in the austere conditions of the battlefield.

Prophylaxis

Presenters at the workshop highlighted the dangers of infectious diseases, which have had the greatest role in casualty production, resulting in more hospitalizations than wounds and injuries do. More than 50 etiological agents were cited as having either historical or future impact on the health of service members on the modern battlefield. These infectious diseases can affect three different phases of military operations: training, deployment, and mission execution. Endemic diseases that affect training and deployment can be categorized as those that can be transmitted easily in the close quarters of military barracks and workspaces. Examples include influenza, adenoviral infections, and diarrheal diseases. These communicable diseases are usually transmitted by close personal contact or respiratory droplet spread.

Threats can come from naturally occurring endemic diseases or from etiologic agents intentionally delivered by an adversary as in the case of biological warfare. Vector-borne parasites and viruses dominate the diseases that commonly affect mission execution. Examples of the most serious arthropod-borne diseases include malaria, yellow fever, dengue fever, and leishmaniasis.

Since the Revolutionary War and beginning with smallpox, vaccination has been the method of choice to counter infectious disease threats. Effective vaccines can decrease the amount of medical

resources required in a theater of operations. Approximately 20 federally licensed vaccines or antitoxin preparations are available for use in military populations.[14] Presenters mentioned another approximately 11 preparations that are in investigational new drug status and could be used if an imminent threat were identified. However, breakout session members estimated that at least double the current number of vaccines may be required in the future. This large number of vaccines represents not only a significant number of inoculations for service members, but also an enormous logistical and medical administration challenge given that most vaccines require multiple booster immunizations to achieve full protection.

These problems are magnified by the need to immunize as many as 100,000 to 500,000 troops on short notice prior to an operation. In the case of anthrax protection, at least six immunizations are required over an 18-month period.[15] This requirement has left the Department of Defense with various categories of service members in different stages of immunization. Lastly, many of the vaccines that are currently available must be kept cold during storage and transport, and the lack of reliable refrigeration throughout the logistics chain precludes their use in many areas. Breakout group members identified the need for advanced biomaterials to improve the thermal stability of vaccines, decrease the number of immunizations, and improve the effectiveness of delivery of vaccine antigens.

In addition to vaccinations, barrier methods to prevent infection have also been used by the military. In the case of vector-borne diseases, the most effective barrier used for more than 50 years has been N,N-diethyl-*m*-toluamide (DEET).[16] Currently, repeated applications of insect repellents are required to maintain an effective dose, especially in hot and humid environmental conditions. However, repeated exposures to DEET have been cited as responsible for a variety of neurological or other medical effects.[17] The lack of acceptance by soldiers of products containing DEET may decrease the effectiveness of these barriers. DEET has been incorporated into military clothing, sun protection creams, and camouflage face paints with limited success.

Barrier creams are designed to confer protection against toxic compounds. They may be applied to protect against a wide spectrum of compounds, or may confer particular protection against specific groups of compounds. For example, specific barrier creams have been developed against chemical warfare agents. Ongoing research includes the development of barrier creams that protect against heat.[18] Barrier creams that offer wide protection are based on materials with high repellence to both oil and water. Creams against specific groups of toxic compounds contain reactive species that act to neutralize the compounds before they can penetrate through the skin into the circulation. Barrier creams offer a simple and direct approach that has the potential to confer protection from toxic chemicals. They may have broad commercial application, for example as a backup to protective clothing or as protection against such industrial chemicals as pesticides. Workshop attendees observed great potential for research and development in this area.

Infection Control

It is always preferable to prevent wound infections rather than treat them. Ballistic wounds on the battlefield are especially troublesome because of the amount of foreign material that may be carried into the wounds, including dirt, contaminated shrapnel, and clothing fragments. Wound infection from burns

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[14] Office of the Secretary of Defense. Vaccines typically administered to U.S. military personnel. Available at *http://www.tricare.osd.mil/immunization/vaccines.html*. Accessed July 2004.

[15] Defence Journal. 2003. Anthrax as a weapon of terrorism and difficulties presented in response to its use. Available at *http://www.defencejournal.com/dec98/anthrax.htm*. Accessed July 2004.

[16] S. Nano. 2002. Study shows repellents with DEET most effective against mosquito bites. Available at *http://www.mindfully.org/Pesticide/2002/DEET-Mosquito3jul02.htm*. Accessed July 2004.

[17] A.W. Abu-Oare and M.B. Abou-Donia. 2001. DEET (N,N-diethyl-*m*-toluamide) alone and in combination with permethrin increased urinary excretion of 6g-hydroxycortisol in rats, a marker of hepatic cyp-3a induction. J. Toxicology and Environmental Health 64(5):373-384.

[18] Maran and Co. 2003. Barrier creams. Available at *http://www.maran.co.uk/technologies/dera/healthcare/barrier_creams/intro.htm*. Accessed July 2004.

and compound fractures has contributed often to the need for limb amputation.[19] Workshop participants observed that no effective infection control or prevention tools currently exist for the battlefield medic, and many are not available for complex wounds.

Because of the number of bacterial species that can cause wound infections and also because of the emergence of antibiotic resistance, military care facilities are constantly challenged by the number and types of antibiotics required. The austere nature of battlefield facilities may also inhibit the use of complex treatment protocols.[20] In the case of biological warfare agents, therapeutic intervention should be started within hours to prevent morbidity and mortality. Workshop participants noted that advanced biomaterials research is required to improve prevention of wound infections, decrease the need for repeated dosing, and simplify administration.

Pain Management

Pain management in the context of mass casualties and austere treatment facilities is challenging. Often, the most powerful drugs, such as morphine, are used when lesser pain management formulations could be effective. Studies suggest that up to 50 percent of all patients do not have their pain managed effectively after trauma.[21] Workshop participants observed that the need for repeated dosing and lack of targeted drug preparations may contribute to this problem. Logistics, drug pharmacology and safety, etiology of the pain, and the experience of the expected administrator may affect the availability of effective pain management in military theaters of operation. Advanced biomaterials are required that increase the effectiveness of analgesics, decrease the requirement for repeated dosing, and allow topical or regional application.[22]

Enabling Biomaterial and Drug Delivery System Technologies

Enabling technologies are those that generally improve the development of biomaterials for many applications. Biomaterials are the underpinning of any method of drug delivery.[23] Relevant factors noted by breakout session members include the development of new biomaterial drug or vaccine carriers or other delivery systems, new methods of administration, new combinatorial approaches for materials design, and rapid effective screening methods. New approaches are required to shorten the current drug development cycle, which is typically 12 to 15 years,[24] and can be as long as 20 years according to some workshop participants.

Desired Future Vision

Prophylaxis

Members of the breakout session proposed that a goal for the military should be to reduce the number of needed prophylactic administrations by 50 percent. This goal was intended to apply to vaccinations and boosters as well as to the application of topical barriers for protection against insect bites and chemical or biological agents.

Because the ultimate, and ultimately preferable, vaccine product would require only a single shot, attendees discussed a variety of strategies to accomplish this goal. One strategy is to enhance the immunogenicity of certain vaccine antigens by the development of more effective carriers. Another

[19] P. Shouler and R. Leicester. 1987. The pathophysiology of combined injury and trauma: Management of infectious complications in mass casualty situations. In Management of Infectionsl and Complications DuringCD the Falkland Islands Campaign,C, D. Gruber, ed. Orlando, Fla.: Academic Press, pp. 365-374.

[20] R. Langer. 2003. Where a pill won't reach. Scientific American 288(4):50-57.

[21] Department of Health and Human Services, Agency for Healthcare Research and Quality. 1994. Acute pain management: Operative or medical procedures and trauma. Clinical Practice Guideline at *http://www.ahrq.gov/clinic/medtep/acute.htm.* Accessed July 2004.

[22] N.A. Peppas. 1997. Hydrogels and drug delivery. Current Opinion in Colloid and Interface Science 2(5):531-537.

[23] R. Langer. 2001. Perspectives: Drug delivery—drugs on target. Science 293(5527):58-59.

[24] The Independent Institute. 2003. The drug development and approval process. Available at *http://www.fdareview.org/approval_process.shtml.* Accessed July 2004.

approach to decrease the number of booster immunizations could be to develop materials that would enable the timed release of antigens over the course of several months. This technology could be tailored to individuals to release antigens at optimal times as required to stimulate the immune system. In other approaches, agent-specific DNA or antigens could be targeted directly to cellular components of the immune system. Lastly, large combinatorial libraries that contain essential information about the potential for antigenic molecules to produce antibodies could replace the need for individual vaccines.

Vaccine preparations for diseases of greater military importance could be formulated using epitopes, or smaller components of antigens, embedded in biomaterial substrates to improve their effectiveness. Workshop attendees noted that as an alternative to vaccines, effective barrier creams may be able to prevent vector-borne diseases.

Some additional suggestions by breakout group members were that vaccine preparations should be thermally stable and not require constant cold temperatures during storage or transportation. Finally, it was suggested that an alternative insect repellent to DEET with the same effectiveness but with less chance for neurological reactions is needed.

Infection Control

The breakout session attendees proposed that a goal for this area is reduce infections by 50 percent and increase return-to-duty rates by 50 percent without additional increases in current medical resources. Improving the formulation of antibiotics, anti-infectives, or disinfectants that could be applied directly to wounds were mentioned as tasks that could lead to accomplishing these goals. Attendees indicated that new formulations are required that decrease the requirement for multiple dosing. Products also should be directed for use at the first echelon of care, and requirements for extensive management, such as multiple boosters, should be minimized.

Pain Management

Breakout session members proposed that the goal of this area should be to reduce the pain management burden by 50 percent on the battlefield after trauma. Accomplishments that would reduce the burden might include the development of better analgesics that could (1) directly target the source of pain, (2) decrease the amount of pain medication needed, (3) decrease the number of times medication must be administered, and (4) decrease the deleterious effects suffered by the recipients of the medication. In some cases, pain management could be combined with infection control in appropriate wound coverings or bandages. Finally, spray-on applications were mentioned as warranting further investigation.

Enabling Biomaterials and Drug Delivery Technologies

A goal identified by breakout session members was to decrease the time required to deliver new biomaterials to these applications by 50 percent. Incumbent in this is a need to develop better combinatorial libraries and screening methods for specific compounds. Investment in this area could shorten development times for all biomaterials and facilitate federal regulatory approval.

Path Forward for Drug Delivery

The roadmap delineates a series of tasks and requirements for research and development that will lead to the development of medical products with improved outcomes, cost-effectiveness, and better delivery of medicine and medical care for warfighters. The tasks and requirements needed to reach this vision can be broken down into three major elements: prophylaxis, infection control, and pain management. Elements of this development may include, first, analyzing the unmet needs of drug and drug delivery systems, the military medicines that are used in battlefield and postbattlefield situations, and the costs of medical management. Next, the potential for new therapeutic drug and biotechnology molecules and for potential drug delivery systems and biomaterials must be assessed. Finally, the

potential drug and delivery system can be assessed based on time of onset, duration of action, therapeutic blood level, pharmacokinetics, physical chemical properties, portal of entry to body, and other factors.

Other considerations mentioned by workshop attendees include the following:

- Drug, biomaterial, delivery platform, and selection process that meet the military performance requirements
- Drug and biomaterial production requirements
- Determining the best route of drug administration based on product requirements and better medical outcomes
- Ease of use under battlefield conditions as well as in hospital settings
- Prioritizing the product requirements based on improving recovery time or return to duty; ease of use; lighter weight; reduction of administration, infection, pain, and inflammation; introducing enabling materials technologies, and so forth
- Development of screening methods for enabling materials technologies

Once the need has been identified, a valuable step is to determine whether a drug delivery product already exists in the civilian market or whether the military, industrial, or academic sectors are currently developing a similar drug delivery product.

Measures of Success

The following performance metrics were suggested by workshop participants for products developed for drug delivery in military applications:

- In the near term, implement methods to deliver bioactives to wounds using powders, films, and dressings.
- In the mid-term, reduce by 50 percent the pain management burden on the battlefield after trauma.
- In the long term, improve the efficacy and reduce the administration requirements of prophylactic vaccines and drugs by 50 percent.
- In the long term, reduce infections by 50 percent and thereby increase return-to-duty rates by 50 percent.
- In the long term, fully integrate drug delivery into wound care and tissue engineering products.

PHYSIOLOGICAL SENSORS AND DIAGNOSTICS

Workshop attendees assigned to assess physiologic sensors and diagnostic needs began with a discussion of the current state of development by the U.S. Army of a system to monitor the physiological status of the foot soldier.[25] The prototype system under development consists of an array of wearable sensors that monitor heart rate, respiratory rate, and skin temperature. Additional capabilities for situation-dependent missions may include measurement of core temperature, body orientation, and actigraphy, a measure of acceleration that can be used to infer whether a soldier is moving around and also the number of hours of sleep. Any one of these physiological parameters can be attained from a number of different technologies involving sensor location in different parts of the body. For example, actigraphy can be measured using a device similar to a wristwatch.

[25] R. Hoyt, J. Reifman, T. Coster, and M. Buller. 2002. Combat medic informatics: Present and future. In Proceedings of the Application of Medical Informatics Association 2002 Annual Symposium, San Antonio, Tex., November 9-13.

Workshop participants noted and emphasized that such devices are in the prototype and proof-of-principle phase. Soldiers involved in current conflicts in Iraq or Afghanistan are not wearing these systems.

Field monitoring of soldiers' physiological status is a very desirable tool and could be used for such beneficial activities as (1) sustenance of physical and mental performance, (2) prevention of such nonbattlefield injuries as heat stroke and hypothermia, and (3) improvement of casualty management. As a first step, the Army is developing a system employing the array of sensors noted above for remote life sign detection (that is, to automatically—based on the sensor measurements and computer-implemented algorithms—determine whether a soldier is dead or alive, or in an unknown state. The Department of Defense is also developing handheld systems for detecting and diagnosing soldier exposure to biological and infectious disease agents. However, these systems are not wearable.

In addition, the Army's Institute for Soldier Nanotechnologies is charged to pursue a long-range vision for how technology can make soldiers less vulnerable to enemy and environmental threats. The ultimate goal is to create a 21st century battle suit that combines high-performance sensor and diagnostic capabilities with light weight and comfort.[26]

Monitoring Strategies

Monitoring today is limited to on-the-skin sensors that a soldier wears. The adhesives used in these sensors are problematic in that they can cause rashes, are not water resistant, and generate poor signal quality due to artifacts. These sensors are typically powered by alkaline batteries, which have a short useful life and are relatively heavy.

Periodic monitoring is done of the heart rate using commercially available electrocardiogram sensors. Respiration is currently monitored using inductance plethysmography to measure breathing rate and depth and also to assess stoppage of breathing in the case of sleep apnea. These are commercial products and sometimes have problems when deployed in battlefield conditions. In addition, workshop participants observed that algorithms specific to military needs may not be available. A specific example is the need to make a remote determination if a soldier is dead or alive, which is something not normally needed in the civilian world.

The Army is moving toward monitoring that can be done without contact with the skin or through clothing. This may include invasive implantation of sensors, but this strategy will depend strongly on acceptance by the soldier and must also have a long life to help amortize its generally high cost. For example, a pill that a soldier can ingest to measure core temperature has a useful life in the body of 24 to 48 hours. Workshop participants did not see this technology as cost-effective today.

Some workshop attendees proposed that the most important fact that a forward medic needs to know is the location of each of his charges. Global Positioning System (GPS) sensing is currently being used only with the radio soldier. Breakout group members noted that lightweight GPS sensors for the field soldier are near-term technology that should be implemented as soon as possible.

Assessment Strategies

Much discussion ensued at the workshop on the parameters needed to accurately assess and treat soldiers in the field. This is a critical technology obstacle that must be addressed to identify the appropriate sensor, either a commercial product or one specifically developed for the Army's use, and to successfully develop and implement the necessary algorithms to interpret the sensed data. The current effort described by presenters is one of system integration of commercial sensors and development of decision algorithms. However, some workshop attendees cautioned that the potential for new sensor development must also be considered.

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[26] The Institute for Soldier Nanotechnology was founded in March 2002 by a $50 million contract from the U.S. Army at the Massachusetts Institute of Technology. More information is available at *http://web.mit.edu/isn/research/researchprojects.html*. Accessed July 2004.

An important goal identified was to provide early remote assessment of the field soldier. If the forward medic could monitor the exact location of any soldier in his squad and the soldier's wearable sensors could measure heart rate, respiration, core and skin temperatures, blood pressure, cardiac output, fatigue, blood oxygen, total weight, and hydration, the overall effectiveness of the medic and the unit would be greatly improved. This goal could be accomplished using multifunctional, lightweight, off-the-skin, micromachine sensors that are integrated with the soldier's uniform or implanted.

Because field medics are typically young, inexperienced, or both, a major challenge is to develop an integrated physiological monitoring system that can provide the medic with real-time information presented as simple decision-making symbols. For example, if a soldier is injured but still alive, the integrated monitoring system would measure vital signs and then flash red or yellow depending on the severity of the soldier's condition. In this way, the medic would be able to make quick decisions as to which soldiers require immediate evacuation or need lifesaving intervention. Such programs as the Virtual Soldier are investigating means of communicating these data in ways that are easy to interpret.[27]

Another human factor need identified is to research which physiological parameters are key in predicting particular clinical outcomes in order to prioritize a need for lifesaving intervention. Ongoing research involving the mining of physiological data from trauma victims in the civilian environment could provide insights on what data should be monitored when a soldier becomes a casualty. Currently, the data needs for prevention of nonbattlefield injuries are known and include heart rate, core temperature, hydration, and metabolic rate. Research is ongoing for casualty management and for sustenance of performance. Currently the only tool available is actigraphy, used to estimate sleep time and predict soldier performance subject to sleep deprivation. A number of gaps have been identified for the development of biomathematical models for prediction of soldier performance subject to sleep deprivation.[28]

Ultimately, sensors will be integrated with controls into systems to treat conditions remotely. This could include dispensing medications, providing hydration, warming boots, or cooling clothing. In the far future, nanosensors could circulate throughout the body, sending information and also controlling function. To this end, it is important that the biomaterials community work with the existing silicon-based devices to ensure compatibility for the next-generation biosensor.

Chemical and Biological Agents

Several presenters at the workshop noted that the threat of chemical or biological weapons attack is real in many locations where soldiers operate today. Such chemical agents as phosgene, chlorine, chloropicrin, and cholinesterase inhibitors may be categorized as blistering agents or toxins in the nervous, blood, and respiratory systems. Biological agents include bacteria, viruses, ricksettiae, and genetically engineered microorganisms. Biological agents can be more lethal than chemical agents but generally offer more time to respond to the threat. In either case, it is desirable to protect the soldier from exposure through early warning sensors that provide ample time to employ protective biomaterials for the skin and biofilters to protect respiration.

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[27] The Virtual Soldier Program seeks to establish a new capability that will revolutionize medical care to support the soldier. The program will create the mathematical modeling approaches to develop an information (computational) representation of an individual soldier (a holographic medical electronic representation, or holomer) that can be used to augment medical care on and off the battlefield with a new level of integration. This virtual soldier will be based on a highly complex model that is derived from biologically driven principles and populated with properties that are extracted from evidence-based data. The initial Phase 1 effort will consist of a two-component, three-dimensionally displayed model: (1) ana organ-tissue system model component and (2) a properties-level model component. Once derived, the virtual soldier will provide multiple capabilities, including but not limited to automatic diagnosis of battlefield injuries, prediction of soldier performance, testing and evaluation of nonlethal weapons, and virtual clinical trials. From *http://www.darpa.mil/dso/thrust/biosci/virtualsoldier.htm*. Accessed July 2004.

[28] D.F. Neri. 2004. Preface: Fatigue and Performance Modeling Workshop, June 13-14, 2002. Aviation, Space, and Environmental Medicine 75(3), pp. A1-A3.

Power Sources

Workshop attendees noted that power is a limiting factor in many devices. For example, more than 75 percent of the weight of many devices is in the battery. The goal of many of the sensor systems discussed is to make them as small as possible in order to reduce the burden on the warfighter. This means that the power supply must also be made smaller. It could also allow the use of very low power sources that have previously been ignored, such as harvesting power from temperature differentials in the human body or using available insolation on clothing surfaces. Currently, there is little commercial demand for such specialized power sources.

Batteries present a variety of materials challenges in their electrodes, electrolytes, cases, and connections. These components are required to be physically robust while they maintain electrolytic function, meaning that the materials must exhibit mechanical stability during cycling and resistance to mechanical shock.[29] Commercial battery systems for small electronics have made great strides in recent years, and in theory, the military should be able to utilize this progress for its own purposes. However, a recent NRC report on advanced power systems describes some of these materials needs. For example, although thin-film, lithium-based batteries show tremendous promise in the laboratory, known challenges include (1) battery development on thinner, more flexible substrates, (2) stacking for creation of three-dimensional batteries, (3) improving yield (currently only 10 percent), and (4) packaging. At present, there is insufficient market pull to drive low-cost solutions to these problems. This implies that the military will have to make directed investments to achieve its specialized power goals for the future.

For many military applications, fuel cells were mentioned as attractive alternative to batteries. An interesting possibility is to use parts of the human body as components of the cell. For example, one could view the nervous system as an electrical system powered by glucose through oxidative phosphorylation. Although these technologies show promise in theory, there is currently little commercial demand for such innovations as energy harvesting. In addition, biomaterials have been shown to enable improved capabilities for future fuel cell configurations.[30]

Desired Future Vision

Near-term Advances (1 to 3 years)

Predicted near-term advances encompass the transition of proven technology to the field. Achieving this will require validation over extended operational periods. Examples of near-term advances include the following:

- Equipping all soldiers with lightweight identification and location sensors.
- Improved adhesive materials to ensure that sensors remain on the skin under all battlefield conditions—an early implementation might include a wired system used to transmit data from the sensors to the soldier's computer where data are processed. In the future, wireless technologies could be used, including magnetic induction, which is desirable because of its low signature level. From the soldier to the medic, data could be transmitted using radio-frequency signals.
- Determination of useful physiological data that the field medic may be able monitor with sensors for casualty management—respiration, heart rate, and the core and skin temperature of each field soldier are the first needs. Blood pressure is a useful parameter that is easy to measure, but cardiac output may be a better indicator. Other parameters may be useful only in combination with additional information.

[29] National Research Council. 2003. Materials Research for 21st Century Defense Needs. Washington, D.C.: The National Academies Press, pp. 198-199.

[30] National Research Council. 2004. Summary of the Power Systems Workshop on Nanotechnology for the Intelligence Community. Washington, D.C.: The National Academies Press.

Mid-term Advances (5 to 7 years)

Predicted mid-term advances include concepts that are currently in research and development. An example is sensors that do not require contact with the skin. Some potentially enabling technologies under investigation for this include micro-impulse radar technology that can detect respiratory rate and heart rate through clothing; range-finding radar that can operate with very low power, in the range of 1/1,000 of the power of a cell phone battery; and capacity-coupled noncontact electrocardiogram systems that have been shown to get good results through clothing.

Long-term Advances (7 to 10 years)

Anticipated long-term advances are sensors that are integrated with soldiers' clothing and other equipment using micro- and nanotechnology. Another long-term goal is the development of algorithms that integrate physiological information for quick decision making and the availability of the multitude of data necessary to make these decisions reliably.

Development Issues for Sensors

It is most important to determine what data are most useful to sense. Data collected will be used by soldiers in the field to make decisions, and these data must be useful and understandable. A number of other factors must be considered, including the following:

- Sensors should not add to the weight or cube of the soldier.
- Sensors must be robust to function in multiple environments and conditions.
- Sensors must provide precise and accurate data. It is tremendously important that sensors be reliable under strenuous environmental and operational conditions. The environment in which soldiers work, the things they do, and the notoriously poor connections between the sensors and the human body generally produce any number of artifacts that make data suspect and decisions unreliable.
- A long-term goal is the development of smart sensors that have self-diagnostics and are able to process information locally with minimal power consumption.
- Sensors should operate with low signature to avoid detection by enemy forces.
- Sensors embedded in clothing may fail when clothing tears.
- Ambulatory modalities are needed for monitoring blood pressure. This measurement currently requires either an electrocardiogram or a carbon monoxide monitor.
- The effects of high-altitude environments on monitoring blood oxygen and carbon monoxide levels must be considered.
- Implanted sensors may pose ethical questions in addition to questions of their impacts on health.

Finally, workshop attendees noted the importance of remembering that people will be using the technology. The forward medic operates in a difficult environment. Many times the environment is dark, dangerous, extremely hot or cold, and usually a high-stress situation. Medics are generally assigned 48 soldiers to monitor and must deal with a 3-day resupply cycle. Often, medics have little training and experience and, thus, need sensors that provide resolution and clear indicators of the situation.

Soldiers also operate in very high stress environments, and their comfort is always an issue. Some workshop attendees suggested that researchers should wear a MOPP[31] to know what it feels like. Soldiers generally do not like the current adhesive electrodes. A major materials need for the soldier was identified as adhesives that stick to sweaty skin with no irritation and strong, light materials for packaging new sensors.

[31] MOPP is mission-oriented protective posture and refers to a protective gear-laden suit.

It is also important to remember that field soldiers are unique individuals with unique baseline vital signs for blood pressure and stress levels. This highlights the importance of access to a soldier's historical data during trauma in the field.

Measures of Success

The following performance metrics were suggested by workshop participants for products developed for physiological sensors and diagnostics in military applications:

- In the near term, make lightweight location transmitters available for every field soldier.
- In the near term, develop a high-level system of diagnostic needs that will help to optimize sensor needs and facilitate the development of the most important combinations of sensors.
- In the mid-term, implement 50 percent smaller batteries using micro- and nanotechnology.
- In the long term, implement integrated, off-the-skin sensors for multiple diagnostic needs.

Success in this endeavor is intended to decrease the volume of the sensor system by 50 percent.

TECHNOLOGY INTEGRATION

A final consideration comes from the realization that it is in many cases the same soldier who needs to be monitored remotely, treated on the battlefield, carefully medicated throughout these steps, and then reconstructed to original functionality. The integration of new technologies for acute care may present some interesting challenges that have implications for the therapeutics provided by the biomaterials-based devices. For example, wound care treatments need to be compatible with potential decontamination for biological and chemical warfare agents. Furthermore, treatments need to be optimized not only to stabilize the patient, but to have minimal impact on the reconstructive therapies to follow, particularly for potential regenerative therapies based on tissue engineering. For example, antimicrobial treatments from drug-eluting dressings should not damage or kill viable tissue.

3

Enabling Biomaterials Development

Workshop participants observed that all of the technologies discussed the workshop had one thing in common, which was that new materials and processes will be needed to transition ideas into products.

EVALUATION PROTOCOLS

It is of particular importance when working with materials that will be used in the human body to understand the variety and range of new materials evaluation protocols.[1] While all of these protocols may not be critical to the final application, workshop participants advocated the consideration of each item before materials development proceeds. Important characteristics listed by the participants include the following:

- The ability to easily form the product to fit a variety of shapes, ideally in situ;
- Erosion resistance;
- Environmental durability in a variety of conditions;
- Well-characterized bioactivity;
- Appropriate mechanical properties;
- Potential for use in multiple applications;
- Cost-effectiveness; and
- The ability to deliver the material in a sterile and bioactive state out of the package and directly into the application.

Workshop participants also described the usefulness of establishing minimum or optimum design characteristics for materials in a number of product applications. Other useful guidance mentioned was for rapid screening techniques for new materials.

A time line for the development of new materials and drug formulations is presented in Table 3.1. Each stage consists of tasks and requirements that must be satisfied as product development proceeds.[2] The time needed to get a product to the battlefield will depend on where it is on this time line, ranging from the early concept stage to commercial availability. Certain assumptions also must be made as progress along time lines is estimated. These assumptions, along with regulatory, military, industrial, and academic requirements, have a great impact on time to reach the battlefield. Because of their experience with extensive regulatory and testing requirements, workshop attendees believed that few new products could be available to the warfighter in less than 2 to 4 years. Many of these new products will depend on the identification and maturation of enabling materials technologies.

[1] N.A. Peppas and R. Langer. 1994. New challenges in biomaterials. Science 263(5154):1715-1720.
[2] R. Langer and D.A. Tirrell. 2004. Designing materials for biology and medicine. Nature 428(6982):487-492.

TABLE 3.1 Path Forward for Product Approval

Concept	Feasibility	Clinical Trials	Battlefield Use
Approved drugs[a]	Prototypes[a,c]	Clinical supply[a,b,c]	Continuous supply from a commercial manufacturer[c]
Approved biomaterials[a] (GRAS)[d]	Preclinical studies[a,b,c]	Phase I, II, III[b,c]	
New biomaterials[b,c]		Quality assurance, documentation[b,c]	Quality control, regulatory stability[c]
New drugs[c]		Predicate device[a,b]	
Production development[b,c]	Manufacturer research and development[b,c]	Packaging, stability[c] Manufacturer scale-up[a,c]	Marketing and distribution[c]

[a] 2-4 years.
[b] 5-7 years.
[c] 7+ years.
[d] Generally regarded as safe.

NEAR-TERM CROSSCUTTING AND ENABLING TECHNOLOGIES

A number of new materials technologies offer the potential for rapid application to identified military needs; these include the following:

- Biomaterials incorporating controlled-release antibiotics; these are especially useful when an antibiotic can be tailored to the clinical indication.
- Ways to ensure shelf life for biomaterials and combination products
- Improved understanding of the three-dimensional interactions of cells on materials
- Improved understanding of the immune response to biomaterials
- Techniques for rapid prototyping, micropatterning, and manufacturing of devices

Workshop attendees also offered a short list of near-term applications in which impact may be relatively easy to achieve. These included combining existing technologies, for example, new coatings on existing materials. Another short-term opportunity is to leverage existing approved technologies, as in drug-eluting stents.

NONTECHNICAL CONSIDERATIONS

While the technologies themselves set an interesting array of challenges for researchers, a number of nontechnical issues must also be considered. There was overwhelming agreement among workshop participants that primary among these is the need to predetermine a regulatory approval path. Some very useful lessons can be taken from the Accelerated Insertion of Materials (AIM) program, funded by the Defense Advanced Research Projects Agency. This program is intended to create and validate new approaches for materials development that will accelerate the insertion of materials into production hardware. The program works to establish approaches to use the required technical content and fidelity of identified military needs to drive the optimized development and use of models and experiments.

In the AIM program, efforts center on understanding how to use materials models effectively, how to link them across various length and time scales, and how to couple them with an optimized series of experiments to yield the appropriate information for the designer. When dealing with new materials for

medical applications however, different guidelines prevail. For example, the regulatory process does not recognize the results of accelerated testing, a protocol that forms the basis for a large fraction of materials modeling. One near-term process improvement offered by attendees included standardizing procedures to enable a clear path to prove the efficacy of new materials.

The need for an easy path to make new materials available to product developers was also noted. Although this may seem trivial, workshop attendees pointed out that some new materials were not available for research because of a new interpretation of intellectual property laws. Improved communication is needed among materials developers and device designers to gain the most from all.

Finally, it was noted at the workshop that the regulatory governance of medical devices does not control their use outside the United States. Because the bulk of military combat takes place overseas, some discussion ensued as to whether the military needed to follow these approval protocols at all. Regardless of the letter of the law, the U.S. military has chosen to abide by U.S. guidelines, including operating with the informed consent of the soldier. However, the demands of battlefield care can provide the opportunity to gain valuable clinical trial information in the field. Many workshop attendees felt that a recognized path for using field trials to prove efficacy would be very useful.

MEASURES OF SUCCESS

Throughout the meeting, workshop participants discussed the outcomes of their efforts to develop and implement new materials for military medicine. Success in the implementation of these suggested goals was linked in the breakout sessions to a number of benefits for the nation's defense, as follows:

- Preserving fighting strength—improving soldier health and well-being could result from improved battlefield diagnostics and care that would keep soldiers at their best and could also allow wounded soldiers in the field to complete their mission. It would result as well from successful tissue engineering technologies that could heal more serious wounds quickly and allow a soldier to return to duty.
- Improving the benefit of medical spending—new materials and processing technologies can reduce the cost of medical care and therefore stretch the funding available and provide better care.
- Transferring cutting-edge technologies developed for the military to civilian medical practice—in many ways, military needs are the most demanding. Success in transitioning technology to field use can push new technologies into other applications. This will require the involvement of new partners, including civilian practitioners and the reimbursement industry.
- Strengthening the biomedical technology industry—by creating and nurturing a critical mass of innovative researchers and product developers, the growth and impacts of biomaterials technology could multiply accordingly.
- Improving troop morale and public perception—confidence that medical technology can save lives in the field and can repair the damage from severe battlefield wounds is important to many soldiers as well as to their families and the general public.

The following performance metrics were suggested by workshop participants the accelerate the availability of biomaterials and related products developed for military applications:

- In the near term, make field clinical trials for new battlefield products routine.
- In the mid-term, establish a transition path to move existing new biomaterials into military applications.

- In the long term, decrease the time required to develop new biomaterials by 50 percent by using emerging techniques.

APPENDIXES

Appendix A

Biographical Sketches of Committee Members

James M. Anderson is professor of pathology, macromolecular science, and biomedical engineering at Case Western Reserve University. Dr. Anderson's research interests focus on mechanistic studies of biological interactions with biomaterials, prostheses, and medical devices. His interests include mechanisms of monocyte, macrophage, and foreign-body giant cell adhesion and activation; bacteria-blood-biomaterial interactions; biology-based design criteria for the development of new medical devices and biomaterials; and the biocompatibility of biosensors and tissue-engineered devices. Clinically, Dr. Anderson's interests include human implant retrieval and evaluation from both the materials and the pathobiology perspectives. Dr. Anderson also works with the International Standards Organization to develop safety standards for medical devices and prostheses. He received his Ph.D. at Oregon State University and his M.D. from Case Western Reserve University. In 2003, he was elected to the Institute of Medicine.

Gary W. Cleary is cofounder, president, and chief technology officer of Corium International, Inc. He is also the founder and served as president, chairman, and chief technical officer of Cygnus, Inc. His research and technology interests are all associated with the development of controlled drug delivery systems. During his career he has served as investigator with the U.S. Public Health Service and the Food and Drug Administration and has held research and management positions at various companies. Dr. Cleary received a Pharm.D. in pharmacy from the University of California, San Francisco; an M.B.A. in health sciences from the University of Miami; and a Ph.D. in pharmaceutics from Rutgers, the State University of New Jersey. Dr. Cleary holds 25 issued U.S. patents related to transdermal, mucosal, polymer, and other drug delivery technologies. His professional affiliations include the Controlled Release Society, American Association of Pharmaceutical Scientists, New York Academy of Sciences, American Association for the Advancement of Science, Rho Chi, and Sigma Xi. He is a fellow of the American Association of Pharmaceutical Scientists and the American Institute of Medical and Biological Engineering. Dr. Cleary is also chairman of the advisory board for the Purdue University Biomedical Engineering Program on Therapeutic and Diagnostic Devices and a member of the University of California, San Francisco, and University of Pacific pharmacy and chemistry programs. He is a former president and board member of the Controlled Release Society of the International Scientific Organization. Dr. Cleary has been a board member of several corporations in the past and is currently on the Corium and Anterion boards of directors.

Erik A. Henchal is commander of the U.S. Army Medical Research Institute of Infectious Diseases of the U.S. Army Medical Research and Materiel Command. Colonel Henchal joined the institute in 1992 and has served as principal investigator and deputy division chief in the Virology Division, division chief of the Diagnostics Systems Division, and coordinator for a joint service research program in medical diagnostics for infectious diseases and biological warfare threats. Prior to this, Colonel Henchal served the command in a broad variety of positions of increasing responsibility. He also served as a deployment team leader for a special pathogens field laboratory, 7th Medical Command, during Operation Desert Shield and Storm (1990 to 1991). He received his B.S. in microbiology from the University of Maine. After receiving his Ph.D. in microbiology from Pennsylvania State University, Colonel Henchal entered active duty in the Medical Service Corps as a first lieutenant. Colonel Henchal has served on national panels and research review committees for the Defense Advanced Research Projects Agency, the National Institutes of Health, the Centers for Disease Control and Prevention, and the American Academy of Microbiology. He

has appeared as a speaker and consultant at numerous medical, professional, and government conferences and has published extensively on the development of diagnostic approaches for agents of military concern. He is also an adjunct assistant professor in pathology at the Uniformed Services University of the Health Sciences. Colonel Henchal is a fellow of the American Academy of Microbiology. His military awards include the Meritorious Service Medal with three oak leaf clusters, the Army Commendation Medal, and the Overseas Ribbon. He is also a recipient of the Surgeon General's "A" Proficiency Designation in microbiology and the Order of Military Medical Merit.

John B. Holcomb is commander of the U.S. Army Institute of Surgical Research and chief of the Trauma Division at Brooke Army Medical Center. He is also an associate professor of surgery at the Uniformed Services University of the Health Sciences. Additionally, Colonel Holcomb is the trauma adviser to the U.S. Army Surgeon General and to the U.S. Special Operations Command Biomedical Initiatives Steering Committee. He is also actively involved in the care of trauma patients and the teaching of surgical residents and students. His research interests include developing novel methods of hemorrhage control, optimal resuscitation techniques, and medical informatics. Colonel Holcomb earned his M.D. from the University of Arkansas Medical School and has held positions at the Womack Army Medical Center, Joint Special Operations Command, and Ben Taub General Hospital. Colonel Holcomb also completed a surgical critical care fellowship at the University of Texas at Houston. His military awards include the Combat Medical Badge, the Bronze Star, and the Defense Meritorious Service Medal. He has also received the "A" Designation for general surgery and the Order of Military Medical Merit. Colonel Holcomb is a fellow of the American College of Surgeons.

Jeffrey O. Hollinger is the director of the Bone Tissue Engineering Center at Carnegie Mellon University and is a tenured professor of biomedical engineering and biological sciences. In 1993, Dr. Hollinger retired as a colonel after 20 years of active military duty in the United States Army. He received several military commendations, including the Army Commendation Medal, the Order of Military Medical Merit, the Meritorious Service Medal, the Army Achievement Medal, the Army Service Ribbon, and the National Defense Ribbon. For most of his career, he was assigned to the Walter Reed Army Medical Center in Washington, D.C. Dr. Hollinger's research focus is on bone tissue engineering and includes polymers, gene therapy, cells, signaling molecules and surgical models to test bone regenerative therapies. Dr. Hollinger has several patents and has published more than 150 peer-reviewed articles, abstracts, chapters in texts, and books, including an in-press textbook on bone tissue engineering fundamentals. He has a D.D.S. and a Ph.D. degree in physiology from the University of Maryland and a B.A. in biology from Hofstra University.

Alan Letton is vice president for research for the Polymerix Corporation. He has held positions at Avon Products, Allied Signal, Dow Chemical, and Sandia National Laboratories. In addition, Dr. Letton was dean of engineering, architecture, and physical sciences and a full professor in chemistry and chemical engineering at Tuskegee University. Prior to that, he was a professor of mechanical engineering and director of the Polymer Technology Consortium at Texas A&M University. During his career, Dr. Letton has managed a consulting company that specializes in expert witness consulting, K-12 education strategic planning, and technology-based business development. He has also served on the National Research Council's Graduate Panel on Engineering. Dr. Letton has published more than 100 articles, contributed to 10 books, and made hundreds of presentations throughout the world. He received his B.S. in chemical engineering from the Massachusetts Institute of Technology and his Ph.D. in chemical engineering and polymer science from the University of Cincinnati.

Aruna Nathan is a principal scientist at the Center for Biomaterials and Advanced Technologies, Medical Devices Group, of Ethicon, Inc. Dr. Nathan works on development of new materials for medical devices, drug delivery, and tissue engineering. Her research includes development of controlled release formulations for small-molecule drugs and proteins with applications including oral, parenteral, and local drug delivery. She previously worked for ConvaTec–Bristol Myers Squibb and performed postdoctoral

work at the Massachusetts Institute of Technology. Dr. Nathan received her B.Sc. in chemistry from the University of Madras, India, and her Ph.D. in chemistry from Rutgers, the State University of New Jersey. She received the Johnson and Johnson Corporate Biomaterials Center Silver Award in 2001 for outstanding teamwork, contributions, and continuous achievement of project goals. During her training, she received the Center for Advanced Biotechnology and Medicine summer fellowship in 1991 and was a University of Madras Gold Medalist in 1987.

Jaques Reifman is a senior research scientist in the Department of the Army. He serves in the U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center. He is also director of the command's bioinformatics cell, which he was instrumental in creating. Dr. Reifman advises, consults, and conducts research in a broad range of disciplines, including bioinformatics, medical informatics, artificial intelligence, data mining, databases, computer modeling and simulation, computer-based decision support systems, robotics, and computer science technologies for medical applications. Dr. Reifman interacts with senior military leaders, scientists, and investigators throughout the command and the Department of Defense and with scientists and executives from other government agencies, academia, and the private sector. Recently, he was appointed to chair the Armed Services Biomedical Research Evaluation and Management Committee, Joint Technical Coordinating Group on Bio and Medical Informatics. He previously served as section manager at the U.S. Department of Energy's Argonne National Laboratory. Dr. Reifman received his Ph.D. and M.S. in nuclear engineering from the University of Michigan, his B.S. in business administration from the Rio de Janeiro Federal University, and his B.S. in engineering from the Rio de Janeiro State University. Dr. Reifman has authored more than 55 peer-reviewed technical publications and book chapters and is the inventor of five U.S. patents. He is the recipient of the 1998 R&D 100 Award, presented annually by *R&D Magazine* for the "most significant technical products of the year," and Argonne National Laboratory's Productivity Award in 1995, 1997, and 1999 "in recognition of performance significantly beyond job expectations in areas of importance to the Laboratory."

James Scheirer is associate dean for clinical research at the Robert Wood Johnson Medical School of the University of Medicine and Dentistry of New Jersey. He also holds appointments as associate professor of medicine and associate professor of surgery. Dr. Scheirer had a 20-year career at the National Institutes of Health, most of it with the National Heart, Lung, and Blood Institute. There, Dr. Scheirer was chief of the Review Branch, directing peer review operations for the institute, and was concurrently deputy director of the Division of Extramural Affairs. Prior to the National Institutes of Health, he was a tenured associate professor of psychology at the State University of New York at Binghamton. Dr. Scheirer received his B.S. in mathematics from the Massachusetts Institute of Technology and his Ph.D. in cognitive psychology and statistics from the University of Pittsburgh. Dr. Scheirer has published more than 40 peer-reviewed articles and chapters in the areas of cognitive psychology and statistics and has edited several books. He is a fellow of the American Heart Association and a fellow of the American Psychological Society.

Peter P. Tolias is worldwide vice president of the Department of Advanced Research and Technology Assessment at Ortho-Clinical Diagnostics, a Johnson and Johnson company. He is a member of the Global Management Board that oversees all functions of the corporation's activities. Dr. Tolias' work includes defining and driving the scientific long-term strategic direction of the company and striving to performing cutting-edge research in genomics, bioinformatics, proteomics, and micro- and nanoengineering. He also identifies diagnostic opportunities for therapies developed by Johnson and Johnson companies and others. Dr. Tolias is adjunct professor in the Department of Molecular Genetics, Microbiology, and Immunology at the Robert Wood Johnson Medical School of the University of Medicine and Dentistry of New Jersey. Prior to Ortho-Clinical Diagnostics, Dr. Tolias was on the board of directors for the Public Health Research Institute and was founder and executive director of the Center for Applied Genomics. He received his B.S. and Ph.D. from McGill University in microbiology and immunology. His postdoctoral training was at Harvard University, and he spent two summers as a visiting postdoctoral

research fellow at the Institute for Molecular Biology and Biotechnology, Foundation of Research and Technology in Crete, Greece.

Robert H. Vandre serves as research area director for combat casualty care research at the U.S. Army Medical Research and Materiel Command. He is also chairman of the Armed Services Biomedical Research Evaluation and Management Committee's Joint Technical Coordinating Group on combat casualty care, which manages and coordinates all Defense Department combat casualty care research. He also serves as the U.S. representative to the Technical Cooperation Program technical panel and chairman of the American Dental Association's working group 12.2 on digital radiographic systems. He has served in the Army since 1977, serving the first 5 years as a clinician and subsequent years in research. He also managed the Army's telemedicine program in Bosnia for 2 years. Colonel Vandre graduated from the University of California at Los Angeles with a D.D.S. and a B.S. and M.S. in physics. He has published on subjects varying from electromagnetic pulse and radiation effects on semiconductors to, more recently, digital dental radiography and telemedicine. He has a patent on a dental endoscope and also consults on digital dental radiology.

Appendix B

Workshop Agenda and Attendees

Capturing the Full Power of Biomaterials for Military Medical Needs
A Science and Technology Roadmap Workshop

February 2-4, 2004 Woodbridge Hilton, Iselin, New Jersey

WORKSHOP AGENDA

Day 1–February 2, 2004

12 noon-1:00 p.m.	Registration and Lunch	
1:00-1:20 p.m.	*Welcome and Charge to the Workshop*	MG Lester Martinez-Lopez M.D., Commanding GEN, U.S. Army Medical Research and Materiel Command
1:20-1:30 p.m.	*Vision for Military-Academic-Industrial Collaboration*	Joachim Kohn, Ph.D., Rutgers and the Center for Biomaterials Research
1:30-1:40 p.m.	*Roadmap: Workshop Goals and Process*	James Anderson, Ph.D., Case Western Reserve University

Military Needs for Biomaterials—Acute Trauma and Tissue Restoration

1:50-3:30 p.m.	*Acute Battlefield Needs*	LTC Leopoldo Cancio, M.D., U.S. Army Institute of Surgical Research
	Hemostasis: Needs and Research	Kathy Ryan, Ph.D., U.S. Army Institute of Surgical Research
	Tissue Restoration Needs for Combat Injuries	CPT Dave Baer, Ph.D. U.S. Army Institute of Surgical Research

Panel Discussion–Moderator, James Anderson, Ph.D., M.D., Case Western Reserve University
All session speakers with
Gary Nackman, M.D., Robert Wood Johnson Medical School
COL Robert Vandre, D.D.S., Director of Combat Casualty Care Research, U.S. Army Medical Research and Materiel Command
Ben Walthall, Ph.D., Johnson and Johnson Wound Care

3:30-4:00 p.m. Break

Military Needs for Biomaterials—Agent Delivery Using Skin

4:00-5:10 p.m.	*Dermal Protective Agents for the Military*	Ernest Braue, Jr., Ph.D., U.S. Army Medical Research Institute of Chemical Defense
	Skin Barrier Technologies	Bozena Michniak, Ph.D., New Jersey Medical School

Panel Discussion–Moderator, Patrick Sinko, Ph.D., Rutgers University
All session speakers with:
Kathryn Uhrich, Ph.D., Rutgers University, and Gary Cleary, Ph.D., Corium

5:30-7:15 p.m.	Reception and Dinner	
7:15-7:45 p.m.	*Lessons from Iraq*	LTC Leopoldo Cancio, M.D., U.S. Army Institute of Surgical Research

Day 2–February 3, 2004

7:00-8:00 a.m.	Breakfast	
8:00-8:30 a.m.	*Biomaterials Science—A Wealth of Opportunities*	Joachim Kohn, Ph.D., Rutgers University and the Center for Biomaterials Research

Agent Delivery and Sensors

8:30-9:30 a.m.	*Polymers for Drug Delivery*	Kathryn Uhrich, Ph.D., Rutgers University
	Advanced Drug Delivery Systems	Patrick Sinko, Ph.D., Rutgers University
	Infectious Disease and Biodefense Medical Products	COL Erik Henchal, Ph.D., Commander, U.S. Army Medical Research Institute of Infectious Disease

Panel Discussion–Moderator, Joachim Kohn, Ph.D., Center for Military Biomaterials Research
All session speakers

9:30-10:15 a.m.	*Advanced Diagnostics for the Combat Medic*	Victor Convertino, Ph.D., U.S. Army Institute of Surgical Research
	Embedded Sensors in Artificial and Biological Systems	Paul Calvert, Ph.D., University of Massachusetts at Dartmouth

Panel Discussion–Moderator, Michael Jaffe, Ph.D., New Jersey Institute of Technology
All session speakers

10:15-10:30	Break	

Wound Healing and Tissue Restoration

10:30-12:00 noon	*Biomaterials for Cardiovascular Repair*	Gary Nackman, M.D., Robert Wood Johnson Medical School
	Biomaterials for Musculoskeletal and Craniofacial Repair	Jeffrey Hollinger, D.D.S., Ph.D., Carnegie Mellon University
	Management of Massive Bone Defects	Joseph Benevenia, M.D., New Jersey Medical School

	Biomaterials for Nerve Repair	LTC Geoffrey Ling, M.D., Ph.D., Uniformed Services University of the Health Sciences and LTC James Ecklund, M.D., Uniformed Services University of the Health Sciences

Panel Discussion–J. Russell Parsons, Ph.D., University of Medicine and Dentristy of New Jersey, Moderator
All session speakers

12:00-1:00 p.m.	Lunch	
1:00-2:45 p.m.	New Concept Showcase—Moderator: David Devore, Ph.D., Rutgers University	
	Biocure, Inc. *Corium International* *Johnson and Johnson Wound Care* *Lifecell Corporation*	*Osteotech, Inc.* *TyRx Pharma, Inc.* *ECI Biotech* *Tepha*
2:45-3:00 p.m.	Break	
3:00-3:45 p.m.	Priorities and Roadmapping	Toni Marechaux, Ph.D., National Materials Advisory Board
3:45-6:00 p.m.	Breakout Sessions	
6:15-7:45 p.m.	Dinner	
7:45-8:45 p.m.	*Regulatory Processes and Hurdles for the Introduction of Biomaterials into the Clinic*	Donald Fink, Ph.D., Food and Drug Administration Center for Biologics Evaluation and Research

Day 3–February 4, 2003

7:15-8: 15 a.m.	Breakfast	
8:15-9:00 a.m.	*The Biomaterials Technology Roadmap*	Michael Jaffe, Ph.D., New Jersey Institute of Technology
	The Center for Medical Biomaterials Research and the Telemedicine and Advanced Technology Research Center—Partners in Technology Transfer	Conrad Clyburn, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command
9:00-11:00 a.m.	Breakout Sessions	
11:00-12:00 Noon	Breakout Groups Report	
12:00-2:00 p.m.	Lunch and One-on-one Meetings Concurrent with NRC Committee Meeting	
2:00-3:00 p.m.	*Concluding Remarks*	James Anderson, NRC Committee Chair
3:00 p.m.	Adjourn	

WORKSHOP ATTENDEES

Ajay Ahuja, Tepha, Inc.
James Anderson, Case Western Reserve University
Linda Anthony, Rutgers University
Treena Arinzeh, New Jersey Institute of Technology

David Baer, U.S. Army Institute of Surgical Research
Joseph Benevenia, University of Medicine and Dentistry of New Jersey
Pat Black, U.S. Army Picatinny Arsenal
Barbara Boyan, Georgia Institute of Technology
Ernest Braue, Jr., U.S. Army Medical Research Institute of Chemical Defense
Anthony Brennan, University of Florida
Paul Calvert, University of Massachusetts at Dartmouth
Douglas Campbell, ECI Biotech
Leopoldo Cancio, U.S. Army Institute of Surgical Research
Gary Cleary, Corium International, Inc.
Conrad Clyburn, U.S. Army Medical Research and Materiel Command
Vic Convertino, U.S. Army Institute of Surgical Research
Hal Craig, FMC Corporation
Ronald DeMartino, New Jersey Center for Biomaterials
David Devore, New Jersey Center for Biomaterials
Daniel Di, Vincogen, Inc.
Joseph Didonato, Rutgers University
Jim Ecklund, Uniformed Services University of the Health Sciences
Eric Erickson, Jr., Picatinny Arsenal
Donald Fink, Food and Drug Administration
Dennis Goupil, Biocure, Inc.
Scott Guelcher, Carnegie Mellon University
Erik Henchal, U.S. Army Medical Research Institute of Infectious Disease
Patrick Hiu, Paul Magliochetti Associates, Inc.
Jeffrey Hollinger, Carnegie Mellon University
Henry Hsia, New Jersey Center for Biomaterials and Princeton University
William Hunter, New Jersey Institute of Technology
Michele Iacoletti, The National Academies
Michael Jaffe, New Jersey Institute of Technology
Carole Kantor, New Jersey Center for Biomaterials
Joachim Kohn, New Jersey Center for Biomaterials and Rutgers University
Elizabeth Lande, New Jersey Center for Biomaterials
Alan Letton, Polymerix Corp.
Geoffrey Ling, Uniformed Services University of the Health Sciences
Qing Liu, Celgene
Toni Marechaux, The National Academies
Nicholas Megjugorac, University of Medicine and Dentistry of New Jersey
Millard Mershon, Consultant
Bozena Michniak, University of Medicine and Dentistry of New Jersey
Jeffrey Miller, Celgene
Gary Nackman, University of Medicine and Dentistry of New Jersey
Aruna Nathan, Ethicon, Inc., a Johnson and Johnson company
James Pachence, VectraMed, Inc.
J. Russell Parsons, University of Medicine and Dentistry of New Jersey
Marian Pereira, New Jersey Center for Biomaterials and Rutgers University
Satish Pulapura, TyRx Pharma, Inc.
Frank Rauh, FMC Corporation
Jaques Reifman, U.S. Army Medical Research and Materiel Command
Ronni Rubenstein, New Jersey Center for Biomaterials
James Russell, Osteotech, Inc.
Randy Rutherford, Corium International, Inc.
Kathy Ryan, U.S. Army Institute of Surgical Research
Mitchell Sanders, ECI Biotech
Bonnie Scarborough, The National Academies
James Scheirer, University of Medicine and Dentistry of New Jersey
Howard Schrayer, Regulatory Consultant

Donald Sebastian, New Jersey Institute of Technology
Vikas Sharma, Advanced BioAdjuvants, LLC
Judith Sheft, New Jersey Institute of Technology
David Shreiber, Rutgers University
Patrick Sinko, Rutgers University
Gene Slowinski, Advanced BioAdjuvants, LLC
Susan Sutton, New Jersey Center for Biomaterials
Raymond Thek, Hale and Dorr
Peter Tolias, Ortho-Clinical Diagnostics, a Johnson and Johnson company
Sherylyn Tucker, New Jersey Center for Biomaterials
Kathryn Uhrich, Department of Chemistry, Rutgers University
Michiel Ultee, Laureate Pharma LP
Ranji Vaidyanathan, Advanced Ceramics Research, Inc
Robert Vandre, U.S. Army Medical Research and Materiel Command
Nancy Vause, U.S. Army Medical Research and Materiel Command
Chris Wagner, LifeCell Corporation
Ben Walthall, Johnson and Johnson
Pablo Whaley, The National Academies
Simon Williams, Tepha, Inc.

Appendix C

Roadmapping Process

BEFORE THE WORKSHOP

- Define the scope of the roadmap
  - Define the charter, mission, system boundary, scope, and team participants
  - Identify priority focus areas: biomaterials for
    - Wound healing
    - Tissue engineering
    - Agent delivery
    - Sensor and detectors
- Recruit leaders and experts
  - Identify all stakeholder groups
  - Military departments, product developers, device manufacturers, materials suppliers, academics, interested consortia, others

AT THE WORKSHOP

- Hold inclusive sessions
  - Provide overviews of focus areas
    - Military medicine and its importance to missions and personnel
    - Biomedical materials, current and potential
  - Hold panel discussions
    - Describe facts, issues, challenges, opportunities
    - Differentiate between facts and assumptions
  - Conduct open brainstorming session
    - Welcome all input
    - Forecast any and all candidate technologies, projects, goals, barriers, ideas
    - Identify overarching groups of ideas, and transfer to breakout sessions
- Hold breakout sessions
  - Refine and add to list of potential roadmap elements
    - Identify long-term goals, mid-term targets, and near-term achievables
    - Identify gaps and "showstoppers" in the existing technology
  - Time phase: near-term (0-2 years), mid-term (2-7 years), and long-term (>7 years) activities
    - Include example elements
      - When a product characteristic will be achieved
      - When a technology goal will be reached
      - When a basic research project will begin and end
      - When an applied research project will begin and end
      - When a processing or manufacturing technology will be needed
      - When a technology demonstration is warranted
      - When clinical trials will being and end
      - Others
  - Network roadmap elements

- Identify critical paths, higher-level goals, and decision points
- Identify fundamental research with the greatest potential for multiple impacts
- Point out critical capabilities as focal points for R&D priority
- Highlight specific opportunities for partners and projects, programs, and partnerships
- Find highest risks and highest payoffs
- Identify relevant barriers as they affect these goals and paths forward

WITH ROADMAP IN HAND

- Critique and validate
  - Refine product and technology definitions
  - Gather data to back up any uncertainties or assumptions made in roadmapping process
  - Develop consensus on needs and actions
- Develop implementation plan
  - Focus resources on roadmap elements with the most promise
  - Leverage resources to accomplish roadmap goals
    - Coordinate with other organizations
    - Identify common elements and synchronize time lines
- Communicate goals and planning
  - Utilize professional societies, parallel organizations
- Review and update as needed