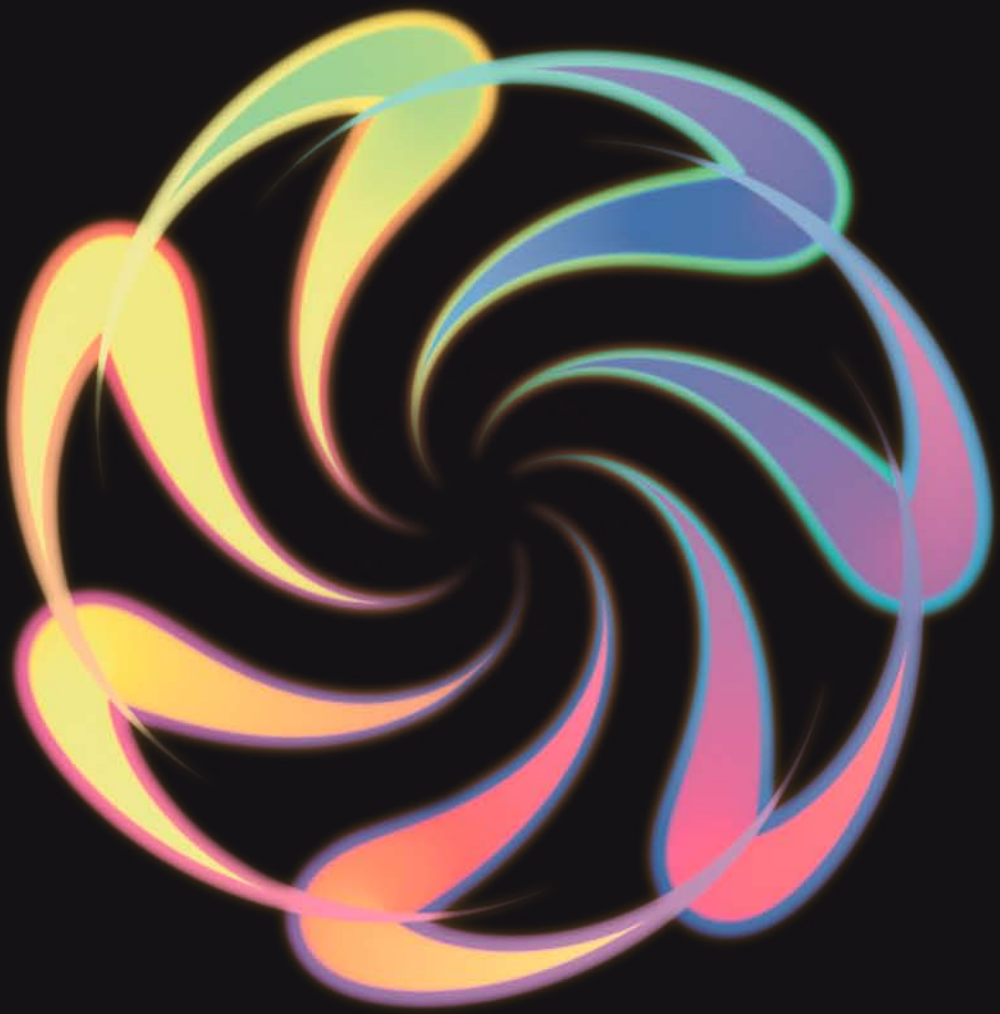
ADVANCING TISSUE SCIENCE AND ENGINEERING



A MULTI-AGENCY STRATEGIC PLAN

ABOUT THE MATES IWG

The Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group (IWG), organized under the auspices of the Subcommittee on Biotechnology of the National Science and Technology Council (NSTC), is the means by which Federal agencies involved in tissue engineering stay informed of each other's activities and coordinate their efforts in a timely and efficient manner.

The goals of the MATES IWG are:

- To facilitate communication across departments/agencies by regular information exchanges and a common website
- To enhance cooperation through co-sponsorship of scientific meetings and workshops, and facilitation of the development of standards
- To monitor technology by undertaking cooperative assessments of the status of the field
- To provide for support of tissue engineering research through interagency tissue engineering funding opportunity announcements

For more information, see the MATES website at http://www.tissueengineering.gov.

ABOUT THE NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

The National Science and Technology Council (NSTC) was established by Executive Order on November 23, 1993. This cabinet-level council is the principal means by which the President coordinates science, space, and technology policies across the Federal Government. NSTC coordinates diverse paths of the Federal research and development enterprise.

An important objective of the NSTC is the establishment of clear national goals for Federal science and technology investments in areas ranging from information technologies and health research to improving transportation systems and strengthening fundamental research. The Council prepares research and development strategies that are coordinated across the Federal agencies to form a comprehensive investment package aimed at accomplishing multiple national goals.

For more information visit http://www.ostp.gov/nstc/html/NSTC_Home.html.

ABOUT THE OFFICE OF SCIENCE AND TECHNOLOGY POLICY

The Office of Science and Technology Policy (OSTP) was established by the National Science and Technology Policy, Organization and Priorities Act of 1976. OSTP's responsibilities including advising the President in policy formulation and budget development on all questions in which science and technology (S&T) are important elements; articulating the President's S&T policies and programs; and fostering strong partnerships among Federal, state, and local governments, and the scientific communities in industry and academe.

Every fiscal year, OSTP and the Office of Management and Budget (OMB) issue a memorandum entitled "Administration Research and Development Budget Priorities." The memorandum highlights the Administration's research and development priorities and emphasizes improving management and performance to maintain excellence and leadership in science and technology. The FY '08 memorandum is available at http://www.ostp.gov/html/budget/2008/m06-17.pdf.

For more information visit http://www.ostp.gov.

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The predominant mission of the Office of Management and Budget (OMB) is to assist the President in overseeing the preparation of the Federal budget and to supervise its administration in Executive Branch agencies. In helping to formulate the President's spending plans, OMB evaluates the effectiveness of agency programs, policies, and procedures, assesses competing funding demands among agencies, and sets funding priorities. OMB ensures that agency reports, rules, testimony, and proposed legislation are consistent with the President's Budget and with Administration policies.

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For more information visit http://www.whitehouse.gov/omb/.

ABOUT THIS DOCUMENT

This document is a strategic plan for Federal Government investments in tissue science and engineering, including the activities of both research and the regulatory agencies with interests related to tissue engineering or regenerative medicine. The plan was drafted by the members of the MATES IWG, and reviewed and approved by OSTP and NSTC.

Central image on front cover, "Mindflower," courtesy of Ned May. Cover design and layout by Nicolle Rager of Sayo-Art.

Advancing Tissue Science and Engineering

A Foundation for the Future

A Multi-Agency Strategic Plan

June 2007

Report prepared by

MULTI-AGENCY TISSUE ENGINEERING SCIENCE (MATES)
INTERAGENCY WORKING GROUP (IWG)

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EXECUTIVE OFFICE OF THE PRESIDENT
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Washington, D.C. 20502

June 7, 2007

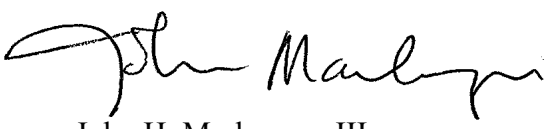
Dear Colleague:

I am pleased to transmit this strategic plan for Federal efforts regarding tissue science and engineering. Over the past two decades significant progress has been made toward understanding and harnessing the structure-function relationships in living organisms. Out of this fundamental understanding, a new and burgeoning field, tissue science and engineering, has developed. Applications in medical therapeutics have begun to emerge, under the rubric of regenerative medicine. Non-therapeutic medical uses such as surrogates for animal models in drug discovery and toxicology screening are under development. And tissue science and engineering has led to the development of potentially important non-medical applications such as tissue-based sensors to detect biological or chemical threats.

Advancing Tissue Science and Engineering: A Multi-Agency Strategic Plan identifies opportunities for dramatic advances in this and the related field of regenerative medicine. Some specific opportunities include regeneration of lost limbs or organs, rapid identification of deadly biological or chemical agents, reduced reliance on animal testing, and more efficient and less costly drug development and chemical testing. The plan sets four long-term goals for the development of this field as a whole, identifies eight strategic priorities where Federal investments in tissue science and engineering will accelerate progress, and outlines implementation steps that Federal agencies will employ to carry out the plan.

This plan was developed by the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group (IWG) under the Subcommittee on Biotechnology of the Committee on Science of the National Science and Technology Council. The MATES IWG coordinates Federal activities related to tissue science and engineering. The implementation of this plan, under the guidance of the MATES IWG, will contribute significantly to the Administration's interagency R&D priority on research aimed at improving our understanding of complex biological systems, with multiple agencies supporting highly interdisciplinary research that involves close collaborations among physical, computational, and biological scientists and engineers. The MATES IWG activities outlined in this plan comprise a thoughtful approach for coordinating and prioritizing programs across the Federal Government to ensure full realization of the potential of the field for addressing needs in healthcare, national security and economic vitality.

Sincerely,



John H. Marburger, III
Director, Office of Science and Technology Policy

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EXECUTIVE SUMMARY

This strategic plan identifies the underpinning technological needs that will advance the field of tissue science and engineering, and steps that can be taken by various agencies of the U.S. Federal Government to achieve this end. Engineered tissues have applications in medical therapeutics, including regenerative medicine, and a growing number of non-therapeutic medical uses such as surrogates for animal models in drug discovery, toxicology screening, and pharmacogenomics. Engineered tissues are also being developed for non-medical uses such as tissue-based sensors to detect biological or chemical threat agents, and tissue-based factories producing high-quality proteins on an industrial scale. Neural cell networks and other hybrid computational devices are also being investigated. Such advances both draw from and contribute to advances in the biological, chemical, and physical sciences, especially at the intersections of these fields. Thus, these projects are supported by a variety of U.S. Federal Government agencies as well the private sector, and promise to have broad application across many sectors of the economy.

In this document, tissue science and engineering is defined as *the use of physical, chemical, biological, and engineering processes to control and direct the aggregate behavior of cells*. Recent advances in molecular, cellular, and systems biology allow an ever finer dissection of the internal dynamics of individual cells, including the beginnings of the "circuit diagram" for how various intracellular networks are integrated to produce these highly adaptable units of biological function. The role of the extra-cellular matrix beyond its structural support for cell assemblies (i.e., as a key element in creating the physical and chemical signaling necessary to direct cellular aggregation) is being increasingly appreciated. Additionally, biomarker-based assays and imaging tools are gaining the sophistication necessary to give real-time, non-invasive views of cell-based events as they occur within an organism. Information management and computational modeling is maturing to the level that rapid data analysis powers cycles of rational design and testing of experimental constructs. However, there is an urgent need for an overarching paradigm, informed by the organizing principles of systems biology, that will channel the knowledge gained from these diverse disciplines toward the problem of how cells specifically process the signals received from their environment, and organize into the tissues and organisms. *Advancing Tissue Science and Engineering: A Foundation for the Future* attempts to define these questions in qualitative and quantitative terms, and then suggest ways that the Federal agencies involved in tissue science and engineering can leverage their resources to find answers and capitalize on the results.

Chapter 1 of the strategic plan briefly reviews the history of tissue science and engineering, and outlines the current state of commercial and international interest. It then lays out a rationale for collaborative efforts across the Federal Government, under the aegis of the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group (IWG), to maximize the benefits of tissue science and engineering.

Chapter 2 identifies four overarching goals for tissue science and engineering that such a collaborative research and development (R&D) effort would address:

1. Understanding and controlling the cellular response: A fundamental challenge is to understand how cells—the building blocks of tissues—receive and respond to information from their local environment in establishing and maintaining tissues.
2. Formulating biomaterial scaffolds and the tissue matrix environment: The scaffolding that supports cells and gives tissues their form is increasingly appreciated as an important source of information that drives cell fate determination. A deeper understanding of the biology underlying this relationship will allow more effective tissue design and engineering.

3. Developing enabling tools: Complex, multiparametric inputs are required to assess the state of a tissue and the cells within it. This information will be supplied by improvements in high-throughput assays and instrumentation, imaging modalities, fabrication technologies, computational modeling, and bioinformatics. Additionally, tissue preservation technologies and bioreactors will facilitate the generation of tissues on demand.
4. Promoting scale-up, translation, and commercialization: Demonstrating the feasibility of designing an engineered tissue is not enough. Realizing the full benefits tissue engineering science requires increased reproducibility, robustness, and user-friendliness that will enable the broad distribution of products.

Chapter 3 lays out eight strategic priorities for Federal Government agencies, identifying where the agencies can focus their activities now to have the greatest impacts in furthering the overarching goals outlined in Chapter 2:

- Understanding the Cellular Machinery
- Identifying, Validating Biomarkers and Assays
- Advancing Imaging Technologies
- Defining Cell/Environment Interactions
- Establishing Computational Modeling Systems
- Assembling and Maintaining Complex Tissue
- Improving Tissue Preservation and Storage
- Facilitating Effective Applications Development and Commercialization

Chapter 3 also includes implementation strategies that the MATES IWG will employ to carry out the plan, including the following:

- Agency-specific and interagency funding opportunity announcements (FOAs) or other funding vehicles in targeted areas
- Interagency research collaborations, postdoctoral programs, personnel details and sabbaticals, and mid-career training opportunities, to ensure exchange of knowledge, technical expertise, priorities, and cultures across agencies
- Improved coordination among agencies to foster technology transfer and translation via Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) programs, centers of excellence, engineering research centers, joint R&D ventures, bioengineering research partnerships, and other formal and informal structures to accelerate practical, clinical, and commercial development
- Coordinated policy development including participation in the development and adoption of industry-wide standards

The final section of Chapter 3 identifies the intersections and opportunities for leveraging between the strategic plan for tissue science and engineering and other Federal initiatives.

Advancing Tissue Science and Engineering: A Foundation for the Future outlines a role for an integrated Federal effort that leverages each agency's strengths and contributions. By coordinating efforts in the strategic priorities, the agencies of the MATES IWG will advance tissue science and engineering by supporting and extending the critical underpinning science and engineering that will lead to success. This strategic plan describes how contributions from the physical, chemical, biological, and computational sciences and engineering will provide the tools by which better understanding and control of biological systems will be achieved.

Each of the agencies involved in the IWG has a critical role to play in moving this emerging field forward, hence a coordinated interagency effort is an essential element of this strategic plan.

1. INTRODUCTION

What if lost limbs or organs could be regenerated?

What if drug development and chemical testing were more efficient and less costly?

Can deadly biological and/or chemical agents be rapidly identified?

Are there ways to reduce our reliance on animal testing?

These questions and others reflect the goals of the current programs on tissue science and engineering in the public and private sector. Success at achieving these goals will have great benefit to society by minimizing the human tragedy of physical trauma, reducing the cost of drug development, understanding the effects of chemical exposures and enhancing chemical testing approaches, protecting us from biological threats, and offering new functionalities in consumer products. However, hurdles must be overcome for these potential benefits to be realized. **The purpose of this strategic plan is to identify the overarching goals in tissue science and engineering that will serve as the basis for coordinated program efforts among U.S. Federal Government agencies seeking to extend scientific knowledge, advance technology development, improve public health, protect the environment, enhance national defense, and support a strong U.S. economy.**

For the purposes of this document, *tissue science and engineering* is *the use of physical, chemical, biological, and engineering processes to control and direct the aggregate behavior of cells*. Tissue science and engineering rests on the core foundations of science—the physiochemical/mechanistic understanding of basic biological processes—and engineering—the quantitative and systematic application of scientific principles to practical ends. The result is cells functioning in concert, integrating cellular communication pathways and molecular interactions, across many time domains and spatial scales from the subcellular through to the whole organism.

EVOLUTION OF TISSUE SCIENCE AND ENGINEERING

Tissue science and engineering has grown to incorporate many disciplines, but has its roots in tissue engineering, which Skalak and Fox defined as:

> …the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue functions. (Skalak and Fox 1988)

This document takes a broader view of tissue engineering than the more traditional definition shown above. In particular, *tissue science and engineering* includes non-medical applications of tissue engineering such as biosensors. Since the term *tissue engineering* was first used in 1985 (Viola et al. 2003) significant progress has been made toward understanding and harnessing the structure-function relationships in living organisms, and first-generation tissue-engineered medical products are commercially available (e.g., skin and cartilage). Yet, unsolved fundamental questions about how cells work within engineered matrices compromise further advancement. These new innovations will be launched into an increasingly complex and sophisticated medical marketplace in which traditional risk-benefit analyses must be complemented with cost-benefit analyses. As the cost of medical care continues to grow faster than overall inflation, such assessments will soon need to be made at both the individual and societal levels. Tissue science and engineering is expected to contribute to revolutionary products for the full spectrum of biotechnology from the earliest diagnostic testing to the advanced stages of therapy. Thus, this field will be an integral part

of the national debate on moving to a health care system that emphasizes prediction, personalization, and prevention, while continuing to improve treatments for end stage disease.

Early successes in tissue engineering have led to an evolution in thinking about organ repair and replacement. An overlapping field, *regenerative medicine*, encompasses some of the knowledge and practice of tissue engineering but also includes *self-healing through endogenous recruitment or exogenous delivery of appropriate cells, biomolecules, and supporting structures.* What differentiates regenerative medicine from other disciplines is its focus on cure rather than treatment (HHS 2005).

Engineered Tissues Provide Alternatives to Animal Testing

Millions of animals are used each year in pre-market testing of products and procedures that range from cosmetics to cleaning agents, pesticides, and surgical procedures. Tissue science and engineering is providing alternatives to traditional animal testing. A number of companies market such tissue-engineered products and their use is increasing in the pharmaceutical and personal product industries. In fact, U.S. and European government regulators have evaluated several tissue-engineered skin products as alternatives to animals for testing the potential of chemicals to cause a type of skin damage (corrosivity). Currently, engineered skin products are the most widely used, but the future could bring more complex tissues, further reducing the need for animal use in toxicology and drug development.

(photos, left: courtesy of MatTek Corporation; right: courtesy of pdphoto.org)

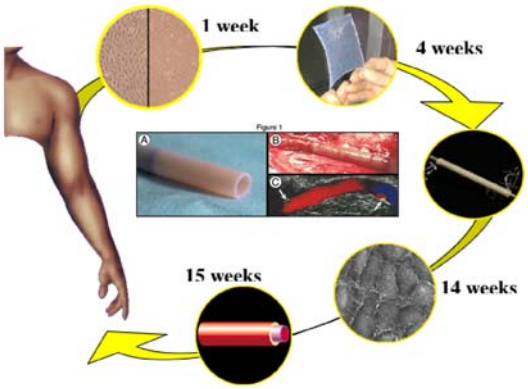
While there is significant overlap in these rapidly evolving fields, therapeutic applications of tissue engineering aim to assemble fully functional constructs, while regenerative medicine attempts to engage innate physiological processes to rebuild organs. Additionally, a growing number of non-therapeutic applications depend on engineered tissues. Tissue-based sensors detect biological and/or chemical threat agents. Engineered human tissues are in development as surrogates for animal models in drug discovery, toxicology screening, and pharmacogenomic analyses. Cells cultivated as tissues serve as factories to produce complex and delicate proteins on an industrial scale. Neural cell networks and other hybrid computational devices are being investigated.

Thus, a new vision for tissue science and engineering as a broad field of study supported by a vigorous, diverse, yet integrated Federal effort is built upon a strong and expanding foundation. Federal science, engineering, technology development, and regulatory agencies; private foundations; academia; and industry have already collaborated to address some pressing issues. For example, Federal agencies played a very large role in fostering the formation of the American Society for Testing and Materials (ASTM) Committee on Tissue Engineered Medical Products (TEMPs) that is actively promulgating voluntary standards for engineered tissues. Standards help establish a common language and understanding, and manage expectations across the spectrum of scientific, engineering, regulatory, and sociological arenas in which tissue science and engineering advances must be considered. The challenge ahead will be to better integrate and accelerate that progress.

COMMERCIAL AND INTERNATIONAL INTEREST

Between 1990 and 2002, the worldwide cumulative capital investment in the tissue engineering industry was over $4.5 billion (Lysaght 2004), with more than 90% from the private sector. Living skin equivalents and autologous cartilage have been available for several years for limited repair and regeneration in humans. There are publicly traded companies as well as groups within large multi-national corporations dedicated to tissue engineering. Since capitalization and venture capital investments have varied with market conditions over the past several years, the industry is still young, with evolving business models. Challenges include market acceptance of complex products; scale-up, manufacturing, storage, and delivery costs; regulatory pathways; and reimbursement strategies. Yet, estimates of the near-term market potential for medical applications for tissue engineering/regenerative medicine in the dozens of billions of dollars keep interest high. In 2002, 89 biotechnology organizations—both start-up companies and business units of larger firms—were involved in tissue engineering research and development worldwide.

Engineered Blood Vessels May Be an Option in Heart Bypass Surgery



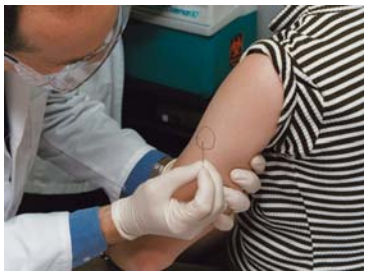
Using skin biopsies from patients with advanced cardiovascular disease, researchers in California have constructed tissue-engineered blood vessels (TEBVs) that serve as arterial bypass grafts in long-term animal models. These TEBVs have demonstrated burst pressure, compliance, and suture retention strength similar to that of human blood vessels without relying upon synthetic or exogenous scaffolding. This technology uses adult skin to provide adequate mechanical strength without relying on synthetic scaffolds or exogenous biomaterials. Currently, the process takes six to nine months and costs about $10,000. Initial clinical trials are beginning in Argentina and the UK, and the researchers have announced plans to conduct a U.S.-based safety trial in 2007.

(image courtesy of Nature Publishing Group, reprinted by permission from L'Heureux et al. 2006)

There is growing commercial interest in application of tissue science and engineering beyond medical therapeutics. For example, the following emerging markets are all available to tissue-based products:

- Theragnostics (the pairing of diagnosis with treatment) is anticipated to be $3.7 billion by 2009.
- Human tissue models may in part replace expensive and increasingly unpopular animal studies and impact the total investment in bringing a new drug to market, now conservatively estimated at $800 million over 12 years (Boston Consulting Group 2001).
- Projections vary widely for the biological and chemical warfare agent detection market, from several to tens of billions of dollars over the next five years.

Engineered Immune Systems for Rapid Vaccine Assessment (RVA)



The development of effective protective measures and appropriate post-exposure treatments against biological threat agents is a matter of urgency. Since mortality rates can be high, the ability to rapidly develop biological weapons countermeasures is of utmost importance. In order to meet these needs, the Federal Government established a program to explore the technologies and science necessary to create an artificial human immune system to serve as a high-throughput testbed for preclinical testing of vaccines and other therapeutics. This will do away with costly, time-consuming, labor intensive animal experiments and should have more direct relevance to human response than animal studies currently allow. To date, the development of an artificial lymph node has been successful and it is anticipated that it will accelerate the development of superior anti-biological weapons agents.

(photo courtesy of the National Institute of Allergy and Infectious Diseases)

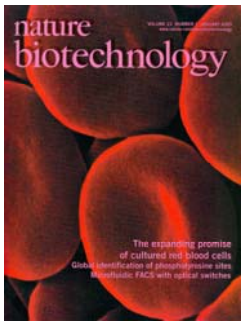
Other countries are rapidly stepping up to fill investment gaps in the U.S. research and development landscape. The most recent global assessment of tissue engineering, the 2002 World Technology Evaluation Center, Inc. (WTEC) study, documented diverse and widespread interest across Europe and Japan, as reflected by fledgling efforts at support for biotechnology incubators, and the establishment of large research centers in Japan, the United Kingdom, China, and Germany. Outside the United States, support for the field has come predominantly from government funding, whereas domestically, the U.S. Federal Government provided only 5-10% of the total spending (Hellman 2000). While much of this data is qualitative rather than quantitative, and difficult to compare across diverse information gathering processes, the emerging trend is that coordinated government programs in other countries may increasingly challenge U.S. leadership in this field (McIntire et al. 2002).

Regenerative Medicine in Europe

Research groups in Europe have active preclinical and clinical studies in many areas of regenerative medicine such as:

- Preclinical development of models for lung tissue repair using embryonic stem cells
- Development of preclinical models for treatment of wound infections using bioactive glass in the dermatology field
- Preclinical development of novel, recombinant proteins, such as collagen, fibrinogen, and lactoferrin
- Maintenance and growth of stem cells, including large-scale production of specialized cell types and processes for practical manufacture of cells for clinical trials
- Clinical trials of autologous cells from various sources for the treatment of ischemic heart disease
- Clinical trials in allogeneic islet transplantation for the treatment of diabetes

Growing Red Blood Cells—A European "First" in Tissue Science and Engineering



Researchers in France are exploring methods for producing red blood cells on a large scale. Hematopoietic (blood-producing) stem cells are taken from a variety of sources and grown in an environment mimicking bone marrow. Tests involving the transplant of the engineered blood into mice have shown encouraging results. In addition to the promise of unlimited supplies of blood for routine and emergency medical needs, this research promises to lead to a better understanding of how red blood cells are formed—through a process called erythropoiesis—and can serve as a model for studying important viral or parasitic infections that target red blood cells. This is an example of how adult stem cells may potentially be used in significant therapeutic applications.

(image courtesy of Nature Publishing Group, reprinted by permission from cover of *Nature Biotechnology* Jan. 2005)

NEED FOR A COLLABORATIVE FEDERAL AGENCY EFFORT

In this document, the MATES IWG defines four overarching goals for the tissue science and engineering field as a whole. Based on examination of the opportunities presented by tissue science and engineering, the MATES IWG has identified eight strategic priorities in which Federal agencies can leverage their specific interests and contributions to accelerate short-term successes and foster longer-term commitments. These strategic priorities are not the purview of any one agency. For example, scientific success will require discovery in and application of advancements in biological and materials science at the cellular, tissue, and organism level, based upon better physical measurement tools, measurement standards, and predictive models. To achieve the full promise of tissue science and engineering, the U.S. Government will also need to provide leadership in the interdisciplinary fields of bioethics, logistics, premarket review, standards development, and patient reimbursement.

Consistent with their respective missions, some of the agencies of the MATES IWG will be contributors of basic biochemical knowledge and physical and computational technologies; other agencies have applications or regulatory needs that will benefit from these advancements. Some agencies will transition the knowledge and technologies gained to clinical applications, others will be involved in non-clinical applications, and some will focus solely on the development of relevant but broadly applicable technologies. Thus, the roles for, and benefits to, the agencies of the MATES IWG will vary from agency to agency. Because of the inherent complexities of tissue science and engineering processes and products—the science behind them, the technologies that create them, the products that result from them, the regulations that protect those who use them, and the health care enterprise and individuals who pay for them—the Federal Government has a number of roles to play in advancing this field.

The MATES IWG was established in 2000, and its five-year plan was renewed in 2002. The principal purpose of the MATES IWG is to provide a platform across which member agencies can interact and exchange information on tissue engineering efficiently and effectively. MATES IWG accomplishments to date include the following:

- Commissioning the *WTEC Panel Report on Tissue Engineering Research*, which was published in 2002 (McIntire et al. 2002)
- Joint progress report presentations at meetings of grantees, industry-sponsored groups, and the National Science and Technology Council (NSTC) Biotechnology Subcommittee
- Use of Federal reviewers from many agencies for program and proposal evaluation

- Joint development of the language for a National Institute of Biomedical Imaging and Bioengineering (NIBIB) RFA on tissue engineering
- Subsequent development and release of a funding opportunity announcement for research on "Enabling Technologies for Tissue Engineering and Regenerative Medicine," and an associated interagency memorandum of understanding to carry out that program
- Interagency knowledge-sharing via MATES IWG meetings and conferences
- Development of the MATES IWG website (www.tissueengineering.gov), which serves as a one-stop source for information on the Federal Government's activities in tissue engineering

The membership and interests of the MATES IWG have expanded as both the number of tissue engineering applications and the need to advance the underpinning science have increased.

Advancing Tissue Science and Engineering: A Foundation for the Future outlines a role for a coordinated Federal effort that leverages each agency's strengths and contributions. Leadership from the Federal agencies involved in tissue science engineering will be required if the United States is to:

- Set the standards for the efficient and effective management of tissue science and engineering research and products
- Maintain U.S. scientific and engineering preeminence in this field and ensure that the potential of this promising technology is fulfilled
- Support the national research priority of developing a deeper understanding of complex biological systems, which requires collaborations among physical, computational, behavioral, social, and biological scientists and engineers
- Capture the potential benefits to society from both medical and non-medical applications of tissue science and engineering

2. OVERARCHING GOALS FOR TISSUE SCIENCE AND ENGINEERING

The numerous potential applications for engineered tissues—as sensors, as information processing components, as diagnostics tools, and as therapies—present a progression of scientific and technical hurdles. Therapeutic applications of tissue science and engineering are arguably the most challenging, but all applications have common elements and scientific and technical challenges that will have to be overcome. This chapter outlines the overarching goals articulated by the tissue science and engineering community and serves as the basis for identifying, in Chapter 3, eight strategic priorities for the Federal Government agencies to pursue within this strategic plan.

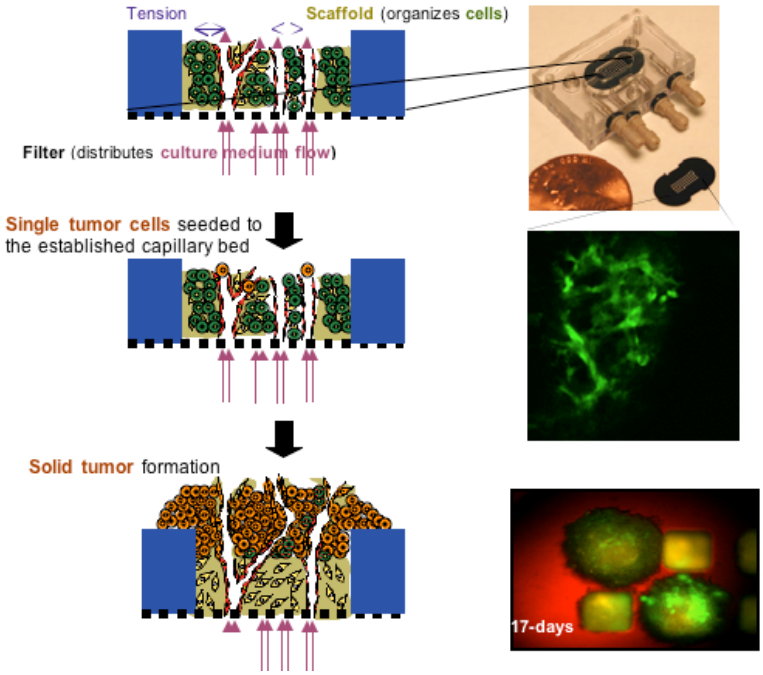
Tissue engineering can involve both living and biologically-derived components such as cells and proteins, as well as manufactured components such as organic polymers and inorganic materials. Combining such components into a fully functional unit requires control of many physical, chemical, and biological characteristics simultaneously. For example, at a minimum an engineered tissue is likely to require: (1) blood vessels for efficient transit of soluble nutrients and wastes; (2) suitable compliance and tensile strength; (3) molecular recognition sites that cells will respond to appropriately *vis à vis* growth and gene expression; (4) cells with the sufficient biological capacity to develop or retain the desired biological functions over time; and (5) biocompatibility within the host tissue if transplanted. Measurement, modeling, integration and assessment of these factors will require increasingly sophisticated tools and technologies. Orchestration of diverse elements into a functional tissue that can be reliably made to exacting specifications and delivered on demand presents unique technical, organizational, and logistical challenges as well.

The following sections outline progress to date and overarching goals that must be addressed to move forward in tissue science and engineering. Issues are described in three major groups: (1) cells and matrices; (2) the tools available and needed to obtain the required qualitative and quantitative data; and (3) the practical and regulatory considerations involved in bringing the promise of tissue-based technologies to fruition.

UNDERSTANDING AND CONTROLLING THE CELLULAR RESPONSE

Cells are the functional elements of tissue science and engineering. A fundamental challenge for the field is to model organogenesis—the normal process by which cells self-assemble into tissues and then organs. This complex process requires that cells proceed down a programmed differentiative pathway, which in most cases has not been well defined. However, information accumulating from studying the developmental programs of many different organisms reveals an evolving understanding that tissue architectures seem to be assembled from common building blocks and regulatory signals. Cells respond to a huge array of spatial and temporal choices by assembling and reassembling to give the variety and complexity that leads to tissue and organ formation. Recent evidence has shown that the path is not one-way, and cells can de-differentiate and even transdifferentiate (i.e., enter a different developmental program) if given the appropriate signals. Understanding, much less controlling, such intricate possibilities will entail a greater knowledge of the ways that cells receive, order, and respond to information and how the resultant messages are integrated into the cell's state in real time to present a particular phenotype.

Tissue-Engineered Disease Models

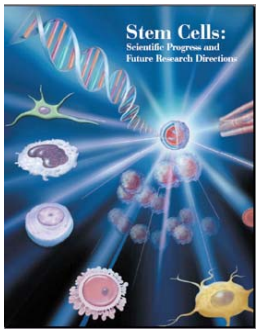


Tissue science and engineering offers a promise of cheaper and better testbeds for clinical research such as drug and chemical testing and disease models, thereby reducing or eliminating the current use of millions of animals annually. Appropriate complex tissue models may more accurately reflect human responses. Researchers in Massachusetts, supported by Federal and private funds, are developing 3D tissue models to study the growth of tumors in tissue beds and for use in drug screening. The figure shows a schematic of a small tumor grown from prostate tumor cells seeded into a capillary bed, the experimental system for growing a liver capillary bed, and the tumor spilled out of the tissue bed and grown along the surface of the scaffold at Day 17.

(images courtesy of Nature Publishing Group, reprinted by permission from Griffith and Swartz 2006)

Cells receive messages from multiple sources, each of which initiates a cascade of intracellular responses that ultimately determines a phenotypic change. Additionally, nutrient stores and highly interactive molecules may help establish intracellular depots and cellular energy budgets determining cell fate. Some signaling pathways can result in an "auto destruct" response in which the cell undergoes apoptosis—programmed death—via breakup of its DNA and dissolution of its membranes. Cells also share information by elaborating molecular signals that regulate their own behavior and that of other nearby or even distant cells. In addition, cells secrete a variety of structural and enzymatic proteins that chemically and physically remodel their neighborhood—the extracellular environment. Researchers are compiling lists of molecules that control intracellular checkpoints, cell-cell interactions, cell-matrix remodeling, and that stimulate migration, proliferation, differentiation, and/or apoptosis of cells in appropriate locations and sequences to form functional multicellular organs.

Stem Cells for Tissue Science and Engineering



Broadly defined, a stem cell is any cell that can self-renew—propagate indefinitely—and can also be induced to differentiate—change to take on a more specialized function—when it receives an appropriate physical or chemical signal. Properly understood and harnessed, stem cells can play important roles in understanding how cells develop, communicate, and differentiate under normal and abnormal conditions. Further, their ability to grow rapidly and potentially, under controlled laboratory conditions, to develop into specialized tissue cells is considered critical for generating tissue-engineered products.

(image courtesy of Terese Winslow, © 2001, reprinted by permission from cover of NIH 2003)

Researchers are investigating the potential contributions of adult and embryonic stem cells to tissue science and engineering. Broadly defined, a stem cell is any cell that can self-renew (i.e., propagate indefinitely) and also be induced to differentiate given the appropriate physical and chemical signals. To date, stem cells have been obtained from six general sources (with varying degrees of success):

- The interior of long bones houses the precursor compartment for renewing the cellular components of blood, and hematopoietic (blood forming) stem cells can be reliably harvested to generate red and white blood cells, as well as other cell types.
- Various tissues of the adult body (e.g., fat, muscle, skin) have been used as a source of stem cells.
- Gestational tissues (e.g. umbilical cord, yolk sac, and amnionic fluid) have become a robust source of multipotent stem/progenitor cells.
- Embryonic stem cells have been obtained from the inner cell mass of the pre-implantation embryo as well as from blastomeres of very early-stage embryos.
- Embryonic germ cells (functionally equivalent to embryonic stem cells) can be isolated from the developing gonads of the fetus.
- Finally, there is early evidence that addition of extracts of pluripotent cells (e.g., fertilized or unfertilized eggs, or other stem cells) can cause reversion of differentiated cells into less specialized cells with stem-like properties.

Properly understood and harnessed, stem cells can be important elements in the generation of products based on tissue science and engineering. The ability to grow, under controlled laboratory conditions, large numbers of cells that will reliably and stably develop into the cellular portion of a complex tissue is considered critical to production of tissue-engineered products.

The ability to control cell phenotype and direct tissue formation is the ultimate goal of tissue science and engineering. Cell sourcing, expansion in culture, and the power to modify the differentiation state of a cell are critical parameters that must be controlled. Obtaining a sufficient source of cells is often a challenge due to the difficulty in isolating cells from a biopsy or tissue sample, and expanding the population is a challenge due to inherent biological limitations on the number and rate of cell doublings. This is an acute problem for *in vitro* expansion, since the supply of fully characterized and microbiologically tested cells can become rapidly exhausted. Adjusting the cellular machinery to allow greater proliferation can lead to other unwanted outcomes, such as unmanageable pre-cancerous changes, or differentiation down an undesired pathway. Design and

engineering of culture conditions that allow such control are currently a topic of significant research effort. The variety of culture conditions employed in different research laboratories also needs to be standardized so that data and outcomes can be compared and build upon one another into a unified description. Overall, improved cell culture protocols and reliable sources of stored cells for use in tissue engineering applications would help speed applications development.

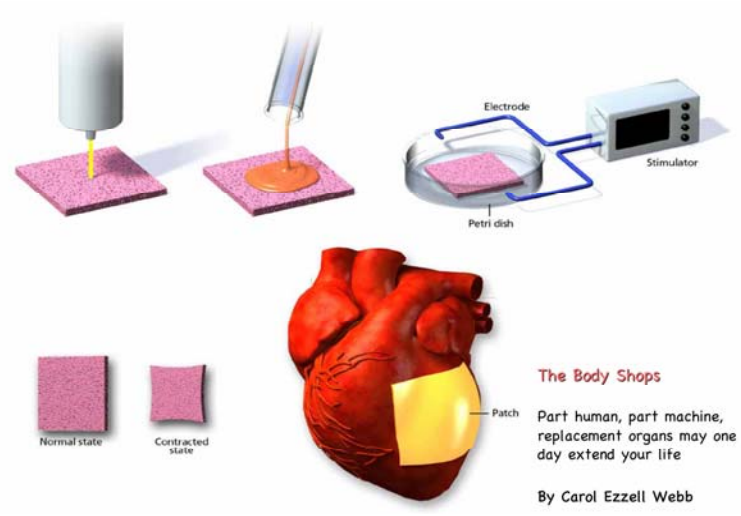
Understanding and Controlling the Cellular Response: Implications for the Future

Present:	Cell-based drug screening is used in pharmaceutical development. Animals are used as disease models.
Future:	*Tissue-based drug screening will be a more accurate assessment of drug action. 3D human tissue disease models will be created to understand human disease processes to minimize animal use.*
Present:	Risk of tissue and organ rejection means transplants are often unsuccessful, even with the use of expensive drug regimens that leave recipients with compromised immune systems.
Future:	*Tissues composed of the patient's own cells will not be rejected.*
Present:	Relatively simple tissues with limited functions (e.g., skin) can be constructed.
Future:	*Tissue and organ constructs with more complex functions (e.g., liver and pancreas) will be engineered and available.*
Present:	Complex tissues are often obtained from animals, with the possible risk of transmitting unknown microbes that could cause new diseases in human hosts.
Future:	*Engineered tissues will be assembled from pre-screened, non-animal sources to ensure the absence of disease-causing microbes, or other undesired elements.*
Present:	Damaged tissues are replaced with implants and components that cannot grow with the patient, that can wear out, or that provide only partial function.
Future:	*Damaged tissues will be replaced with tissues that can grow and regenerate.*
Present:	Blood is transfused from person to person to ensure oxygen-carrying capacity to tissues.
Future:	*Tissue-engineered red blood cells will be immunologically compatible with the patient and serve to carry oxygen to avoid the risks associated with transfusion.*

FORMULATING BIOMATERIAL SCAFFOLDS AND THE TISSUE MATRIX ENVIRONMENT

The engineering of tissues *in vivo* and *in vitro* requires biomaterials that function as scaffolds to guide the growth, differentiation, and organization of cells, thus giving support, strength, and form to tissues and organs. Since the process of forming tissues from cells is a highly orchestrated set of temporal and spatial events, research on scaffold materials must address problems across this spectrum. For tissue science and engineering applications, the supporting material may be either biologically-derived or artificial, inert or bioactive, durable or subject to remodeling. There is a growing appreciation that the extracellular matrix (ECM) that surrounds the cells in a tissue also supplies critical chemical and physical signals to initiate or sustain cellular functions within that tissue. The cellular response to the nature and density of molecules encountered in the ECM must be catalogued and characterized if it is to be used for engineering specific responses.

Blueprint for Growing Heart Tissue



Our inability to vascularize and perfuse thick cell masses has blocked efforts to make many types of functional tissues including, most critically, cardiac muscle. As shown here, porous support structures, or "scaffolding" allows researchers to optimize heart cell proliferation into 3D tissue. The cell-seeded scaffolding is then placed into a culture vessel where the cells are bathed in nutrients and gases. An electrical field stimulates the organization and growth of the cells, helping them to become synchronized. The cells within the engineered tissue begin to communicate with one another when a clinical pacemaker generates similar electrical signals like those found in a developing heart. A working piece of heart tissue is produced after eight days. This is the first time scientists have succeeded in using an electrical current to produce dense heart tissue that beats in rhythm with that of a live animal's heart.

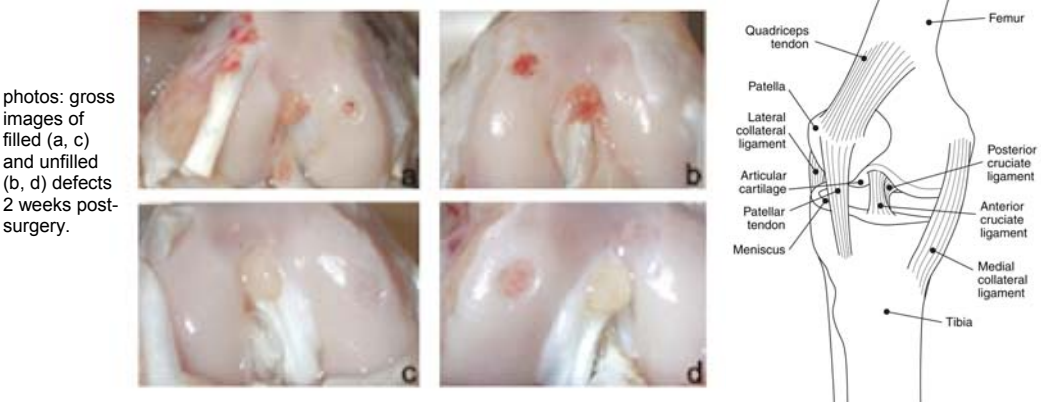
(images courtesy of the National Academy of Sciences, © 2004, reprinted by permission from Radisic et al. 2004)

Scaffolds

Biomaterial scaffolds can be broadly divided into two categories based on their basic composition: synthetic and naturally-derived materials. At a minimum, the scaffold for engineered tissue should: (1) possess adequate mechanical properties to match the intended site of implantation (if any); (2) possess interconnecting pores of appropriate scale to favor cellular infiltration, tissue integration, and vascularization; (3) be made from material with controlled biodegradability or bioresorbability; (4) have appropriate surface chemistry for cellular attachment, differentiation and proliferation; (5) not induce any adverse response; and (6) be easily handled and fabricated into a variety of shapes and sizes (Hutmacher 2001).

Historically, the choice of scaffold has been largely dependent upon available materials, but increasingly, due to advances in the science, materials are being selected based on the properties needed for a particular application. The earliest engineered tissues utilized synthetic polymers that were biocompatible, biodegradable, and provided appropriate strength, resilience, toughness, and porosity. However, these materials are not instructive for cells. Many tissues are still designed using these "workhorse" scaffolds because of their proven safety. Examples include a large library of scaffold materials based on derivatized polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolactone (PCL). The popularity of these materials is largely based on their use in a wide variety of FDA-approved products suitable for implantation, and the fact that their breakdown products are common metabolites (glycolic or lactic acid). While adaptation of such existing materials has fulfilled some needs in the field, most applications demand the development of new materials that allow for better control of bulk and surface properties, along with mechanical, chemical, and biological cues.

Synthetic Biomaterials for Replenishing Damaged Cartilage



photos: gross images of filled (a, c) and unfilled (b, d) defects 2 weeks post-surgery.

Cartilage, the tough connective tissue in joints such as knees and elbows, is almost impossible to repair naturally due to the lack of blood vessels through which the body can deliver healing nutrients. Researchers in North Carolina have developed a liquid polymer gel that helps cartilage heal itself. The gel is "poured" into the torn tissue, and then hardened through exposure to laser light. After only 30 seconds, the gel is hard enough to serve as a scaffold on which new chondrocyte cells—the raw material that makes cartilage tissue—grow and repair the cartilage naturally. Tests carried out *in vivo* in rabbits have shown promising results.

(photos at left courtesy of Springer, reprinted by permission from Nettles et al. 2004; image at right courtesy of the National Institute of Arthritis and Musculoskeletal and Skin Diseases)

Matrix

Many of the matrix materials currently under development are extracted from or modeled on extracellular matrix. As such, major components include collagen, elastin, proteoglycans, and a wide variety of other proteins and signaling molecules. Popular variations include formulations that are fluid at one temperature and then self-assemble into a solid form at the working temperature.

A primary concern for the choice of matrix material is a set of appropriate physical properties to support and sustain cells over time within the resident environment—either in the body and/or under defined culture conditions. Since tensile, compressive, shear, and bending forces all contribute to material toughness, resilience, and durability, all new candidate materials must be characterized before any predictions about performance can be made. Understanding the limits of these processes is also important in determining and controlling the persistence of engineered constructs—their biodegradation and remodeling *in situ*.

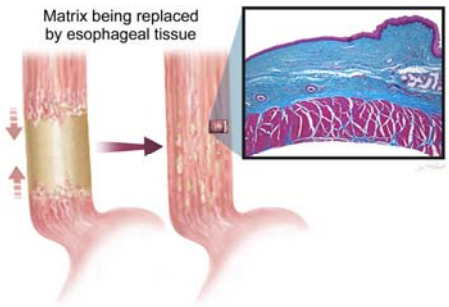
Scaffold porosity is an important consideration for tissue strength and structural integrity. It is also a key determinant for cellular and vascular infiltration. Pores that are too small for cells to enter the matrix, or that are not continuous, allow only surface colonization of the structure. Insufficient porosity also limits the size of viable engineered constructs because blood vessels do not develop where cells cannot penetrate. Such low porosity structures have generally poor biocompatibility over time.

The matrix stiffness controls limits on diffusion of nutrients, wastes, and growth regulators. Spongy, highly flexible gel-based matrices generally impede fluid flow and rapid diffusion. A stiffer matrix can produce structural stress within the component cells that leads to intracellular and

extracellular remodeling, especially in tissues with cells that are tightly adhered to the scaffold. Such parameters are important in driving terminal differentiation of cells into a specific tissue type.

Design of new materials that meet specific performance criteria is a challenge for the field. Equally challenging is the development of design principles for new materials based on a physical and quantitative understanding of how cells respond to molecular signals and integrate multiple inputs to generate a given response in their physiological environment. In addition, these new biomaterial scaffolds better address physiological responses such as toxicity, immunogenicity, foreign body response, complement activation, and evolving structural integrity over time. Understanding and quantifying the relationship between biomaterial scaffolding characteristics (such as bulk composition and surface topography) and physiological responses (such as integration of biomaterial constructs into living organisms) remain among the most pressing materials challenges today.

Naturally-Derived Biomaterials for Esophageal Tissue Engineering



Extracellular matrix (ECM) is a complex structure of proteins and other molecules that surround and support cells in the body. ECM is often called connective tissue.

An interdisciplinary research team is currently investigating the use of ECM as a scaffold material to aid in the reconstruction of tissues in the esophagus and trachea. The team is exploring ways to use skeletal muscle cells, esophageal epithelial cells, vascular endothelial cells, fibroblasts, and ECM proteins to build a structural framework on which the body's own cells can then grow and repair the damage.

(images courtesy of Stephen Badylak, McGowan Institute for Regenerative Medicine)

Cellular Organization

A special challenge is to understand how to control and direct the 3D organization of cells into tissues. Cell phenotype and function is dependent on the aggregate response to various chemical signals, physical stresses via substrate adhesion, and spatial/temporal changes in the internal and external environment. Culturing cells in 3D allows establishment of more complex (and physiologic) gradations of growth and differentiation factors. Such tissue-level gradients supplement the immediate cellular environment providing each cell with an "address" in the tissue architecture that governs its state. Additionally, once grown beyond the dimensions allowing efficient diffusion-based nutrient and waste exchange, functional tissues require vascularization. Understanding and controlling the formation of substantial blood-carrying vessels has been elusive.

Biomaterial Scaffolds and the Tissue Matrix Environment: Implications for the Future

Present: The complexity of clinical studies on combination products often drives tissue engineers to design to the properties of materials that have already been approved by the FDA for previous applications.

Future: *Better understanding of the host's integration of implanted tissues will allow scaffolds that are uniquely suited to the purpose with controlled mechanical/physical properties and degradation rates.*

Present: Cell or tissue cultures (usually 2D) can be used to screen for drug toxicities.

Future: In vitro *models of human systems will be built to the scale and complexity desired for the application to be evaluated. Many "cassettes" of living tissue can be integrated to simulate tissue, organs, or whole systems.*

Present: Engineered tissues are designed for the "best fit" to the current conditions within a host. Once transplanted, remodeling to suit evolving conditions is largely "hit or miss."

Future: *Constructs will be remodeled over time by a combination of host responses and additional material added by the therapist to achieve the desired reconstruction at the structural and chemical level.*

Present: Chemical/biological sensors are delicate, complex devices with very limited range and scope that do not accurately predict the organismal response to environmental toxins.

Future: *Robust sensors based on tissues and/or organ fragments will be used to rapidly detect biological or chemical threats in a wide variety of public spaces.*

Present: Scaffolds are not fully biocompatible, causing mild to severe inflammation upon transplantation and limiting usable implant lifetimes.

Future: *Biomaterials with tunable properties will be available on demand for a range of clinical applications*

Present: Comparative analysis of the characterization and performance of scaffolds cannot be conducted to advance technologies due to the lack of standard reference materials.

Future: *Standard reference scaffolds with known geometries and 3D properties will be available to benchmark R&D and inter/intra-laboratory analysis.*

Present: *In vitro* testing to determine performance of biomaterials is based on a limited number of fluorescent markers used to image biological behavior.

Future: In vivo *biomedical imaging techniques can be adapted to monitor therapeutic delivery, biological factor release, and scaffold performance by doctors using materials engineered with markers.*

DEVELOPING ENABLING TOOLS

The development of tissues is the result of molecular and supramolecular interactions that occur on a continuum of time and spatial scales in response to the many chemical and physical parameters within cells, between cells, and within organisms. Thus, tissue science and engineering research resides at the interface of the life and physical sciences, and basic principles from both are needed to advance this area of biotechnology. While great progress has been made towards understanding these interactions, additional research in the life sciences and the physical sciences is required to improve understanding of the interactions between the living and nonliving components of engineered tissues. Such explorations will be critically dependent on the development of enabling technologies from the physical and engineering sciences that will expedite and facilitate accurate measurements and assessments of molecular and cellular interactions. In some cases novel methods and tools are required while in other instances tools and technologies could be adapted from other fields and tailored for use in tissue science and engineering. Further progress in tissue science and engineering is dependent upon this effort to develop new and improved measurement and monitoring tools and technologies.

Achieving sufficient insight into these complicated relationships will require both measurement-based knowledge of molecular components and computational models that provide insight into the relationships of these molecular components to one another. The cycle of quantification, evaluation, prediction, and verification is a common theme in all the current challenges for tissue science and engineering.

Biomarkers, High-Throughput/Content Assays and Instrumentation

Assessing the physiological state or condition of a cell or tissue requires measurable surrogates or indicators called biomarkers. Biomarkers can take many forms and include intracellular molecules and image contrast characteristics. Biomarkers must be validated by multiple techniques to ensure that they are accurate indicators of cell and tissue physiology. For example, the identification of

stem cells and the determination of their state of differentiation require biomarkers appropriate to the interim stages of development. Biomarkers are also needed to understand the intracellular machinery that guides cells to become functional tissues.

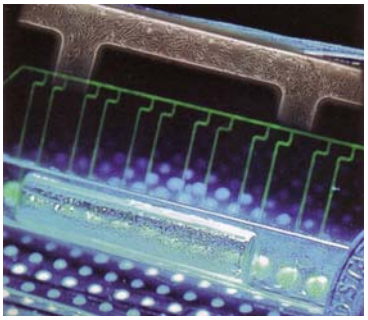
Reliable imaging, sorting, and assays to identify and assess biomarkers are required for collecting accurate, reproducible data. High-throughput and multiparametric approaches are increasingly recognized as critical for collecting sufficient data to inform predictive models and to allow unequivocal determination of the state of tissues *in situ* (i.e., in the body) over time.

High-throughput technologies based on automation, miniaturization, and multiplexing are becoming available to the systematic study of cells and tissues. For example, genomics, proteomics and metabolomics are methods that allow for the rapid and simultaneous quantitation of information about the functional state of cells and tissues. This knowledge is fundamental to our understanding of the correlations between molecular signature(s) and tissue function (i.e., mechanical, metabolic, and structural activities).

Improved success with cell-based therapies is also being enabled by recent advances in technologies for cell sorting and analysis. The performance of flow cytometers is being pushed to new levels of sensitivity and discriminatory power. The development of devices that enable simultaneous processing of an increasing number of parameters on higher throughput platforms on the microfluidic scale allow for the determination of how cells behave under a large number of defined circumstances. These results can be coupled with tissue-level data to provide an understanding of the overall processes of importance in tissue science and engineering.

Advanced high-throughput assay approaches are essential for rapid screening of novel materials as candidates for scaffolding, and for optimizing the many parameters of culture conditions. These tools will also enable the development of increasingly sophisticated tissue analogs that can process complex environmental information and serve as smart sensors in public health surveillance, or partially replace animals in pre-clinical drug testing.

Engineered Tissue for High-Throughput Screening



Scientists studying the behavior of complex, highly specialized cells (neurons in the brain, for example) face a fundamental constraint: such cells require other specialized cells to feed, clean, and protect them. Federal agencies are sponsoring the development of “labs-on-a-chip”—highly complex environments where specialized cells can grow and thrive. The chips contain all the necessary support cells plus the heat and fluid flow necessary to simulate the specialized cells’ natural environment. Labs-on-a-chip can be used for high-throughput screening; chips containing small-scale biological environments can be “slotted” into and out of testing devices such as sensors, and used to test for drug side-effects and toxicity.

(photo courtesy of the National Academy of Science, © 2004, reprinted by permission from Gu et al. 2004 and Weiss 2005)

Imaging Technologies

Currently, studies of engineered tissue constructs often are conducted by implantation of the construct into an animal, and after some time sacrificing the animal to assess the result. This approach does not provide sufficient nor efficient information. Imaging techniques have the potential for tracking small numbers of cells, functional assessment and characterization of engineered tissue constructs, and monitoring changes over time in a non-invasive manner. Imaging challenges include development, optimization, and integration of technologies at the many levels of

scale, resolution, and dimensionality needed—from molecular to tissue to whole body. Validated methods and protocols will improve interoperability of data. High-resolution imaging methods that allow real-time, non-invasive study of processes on the tissue, cellular and sub-cellular levels could significantly advance the field of tissue science and engineering. There is a need to improve correlation between *in vitro* assays in the laboratory and *in vivo* conditions in the body.

Magnetic resonance imaging with improved resolution and sensitivity promises to be applicable to sensing inflammation, apoptosis, cell trafficking, and gene expression. High-energy photon imaging (such as single photon emission computed tomography and positron emission tomography) has high sensitivity, and has been shown to be successful for imaging of stem cell survival in infarcted heart and in pancreatic islet cell transplantation. Optical imaging methods that circumvent challenges such as thickness and highly-scattering properties of tissues also offer potential for non-invasive assessment of tissue structure and function in real time. Approaches to be pursued include multi-photon microscopy, optical coherence tomography (OCT), which promises to be capable of providing chemically-specific structural information, and Doppler OCT. Other optical techniques with the potential to yield spatially and temporally resolved chemical and physical information include Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy. Currently, signals can be weak and spectral information can be complex and difficult to interpret.

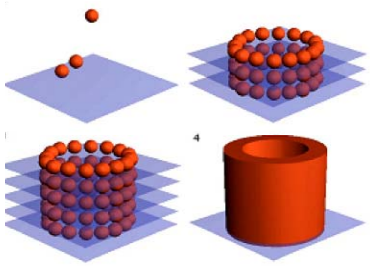
Reliable tests and imaging are required for collecting accurate data that are comparable between different laboratories. High-throughput and multiparametric approaches are increasingly recognized as critical for collecting sufficient data to inform predictive models and to allow unequivocal determination of the state of tissues *in situ* (such as in the body) over time. Imaging challenges include quantification, the many levels of resolution needed (from molecular to tissue to whole body), and imaging of tissue mass in 3D. Validated methods and protocols will improve interoperability of data. Correlation between *in vitro* assays in the laboratory and *in vivo* conditions in the body must be improved.

Fabrication Technologies

Substantial progress has been made in 2D patterning of biological substrates for controlled cell-material interactions at micrometer scales. The literature is replete with examples of cellular patterning achieved through deposition of cell adhesive/trophic biomolecules using photolithography or microstamping, or through topographical features etched in silicon for guidance. Tissue engineering poses additional challenges for controlling the 3D cell-material interface.

Successful fabrication of tissue-engineered scaffolds depends on an array of biomaterial properties that are expressed over nanometer to micrometer scales. These properties include matrix composition, architecture, porosity, surface chemistry, and degradation dynamics, as well as scaffold strength, shape, and compliance. A process borrowed from industrial design that has impacted tissue engineering science is rapid prototyping (RP) technology (also known as solid freeform fabrication), involving layered fabrication from computer-aided designs. Innovation in the fabrication of 3D biological scaffolds has resulted from the adaptation of RP technologies to accommodate aqueous-based, bioactive components. While there have been efforts to deposit cells in the layers during the fabrication process, the majority of effort has been directed towards fabricating scaffolds that are permissive for cellular integration.

Organ Printing



Biological systems exhibit a phenomenon called "self-assembly" in which the molecular building blocks of life assemble into cells, tissues, and entire organisms. With Federal funding, researchers in Missouri are trying to fill in the gap between gene expression and 3D structure by correlating biophysical properties of cell aggregates with known gene expression patterns to assess the effects of molecules on cardiac and limb development. The results will elucidate new principles of multicellular self-assembly and may enable novel approaches to engineering regenerative tissues.

(images courtesy of Gabor Forgacs, University of Missouri)

Computational Modeling and Bioinformatics

A large and expanding array of high-throughput tools—genome sequencing, microarray-driven gene expression studies, post-translational modifications and proteomics scans, metabolomics breakdowns, and defining network topologies—are providing vast amounts of data, over several measurement scales, about the state of a cell within its environment. A systems approach—new representations that transcend cataloging and organizing the "parts list"—will be needed. Integrating information into a knowledge base for tissue formation and maintenance will require understanding the intracellular machinery that conveys cellular identity; suggesting testable hypotheses of how the extracellular components of tissues elicit cellular responses such as migration, proliferation, and differentiation; and predicting temporal changes in cell-scaffold composition. Through iterative cycles of model building, we should acquire an understanding of how such cells aggregate to become tissues, which tissues integrate into organs, and how organs respond to their environment over time. Ultimately, sufficiently complex models, developed with the aid of validated experimental data, will enable rational design and implementation of engineered tissues.

Future advances in tissue science and engineering will be driven not only by improved modeling approaches that allow more efficient multiscale predictions but also by well-characterized and validated experimental data from which the models will be developed. Databases that allow easy addition and extraction of validated data will be essential to support model development. A bioengineered 3D tissue system that can be reproducibly quantified and modeled could radically increase the rate at which functional tissues are produced.

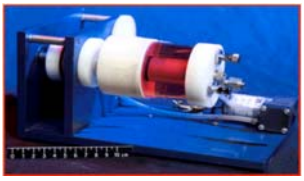
Understanding the intracellular machinery—how cells become tissues, how tissues become organs, and how organs respond to their environment over time—will require assimilating vast amounts of data into computational models. Time- and computationally-efficient methods through multiscale modeling of systems biology to link gene and protein expression to cellular phenotypic dynamics will turn information into knowledge. Such models will be critical for allowing prediction and subsequent testing of the large number of parameters that influence cells, tissues, and organs.

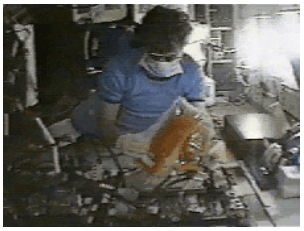
Bioreactors

Producing 3D tissues *in vitro* requires appropriate bioreactors that simulate physiological environments for the creation, physical conditioning, integration, and testing of cells and their support structures. Currently, bioreactors are generally designed to meet the requirements of controlling the culture environment such as temperature, oxygen, pH nutrients, metabolites, and biologically-active molecules. In addition, state-of-the-art bioreactors ensure automated feeding, provide effective mass transfer, and allow coupling to external mechanical and physical stimuli as well as real-time imaging for assessment of tissue function. Since the current generation of

bioreactors was developed to support the rapid growth of cells in solution, much work in this arena is required to design devices that can support self-assembly of multiple cell types into complex tissue structures.

A Rotating Cell Culture System (RCCS)





Heat, cold, salt, darkness—over a billion years, life has adapted to many stressful environments. A joint Federal research program is investigating how cells adapt to a new environment—weightlessness. In normal gravity, cells grow as a single monolayer on the bottom of a flask. In low gravity, cells assemble into tissue-like aggregates.

This Rotating Cell Culture System simulates zero gravity by rotating at a rate that causes cells to remain in continual free fall at less than 1% of Earth's gravity. RCCS may be an important tool for understanding how cells aggregate and function as complex tissues.

Left: Astronaut John Blaha operating the bioreactor aboard the Mir Space Station.

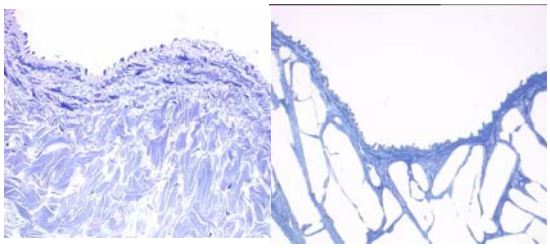
(photos courtesy of the National Aeronautics and Space Administration)

Tissue Preservation and Storage Methodologies

The preservation of engineered tissues will enable a consistent supply of off-the-shelf tissues for basic research, device development, and clinical applications. Yet preservation techniques are far from perfect, and often the damage that is done to cells and tissues is not immediately apparent or easily quantified. Additionally, the use of cryopreservation to store tissues is rudimentary, with tissue integrity generally lost upon thawing.

Tissue Preservation Technologies

Federally-funded researchers in South Carolina have developed a novel tissue preservation technology that prevents ice formation in cryopreserved tissues. Chemical compounds interact with the water in the tissue, causing it to vitrify—form a liquid that is too cold to flow, like a glass—rather than turn into ice, preventing the tissue from being damaged by ice formation.



Photos of rabbit veins cryopreserved using vitrification technology appear normal (left), in contrast to traditional methods in where huge holes are created by the formation of ice (right). When implanted in a rabbit, the vitrified vein maintained its normal function for four weeks.

(photos courtesy of Nature Publishing Group, reprinted by permission from Song et al. 2000)

Other preservation methods need to be explored. Achieving maximal function across the range of applications will require long-term dry storage at ambient temperature, and studies aimed at such "freeze-dried" storage for living cells and tissues are just beginning. Universal standards and protocols for preservation, and criteria by which to assess the effects of preservation, will also be the key. Improving tissue preservation technologies will be one of the most significant factors in reducing the cost of tissue-engineered products, because the majority of constructs will have very short shelf lives.

Learning from Nature's Own Freezing Process

Wood frogs can be found from Georgia to Alaska. As temperatures drop below freezing, ice crystals begin to form beneath the frog's skin; if the temperature drops far enough, even the veins, arteries, and internal organs freeze. When the temperature eventually climbs above freezing and the frog thaws, normal blood circulation and neural activity return. Wood frogs undergo this process many times without harm; if medical researchers can figure out how and why, they may be able to apply the same technique to preserve transplant organs.

(photo courtesy of Kenneth Storey, reprinted by permission from Fahrenthold 2004)

Enabling Tools: Implications for the Future

Present: Cell biology experiments frequently test one variable at a time, and in a limited time domain.

Future: *Quantifying hundreds of parameters simultaneously over large spatial and time scales will speed our understanding of complex biological phenomena.*

Present: Current methods are insufficient to fully evaluate the safety, functionality or state of tissue engineering products.

Future: *Manufacturers will have biomarkers to test for specific criteria that will indicate the condition of the engineered tissue.*

Present: Assessments of function of engineered tissues or fate of implants require destruction of the samples.

Future: *Non-invasive and non-destructive measurement methods will allow determination of the health of an implanted tissue over time.*

Present: Cell-based drug screening is used in pharmaceutical development, followed by several rounds of testing in animal models of disease.

Future: *Tissue-based drug screening will be a more accurate assessment of drug action. 3D human tissue models will be created to understand human disease processes to minimize use of animals in research.*

Present: Molecular sensors are capable of detecting only single pathogens or chemicals.

Future: *Tissue-based sensors using cell signaling pathway components as a detection mechanism will be able to detect and identify a wide range of pathogens and chemicals.*

Present: Rudimentary models are being designed for describing cell signaling pathways.

Future: *Accurate prediction of currently unexpected adverse effects in cellular and tissue response to environmental stresses and pharmacological treatments.*

Present: Many commercial living skin products have a shelf life of five days or less, resulting in much waste and an expensive product. In addition, limited time that organs and blood products can be stored severely limits their effective distribution and deployment.

Future: *Improved shelf life through better preservation technology will reduce the cost of living tissue products, and will also permit the completion of standardized sterility tests for medical products being completed before clinical application. Longer-term storage will allow greater availability of vitally needed organs and blood cells.*

PROMOTING SCALE-UP, TRANSLATION, AND COMMERCIALIZATION

If the benefits of tissue engineering are to be realized, the field must deliver products for clinical or non-clinical applications that can be commercialized. There is much work to be done on the technical side in translating laboratory-scale fabrication techniques into large-scale production of high-quality products that meet good manufacturing practice (GMP) standards. Additionally, many tissue-engineered products are complex constructs involving cells, scaffolds, and signaling molecules, which will undoubtedly need regulation as "combination products". Finally, these cell-based therapies are relatively new and untested *vis-à-vis* long-term health benefits. While the promise of engineered tissues offers hope for curative rather than palliative care, careful attention must be paid to the data collection that will support and empower robust reimbursement strategies.

Enabling technologies that will be needed include techniques to cost-effectively grow tissues and organs on a commercially relevant scale, criteria and testbeds that assure physiological functionality, and methods to establish biosafety, quality assurance, stability, and predictable performance. Better storage, shipping, and packaging techniques are required.

Advances in both measurement-based instruments and reference materials are needed to characterize, evaluate, and certify products for commercialization. Standards are also necessary to qualify scaffolds, cells, and tissue constructs and to address the major barriers to the introduction of new technologies.

Progress will be accelerated by development of appropriate *in vitro* and *in vivo* pre-clinical models to address biocompatibility, toxicity, immunogenicity and inflammatory responses.

The use of engineered tissues will break new ground in many applications. As mentioned above, tissue-engineered medical products will most likely be regulated as "combination products" by the FDA, and require a very sophisticated understanding of the interplay between cells, scaffolds, and growth factors over the long term within an intact organism. Post-marketing studies will help assess the continuing safety and efficacy issues of such cell-based systems. Additionally, in the newly dawning era of true "regenerative medicine" the ability to fine tune the host's response to trauma and injury raises ethical and societal questions. Fortunately, the developers of cell-based therapies will make ample use of the well-established system of human subjects protections that are overseen by the nation's Institutional Review Boards (IRBs) and Federal regulations.

Promoting Scale-Up, Translation, and Commercialization: Implications for the Future

Present:	Tissue-engineered products are labor-intensive to produce with small lot sizes, variation in fabrication techniques, and challenging cell and matrix sourcing.
Future:	*Standard preparations of engineered tissues will be available for "on demand" use.*
Present:	The "boutique" nature of many tissue engineering processes and companies can delay regulatory approval as applicants cannot take advantage of time-tested and widely available practices and procedures.
Future:	*Widespread implementation of standard GMP fabrication techniques and assessments will increase the number and quality of "off the shelf" tissue-engineered products.*
Present:	Limited availability, complex storage and shipping requirements, and uncertainty in implantation techniques reduce the use of cell-based therapies.
Future:	*Better business models for product dissemination and implementation will empower robust marketing and data-driven reimbursement resulting in widespread use of engineered tissues.*

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3. STRATEGIC PRIORITIES FOR FEDERAL GOVERNMENT AGENCIES

The objectives of this MATES IWG strategic plan for tissue science and engineering are twofold: first, to present the overarching strategic goals for tissue science and engineering as set out in Chapter 2, and second, to define the role of the Federal agencies and their proposed activities to advance the field. The following sections describe two aspects of an implementation plan directed towards the latter objective. The first part identifies eight strategic priorities for Federal agencies where Government investments in research and development can have the most impact in furthering the overarching goals. Identification of these goals and priorities reflects the unique perspective of Federal agencies that: (1) conduct and support research in tissue science and engineering and related fields, (2) define the funding priorities and monitor the progress of Government-funded programs on the disparate disciplines related to tissue science and engineering, and (3) regulate the commercial distribution and Federal reimbursement of medical products derived from tissue science and engineering.

The second portion of this chapter outlines strategies for implementation of this strategic plan. It begins with a brief overview of previous and ongoing agency activities, followed by a discussion of general implementation strategies for promoting future progress towards all of the strategic priorities, concluding with a review of specific implementation strategies for each of the strategic priorities. Finally, the chapter concludes with a review of connections between tissue science and engineering and existing Federal research initiatives; leveraging from these complementary investments is key to helping realize the promise of this revolutionary technology.

ESTABLISHING PRIORITIES

Tissue science and engineering is at a crossroads. Much progress has been made, especially in the development of first generation products, and the growth in our understanding of cell-to-cell and cell-matrix interactions. Yet, critical gaps in basic biology, for example, mechanistic information and cell-substrate dynamics, as well as key deficiencies in technology development prevent further rapid advancement. Based upon these accomplishments and challenges, the MATES IWG member agencies have defined eight strategic priorities for the short-term focus of the U.S. Government's ongoing efforts in tissue science and engineering (Table 1). These priorities are drawn from the description of the state-of-the-art found in the preceding chapter and reflect gaps in the fundamental knowledge or operational capabilities that must be addressed for tissue science and engineering to advance.

Early visions for tissue engineering generally involved engineered scaffolding materials—either based on artificial, biocompatible polymers or processed natural matrix—and phenotypically defined cells—usually added into the construct or sometimes recruited post-implantation. Such constructions were seen as replacement parts for damaged or diseased organs within living individuals. Thus, tissue engineering has been used to produce commercially available skin substitutes and chondrocytes for articular cartilage repair. In addition, many engineered tissues and organs are in late stage animal studies or early clinical trials for use as implants. However, as our knowledge of the increasingly complex possibilities for cells as basic units for biological processes has grown, so has our need to use the integrated collections of cells known as tissues. This expanding vision has created both challenges and opportunities across the array of Federal programs supporting this field. Any discussion of tissue science and engineering reflects a broader view that goes beyond replacement of lost organ function to the use of tissues as the functional unit in a biologically-based application or system. Most assuredly, tissue transplantation and organ repair will remain a major goal. However, tissues are also being developed as chemical/biological

warfare agent sensors, information integrators/processors, miniature factories, models of intact animals, etc.

Table 1. Strategic Priorities for Federal Agencies*	
1. Understanding the Cellular Machinery	Obtain a molecular-level understanding of the basic physical, chemical, and biological conditions that direct cells to assemble into and maintain complex communities and functional 3D tissues.
2. Identifying and Validating Biomarkers and Assays	Identify biomarkers that can be used to specify cells in tissue-engineered constructs, assess their physiological state and/or condition such as their state of differentiation. Develop high-throughput, high-content assays for collecting multiparametric data and correlating that information with biologically significant outcomes.
3. Advancing Imaging Technologies	Develop high-resolution, non-destructive imaging technologies to assess engineered tissue function *in vivo* and *in vitro* in real time.
4. Defining Cell/Environment Interactions	Develop design principles for new materials based on a physical and quantitative understanding of how cells respond to molecular signals and integrate multiple inputs to generate a given response in their physiological environment. Test new matrices for biocompatibility and successful integration into relevant hosts or *in vitro* platforms.
5. Establishing Computational Modeling Systems	Make available user-friendly, predictive (physiological, biological, and mechanical) computational models whose simulations will aid in the engineering of reproducible tissue constructs. Such tools will drive the development of a systems-level capacity to analyze and understand cells, tissues, and organs.
6. Assembling and Maintaining Complex Tissue	Develop novel tools and bioreactors to precisely control rapid stem/progenitor cell expansion as well as the chemical and mechanical environment for phenotype-directed 3D tissue growth and function.
7. Improving Tissue Preservation and Storage	Optimize methods for long-term, low cost, low maintenance preservation that allow recovery of viable and functional cells/tissues. Develop better storage, shipping, and packaging techniques to provide tissues on demand.
8. Facilitating Effective Applications Development and Commercialization	Facilitate cost-effective production and scale-up of tissues and organs that can effectively meet regulatory requirements for good manufacturing practices and meet aggressive cost-benefit targets for a wide variety of applications.

*** Numerical order does not imply level of priority; instead it reflects approximate flow from basic understanding to application and commercialization.**

Bioartificial Engineered Human Bladder

This picture shows a bioartificial engineered human bladder prior to implantation. Tissue-engineered bladders are among the first of a new type of custom-made replacement organs to be developed. Bladder cells from the patient are seeded onto a biodegradable material molded into the form of the organ. The structure may then be implanted and the cells continue to grow *in vivo*, where they gradually take the shape of the scaffold. Preliminary results suggest that when the scaffold eventually biodegrades a fully functioning organ remains.

(photo courtesy of Anthony Atala, Wake Forest University)

The ongoing development of these diverse applications has revealed some common technical roadblocks preventing rapid advancement. Indeed, the WTEC report (McIntire et al. 2002) identified a better understanding of the underlying mechanisms of cell differentiation as a key "missing link" in positioning tissue engineering as a maturing therapeutic field. There was a consensus among the WTEC panelists that more basic studies in cell biology were critically needed. Yet, much of the necessary work is impeded by a lack of biomarkers, cell imaging techniques, sorting and assay systems, and computational tools for consistent, reliable, repeatable assessments. Cellular interactions with and within supporting matrices are not well understood. The behavior of cells within a 3D scaffold is closer to that seen *in vivo* than that of cells grown in a flat sheet in a culture dish, but the biological basis of this observation is not clear. Scale-up and manufacturing issues also have been frequently cited as barriers to the effective product development that precedes commercialization. In order to provide the robust and predictable function and "on demand" practicality needed for broad use, engineered tissues must be made less fragile, with improved long-term storage and preservation techniques. These common challenges that underpin virtually all applications of tissue science and engineering drive the need for information sharing and cooperation across the Federal agencies that comprise the MATES IWG.

What if There Were No Waiting Lists for Organ Transplants?

Organs for medical transplantation are in such short supply that patients are advertising over the Internet in the hopes of finding an appropriate organ donor. Transplantation of organs from donors requires replacement of one condition—organ failure or limb loss—with a second condition—pharmacologic immunosuppression. A long-range goal of tissue engineering is to minimize the need for organ donors and for pharmacologic immunosuppression of transplant recipients by making it possible to manipulate a patient's own cells to recapitulate organ function outside of the body, and then implant that tissue into the patient.

While the strategic priorities each have a discrete focus of critical importance, they are also interdependent and reflect a progression of enabling competencies, capacities and concerns. The Federal agencies that participate in the MATES IWG bring distinct missions, capabilities, and needs to tissue science and engineering, and thus will vary in their abilities to contribute to and derive from the common platforms that develop. Thus, the role for each agency within the full scope of this strategic plan is specifically identified (Table 2). MATES IWG agencies act as both contributors of needed expertise (via in-house expertise or support for specific projects) and users of the advances in one or more of the strategic priorities outlined below.

Table 2. Roles of Agencies in Strategic Priorities

Strategic Priorities (c=contributor of basic tissue science and engineering knowledge; u=user of tissue science and engineering knowledge)								
Agency *Mission relevance*	1. Understanding the Cellular Machinery	2. Identifying and Validating Biomarkers and Assays	3. Advancing Imaging Technologies	4. Defining Cell/Environment Interactions	5. Establishing Computational Modeling Systems	6. Assembling and Maintaining Complex Tissue	7. Improving Tissue Preservation and Storage	8. Facilitating Effective Applications Development and Commercialization
DOD *Engineering, battlefield applications*	u/c	u/c	u/c	u/c	u	u/c	u/c	u
DOE *Imaging technologies,* in vivo *gene assays*	u/c	u/c	u/c	u/c	u/c			
EPA *Molecular, cellular & computational approaches for prioritizing and screening chemicals for toxicity*	u/c	u/c	u/c	u/c	u/c			
FDA *Regulation of diagnostic and therapeutic products*	u/c	u/c	u	u/c	u	u/c	u	u/c
NASA *Engineering, in-space technologies*						c		
NIH *Biomedical applications*	u/c	u/c	u/c	u/c	u/c	u/c	u/c	u/c
NIST *Measurement science, standards, and technology*	c	c	c	c	c			
NSF *Fundamental science and engineering*	c	c	c	c	c	c	c	c
CMS *Health care payer*		u	u	u		u	u	u

Contributors have resources, facilities and technical programs that generate capabilities or knowledge that can be harnessed and brought to bear to advance tissue science and engineering, even if such concerns are generally peripheral to their mission.

Users will derive benefit from research, technology and engineering that originates in other agencies to apply to their agency's mission in tissue science and engineering, even if they do not actively perform such research.

IMPLEMENTATION STRATEGIES FOR TISSUE SCIENCE AND ENGINEERING

Introduction

While each of the participating agencies will develop its own approach for implementing this strategic plan, the agencies will also work in concert to develop an integrated, interagency implementation strategy. The agencies identified within each strategic priority area will work together to hold public meetings or workshops at which representatives from the various stakeholders—academe, industry, and the regulatory community—will be invited to provide input to defining the state of the art, specific technical goals, requirements for commercialization, and the regulatory landscape. The guidelines that result will form the basis of interagency implementation plans for advancing the aspects of tissue science and engineering that fall within missions of the relevant agencies. This approach will ensure that the implementation plans represent the best ideas of the experts and leaders in each field. Regular MATES IWG meetings and periodic MATES-sponsored conferences will ensure the integration of activities and help MATES member agencies assess overall progress in the field.

MATES IWG members are particularly interested in accelerating the transition from discovery science to product development. Thus, the IWG will foster interactions that encourage data sharing among agencies and the groups they support as well as early outreach to product developers concerning regulatory requirements. For example, regulatory officials will be invited to participate in panel reviews of proposals submitted to the research agencies.

WTEC Study on Tissue Engineering Research

In 2000 the MATES IWG member agencies funded the World Technology Evaluation Center (WTEC) to organize a comparative review of tissue engineering research and development activities in the United States, Japan, and Western Europe. The study was conducted by a panel of leading U.S. experts in the field, and covered biomaterials, cells, biomolecules, non-medical applications, engineering design, informatics, and legal and regulatory issues associated with tissue engineering research and applications. In its report, published in early 2002, the panel found that the United States was the world leader in tissue engineering, particularly in privately-funded applied research; however, governments in both Japan and Europe had initiated major new research programs in this area that were expected to challenge the U.S. lead. The panel also concluded that:

> *In order for the immense potential of tissue engineering to be realized in the United States, an intensive national effort will be required to provide the basic structure-function relationships from the molecular to the tissue level and to develop the engineering systems and analysis needed to produce functional tissue replacements. Developing focused large-scale initiatives to fill the gap areas in basic science and engineering will be crucial for the United States if it is to continue to lead in the development of actual products for this exceptionally important emerging field. As our population ages, tissue engineering and regenerative medicine will become important economic forces, and the United States must be prepared to lead.*

This MATES IWG strategic plan is being formulated in part to address the issues raised in the WTEC study (McIntire et al. 2002).

Previous and Ongoing Activities Supporting Tissue Science and Engineering

The MATES IWG and its member agencies already are involved in a number of activities that support the strategic priorities identified in this plan. These are reviewed in detail in Appendix A. A brief summary of these activities includes the following:

- Technology assessments (e.g., the WTEC study discussed in the sidebar above)
- Individual agency and interagency research/funding programs
- Efforts designed to streamline regulatory and reimbursement approval processes

- Measurement science, standards, and technology
- Government outreach to industry and academia

The implementation strategies outlined in this strategic plan are intended to build and improve on these previous and ongoing activities.

General Implementation Strategies

The following is a list of implementation mechanisms that apply to any or all of the strategic priorities for Federal agencies identified in this plan. This is followed by a section outlining implementation strategies that apply to specific strategic priorities.

- Develop agency-specific and interagency funding opportunity announcements (FOAs), or other funding vehicles in targeted areas, e.g., the National Institute of Biomedical Imaging and Bioengineering (NIBIB)-led, MATES (interagency) FOA on "Enabling Technologies for Tissue Engineering and Regenerative Medicine." For this FOA, MATES member agencies assisted in the drafting the FOA, and six NIH institutes as well as two other agencies (NIST and NSF) are providing funding contributions.
- Ensure exchange of knowledge, technical expertise, priorities, and cultures across agencies through interagency research collaborations, postdoctoral programs, personnel details and sabbaticals, and mid-career training opportunities.
- Improve coordination among agencies to foster technology transfer and translation via SBIR/STTR programs, centers of excellence, engineering research centers, joint R&D ventures, bioengineering research partnerships, and other formal and informal structures designed to accelerate practical, clinical, and commercial development.
- Coordinate policy development including participation in the development and adoption of industry-wide standards.
- Track and coordinate information exchange by developing a living database of tissue science and engineering research projects funded or conducted by the MATES member agencies.
- Continuously collect information and assess the state of the art in tissue science and engineering and identify, together with the community, the most promising research areas to move forward toward application, through interagency collaboration on proposal review, international benchmarking studies, and a variety of public and research community outreach activities (e.g., websites).
- Serve as a catalyst for bringing investigators in disciplines that could have a big impact on tissue engineering to the field. For example, MATES member agencies could identify researchers who are developing methods such as reporter genes for imaging of stem cells in cancer but who are not working on tissue engineering applications.
- Support activities intended to track commercial developments in tissue engineering and regenerative medicine, not only domestically but also worldwide.
- Organize an ongoing series of workshops targeted at gathering input from the research community. Topics to be addressed may include the most promising approaches for achieving the overarching goals outlined in Chapter 2 of this strategic plan, as well as the appropriate Federal roles in promoting progress in the strategic priorities identified in Chapter 3. Other topics may include forging collaborative partnerships and gathering input for future updated strategic plans. Outcomes from such workshops may include development of multi-agency funding initiatives, establishment of public/private and State/Federal partnerships to leverage Federal funding in this area, or identification of opportunities for international collaboration.

Implementation Strategies Specific to Eight Strategic Priorities (SPs) for Federal Agencies

In addition to the general implementation strategies listed above, the following are examples of implementation strategies proposed to specifically address the eight strategic priorities identified in this plan.

SP 1: Understanding the Cellular Machinery

Obtain a molecular-level understanding of the physical, chemical, and biological conditions that direct cells to assemble into and maintain complex communities and functional 3D tissues.

Implementation steps:

- Convene a workshop on stem cells in regenerative medicine and tissue engineering to bring together leading stem cell biology researchers and tissue engineering/regenerative medicine researchers in order to advance understanding of the cellular machinery and how stem cell research can be applied to regenerative medicine and tissue engineering.
- MATES IWG participation in, and presentations at, leading national and international conferences on tissue engineering and regenerative medicine; distribution of MATES materials at national and international conferences.
- MATES IWG networking with and participation in complementary interagency activities related to understanding of cellular machinery, e.g., systems biology and metabolic engineering.
- Include language soliciting proposals on this topic in funding opportunity announcements released by individual agencies.

SP 2: Identifying, Validating Biomarkers and Assays

Identify biomarkers that can be used to specify cells in tissue-engineered constructs, assess their physiological state and/or condition such as their state of differentiation. Develop high-throughput, high-content assays for collecting multiparametric data and correlating that information with biologically significant outcomes.

Implementation steps:

- Hold an evaluation science workshop to form a consensus on the best scientific approaches for the development of biomarkers for tissue science and engineering products. Approaches will address the goals of the FDA Critical Path Initiative, the NIH Roadmap Initiative, and other agency and interagency activities.

SP 3: Advancing Imaging Technologies

Develop high-resolution, non-destructive imaging technologies to assess engineered tissue function *in vivo* and *in vitro* in real time.

Implementation steps:

- List "quantitative, non-invasive tools to monitor structure, composition, and function of engineered tissues in real time" as a priority topic in the NIBIB-led, MATES (interagency) FOA, "Enabling Technologies for Tissue Engineering and Regenerative Medicine."
- Sponsor meetings with other NSTC interagency working groups and subcommittees to identify and leverage the large amount of ongoing and planned basic physics and engineering research relevant to biomedical imaging, e.g., development of quantum dots as biomarkers.

SP 4: Defining Cell/Environment Interactions

Develop design principles for new materials based on a physical and quantitative understanding of how cells respond to molecular signals and integrate multiple inputs to generate a given response in

their physiological environment. Test new matrices for biocompatibility and successful integration into relevant hosts or *in vitro* platforms.

Implementation steps:

- Conduct an interagency supported workshop, program survey, or a web-based conference to obtain a consensus-based roadmap of standardized methods and tools that will verify, validate, and enable descriptive or predictive modeling and analysis.
- Develop an integrated information network that contains data sets, reference data, performance data, etc. obtained from standards/pre-standards organizations like the Versailles Project on Advanced Materials and Standards (VAMAS), ASTM International (ASTMi), and participating institutions involved in collaborative research.
- Utilize such networks to support or challenge solicited agency projects and programs.
- Participate in ASTM International Committee F04.46 on Standards for Cell Signaling.
- Participate in NIST's U.S. Measurement System (USMS) program for tissue engineering and regenerative medicine.
- Establish partnerships in the area to advance design technologies, establish incubators, centers of expertise, or industry-academic consortia.

SP 5: Establishing Computational Modeling Systems

Make available user-friendly, predictive (physiological, biological, and mechanical) computational models whose simulations will aid in the engineering of reproducible tissue constructs.

Implementation steps:

- List "predictive computational models for engineering functional 3D tissues" as a priority topic in the NIBIB-led, MATES (interagency) FOA on "Enabling Technologies for Tissue Engineering and Regenerative Medicine."
- Jointly sponsor a meeting with other interagency working groups and subcommittees to identify and leverage the large amount of ongoing and planned basic physics and engineering research relevant to modeling of biological systems, e.g., systems biology.

SP 6: Assembling and Maintaining Complex Tissue

Develop novel tools and bioreactors to precisely control rapid stem/progenitor cell expansion as well as the chemical and mechanical environment for phenotype-directed 3D tissue growth and function.

Implementation steps:

- List "3D fabrication technologies for tissue engineering" and "novel bioreactors to precisely control the chemical and mechanical environment for functional 3D tissue growth or to rapidly expand functional stem cells" as priority topics in the NIBIB-led, MATES (interagency) FOA on "Enabling Technologies for Tissue Engineering and Regenerative Medicine."
- Leveraging of other agencies' previous and ongoing work in this area, e.g., NASA's microgravity bioreactor.

SP 7: Improving Tissue Preservation and Storage

Optimize methods for long-term, low-cost, low-maintenance preservation that allow recovery of viable and functional cells/tissues. Develop better storage, shipping, and packaging techniques to provide tissues on demand.

Implementation steps:

- List "technologies for manufacturing of tissue-engineered products including preservation, sterilization, packaging, and transport" as a priority topic in the NIBIB-led, MATES

(interagency) FOA on "Enabling Technologies for Tissue Engineering and Regenerative Medicine."

- Networking with other interagency working groups and subcommittees to identify and leverage their complementary R&D activities, including those sponsored by DOD agencies to improve the long-term storage of blood products.

SP 8: Facilitating Effective Applications Development and Commercialization

Facilitate cost-effective production and scale-up of tissues and organs that can effectively meet regulatory requirements for good manufacturing practices and meet aggressive cost-benefit targets for a wide variety of applications.

Implementation steps:

- Federal agencies—including the Food and Drug Administration (FDA), the National Institute of Standards and Technology (NIST), the National Institutes of Health (NIH), and the U.S. Department of Agriculture (USDA)—will continue to work with industrial and academic partners to develop standards for tissue-engineered medical products (TEMPs) through standards development organizations such as the American Society for Testing and Materials International (ASTMi). Standards are being developed in six broad categories:
  - Classification and Terminology
  - Tissue-engineered Biomaterials and Biomolecules
  - Cells and Tissue-engineered Constructs
  - Assessment
  - Adventitious Agents Safety
  - Cell Signaling

  More than 20 standards have been published so far, and more are in the development stage. Use of published standards can significantly improve and simplify the premarket review process. Efforts are also underway to develop pre-standards in materials research for tissue engineering through international collaborations via VAMAS: the Versailles Project on Advanced Materials and Standards.
- FDA researchers will collaborate with other Federal agencies to develop methods and reagents that will enable the evaluation of cells and tissue-engineered products.
- FDA and CMS product development requirements should be considered during the review of proposals submitted in response to tissue engineering funding opportunity announcements.
- CMS will participate with other agencies within the Department of Health and Human Services to implement Secretary Michael Leavitt's four specific initiatives (announced March 14, 2006) for competition and transparency, with special focus on the Quality and Price Transparency initiatives.
- CMS will implement revised guidance (released July 12, 2006) for Coverage with Evidence Development (CED) approach for national coverage determinations (NCD). The CED process may also prove helpful when there have been significant barriers to conducting research about an item or service at the time of the NCD review. According to CMS Administrator Mark McClellan: "The results of the data collection achieved through CED have the potential to improve patient health and physician decision making while speeding access to innovative technologies. This policy should encourage industry efforts to invest in innovations that enhance the care of our beneficiaries."

Connections between Tissue Science and Engineering and Existing Federal Research Initiatives

Tissue science and engineering is dependent on a better understanding of subcellular biological pathways; this understanding in turn requires the availability of advanced technologies at the

nanometer-, micrometer- and meso-scales. Tissue science and engineering applications will include medical therapeutics and highly innovative non-medical applications. As a result, it is appropriate to understand how tissue science and engineering contributes to or benefits from other Federal initiatives such as the National Nanotechnology Initiative, the National Institutes of Health (NIH) Roadmap, the FDA Critical Path Initiative, and the Medical Innovations Report.

Furthermore, the strategic priority areas described in this strategic plan dovetail with many agency research efforts related to systems biology. Agency interests and technical needs with respect to tissue science and engineering also intersect with other NSTC IWGs such as the Metabolic Engineering Working Group (USDA, DOD, DOE, EPA, NASA, NIH, NIST, NSF). Other related interagency collaborations include the Human Genome Program (DOE, NIH, Celera Genomics), Bioengineering Research Partnerships (NSF, NIH); and the Interagency Microbial Genome Sequencing Project (USDA, NSF).

As part of its implementation strategy, the MATES IWG will leverage all of these other interagency initiatives by sponsoring joint planning meetings and exchanging information on ongoing and planned activities with other interagency working groups and subcommittees.

4. CONCLUSIONS

The goals of this strategic plan are to better coordinate agency activities to address the gaps in enabling technologies for tissue science and engineering and to promote improvements in public health and safety. This plan provides an assessment of the current highest priority research in enabling technologies, which the field needs in order to progress efficiently. The participating Federal agencies have an essential role to play in defining and coordinating these activities because of the potential broad economic, national security, and public health impacts of the technologies and because of the diverse science and engineering fields that are needed to contribute to the enabling technologies. The varied roles of the Federal agencies include support for fundamental research in the physical and biological sciences, transitioning of basic science to technology, standards development, and regulation of medical products. Advances in the understanding of the complex biology of tissue engineering will be made possible by advances in the biological and physical sciences and engineering that improve cell and tissue imaging, quantitative methods, predictive models, and tissue preservation and other technologies.

The agencies of the MATES IWG have a proven track record of working effectively together. The responsibility for crafting specific implementation plans in the identified technical areas will be assumed by the agencies in accord with their agency missions and goals. The expected advances from focused implementation plans will be quantitatively assessed. The overarching goals and strategic priorities will be modified as appropriate to advances that occur in the field.

Advancements in tissue science and engineering will occur more rapidly with a coordinated and focused multi-agency effort as described in this strategic plan. The strategic priorities identified in this plan will help provide that focus. Advancements in tissue science and engineering will lead to improved medical therapies, better sensors, greater protection from biological threats, more cost-effective development of pharmaceuticals and screening of chemicals for toxicity, and new paradigms for advanced computing.

APPENDICES

APPENDIX A. PREVIOUS AND ONGOING ACTIVITIES SUPPORTING TISSUE SCIENCE AND ENGINEERING

The following are examples of activities that the MATES member agencies have engaged in previously and are continuing to pursue in the interests of promoting progress in tissue science and engineering.

Technology Assessments

- From 2000–2002, MATES IWG funded a worldwide benchmarking study assessing tissue engineering R&D in other countries in comparison to that in the United States.

Individual Agency and Interagency Research/Funding Programs

- Based partly on input from the international benchmarking study, MATES member agencies have cooperated in preparing an interagency (NIBIB-led) funding opportunity announcement, "Enabling Technologies for Tissue Engineering and Regenerative Medicine."
- With support from NIH, NIST developed microscopic, broadband coherence anti-Stokes Raman spectroscopy (CARS) techniques to image the morphology and function of tissue-engineered constructs. Broadband CARS can be used to acquire volumetric, chemically specific images with sub-micrometer resolution.
- NSF, NIH, NASA, and DOE have teamed to offer support through a solicitation entitled "Interagency Opportunities in Multi-Scale Modeling in Biomedical, Biological, and Behavioral Systems," which includes 3D multiscale modeling of complexity in engineered tissues**.**
- ATP/NIST and NIBIB/NIH have partnered via an interagency personnel detail to research mechanisms and models for public-private partnerships at different Federal agencies and developed a report with recommendations to NIBIB for developing and strengthening public-private research partnerships.
- In 2000, FDA and NIDCR initiated an interagency working group on disorders of the temporomandibular (jaw) joint. This group meets quarterly to discuss research needs and developments in diagnostic and treatment regimens.
- In 1995, CMS and FDA initiated a program by which Medicare payments may be received to cover the cost of specific investigational devices and related patient care. This program provides reimbursement for studies including tissue-engineered skin constructs reviewed as medical devices.
- Since 1990, FDA staff has participated in the review of NIST/ATP and NIH research proposals. This sharing of staff has increased the available number of non-conflicted reviewers and permitted FDA staff to maintain an awareness of developing trends in materials and biological sciences.
- NIH, DOE, NSF, and other agencies support the development of real-time medical imaging technology.
- ATP/NIST, DARPA, NIH, and NSF have supported the development of technologies to enable long-term tissue storage and transport.
- NSF has underpinned the field from the beginning by funding basic cell and developmental biology and engineering research that provides for the fundamental understanding of tissue formation and function. The Directorate for Engineering and the Directorate for Biological Sciences continue to provide strong support for basic and applied research in ways that range from single-investigator grants through group grants and Engineering Research Centers.

- DOD, via its exploratory research arm at DARPA, has played a pivotal role during the early explorations into the use of cells and tissues as the sensing units in biological and chemical warfare detection. DARPA is pushing the envelope of prevention and medical intervention for the healing of traumatic wounds and the management of physiological stress, and for tissue regeneration. These research areas continue to be strong drivers in this highly productive program. DARPA:
  - Pioneered research into the use of cells and tissues as sensing units in biological and chemical warfare detection. Research efforts now include the use of tissue science and engineering for vaccine development, healing of traumatic wounds and management of physiological stress, and tissue regeneration.
  - Supported commercial efforts to realize high-content screening as a potential biosensor platform for environmental threat detection. DARPA has supported tissue-based biosensor development at the Naval Research Laboratory (NRL).
  - Invested substantially in the research that led to the development of the Biological Simulation Program for Intra- and Inter-Cell Evaluation (BioSPICE), a computational framework and set of analytical techniques and bioinformatics tools that is capable of predicting cellular processes and controlling their spatio-temporal behavior.
  - Supported the development of novel methods to achieve freeze-dried nucleated mammalian cells, and ambient temperature storage of blood cells.
  - Conducted research that led to the generation of test beds for faster, better, and cheaper vaccine development.
- The U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center as well as the Combat Casualty Care Research Directorate and its component labs have been actively managing and/or engaging in tissue engineering efforts. Projects include development of improved scaffolding for bone, hepatic, and dermal tissue growth; methods for utilizing various adult stem cell lines to allow improved bone and wound healing, as well as tooth generation; manipulation of growth factors and genes for potential limb regeneration and vascularization/development of replacement vessels; and combinations of biomaterial, adult stem cell, growth factor, and gene manipulations for repair of the central and peripheral nervous system. Beginning in 2008 the Combat Casualty Care Research Directorate will fund a competitively selected "Institute of Regenerative Medicine" and is exploring multi-agency sponsorship of this effort. The goal of the institute will be to develop militarily-relevant solutions for the management of complex tissue injuries and burns.
- The Office of Naval Research (ONR/DOD) has supported neural tissue engineering at NRL.
- DOE's Office of Biological and Environmental Sciences (BER) has a vigorous program dedicated to mapping the genomes of a wide range of organisms of interest to environmental studies and microbial ecology in order to better understand cellular machinery and cell-matrix interactions. Biomarker development and validation and computational modeling are an integral part of these studies. Important insights into the behavior of collective cells versus single cells are expected to emerge from a large-scale comparison across the multitude of organisms being mapped. BER also supports extensive research on the development of biocompatible materials. Highly reliable biocompatible materials, while essential for DOE's retinal prosthesis program, are also important for tissue engineering applications such as scaffolds for engineered tissues, tissue storage devices, and bioreactors.
- New funding mechanisms focused more on "technology driven" rather than "hypothesis driven" science have been created with tissue engineering in mind. The formation of the Bioengineering Consortium (BECON) and later NIBIB at NIH have augmented a diverse portfolio with its roots in the National Heart, Lung, and Blood Institute (NHLBI), the National

Institute of Dental and Craniofacial Research (NIDCR), NINDS, the National Institute of General Medical Sciences (NIGMS), and others.

- NIH has funded a private industry effort to grow blood vessels from patients' skin.
- NIH has supported the development of cryopreservation cocktails for storage of peripheral blood mononuclear cells and whole blood.
- NASA's space technology program has supported tissue engineering studies and the development of the microgravity bioreactor to understand the processes of tissue formation and function. This research led to the creation of highly effective rotating wall vessel bioreactors.
- In related research but with different goals and objectives, EPA is developing approaches using high-throughput screening assays to characterize the biological activity of chemicals. These activity profiles will help identify chemicals with disparate chemical structure, but similar potential to interact with critical metabolic pathways, and hence aide in the prioritization of chemicals for additional toxicological evaluation. On a higher level of biological organization, systems models are being developed that build on the basis of normal biochemical and physiological processes and help understand through computer simulations the health effects that are likely to be observed when those processes are perturbed by environmental stressors.

Efforts Designed to Streamline Regulatory and Reimbursement Approval Processes

- FDA has enhanced its cross-center collaborations between the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) with standing working groups focused on tissue-engineered medical products.
- FDA performs research to identify biomarkers to help evaluate the safety and efficacy of cell therapy products. Projects range from the identification of highly expressed genes in embryonic stem cells to functional analysis of key signaling pathways in a variety of animal systems.
- In 2003, FDA established the Office of Combination Products to serve as a single point of contact organization for manufacturers of complex products containing drug, biologic and/or device components. The majority of tissue-engineered products meet this definition.
- Since 1998, NIST and FDA have worked with the Tissue-Engineered Medical Products Subcommittee of ASTM International to develop consensus standards and reference materials for classifying and characterizing biomaterials.
- FDA continues to hold public meetings and publish Guidance Documents on scientific and medical topics related to medical applications of tissue engineering products. In 2006 FDA drew upon scientists from NIST during a public meeting to discuss the development of potency assays. In 2004 CBER hosted a public meeting to discuss Critical Path issues associated with premarket review of cellular products.
- CMS has become the "new frontier" for complex medical treatments, as the biotechnology sector integrates the need to encompass value as well as safety and efficacy in its market projections. For example:
    - The Council on Technology and Innovation (CTI), launched in August 2004, works to anticipate new technologies and improve ways to make their transition to Medicare coverage as predictable and timely as possible, including facilitating the exchange of information between CMS and other entities making similar decisions.
    - Coverage with Evidence Development (CED), introduced in April 2005, is an alternative approach to making Medicare coverage decisions for certain medical services, items, and devices in the context of protocol-specified prospective data collection, thus recognizing the value of linking technology diffusion to timely practical clinical research.
    - CMS is carrying out the provisions for medical technology in the Medicare Prescription Drug and Modernization Act of 2003:

  - expand coverage for clinical trials
  - improve payments for new technologies
- CMS is implementing significant revisions to the billing code sets process for the Health Insurance Portability and Accountability Act (HIPAA)-compliant Health Care Financing Administration (HCFA) Common Procedural Coding System (HCPCS):
  - improved development of codes for new technologies
  - easier for health plans to make decisions on coverage and payment
  - more transparent coding process

Measurement Science, Standards, and Technology

- NIST's mission is to develop and promote measurements, standards, and technology to enhance productivity, facilitate trade, and improve the quality of life. NIST develops validated protocols, standards, and improved technologies to facilitate quantitative methods in biological samples, including cells and tissues. Such tools will assist the interoperability of measurements across laboratories, which will improve the quality of data available for databases and predictive modeling.
- NIST also advances imaging technologies that are applicable to cells, tissues, and medical imaging, particularly through the Advanced Technology Program at NIST:
  - Performs measurement and standards science and development in this intersection of biology, physics, and chemistry.
  - Has developed an integrated multi-photon fluorescence microscope (MPM) and optical coherence tomography (OCT) for visualizing 3D engineered tissue scaffolds and tracking the growth of engineered tissues on a micrometer scale. This technique permits deeper imaging into highly-scattering tissues than is possible with OCT or multi-photon microscopy alone.
  - Through its significant investment in high-risk/large benefit projects, ATP/NIST has been largely responsible for the rapid growth of the tissue engineering industry. ATP support enabled firms to explore the technological frontier and thereby develop alternatives to organ transplantation, extra-corporeal support devices, stem cells as reservoirs for tissue regeneration, and methods for preserving tissue and organ constructs.

Government Outreach

- The MATES IWG public website, www.tissueengineering.gov, serves as a single source of information for the public and the research community on U.S. Government activities and funding opportunities with respect to tissue engineering and regenerative medicine.
- Representatives of MATES member agencies have participated in numerous national and international conferences, explaining their tissue engineering and regenerative medicine funding programs and other related activities (e.g., regulatory policies).
- In particular, MATES member agencies helped to organize a workshop at the 2006 Society for Biomaterials conference on the "Next Generation Measurement Tools to Advance Tissue Engineering & Regenerative Medicine." Businesses and universities were invited to help define the needs, tools, and barriers to testing biomaterials interaction with cells and tissues for the rational design of materials.

APPENDIX B. BIBLIOGRAPHY

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APPENDIX C. ABBREVIATIONS

2D: two dimensions (n) or two-dimensional (adj)

3D: three dimensions (n) or three-dimensional (adj)

ASTMi: American Society for Testing and Materials International

ATP: Advanced Technology Program, National Institute of Standards and Technology

BW: Biological weapon

BECON: Bioengineering Consortium

BER: [Office of] Biological and Environmental Research, within the Department of Energy's Office of Science

BioSPICE: Biological Simulation Program for Intra- and Inter-Cell Evaluation (DARPA program)

BISTI: Biomedical Information Science and Technology Initiative, National Institutes of Health

CARS: Coherence anti-Stokes Raman spectroscopy

CBER: Center for Biologics Evaluation and Research, Food and Drug Administration

CCCRP: Combat Casualty Care Research Program, U.S. Army

CDRH: Center for Devices and Radiological Health, Food and Drug Administration

CMS: Centers for Medicare & Medicaid Services, Department of Health and Human Services

DARPA: Defense Advanced Research Projects Agency

DOC: Department of Commerce

DOD: Department of Defense

DOE: Department of Energy

ECM: Extracellular matrix

EOP: Executive Office of the President

EPA: Environmental Protection Agency

EUCOMED: European Medical Technology Industry Associations Group

FDA: Food and Drug Administration

FOA: Funding Opportunity Announcement (U.S. Government)

FTIR: Fourier transform infrared spectroscopy

HHS: Department of Health and Human Services

IDE: Investigational Device Exemption

IND: Investigational New Drug Application

MATES IWG: the Multi-Agency Tissue Engineering Science Interagency Working Group, NSTC

MPM: Multi-photon fluorescence microscope

NASA: National Aeronautics and Space Administration

NHLBI: National Heart, Lung, and Blood Institute, NIH

NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

NIBIB: National Institute of Biomedical Imaging and Bioengineering, NIH

NIDCR: National Institute of Dental and Craniofacial Research, NIH
NIGMS: National Institute of General Medical Sciences, NIH
NIH: National Institutes of Health, Department of Health and Human Services
NINDS: National Institute of Neurological Disorders and Stroke, NIH
NIST: National Institute of Standards and Technology, Department of Commerce
NRL: Naval Research Laboratory
NSF: National Science Foundation
NSTC: (U.S.) National Science and Technology Council
OCSQ: Office of Clinical Standards and Quality, CMS
OCT: optical coherence tomography
OMB: Office of Management and Budget, Executive Office of the President
ONR: Office of Naval Research, U.S. Navy
OSTP: Office of Science and Technology Policy, Executive Office of the President
R&D: Research and development
RFA: Request for Applications
RP: Rapid prototyping
RVA: Rapid vaccine assessment
SBIR: Small Business Innovation Research Program, Small Business Administration
STTR: Small Business Technology Transfer Program, Small Business Administration
TATRC: Telemedicine and Advanced Technology Research Center, U.S. Army
TEBV: Tissue-engineered blood vessel
TEMP: Tissue-engineered medical product
UK: United Kingdom
USAMRMC: U.S. Army Medical Research and Materiel Command
USDA: (U.S.) Department of Agriculture
WTEC: World Technology Evaluation Center, Inc.

National Science and Technology Council
Committee on Science
Subcommittee on Biotechnology
Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group