

# EXECUTIVE SUMMARY

Larry V. McIntire

## INTRODUCTION

Tissue engineering is 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 function. Sometimes also called reparative and regenerative medicine, tissue engineering is an emerging interdisciplinary area of research and technology development that has the potential to revolutionize methods of health care treatment and dramatically improve the quality of life for millions of people throughout the world. Some products are already in use clinically, and their number will assuredly increase rapidly in the future.

A worldwide study of the status and trends in tissue engineering research and development was carried out during the period 1999-2001 by an eight-person panel under the auspices of the World Technology (WTEC) Division of the International Technology Research Institute at Loyola College in Maryland. Led by the National Science Foundation, a wide range of U.S. Government organizations commissioned this study: the National Institutes of Health, the National Institute for Standards and Technology, the Defense Advanced Research Projects Agency, the National Aeronautics and Space Administration, and the Food and Drug Administration. This support indicates the breadth of interest in and immense potential of this rapidly growing new field. The purpose of this study was to gather and disseminate information for the U.S. tissue engineering and science policy communities on the current status and future trends in research and development in the field of tissue engineering in Europe and Japan, in comparison to U.S. activity in this field. The goals included the following:

1. Gain a broader understanding of the work being performed globally in the design, fabrication, and use of engineered tissues by identifying, visiting, and assessing the work at key research centers
2. Reveal new cross-disciplinary strategies that are being used to advance novel research approaches to specific application areas within the field of tissue engineering, including exploration of models of cooperation across industry, government, and academia in different countries
3. Examine the scientific basis for advancing methodologies focused on evaluating the cellular response to implants, the quality and fabrication of implants, and human acceptance
4. Assess the effect of the regulatory environment on progress of critical work in tissue engineering
5. Identify and encourage opportunities for international collaboration in this emerging field

This executive summary of the WTEC panel's final report presents an overview of the panel's observations and conclusions regarding tissue engineering science and technology worldwide. The chapters written by panel members report on critical areas that form the building blocks necessary for substantial growth of the tissue-engineering field. Site reports documenting the panel's visits to university, government, and industry laboratories in Europe and Japan are included in this volume as appendices. A companion report, also available from WTEC, contains the proceedings of a WTEC tissue-engineering workshop held on the NIH campus in Bethesda, Maryland, on June 5-6, 2000, with the purpose of assessing the current state of the U.S. tissue-engineering enterprise.

## FINDINGS

Table ES.1 summarizes the panel's comparisons between U.S., Japanese, and European tissue-engineering R&D activities, at a fairly gross level of generalization. In addition, several other general conclusions can be drawn from the information assembled in the WTEC Study:

1. Until recently, most of the funding to support activities in tissue engineering in the United States has been in support of commercial development (companies, NIST/ATP Program), leading to large amounts of applied research, but lesser amounts of fundamental research. In Japan and Europe, the tissue engineering field is being largely driven by government funding, allowing researchers to perform more basic research, which offers greater potential for generating intellectual property. Examples include London's Imperial College Tissue Engineering Center with its focus on stem cell research and the new Manchester/Liverpool Tissue Engineering Center, built on the foundations of the long standing Welcome Trust-funded Centre for Cell-Matrix Research.
2. Use of autologous cells is predominant in both Europe and Japan. In Europe there was surprisingly little discussion of the development of allogeneic cell products. Allogeneic products are amendable to large-scale manufacturing at single sites, while autologous therapies will likely lead to more of a service industry, with a heavy emphasis on local or regional cell banking/expansion. In the United States, both autologous and allogeneic cell products are being developed, but the largest companies (e.g., Advanced Tissue Sciences and Organogenesis) are focused on allogeneic products. Different technologies will be needed to achieve success in these two different models.
3. Many centers of tissue engineering in both Europe and Japan devote much of their efforts to challenges in cell technologies, often combining cells with existing materials in clinically driven application approaches to regenerating tissues. Many of these tissue engineering programs employ off-the-shelf biomaterials, with the aim of creating novelty through applications of cells, and thus do not explicitly focus on development of new biomaterials or even on significant modification of existing biomaterials. In general, the United States leads in the development of novel biomaterials. There are several important exceptions in both Europe and Japan, however, where there is a focus on utilization of biological molecular design principles, including a fairly sophisticated knowledge of receptor-mediated cell interactions, to develop new and novel biomaterials.
4. Rapid advances in the tissue-engineering field will require linkage between basic biological scientists, bioengineers and material scientists, and clinical researchers. The United States is currently ahead in generating these cross-disciplinary environments, but there is strong movement in both Europe and Japan to promote the interactions among different laboratories specifically to advance tissue-engineering applications, often by establishing centers with links to private industry. Examples include the tissue-engineering aspects of the Japanese Millenium Project and the UK Manchester/Liverpool Tissue Engineering Centre.
5. The United States has a leadership position in the genomics-based development of databases to which data mining tools can be directed for drug discovery. The use of informatics approaches in tissue engineering is in its infancy. Notable exceptions to the absence of informatics solutions for tissue engineering approaches were found at Keio University, where the e-Cell initiative is pursuing goals similar to those being undertaken by many U.S. universities and by Physiome Sciences—that is, the development of a computer model of a virtual cell. At Heidelberg, the European Molecular Biology Laboratory has long been a leader in the application of informatics solutions to biological problems, particularly in the area of molecular analysis and genomics. With its development of the BioImage database, an increasing interest has been shown in the role of shared tissue images and related information in the understanding of the mechanism of disease; however, the direct application to tissue engineering has apparently not been organized. Several institutions have ongoing functional genomics activities and 3D modeling activities, but in most cases these remain confined to the genomics sector.

**Table ES.1.**  
**Comparisons Among U.S., Japanese, and European Tissue Engineering R&D Efforts**

	Topic	Knowledge Base	Work to Date	Leading Region
<b>Biomaterials</b>	Adapted biomaterials	Advanced	Extensive	Equivalent
	Adapted bioactive materials	Advanced	Extensive	Equivalent
	Biomaterial design	Incomplete	Extensive	U.S.>Europe>Japan
	Linkage of biomaterial Design to cell biology/ development	Incomplete	Modest	U.S.
	Clinical application of novel concepts	Incomplete	Little	Equivalent
<b>Cells</b>	Enabling methodology	Moderate	Moderate	Equivalent
	Allogeneic cells/ immunological manipulation	Extensive	Active in U.S. Modest in EU Little in Japan	U.S.
	Stem cell research	Extensive in hematopoietic system	Widely dispersed activity	Equivalent
	Commercialization of cell therapies	Moderate	Extensive activity in U.S. Modest in EU Early in Japan	U.S.
<b>Biomolecules</b>	Gene transfer	Incomplete	Extensive	U.S.
	Angiogenic factors	Incomplete	Limited	I.D. of factors: U.S. Delivery of factors: equivalent
	Growth factors	Extensive	Moderate	I.D. of factors: U.S. Delivery of factors: equivalent
	Differentiation factors	Little	Limited	Too early to determine
	BMPS	Incomplete	Moderate	U.S. (close)
<b>Engineering Design (Mass Transport)</b>	2-d cell expansion	Advanced	Extensive	U.S.
	3-d tissue growth	Incomplete	Significant	U.S.
	Liver devices	Little	Significant	Equivalent
	Promoting vascularization	Incomplete	Little	Too early to determine
	Cell storage	Advanced	Extensive	Equivalent
	Tissue storage	Incomplete	Little	Too early to determine
<b>Engineering Design (Biomechanics)</b>	Properties of native tissues	Incomplete	Extensive	Equivalent
	ID minimum props. of engineered tissues	Little	Little	Too early to determine
	Biomechanics input to cells	Advanced	Significant	Equivalent
	Biomechanics input to eng. tissues	Incomplete	Little	U.S.
<b>Informatics</b>	Genomics	Advanced	Extensive	U.S.>UK>Switz
	Proteomics	Incomplete	Significant	U.S.
	Microarray	Advanced	Extensive	U.S.
	Cell informatics	Incomplete	Significant	U.S.
	Tissue informatics	Little	Little	U.S., Germany
	Physiome (system)	Incomplete	Significant	U.S.>Japan
	Commercial	Incomplete	Significant	U.S.>Germany
<b>Cell-Based Tech., Non-Medical Apps.</b>	Cell-based sensors	Moderate	Significant	U.S.
	Neural networks	Incomplete	Significant	Equivalent
	Other applications	Incomplete	Little	Too early to determine
	Engineering active interfaces	Incomplete	Little	Equivalent

6. A number of engineering areas/technologies will be critical to developing tissue-engineered products. These include bioreactor design, optimization of mass transport following cell transplantation, understanding of the biomechanical requirements of engineered tissues, and using electrical/mechanical stimulation to promote desired development of engineered tissues. A great deal of work has been done in the United States to develop novel bioreactors for expansion of a variety of cell types and sources, both in 2D and 3D culture. The potential importance of autologous cell therapies in Europe and Japan will demand significant attention to this topic, but most bioreactor work in these regions currently follows the U.S. lead. The importance of vascularization to enhance mass transport in engineered tissues is widely acknowledged, but little progress has been made to date in any region. The biomechanics issues in tissue engineering have not been addressed to the extent that biochemistry issues (e.g., composition of tissues, protein secretion) have been in the past. Little is known regarding the necessary or desired mechanical properties of many potential tissue-engineering products. Compared to Europe or Japan, the potential role of mechanical signals in tissue development has been explored in the United States to a greater, albeit still very limited, extent.
7. Regulatory issues present a major challenge to the worldwide development of the tissue engineering industry. The FDA approach to the regulation of products incorporating human tissues is comprehensive but not fully implemented. In the absence of a European Union regulatory program, those European governments that have addressed the status of engineered tissue products have employed an array of classification schemes that further complicate international application of this technology. Like a number of European states, Japan has yet to articulate its own regulatory policy. Uncertainty in classification between states and, with that, unpredictability in marketing approval strategies may impede product development, especially in the case of engineered tissues developed for smaller patient populations.

The implications of governmental authority over access to human tissues for research and development purposes are equally clouded by multiple responses to the legal, ethical, and cultural issues, with the recent debate over the use of embryonic stem cells highlighting these different approaches. In both Europe and Japan, the availability of tissues within academic institutions and their researchers' ability to employ manipulated tissues in small-scale applications in humans contrasted with the barriers faced by commercial entities in acquiring tissues (especially in Japan) and the greater scrutiny given to their clinical uses of engineered tissues. Differentiating between academic and industrial uses of research tissues may ameliorate possible concerns over the commercialization of tissue transfer, although it may slow the scaling of new tissue-engineering technologies to meet regulatory approval requirements.

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.