

Chapter 1: Tissue Engineering: An Introduction

Setting the Stage for a Biomedical Revolution

For millennia, humans have been interested in manipulating the vast body of life surrounding them. As social systems and resultant technology have progressed, the motivation and ability to alter life has steadily increased. In actuality, much of the “biotechnology revolution” that so enralls us today had its roots at the dawn of civilization. For example, humans have been practicing various forms of tissue engineering in its broadest sense for thousands of years. The manipulation of crops and domesticated animals has been a persistent and widespread practice across the planet. The simple act of the castration of a farm animal dramatically alters tissue function, yielding desired morphologic, chemical, and behavioral changes. Exponential increases in our understanding of the molecular basis of cell interactions have provided the means to more precisely manipulate, and perhaps duplicate, tissue function. Plant tissue engineering is becoming commonplace, and food, fiber, and pharmaceutical production may well be changed irrevocably. In addition, the biomedical application of tissue engineering is entering its infancy, and the imagination of researchers and laymen alike has been awakened to wonders that blur the line between reality and science fiction.

The 20th century will be remembered as a time of revolutionary change in the fields of basic and applied science. New ideas and new tools provided both an increased understanding of the natural world as well as an unparalleled ability to alter the environment and human society. The field of biomedicine reaped the windfall of new discoveries from virtually every area of science, dramatically improving health care throughout the world. The revolution in molecular biology has afforded scientists and clinicians the opportunity to examine the chemical basis of human health and to develop a number of novel therapeutic strategies. Advances in biophysics and biochemistry have allowed a more intimate glimpse of the structure and functioning of human tissue, providing material scientists and roboticists the opportunity to more accurately mimic living structures. Cell and developmental biologists continue to unravel the complexities of the establishment and maintenance of multicellularity, tantalizing the populace with possibilities including tissue regeneration, cloning, and longevity.

With greater insight into the structural and behavioral characteristics of living tissues, researchers have begun to investigate the possibility of designing and creating tissues. The natural outcome or goal of this multidisciplinary field involves the development of replacement tissues for disease and trauma. The great success of skin engineering has generated optimism and support for the expansion of tissue-engineering projects. It has been projected that tissue engineering will be one of the most significant health/science employment fields of the next few centuries, in addition to initiating a revolution in health care and biomedical research. The cover story of the May 22, 2000, issue of TIME Magazine includes predictions relating to future careers with great promise, and lists Tissue Engineer as the Number 1 projected career (**Figure 1.1**). Interestingly, three of the other top five careers involve technologies that readily overlap with the field of tissue engineering.



Figure 1.1: Tissue engineering job prospects for the 21st century.

The Role of the Pittsburgh Tissue Engineering Initiative

A number of collaborative efforts have been established across the world to facilitate tissue-engineering research. Pittsburgh is proud of its leadership position in this field, and continues to serve as a model for such enterprises. The Pittsburgh Tissue Engineering Initiative, Inc. (PTEI) is a network strategy to promote regional economic growth through the advancement and creation of university-developed technology. It focuses on biomedical and related technologies that are associated with engineered tissues, including cell culturing, gene therapy, organ transplant and regeneration, **biomaterials**, and computer-assisted analysis and design. The PTEI network includes researchers at Allegheny General Hospital, Carnegie Mellon University, Children's Hospital of Pittsburgh, Duquesne University, University of Pittsburgh, and UPMC Health System, as well as persons from the business, government, and educational sectors.

The Pittsburgh Tissue Engineering Initiative strives to facilitate the recognition of Pittsburgh as an international center of excellence in tissue-engineering research and education. Using this emerging national resource as a driving force, the organization seeks to foster and encourage the growth of a regional biotechnology industry rooted in tissue engineering. PTEI achieves its goals by sponsoring research, providing educational programs for a broad spectrum of students, and facilitating access to efficient technology transfer systems.

This curriculum activity outreach manual was developed as a basic introduction to the concepts and potentials of tissue engineering. Teachers are encouraged to use and modify the exercises as they see fit, and to take advantage of the programs offered by PTEI. PTEI plans to update and expand this manual on an annual basis.

Tissue Substitutes: Statement of the Problem

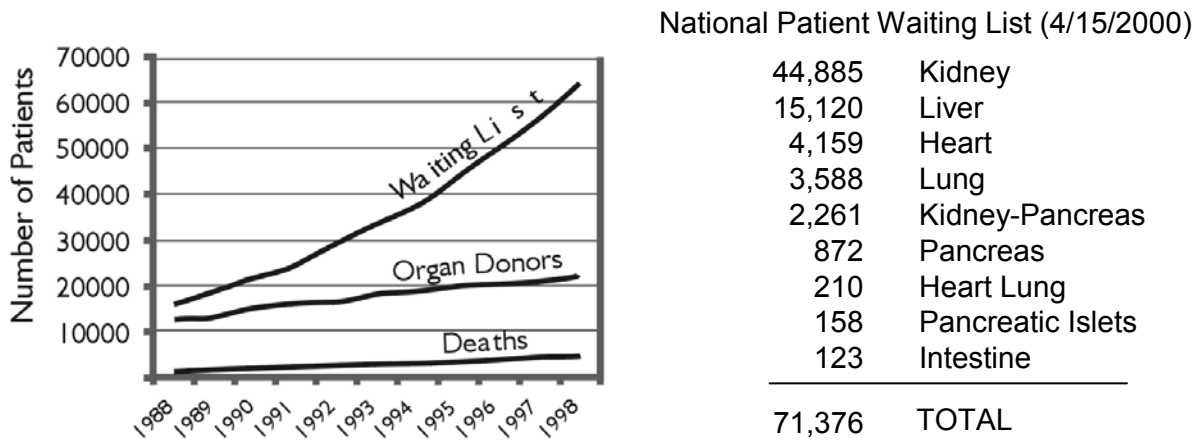


Figure 1.2: Tissue substitute need

The loss or failure of an organ or tissue is one of the most frequent, devastating, and costly problems in human health care. The need for substitutes to replace or repair tissues or organs because of disease, trauma, or congenital problems is overwhelming. Studies have estimated that more than \$400 billion is spent each year in the United States on patients suffering from organ failure or tissue loss, accounting for almost half of the national health-care bill. More than eight million surgical procedures are performed annually to treat these cases, yet every year 4,000 people die while waiting for an organ transplant, and an additional 100,000 patients die without even qualifying for the waiting list. **Figure 1.2** illustrates the great need for donor organs and/or tissue substitutes.

Current Therapies and Future Prospects

The growing need for tissue substitutes is being addressed by researchers and physicians across the world. Three major types of clinical therapies are currently being utilized:

1. **Autografting** involves harvesting a tissue from one location in the patient’s body and transplanting the tissue into another part of the same patient. Autologous grafts, those derived from within the patient, typically produce the best clinical results since tissue rejection is not an issue. However, there are several associated problems with autografting that include a lack of suitable harvest sites in some patients, additional surgical costs for the harvesting procedure, pain, infection, and blood loss (requiring transfusion and its accompanying risks).
2. **Allografting** involves harvesting tissue or organs from a donor and then transplanting it to the patient. Deceased or living donors have been used to donate such organs as heart, kidneys, lungs, and liver, and such tissues as bone marrow, tendons, ligaments, cartilage,

eye lens, and blood vessels. With the advent of anti-rejection drugs, transplantation technology has dramatically improved over the past several decades. However, large shortages in donor availability remain a problem. In addition, life-long medication and potential rejection complications make this an imperfect solution.

3. **Xenografting** Xenografting involves removing tissue from animal sources for transplantation into a human recipient. As in allografting, the potential for tissue rejection and the possible transmission of disease remains a concern. In addition, ethical concerns regarding this use of animals continue. However, the advantages of a readily available potential supply and the possibility of a standardized product make this option attractive to biomedical researchers. Researchers, bolstered by the expanding strategies and techniques of DNA science and the human genome project, continue to investigate the possibility of producing transgenic animals that are recognized as human.
4. **Man-made, biomimetic materials and devices** have been created by engineers and scientists to try to replicate, augment, and extend functions performed by biological systems. Examples include artificial hearts, heart valves, prosthetic hips, and breast implants, and these have had an enormous positive impact. However, the materials used are subject to fatigue, fracture, toxicity, and wear, and they do not remodel with time (for example, a metal bone implant cannot grow with the patient and it cannot change shape in response to the loads placed upon the implant). In addition, these material constructs do not behave physiologically like true organs or tissues. Thus, devices like an artificial heart are currently best suited as temporary therapies until a donor organ becomes available.

While all the aforementioned therapies have had a significant medical impact, there are newer technologies on the horizon that seek to overcome the limitations of these traditional approaches. The next-generation therapies include harvesting tissues and organs from genetically engineered and cloned animals, gene therapies, and cell and tissue engineering. While cloning and gene therapies have received much publicity, there are still significant technical, economical, political, and ethical issues that must be overcome before they are used. Many of the tissue-engineering approaches hold the promise of providing more immediate solutions.

Tissue Engineering is an emerging interdisciplinary field that applies the principles of biology and engineering to the development of viable substitutes that restore, maintain, or improve the function of human tissues. This form of therapy differs from standard drug therapy in that the engineered tissue becomes integrated within the patient, affording a potentially permanent and specific cure of the disease state.

Three general approaches have been adopted for the creation of new tissue:

1. Design and grow human tissues outside the body for later implantation to repair or replace diseased tissues. The most common example is the skin graft that is used for

treatment of burns. Skin graft replacements have been grown and used clinically for over 10 years.

2. Implantation of cell-containing or cell-free devices that induce the regeneration of functional human tissues. This approach relies on the purification and large-scale production of appropriate “signal” molecules, such as **growth factors**, to assist in biomaterial-guided tissue regeneration. Novel **polymers** are being created and assembled into three-dimensional configurations, to which cells attach and grow to reconstitute tissues. An example is the biomaterial matrix used to promote bone regrowth for periodontal disease.
3. The development of external or internal devices containing human tissues designed to replace the function of diseased internal tissues. This approach involves isolating cells from the body, using such techniques as **stem cell** therapy, placing them on or within structural matrices, and implanting the new system inside the body or using the system outside the body. Examples of this approach include repair of bone, muscle, tendon, and cartilage, as well as the cell-lined vascular grafts and artificial liver that are being developed in Pittsburgh.

Tissue-engineering researchers are attempting to engineer many human tissues. As the field of tissue engineering progresses, it will inevitably provide the following outcomes:

- By growing tissues outside the body for later implantation, the costs of tissue harvest, surgical costs, and postoperative patient costs will be significantly reduced.
- By actually designing tissue to mimic the site being reconstructed, the adequacy of the tissue replacement will be optimized, leading to improved patient care at less expense.
- In a cost-controlled health care environment, many experts believe that only those technologies capable of providing a major enhancement to quality of life and a reduction of cost will be driven forward. Engineered tissues represent a technology with the clear potential to meet this criterion.

Tissue Engineering: Discussion Questions

The following questions may serve as an effective introduction for students and educators alike. Class discussion, group classwork (perhaps cooperative learning units), or home research assignments may all provide appropriate forums for student comprehension of tissue-engineering concepts and challenges.

1. In general terms, what is tissue engineering?
2. What areas of life science and/or technology have been affected by tissue engineering?
3. Create a list of five major developments or contributions related to tissue engineering.
4. List and briefly describe five potential applications for tissue engineering within the 21st century.

Biomedical Focus

5. Specifically, and with greater emphasis on biomedical science, how might one more narrowly define tissue engineering?
6. In the area of biomedical science, what are the immediate and long-term applications of tissue engineering?
7. As of 2000, what has been the most successful clinical application of this field? Why is it not considered a complete success?
8. Tissue engineering is claimed to require a multidisciplinary approach. What areas of science or technology might or should interact?
9. In an attempt to build a tissue for incorporation into a host body, what major obstacles must be overcome? List and describe these obstacles.

Tissue Engineering: Discussion Answers

1. In its broadest sense, tissue engineering encompasses any manipulation of an organism in which tissue function or structure is altered. Thus, almost any manipulation that produces this change can be considered tissue engineering, including genetic manipulation, alteration of diet, surgical intervention, chemical (for example, hormonal) therapy, and simple selective breeding. However, many researchers now accept a more restricted definition, enabling them to more precisely identify and characterize the field. Refer to answer 5 below.
2. There are many possible answers. Agriculture has been tremendously affected, yielding plants with altered, favorable characteristics such as drought, temperature, and pest resistance. Plants may produce more of a given product (food, pharmaceuticals, etc.), may grow larger, or even interact in new ways with their surroundings. Biomedicine has begun a revolution, with greater insights into mimicking tissue function and the disease state. Biophysics has become an even more applied field, as have biomaterial research and computer modeling of life structure and function.
3. Answers will vary. Refer to the general articles listed in the reference section.
4. Answers will vary. Students are left to extrapolate from current technologies, therapies, etc. General articles listed in the reference section provide many potential answers.
5. One restricted definition describes tissue engineering as the laboratory construction of a living tissue system that can be implanted into a body and is able to duplicate the structural and functional parameters of normal tissue. This implies that the tissue construct can be designed and produced artificially, though not necessarily consisting of completely inorganic materials. In fact, a crucial aspect of most definitions is the requirement that the tissue have a critical cellular component, distinguishing tissue engineering from bioengineered products such as artificial organs.
6. There are a number of possible answers. Immediately, tissue engineering may be used to replace tissues damaged by trauma or disease. Down the road, the technology may allow people to supplement tissue function, perhaps improving performance, general health, or reducing age or disease risks. Liver, neural, circulatory, pulmonary, intestinal, integumentary musculoskeletal, and pancreatic tissue appear to be likely targets.
7. The development of engineered skin is one of the great initial success stories, though it is actually far from able to mimic all of the biological characteristics of normal skin. It does not contain sweat pores for temperature and liquid balance, it does not possess any of the glands such as oil glands, and it does not have hair follicles. Melanocytes also are lacking, as are other cellular features. In spite of these and other structural limitations, the engineered skin can allow one to reconstitute the integumentary covering of the body, rectifying the primary problem of possible infection.
8. Biology, chemistry, physics, materials science, engineering, computer science, and biomedicine can make significant contributions to this field. Subsets of each discipline abound, making the list quite formidable.
9. At this point, there are a number of obstacles or questions to be resolved, including:

- a. The **extracellular matrix** (the chemical environment surrounding the cells within a tissue) must be characterized.
- b. The constructed matrix, or **scaffold**, must be compatible with the living host.
- c. The scaffold must allow cells to migrate and populate properly, as well as to properly interact with the living matrix.
- d. The proper development and subsequent functioning of the cells within the scaffold must be established and maintained. This must include properly stimulating cell proliferation and **differentiation** by the delivery of appropriate growth factors or other chemical agents, and ensuring a constant and adequate vascular supply.

Biological considerations are vast and include the concerns described above. Physical and material science considerations generally relate to the mimicking of the physical characteristics of the tissue, including resistance to physical and chemical stresses. Chemical considerations often relate to the properties of the scaffold as it interacts with the living system. In addition, chemical delivery systems for regulatory molecules remain a challenge. Overall, computer-modeling systems enable the engineers to better predict outcomes and improve design parameters for the tissue product.