TISSUE ENGINEERING

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Summary

This chapter is aimed to present tissue engineering and regenerative medicine has the potential of revolutionizing treatment and therapies for patients. Regenerative medicine is a term that is often used synonymously with tissue engineering, though the former often neglects the scaffold and focuses on tissue regeneration via application of stem cells. Since tissue engineers also may make use of stem cells, there is some overlap between the two fields.

Tissue engineering aims to create medical devices that, once implanted, will replace or enhance tissue function that has been impaired by disease, injury, or age. These devices are typically created by seeding a biomaterial scaffold (a sculpted porous sponge) with cells. It is preferable that the cells be harvested from the patient - a device made from cells that are a genetic match are less likely to be rejected by the immune system. If the patient's own cells are not an option, cells from another human donor can be used. There are already several types of tissue engineered skin in clinical use, and a great deal of research going into tissue engineered liver, bone, blood vessel, nerve grafts, and pancreas.

1. Introduction

The world of medical devices and implants has entered an era where the future will be more and more driven by the desire to in some way imitate nature and to harness this into clinical treatments and therapies. A variety of terms are being used. These include the term bioengineered tissues, tissue engineering, or regenerative medicine, cell therapies; however, what one in general means is the replacement, repair, and/or regeneration of tissues and organs. In these one is using more biologically-based approaches to treat problems associated with failing tissues and organs.

Historically the term tissue engineering dates back to the Fall of 1987 when it was "coined" at a meeting at the National Science Foundation in Washington, D.C. This led to the first meeting called "tissue engineering," a small conference held in early 1988 at Lake Tahoe, California (1). The term "Regenerative medicine" is a more recent one that came into use during the 1990s. Although to some it is synonymous with stem cell technology, regenerative medicine must be more than just stem cells if one is to move from basic biology to clinical applications. Thus, tissue engineering and regenerative medicine are very much complementary, with many using the two terms interchangeably. Even so, it must be recognized that early research in this general area predates by decades the origin of these terms, with the earliest mention of the concept of a more biological approach dating back to a book published in 1938(2).

Tissue engineering and regenerative medicine have the potential of revolutionizing treatment and therapies for patients, and in the process also revolutionizing the medical device industry as will be discussed later. Even though as already indicated research in tissue engineering goes back well into the 20th century the 1990s represented a decade of considerable excitement. This was a time where research in this field was rapidly expanding at universities, a time led by bold visions for the future (3,4), a time when a number of start ups were being formed, and a time when there was considerable commercial activity. With all this there was considerable attention to this field provided by the media. An example is the respected business journal Barron's that touted the future of tissue engineering in an article entitled "Spare Body Parts," headlining a $100 billion industry(5). Another example is Dr. Michael Guillen, an ABC television science correspondent, who stated in a September 29, 1999 broadcast that "when historians look back at the twentieth century … the greatest achievement will not be space travel or computers … but will be in the fields of tissue engineering and genetic medicine." Scientists, perhaps in the excitement of their research, have also contributed by sometimes overstating the potential benefit for patients and/or talking about unrealistic timelines for a product or a treatment to reach the patient bedside. In spite of this hype, the hope for new innovative approaches in the future remains (6).

2. Clinical Applications

The medical device/implant industry has made enormous contributions to healthcare over the past half century. Each of us knows individuals who either have a pacemaker, a prosthetic heart valve, a hip or knee implant, or some other medical device/implant(7). The biological revolution, however, is spawning a revolution in this industry. It is one where in this 21st century the products will be different and the way products are engineered will be different. Tissue engineering and regenerative medicine will not only lead to the next generation of medical implants, but also to strategies that bypass the need for replacement through fostering repair and regeneration. It is these three Rs, i.e. replacement, repair, and regeneration, that offers hope to millions of patients who today have diseases where existing treatments are inadequate or in many cases do not exist at all.

By replacement what is meant is the actual growing or fabricating of a tissue or organ substitute outside the body and then surgically implanting it. An example is the making of a blood vessel substitute as illustrated in Figure 1. A blood vessel is a complicated multi-cellular structure involving three layers. These are (i) the media in which smooth muscle cells are incorporated, (ii) the intima which is the inner lining of endothelial cells that provides for non-thrombogenicty, i.e. to prevent clotting, and (iii)the adventia which is the outer layer with fibroblasts, a layer that not only provides mechanical strength but one where nutrients come in from the outside through small blood vessels, what is called the vasa vasorum. It is the last of these three layers that is the most complicated, and thus most attempts to tissue engineer a blood vessel substitute have focused on just two layers, the media and the intima. This is what is illustrated in Figure 1 where the media is fabricated by seeding smooth muscle cells into a porous polymeric scaffold and then an inner lining of endothelial cells is added. This must be viewed as a "simplistic" model of an actual blood vessel. Still, it illustrates the basic concept of creating a replacement tissue through tissue engineering.

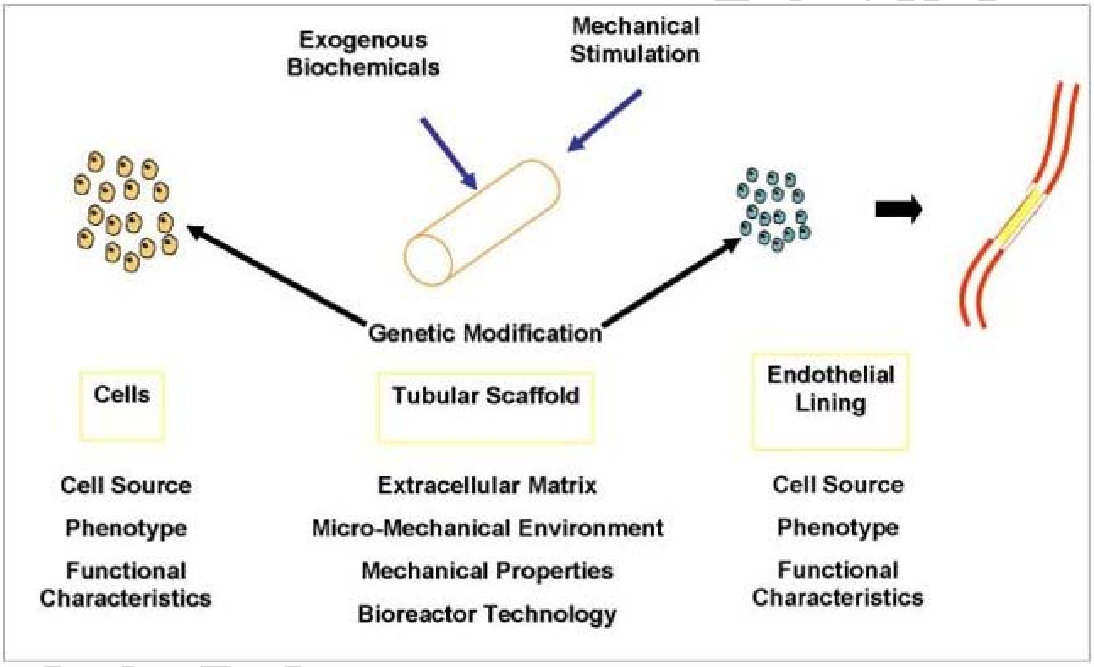

Figure 1. Illustration of the Tissue Engineering of a Blood Vessel Substitute

Then there is the concept of repair, i.e. biological repair done through altering the biological events. This really requires that one is able to detect disease at what might be called a pre-clinical state, i.e. before the disease manifests itself with clinical symptoms. This only can be done at an earlier stage in the disease process when in effect the pathological events can be reversed. Finally, there is regeneration. At times there may be some confusion between the terms repair and regeneration; however, as used here repair does not involve replacing tissue or regenerating, i.e. creating, tissue that is no longer there, but simply repairing existing tissue through biological processes so as to bring it back to its normal physiological state.

There will be cases where there will be a need for replacement, others where the strategy will be repair, and others yet where the approach will be the regeneration of new healthy tissues. Table 1 summarizes the different tissues and organs where progress is being made today in advancing clinical treatments and therapies through tissue engineering and regenerative medicine.

These range from the more structural tissues like skin, cartilage, and bone to the vital organs, e.g. kidney, liver, and pancreas, and to neural repair. It is for these latter applications that tissue engineering and regenerative medicine may have the greatest impact. Today, at least in the Western, developed world, we are facing a “transplantation crisis”(8). It is a crisis because there is an ever increasing patient need, but little increase in the availability of donor organs.

Tissue engineering has the potential to confront this crisis by providing an alternative supply of the organs that are needed. Neural injury also represents a major challenge. Although some progress is being made in the regeneration of the peripheral nervous system, there needs to be advances made in the repair of the central nervous system.

Severe Burns	Blood Vessels
Skin ulcers	Heart Valves
Facial reconstruction	Myocardial Patches
Cartilage	Heart
Tendons	Bioartificial Pancreas
Ligaments	Kidney
Bone	Liver

- **Neural Repair**

Table 1. Some Tissue Engineering Applications

Out of what has been learned so far, there are a number of critical issues that can be identified. These are highlighted in Table 2, and these will be addressed in the next few sections. With all this potential, with this hope for the future, what are the barriers that stand in the way. What are the challenges that are facing tissue engineering? There are a number of these, both in terms of the basic science and issues related to product development (9,10), and these are discussed next.

Cell Source
Smart Scaffolds
Delivery Vehicles
Vascularization
Innervation
Immune Acceptance
Scaleup of Manufacturing
Product preservation and shelf life

Table 2. Critical Issues for the Field of Tissue Engineering and Regenerative Medicine

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Biographical Sketch

Robert Nerem has been active in bioengineering for more than thirty-five years. His initial interest was motivated by the possible role of fluid dynamics in atherosclerosis, and he has conducted fundamental research on problems in cardiovascular fluid dynamics. In 1981 he established a cell culture laboratory and began to study the influence of physical forces on anchorage-dependent mammalian cells, with much of this work focusing on the cells which make up a blood vessel. This work led to his interest in tissue engineering, and he now is director of the Georgia Tech/Emory Center for the Engineering of Living Tissues (GTEC), an Engineering Research Center established in 1998 and funded by the National Science Foundation.

Since 1995, Dr. Nerem has served as the director of the Parker H. Petit Institute for Bioengineering and Bioscience (IBB), a research institute whose mission is to integrate engineering, information technology, and the life sciences in the conduct of biomedical research. In addition, he served on a part-time basis from 2003 to 2006 as the senior advisor for bioengineering in the National Institute of Health's (NIH) newest institute, the National Institute for Biomedical Imaging and Bioengineering.

In recognition of his work, he was elected to the National Academy of Engineering in 1988 and to the Institute of Medicine of the National Academy of Sciences in 1992. He was elected a fellow of the American Academy of Arts and Sciences in 1998. Nerem is past president of the International Federation for Medical and Biological Engineering and past president of the International Union for Physical and Engineering Sciences in Medicine. He was also the founding president of the American Institute of Medical and Biological Engineering and he served on the Science Board of the Food and Drug Administration from 2000 to 2003. In 2008 he received the Founders Award from the National Academy of Engineering.

Dr. Nerem came to Georgia Tech in the winter of 1987 as a professor in the School of Mechanical Engineering and as the Parker H. Petit Distinguished Chair for Engineering in Medicine. He also has an appointment in the School of Chemical & Biomolecular Engineering. Prior to coming to Georgia Tech, he was a professor and chairman in the Department of Mechanical Engineering at the University of Houston from 1979 to 1986 and on the faculty at the Ohio State University from 1964 to 1979.