

Chapter 1

An Introduction

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Abstract

In the last few decades tissue engineering has emerged as a technology, and this has now evolved into what is called regenerative medicine, including not only the replacement of tissues and organs, but also repair and regeneration. This field is an outgrowth of the biological revolution. Although research in this field goes back well into the 20th century, it was in the 1990s that research accelerated and that an industry began to emerge. In this same period the Tissue Engineering Society was formed, and this has evolved into what is now the Tissue Engineering and Regenerative Medicine International Society. Although the industry still may be characterized as being in a fledgling state, there are some positive signs appearing. Furthermore, the field has become a global activity, one that has the potential to alter the practice of medicine as we know it. Thus, building on the past, the future of tissue engineering and regenerative medicine remains extremely promising.

Keywords: Tissue Replacement and Repair; Regeneration; Stem Cell Technology; Industry.

Outline

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1. Introduction

Over the last few decades tissue engineering has emerged as a technology, and this now has evolved into what is called regenerative medicine. For many tissue

engineering has had a broad meaning, one that includes not only the replacement of tissues and organs, but also repair and regeneration. For others, however, it is the term regenerative medicine that has the broader meaning. Whatever the use of these terms, it is a more biologic approach to treating tissues and organs that represents the future, and what one in general means is the triad of replacement, repair, and/or regeneration of tissues and organs. It is this combination of approaches that represents a new era in our efforts to treat problems associated with failing tissues and organs, an era where our goal is to harness the intrinsic power of biology and where our thinking is driven by the desire to in some way imitate nature.¹

It should be noted that for this author replacement involves the growing/fabricating of tissues and organs outside the body and these then being implanted. Repair is not what has been afforded by the electromechanical devices/implants of the 20th century where there was no biological function. Rather, repair is a biological one at the cell and molecular level, including the repair of DNA. Finally, regeneration means to literally grow *in vivo* a new tissue or organ, where the challenge is to cause this regeneration without scarring.

The medical device/implant industry started to emerge in the middle of the last century, and this industry and the technology it has fostered has made enormous contributions to healthcare. All of us know individuals who have a medical device/implant and who thus have benefited from the products of this industry.² These have reduced pain and alleviated symptoms, but they have not been cures. Thus, as will be discussed later, the biological revolution is spawning a revolution in this industry, one where the products will be different and the way products are engineered will be different. This is due, at least in part, to the advent of tissue engineering and regenerative medicine. This more biologic approach brings the potential of revolutionizing treatments and therapies for patients, and it is this emerging science and technology that will lead to the next generation of medical implants. It also will lead to strategies that bypass the need for replacement through the fostering of repair and regeneration. All of this will in turn offer hope to millions of patients who today have conditions where existing treatments and therapies are inadequate or in many cases do not exist at all.

2. The Early Years

The field of tissue engineering and regenerative medicine is a product of the biological revolution. This revolution in biology dates back to the early part of the 20th century and the advent of cell culture, i.e. the ability to grow cells in the laboratory, outside of the body. The next major step was the identification of DNA as a double helix, this in the early 1950s, and by the 1970s recombinant DNA

technology had been established. More recently we have the Human Genome Project, and this will be followed by the proteome and the physiome, areas now of significant activity. It was the advent of cell culture, however, that in a very real way initiated the biological revolution.

Another important development in these early years was the field of transplantation, i.e. the ability to transplant an organ from one individual to another individual. The earliest report of an attempt to carry out such a transplantation was reported in a *New York Times* article published November 14, 1911. This attempt apparently was not successful, and it was not until four decades later that such an operation was successfully performed, this at Massachusetts General Hospital in Boston. The transplantation of organs such as the heart, kidney, liver, and pancreas are now all routinely carried out and have helped thousands of patients. Even so, there are more than 90,000 individuals in the United States alone waiting for an organ for transplantation. The patient need far exceeds the availability of organs from donors, and one cannot foresee this transplantation crisis going away without there being an alternative to donated organs. Tissue engineering and regenerative medicine has the potential to be that alternative.

The earliest mention of the concept of a more biological approach dates back to a book published in 1938.³ It was not until the second half of the 20th century, however, that one began to see more and more research in this emerging field. This is when many of the pioneers in research began to make their mark. Leaders that emerged in the 1970s and 1980s include Anthony Atala, Francois Auger, Stephen Badylak, Eugene Bell, Robert Langer, Gail Naughton, Julia Polak, Charles Vacanti, his brother Joseph Vacanti, and Ioannis Yannas. In fact, one of the early publications was that of Professor Yannas, who with his collaborators described in 1982 the partial regeneration of skin following the grafting of an animal with a cell seeded scaffold.⁴

The term tissue engineering was in fact not “coined” until Autumn 1987, this at a meeting at the National Science Foundation. This led to the first meeting called “tissue engineering” which was held in early 1988 at Lake Tahoe, California,⁵ and it was that same year that the first research grants were awarded through a Federal program labeled tissue engineering. This was a National Science Foundation program, and I and my collaborator were fortunate enough to get one of these first six grants. Our goal in 1988 was to create a tissue engineered blood vessel; however, the application was not for clinical use, but rather to develop a better *in vitro* model for vascular biology studies.

The 1980s also was a time when startups were being formed. This included two pioneering companies, Organogenesis in 1986 and Marrow Tech in 1987, with the latter becoming later Advanced Tissue Sciences. More will be said about these companies in a later section.

3. The 1990s

Although as indicated previously, research in tissue engineering goes back well into the 20th century, it was in the 1990s that research in the field accelerated. This thus was a decade of considerable excitement. Not only was research in this field rapidly expanding in the academic arena, but it was a time when there was considerable activity on the commercial front, and there were bold visions of the future.^{6,7}

This also was the decade when tissue engineering as a community began to organize. In 1995 the Tissue Engineering Society was formed, and it was Charles Vacanti who was the first president of the society. The journal *Tissue Engineering* was launched in 1996, and in that same year the first meeting of the Tissue Engineering Society was held in Orlando, Florida. In addition, this was the decade when major centers of activity began to emerge including our own center in Atlanta, the Georgia Tech/Emory Center for the Engineering of Living Tissues, established in 1998 as a National Science Foundation Engineering Research Center.

With all this there was considerable hype in the media. An example of this is the respected business journal *Barron's* touting the future of tissue engineering in an article entitled "Spare Body Parts" and that headlined a US\$100 billion industry.⁸ The television media also contributed to the excitement and the hype. An example of this is Dr. Michael Guillen, an ABC science correspondent, stating in a September 29, 1999 broadcast that "when historians look back at the 20th century [...] the greatest achievement will not be space travel or computers [...] but will be in the fields of tissue engineering and genetic medicine." Furthermore, the fault for all of this does not entirely lie with the media as scientists have also contributed to the hype by overstating the potential benefit for patients and/or by talking about unrealistic timelines for a product or a treatment to reach the patient bedside. The result, however, was that pioneering companies were caught in a circle where the hype helped with the need to continue to raise funds but also lead to increased expectations by investors and by the public.

It also was in the 1990s when the term "regenerative medicine" came into use. For some this term is synonymous with stem cell technology; however, regenerative medicine must be more than just stem cells if one is to move from basic biology to clinical applications. The two areas of tissue engineering and regenerative medicine in fact are very much complementary, and there are many who use the two terms interchangeably.

4. 2000 to Present

The industry that grew up in the 1990s did bring some products to the market. These were largely skin substitutes, with the one exception being Carticel, an

autologous cell procedure for treating cartilage defects. These were developed by pioneering individuals such as Professor Yannas whose dermal regeneration template received regulatory approval in 1996. Then there were other skin substitutes, TransCyte, Apligraf, and Dermagraft, developed by Advanced Tissue Sciences and Organogenesis.^{9,10} These pioneering companies, however, had their own set of problems. These were addressed as part of a meeting at Georgia Tech held under the auspices of the Medical Technology Leadership Forum (MTLF) in 2007.¹¹ These problems ranged from an insufficient science base, e.g. not understanding the mechanism of action, to overestimating the patient need, i.e. market size, to underestimating the disruptiveness of this new technology. It was hampered by delays in regulatory approval and in reimbursement approval, and there were a variety of less than optimal business/management decisions. The “bottom line” was that the time from the benchtop to a marketable product was far too long, with a result that several of these pioneering companies, including both Advanced Tissue Sciences and Organogenesis, ran into severe financial problems.

This industry continued into this century in a fledgling state. This is an industry that in some ways is still in the process of being born; however, it is an industry that continues to progress. Whereas *Barron's* talked about a US\$100 billion industry, Michael Lysaght¹² estimates that in 2006 total sales was US\$240 million, this as compared to less than US\$100 million in 2000. Furthermore, in an expanded study using a broader definition that attempts to include all aspects of tissue engineering, regenerative medicine, and stem cell therapeutics, Lysaght and co-workers estimate annual sales at US\$1.5 billion for 2007 with another US\$860 million in development stage spending, a total of 170 companies, and more than 6000 employees.¹³ Of those using cellular approaches, 62% are employing allogeneic cells, and of the stem cell companies, 61% are based on adult stem cells, 27% cord blood-derived cells, and only 12% embryonic stem cells. Whereas this industry in the 1990s appeared to be dominated by US companies, it clearly is now becoming a global industry, with a high percentage of new firms being located outside of the US. Also many of the new firms are in the stem cell area.

There thus are some positive signs appearing. Organogenesis, one of the pioneering skin substitute companies with their product Apligraf, is now turning a profit, and Advanced Tissue Sciences, having gone bankrupt and then acquired by Smith & Nephew, now has its skin substitute products manufactured and marketed by Advanced Biohealing. One of the real successes in bringing tissue engineering to the patient bedside has been the use of the acellular small intestine submucosa (SIS) for a variety of purposes, including musculoskeletal repairs.¹⁴ It thus would be wrong to describe the 1990s as a decade of failures as there are products on the market and these products are helping patients.

Furthermore, the development of these products in the 1990s represented learning experiences, and they have provided insight into what some of the critical issues were and continue to be. Some even say that the industry has come of age, that it has moved into a new era.¹⁵ This may be an overstatement; however, the good news is that the “big boys” of the medical device industry are increasingly investing in tissue engineering and regenerative medicine. They realize that the convergence of biologics with medical devices eventually will have an enormous impact on the industry.¹¹ To ultimately commercialize a technology, however, requires addressing a variety of other issues that go beyond the science. These will be addressed in various chapters of this publication; however, clearly, scientific success does not ensure commercial success as the issues are very different.

Finally, it should also be noted that the organization of the community has continued to evolve. The Tissue Engineering Society became the Tissue Engineering Society International (TESI) and held meetings in Freiburg, Germany and in Kobe, Japan in 2001 and 2002 respectively, and then in 2003 TESI returned to Orlando, Florida. At that time discussions began to take place to make the society a truly international organization, and in 2005 out of TESI the Tissue Engineering and Regenerative Medicine International Society (TERMIS) was established. As part of this three regional chapters were formed, one in North America, one in Europe, and one in Asia. The plan included holding a World Congress once every three years, with 2006 being in Pittsburgh, 2009 in Korea, and 2012 somewhere in Europe. In years not corresponding to a TERMIS World Congress, the chapters are each authorized to hold a regional meeting.

5. What About the Future?

Even though tissue engineering has been over promised and under delivered in the past, and the same can be said for the more recent development of regenerative medicine, the potential is still there. Advances that are envisioned include the following:¹⁶

- *in vitro* models for the study of basic biology and for use in drug discovery;
- blood cells derived from stem cells and expanded *in vitro*, thus reducing the need for blood donors;
- an insulin-secreting, glucose responsive bioartificial pancreas;
- heart valves that when implanted into an infant grow as the child grows; and
- repair/regeneration of the central nervous system.

What is necessary in order to create this brighter future? To start with, as with many new technologies, it is only when the second generation of products comes

along that there develops a strong scientific foundation upon which the product development/treatment strategy can be established. This is true of tissue engineering and regenerative medicine, and this foundation is very much needed. The critical issues that need to be addressed have been identified recently through two different studies. One of these is a report published by the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group, a consortium of six Federal agencies.¹⁷ The other is published in late 2007.¹⁸ These represent a road map, and if we address what is identified in these two separate studies, we will be laying the foundation. To do this, however, will require the expanded and accelerated efforts of the tissue engineering and regenerative medicine community. As part of the expansion of this effort, more attention will need to be given to the biology. We need to understand basic biological mechanisms and this includes developmental biology. This in turn requires that more biologists join the multi-disciplinary efforts now in progress.

It also must be recognized that the science and the basic technology represents only the beginning. As one moves from the benchtop of the research laboratory ultimately to the patient bedside, there are a variety of other issues that will need to be addressed.¹⁹ One of these is the manufacturing process as it must be recognized that it is one thing to make one of a kind of a product, a substitute or delivery vehicle in a research laboratory, it is quite different to make 1000 per week with the reproducible quality that would be required to obtain regulatory approval. There also are problems that arise in the testing of the initial cells, in the growth and handling of large volumes of cells, and in maintaining sterility and phenotype. In this the optimization of bioreactor design is critical to meeting the needs of cell expansion and tissue production. Furthermore, the manufacturing process of a living cell product needs to be critically controlled, and the development of new manufacturing techniques will be needed. There will need to be greater attention given to the quality control of what has been engineered. For long-term success a better understanding of the mechanism of action will be needed for use in setting product specifications and for quality control. Once manufactured, how is off-the-shelf availability of a cell-based product to be provided? Is it to be stored fresh in which case its shelf life will be limited or is it to be cryopreserved so as to have extended shelf life? What is the best approach if a particular product or cell-based strategy is to be implemented in the variety of hospitals that make up our health-care system?

The ultimate success of a tissue-engineered product is also dependent on the market for the product. This is influenced by its uniqueness, accessibility, and cost, as well as the market competition and physician acceptance. There needs to be appropriate business models. In developing these, we need to learn from the problems encountered by the early pioneering companies. Their experiences

should be viewed as case studies from which we all can learn as we move towards the next generation of products, and the MTLF meeting held at Georgia Tech in June 2007 represented a start in this.¹¹

6. Concluding Discussion

In summary, the advances in the science and the technology have been and continue to be exciting; however, to date tissue engineering and regenerative medicine have been over-promised and under-delivered. Still, if the tremendous potential that exists could be realized, this would dramatically alter the practice of medicine in the future.²⁰ If we are able to address the critical issues, then there will be a whole new generation of totally biologic products and strategies.

It should be noted that there are significant, multi-disciplinary national initiatives that have been or are being established in countries in Europe and also in Asia. In some cases these have resulted or are resulting in the formation of centers and in others these are taking the form of a broader type of initiative. Example countries in Europe include Germany, Ireland, the Netherlands, and the United Kingdom and in Asia examples are China, Japan, and Korea. The US itself needs a national initiative. Stem cell technology²¹ has become an important part of tissue engineering and regenerative medicine, and the US should not let the controversy surrounding human embryonic stem cells prevent a major expansion and acceleration of the US effort in tissue engineering and regenerative medicine. Now that there is the road map provided by the recent studies, how is this to be implemented in the US and elsewhere?

The fact that this field has become a global activity bodes well for the future, in particular with the current constraints on human embryonic stem cell research in the US where as a result other countries are taking the lead. It is this global effort that will write the future history of tissue engineering and regenerative medicine. As we look into this future, in some cases the advances in a treatment or therapy will be made through the development of a replacement tissue or organ. In other cases, for example where the biological complexity prevents us from growing replacement parts in the laboratory, the solution in the future may be the fostering of repair or regeneration. Perhaps we will even be able to diagnose disease at what we now consider to be a preclinical stage and to induce a biological repair and/or regeneration at an early state. All of this will be part of the future of this still emerging field of tissue engineering and regenerative medicine, a future that has the potential of altering the practice of medicine as we know it today.

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