Chapter TWO

The Challenge of Imitating Nature

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I. INTRODUCTION

Tissue engineering, through the imitation of nature, has the potential to confront the transplantation crisis caused by the shortage of donor tissues and organs and also to address other important, but yet unmet, patient needs. If we are to be successful in this, a number of challenges need to be faced. In the area of cell technology, these include cell sourcing, the manipulation of cell function, and the effective use of stem cell technology. Next are those issues that are part of what is called here *construct technology*. These include the design and engineering of tissuelike constructs and/or delivery vehicles and the manufacturing technology required to provide off-the-shelf availability to the clinician. Finally, there are those issues associated with the integration of cells or a construct into the living system, where the most critical issue may be the engineering of immune acceptance. Only if we can meet the challenges presented by these issues and only if we can ultimately address the tissue engineering of the most vital of organs will it be possible to achieve success in confronting the crisis in transplantation.

An underlying premise of this is that the utilization of the natural biology of the system will allow for greater success in developing therapeutic strategies aimed at the replacement, maintenance, and/or repair of tissue and organ function. Another way of saying this is that, just maybe, the great creator, in whatever form one believes he or she exists, knows something that we mere mortals do not, and if we can only tap into a small part of this knowledge base, if we can only imitate nature in some small way, then we will be able to achieve greater success in our efforts to address patient needs in this area. It is this challenge of imitating nature that has been accepted by those who are providing leadership to this new area of technology called *tissue engineering* (Langer and Vacanti, 1993; Nerem and Sambanis, 1995). To imitate nature requires that we first understand the basic biology of the tissues and organs of interest, including developmental biology; with this we then can develop methods for the control of these biologic processes; and based on the ability to control, we finally can develop strategies either for the engineering of living tissue substitutes or for the fostering of tissue repair or regeneration.

The initial successes have been for the most part substitutes for skin, a relatively simple tissue, at least by comparison with most other targets of opportunity. In the long term, however, tissue engineering has the potential for creating vital organs, such as the kidney, the liver, and the pancreas. Some even believe it will be possible to tissue engineer an entire heart. In addressing the repair, replacement, and/or regeneration of such vital organs, tissue engineering has the potential literally to confront the transplantation crisis, i.e., the shortage of donor tissues and organs available for transplantation. It also has the potential

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to develop strategies for the regeneration of nerves, another important and unmet patient need.

Although research in what we now call tissue engineering started more than a quarter of a century ago, the term *tissue engineering* was not coined until 1987, when Professor Y. C. Fung, from the University of California, San Diego, suggested this name at a National Science Foundation meeting. This led to the first meeting called "tissue engineering," held in early 1988 at Lake Tahoe, California (Skalak and Fox, 1988). More recently the term *regenerative medicine* has come into use. For some this is a code word for stem cell technology, while for others regenerative medicine is the broader term, with tissue engineering representing only replacement, not repair or regeneration. Still others use the terms *tissue engineering* and *regenerative medicine* interchangeably. What is important is that it is a more biologic approach that has the potential to lead to new patient therapies and treatments, where in some cases none is currently available.

It should be noted that the concept of a more biologic approach dates back to 1938 (Carrel and Lindbergh, 1938). Since then there has been a large expansion in research efforts in this field and a considerable recognition of the enormous potential that exists. With this hope, there also has been a lot of hype; however, the future long term remains bright (Nerem, 2006). As the technology has become further developed, an industry has begun to emerge. This industry is still very much a fledgling one, with only a few companies possessing product income streams (Ahsan and Nerem, 2005). A study based on 2002 data documents a total of 89 companies active in the field, with $500 million annually in industrial research and development taking place (Lysaght and Hazlehurst, 2004). Although this study will soon be updated, based on the 2002 data, 80% of the new firms were in the stem cell area and 40% were located outside of the United States.

Tissue engineering is literally at the interface of the traditional medical implant industry and the biological revolution (Galletti *et al.*, 1995). By harnessing the advances of this revolution, we can create an entirely new generation of tissue and organ implants as well as strategies for repair and regeneration. Already we are seeing increased investments in this field by the large medical device companies. A part of this is a convergence of biologics and devices, which is recognized by the medical implant industry. It is from this that the short-term successes in tissue engineering will come; however, long term it is the potential for a literal revolution in medicine and in the medical device/implant industry that must be realized.

This revolution will only occur, however, if we successfully meet the challenge of imitating nature. Thus, in the remainder of this chapter the critical issues involved in this are addressed. This is done by first discussing those issues associated with cell technology, i.e., issues important in cell sourcing and in the achievement of the functional characteristics required of the cells to be employed. Next to be discussed are those issues associated with construct technology. These include the organization of cells into a three-dimensional architecture that functionally mimics tissue, the development of vehicles for the delivery of genes, cells, and proteins, and the technologies required to manufacture such products and provide them off the shelf to the clinician. Finally, issues involved in the integration of a living cell construct into, or the fostering of remodeling within, the living system is discussed. These range from the use of appropriate animal models to the issues of biocompatibility and immune acceptance. Success in tissue engineering will only be achieved if issues at these three different levels, i.e., cell technology, construct technology, and the technology for integration into the living system, can be addressed.

II. CELL TECHNOLOGY

The starting point for any attempt to engineer a tissue or organ substitute is a consideration of the cells to be employed. Not only will one need to have a supply of sufficient quantity and one that can be ensured to be free of pathogens and contamination of any type whatsoever, but one will need to decide whether the source to be employed is to be autologous, allogeneic, or xenogeneic. As indicated in Table 2.1, each of these has both advantages and disadvantages; however, it should be noted that one important consideration for any product or treatment strategy is its off-the-shelf availability. This is obviously required for surgeries that must be carried out on short notice. However, even when the time for surgery is elective, it is only with off-the-shelf availability that the product and strategy will be used for the wide variety of patients who are in need and who are being treated throughout the entire health care system, including those in community hospitals.

With regard to the use of autologous cells, there are a number of potential sources. These include both differenti-

Table 2.1. Cell source

Type	*Comments*
Autologous	Patient's own cells; immune acceptable, but does not lend itself to off-the-shelf availability unless recruited from the host
Allogeneic	Cells from other human sources; lends itself to off-the-shelf availability, but may require engineering immune acceptance
Xenogeneic	From different species; not only requires engineering immune acceptance, but must be concerned with animal virus transmission

ated cells and adult stem/progenitor cells. It is only, however, if we can recruit the host's own cells, e.g., to an acellular implant, that we can have off-the-shelf availability, and it is only by moving to off-the-shelf availability for the clinician that routine use becomes possible.

The skin substitutes developed by Organogenesis (Canton, MA) and Advanced Tissue Sciences (La Jolla, CA) represented the first living-cell, tissue-engineered products, and these in fact use allogeneic cells. The Organogenesis product, Apligraf™, is a bilayer model of skin involving fibroblasts and keratinocytes that are obtained from donated human foreskin (Parenteau, 1999). Apligraf™ is approved by the Food and Drug Administration (FDA); however, the first tissue-engineered products approved by the FDA were acellular. These included Integra™, based on a polymeric template approach (Yannas *et al.*, 1982), and the Advanced Tissue Sciences product, TransCyte™. Approved initially for third-degree burns, TransCyte™ is made by seeding dermal fibroblasts in a polymeric scaffold; however, once cryopreserved it becomes a nonliving wound covering. Advanced Tissue Sciences also has a living-cell product, called Dermagraft™. It is a dermis model, also with dermal fibroblasts obtained from donated human foreskin (Naughton, 1999). Even though the cells employed by both Organogenesis and Advanced Tissue Sciences are allogeneic, immune acceptance did not have to be engineered because both the fibroblast and the keratinocyte do not constitutively express major histocompatibility complex (MHC) II antigens.

The next generation of tissue-engineered products will involve other cell types, and the immune acceptance of allogeneic cells will be a critical issue in many cases. As an example, consider a blood vessel substitute that employs both endothelial cells and smooth muscle cells. Although there is some unpublished data that suggest allogeneic smooth muscle cells may be immune acceptable, allogeneic endothelial cells certainly would not be. Thus, for the latter, one either uses autologous cells or else engineers the immune acceptance of allogeneic cells, as is discussed in a later section. Undoubtedly the first human clinical trials will be done using autologous endothelial cells; however, it appears that the use of such cells would severely limit the availability of a blood vessel substitute, unless the host's own endothelial cells are recruited.

Once one has selected the cell type(s) to be employed, then the next issue relates to the manipulation of the functional characteristics of a cell so as to achieve the behavior desired. This can be done either by (1) manipulating a cell's microenvironment, e.g., its matrix, the mechanical stresses to which it is exposed, or its biochemical environment, or by (2) manipulating a cell's genetic program. With regard to the latter, the manipulation of a cell's genetic program could be used as an ally to tissue engineering in a variety of ways. A partial list of possibilities includes the alteration of matrix synthesis; inhibition of the immune response; enhancement of nonthrombogenicity, e.g., through increased synthesis of antithrombotic agents; engineering the secretion of specific biologically active molecules, e.g., a specific insulin secretion rate in response to a specific glucose concentration; and the alteration of cell proliferation.

Much of the foregoing is in the context of creating a cell-seeded construct that can be implanted as a tissue or organ substitute; however, the fostering of the repair or remodeling of tissue also represents tissue engineering as defined here. Here a critical issue is how to deliver the necessary biologic cues in a spatially and temporally controlled fashion so as to achieve a "healing" environment. In the repair and/or regeneration of tissue, the use of genetic engineering might take a form that is more what we would call *gene therapy*. An example of this would be the introduction of growth factors to foster the repair of bone defects. In using a gene therapy approach to tissue engineering it should be recognized that in many cases only a transient expression will be required. Because of this, the use of gene therapy as a strategy in tissue engineering may become viable prior to its employment in treating genetically related diseases.

Returning to the issue of cell selection, there is considerable interest in the use of stem cells as a primary source for cell-based therapies, ones ranging from replacement to repair and/or regeneration. This interest includes both adult stem cells and progenitor cells as well as embryonic stem cells (Ahsan and Nerem, in press; Vats *et al.*, 2005). With regard to the latter, the excitement about stem cells reached a new height in the late 1990s with articles reporting the isolation of the first lines of human embryonic stem cells (Thomson *et al.*, 1998; Solter and Gearhart, 1999; Vogel, 1999). Since then considerable progress has been made; however, the hype continues to outpace the progress. This reached an unfortunate crescendo in the latter part of 2005 with the revelation that the major advances reported by the Korean scientist Woo Suk Hwang were based on the fabrication of results (Normile and Vogel, 2005; Normile *et al.*, 2005, 2006). This was compounded by ethical issues and by the inclusion of Dr. Gerald Schatten from the University of Pittsburgh as a senior author (Guterman, 2006). Korea must be credited with launching a full investigation that led to Dr. Hwang's losing his position. The University of Pittsburgh also conducted an investigation and found Dr. Schatten guilty of "research misbehavior," a term not fully understood by the scientific community (Holden, 2006). The unfortunate thing is that this all happened at a time of considerable ethical and political controversy surrounding human embryonic stem cell research. From this we must all learn (Cho *et al.*, 2006), and, in spite of this setback in the public arena, research in the human embryonic stem cell area continues to hold considerable promise for the future.

There is in fact a variety of different stem cells, and several comprehensive reviews of a general nature have recently appeared (Vats *et al.*, 2005; Ahsan and Nerem, in

press). It is the adult stem cells and progenitor cells that are being and will be used first clinically; however, long term there is considerable interest in embryonic stem cells. These cells are pluripotent, i.e., capable of differentiating into many cell types, even totipotent, i.e., capable of developing into all cell types. Although we are quite a long way from being able to use embryonic stem cells, a number of companies are working with stem cells in the context of tissue engineering and regenerative medicine. It needs to be recognized, however, that immunogenicity issues may be associated with the use of embryonic stem cells. Furthermore, different embryonic stem cell lines, even when in a totally undifferentiated state, can be significantly different. This is illustrated by the results of Rao *et al.* (2004) in a comparison of the transcriptional profile of two different embryonic stem cell lines. This difference should not be considered surprising, since the lines were derived from different embryos and undoubtedly cultured under different conditions.

To take full advantage of stem cell technology, however, it will be necessary to understand more fully how a stem cell differentiates into a tissue-specific cell. This requires knowledge not just about the molecular pathways of differentiation, but, even more importantly, about the identification of the combination of signals leading to a stem cell's becoming a specific type of differentiated tissue cell. As an example, with the recognized differences between large-vessel endothelial cells and valvular endothelial cells (Butcher *et al.*, 2004), what are the signals that will drive the differentiation toward one type of endothelial cell versus the other? Only with this type of knowledge will we be able to realize the full potential of stem cells. In addition, however, we will need to develop the technologies necessary to expand a cell population to the number necessary for clinical application, to do this in a controlled, reproducible manner, and to deliver cells at the right place and at the time required.

III. CONSTRUCT TECHNOLOGY

With the selection of a source of cells, the next challenge in imitating nature is to develop an organized three-dimensional architecture (with functional characteristics such that a specific tissue is mimicked) and/or a delivery vehicle for the cells. In this it is important to recognize the importance of a cell's microenvironment in determining its function. *In vivo* a cell's function is orchestrated by a symphony of signals. This symphony includes soluble molecules, the mechanical environment, i.e., physical forces, to which the cell is exposed, and the extracellular matrix. These are all part of the symphony. And if we want the end result to replicate the characteristics of native tissue, attention must be given to each of these components of a cell's microenvironment.

The design and engineering of a tissuelike substitute are challenges in their own right. If the approach is to seed cells into a scaffold, then a basic issue is the type of scaffold that will allow the cells to make their own matrix. There are, of course, many possible approaches. One of these is a cell-seeded polymeric scaffold, an approach pioneered by Langer and his collaborators (Langer and Vacanti, 1993; Cima *et al.*, 1991). This is the technology that was used by Advanced Tissue Sciences, and many consider this the classic tissue-engineering approach. There are other approaches, however, with one of these being a cell-seeded collagen gel. This approach was pioneered by Bell in the late 1970s and early 1980s (Bell *et al.*, 1979; Weinberg and Bell, 1986), and this is used by Organogenesis in their skin substitute, Apligraf™.

A rather intriguing approach is that of Auger and his group in Quebec, Canada (Auger *et al.*, 1995; Heureux *et al.*, 1998). Auger refers to this as *cell self-assembly*, and it involves a layer of cells secreting their own matrix, which over a period of time becomes a sheet. Originally developed as part of the research on skin substitutes by Auger's group, it has been extended to other applications. For example, the blood vessel substitute developed in Quebec involves rolling up one of these cell self-assembled sheets into a tube. One can in fact make tubes of multiple layers so as to mimic the architecture of a normal blood vessel.

An equally intriguing approach is that pioneered by the Campbells in Australia and their collaborators (Chue *et al.*, 2004). In this they literally use the peritoneal cavity as an *in vivo* bioreactor to grow a blood vessel substitute. The concept is that a free-floating body in the peritoneal cavity initiates an inflammatory response and becomes encapsulated with cells. This is an autologous-cell approach, and it is also one where the cells make their own matrix.

Any discussion of different approaches to the creation of a three-dimensional, functional tissue equivalent would be remiss if acellular approaches were not included. Although in tissue engineering the end result should include functional cells, there are those who are employing a strategy whereby the implant is without cells, i.e., acellular, and the cells are then recruited from the recipient or host. A number of laboratories and companies are developing this approach. Examples include the products Integra™ and TransCyte™, already noted, and the development of SIS, i.e., small intestine submucosa (Badylak *et al.*, 1999; Lindberg and Badylak, 2001). One result of this approach, in effect, is to bypass the cell-sourcing issue and replace this with the issue of cell recruitment, i.e., the recruiting of cells from the host in order to populate the construct. Because these are the patient's own cells, there is no need for any engineering of immune acceptance.

Whatever is done, an objective in imitating nature must be to create a healing environment, one that will foster remodeling and ultimately repair. To do this requires delivering the appropriate, necessary cues in a controlled spatial and temporal fashion. This is needed whether the goal is replacement or repair or regeneration. Whatever the approach, the engineering of an architecture and of func-

tional characteristics that allow one to mimic a specific tissue is critical to achieving any success and to meeting the challenge of imitating nature. In fact, because of the interrelationship of structure and function in cells and tissues, it would be unlikely to have the appropriate functional characteristics without the appropriate three-dimensional architecture. Thus, many of the chapters in this book describe in some detail the approach being taken in the design and engineering of constructs for specific tissues and organs, and any further discussion of this is left to those chapters.

The challenge of imitating nature, however, does not stop with the design and engineering of a specific tissuelike substitute or a delivery vehicle. This is because the patient need that exists cannot be met by making one construct at a time on a benchtop in some research laboratory. Accepting the challenge of imitating nature must include the development of cost-effective manufacturing processes. These must allow for a scale-up from making one at a time to a production quantity of 100 or 1000 per week. Anything significantly less would not be cost effective; and if a product cannot be manufactured in large quantities and cost effectively, then it will not be widely available for routine use.

Much of the research on manufacturing technology has focused on bioreactor technology. A bioreactor simply represents a controlled environment — both chemically and mechanically — in which a tissuelike construct can be grown (Freed *et al.*, 1993; Neitzel *et al.*, 1998; Saini and Wick, 2003). The design of a bioreactor involves a number of critical issues. The list starts with the configuration of the bioreactor, its mass transport characteristics, and its scaleability. Then, if it is to be used in a manufacturing process, it is desirable to minimize the number of asceptic operations while maximizing automation. Reliability and reproducibility obviously will be critical, and it needs to be user friendly.

Although it is generally recognized that a construct, once implanted in the living system, will undergo remodeling, it is equally true that the environment of a bioreactor can be tailored to induce the *in vitro* remodeling of a construct so as to enhance characteristics critical to the success to be achieved when it is implanted (Seliktar *et al.*, 1998). Thus, the manufacturing process can be used to influence directly the final product and is part of the overall process leading to the imitation of nature. An important issue in developing a substitute for replacement, however, is how much of the maturation of a substitute is done *in vitro* in a bioreactor as compared to what is done *in vivo* through the remodeling that takes place within the body itself, i.e., in the body's own bioreactor environment. As pointed out by Dr. Frederick Schoen (private communication), in this one needs to recognize that the rate at which remodeling *in vivo* takes place will be extremely different from individual to individual. It is equally true that the extent of remodeling also will be different. Thus, the degree of maturation that occurs *in vivo* will be highly variable, depending on the host response.

Once a product is manufactured, a critical issue will be how it is delivered and made available to the clinician. The Organogenesis product, Apligraf™, is delivered fresh and originally had a 5-day shelf life at room temperature (Parenteau, 1999), although recently this has been extended. On the other hand, Dermagraft™, the skin substitute developed by Advanced Tissue Sciences, is cryopreserved and shipped and stored at –70°C (Naughton, 1999). This provides for a much more extended shelf life but introduces other issues that one must address. Ultimately, the clinician will want off-the-shelf availability, and one way or another this will need to be provided if a tissue-engineered product or strategy is to have wide use. Although cryobiology is a relatively old field and most cell types can be cryopreserved, there is much that still needs to be learned if we are successfully to cryopreserve three-dimensional tissue-engineered products.

IV. INTEGRATION INTO THE LIVING SYSTEM

The final challenge to imitating nature is presented by moving a tissue-engineering concept into the living system. Here one starts with animal experiments, and there is a lack of good animal models for use in the evaluation of a tissue-engineered implant or strategy. This is despite the fact that a variety of animal models have been developed for the study of different diseases. Unfortunately, these models are still somewhat unproved, at least in many cases, when it comes to their use in evaluating the success of a tissue-engineering concept.

In addition, there is a significant need for the development of methods to evaluate quantitatively the performance of an implant, and a number of concepts are being advanced (Guldberg *et al.*, 2003; Stabler *et al.*, 2005). This is not only the case for animal studies, but is equally true for human clinical trials. With regard to the latter, it may not be enough to show efficacy and long-term patency; it may also be necessary to demonstrate the mechanism(s) that lead to the success of the strategy. Furthermore, it is not just clinical trials that have a need for more quantitative tools for assessment; it also would be desirable to have available the technologies necessary to assess periodically the continued viability and functionality of a tissue substitute or strategy after implantation into a patient.

Also, one cannot state that one has successfully met the challenge of imitating nature unless the implanted construct is biocompatible. Even if the implant is immune acceptable, there can still be an inflammatory response. This response can be considered separate from the immune response, although obviously interactions between these two might occur. In addition to any inflammatory response, for some types of tissue-engineered substitutes thrombosis

will be an issue. This is certainly an important part of the biocompatibility of a blood vessel substitute.

Finally, important to the success of any tissue-engineering approach is the immune response and that it be immune acceptable. This comes naturally with the use of autologous cells; however, if one moves to nonautologous cell systems (as this author believes we must, at least in many cases, if we are to make the products of tissue engineering widely available for routine use), then the challenge of engineering immune acceptance is critical to our achieving success in the imitation of nature. Today we have immunosuppressive drugs, e.g., cyclosporine; however, transplant patients treated this way face a lifetime where their entire immune system is affected, placing them at risk of infection and other problems.

It should be recognized that the issues surrounding the immune acceptance of an allogeneic cell-seeded implant are no different than those associated with a transplanted human tissue or organ. Both represent allogeneic cell transplantation, and this means that much of what is being learned in the field of transplant immunology can help us understand implant immunology and the engineering of immune acceptance for tissue-engineered substitutes. For example, it is now known that to have immune rejection there must not only be a recognition by the host of a foreign body, but there also must be present what is called the *costimulatory signal*, or sometimes simply signal 2. It has been demonstrated that, with donated allogeneic tissue, if one can block the costimulatory signal, one can extend survival of the transplant considerably (Larsen *et al.*, 1996). There also is the chimeric approach, where one transplants into the patient from the donor both the specific tissue/organ and bone marrow. This suggests that perhaps in the future one will be able to use a stem cell–based chimeric approach. As an example, if one were to differentiate an embryonic stem cell both into the tissue-specific cells needed and into the cells required for implantation into the bone marrow, then from a single cell source one would create the chimerism desired.

Another approach is that of therapeutic cloning. Here a patient's DNA is transferred into an embryonic stem cell, which in turn is differentiated into the cells needed for a particular tissue-engineering approach. As attractive as this approach appears, many think it is unrealistic, simply because of the scarcity of eggs and embryonic stem cells. Furthermore, as our knowledge of immunology continues to advance, other approaches might make the need for therapeutic cloning disappear (Brown, 2006). Thus, strategies are under development, and these may provide greater opportunities in the future for the use of allogeneic cells.

V. CONCLUDING DISCUSSION

If we are to meet the challenge of imitating nature, there are a variety of issues. These have been divided here into three different categories. The issue of cell technology includes cell sourcing, the manipulation of cell function, and the use of stem cell technology. Construct technology includes the engineering of a tissuelike construct as a substitute or delivery vehicle and the manufacturing technology required to provide the product and ensure its off-the-shelf availability. Finally is the issue of integration into living systems. This has several important facets, with the most critical one being the engineering of immune acceptance.

Much of the discussion here has focused on the challenge of engineering tissuelike constructs for implantation. As noted earlier, however, equally important to tissue engineering are strategies for the fostering of remodeling and ultimately the repair and enhancement of function. As the field moves to the more complex biological tissues, e.g., ones that require innervation and vascularization, it may well be that a strategy of repair and/or regeneration is preferable to one of replacement.

As one example, consider a damaged, failing heart. Should the approach be to tissue engineer an entire heart, or should the strategy be to foster the repair of the myocardium? In this latter case, it may be possible to return the heart to relatively normal function through the implantation of a myocardial patch or even through the introduction of growth factors, angiogenic factors, or other biologically active molecules. Which strategy has the highest potential for success? Which approach will have the greatest public acceptance?

Even though short-term successes in tissue engineering may come from the convergence of biologics and devices, long term it is the generation of totally biologic products and strategies that must be envisioned. These will result in advances that include, for example, the following: *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; and heart valves that when implanted into an infant grow as the child grows. In addition, the repair/regeneration of the central nervous system will become a reality. Furthermore, as one thinks about the future, medicine will move to being more predictive, more personalized, and, where possible, more preventive. It is entirely possible that we will be able to diagnose disease at a preclinical stage. In that event, the concept of inducing biological repair prior to the appearance of the clinical manifestations of disease becomes even more attractive.

Thus, the strategy being evolved in Atlanta, Georgia, by the Georgia Tech/Emory Center for the Engineering of Living Tissues, an engineering research center funded by the National Science Foundation, is one that more and more is placing the emphasis on repair and/or regeneration. It is moving beyond replacement that may provide the best opportunity to meet the challenge of imitating nature. Fundamental to this is understanding the basic biology, including developmental biology, even though the biological

mechanisms involved in adult tissue repair/regeneration are far different from those involved in fetal development. Furthermore, to translate a basic biological understanding into a technology that reaches the patient bedside will require a multidisciplinary, even an interdisciplinary, effort, one involving life scientists, engineers, and clinicians. Only with such teams will we be able to meet the challenge of imitating nature, and only then can the existing patient need be addressed and will we as a community be able to confront the transplantation crisis.

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