

4.0 Development of the Field: 1987-2002

The publication record indicates that the volume of research carried out under the rubric of tissue engineering has increased substantially since 1987, and especially since the mid-1990s, though it is difficult to determine this volume exactly because of the challenge inherent in attempting to precisely specify the scope of the field.

A convenient proxy for the scope of TE today is arguably the pair of reference volumes *Principles of Tissue Engineering* (first edition published in 1997, second edition in 2000) and *Methods of Tissue Engineering* (published in 2002), which cover an impressively broad range of research subtopics and researchers.⁵³ The chapter-end bibliographies of *Methods* alone record thousands of citations to the research literature, with well over 5,000 individual researchers represented in the corpus of research thus defined.⁵⁴ The scope of research referenced by these volumes overstates to some extent the reach of tissue engineering today, because many of the citations refer to prior art or to adjacent fields from which current lines of research have drawn concepts and methods. Much of the scope of knowledge represented in these volumes was created through research efforts not originally conceptualized as investigations in tissue engineering, but which have, nevertheless, contributed to the field's emergence.

Nevertheless, the growth in tissue engineering proper – defined here as work perceived or designated by its participants as TE – has been substantial. This growth derives from multiple sources:

- New graduates or established researchers who have chosen to enter the field have initiated or expanded work under established research themes.
- Established researchers who have begun to collaborate with tissue engineers, or who have recognized similarities between their own work and that of tissue engineers as awareness of the field has grown, have relabeled existing lines of research as TE. One example is an apparent increase in the propensity of researchers in orthopedic surgery to conceive of their work as tissue engineering.
- The definition of the field undergoes an implicit expansion when adjacent fields report advances that appear to address core challenges in tissue engineering. A prominent example of this phenomenon is the explosion of research on stem cells within the past few years, in the wake of discoveries in the late 1990s related to embryonic stem cells. Sourcing and cultivation of cells with desired and stably expressed properties has been recognized as a central research challenge for TE since it was defined as a field. In the words of one prominent researcher, however, “prior to the burst of stem cell activity, there would have been surprisingly little to say regarding progress in living cell therapy or knowledge of the conditions that would enable the practical use of cells in tissue engineering beyond skin.”⁵⁵ Today, stem cell research is a vigorous and important component of TE, partly through pursuit by researchers who consider themselves tissue engineers, and partly by extension of the concept of TE to incorporate the freshly relevant work of investigators who see their research as situated within other intellectual domains.

⁵³ Lanza RP, Langer R, Vacanti J, eds., *Principles of Tissue Engineering* (San Diego: Academic Press, 2000); Atala A, Lanza RP, eds., *Methods of Tissue Engineering* (San Diego: Academic Press, 2002).

⁵⁴ Abt Associates analysis.

⁵⁵ Parenteau NL, “Cells”, pp. 19-32 in McIntire LV, Greisler HP, Griffith L et al., *WTEC Panel Report on Tissue Engineering Research* (Baltimore, MD: International Technology Research Institute, January 2002), available at http://www.wtec.org/loyola/te/final/te_final.pdf (URL verified Sept. 7, 2002).

The individuals interviewed for this study found it difficult to identify seminal papers, events or specific discoveries or technical advances that could be characterized as having defined the direction or character of the field. Tissue engineering's growth and development might be better described as the result of incremental progress along several originally independent lines of work, rather than the product of a handful of major breakthroughs or discoveries. Interviews and bibliometric analysis, pointed to two early papers that have played especially important roles in shaping the overall character of the field. While the 1987 Granlibakken conference officially presented and defined the term "tissue engineering", the 1993 Langer/Vacanti review paper in *Science* introduced the concept of tissue engineering to a wider audience, alerted many researchers who were independently pursuing related work that others shared similar interests within a larger framework, and provided a convenient label for these activities. The Langer/Vacanti collaboration was also responsible for the paper that has probably been most influential from a substantive point of view, an article published at the beginning of 1988 describing the method of using resorbable polymer matrices as a vehicle for cell transplantation.⁵⁶

On the face of it, the work presented in this paper represented a modest advance. Conceptually, it reflected a logical combination of existing approaches – cell-seeding of two-dimensional matrices of biological origin, as in the early work on artificial skin; three-dimensional cell culture on synthetic matrices;⁵⁷ and selective cell transplantation, as in the early work on islet cell transplantation. However, the method of seeding cells on resorbable polymer scaffolds was unique and rapidly became both the most important enabling technology and the most important organizing concept in the field, serving as a common element across lines of research addressing a wide range of therapeutic challenges. As a technique for building tangible objects, it also became a vehicle for enhanced public visibility – if not enhanced public understanding – of the field and its goal of "growing organs".⁵⁸

The scaffolds-and-cell-seeding technique catalyzed a flurry of tinkering on a wide range of tissue and organ systems, overshadowing to some extent the more fundamental efforts proceeding in parallel to develop the underlying knowledge needed to make the products of this technique viable as therapies. Beyond the obvious need for new scaffold materials with properties optimized for specific tissue engineering applications, key knowledge gaps in the late 1980's and early 1990's included, among others:

- sources of large quantities of cells reliably and controllably expressing desired phenotypes
- details of the immune response to implanted tissues, and means of controlling it
- the role of chemical and physical signals in morphogenesis and in the *in vivo* remodeling of implanted tissues
- means of controlling angiogenesis in order to achieve adequate vascularization of three-dimensional tissue constructs
- design principles to create and optimize bioreactors and bioprocessing techniques for the manufacture of specific tissue-engineered products
- means of preserving TE products between the point of manufacture and the time of usage

⁵⁶ Vacanti JP, Morse MA, Saltzman WM *et al.*, "Selective Cell Transplantation Using Bioabsorbable Polymers as Matrices", *J Pediatr Surg* 1988 Jan;23(1 Pt 2):3-9.

⁵⁷ Bottaro DP, Liebmann-Vinson A, Heidaran MA, "Molecular Signaling in Bioengineered Tissue Microenvironments", pp. 143-53 in Sipe JD, Kelley CA, McNicol LA, *eds.*, *Reparative Medicine: Growing Tissues and Organs* (Annals of the New York Academy of Sciences, vol. 961, June 2002).

⁵⁸ This was notoriously so in the case of the tissue-engineered "ears" grown by implantation of suitably-shaped polymer templates, seeded with chondrocytes, on the backs of mice. Cao Y, Vacanti JP, Paige KT *et al.*, "Transplantation of Chondrocytes Utilizing a Polymer-Cell Construct to Produce Tissue-Engineered Cartilage in the Shape of a Human Ear", *Plast Reconstr Surg* 1997 Aug;100(2):297-302; "Artificial Liver 'Could be Grown'", BBC News Online, 25 April 2002, <http://news.bbc.co.uk/1/low/health/1949073.stm> (URL verified Dec. 26, 2002).

- methods for characterization and functional assessment of engineered tissues both *in vitro* and *in vivo*

Many researchers began – or continued – to pursue these questions in their own work, and to draw relevant insights from developments in research outside of tissue engineering.

In 2002, after 15 years since the initial NSF meetings, TE remains a mix of topical foci and research styles, reflecting in part the heterogeneous origins, intellectual traditions, and disciplinary affiliations of the mix of clinicians, engineers and scientists who work in the field.

Although recognition of the importance of gaps in the fundamental knowledge underlying tissue engineering is widespread, many of the individuals interviewed for this study referred to the persistently “Edisonian”⁵⁹ character of much of the work in TE, by which they meant a sort of inspired, *ad hoc* tinkering focused on the solution of specific practical problems in the creation of usable products. Some considered this a positive attribute while others viewed it as a drawback, reflecting a persistent tension between two different strategies for TE. Is it best to invest in fundamental research that will lay strong theoretical and methodological foundations for the long-term productivity of TE, or are clinically-significant products sufficiently close to being within reach as to warrant an Edisonian sprint toward their creation?

It might be expected that Edisonian approaches would be most strongly associated with TE research and development efforts in the corporate sector, while the academic sector would be more strongly focused on fundamentals. The former is certainly true, and because the corporate sector has accounted for the great majority of the funds invested in TE,⁶⁰ it necessarily follows that the character of corporate R&D has had a substantial impact on the character of the TE enterprise overall.

Many of our informants observed that corporate R&D efforts in tissue engineering have had a modest effect on the progress of the field. Corporate R&D has focused on the creation of proprietary intellectual content centered on the challenges of bringing products to market, and less on the solution of broader challenges in science or engineering. Knowledge transfer from industry back to academia has been limited.

However, many respondents suggest that the Edisonian approach remains a powerful force within the academic sector as well. In part, this reflects the natural inclination of some workers in the field, many but not all of these clinicians who bring to their work a strong practical bent. Some observers believe that another influence – a deleterious one – has been the combined effect of a shortage of funding from traditional sources of support for academic research together with the incentives created by the venture-capital-funded boom in biotechnology startup companies during select periods in the 1980s and 1990s, that has induced some researchers to attempt prematurely to “productize” their ideas or research findings.

Given the eclectic nature of the field, it is difficult to make judgments as to the level of progress that has been made in the years since 1987. One way of interpreting the significance of the events of 1987 is that they marked the beginning of an attempt by engineers to systematize and formalize the field of tissue engineering. The principle of rational design is central to the engineering approach. In turn, rational

⁵⁹ The term “Edisonian” was used independently by several researchers we spoke to during the course of our interviews. The term itself originates from the book *Pasteur’s Quadrant: Basic Science and Technological Innovation* (Brookings Institution Press, 1997) by Donald E. Stokes.

⁶⁰ Investment in TE has been tracked most systematically in a series of studies by Michael Lysaght; the most recently published installment in the series is Lysaght MJ, Reyes J, “The Growth of Tissue Engineering”, *Tissue Eng* 2001 Oct;7(5):485-493.

design is made possible by the elucidation of theoretical principles of broad generalizability and by the systematic characterization of available materials and methods in terms of the parameters that comprise these theoretical models. In the tissue engineering context, some of these principles would need to come from engineering – for example, those related to mechanical aspects of tissues, the behavior of biomaterials, and processes for producing, preserving and distributing TE products. Others would need to come from biology – for example, the behavior of cells and of growth factors. Still others would need to come from clinical medicine – for example, principles of physiology and pathophysiology. No matter whether their disciplinary roots have been in medicine, in engineering or in biology, TE researchers have from the earliest days of their involvement recognized that the future success of the field depends heavily on strengthening the base of systematic knowledge underlying TE applications. Yet it was engineers who first sought to articulate this point clearly and make it the foundation for a formalization of the field.⁶¹

While this principle is sound, however, the development of the field since 1987 reflects little progress toward a systematization of TE through the creation of a foundation of broadly applicable theory or even a well-structured phenomenology. Although a great deal of new knowledge has been accumulated, deficits in fundamental understanding cataloged in recent reviews⁶² are similar in general outline to those recognized in the late 1980s and early 1990s. Researchers today have gained a much more detailed and sophisticated understanding of the specific challenges that must be addressed, however, and some progress has been made in framing research challenges in particular areas of TE in a more systematic way.⁶³

Perhaps the most important explanation for this slow progress is simply that the rationalization of TE represents an intellectual challenge of enormous magnitude. Construction of replacement tissues and organs, or controlled induction of endogenous reparative capacities to restore tissue structure and function, represent extraordinarily difficult *systems engineering* problems, and knowledge both of the behavior of the system components and of the necessary principles of systems integration remains primitive in relation to what is required.

Another factor affecting the rate of progress may be important gaps in the intellectual resources that have been brought to bear on the challenges of tissue engineering, and in the degree of cross-disciplinary integration that has been achieved. In her plenary address at the 2001 BECON symposium, Nancy Parenteau articulated these concerns:

The need for cell therapy is well recognized even by the nonscientist, as evidenced by the perceived need for some form of stem cell research. Yet the complex nature of dealing with actual cells themselves to achieve an outcome is still not fully realized. While there is burgeoning information on the genetics front, advances in technology for rapid proteomic analysis, rapidly growing information on factors that effect (*sic*) cell lineage, identification of transcription factors involved in the development of tissue structure and control of morphogenesis, and advancing preclinical and clinical research on cell implantation, there is a very important need to bring all aspects together. Engineers and physician scientists have been

⁶¹ The 1985 ERC proposal from UCSD is emphatic and articulate on this point. Pp. 8-9, “A Proposal to the National Science Foundation for An Engineering Research Center at UCSD, CENTER FOR THE ENGINEERING OF LIVING TISSUES”, UCSD #865023, courtesy of Y.C. Fung, August 23, 2001.

⁶² WTEC Panel Report on Tissue Engineering Research (Baltimore, MD: International Technology Research Institute, January 2002), available at http://www.wtec.org/loyola/te/final/te_final.pdf (URL verified Sept. 7, 2002); Sipe JD, Kelley CA, McNicol LA, eds., *Reparative Medicine: Growing Tissues and Organs* (Annals of the New York Academy of Sciences, vol. 961, June 2002).

⁶³ See, for example, Butler DL, Goldstein SA, Guilak F, “Functional Tissue Engineering; The Role of Biomechanics”, *J Biomech Eng* 2000 December;122:570-575.

instrumental in leading the way in academic tissue engineering research, although they desperately need the participation of workers in other disciplines, such as molecular biologists and cell biologists, to fill the important gaps in understanding between them. We must not be naïve.

How do we stimulate interest in critical areas such as applied research in cell biology and foster interdisciplinary collaboration? How do we provide academic recognition for being an important part of a significant achievement? Academic laboratories must be given an incentive to work on common goals.... New paradigms and metrics must be established both in academics and industry as we delve into complex biological problems that are well beyond a single scientific or engineering discipline....⁶⁴

With respect to its headline goal as well – to create living replacement parts for the human body – the progress of TE has been slow. As with the underlying scientific challenges, the work of the past fifteen years in tissue engineering has served above all to clarify our understanding of how difficult it will be to achieve the full extent of TE's therapeutic vision.

In his 1987 draft concept memo, NSF's Allan Zelman identified a list of "types of tissues most likely to bring early success". In Zelman's words, these were:

1. Skin: replacement of existing skin damaged from burns, scars, etc.
2. Bone: present artificial hips and other joints could be replaced with hips and joints composed primarily from the patients' own tissue
3. Blood vessels: arteriovenous shunts for hemodialysis patients and heart bypass patients would benefit greatly
4. Cornea: this could eliminate rejection, bring sight to those who reject corneal transplants and as success grows possibly provide an alternative to eye glasses
5. Cartilage: providing cartilage replacement for arthritic patients could bring relief from pain to millions
6. Nerves: every year thousands of paraplegics are generated and this may be the means to reconnect nervous tissue too damaged for self-repair
7. Blood or blood components: production of viral free blood and blood components could justify a great research effort⁶⁵

Preliminary progress has been made in the development of many of these tissues, though it is understood that much more work is required before "off-the-shelf" products will be available:

Skin. Skin is perhaps the most successful of the tissue engineered therapies, with several products having completed clinical trials, met with FDA approval, and made the transition to market. In 1997, the FDA approved *TransCyte*⁶⁶, a skin replacement tissue made by Advanced Tissue Sciences, which consists of dermal keratinocytes grown on a biodegradable polymer. *TransCyte* serves as a temporary wound cover

⁶⁴ Parenteau NL, Young JH, "The Use of Cells in Reparative Medicine", pp. 27-39 in Sipe JD, Kelley CA, McNicol LA, eds., *Reparative Medicine: Growing Tissues and Organs* (Annals of the New York Academy of Sciences, vol. 961, June 2002).

⁶⁵ Zelman A, "Tissue Engineering: A Fundamentally New Concept in Health Care", internal discussion memo, first draft, Sept. 22, 1987, courtesy of NSF.

⁶⁶ *TransCyte* is now sold by Smith & Nephew, see: http://www.smith-nephew.com/businesses/W_TransCyte.html

for burns as new tissue forms. *Apligraf*⁶⁷, manufactured by Organogenesis, utilizes live human skin cells to form a dual layer skin equivalent approved by the FDA to treat diabetic leg and foot ulcers.

Recent advances in skin tissue engineering have resulted in the following examples of products in the last 5 or so years:

- *EpiDex*⁶⁸, from Swiss-based Modex Therapeutics for treatment of chronic skin ulcers; EpiDex grafts are grown from hair follicle stem cells.
- *Dermagraft*⁶⁹ was introduced in 1998 by Advanced Tissue Sciences. Dermagraft is a cryopreserved human fibroblast-derived dermal substitute, composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold.
- *Integra* – Integra is a two-layered dressing and is completely acellular. The top layer serves as a temporary synthetic epidermis; the layer below serves as a foundation for re-growth of dermal tissue. The underlying layer is made of collagen fibers that act as a lattice through which the body can begin to align cells to recreate its own dermal tissue.
- *Epicel*, also manufactured by Genzyme Biosurgery, is the only autologous skin graft that can permanently close a burn wound⁷⁰. Epicel was developed based on original research done by Howard Green.
- *Alloderm*⁷¹ (LifeCell) is a cell-seeded allogenic skin replacement. The product consists of human dermal collagen seeded with allogenic fibroblasts. The material has recently been launched in the US - initially for patients with third degree burns and limited donor-site tissue.
- *Xenoderm*, another product from LifeCell consists of porcine dermis used as a replacement for burn wounds. LifeCell claims that experimental data shows consistent incorporation of the matrix into the wound bed, low immunogenicity, and re-population with host cells.

Companies have approached the development of skin equivalents from different perspectives: autologous cellular replacements (Genzyme Biosurgery), allogeneic cellular replacements (Advanced Tissue Sciences and Organogenesis), and completely acellular replacements (Integra). Each of these appear to achieve success as wound coverings. However, scar tissue formation and wound contraction issues remain problematic. Available products also fail in several ways to mimic the structure and function of native skin. Substitutes have long acted as passive wound covers, lacking certain essential

⁶⁷ Apligraf is indicated for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional therapy, and also for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure. Apligraf prescribing information, Novartis Pharmaceuticals Corporation, June 2000.

⁶⁸ <http://www.epidex.com>

⁶⁹ Dermagraft is now marketed by Smith and Nephew, see: <http://wound2.snwmd-us.com/us/Product.asp?NodeId=2550> (URL verified April 12, 2002)

⁷⁰ Epicel was first introduced in 1987, but is still a popular treatment for severe burns: www.genzymebiosurgery.com (URL verified April 12, 2002)

⁷¹ <http://www.lifecell.com/healthcare/products/alloderm/index.cfm> (URL verified April 12, 2002)

functions/components—including hair follicles, and glands⁷². Development of such enhancements are the focus of current research in living skin equivalents and suggests the use of stem cells as a basis for development of fully differentiated skin equivalents. Choice of matrix support to maintain fibroblasts and keratinocytes is also still being investigated.

Vascular grafting. Progress to date in the development of tissue engineered vascular grafts has focused on mimicking the three layers of the normal muscular artery, using combinations of live cells, bioresorbable and non-bioresorbable scaffolding constructs. At present, there are no FDA approved live vascular replacement therapies. Several techniques are in pre-clinical trial but face challenges that may prevent their widespread use/application in the near future.⁷³

Huynh and colleagues at Organogenesis and Duke University, for example have used porcine intestine as a graft base for seeding of endothelial cells, which will grow and develop into vessel like structures⁷⁴. The use of porcine cells, while important for clinical research, have unknown effects if transplanted into humans. Other sources for graft bases are also being explored, including fibrillar collagen and bovine collagen gels. However, none of these have produced a vascular substitute with the mechanical properties and strength of native blood vessels. Traditional problems plaguing the field, including clotting and scar tissue formation also persist in cellular replacements and prevent laboratory products from making it to the clinical trial stage. To combat such problems, researchers have attempted to embed the graft materials with antibiotics and antithrombotic coatings with limited success. There is also the need to create a functional nerve supply and capillary network in vitro to support live vascular tissues. Until such challenges are remedied, prosthetic grafts, made of substances like Dacron and polytetrafluoroethylene, will continue to serve as the major therapy.

Kidney. As a highly complex organ, whole kidney replacement organs are far from being a reality. However, progress has been made in development of temporary replacement devices, such as extracorporeal kidney assist devices. Dr. David Humes, Chairman of The Department of Internal Medicine at The University of Michigan, Ann Arbor, has successfully completed *in vivo* testing of a *Renal Tubule Assist Device* (RAD) for treating acute renal failure⁷⁵. The only other treatments currently available for acute renal failure are hemofiltration and dialysis. Extracorporeal devices may improve the outcomes of these patients while making treatment much less costly.

Pancreas/Islet cells. Islet cell transplantation techniques have consisted of two major approaches: perfusion devices and microencapsulation. Perfusion devices, though developed as early as 1970, have failed to make it to the clinical trial stage due to long-term biocompatibility issues, membrane breakage, and size limitations (a problem which plagues bioartificial implantable livers as well). Microencapsulation, has also been in existence for several decades. Refinements to this technique over time involved improving the biocompatibility of the encapsulating materials. Some researchers suggest that widespread clinical application of microencapsulation techniques is just around the corner.⁷⁶

Several commercial tissue engineering approaches to repair/replace pancreatic function describe the current state of the field:

⁷² Bren L, “Helping Wounds Heal”, *FDA Consumer*, May-June 2002, http://www.fda.gov/fdac/features/2002/302_heal.html, (URL verified September 2, 2002).

⁷³ Niklason, LE. “Replacement Arteries Made to Order.” *Science*, 286: 19 November 1999; 1493-1494.

⁷⁴ Huynh T, et al. *Nature Biotechnology*. 17(1083); 1999.

⁷⁵ The technology is now being developed by Nephros Therapeutics; see <http://www.nephrostherapeutics.com/news/pr/pr-20020918-01.htm> (URL verified April 12, 2002)

⁷⁶ Macluf M., Atala A. “Tissue Engineering: Emerging Concepts.” *Graft*. 1(1): March-April, 1998.

- *Metabolex* is developing proprietary technologies for the microencapsulation of insulin-producing tissues using thin, conforming, biocompatible coatings.
- *BetaGene* is a privately held biotechnology company developing innovative strategies for the detection and treatment of diabetes. This company was formed for the purpose of developing proprietary technology originating at the University of Texas Southwestern Medical Center. BetaGene retains exclusive license to aspects of this technology including the use of engineered cell lines for the treatment of type I and Type 2 diabetes and the use of these cells for bulk insulin production.
- *Circe Biomedical* has developed the *PancreAssist System*, consisting of a single tubular membrane surrounded by insulin-producing islets, which are, in turn, enclosed within a disk-shaped housing. The tubular membrane is porous and permeable to glucose and insulin.⁷⁷

Liver. Several bioartificial liver (BAL) bioreactor designs have been developed in the laboratory to replace liver function. The basic design of a BAL device consists of circulating patient plasma extracorporeally through a bioreactor that houses/maintains liver cells (hepatocytes) sandwiched between artificial plates or capillaries.⁷⁸ Bioreactor materials have either a spherical shape, large surface area, large pores or high porosity, or are hydrophilic and biocompatible.⁷⁹ These features can help to achieve the high density cultures of hepatocytes required. However, there is no one material that possess all of these desired properties. Researchers are actively seeking a support matrix that could provide all these properties in order to have a BAL with improved efficiency and effectiveness. Clinical trials of some BAL devices are already underway in the United States and the UK. *Circe Biomedical* currently has the *HepatAssist* liver device in clinical trial, which is a extracorporeal device consisting of a hollow-fiber bioreactor lined with porcine cells⁸⁰.

Numerous other challenges plague the development of tissue engineered livers:

- Human hepatocytes are limited in supply which make harvest and culture for liver assist devices difficult
- Hepatocytes are extremely difficult to stabilize and maintain in culture and lose their specificity rapidly. Several devices have made it to clinical trial but fail to seek FDA approval based on the lack of stabilization of the cellular component.
- The liver is so complex and varied in its functions that generating a replacement device that performs all these duties is far from a reality.
- Microencapsulation techniques have also been tried, but have been unsuccessful, again, due to the rapid loss of functionality of liver cells once removed from the body.

Bone, cartilage. Like skin, tissue engineering of bone and cartilage has experienced relative success as compared to other tissue engineered products. Current strategies consist of two major approaches:

⁷⁷ <http://www.circebio.com/technology/pancreassist.html> (URL verified April 12, 2002)

⁷⁸ Strain A, Neuberger JM. "A Bioartificial Liver—State of the Art." *Science*. 295(5557): 8 Feb 2002; 1005-1009.

⁷⁹ http://mtel.ucsd.edu/publications/Advances_in_Bioartificial_Liver_Devices.pdf (URL verified April 12, 2002)

⁸⁰ <http://www.circebio.com/technology/hepatassist.html> (URL verified April 12, 2002)

transplantation of osteochondral grafts and transplantation of chondrocytes⁸¹. Cell populations from cultured periosteum have the ability to form new bone and cartilage under the appropriate conditions and with the addition of the appropriate growth factors.⁸² Transplantation of osteochondral grafts, however, runs a possible risk of rejection in the recipient.

Current products and strategies include:

- *Carticel*⁸³, by Genzyme Biosurgery of Cambridge, MA, which has received FDA approval to replace damaged knee cartilage. The product uses autologous chondrocytes and grows them in a biodegradable matrix, which is then transplanted in place of the damaged tissue.
- Stryker Biotech of Hopkinton, MA has an FDA approved OP-1 Implant under the Humanitarian Device Exemption (HDE). The OP-1 Implant is now available across the country and is indicated for use as an alternative to patients' own bone in recalcitrant long bone nonunions where an autograft is unfeasible and alternative treatments have failed.⁸⁴
- Arnold Caplan of Case Western Reserve has performed mesenchymal stem cell (MSC) transplants in animals, and is working on similar transplants in humans. MSC's have been found to induce bone and connective tissue growth.
- Antonios Mikos at Rice University has developed an injectable copolymer that hardens quickly in the body and provides a surface to guide severed long bone regeneration⁸⁵.

To our knowledge, no other allogeneic, cell-based organ- or tissue-replacement product is close to market. Autologous efforts remain dominant. Efforts to bring to market tissue-engineered products that address defects in complex metabolic functions or replace vital organs will require more time and effort before reaching success. Research and development programs on various approaches to the bioartificial pancreas are said to have consumed over \$200 million of private sector funds to date, but designs capable of routine success in large animal models are yet unavailable, while encapsulated cell therapy has failed to demonstrate efficacy in phase III clinical trials.⁸⁶ Extracorporeal replacement of critical metabolic functions of the kidney and liver has reached the stage of small clinical trials – Phase I (safety) for the former and Phase II (preliminary safety and efficacy) for the latter.⁸⁷ In both cases, the devices' mode of operation involves extracorporeal blood circulation comparable to that of a dialysis machine, and both are initially targeted toward treatment of acute, life-threatening metabolic failure. The tissue-engineered replacement heart remains a distant vision.⁸⁸

⁸¹ Macluf M., Atala A. "Tissue Engineering: Emerging Concepts." *Graft*. 1(1): March-April, 1998.

⁸² Breitbart AS, Grande DA, Mason JM, Barcia M, James T, Grant RT. Gene-enhanced tissue engineering: applications for bone healing using cultured periosteal cells transduced retrovirally with the BMP-7 gene. *Ann Plast Surg* 1999; 42:488-495.

⁸³ <http://www.carticel.com> (URL verified April 14, 2003)

⁸⁴ <http://www.op1.com> (URL verified April 14, 2003)

⁸⁵ Ferber D. "From the Lab to the Clinic." *Science* 284(5413); 16 April 1999: 423.

⁸⁶ Michael Lysaght, interview, July 2, 2001.

⁸⁷ See <http://www.nephrotherapeutics.com> (Nephros Therapeutics Renal Assist Device) and <http://www.vgen.com> (Vitagen ELAD® Artificial Liver device) URLs verified September 6, 2002).

⁸⁸ Sefton MV, "The LIFE Initiative: Creating Transplant Organs Through Tissue Engineering", *e-biomed: The Journal of Regenerative Medicine* 2002;3:25-28.

As noted previously, from the beginning, more subtle conceptions of TE have extended its scope to encompass not only the production of replacement parts that embody the necessary structure and function, but the possibility of induction of endogenous reparative capabilities as well. In principle, such induction may be achieved via a variety of approaches, including implantation of cells that express growth factor molecules, implantation of non-living materials (for example, a collagen sponge) containing growth factor molecules, delivery of genes that encode the required growth factor, or by local or systemic infusion of growth factor molecules. The observed physiologic effects of the “skin replacement” products in promoting wound healing suggest that they might also be described as the first “induced repair” products rather than as replacement organs. Acellular “skin replacement” products on the market, such as the INTEGRA® dermal regeneration template derived from the work of Yannas,⁸⁹ are designed to function in this way. After more than 30 years of research on bone morphogenetic proteins, a BMP product has also recently reached the market – Medtronic’s INFUSE™ bone graft product, incorporating recombinant human bone morphogenetic protein rhBMP-2.⁹⁰ Several companies market acellular matrix materials for bulk applications in orthopedic and reconstructive surgery.

In bringing therapeutic products to market, tissue engineers must surmount not only daunting technical challenges, but regulatory and business obstacles as well. The regulatory environment for cell-containing products is complex and still at an early stage in its evolution; it imposes a substantial financial burden on the product development process, directly through the efficacy standards the product must meet and through the cost of funding the trials needed to demonstrate that efficacy, and indirectly through the financial effects of delay in bringing products to market. Finally, for a product to be viable, it must be possible to develop it, achieve regulatory approval, manufacture it, distribute it and market it at a price adequate to yield a positive economic return.

The difficulty of companies like Organogenesis and Advanced Tissue Sciences in recent times also raises concerns around the financial viability of some tissue engineered products. As of this writing, both Organogenesis and Advanced Tissue Sciences are undergoing reorganization under Chapter 11 bankruptcy protection, and on trends to date it appears unlikely that revenues from their artificial skin products will ever cover the cost of the capital invested in their development. At the aggregate level, cumulative investment in tissue engineering research has been estimated to exceed \$3.5 billion, of which well over 90% has been provided by private sources, with negligible financial return.⁹¹ Such concerns are well known by individuals in the public and private sectors and will be important considerations in strategy development for building not only clinically viable, but commercially viable products.

It is clear from these examples that despite notable contributions and advancements, tissue engineering is still a field in its infancy. Whether tissue engineering as we know it today will prove to be a powerful general strategy for developing therapeutic products and methods that can meet the dual hurdles of therapeutic efficacy and commercial viability remains to be seen. A strong research effort is underway,

⁸⁹ INTEGRA® Dermal Regeneration Template product description, http://www.integra-ls.com/bus-skin_product.shtml (URL verified December 25, 2002).

⁹⁰ “INFUSE™ Bone Graft / LT-CAGE™ Lumbar Tapered Fusion Device”, Medtronic Sofamor Danek press release, July 2, 2002 (<http://www.sofamordanek.com/press-infuse.html>, accessed Sept. 7, 2002). An additional BMP, Curis’ OP-1, has been approved by the FDA for limited use under a Humanitarian Device Exemption, and has also been approved for sale in certain international markets. “Curis’ OP-1 Received HDE Status in the United States”, Curis press release, October 18, 2001 (http://www.curis.com/news_101801.html, URL verified Sept. 7, 2002). Hematopoietic growth factors (such as recombinant erythropoietin), have been on the market for a number of years, but this line of research has not been characterized as tissue engineering by any of the informants consulted by the study team.

⁹¹ Lysaght MJ, Reyes J, “The Growth of Tissue Engineering”, *Tissue Engineering* 2001 Oct;7(5):485-493.

however, and advances in other emerging areas of science, such as stem cell research, are likely to make significant contributions toward helping tissue engineering to become a viable field.