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Tissue Engineering: The End of the Beginning

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This is not the end. It is not even the beginning of the end.
But it is, perhaps, the end of the beginning.
(Sir Winston Churchill, 1942)

ABSTRACT

This study was undertaken to assess the impact of current economic conditions and recent disappointing product launches on the field of tissue engineering. Data were collected on all firms known to be active in the field, analyzed, and compared with analogous data collected in 1995, 1998, and 2000. As of December 31, 2002, more than 2600 full-time equivalents (FTEs) in 15 countries and 89 firms were engaged in tissue-engineering research and development. Annual spending was $487 million, down about 20% since 2000—a reasonable performance in the face of a stagnant economy and difficult capital markets. Individual sectors proved far more volatile. Activity in skin, cartilage, and other structural applications declined by more than 50% with a loss of 800 FTEs. This downsizing was somewhat counterbalanced by a 42% increase in stem cell firms, which added more than 300 employees. Consistent with general disenchantment with technology sector equities, capital value of publicly traded tissue-engineering corporations has decreased by almost 90% from $2.5 billion at the end of 2000 to $300 million at the end of 2002. The United States' fraction of the total workforce declined from 80% in 2000 to 54% in 2002. By the close of 2002, twenty tissue-engineered products had entered Food and Drug Administration clinical trials. Four were approved but none of these are yet commercially successful. Six other applications were either abandoned or failed to achieve product approval. Ten products were still in clinical trials, some of which were investigator sponsored, and most of which were at the phase I/phase II stage. The field has yet to produce a profitable product despite an aggregate research and development investment exceeding $4.5 billion. Tissue engineering is clearly having difficulty transitioning from a development stage industry to one with a successful product portfolio. This is often the case for breakthrough medical technologies.

INTRODUCTION

THE VISION OF TISSUE ENGINEERING is readily grasped and has a high intrinsic appeal to scientists, investors, and the media. During the bull market of the late 1990s, media attention became almost euphoric. In 1999, Dr. Michael Gillian, ABC science correspondent, reported on *Good Morning America* that advances in tissue engineering and genetic medicine were likely to be "the greatest scientific achievements of the twentieth century."[1] A year later, in 2000, *Time* magazine deemed a career in tissue engineering one of the "10 Hottest Jobs of the Future."[2] That same year a report in *Barron's* estimated that regenerative medicine was on a path to become a $100 billion industry.[3] In 2001, Massachusetts Institute of Technology's *Technology Review* stated in a cover story,

Center for Biomedical Engineering, Brown University, Providence, Rhode Island.

"what if getting a replacement for a failing heart were as easy as buying a new car muffler? Advances in tissue engineering could make it happen sooner than you think."[4] *Science* magazine ran a special 2002 issue on the bionic human that fully endorsed the field's potential to generate "off-the-shelf replacement parts for the human body."[5] As recently as February 2003, the normally skeptical *Economist* reported, "these are exciting times for tissue engineers. The technology for growing human body parts is advancing rapidly. Already it is possible to cultivate sheets of human skin. And huge efforts are underway to develop even more complex structures, such as heart valves and whole organs such as the liver."[6] Such highly favorable media treatment has its benefits, but research-minded professionals increasingly recognized a disconnect with the realities. And such disconnects rarely lead to happy endings.

This study was undertaken to characterize and quantitate the current economic scope and demographic magnitude of worldwide private sector activity in tissue engineering. All data are referenced to December 31, 2002, and compared with historical performance based on similar surveys published in 1995,[7] 1998,[8] and 2000.[9] In addition, we describe and discuss the regulatory fate of tissue-engineered products, and the clinical performance of approved products.

MATERIALS AND METHODS

For the purposes of this report, tissue engineering is defined to include products or processes that (1) combine living cells with biomaterials, (2) utilize living cells as therapeutic or diagnostic reagents, (3) generate cells or tissues *in vitro* for therapeutic implantation, and (4) provide materials or technology to enable any of these approaches. The same definition was employed in our previous surveys. It includes living skin equivalents, cartilage replacement, tissue substitutes, biohybrid organs, organs or tissue prepared by nuclear transfer, *in vitro* organogenesis, stem cell therapies, and biomaterials which enable any of these approaches biomaterials. Specifically excluded are allografts, first-generation xenografts, bone marrow transplants, blood substitutes, bulking agents, orthopedic biomaterials, small molecule drugs, and biopharmaceuticals. A more expansive definition would have increased the number of firms and other parameters of economic activity.

A list of companies operating within our definition was derived from keyword Web searches, relevant hard literature and trade publications, participant and registrant lists from technical and investor conferences, discussions with venture capitalists, previous surveys, and general awareness of the field. The following data were obtained for each firm found to be active in the field: date of formation, number of full-time equivalents (FTEs) as of December 31, 2002, total spending in 2002, product focus, percentage of resources devoted to tissue engineering, source of funding, and geographic location. In many cases, the desired information was available at the company's Web site. If not, a direct inquiry was made to the company either by e-mail or phone. For publicly traded companies, pertinent information could be found in annual reports or Security and Exchange Commission (SEC) filings. Whenever possible, data were directly verified with each firm. When tissue engineering accounted for only a fraction of a firm's activities, a factor between zero (no tissue engineering) and one (all tissue engineering) was applied to the data. Privately held companies have become increasingly reluctant to disclose their annual spending or "burn rate"; when necessary a previously validated lump sum correlation of $190,000 per FTE was utilized to estimate spending based on total employment.[8]

Each tissue-engineering firm was assigned to one of three general categories based on requisite skills, technologies, and development culture: cellular, metabolic, or structural. These were further subclassified as follows: *cellular*—stem cell/therapeutic cloning, encapsulated cell therapy; *metabolic*—bioartificial liver, bioartificial pancreas, bioartificial kidney; *structural*—skin, cardiovascular disease, and muscloskeletal. Companies that did not fit into any of the stated categories were listed under *other*. A few firms were included in multiple categories.

The capital value of publicly traded firms was calculated as the product of the number of shares outstanding times the value per share on December 31, 2002. For firms listed on non-U.S. stock exchanges, the capital value was converted using the exchange rate that prevailed on December 31, 2002. When only a percentage of the firms' efforts were devoted to tissue engineering, the capital value was prorated appropriately. Large firms with a small fraction of their resources devoted to tissue engineering, for example, Medtronics or Smith & Nephew, were not included in capital value calculations.

Annual sales volume was the key criteria for success of Food and Drug Administration (FDA) approved products; these were either available from company reports or provided directly by the companies. When the sales of products were known for only part of the year the total annual sales were estimated by projecting sales by the company over the full year.

Data on FDA filings, and the outcomes of those filings, were obtained from company Web sites and press releases, from reports in trade literature, or from individuals involved with the filings. No information was obtained from the FDA, which does not release data on applications before approval.

Earlier surveys employed a +10% correction factor to all totals to correct for data lag in a rapidly growing in-

dustry segment. No such correction factor needed to be applied to the current study because the field is no longer increasing rapidly. All comparisons made between 2002 data and 2000 data are based on the corrected data for 2000.

RESULTS

Table 1 summarizes the overall status of the tissue-engineering industry as of December 31, 2000. Eighty-nine firms are operating in 16 countries, with a combined workforce of 2611 FTEs. Total aggregate spending for the 2002 calendar year was just under $500 million, and the capital valuation of publicly trading companies rounded out at $300 million. The compound annual growth rate from 1995 to 2002 is ~11%. Table 2 provides a breakdown of the industry by sector—cellular, metabolic, or structural—and their percentage growth and decline since year-end 2000. The cellular sector has become the largest segment, now accounting for almost 50% of the field. This is a change from the structural segment's dominance in 2000.

Figure 1 is a "mass balance" giving details of the industry dynamics between 2000 to 2002, and illustrating the sources of expansion and contraction for the industry as a whole and also by industry segment. The boxes on the left in Fig. 1 represent new firms or expansion of existing firms. The boxes on the right chronicle contraction or outright closure. The box in the middle summarizes overall changes for the industry. Figure 2 depicts the trend line in worldwide annual spending in 1995, 1998, 2000, and 2002, and illustrates the ~20% contraction during 2001 and 2002. Figure 3 summarizes the combined capital value of public companies in 1998, 2000, mid-2002, and end-2002, and highlights the precipitous decline in share values since the end of the bull market in 2000. Figure 4 illustrates how tissue-engineering resource allocation between the various sectors has changed since 2000; most pronounced is a shift of emphasis away from structural applications and toward stem cells.

Table 3 lists tissue-engineered products currently approved by the FDA and their estimated sales in 2002. Table 3 includes all tissue-engineering products whether or not classified as "combination" products (e.g., Carticel); it excludes combination products outside the realm of tissue engineering as defined for this article. Table 4 lists products that are still in clinical trials or that failed or were abandoned after entering such trials.

Appendix 1 provides a list of all the companies in the field, national location, sector activity, and Web site address. Appendix 2 provides a breakdown of companies by sector and principal activity.

DISCUSSION

In the face of a poor-to-dismal worldwide economic climate during 2001 and 2002, the tissue-engineering industry has remained highly viable with 89 firms and 2611 staff as of December 31, 2002. Although much of the industry now finds itself grappling for funding, while being forced to restructure business models and/or downsize, these stresses are similar to those facing the biotechnology industry as a whole and are not necessarily predictive of long-term failure.[10] In fact, many of the contractions taking place may ultimately benefit the field because they will eliminate those failures due to weak management and nonviable product applications. As is apparent from Table 1, Table 2, and Fig. 3, the general stability of the entire industry masks a higher volatility in the constituent sectors. Skin, cartilage, and other structural applications were especially hard hit, contracting by about 50%. Cellular applications, driven by the popularity of stem cells, increased by about the same amount albeit off a smaller base. Contraction is due to both the decline in the number of firms and to downsizing in those which persist. Similarly, growth can be attributed to both the formation of new firms, especially in stem cells, and to increase in staffing level within existing firms.

One clear trend is for a larger number of smaller companies. The number of firms increased by 16 from 73 to 89, since 2000 but the number of FTEs decreased by more than 450 (Fig. 1). This reflects both a willingness of investors to support smaller (and thus perceived as lower risk) undertakings, and also a movement of the field toward basic and applied research, which can be conducted with smaller groups, and away from development, which requires larger staff levels and investment in Good Manufacturing Practice (GMP) facilities and generation of FDA databases.

By extrapolation and interpolation of the data in Fig. 2, aggregate spending in the field since the early 1990s

Table 1. Overview of the Contemporary Tissue-Engineering Industry

Number of firms, December 31, 2002	89
Compound annual growth rate, 1995–2002	11%
Number of full-time equivalents, December 31, 2002	2611
Annual spending, calendar 2002	$487 million
Capital value of publicly traded companies, December 31, 2002	$307 million

TABLE 2. SECTOR ANALYSIS[a]

	Cellular	*Metabolic*	*Structural*
Number of FTEs	1225	381	975
Percentage of total	48%	15%	37%
2002 spending ($million)	$230	$72	$185
Growth since 2000 survey	+37%	−33%	−50%

[a]*Note:* Percentages may not total 100 because some firms were included in more than one group. FTE, full-time equivalent.

exceeds $4.5 billion with an averaged compound annual growth rate of 11%. The ~20% decline in spending over the past 2 years is far more modest than has been experienced by the dot.coms, a very different high-tech sector also relying on investment capital. In contrast, the net capital value of publicly traded tissue-engineering firms declined precipitously, dropping 88% between YE 2000 and YE 2002. This decline is partially due to diminished investor appetite for the sector, and also to the dissolution of both Organogenesis and Advanced Tissue Sciences, which extinguished to zero their previous combined capital value of well over $1.5 billion.

Comparison of the pie charts in Fig. 4 illustrates how dramatically the advent of stem cell technology and therapeutic cloning, along with the demise of firms vested in structural areas, have altered the landscape of the tissue-engineering business. In 2000, the structural segment accounted for ~60% of the industry and had grown by 85% since 1998. Since that time, the sector has contracted by ~50% while the cellular segment has expanded by ~37%. The majority of stem cell firms are in early stages of development and thus tend to be small, employing fewer than 25 FTEs. The result is a field that, despite its maturation in age, continues to be predominated by start-up and early stage firms: 82% of firms employ fewer than 50 FTEs.

The United States no longer enjoys its earlier advantage over the rest of the world (Fig. 5). In 2000 ~80% of the total tissue engineering workforce was stationed within U.S. borders as compared with ~54% in 2002. Several factors have contributed to this loss in preeminence and it is difficult to know which are most important. The door-closing of Advanced Tissue Sciences and Organogenesis fell exclusively on the United States. Europe and the rest of the world, arriving late to the field, are now expanding more rapidly. Some member states of the European Union require less stringent regulatory procedures related to the marketing and clinical application of medical devices, and as a result companies can collect valuable clinical data at lower cost. Emerging government policies related to the use of stem cells and therapeutic cloning, that is, the application of nuclear transfer to human cells, may be impacting the geographic distribution of the firms in this subset of the field.

United States government funding in the tissue-engineering field remains between 5 and 10% of spending total.[11] A World Technology Evaluation Center (WTEC) Panel Report on Tissue-Engineering Research suggests that while in the United States tissue engineering is funded primarily by the private sector, in Europe and Japan support for the field comes predominantly from federal funding.[12] Because federal funding tends to go to academic institutions and research centers, whose environment is conducive to conducting discovery level science, whereas industry tends to benefit from technology-based product development, concurrent development of both sectors could accelerate advances in the field. The National Institutes of Health (NIH), National Science Foundation (NSF), National Institute of Standards and Technology (NIST), Food and Drug Administration (FDA), and other federal agencies have begun taking steps to encourage increased federal support of the field.

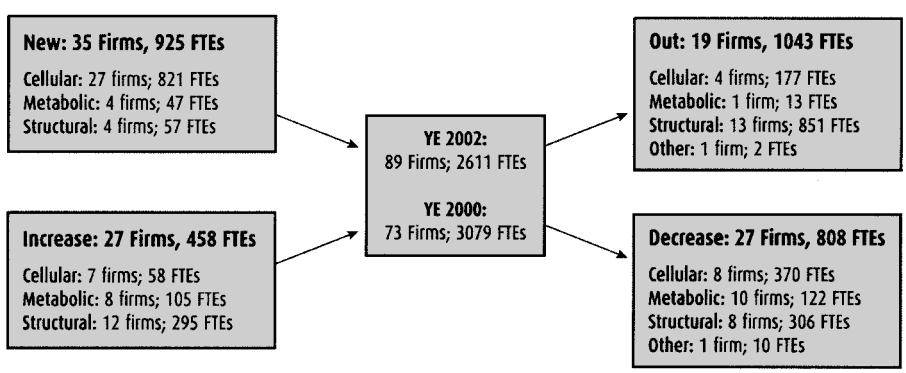

FIG. 1. Flow chart illustrating industry dynamics between 2000 and 2002. Flow chart is a mass balance illustrating dynamics of industry over a 2-year period, and details the firms that commenced operations (new), went bankrupt, or discontinued operations (out), grew (increased), or downsized (decreased). The central box summarizes the net result for the field as a whole. Gains and losses are further broken out for each category. About 80% of new firms were stem cell based. Of the firms that discontinued operations, about 70% were engaged in skin, cartilage, or other structural applications.

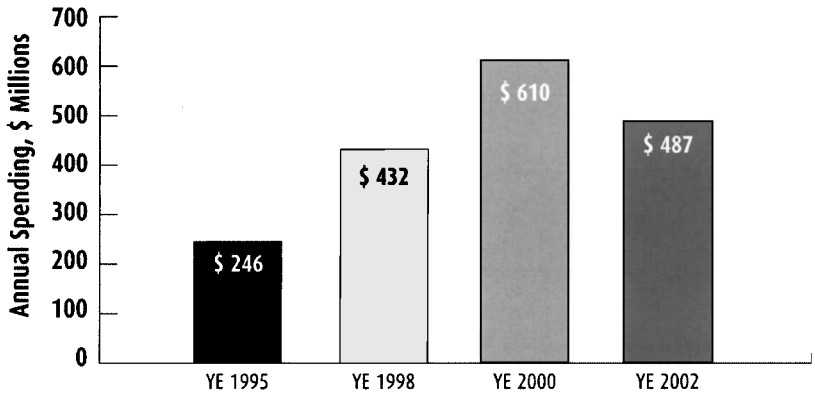

FIG. 2. Overall spending by the industry. Present expenditure is slightly above that of 1998. Diminished spending is consistent with a bear economy, a risk-averse investor community, and an industry not yet living up to general expectations. Aggregate spending to date is an impressive $4.5 billion. The compound annual growth rate (CAGR) is 11%. The decline between 2000 and 2002 is much less than that experienced by other high-tech sectors such as the dot.coms, which rely on investor capital, rather than sales, as a source of funds.

In 2002 alone, the NIH awarded ~$25 million in stem cell research grants, and new initiatives aim to increase federal activity in the field further.[11] The FDA established the Office of Combination Products in December 2002, which will coordinate regulation of all combination products utilizing tissue-engineering approaches.

The most difficult issue for industry enthusiasts is the poor market acceptance of those products that have been introduced into the market after FDA approval (Table 3). Of the four firms whose products have entered the clinical market, one has filed bankruptcy (Organogenesis), one has discontinued operations (Advanced Tissue Sciences [ATS]), one is operating under a "going financial concern warning" (Ortec), and one has downsized and been assimilated into a larger division of its parent corporation (Genzyme). Dermagraft (ATS) continues to be marketed by Smith & Nephew, but sales data following the transition are not yet available. Several factors appear responsible for this rather plaintive performance, although not all factors apply to all firms, and it is difficult to weight the importance of the different issues: (1) initial sales were very disappointing because the improvements over existing therapies were either limited to small subsets of patients, or were not generally compelling enough to attract large numbers of customers; (2) although scientifically strong, the companies lacked the skill sets required to develop low-cost manufacturing procedures; (3) high regulatory costs and protracted approval processes (especially for Dermagraft) placed an unrealistically high burden for return on investment (ROI) on the fledgling products; (4) marketing was haphazard either because the startups lacked experience in this area or because of dissonance between the startups and their corporate partners; and (5) the firms did not have clear reimbursement strategies, which limited end-user acceptance. In contrast to commercial aircraft, startups that

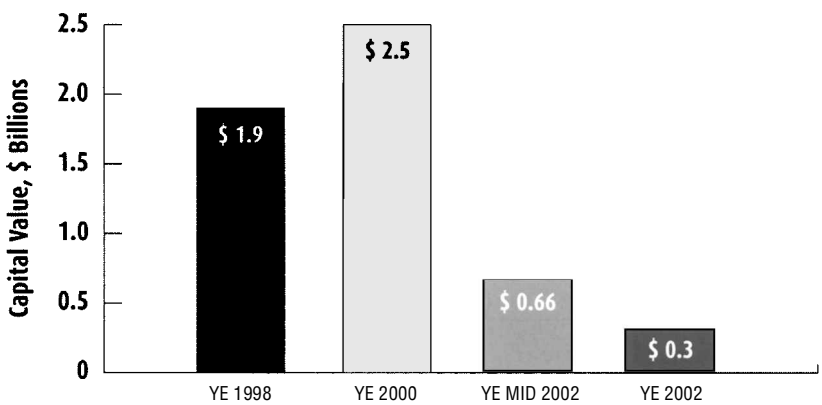

FIG. 3. Reduction in the capital valuation of publicly traded firms. The demise of two of the largest firms in the industry and general investor disenchantment with high-tech equities are responsible for this decline of almost 90%.

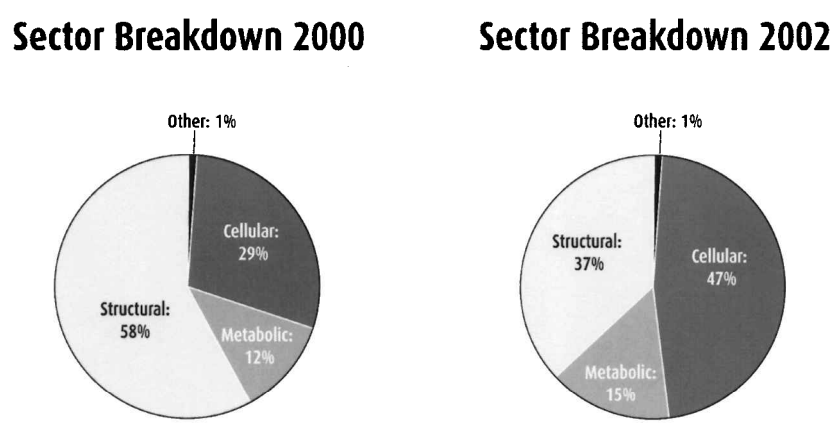

FIG. 4. Alteration in the makeup of the industry between 2000 and 2002. The driving force for the shifts is the demise of the large firms in living skin equivalents and the rise of small stem cell-based firms.

crash and burn do not have "black box flight recorders" and the causes of their final fate may ultimately be very difficult to sort out.

Close analysis of the sales history of Apligraf and Dermagraft support the hypothesis that these products have genuine clinical potential. Initial poor sales may simply reflect that they were undergoing an incubation period common to medical products. Sales of Dermagraft more than tripled from Q1–Q2 2002 sales of ~$1 million to ~$3.5 million in Q3–Q4 2002. This 300% improvement in sales, if sustained, would eventually have brought the product to a critical viable market level. In contrast, Carticel sales have been nearly flat for the past 3 years, at a level of about $22 million. Lack of interest in the conceptually appealing product may be due to relatively modest advantages over traditional approaches, as well as the need for surgeons to retrain to learn the procedure. In addition, clinical trials that tested the product in young patients with traumatized joints, not a representative pool of the typical candidate, may have led to miscalculations regarding the market potential.

As of December 31, 2002, 10 tissue-engineered products were still engaged in clinical trials while 6 had either failed to meet efficacy in phase III or been abandoned during phase I or II. Failure in a phase III trial is usually fatal for a biotech startup. Circe downsized and essentially ceased operations; Cytotherapeutics remained in the field but restructured its business model and now operates as Stem Cell, Inc. Curis abandoned the field of tissue engineering, after announcing that it would not go forward with phase III trials of Chondrogel and Vascugel because potential profit from sales of the products would not recover the costs of regulatory approval.

By all accounts, CytoTherapeutics and Circe's products failed on efficacy because their phase III trials were not sufficiently powered, that is, not large enough to reach statistically significant end points. Both products are reported to have functioned very effectively in certain sub-

TABLE 3. FDA-APPROVED TISSUE-ENGINEERED PRODUCTS[a]

Product	*Launch*	*Description*	*2002 annual sales*
Apligraf (Organogenesis)	1998	Living skin equivalent for diabetic and venous ulcers	$23 million; 25,000 units
Carticel (Genzyme Biosurgery)	1999	Autologous chondrocytes for cartilage repair	$25 million; 2,500 units
Dermagraft (ATS)	2001	Living skin equivalent for diabetic and venous ulcers	$4.5 million 4,500 units
OrCel (Ortec)	2001	Living skin equivalent for burn patients	<$100,000

[a]*Note:* Both Organogenesis and Advanced Tissue Sciences have discontinued operations. Smith & Nephew has taken over production, marketing, and sales of Dermagraft. The future of Apligraf is unclear.

Table 4. Products Engaged, Failed, or Abandoned in Clinical Trials as of December 31, 2002

Product	*Description*
Described by firm as engaged in trials	
Aastrom Replicell (Aastrom)[a]	*Ex vivo* cell production kits for specific disease
E-Matrix (Encelle)	Treatment of diabetic foot ulcers
Bioartificial liver support system (Excorp)	Bioartificial liver
Activated macrophage therapy (Proneuron)	Treatment of spinal cord injury
Spheramine (Titan Pharmaceuticals)	Encapsulated cell therapy for Parkinson's disease
ELAD (VitaGen)	Bioartificial liver
Renal assist device (Nephros)	Treatment of acute renal failure
LIVERX 2000 (Algenix)	Bioartificial liver
MyoCell (Bioheart)	Myocardiogenesis
Myocardial stem cells (Genzyme)	Myocardiogenesis
Failed or abandoned	
HepatAssist (Circe)[b]	Bioartificial liver
Cerecrib (CytoTherapeutics)[b]	Encapsulated cells for chronic pain
Acticell (BST)[b]	Keratinocyte burn dressing
Neurocell (Diacrin)[c]	Intracerebral porcine islets
Chondrogen (Curis)[c]	For bladder reflux and adult incontinence
Vascugel (Curis)[c]	To improve patency in coronary grafts

[a]Indicates product engaged in phase III, all others are in phase I/II.
[b]Indicates products that failed to meet efficacy during phase III.
[c]Indicates products abandoned during phase I/II.

sets of the trial population: CytoTherapeutics in patients with neuropathic pain and Circe in patients with sudden onset rapidly progressive acute hepatic failure. However, these were identified retrospectively and the FDA gives little weight to post-hoc analysis. Many advocate that larger trials would have led to approval for both firms' products. Table 5[13,14] compares the size of clinical trials conducted for tissue-engineered products and some recent biopharmaceuticals. There is a one to two order of magnitude difference in the number of test subjects. "Big pharma" can afford big trials and invests in them simply because high statistical power is often needed to demonstrate efficacy to FDA standards. We speculate that if tissue-engineered products had the funding to initiate trials on a par with those of big pharma and medical device companies, their clinical trial track record would almost certainly be better.

As of December 31, 2002, 10 tissue-engineered products were known to be in various stages of clinical trials (Table 4). (Since that time, VitaGen has discontinued operations, thus halting the ELAD trial). Some of the trials are investigator sponsored, and some are company spon-

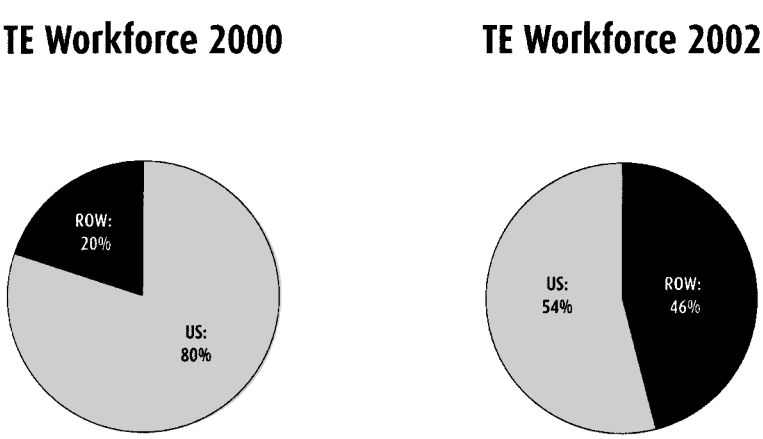

FIG. 5. Increasing globalization of the TE workforce between 2000 and 2002. Data are based on employee location, not location of firms. This trend is not necessarily a consequence of U.S. policies toward stem cell research. ROW, Rest of world.

Table 5. Comparison of the Size of Selected Clinical Trials

Product	*Clinical trial size*
Coated stent (Johnson & Johnson)[a]	5233 patients (4780 study, 525 control)
Viagra (Pfizer)[b]	3860 patients (3476 study, 384 control)
Cerecrib (Cytotherapeutics)[a]	85 patients (equally split study + control)
HepatAssist (Circe)[a]	175 patients (90 study, 85 control)
Dermagraft (Advanced Tissue Sciences)[b]	695 patients (389 study, 306 control)

[a]Data obtained directly from the firm.
[b]Data obtained from FDA files.[13,14]

sored. Some are active, others are dormant. It is not possible to judge the time-to-market for these products nor to predict their ultimate commercial success.

The challenges tissue engineers face in bringing products to market neither begin nor end with the regulatory process. In future more careful consideration must be given to marketing and sales, reimbursement, and to the development of large-scale production techniques, with attention to factors such as viable and safe sources of cells, bioreactor design, and preservation and shelf-life of products.[15]

In 1995, Frost and Sullivan forecast $2.0–$3.0 billion in sales for tissue-engineered products by 2002. The reality of ~$50 million is somewhat sobering. Sales of this magnitude cannot sustain present expense levels in the field, much less offset investing the $300–$500 million required to increase clinical trial patient populations to the levels found in drug trials. One constructive approach being advocated by the Medical Technology Leadership Forum (MTLF)[16] is enactment of a special approval pathway for tissue-engineered products.

Those in the field need to face the realities of the time frames and costs associated with bringing complex regulated products to market. Short-cutting either of these areas is likely to result in failure during clinical trials or after approval . . . and few firms survive such failures. If tissue engineering is to represent the basis for the next generation of organ replacement therapies, adequate funding and effective tactics for transitioning from research to product-based enterprises must emerge and take form. Viable options to consider are as follows: (1) diversification by private sector firms into revenue-generating areas to offset costs, (2) recruitment of funding from large, affluent pharmaceutical and medical device companies, (3) collaborations between the private and federal sectors that enable successful integration of discovery level science, product development, and marketing, and (4) a national initiative that provides adequate funding and regulatory frameworks which promote clinical application.

The initial poor performance of tissue-engineered products in the market and in latter-stage clinical trials is manifestly disappointing, especially to those involved with the firms and products that failed. But it is important to view these early-stage difficulties with a balanced perspective, and to bear in mind that innovative medical therapies more often than not endure a period of "blood, sweat, and tears" before final triumph. Consider, for example, (1) the pharmaceutical industry itself as well as (2) controlled release approaches, and (3) monoclonal antibody technology. After World War II, the emerging pharmaceutical industry was in jeopardy. In the late 1940s, the cost of producing cortisone had almost resulted in Merck's near bankruptcy. Penicillin, the most revolutionary drug of all, brought meager profit to any of its vendors. Fifteen years later the pharmaceutical industry had gotten past these "going in problems" and was well on its way to becoming the most outstanding wealth creation paradigm of the latter twentieth century. In the early 1970s, Alza Corporation's first two controlled release products (Occusert and Progesert) crashed and burned far more catastrophically than either Dermagraft or Apligraf. The scopolamine patch for motion sickness and nitroglycerin patch for angina followed and were the only commercially successful application of controlled release technology until the late 1980s and early 1990s. Today, controlled release represents a $25 billion global enterprise with enormous growth potential. In the late 1980s, monoclonal antibodies were little more than a source of frustration and failure within the biotechnology community; today they are the "new new thing." We advocate that tissue engineering will follow the same pattern, and that today's "going-in" problems will be regarded in retrospect as a part of the inevitable learning curve of what will have proven to be a medically successful and commercially rewarding venture.

CONCLUSION

Despite an unfavorable economy, the field of tissue engineering remains highly viable, with the number of firms in the field continuing to increase. To date the field includes 89 firms, employing more than 2600 workers and operating out of 16 countries. There has been a sub-

stantial increase in activity outside the United States: only ~54% of the 2002 workforce is based in the United States as compared with ~80% in 2000. A notable shift of focus toward stem cell-based technology has resulted in the field continuing to be characterized by small-scale, technology-based firms. Although aggregate development costs exceed $4.5 billion, the field has yet to produce a single profitable product. The marked difficulty the field has encountered as it transitions from discovery level science to clinical markets is not predictive of long-term failure, and is consistent with the difficulties encountered by other breakthrough medical technologies.

ACKNOWLEDGMENTS

This report would not have been possible without the help of the individuals at each firm who provided information and insights. Special thanks to Frank Gentile at Hambrecht & Quist and to Michael Ehenreich at Techvest for support and assistance.

Appendix 1. Directory of Tissue-Engineering Firms in This Study

Name	*Location*	*Category*	*Web address or telephone*
Aastrom	USA	Cellular	www.aastrom.com
Acorda (X%)	USA	Cellular	www.acorda.com
Advanced Cell Technology (ACT)	USA	Metabolic	www.advancedcell.com
Algenix	USA	Metabolic	www.algenix.com
Amcyte	USA	Metabolic	www.amcyte.com
Anterogen	USA	Structural	www.anterogen.com
Articular Engineering	USA	Cellular	www.articular.com
Befutur Technologies	Switzerland	Cellular	www.befutur.com
Bioheart	USA	Structural	www.Bioheartinc.com
BioTissue Technologies	Germany	Structural	www.biotissue-tec.com
BresaGen, Inc.	Australia/USA	Cellular	www.bresagen.com.au
Cardion AG	Germany	Cellular	www.cardion-ag.de/cardion.cfm#
Celgene	USA	Cellular	www.celgene.com
Cell Based Delivery	USA	Cellular	www.cellbaseddelivery.com
CellECT Bio, Inc.	USA	Metabolic	www.cellectbio.com
Cellexsys	USA	Cellular	www.targen.com/cellexsys
CellFactors, PLC	UK	Cellular	www.cellfactors.com
CellGenix	Germany	Cellular	www.cellgenix.com
Circe	USA	Metabolic	www.circebio.com
Co.don	Germany	Structural	www.codon.de
CyThera, Inc.	USA	Cellular	www.cytheraco.com
Cytomatrix, LLC	USA	Cellular	www.cytomatrix.com
Develogen	Germany	Cellular	www.develogen.com
Diacrin	USA	Metabolic	www.diacrin.com
Edwards	USA	Structural	www.edwards.com
Encelle	USA	Metabolic	www.encelle.com
ES Cell International	Australia	Cellular	www.escellinternational.com
Excorp	USA	Metabolic	(612)789-5940
Exten	USA	Metabolic	www.exten.com
Fidia Advanced Biopolymers	Italy	Structural	www.fidiapharma.it
Gamida Cell, Ltd.	Israel	Cellular	www.gamida-cell.com
Genevrier	France	Structural	www.laboratoires-genevrier.com
Genzyme Biosurgery	USA	Structural	www.genzymebiosurgery.com
Geron	USA	Cellular	www.geron.com
Human Genome Sciences (7.5%)	USA	Cellular	www.hgsi.com
Hybrid Organs	Germany	Metabolic	www.hybrid-organ.com
Infigen	USA	Cellular	www.infigen.com
Intercytex	UK	Structural	www.intercytex.net
Islet Sheet Medical	USA	Metabolic	www.isletmedical.com
Islet Technology	USA	Metabolic	www.islet.com
Isotis	The Netherlands	Structural	www.isotis.com
ISTO Technology	USA	Structural	www.istotech.com

(*continued*)

Appendix 1. Directory of Tissue-Engineering Firms in This Study (*Continued*)

Name	*Location*	*Category*	*Web address or telephone*
Ixion	USA	Cellular	www.ixion-biotech.com
Kaleidos Pharma	USA	Cellular	www.stemcellrx.com
Kourion Therapeutics AG	Germany	Cellular	www.kouriontx.com
Kuros	Switzerland	Structural	011-41-254-9933
Layton Biosciences (7.5%)	USA	Cellular	www.laytonbio.com
Maria Biotech Company, Ltd.	Korea	Cellular	
MaxCyte, Inc.	USA	Cellular	www.maxcyte.com
Medtronics	USA	Structural	www.medtronic.com
MicroIslet, Inc.	USA	Metabolic	www.microislet.com
Nephros	USA	Metabolic	www.nephrostherapeutics.com
NeuralSTEM	USA	Cellular	www.neuralstem.com
NeuroNova	Sweden	Cellular	www.neuronova.com
NeurotechSA	France	Metabolic	www.neurotech.fr
Neuronyx	USA	Cellular	www.neuronyx.com
Novocell	USA	Metabolic	www.novocell.com
Organogenesis	USA	Structural	www.organogenesis.com
Ortec	USA	Structural	www.ortecinternational.com
Osiris	USA	Structural	www.osiristx.com
Primegen	USA	Cellular	www.primegenbiotech.com
Proneuron	USA	Cellular	www.proneuron.com
Reliance Life Sciences	India	Cellular	www.relbio.com
Reneuron	UK	Cellular	www.reneuron.com
SCS KK	Japan	Cellular	81 0 78 306 0381
Selective Genetics	USA	Cellular	www.selectivegenetics.com
Sertoli	USA	Metabolic	www.sertoli.com
Skinethic	France	Structural	www.skinethic.com
Smith & Nephews	UK	Structural	www.smith-nephew.com
St Jude	USA	Structural	www.sjm.com
Stem Cell Sciences	Australia	Cellular	www.stemcellsciences.com.au
Stem Cell, Inc.	USA	Cellular	www.cyto.com
StemCell Technologies	Canada	Cellular	www.stemcell.com
Stemron	USA	Cellular	www.stemron.com
StemSource, Inc.	USA	Cellular	www.stemsource.com
Sulzer	Switzerland	Structural	www.sulzermedica.com
TEI biosciences	USA	Structural	www.teibio.com
TheraCyte	USA	Metabolic	www.theracyte.com
TiGenix	Belgium	Structural	www.tigenix.com
Tissue informatics	USA	Other	www.tissueinformatics.com
Titan Pharmaceuticals (Theracell)	USA	Metabolic	www.titanpharm.com
Transtissue Technologies	Germany	Structural	www.transtissue.com
Verigen	Denmark	Structural	www.vtsi.de
Vesta Therapeutics	USA	Cellular	www.vestatherapeutics.com
ViaCell	USA	Cellular	www.viacellinc.com
VitaGen	USA	Metabolic	www.vgen.com
VistaGen, Inc.	USA	Cellular	www.vistagen-inc.com
Wyeth	USA	Structural	www.wyeth.com
Ximerex	USA	Cellular	www.ximerex.com

APPENDIX 2. BREAKDOWN OF COMPANIES BY SECTOR AND PRINCIPAL ACTIVITY

*Primary classification for firm active in more than one area.

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