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Great Expectations: Private Sector Activity in Tissue Engineering, Regenerative Medicine, and Stem Cell Therapeutics

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"The future ain't what it used to be"
—Yogi Berra

ABSTRACT

This report draws upon data from a variety of sources to provide a detailed estimate of the current scope of private sector development and commercial activity in the aggregate field comprising tissue engineering, regenerative medicine, and stem cell therapeutics. Economic activity has grown a remarkable fivefold in the past 5 years. As of mid-2007 approximately 50 firms or business units with over 3000 employees offered commercial tissue-regenerative products or services with generally profitable annual sales in excess of $1.3 billion. Well over a million patients have been treated with these products. In addition, 110 development-stage companies with over 55 products in FDA-level clinical trials and other preclinical stages employed ~2500 scientists or support personnel and spent 850 million development dollars in 2007. These totals represent a remarkable recovery from the downturn of 2000–2002, at which time tissue engineering was in shambles because of disappointing product launches, failed regulatory trials, and the general investment pullback following the dot-com crash. Commercial success has resulted in large measure from identification of products that are achievable with available technology and under existing regulatory guidelines. Development-stage firms have become much more adept at risk management. The resilience of the field, as well as its current breadth and diversity, augurs well for the future of regenerative medicine.

INTRODUCTION

ROUTINE AND COST-EFFECTIVE REPLACEMENT of the function of failed organs or deteriorated tissues with man-made substitutes represents one of the great accomplishments of biomedical science and engineering during the last half of the 20th century. Substitutive medicine, as it was termed by the late Pierre Galletti,[1] began in earnest in the decade between 1955 and 1965 with simultaneous development of enabling technology for artificial hips, blood oxygenators (artificial lungs), maintenance hemodialysis, and pacemakers. The field grew slowly at first but then accelerated rapidly as will also be seen to be the case for tissue engineering products. Growth patterns are well illustrated by hemodialysis, for which accurate demographic records are available. Chronic therapy for renal failure first became feasible in 1960. A few hundred patients were being treated in 1962. This number grew to only 10,000 over the next decade. But by 1982, another decade later, the chronic population had expanded to over 200,000 and today (2007) the hemodialysis patient population exceeds 1.6 million diseased individuals.[2] In aggregate, nearly 50 million patients are living because of one form

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or another of artificial organ therapy, and in developed nations one person in five who reaches 65 is likely to benefit from the organ replacement technology in the remaining years of their lives. The United States spends an astonishing 1% of its gross domestic product (GDP) on organ replacement therapies.[3]

Despite manifold accomplishments, contemporary technico-medical approaches to tissue and organ replacement are both constrained and Procrustean. They rely upon organometallic devices that are, to a lesser or greater degree, inherently bioincompatible and upon inert materials that do not grow, remodel, or repair themselves. Therapy formats can be highly invasive, and the working life of implants is often less than the life expectancy of the patient. Fully aware of these limitations, research-minded investigators have advanced a new paradigm in which man-made organ and tissue replacements will either have a biologic component or, in some instances, be entirely cellular. Individual efforts in this area have eventually coalesced into a functioning subspecialty initially termed tissue engineering and more recently described as regenerative medicine. The manner in which various disciplines came together to enable tissue engineering is recounted in a 2004 study conducted by Viola *et al.*[4] for the National Science Foundation (NSF) and in an exhaustive technically grounded World Technology Evaluation Center (WTEC) report prepared by a distinguished working group under the direction of McIntire[5] in 2002.

The early evolution of tissue engineering followed an unusual pattern. Although seminal ideas originated in universities, the preponderance of research and initial development took place in the private sector, usually inside venture-backed start-up companies. Government-supported research in academia and elsewhere accounted for, at most, 10% of activity.[6] In essence, financial analysts and venture investors had displaced peer reviewers and study sections in deciding which science and technology would be funded and by whom it would be conducted. This naturally led to greater emphasis on applied research and advanced development and less on basic science. Although the balance has been somewhat redressed, this anomalous history makes the growth of tissue engineering particularly interesting and worthy of study. We have published in this journal analyses of the private sector of tissue engineering in 1995,[7] 1998,[8] 2001,[9] and 2004.[6] The growth of the field up until about 2003, as chronicled in these studies, can readily be divided into two distinct phases. The first, running from the early 1990s through 2001 is appropriately described as "the best of times." At the end of the millennial year of 2000, tissue engineering research and development was being pursued by 3300 full-time equivalents (FTEs) in more than 70 start-up companies or business units with a combined annual expenditure of over $600 million. Spending since 1995 had grown at a compound annual rate of 16%, and the aggregate private sector investment exceeded $3.5 billion. The net capital value of 16 publicly traded start-ups exceeded $2.5 billion. Apligraf® skin equivalent (Organogenesis, Canton, MA) and Carticel® (Genzyme Biosurgery, Cambridge, MA) had been FDA approved and had achieved annual sales revenues in the $10–20 million range. Close to a dozen products were in FDA-level regulatory trials, including a bioartificial liver, an intracerebral pain implant, and a second skin equivalent. Small wonder then that a 1999 *Good Morning America* television report described tissue engineering (along with genetic medicine) as the greatest scientific accomplishment of the 20th century[10] and that in 2000 *Time* magazine placed tissue engineering at the top of its list of the hottest new jobs of the 21st century.[11]

Between 2001 and 2003 things went very wrong, very quickly. As documented in our most recent report,[6] several factors combined to make this period "the worst of times" for tissue engineering. After the dot-com crash, investors lost their appetite for risky investments, thus limiting the availability of funds for companies who relied upon investment capital to finance day-to-day operations.

For reasons analyzed extensively elsewhere,[6] sales of approved products, Apligraf©, Dermagraft©, and Carticel©, remained anemic and far too low to cover fixed costs of their production. As a consequence, both Organogenesis and Advanced Tissue Sciences were operating at significant financial losses and chose to apply for Chapter 11 bankruptcy protection in the fall of 2001. Genzyme Tissue Engineering was downsized and folded into a Genzyme Biosurgery, a larger corporate unit. All nine leading tissue engineering product candidates either failed to win FDA approval after submitting clinical trial data or simply abandoned their clinical trials for financial reasons, and this was not counterbalanced by a single regulatory success. The combined effect of the dot-com economy, the failed product launches, and the disappointing results from FDA clinical trails was devastating. Spending in the field, which had been growing at about 16% per year, declined by 20% between 2000 and 2002. Nineteen firms out of a total of 73 either filed for bankruptcy or simply closed their doors. Twenty-seven others downsized significantly. Employment in companies developing metabolic and structural organ replacements declined by a third and a half, respectively. Overall 1800 workers out of 3100 were displaced, but the field as a whole only lost 500 net positions because contractions in metabolic and structural sectors were counterbalanced by growth in stem cells. The capital value of publicly traded tissue engineering companies fell by more than eightfold, from $2.5 billion to $300 million.

The dismal performance of tissue engineering in 2001 and 2002 certainly raised concerns about the validity of its promise and prompted questions as to whether the technology had missed its window of opportunity. Would newfound enthusiasm for nanotechnology and personalized genomic medicine usurp funding and talent that were previously directed toward tissue engineering? Would the field follow in the plaintive footsteps of gene therapy and xenotransplantation as failed undertakings? As it happened, and as described in detail in the following sections, none of these dire

possibilities were realized; instead tissue engineering rebounded from its nadir more robust and more ebullient than ever.

This paper will update our earlier series of reports by providing a quantitative description and an in-depth analysis of the field as of mid-2007. As tissue engineering has expanded, other authors also have begun to either document or analyze the private sector. Bock *et al.* prepared a detailed analysis of European activities in both private and public sectors in 2003.[12] Ehrenreich and Ruszczak have published an insightful review of the commercial development and market status of living skin equivalent and wound healing.[13] Nerem contributed two recent reviews offering insight and perspective into the development patterns of the industry.[14,15] Pangarkar and Hutmacher have analyzed the role of innovation business models of private sector firms.[16] Langer[17] and Vacanti[18] have prepared very interesting editorial perspectives. Mason has written thoughtful overviews of recent commercial and scientific progress in the field and coined the metonymic word ''Regenmed.2'' to describe its current status, in analogy with the term ''Dotcom.2,'' which is applied to Internet commerce after its recovery from the crash of 2002.[19,20] Finally, the online proceedings of a 2007 NSF workshop on translational research in stem cells organized by Shoichet and Caplan[21] are very pertinent as are reviews by Shastri,[22] Wilan,[23] and Kirkpatrick.[24]

Nomenclature expanded as the field grew. According to Viola *et al.*,[4] the term ''tissue engineering'' first appeared in literature searchable on PubMed in an offhand reference in the 1984 *Transactions of the American Ophthalmological Society*,[25] and the expression ''regenerative medicine'' was coined by William Hazletine in the late 1990s.[26] In actuality, several earlier references to both terms, with the very same meaning that is recognized today, are available in media not covered by PubMed.[27–30] Regardless of origin, both expressions have become widespread: a Google search on ''tissue engineering'' and ''regenerative medicine'' results in 1.8 and 1.1 million hits, respectively (July 2007).

But what do the terms actually mean? Langer and Vacanti's original 1993 definition is still perhaps the most popular and widely relied upon: ''an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.''[31] The recent report of Multi-Agency Tissue Engineering Science (MATES) interagency working group defines tissue engineering as ''the use of physical, chemical, biological, and engineering processes to direct the aggregate behaviour of cells,'' but later imputes a somewhat different meaning to regenerative medicine as ''self healing through endogenous recruitment or exogenous delivery of appropriate cells, biomolecules, and supporting structures.''[32] Such constructions, as well as many others, are articulate and aspirational embodiments of the potential of tissue engineering. They are not, however, what is needed for this paper, that is, a working definition that can be applied to a particular product or process or firm to decide whether it should be included in this survey of the field, or should be excluded.

For our purposes, the terms tissue engineering and regenerative medicine are used interchangeably and are defined broadly as biologic approaches to repairing, replacing, and regenerating functional living tissue. Stem cell therapies, adult or embryonic, are included, as are therapies in which a mechanical approach stimulates a biologic response. Pure-play gene therapy, drug-eluting stents, allo- and xenotransplantation, and transfusion medicine are explicitly excluded. Considerable judgment and discretion is involved in applying this definition to specific products and processes. Close cases need to be deconstructed by asking ''what living functional tissue is being repaired, replaced, and regenerated'' and ''to what extent is the mechanism biological rather than mechanical (traditional devices) or biochemical (traditional pharmaceuticals)?'' This working definition is more expansive than that which was applied in our previous surveys,[6–9] which excluded acellular products such as matrices and morphogenic proteins; we believe that the expanded definition is appropriate and necessary because technical consideration and market forces have moved the field in the direction of the products that it now encompasses.

METHODS

Lists of firms active in tissue engineering, regenerative medicine, and stem cell therapeutics were prepared from author affiliations in relevant journals, from programs and attendee registers at scientific congresses and commercial meetings, from Google searches, from available compilations by industry-analyst reports, and finally from personal knowledge. Lists were checked for accuracy and completion against online databases listing firms in the field, the most comprehensive of which is managed by the Network for Regenerative Biology.[33] Contract research organizations manufacturing for other tissue engineering firms were included although their financial contributions were not tallied to avoid double counting. Organizations selling goods (e.g., specialized laboratory equipment) or services (e.g., financial service firms) to operating firms were not included. Bioaesthetic products were excluded (e.g., creams prepared from conditioned media), excepting those involving cell transplantation. Also not included in our database were not-for-profit cord blood banks, veterinary firms, clinical services, organ or tissue allografts, conventional bone marrow transplantation for blood-borne cancers, transfusion medicine, and educational, media-based, or financial services.

Particular attention was given to the question of whether private sector cord cell banking and Medtronic's INFUSE® Bone Graft should be included in our survey. In the end, both were included because they clearly fall under our definition.

Virtually all start-up companies have Web pages explaining their focus, technical approach, and strategy. These were reviewed, and companies were readily classified as

"Biomaterials," "Cells & Biomaterials," "Adult Stem Cells," "Embryonic Stem Cells," or other according to their principle development activity. The type of cells that firms preferred, that is, autologous, allogeneic, or (rarely) xenogeneic cells, was recorded. Companies' development status was categorized as preclinical, clinical trial, or commercial; the latter designation was reserved for operations that derived the bulk of their revenue from product sales. The focus of the company, for example, pancreas, skin, and platform, was recorded. The status of clinical trials for products regulated as drugs or biologics was given as phase I, phase II, or phase III, and for products regulated as medical devices as Investigational Device Exemption (IDE) or pivotal. The cumulative number of patients treated with commercial products was either taken directly from firms' Web pages or back calculated from total sales divided by unit costs.

The size of stand-alone firms was quantified by number of employees or FTEs and overall operating expenditure. Expenditure is simply net income for profitable companies and net income plus loss (burn rate) for companies still operating with investor funds. Data were keyed to mid-2007. Some companies posted this information on their Web pages, while others provided it when contacted by e-mail or phone. For public companies, the information was available in 10-Q or other Securities and Exchange Commission (SEC) filings. Some privately held companies declined to provide information beyond what was given on their Web page; for these firms the data were taken from "Hoovers" database,[34] a company information service of Dunn & Bradstreet. Figures provided by companies were also crosschecked against Hoovers, and the larger of the two values was recorded because in a growing field it was likely to be more recent. A few firms not disclosing financial data were also not found in Hoovers; in those instances, estimates were based upon comparables. In some cases, total annual spending was available but not the number of employees; for others, the number of employees was known but not the annual expenditure. We estimated one from the other using a ratio of $338,000 per employee based upon a linear regression of annual expenditure against the number of employees for those companies for which both sets of data were available. In the case of Medtronic, employees were calculated from company-wide data for cost of goods sold applied to the "Spinal Biologics" operating segments; both figures are available in the company's 2006 annual report.

Increasingly, tissue engineering is found as small pockets in larger firms, for example, J&J, Cook Biotechnology, Genzyme, Biomet, Baxter, and Fidia. While not highly confidential, data on the size and scope of activities of firms in this area are not routinely provided. Data in this report on these companies are estimates, based upon company annual reports, analysts' reports, and discussions with employees, competitors, and industry insiders.

Capital values of companies were calculated as multiplicative product of the number of shares and the share price (July 2007) for traded companies; this information is readily available from company Web pages or SEC filings of public companies, even those traded over the counter (OTC). This parameter was calculated only for stand-alone regenerative medicine companies; no effort was made to estimate, for example, the contribution of J&J's or Genzyme's tissue engineering activities to the firm's overall capitalization.

Where necessary, overseas currency was converted to dollars at the exchange rates prevailing in mid-2007 (~$1.40 per Euro and ~$2.00 per pound, etc.), not at purchasing power parity.

RESULTS

An Excel spreadsheet compiling the data collected in the preparation of this report is available by request to the corresponding author. Appendix A (available online at www.liebertpub.com) contains a list of all 171 firms identified as meeting our inclusion criteria, the countries in which they are located, their websites, and their stages of development.

Table 1 provides a concise overview of key industry parameters. Table 2 breaks down economic data for different industry segments; note that INFUSE® Bone Graft is included under "other," along with other firms within this class of product, for example, Biomemitic Technologies. Table 3 lists both the 2007 sales levels for key product areas and the estimated cumulative total number of patients treated. Figure 1 is a bar chart illustrating the magnitude of the recent growth of the field. Figure 2 places each firm in our database in an *x–y* matrix according to industry segment and development status. Symbols indicate the size of each firm, based upon annual turnover. Figure 3 contains pie charts detailing the geographic distribution of activity, firms' preferences for different available cell types, and estimated split of expenditures between public and private sectors.

Table 1. Key Industry Parameters: Tissue Engineering, Regenerative Medicine, and Stem Cell Therapeutics

Worldwide estimates for 2007 (rounded totals; $ [millions])	
Total private sector activity	$2400
Total commercial sales	$1500
Total development-stage spending	$860
Number of FTEs	6100
Number of firms or business units	171
Number of firms or business units in commercial stage	47
Number of firms or business units with products in clinical trials	57
Percent of companies that are U.S. based	55%
Cumulative patients treated with regenerative medicine products*	1,200,000
Capital value of listed firms (50)	$4700

*Excludes cord cell banks.

Table 2. Breakout of Key Parameters by Industry Segment (Rounded Totals; $ [Millions])

	Biomaterial	*Cells and biomaterials*	*Stem Cells (adult and embryonic)*	*Multiple/other*	*Total*
Preclinical					
No. of firms	5	13	41	4	63
FTEs	48	153	744	47	992
Dollar volume	$13	$55	$230	$8	$306
Clinical trial stage					
No. of firms	6	20	25	6	57
FTEs	199	476	687	154	1516
Dollar volume	$71	$163	$277	$47	$558
Commercial					
No. of firms	6	12	25	4	47
FTEs	791	541	1391	762	3485
Dollar volume	$313	$160	$273	$787	$1533
Total					
No. of firms	17	45	91	14	167
FTEs	1038	1170	2822	964	5994
Dollar volume	$397	$378	$781	$842	$2398

DISCUSSION

Three observations are apparent.

1. The recovery of the private sector from the downturn in 2002 is both remarkable and complete; aggregate economic activity has grown an extraordinary fivefold since our last survey keyed to year-end 2002.
2. Regenerative medicine is now a commercial-stage enterprise with over 60% of economic activity representing product sales compared to only 5% of a much smaller base in 2002.
3. The field has become far more diversified, and much, though certainly not all, of the successful activity is found in acellular products that were not emphasized in the earlier years.

These outcomes are themselves interrelated and depend in a complex fashion on a number of factors: adjustments in business models following the downturn of 2002; entry of established biomedical firms into the field; a subtle change in the approach to regulation; enthusiasm of governmental funding agents; and increased internationalism. This interplay will be discussed after the commercial sales are described in more detail.

Table 3 lists the current sales of products in regenerative medicine, and also lists the estimated cumulative number of patients treated with these products. Three areas predominate: sales of Medtronic's INFUSE® Bone Graft products are approaching $700 million, the aggregate volume of private sector cord banking of adult stem cells now exceeds $270 million, and sales of biomaterials with a propensity for tissue regeneration, including small intestine submucosa

Table 3. Commercial Products (Rounded Totals; $ [Millions])

Commercial products	*2007 sales*	*Cumulative patients*
Bioactive bone grafts	$700	170,000
Regenerative biomaterials	$240	750,000
Cord stem cells	$270	*
LSE and cartilage	$90	250,000

LSE: Living skin equivalent.
*Cord stem cell donors are not classified as patients.

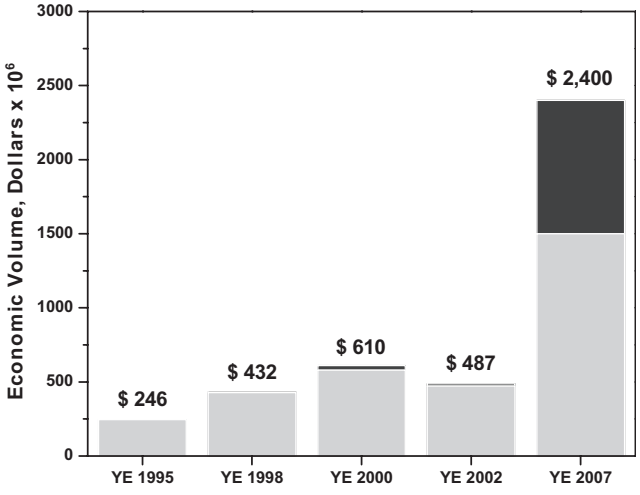

FIG. 1. Growth of the economic value of tissue engineering and regenerative medicine since 1995. Light-gray sections in the column graph refer to spending by companies in preclinical or clinical stage; darker segments refer to sales by firms in the commercial stage. The dip in 2002 is evident as is the subsequent rebound. Data for earlier years from refs 6–9.

	Biomaterials TE	Cells & Biomaterials	Adult SC		Embryonic SC	Multiple/Other
Preclinical	$ SericaTechnologies $ Regentec $ 3DM $ Nanomatrix $ Tepha	$$ Novocell $$ HepaLifeTechnologies $ Microislet $ Arbios $ VitalTherapies $ Mattek $ Bioengine $ Genegrafts Ltd $ Bionova $ Humacyte $ Regentis Biomaterials $ CytomatrixLLC $ Cerco MedicalLLC	$$ Mesoblast Limited $ NeuroNova AB $ Reneuron $ Stelic $ MultiCell Technologies $ ReproCELL $ Cytonet Hannover Gmbh $ Medistem Laboratories $ Neuralstem Biopharmaceuticals, Ltd $ BioE $ EndGenitorTechnologies $ Relnnervate $ BetaCell $ Pluristem LifeSystems $ IxionBiotechnology	$ AegeraTherapeutic $ AntiCancer $ Theradigm $ RhinoCyte $ Calba Tech $ OncoMed $ Regenics A/S $ Stem Path $ Morphogenesis $ Novathera $ PlureonCorporation $ StemnionLLC $ VitroDiagnostics $ Odontis $ Prime GenBiotech Corporation	$$$ Geron $$ Advanced Cell Technology $$ Cellartis $$ Stem Cell Innovations $ Stem Cell Sciences $ Thrombogenics Ltd $ Axordia Limited $ Vistagen $ Stemagen $ Cellular Dynamics Inernational $ ES Cell International Pty. Ltd	$ Cardio $ Tissue Regeneration Therapeutics $ NsGene A/S $ National Stem Cell
Clinical Trials	$$ Kuros Biosurgery Ltd $$ RegenBiologics $ Encelle $ Biosyntech $ Celltrix	$$ Tengion $$ Intercytex $$ Neurotech $$ Ortec $$ Amcyte $$ Pervasis $ Japan Tissue Engineering Co $ LCT $ Genevrier $ Hybrid Organ GMBH $ Excorp $ BCS $ ArBlast $ AdvancedBiohealing $ Educell $ Cytograft $ Histogeneics $ Theregen $ Millenium Biologix $ Euroderm	$$$ Osiris $$ Co.don $$ Cytori Therapeutics $$ Aastrom Biosciences $$ Opexa Therapeutics $$ CellGenix Technologie Transfer GmbH $$ TheraVitae $ Myosix $ Bioheart $ Cellerant Therapeutics $ NeoStem $ BrainStorm Cell Therapuetics	$ MaxCyte $ Gamida Cell Ltd $ Angioblast Systems $ NeuroGeneration $ VelcuraTherapeutics $ Aldagen $ Neuronyx $ Stem Cell Therapeutics Corp $ Stem Cell Therapy International $ Vesta Therapeutics $ Tristem Corporation $ Stemline Therapeutics	$$ StemCells	$$ Biomimetic Therapeutics $$ TiGenix $$ Isolagen $ ISTO $ Innovacell $ TissueGene $ Titan(Spheramineonly)
Commercial	$$$ Lifecell $$$ Orthovita $$ Integra $$ Cook BiotechLtd $$ Fidia Advanced Biopolymers $$ TEI Biosciences	$$$ Organogenesis $$ SEWON Cellontech $$ Arthro Kinetics $ Celltran $ Biotissue Technology $ Imedex Biomateriaux $ Tetec $ Interface Biotech A/S $ Vaso Tissue Technologies $ Skinethic $ Cell Matrix AB $ Karocell Tissue Engineering AB	$$$ Viacell $$ CBR Systems $$ Cryo-Save $$ CryoCell $$ Cordbank $$ Vita 34 AG $$ CordLife $ Stemcyte $ MedCell $ Cord Blood Registry $ VetStem $ Future Health $ Stemlife	$ Cryobanks International $ Cryocord $ Eticur $ LifelineCordBloodBank $ ViviCells $ Cord Blood America $ Lazaron Biotechnologies $ Virgin Health Bank $ Cells for Life $ New England Cord Blood Bank $ Securacell $ Cord Blood Bank of Canada		$$$ Medtronics $$ Genzyme $$ Johnson& Johnson $$ Baxter

FIG. 2. Overview of industry product focus and development stage. Companies are classified according to product type and development stage. Companies within each box are listed according to size. Estimated sales or annual spending is classified by the symbols: $, < 10 million per year; $$, 10–50 million per year; $$$, > 50 million per year.

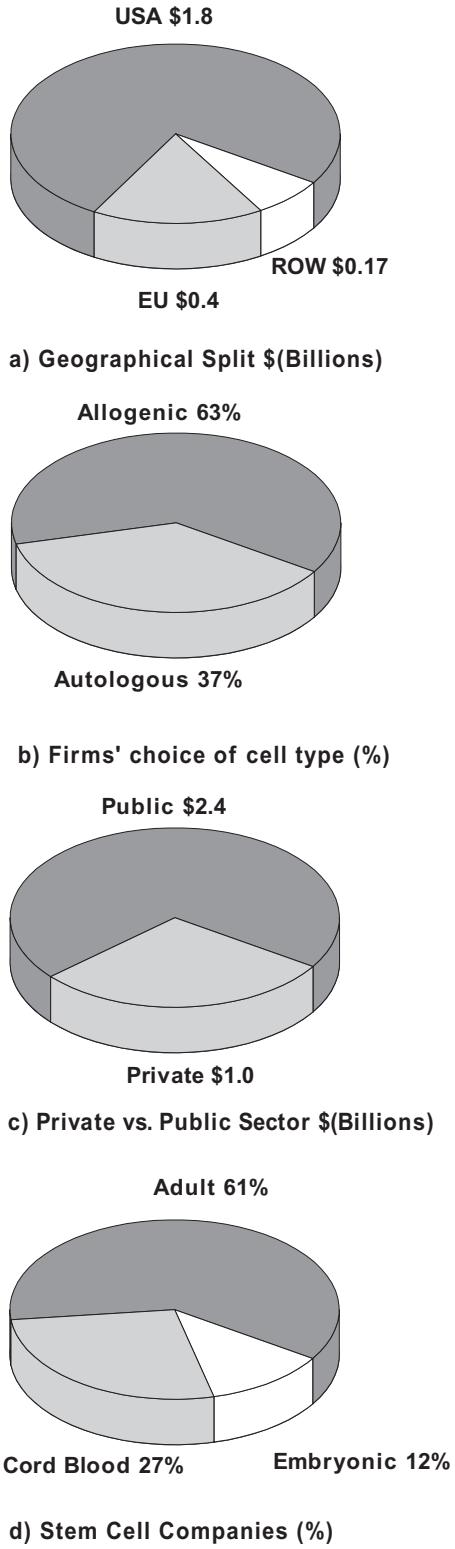

FIG. 3. Industry characteristics. Pie charts show **a**) geographical distribution of industry, **b**) firms' selections of cell types, **c**) the mix of public and private sectors and **d**) the relative industry investment in adult embryonic stem cells. As regenerative medicine has emerged and taken form, the field has become more diverse, which provides advantages in both survival and growth.

(SIS), now exceeds $240 million. Finally, sales of living skin equivalents and cartilage approach $100 million per year, of which the lion's share is Apligraf from Organogenesis.

Both the magnitude and makeup of product sales are somewhat surprising. Cord blood banking is a service, the therapeutic benefit of which lies in the future and will depend in some measure upon medical breakthroughs that have yet to occur. Both INFUSE® and SIS, while unequivocally fostering bone and tissue growth, are acellular products. SIS, for example, supplies only the matrix and relies upon the patient to provide her or his own cells and growth factors. These products are very different from the earlier vision of a "heart in a box" or full-grown organs provided from a laboratory. This may be off-putting to traditionalists but is, in actuality, the logical response of a market-driven industry to commercial realities. Products containing living cells are costly to manufacture, are expensive to shepherd through regulatory approval, and may not offer sufficient benefit to justify the cost to the patient or the risk to the investor. Acellular products predominate at the moment because they avoid the technical challenges and regulatory issues implicit in selling a product containing living cells. As the industry grows in experience, it will have the skill sets and financial resources to tackle the more difficult product challenges.

In addition to the expansion of the commercial sector, the past 5 years have seen a resurgence of development-stage companies, that is, those in preclinical or clinical-trial stage of development. In general and with some exceptions, the character of these firms has also changed. First-generation tissue engineering start-ups were largely financed with venture capital funds, and thus venture capitalists (VCs) had ultimate control over key strategic decisions and business plans. Flush with success from their early investments in recombinant molecular biology, the VCs advocated an expansive and dynamic business model. Firms were guided to identify a large market, and then to carve out a niche where they could be the leading contender and thus attract the most funds. Being number one meant acquiring more "throw weight" than competitors: the most prestigious scientific advisory boards, well-credentialed executives, and the best equipped laboratories. Firms were also encouraged to become fully integrated—the acronym FIPCO or Fully Integrated Pharmaceutical Company was much in vogue—because outsourcing any steps along a critical path would not lead to a sustainable advantage over competitors. Availability of future funding would of course depend upon achievement of defined milestones, for example, an article in a high-impact journal or a "first in man" clinical trial, but also upon maintaining a high level of visibility for the company. Management needed to be effective and articulate spokespersons and had to craft a message readily grasped by the investment community. For sure, not every company was destined to end up a leader and a winner, but investors were confident that the bountiful profits of the successful would more than compensate for those with less-fortunate outcomes. This

paradigm had worked well for an industry that spawned Amgen, Genentech, and their counterparts, so it is important, in retrospect, not to judge the VCs too harshly for attempting to apply it to tissue engineering and regenerative medicine. But, in the end, it proved disastrous. First, the implicit assumption that bountiful profits would immediately follow upon product approval neglected the fact that the pharmaceutical ramp-up rates rarely attend medical devices. In fact, even very successful devices start slowly and build gradually to large volume and high profitability over a period of several years. Small firms particularly may lack the sophistication and experience necessary for successful interactions with physicians and clinicians. Second, widely touted estimates of market size for living skin equivalents and cartilage repair were based upon total replacement of an existing technology when, in fact, the products that were developed were suitable for only a very small subset of patients. There simply were no blockbusters. Third, the burn rate required to sustain the FIPCO leadership infrastructure was very high, and senior management spent most of its time raising funds rather than managing the technology. Fourth, companies quickly learned how to game the milestones, for example, by starting a first-in-man trial prematurely to meet a previously assigned goal. Finally and most importantly, scientist-managers began in some instances to believe their own hype and to loose the critical skepticism, which is a *sine qua non* for effective science.

Few who experienced the difficult days of the early 2000s have any desire to repeat these mistakes. Firms today have lessened their dependency on VCs by seeking funds from other sources, including angels, debt, SBIRs, or other forms of public–private cooperation. Outsourcing, even of manufacturing, is far more common. Firms whose employees' skills are primarily technical are increasingly reluctant to move beyond their areas of core competency, and seek strategies in which established manufacturers and marketers will take on those responsibilities and risks. Business plans have become more realistic: modest but achievable profits based upon reasonable investment have become more attractive than long-shot blockbusters. These trends toward a risk-management-based business model have been accelerated by the entry of very large firms into the field. Big pharma and big medical technology companies have a plethora of skills in manufacturing, marketing, and regulation. They have deep pockets and can nurture developmental products until they are ready. Having multiple alternative investment options, the firms can easily afford to terminate a product if progress lags or perceived risks begin to escalate. In contrast, a small company is wedded to its product and often has no alternative but to go full speed ahead, torpedoes or no.

One of the subtler and perhaps unsettling aspects of the transition in the past 5 years is the dilution of scientific presence and control in the field. The senior management that turned around Organogenesis (of which, more later) was skilled at finance, marketing, and manufacturing, but certainly would best be characterized as technophilic rather than as hard-core scientific. The cord banking business, a major component of regenerative medicine, requires technical competence, but science *per se* is not a source of competitive advantage. (Any reader doubting this should view Richard Branson's video clip on Virgin cell bank's home page.[35]) Similarly, the INFUSE® Bone Graft, likely to become the field's first billion-dollar product, appears to have been driven by orthopedic marketing skills; we were unable to find a single presentation on INFUSE® at any of the TERMIS meetings. As the field goes forward and commercial factors drive decisions and directions, it is probably time for research-minded scientists and biomedical engineers to learn to "let go." The analogy with parenting is clear.

The issue of cell sourcing is unresolved. Figure 3B shows the percent of firms concentrating on autologous cells versus those with a focus on allogeneic cells. (Private cord blood cell banks were considered autologous though allogeneic use, for example for siblings, is certainly possible.) Figure 3D compares the focus of stem cell firms. Adult stem cells lead by a wide margin, but embryonic stem cell activity is nevertheless very robust. In any event, the overall popularity of stem cells persists, even though this source may in fact be associated with more regulatory and developmental risk than other cell types.

Tissue engineering is unique in that a sizable commercial base emerged well in advance of federally supported basic science. The situation has changed, gradually at first and more aggressively in recent years. As chronicled by Christine Kelley of National Institute of Biomedical Imaging and Bioengineering (NIBIB) in a very thorough and complete report of NIH activities in the field,[36] only three requests for applications (RFAs) related to tissue engineering were issued prior to 2000; by this time, the private sector already had more than 3000 employees. However, the NIH issued 10 tissue engineering RFAs in the period 2000–2005, and 3 more in 2006 alone. Based upon the NIH's internal Disease Funding and Tracking System (DFTS), not publicly available, Kelley estimates that the NIH is spending over $600 million on tissue engineering and regenerative medicine in 2007. This total almost certainly includes research that falls well beyond the inclusion criteria of this report, for example, bone marrow transplantation for leukemia, surgical techniques for maxillofacial reconstruction, and/or the use of stem cells in drug discovery and agriculture. Nevertheless, it captures the heightened priority given to tissue engineering and regenerative medicine by the NIH. Further, Kelley's estimates only tally NIH funding, and not funds spent in the area by NSF, Department of Defense (DOD), National Institute of Standards and Technology (NIST), and other agencies. Nor does it include state initiatives in stem cell research. Thus far, seven states—California, Connecticut, Illinois, Maryland, New Jersey, New York, and Wisconsin—have established programs to fund embryonic stem cell research, though the amounts actually disbursed and spent thus

far by these initiatives are very small. European and Asian governments have also invested heavily. Singapore has Biopolis, and Germany has established and significantly funded four very large centers in regenerative medicine; England and Holland have government-supported networks and centers. Government generally supports basic rather than translational research, and it is somewhat oxymoronic to classify basic research into applied fields. Nevertheless, expanding upon Kelley's analysis, a reasonable estimate of worldwide government support for the field is in the range of $500 million to $1 billion. The latter value was employed in Figure 3C. Such a level of support creates a vibrant academic partner for industry and assures the education and training in regenerative medicine of a generation of scientists and biomedical engineers. It contributes a basic science foundation that is conducive to efficient regulation. In addition, the various government programs provide benediction to the technology and validation to the concept, and thus increase the credibility of the field to investors and to decision makers in big pharma and large device companies.

FDA regulation is an enormous barrier to entry of any new healthcare technology. New drugs and biologics are regulated by either the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER). Candidate products must pass through a long and expensive gauntlet to reach the market involving several thousand patients, 6–12 years of testing and review, and a cost ranging from $500 million to $1.5 billion. In contrast, medical devices are regulated by the Center for Devices and Radiological Health (CDRH). The regulatory burden for devices is much lower: class-three medical devices typically require 1–3 years for approval at a cost of $25–100 million, with patient study populations numbering in the hundreds. Generally speaking, tissue-engineered products are combination products and follow the device approval pathway at CDRH if they function by mechanical means (e.g., skin, bone, and cartilage), and follow the drug approval pathway at CDER or CBER if their ultimate mechanism of action is biochemical (artificial pancreas, artificial liver, etc.). Not surprisingly, to our knowledge all tissue engineering products, which have been FDA approved to date, have gone through the cheaper and simpler device pathway. Whilst the overall success rate of tissue-engineered products is comparable to that of small molecules and biologics, it is much lower than that of medical devices. As we noted in an earlier report,[6] a plausible case can be made that early on the regulatory burden of the drug approval pathway prevented worthwhile tissue engineering products from reaching the clinic. However, this analysis may mask a subtler dynamic that has played out in recent years. Early tissue engineering firms approached the FDA with a ''shock and awe'' strategy, trying to establish an environment that would facilitate approval. For its part, the agency had difficulty fitting devices into the rigid-as-haiku phase I–II–III drug approval processes. Whilst the regulations and the basic tenets of regulatory policy have not changed, the posture of both groups seems to have moderated somewhat. Companies are listening to the agency, rather than talking at them. Agency personnel are developing a comfort level with tissue engineering and regenerative medicine in part because of greater experience and in part because of advance in translational and basic science since 2002 that have contributed to the understanding of product's mechanism of action and interaction with the host's clinical sequelae. They are increasingly working with firms to design clinical trials commensurate with the resources of start-ups and early stage companies. Right now over 55 products are in various clinical trials at the agency, the majority of which are following the phase I–III pathway. Details of the trials are not made public, but from the burn rates of the companies it is apparent that the patient population and trial costs are far less than for conventional drugs. For example, Osiris has four cellular products in clinical trials and a total annual expenditure of $< \$50$ million, and the agency has granted two of its products fast-track status. Time will tell how this plays out, but the current trends are encouraging.

Firms that can operate in minimally regulated areas or with more conventional products have a significant advantage in terms of ''time to market.'' This explains the commercial prominence of cord blood banking and of acellular biomaterials. It also accounts for the proliferation of clinical trials with autologous adult stem cells, since most of these can be conducted by physician-investigators with Institutional Review Board (IRB) approval and without involvement of the FDA. Of course, more rapid market access involves a trade-off; it is more difficult to establish a long-term defensible competitive advantage in minimally regulated fields.

In the early to late 1990s, commercial tissue engineering was almost exclusively conducted in the United States. The trend toward internationalization began around 2000, and has continued ever since. Today, and as shown in Figure 3A, commercial activity in the field is about $\sim$75% U.S.-based and the remainder outside the United States. International diversification is clearly a benefit, as it provides the field with broader access to talent, markets, business models, and governments. It also allows firms to gain earlier clinical experience in environments with less expensive and more rapid regulatory approval pathways.

The overall success of the regenerative medicine is certainly mirrored in the stock markets; there is even an online index of representative publicly traded stem cell companies.[37] Forty-two start-ups listed in the appendix are exchange traded, and eight are traded over the counter. The combined market value of these firms is 4.7 billion, twice the highest level reached prior to 2002. This estimate only relates to start-ups and does not include cases where tissue engineering is a small part of larger firms, such as J&J, Medtronic, Baxter, or even Integra.

The recovery of Organogenesis is particularly informative. The firm won approval for its Apligraf Living Skin Equivalent product in 1997. In the next 5 years, sales never exceeded $20 million per year and the company never operated at a profit, since the cost of producing and selling the product exceeded its sales revenue. The firm filed for bankruptcy and essentially closed its doors in the fall of 2002. In the fall of 2003, the firm emerged from bankruptcy and since that time has grown to 260 employees, is operating at breakeven (reinvesting operating profits into future growth opportunities), has treated over 200,000 patients, and enjoys Apligraf sales of $60 million per year with a continuously upward sales trendline. It is by far the largest enterprise selling a cell-based tissue engineering product. Organogenesis has accomplished this with very same product that brought it to bankruptcy: Apligraf in 2007 is essentially the same as Apligraf in 2002. This success is informed by the skill of the new management and in the focus that the company has placed on the nontechnical side of the business: reimbursement, manufacturing cost, and customer satisfaction. Let this be a reminder that good science is necessary but not sufficient; broad-based business skills are determinants of success when companies reach the commercial stage.

Some advocate that the difficulties encountered by the industry in 2000–2002 were caused because commercial development took place without sufficient basic scientific underpinnings[38] and that more public funds should be devoted to academic research to overcome this shortcoming. Basic science and academic support are unquestionably worthwhile in their own right and provide an enormous payback to society. But the Organogenesis history and a company-by-company examination of failures during the downturn simply do not lend credence to an argument that the difficulties of 2002 had anything to do with a lack of basic science support.

Finally, it is important to recognize the limitations of this survey. Our definition and exclusion criteria, while explicit, may differ from those others would use. Some firms, albeit small ones, may have been overlooked and are not present in our database. Big pharma and other very large companies could have significant but largely undisclosed in-house activities in regenerative medicine. Smaller firms may position more pedestrian efforts as regenerative medicine to increase their appeal to investors and customers. Estimates of business activity may have been in error. Further, the field is moving rapidly; a year from now the numbers will be different. It is reassuring, however, that our totals for the size and scope of development-stage industry match well with those of Mason[19,20] of University College London, and our commercial sales tallies are close to those offered by Bonfiglio of Pacific Venture Capital.[38] Our overall estimate is lower, by far, than that of Coury of Genzyme, who argues that regenerative medicine comprises about 25% of the nonpharmaceutical medical products industry or $\sim$$50 billion[39]; this may eventually prove true but seems quite premature. Overall, this survey is best considered to be ''approximately right'' in the Warren Buffet sense that it is better to be approximately right than exactly wrong.

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APPENDIX A

Firm	*Location*	*Stage*	*Website*
3DM	Boston, MA	Preclinical	http://www.puramatrix.com
Aastrom Biosciences	Ann Arbor, MI	Clinical trials	http://www.aastrom.com
Advanced Biohealing	New York, NY	Clinical trials	http://advancedbiohealing.com
Advanced Cell Technology	Worcester, MA	Preclinical	http://www.advancedcell.com
Aegera Therapeutic	Canada	Preclinical	http://www.aegera.com
Aldagen	Durham, NC	Clinical trials	http://www.aldagen.com
Amcyte	Santa Monica, CA	Clinical trials	http://www.amcyte.com
Angioblast Systems	New York, NY	Clinical trials	http://www.angioblast.com
AntiCancer	San Diego, CA	Preclinical	http://www.anticancer.com
Arbios	Los Angeles, CA	Preclinical	http://www.arbios.com
ArBlast	Japan	Clinical trials	http://www.arblast.jp/english
Arthro Kinetics	Germany	Commercial	http://www.arthro-kinetics.com
Axordia	United Kingdom	Preclinical	http://www.axordia.com
Baxter	Deerfield, IL	Commercial	http://Baxter.com
BCS	Japan	Clinical trials	http://www.bcsinc.co.jp/en/index.htm
BetaCell	Belgium	Preclinical	http://www.beta-cell.com
BioE	St. Paul, MN	Preclinical	http://www.bioe.com
Bioengine	Boston, MA	Preclinical	http://www.bioengine.biz
Bioheart	Sunrise, FL	Clinical trials	http://www.bioheartinc.com
Biomimetic Therapeutics	Franklin, TN	Clinical trials	http://www.biomimetics.com
Bionova	Australia	Preclinical	http://www.bionova.com.au/
Biosyntech	Canada	Clinical trials	http://www.biosyntech.com.my
Biotissue Technology	Germany	Commercial	http://www.biotissue-tec.com/
BrainStorm Cell Therapuetics	Israel	Clinical trials	http://www.brainstorm-cell.com
CalbaTech	Irvine, CA	Preclinical	http://www.calbatech.com
Cardio	Japan	Preclinical	http://www.cardio.co.jp
CBR Systems	San Bruno, CA	Commercial	http://www.cordblood.com/
Cell Matrix AB	Sweden	Commercial	http://www.cellmatrix.se
Cellartis	Sweden	Preclinical	http://www.cellartis.com/
Cellerant Therapeutics	San Carlos, CA	Clinical trials	http://www.cellerant.com
CellGenix Technologie Transfer GmbH	Germany	Clinical trials	http://www.cellgenix.com
Cells for Life	Canada	Commercial	http://www.cellsforlife.com
Celltran	United Kingdom	Commercial	http://www.celltran.co.uk/
Celltrix	Sweden	Clinical trials	http://www.celltrix.se
Cellular Dynamics International	Madison, WI	Preclinical	http://www.cellular-dynamics.com
Cerco Medical LLC	San Francisco, CA	Preclinical	http://www.cercomedical.com
Co.don	Germany	Clinical trials	http://www.codon.de
Cognate	Baltimore, MD	Contract research organization	http://www.cognatebioservices.com
Cook Biotech	West Lafayette, IN	Commercial	http://www.cookbiotech.com
Cord Blood America	Los Angeles, CA	Commercial	http://www.cordblood-america.com/
Cord Blood Bank of Canada	Canada	Commercial	http://www.cordbloodbankofcanada.com
Cord Blood Registry	San Bruno, CA	Commercial	http://www.cordblood.com
Cordbank	New Zealand	Commercial	http://www.cordbank.co.nz
CordLife	Australia	Commercial	http://www.cygenics.com
Cryobanks International	Altamonte Springs, FL	Commercial	http://cryo-intl.com
CryoCell	Oldsmar, FL	Commercial	http://www.cryo-cell.com/
Cryocord	Malaysia	Commercial	http://www.cryocord.com.my/
Cryo-Save	The Netherlands	Commercial	http://www.cryo-save.com
Cytograft	Novato, CA	Clinical trials	http://www.cytograft.com
Cytomatrix LLC	Chelmsford, MA	Preclinical	http://www.cytomatrix.com
Cytonet Hannover Gmbh	Germany	Preclinical	http://www.cytonet.de
Cytori Therapeutics	San Diego, CA	Clinical trials	http://www.cytoritx.com
Educell	Slovenia	Clinical trials	http://www.educell.si
Encelle	Research Triangle, NC	Clinical trials	http://www.encelle.com/

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EndGenitor Technologies	Indianapolis, IN	Preclinical	http://www.endgenitor.com
ES Cell International	Singapore	Preclinical	http://www.escellinternational.com
Eticur	Germany	Commercial	http://www.eticur.de
Eufets AG	Germany	Contract research organization	http://www.eufets.com
Euroderm	Argentina	Clinical trials	http://www.euroderm-biotech.de
Excorp	Minneapolis, MN	Clinical trials	http://www.excorp.com/
Fidia Advanced Biopolymers	Italy	Commercial	http://www.fidiapharma.it
Future Health	United Kingdom	Commercial	http://www.futurehealth.co.uk
Gamida Cell	Israel	Clinical trials	http://www.gamida-cell.com
Genegrafts	Israel	Preclinical	http://www.genegrafts.com
Genevrier	France	Clinical (Euro)	http://www.laboratoires-genevrier.com
Genzyme	Cambridge, MA	Commercial	http://genzyme.com
Geron	Menlo Park, CA	Preclinical	http://www.geron.com
HepaLife Technologies	Boston, MA	Preclinical	http://www.hepalife.com
Histogeneics	Waltham, MA	Clinical trials	http://www.histogenics.com
Humacyte	Research Triangle, NC	Preclinical	http://www.humacyte.com
Hybrid Organ GMBH	Germany	Clinical trials	http://www.hybrid-organ.com
Imedex Biomateriaux	France	Commercial	http://www.imedex.fr
Innovacell	Austria	Clinical trials	http://www.innovacell.at
Integra	Plainsboro, NJ	Commercial	http://www.integra-ls.com
Intercytex	United Kingdom	Clinical trials	http://www.intercytex.com
Interface Biotech A/S	Denmark	Commercial	http://www.interfacebio.com/
Isolagen	Eston, PA	Clinical trials	http://www.isolageninc.com
ISTO	St. Louis, MO	Clinical trials	http://www.istotech.com
Ixion Biotechnology	Alachua, FL	Preclinical	http://www.ixion-biotech.com
Japan Tissue Engineering	Japan	Clinical trials	http://www.jpte.co.jp/english/ir/profile.html
Johnson & Johnson	New Brunswick, NJ	Commercial	http://www.jnj.com/home.htm
Karocell Tissue Engineering AB	Sweden	Commercial	http://www.karocell.com/
Kuros Biosurgery	Switzerland	Clinical trials	http://www.kuros.ch
Lazaron Biotechnologies	South Africa	Commercial	http://www.lazaron.co.za
LCT	Australia	Clinical trials	http://www.lctglobal.com
Lifecell	Branchburg, NJ	Commercial	http://www.lifecell.com
Lifeline Cord Blood Bank	Cyprus	Commercial	http://www.lifeline.com.cy
Lonza	Switzerland	Contract research organization	http://www.lonzabiologics.com
Mattek	Ashland, MA	Preclinical	http://www.mattek.com
MaxCyte	Gaithersburg, MD	Clinical trials	http://www.maxcyte.com
MedCell	United Kingdom	Commercial	http://www.vetcell.com/
Medistem Laboratories	Tempe, AZ	Preclinical	http://www.medisteminc.com
Medtronics	Minneapolis, MN	Commercial	http://www.medtronic.com/
Mesoblast	Australia	Preclinical	http://www.mesoblast.com
Microislet	La Jolla, CA	Preclinical	http://www.microislet.com/
Millenium Biologix	Canada	Clinical trials	http://www.millenium-biologix.com
Morphogenesis	Oldsmar, FL	Preclinical	http://www.morphogenesis-inc.com
MultiCell Technologies	Lincoln, RI	Preclinical	http://www.multicelltech.com
Myosix	France	Clinical trials	http://www.myosix.com
Nanomatrix	Addison, TX	Preclinical	http://www.nanomatrix.biz
National Stem Cell	New York, NY	Preclinical	http://www.nationalstemcell.com
NeoStem	Agoura Hills, CA	Clinical trials	http://www.neostem.com
Neuralstem Biopharmaceuticals	Rockville, MD	Preclinical	http://www.neuralstem.com
NeuroGeneration	Beverly Hills, CA	Clinical trials	http://www.neurogeneration.com
NeuroNova AB	Sweden	Preclinical	http://www.neuronova.com
Neuronyx	Malvern, PA	Clinical trials	http://www.neuronyx.com
Neurotech	Lincoln, RI	Clinical trials	http://www.neurotechusa.com
New England Cord Blood Bank	Newton, MA	Commercial	http://www.cordbloodbank.com
Novathera	United Kingdom	Preclinical	http://www.novathera.com/
Novocell	San Diego, CA	Preclinical	http://www.novocell.com
NsGene A/S	Denmark	Preclinical	http://www.nsgene.dk

(*continued*)

APPENDIX A (CONTINUED)

Firm	*Location*	*Stage*	*Website*
Odontis	United Kingdom	Preclinical	http://www.odontis.co.uk/
OncoMed	Mountain View, CA	Preclinical	http://www.oncomed.com
Opexa Therapeutics	The Woodlands, TX	Clinical trials	http://www.opexatherapeutics.com
Organogenesis	Canton, MA	Commercial	http://www.organogenesis.com
Ortec	New York, NY	Clinical trials	http://Ortecinternational.com
Orthovita	Malvern, PA	Commercial	http://www.orthovita.com
Osiris	Baltimore, MD	Clinical trials	http://www.osiris.com/
Pervasis	Cambridge, MA	Clinical trials	http://www.pervasistx.com
Plureon Corporation	Winston-Salem, NC	Preclinical	http://www.plureon.com
Pluristem Life Systems	Israel	Preclinical	http://www.pluristem.com
PrimeGen Biotech Corporation	Irvine, CA	Preclinical	http://www.primegenbiotech.com
Progenitor Cell Therapy	Hackensack, NJ	Contract research organization	http://www.progenitorcelltherapy.com/
Regen Biologics	Franklin Lake, NJ	Clinical trials	http://www.regenbio.com/
Regenics A/S	Norway	Preclinical	http://www.regenics.no
Regentec	United Kingdom	Preclinical	http://www.regentec.net/
Regentis Biomaterials	Israel	Preclinical	http://www.regentis.co.il
ReInnervate	United Kingdom	Preclinical	http://www.reinnervate.com
Reneuron	United Kingdom	Preclinical	http://www.reneuron.com
ReproCELL	Japan	Preclinical	http://reprocell.com/en/
RhinoCyte	Louisville, KY	Preclinical	http://www.RhinoCyte.com
Securacell	Canton, OH	Commercial	http://www.securacell.com
Serica Technologies	Medford, MA	Preclinical	http://www.sericainc.com/
SEWON Cellontech	Korea	Commercial	http://www.cellontech.com
Skinethic	France	Commercial	http://www.skinethic.com
Stelic	Japan	Preclinical	http://www.stelic.com
Stem Cell Innovations	Houston, TX	Preclinical	http://www.stemcellinnovations.com
Stem Cell Sciences	United Kingdom	Preclinical	http://www.stemcellsciences.com
Stem Cell Therapeutics Corporation	Canada	Clinical trials	http://www.stemcellthera.com
Stem Cell Therapy International	Tampa, FL	Clinical trials	http://www.scticorp.com
Stemagen	San Diego, CA	Preclinical	http://www.stemagen.com
StemCells	Palo Alto, CA	Clinical trials	http://www.stemcellsinc.com
Stemcyte	Arcadia, CA	Commercial	http://www.stemcyteinc.com
Stemlife	Malaysia	Commercial	http://www.stemlife.com/
Stemline Therapeutics	New York, NY	Clinical trials	http://www.stemline.com
Stemnion LLC	Pittsburgh, PA	Preclinical	http://www.stemnion.com
StemPath	Canada	Preclinical	http://www.stempath.com
TEI Biosciences	Boston, MA	Commercial	http://www.teibio.com/
Tengion	East Norriton, PA	Clinical trials	http://www.tengion.com/
Tepha	Cambridge, MA	Preclinical	http://www.tepha.com
Tetec	Germany	Commercial	http://www.tetec-ag.de
Theradigm	Baltimore, MD	Preclinical	http://www.theradigm.com
TheraVitae	Israel	Clinical trials	http://www.theravitae.com
Theregen	San Francisco, CA	Clinical trials	http://www.theregeninc.com
Thrombogenics	Ireland	Preclinical	http://www.thrombogenics.com
TiGenix	Belgium	Clinical trials	http://www.tigenix.com
Tissue Regeneration Therapeutics	Canada	Preclinical	http://www.verypowerfulbiology.com/
TissueGene	Gaithersburg, MD	Clinical trials	http://www.tissuegene.com
Titan (Spheramine only)	San Francisco, CA	Clinical trials	http://www.titanpharm.com
Tristem Corporation	United Kingdom	Clinical trials	http://www.tristemcorp.com
VasoTissue Technologies	Germany	Commercial	http://www.vasotissue.com
Velcura Therapeutics	Ann Arbor, MI	Clinical trials	http://www.velcura.com
Vesta Therapeutics	Durham, NC	Clinical trials	http://www.vestatherapeutics.com
VetStem	Poway, CA	Commercial	http://www.vet-stem.com
Viacell	Cambridge, MA	Commercial	http://www.viacellinc.com/
Virgin Health Bank	United Kingdom	Commercial	http://www.virginhealthbank.com

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Vistagen	San Francisco, CA	Preclinical	http://www.vistagen.com
Vita 34 AG	Germany	Commercial	http://www.vita34.de
Vital Therapies	San Diego, CA	Preclinical	http://www.vitaltherapies.com
Vitro Diagnostics	Aurora, CO	Preclinical	http://www.vitrodiag.com/
ViviCells	Evanston, IL	Commercial	http://www.vivicells.com