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Regenerative Medicine: Learning from Past Examples

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Regenerative medicine products have characteristically shown great therapeutic potential, but limited market success. Learning from the past attempts at capturing value is critical for new and emerging regenerative medicine therapies to define and evolve their business models as new therapies emerge and others mature. We propose a framework that analyzes technological developments along with alternative business models and illustrates how to use both strategically to map value capture by companies in regenerative medicine. We analyze how to balance flexibility of the supply chain and clarity in the regulatory pathway for each business model and propose the possible pathways of evolution between business models. We also drive analogies between cell-based therapies and other healthcare products such as biologicals and medical devices and suggest how to strategically evolve from these areas into the cell therapy space.

Introduction

COMPANIES IN REGENERATIVE MEDICINE have shown limited success in capturing value from innovation; in 2007, the market was estimated at \$1.2B,¹ but only two companies out of more than a dozen with approved regenerative medicine products were profitable. The struggle is, in part, rooted in the challenges associated with developing a business model that maximizes the commercial impact of a cell-based therapy.

The business model for a new technology needs to clearly address not just technology, but also supply chain and regulation. In the commercialization of cell-based therapies, limitations and decision making around the therapy have a direct impact on the structure of the supply chain and regulatory approval. Business models for cell-based therapies should be designed to evolve substantially with the therapy as technological limitations are overcome, and new supply chain strategies are enabled. In this article, we summarize lessons learned from past examples of regenerative medicine with stem cells and not scaffolds only and propose a framework that understands business strategies and investment opportunities in this space.

The evolution of Organogenesis and Advanced Tissue Sciences illustrates the challenges associated with developing a business strategy in regenerative medicine that our work seeks to address. Organogenesis (www.organogenesis.com) was founded in 1981, received approval from the FDA to commercialize Apligraf[®] in 1997, and filed for bankruptcy in 2002 with \$20M revenue.² According to Geoff MacKay, Organogenesis' CEO, the company came back from bankruptcy in 2003 with essentially the skin substitute, but a re-

newed business strategy, and became the first company with a cell-based therapy to achieve profitability.² The development of specialized manufacturing, distribution, and commercialization capabilities for Apligraf (previously outsourced to pharmaceutical companies) was critical to Organogenesis's recovery (www.organogenesis.com, A conversation with Geoff MacKay). New skin substitutes from multiple cell sources are currently being developed.³

In 1999, the Food and Drug Administration (FDA) approved another wound healing therapy, Dermagraft[®] by Advanced Tissue Sciences. Similar to Organogenesis, this company also went bankrupt. Dermagraft was bought and commercialized by Smith & Nephew until October 2005, when the company shut down its Dermagraft's operations, after the FDA refused to certify the treatment (www.telegraph.co.uk, Smith & Nephew ditches Dermagraft). In May 2006, Advanced Biohealing bought Dermagraft's global rights and initiated, in 2009, a pivotal safety/efficacy clinical trial for treating patients with venous leg ulcers. After trial completion, in August 2011, the company decided not to pursue this indication. Advanced Biohealing with a specialized sales and marketing team reported \$130 Million in revenue in 2010, with a growing demand for their leading product, Dermagraft, and demonstrated cost effectiveness (www.abh.com, in Press Release). In June 2011, Shire Pharmaceuticals acquired Advanced Biohealing, which became its business unit of regenerative medicine, and Dermagraft is now marketed by Shire (www.abh.com/investor-relations/).

Regenerative medicine business models have previously been described by cell source and cell type.¹ In this work, we present a new categorization that integrates technology, business model, supply chain, and regulation. Our categorization

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TABLE 1. COMPANIES IN REGENERATIVE MEDICINE THAT HAVE PRODUCTS IN CLINICAL TRIALS OR IN THE MARKET

	Cell Modifiers	Donor	Host	On-Site
Skeletal & muscular system	Medtronic , <i>Depuy Spine Therapeutics</i> , <i>TaiGen</i>	<i>Osiris Therapeutics</i> , <i>Mesoblast</i> , Zimmer Holdings and ISTO Technologies^a , <i>RTI biologics</i> , <i>Teva Pharmaceuticals^b</i> , <i>Medipost</i> , <i>Nuvasive</i> , <i>Orthofix</i> , <i>Mesoblast</i>	Genzyme Biosurgery , Arthro Kinetics^c , <i>Histogenics</i> , <i>ProChon Biotech</i> , <i>TiGenix NV</i> , <i>Arblast</i>	Depuy Mitek, CellCoTec, CellGenix^d
Cardiovascular	OrbusNeich , <i>Stem Cell Therapeutics</i> , <i>TaiGen Biotechnology</i>	<i>Pervasis</i> , <i>Athersys</i> , <i>Angioblast Systems</i> , <i>Stempeutics Research</i> , <i>Osiris Therapeutics</i> , <i>Reneuron</i>	<i>Cytograft Tissue Engineering</i> , <i>MG Biotherapeutics^e</i> , <i>Aldagen</i> , <i>Arterioocyte^b</i> , <i>Cardio3 BioSciences</i> , <i>TheraVita</i> , <i>Asklepios Proresearch</i> , <i>Baxter Healthcare Corporation</i> , <i>BioHeart</i> , <i>Cytforti Therapeutics</i> , <i>Harvest Technologies</i> , <i>Medtronic</i> , <i>Miltenyi TCA Cellular Therapy</i> , <i>EMMES</i>	
Oncology and Immunology	<i>Biokine Therapeutics</i> , <i>BiIncept</i> , <i>TaiGen Biotechnology</i>	<i>Osiris Therapeutics</i> , <i>Quintiles^b</i> , <i>Athersys</i> , <i>Pfizer^b</i> , <i>Fate Therapeutics</i> , <i>Innovative Therapies</i> , <i>Kiadis Pharma</i> , <i>Medipost</i> , <i>Miltenyi Biotech</i> , <i>MolMed</i> , <i>Shenzhen Zhongxing Yangfan Biotech</i> , <i>Aldagen</i> , <i>Amgen^b</i> , <i>Celgene</i>	Dendreon , <i>Sangamo Biosciences</i> , <i>Anterogen</i> , <i>ViroMed</i>	
Central Nervous System	<i>BrainCells</i> , <i>Sangamo Biosciences</i>	<i>StemCells</i> , <i>Geron</i>	<i>TCA cellular Therapy</i>	
Diabetes	<i>Transition Therapeutics</i> , <i>Sangamo Biosciences</i>	<i>Osiris Therapeutics</i> , <i>Novocell^f</i>	<i>Genzyme</i> , <i>Adistem</i> , <i>Stematix</i> ,	
Ophthalmology	Genentech , Pfizer , OSI Pharmaceuticals , <i>Jerini Ophthalmic</i> , <i>Ophthotech Corporation</i>	<i>Advanced Cell Technology</i>		
Genitourinary, Gastrointestinal, Wound repair & other		Organogenesis , Advanced Biohealing , <i>Allocure</i> , <i>Pfizer</i> , <i>Osiris Therapeutics</i> , <i>Athersys</i> , <i>Cellerix</i>	<i>Tengion</i> , <i>Anterogen</i> , <i>Miltenyi Biotec</i> , <i>Beike Biotech India</i> , <i>Cellerix</i> , <i>Cytforti therapeutics</i>	

^aZimmer Holdings and ISTO Technologies only market DeNovo[®] ET Engineering Tissue in Europe.

^bTeva Pharmaceuticals Industries, Arterioocyte, Quintiles, Pfizer, Amgen, are collaborators in the respective clinical trial.

^cArthro Kinetics commercializes CaReS in China, Taiwan, and Hong Kong.

^dCellGenix developed and Styker commercializes CartiGro[®] ACT plus Chrondro-Gide[®] in Austria and Germany.

^eMG Biotherapeutics is a joint venture of Medtronic and Genzyme.

^fNovocell has developed a PEG-encapsulated islet allograft regulated as a combination biologic and device product.

Company names in bold, companies with products in the market; Company names in italic, companies with products in clinical trials.

maps the state of the art in regenerative medicine according to the type of therapy and clinical indication, in addition to cell source and cell type. To develop this categorization, we analyzed more than 200 cell-based therapies at the preclinical and clinical stage and as marketed products, sorted by clinical application, cell type, and cell source. Throughout this article, we draw examples from this list to illustrate the advantages of the categorization we propose and identify the business models used to deliver these therapies into the market. We conclude our analysis with a framework that draws analogies between cell-based therapies and other healthcare products such as biologicals and medical devices.

Methodology

We listed and analyzed 175 companies with cell-based therapies at the preclinical and clinical stage of development and as marketer products. This analysis resulted in more than 200 cell-based therapies. These companies are sorted by clinical application and business model. The business model is classified according to the cell type and cell source. We collected data from four types of sources, information on clinical trials, new in the database Factiva.com, financial reports and papers, and companies' Websites.

We retrieved detailed information on clinical trials from the clinicaltrials.gov Website that contained the term "stem cells". Note that this database recognizes the following terms as synonyms of stem cells: blood cell precursor, hematopoietic progenitor cells, precursor cell, and progenitor cell. We focus on clinical trials that were sponsored by the industry and were last updated from January 1, 2005 to July 1, 2010, which generated 545 clinical trials.

We listed companies in clinical and market stages in Table 1. For companies having multiple cell-based therapies in the same clinical application, we considered the most advanced product in development, for simplicity.

Results

The purpose of regenerative medicine is to develop new therapies to repair, regenerate, or enhance tissue function.⁴ Current regenerative therapies involve stem cells or cell modifiers. Cell therapy source can be either autologous or allogeneic; and these are further classified according to the potential of cell differentiation—pluripotent or multipotent. We have considered four categories of cell-based therapies based on the categorization proposed by McKernan *et al.*⁵ Table 2

summarizes the types of cell-based therapies. Each imposes different constraints on the business model. We have considered four categories of business models: cell modifiers, donor, host, and on-site (shown in Fig. 1). We begin with a description of the four categories of cell-based therapies highlighting examples of the advantages and limitations of each. This is followed by linking them to different business models.

Host's cell modifiers are small molecules or biologicals that once administered to the patient will have an active role in the molecular control of stem cell self-renewal and differentiation *in vivo*. Host's cell modifiers are attractive, because they are regulated and supplied as biologicals; regulatory guidelines are well established, and there is no need to ensure sample safety and integrity throughout the supply chain. Some of the advantages of the host's cell modifiers therapy are as follows: scalable cost structure, high manufacturing scale-up capacity, and high commercial viability. These advantages are illustrated by Medtronic's INFUSE[®] Bone Graft (marketed as InductOs in Europe) for accelerating bone healing. INFUSE consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) embedded in an absorbable collagen sponge (www.accessdata.fda.gov, P050053). The rhBMP-2 affects the osteogenesis process by inducing stem cell differentiation into osteoblasts.⁶ This process accelerates bone healing. Since 2002, INFUSE was approved by the FDA to be administered in lumbar spinal fusion procedures (P000058), in bone fractures (P000054), and in dental restoration (P050053). INFUSE generated approximately \$840M in revenue in 2009 and in 2010 (www.medtronic.com, 2009 and 2010 Annual Report, respectively) Medtronic created a simple, high-revenue, and convenient solution when compared with the standard procedures at the time. INFUSE costs \$5,000 to \$8,400 per unit (www.healthpointcapital.com, INFUSE Add-On Payment Extended 1 Year by CMS), and has a shelf life of 2 years; rhBMP-2 is produced on a large scale, and is a ready-to-apply therapy. This example highlights some of the advantages of the host's cell modifiers therapy: scalable cost structure, high manufacturing scale-up capacity, and high commercial viability.

In allogeneic cell therapy, the patient receives a therapy based on the cells collected from a donor, which are ready to apply whenever required. In this case, establishing safety complicates the regulatory pathway, and sample safety and integrity has to be monitored throughout the supply chain. Nevertheless, allogeneic cell therapies enable economies of

TABLE 2. CLASSIFICATION OF CELL-BASED THERAPIES IN REGENERATIVE MEDICINE SORTED BY CELL TYPE AND SOURCE AND CATEGORIZED BY THE KEY REGULATORY, MANUFACTURING, AND BUSINESS CHALLENGES

	<i>Host's cell modifiers</i> 	<i>Allogeneic</i> 	<i>Autologous</i> 	<i>Pluripotent</i> 
<i>Cell Therapy</i>				
Differentiation potential	✓✓	✓✓	✓✓	✓✓✓
Established guidance by the FDA	✓✓✓	✓✓	✓✓✓	✓
Ready to apply	✓✓✓	✓✓✓	✓	✓✓✓
Manufacturing scale-up or scale-out	✓✓✓	✓✓	✓	✓✓
Supply chain integrity and safety	✓✓✓	✓✓	✓	✓✓
Scalable cost structure	✓✓	✓✓✓	✓	✓✓✓
Commercial viability	✓✓✓	✓✓✓	✓	?

✓✓✓ - high; ✓✓ - moderate; ✓ - low; ? - undetermined.

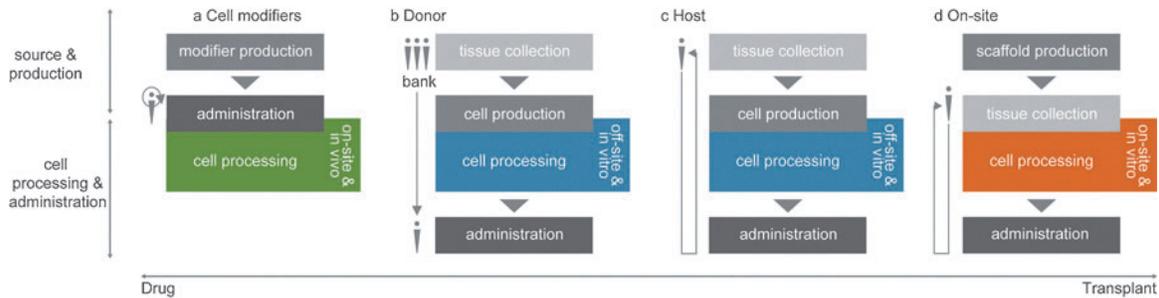


FIG. 1. Successful business models in regenerative medicine. **(a)** Cell modifiers are produced and transported to the healthcare facility, and are ready for on-site administration whenever required. After its administration to the patient, cell self-renewal and differentiation will occur *in vivo* inside the patient. **(b)** In the donor business model, the sample is collected from a donor and typically stored in a tissue or cell bank. The sample is then transported to the manufacturing facility for cell processing (off-site). The processed cells are then stored and transported to the healthcare facility to be administered to the recipient. **(c)** The host business model follows the same path as the donor, but the patient is both the source and the recipient, which eliminates the need for the tissue bank. **(d)** In the on-site business model, the patient is both the source and the recipient, but the sample is applied into a scaffold in the healthcare facility (on-site), and the resultant cell-based therapy is ready to be administered to the patient. Color images available online at www.liebertpub.com/tea

scale through cell expansion, portability across multiple therapies, and storage facilities.⁷ Prochymal[®] from Osiris Therapeutics illustrates these benefits. Osiris created a single technology for multiple applications.

In autologous cell therapy, the patient is both the source and the recipient of the therapy, which limits response time for the patient. The key advantage of autologous cell therapy is the absence of rejection risk. An example is Genzyme's Carticel[®] for cartilage repair. This is a personalized solution that presents key limitations: (1) cost structure scalability; (2) high product cost, as Carticel costs about \$26,000 per procedure;⁸ and (3) manufacturing scale-out. Cost structure and manufacturing limit the long-term viability of autologous cell therapies.

Pluripotent stem cell therapy could be allogeneic or autologous depending on the cell source, but it differs from autologous and allogeneic cell therapy with regard to the higher potential of cell differentiation. However, differentiation challenges and the unknown behavior of these cells when administered to patients increase safety concerns.^{9,10} Regulatory concerns for embryonic stem cells and induced Pluripotent Stem (iPS) cells are very different. Safety issues prompted the FDA to place on hold the first human clinical trial of embryonic stem cell therapy.^{11,12} It received initial clearance in January 2009,¹³ but was effectively started in October 2010 for the treatment of spinal cord injury.¹⁴ This trial was prematurely halted in November 2011 for economical reasons, as pointed out by John A. Scarlett, Geron's CEO. During this period, four patients were treated, and there were neither signs of efficacy nor safety problems (www.geron.com, Investor Relations—Press Release, "Geron Presents Clinical Data Update from GRNOPC1 Spinal Cord Injury Trial," 20 October 2011). According to the *New York Times*, Dr. Scarlett referred that Geron needed to conserve resources at a time when it was extremely difficult for small and nonprofit Biotech companies to raise capital (www.nytimes.com, Geron Is Shutting Down Its Stem Cell Clinical Trial).

Advanced Cell Technologies is the only company that is conducting clinical trials involving human embryonic stem cell-derived retinal pigment epithelium cells (www.clinical

trials.gov, NCT01344993 and NCT01345006) for the treatment of two different forms of macular degeneration. Results were reported for two patients, showing no adverse safety issues, structural evidence that the cells persisted, and improvements in vision for more than 4 months.¹⁵

Besides embryonic stem cells, iPS holds great potential in treating unmet clinical needs with high commercial viability.^{16,17} They have not yet progressed to clinical stages. Animal testing has shown, however, evidence that precursor iPS-derived cells can differentiate into functional adult cells.^{18–20} An example are neural precursor cells derived from iPS cells that can migrate into various brain regions and differentiate into functional glia and neurons on transplantation into the fetal mouse brain.¹⁹

Discussion

In an early technology market such as regenerative medicine, success depends on co-evolving business models and technology. Here, we define success by broadly referring to the ability of companies to reach the market or an exit point (such as being acquired or initial public offer), providing satisfactory return on investment to their shareholders. Our research suggests that given the technological limitations and the business model typically associated with each cell therapy, it is desirable to assess the evolution of the technology strategically to accomplish a sustained economic impact. We identify four business models in cell-based therapies and indicate the possible evolution pathways between them. We also relate business models for cell-based therapies to characteristic business models in healthcare. Figure 1 illustrates four business models in regenerative medicine, emphasizing their similarities, as they emerge from our research.

Companies developing cell modifiers (Fig. 1a) and biotechnology companies that develop biologicals face similar challenges with regard to manufacturing, regulatory approval, and ensuring quality of supply. Therefore, companies developing cell modifiers and biotechnology companies may adopt similar business models. Cell modifiers are manufactured as biologicals, transported to the healthcare facility (not distributed through pharmacies such as many

biologicals), stored at the healthcare facility, and administered to patients as required. Once cell modifiers are administered to the patient, they will act at the cell signaling level and control stem cell growth and differentiation.^{21–23} This process occurs on-site and *in vivo*.

Companies developing allogeneic and pluripotent cell therapies typically adopt a donor business model (Fig. 1b). Donor business models can utilize intermediate storage facilities to decrease waiting time for the patient. The cell-based therapy requires a single procedure on the patient and is ready to apply. Cell processing occurs *in vitro* at the facilities of the company before or after storage. The supply chain and quality and safety standards for donor solutions are similar (modulo storage) to those of transplants or blood.^{24, 25}

Companies that commercialize autologous cell therapies typically adopt the host business model (Fig. 1c). A host business model requires two procedures on the patient, and the patient has to wait anywhere from 3 days to 3 weeks between the two procedures for the full cell processing cycle. Cell processing should occur in a timely manner, *in vitro*, at the facilities of the company.²⁶ The sample collected from the patient should get to that same patient in perfect conditions in order to be administered. Managing the full cell processing cycle and ensuring sample integrity and safety throughout the supply chain is a key challenge in host business models.

As indicated, Figure 1 host and donor-based business models are similar, but have a different impact on the patient. Readiness to apply makes cell modifiers and donor business models attractive, because they can be administered to the patient whenever required by the physician, in a single procedure, without a waiting period of days or weeks. The host business model may, at first, simplify the path to the market for a cell-based therapy, but imposes an extra burden on the patient that may limit its commercial viability in the long term. Moreover, ensuring sample integrity and safety throughout the supply chain is an additional burden in host business models than it is in donor business models.

New on-site solutions (Fig. 1d) have the potential to increase the commercial viability of host solutions as they trade-off transportation logistics for specialized on-site procedures and equipment. Products following this business model are currently used in clinical trials. The patient continues to be both the source and the recipient, but collection and therapy administration may now be a part of the same procedure.²⁷ The tissue sample is collected from the patient, applied into a scaffold on-site, and the scaffold-cell combination is administered back to the patient. Cell processing occurs on-site at the healthcare facility. Companies following the on-site business model and medical device companies face virtually identical manufacturing, monitoring of sample integrity and safety throughout the supply chain, and distribution challenges. Regulation of on-site solutions is expected to follow the pattern of combination products in which the device is considered the primary mode of action.

The host business model may help demonstrate the clinical proof of concept for the technology, but evolution to either on-site or donor business models may increase commercial viability. In Figure 2, we illustrate the evolution pathways for the host business model. This evolution can only be enabled by an evolution of the cell-based therapy

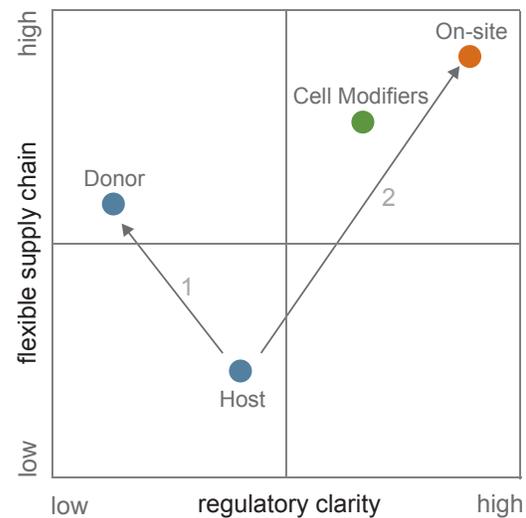


FIG. 2. Business models in cell-based therapies and possible pathways of evolution. The balance between the flexible supply chain and regulatory clarity translates the limitations that the therapy imposes in each business model. A flexible supply chain indicates how adjustable a supply chain is in ensuring sample safety and integrity. Regulatory clarity relates to realize in advance a regulatory path and requirements for approval. Companies developing the host business model present lower commercial viability by combining low regulatory clarity and low flexibility in supply chain management. These companies may evolve to either on-site or donor business models in order to increase their commercial viability. Color images available online at www.liebertpub.com/tea

itself. The particulars of the science that supports each therapy can inform the strategy for the evolution of the business model. Specifically, the ease of development of a device and the procedure for on-site processing of a patient's sample are key to the evolution in an on-site business model. Similarly, the extent to which the therapy applies to autologous and allogeneic cells and the extent to which the processing of donor samples can help manage the risk of rejection by the patient are key to the evolution in a donor business model.

We have identified five basic strategies that have helped companies commercializing cell-based therapies capture value in regenerative medicine. Figure 3 highlights each strategy and how companies can address technological and business challenges to build competitive advantage.

Orphan designation

Companies targeting *orphan diseases* trade potential market breadth to expedite regulatory approval, higher reimbursement, and prolonged market exclusivity.^{28–30} The orphan product strategy focuses resources to accelerate clinical *proof of concept* on a narrowly defined disease, and helps develop expertise in the commercialization of a cell-based therapy to a manageable population. Companies may leverage the expertise of commercializing a therapy for small populations to then expand to broader markets. The orphan product strategy is well aligned with the lower technical barriers typical of a host business model. The restricted nature of the market and the compelling value proposition for an orphan therapy can offset the logistic challenges of a host business model and

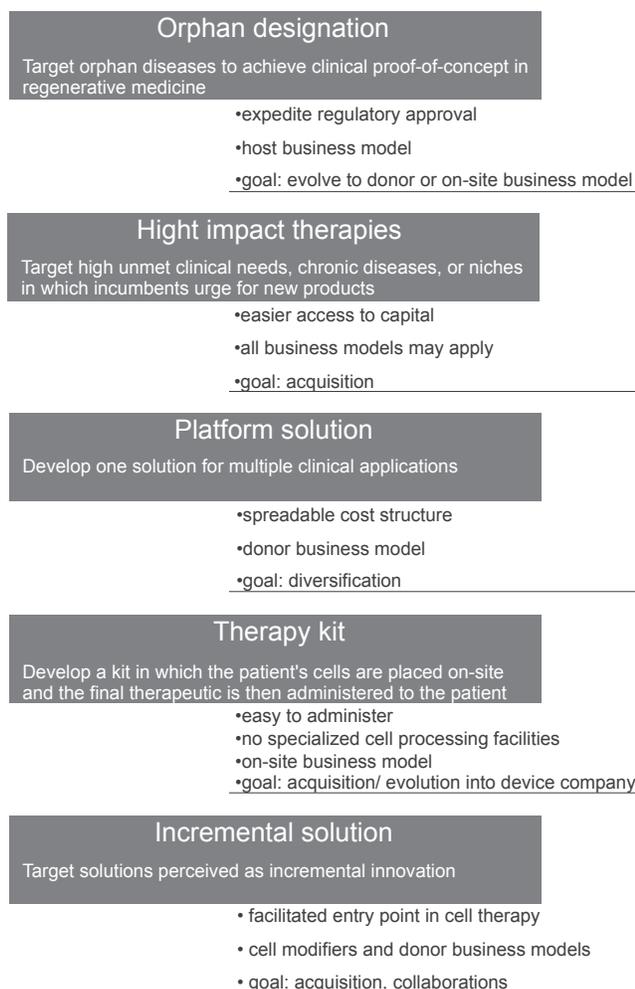


FIG. 3. Strategies to capture value in regenerative medicine. The right column enumerates competitive advantages and strategic goals.

enable rapid access to the market. As they expand to broader markets, however, companies that started with a host business model to serve an orphan disease may consider evolving the technology to enable a donor or on-site approach. An example of a company that is targeting *orphan diseases* with a host business model is Tengion. It received Orphan Medicinal Product designation from the European Medicine Agency in 2008 for Neo-Bladder Augment™, to treat children with neurogenic bladder associated with spinal cord injury and from the FDA in FDA for its Neo-Urinary Conduit for the treatment of bladder dysfunction requiring incontinent urinary diversion in June 2011 (www.tengion.com, in Press Release). Tengion's development provides key lessons for the field; business viability of autologous business models presents serious scale-up limitations that should be considered, even when addressing an orphan designation. Tengion has spent substantial financial resources in advancing these constructs to the patients since its incorporation in July 2003; and in April 2011, decided to redefine its strategy and in June 2011, restructure the management team (www.tengion.com, in Press Release). Tengion has an accumulated deficit of \$230.2 Million since its incorporation through the end of 2011, with \$117.9 Million spent on re-

search and development (www.tengion.com, in 10-k File of 2011). The company decided to restructure their pipeline in an attempt to increase their business viability. Tengion is no longer actively developing their neo-bladder augment (Phase II trials, www.clinicaltrials.com, NCT00419120 and NCT00512148); instead, they are focusing their resources on the Neo-Urinary Conduit (NCT01087697) and Neo-Kidney Augment (submitted IND filing with FDA). This strategic redefinition was due to poor clinical outcomes, namely the observation of serious adverse events and limited efficacy.

High impact therapies

Regenerative medicine companies that target unmet clinical needs, chronic diseases, and clinical applications in which big companies urge for new products are likely to have more success in attracting financing.^{5,31} This strategy is common for startups that develop early collaborations with large corporations and seek to be acquired during the clinical-trial stage. This strategy is not particularly aligned with any of the cell-therapy business models we have enumerated. Rather, the choice of a business model is a function of the terms of the collaboration, the indication, and the therapy. An example of high unmet clinical need is macular eye disease, in which the use of stem cells may treat blindness.³² In 2006, Pfizer's *Mucugen* lost significant market share to Genentech's *Lucentis*. Pfizer reacted by investing in the early-stage development of biologicals for macular eye disease. Pfizer invested \$3 million in EyeCyte in 2008 and in collaboration and licensing deals in cell-based therapies with the University College London in 2009 (www.pfizer.com, in Press Release). EyeCyte is in pre-clinical studies using both autologous and embryonic cell therapy to treat inherited retinal diseases.

Platform solution

If the cell-based therapy is applicable to multiple diseases, there is an opportunity to develop a platform solution and spread cost structure over multiple indications. This strategy is well aligned with donor business models with a storage facility. The platform solution is particularly interesting, because it builds on an advantage of cell-based therapies⁵: control over the cell differentiation process to produce different cell lines helps address multiple clinical needs. Osiris Therapeutics is an example of a company that made the strategic decision of pursuing multiple clinical applications using the same cell-based therapy. Osiris has been testing mesenchymal stem cells in five different clinical applications (www.osiris.com, in Press Release). The phase III trial for the treatment of patients with Graft-versus-Host disease did not show evidence of efficacy for adults. Though the Osiris business strategy seemed very compelling and had attracted interest and relevant investment through major collaborations, such as Genzyme's \$1.4 Billion investment, it will be difficult for the company to raise up, restructure, and raise a new round of financing (www.osiris.com, in Press Release, and in 10-k File of 2009). Genzyme's deal has been terminated, and today, Osiris is in a fragile position to continue clinical developed.

Therapy kit

If manufacturing of the cell-based therapy, specifically, cell processing, does not require specialized manufacturing

facilities, but can be done combining a device and cells in a timely protocol²⁷, there is an opportunity to develop a kit. Kits are stored at the healthcare facility and used as a part of the procedure, very much similar to certain drug-delivery devices and patches that are routinely used in surgery. The role materials in differentiating and processing stem cells bring with them a wealth of opportunities for future therapies.^{33–36} This strategy is well aligned with on-site solutions that may have evolved from a host business. The on-site business model simplifies processing and procedures, is scalable, and has the potential to significantly reduce costs. An example of an on-site business model is the Cartilage Autograft Implantation System, by Johnson & Johnson's Advanced Technologies and Regenerative Medicine, LLC, currently in phase III clinical trials (www.clinicaltrials.com, NCT00881023). It requires surgery, in which the cartilage is collected and fixed in a resorbable implant and the resultant combination of implant and cells is implanted into the patient. Cell expansion and self-renewal that would have been an integral part of the cell processing at the manufacturing facility now occur naturally inside the body of the patient.³⁷ Another example is small intestine submucosa, which provides a restorable scaffold to reinforce weakened or damaged soft tissue repair, such as rotator cuff, biceps, and other tendons. The FDA has approved more than 10 different 510(k) devices formed by small intestine submucosa, such as Restore[®] Orthobiologic Soft Tissue Implant by Depuy (www.fda.gov, Orthopaedic and Rehabilitation Devices Panel, UCM205217).

Incremental solution

Companies developing solutions perceived as incremental innovations have two advantages: decreased uncertainty in both the regulatory process and market introduction, which facilitate entry in the regenerative space. By incremental innovation we mean a solution that sustains the rate of technological improvement, and offers customers a better therapy with regard to attributes they already value.³⁸ Specific benefits of incremental cell-based therapies are as follows: (1) the regulatory route is already paved; (2) physicians are familiar with the product administration; and (3) the distribution channels are established for similar products. This strategy is particularly suited for cell modifiers business models and companies that intend to market and distribute their first products in regenerative medicine. Genous Bio-Engineering Stent[™] by OrbusNeich is an example of an incremental innovation that treats coronary artery disease. It has a coating that captures endothelial progenitor cells to repair damaged blood vessels (www.clinicaltrials.com, NCT00732953). Genous is an example of a product at the frontier between regenerative medicine and medical devices. Genous may be considered a drug-eluting stent, that is, a device. The biological released by the stent, however, is a new cell-based therapy, with proven clinical results (www.orbusneich.com), which in isolation may be considered a host-cell modifier.

In this work, we structure the analysis of the interdependence between business model and technology in cell-based therapies. Our analysis showed that companies which have successfully developed a cell-based therapy had a sophisticated approach to technology, business model, supply chain,

and regulatory approval; and that the technology choices made in the development and evolution of a cell-based therapy enable different aspects of the business model. For companies that seek to develop or acquire cell-based therapies, we recommend them to look beyond the current state of the technology to identify the evolution that is required to reach the desired business model.

New companies can steer the choice of therapy to decrease time to market and mitigate development and commercialization risk by concentrating on the following four aspects: business model, facilitated market entry, regulatory clarity, and identification of a reimbursement policy. Developing a therapy for an unmet clinical need facilitates entry and identification of the reimbursement policy. Similarly, the existence of comparable therapeutics or an orphan designation can expedite regulatory approval. On the other hand, the choice of a business model is strongly influenced by the choice of therapy and can alter the nature of risk. For instance, a host business model translates most commercialization uncertainties into supply chain management, and may result in a shorter time to market.

Companies already developing a cell-based therapy may drive the evolution of their technologies to add value to their products and indirectly determine which incumbents (biotechnology or medical devices companies) are in a better position for an acquisition or a partnership. For instance, companies evolving from the host to donor business model reduce supply chain complexity; those that evolve to the on-site business model reduce supply chain complexity and gain similarity with medical device companies.

Incumbents and new companies can follow an incremental strategy of entry into cell-based therapies by adopting cell modifiers and on-site business models. These are at the boundary between cell-based therapies and other therapeutics. They share the mechanism of action with cell-based therapies and regulatory and supply chain management considerations with either biologicals or medical devices. By including them as cell-based therapies, we were able to identify the pathways of evolution for cell-based therapies as a function of how the end goal relates to other therapeutics. Incumbents may enter this space through the "boundary" business models (cell modifiers and on-site) and as they develop their expertise in cell-based therapies, progress toward host and donor models as pertinent to developing new therapies. Companies that are already pursuing host and donor models have extensive know-how that supports the expansion of incumbents, through acquisitions or partnerships, into the core of the cell therapy space.

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Disclosure Statement

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