Evolution of regenerative medicine business models

Original Research

Evolution of Business Models in Regenerative Medicine: Effects of a Disruptive Innovation on the Innovation Ecosystem

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ABSTRACT

Purpose: This article focuses on 10 case studies of companies/organizations that are part of the current innovation ecosystem of regenerative medicine (RM) in the United Kingdom. It analyzes the actors, linkages, and influences that will determine the future shape of the RM industry sector and its capacity to live up to its initial expectations.

Methods: Using the case study approach, purposive sampling was used to get 18 interview respondents from 10 RM companies/organizations in the United Kingdom. We used semistructured interviews for data gathering and thematic analysis for identifying gaps in the RM value chain (ie, the range of activities required for bringing a product from conception to market and end-use) and the influences of the innovation ecosystem on the evolving RM business models.

Findings: RM promises to address currently unmet health care needs by restoring the normal form and function of cells, tissues, and organs. The innovations emerging to support the progress of RM to satisfy these important health care markets will disrupt the business models of incumbent industry sectors, particularly pharmaceuticals. Companies involved in this area must develop innovative business models and value chains and negotiate the complex influences of the innovation ecosystem, including regulatory systems and standards, financial support systems, and new market dynamics.

Implications: This article highlights the needs for more systemic analyses of the needs of potentially disruptive innovations, in RM and more widely, and for policymakers to give greater attention to these insights in planning regulatory and other supporting initiatives, with the promotion of innovation in mind. (*Clin Ther.* 2018;40:1084–1094)

Key words: business models, regenerative medicine, United Kingdom, disruptive innovation, innovation ecosystems.

INTRODUCTION

Regenerative medicine (RM) is a disruptive innovation set to change therapy for intractable medical conditions. It departs from conventional therapy because of its claim to cure rather than merely treat chronic conditions; and the necessity for new forms of clinical delivery collaborations between therapy manufacturers and surgeons. However, there are concerns that the translation of disruptive RM innovations may be slow or fail to materialize.[1] Gardner et al[1] suggested, "RM products and procedures will have to work very hard to find or create an adoption space if translation into clinic is to be successful." Our article builds on the discussion by Gardner et al[1] of translational challenges in the context of clinical trials; regulatory norms; manufacturing, scale-up, and logistics; reimbursement and commissioning; and clinical adoption. However, we focus on RM business models; gaps in the RM value chain (ie, the range of activities required for bringing a product from conception to market and end-use); and challenges, from the innovation ecosystem, facing the emerging RM business models, in the context of the United Kingdom.

There are 2 important RM therapy categories: (1) *autologous*, in which a patient's own cells are

Accepted for publication June 4, 2018.
https://doi.org/10.1016/j.clinthera.2018.06.003
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harvested; manipulated in a laboratory, factory, or clinical setting; and reintroduced into the same patient; and (2) *allogeneic,* in which different patients receive cells manufactured in a central facility, from a single donor.[2,3] The choice of autologous or allogeneic therapy is determined by disease area, the availability of therapy, or regulatory pressure on developers.[4] We argue that accelerating the clinical adoption of RM will depend on an innovation ecosystem that facilitates faster integration of RM and allied business models to form viable value chains,[3] aided by proportionate and adaptive governance systems.[5] Regarding value chain gaps and innovation ecosystem challenges facing RM business models, we accept Faulkner's[6] assertion that RM is a site for "opposing forces for gatekeeping and innovation." The key to resolving these opposing forces, in keeping with the EU's innovation principle,[7] is to develop regulatory systems that are more proportionate and adaptive to the needs of new technologies than are those currently in operation, involving more creative use of standards and guidelines.[8] Downstream, innovation ecosystem challenges need to be resolved, in particular the adoption of RM therapies by clinical practice, as exemplified by the UK government's effort to establish advanced-therapy clinical centers and reimbursement. Mahalatchimy[9] discussed 2 routes of reimbursement: (1) health technology assessment, for larger-scale disease populations; and (2) highly specialized technology evaluation, for rare diseases (which is more appropriate for many RM therapies).

In this article, we discuss the value chain gaps and innovation ecosystem challenges facing the evolving RM business models in the United Kingdom. The analysis has 3 categories: (1) nonintegrated value chains; (2) technology and delivery models gap; and (3) disproportionate and nonadaptive governance systems. The discussion of each category contains illustrative examples: for nonintegrated value chain, manufacturing gap, clinical adoption gap, and translational services gap; for technology and delivery models gap, different dynamics for autologous and allogeneic therapies, RM logistics issues, and national regulatory and reimbursement systems; and for disproportionate and nonadaptive governance systems, first-mover disadvantages of regulatory learning and costs, and limited patient numbers for clinical trials in small indication.

In the rest of the article, business models, innovation ecosystems, and the framework used by STRATIS (Strategic Planning of Advanced Technological Innovation Systems) framework are briefly discussed; and findings, a discussion, and conclusions are presented.

Materials and Methods

Using the case study approach, purposive sampling was used to get 18 interview respondents from 10 RM companies/organizations in the United Kingdom. We used semistructured interviews for data gathering and thematic analysis for identifying value chain gaps and the influence of the innovation ecosystem on the evolving RM business models.

RESULTS

Regenerative Medicine Business Models and Value Chains

Business models are frameworks of understanding the logic of an enterprise, that is, how it creates and appropriates value from its unique product(s) and service(s) offering(s). A business model describes, "for a sector or subsector, how firms operating within it can create, capture and deliver value. It acts as a guide to incumbent and future businesses aiming to increase the amount of value they can create or capture, often through the adoption of innovative technology."[8] In this article, we use the 6 RM business models (Figure 1) identified by Banda et al (personal communication, [2018]), defined as follows:

- **Materials and service provision business model.** These firms or organizations supply raw materials, reagents, machinery, and other equipment and quality-assurance services to RM firms/organizations. They derive value from offering services and products for RM activities spanning preclinical, efficacy, and tolerability testing.
- **Early exit Phase I/II business model.** These firms or organizations focus on the early stages of development of RM therapy. They capture intellectual property after developing innovative products, processes, and platform technologies. They appropriate value by progressing therapies to proof-of-concept or Phase I/II clinical trials or trials demonstrating efficacy and tolerability, and exit the RM value chain by selling off intellectual property or technology to more resourced firms, for example "big pharma."
- **Manufacturing and scale-up business model.** These firms or organizations specialize in investing in current Good Manufacturing Practice (cGMP)-compliant plants and contract manufacture therapies for other RM firms. They also assist other firms in developing

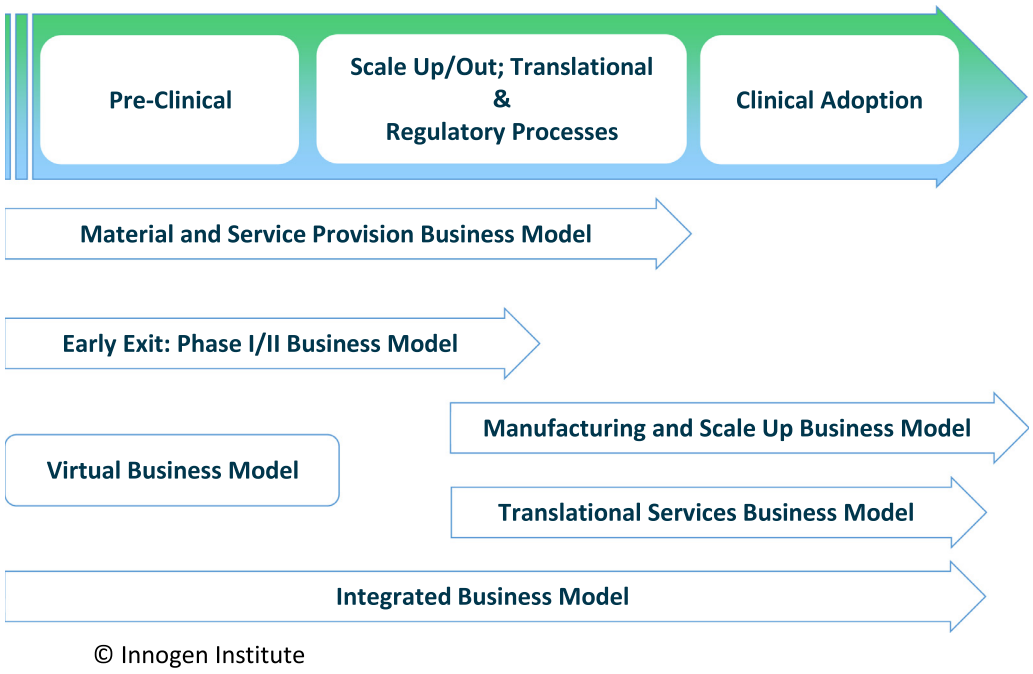

Figure 1. Six emerging UK regenerative medicine business models.

the manufacturing procedure, scaling up their manufacturing capabilities, and producing cells for clinical trials.

- **Translational services business model.** These firms provide technological, business development, and regulatory advisory services as well as physical infrastructure (eg, cGMP plants) to support small to medium enterprises (SMEs) without in-house capabilities. They de-risk the early stages of therapy development, allowing SMEs to delay investing in cGMP plants and related skills.
- **Virtual business model.** These prerevenue SMEs opt to buy-in services and products from manufacturing and scale-up or translational services providers to avoid quickly running down their funds by carrying out the activities themselves.
- **Integrated business model.** This model incorporates all of the other 5 models, and the firm controls the laboratory-to-patient translational activities for a chosen therapy because it has internal technological, financial, and management capabilities. None of the organizations we studied displayed this model.

These business models are interlinked to form value chains. We conceptualize *value chains* as describing "the full range of activities required to bring a product from conception to market and end use, including design, production, marketing, distribution and support to the final consumer. It can be covered by a single, probably large, firm or involve multiple firms, nationally or globally. Each firm will be working to a different business model, appropriate to their role in the overall value chain."[8] We bring together the business models and value chains in the methodology of Stratis,[10] which brings together a range of aspects of value chain analysis for the development of RM therapies, including market identification, complex manufacturing processes and their scale and location in the value chain, distribution processes for vulnerable living materials, partner selection and collaborative/networking approaches, intellectual property and access to cell lines, management of clinical trials and other regulatory approval processes, control of costs, and identification of alternative sources of value.

We borrow aspects of an *innovation ecosystem* from Adner,[11] who defined it as "the collaborative arrangements through which firms combine their individual offerings into a coherent, customer facing solution." Adner[11] argues that the innovation ecosystem leverages synergies across multiple firms/organizations to bring

value to a customer that no firm/organization could singly deliver. We depart from his approach slightly because he describes *mature markets,* and their definition is what we call the *value chain*. We consider the life sciences innovation ecosystem to include the value chain, all of the other things in which the value chain is embedded (the system's environment), as well as external influences such as regulation and national or regional innovation systems. We however adopt the 3 risks that are characteristic of innovation ecosystems—initiative risk, interdependency risk, and integration risk—from a value chain perspective. Adner[11] defines the risks as follows: *initiative risk* is "the familiar uncertainties of managing a project"; *interdependency risk* is "the uncertainties of coordination with complementary innovators"; and *integrative risk* is "the uncertainties presented by the adoption process across the value chain." This conceptualization is relevant to understanding that the RM sector is at a stage at which collaboration with competitors is problematic and thus the firms are likely to face different dynamics for initiative, integrative, and interdependency risks as they negotiate the 6 business models discussed earlier. For example, in integrative risk, the higher the number of actors in a value chain, the higher the number of sequential innovation adopters before a product reaches the market, which we focus on when we discuss value chain gaps. As firms transition from development to clinical adoption, they need to choose other businesses to work with to deliver value to the patient, and the National Health Service will be a key player as industry experts perceive that the value of RM is predicated on the value chain for blood, tissues, cells, and organs—areas of expertise for blood transfusion services.

Value Chain Gaps and Innovation Ecosystem Challenges Facing RM Business Models

The following 3 categories (Table 1) illustrate our argument about the effects of nonintegrated value chains and innovation ecosystem vacuum on evolving RM business models. These findings are based on 10 case studies of RM organizations that we studied between 2015 and 2017. Eighteen semistructured interviews were recorded and transcribed. The names of the organizations and interviewees have been anonymized.

Nonintegrated Value Chains

In the early stages of RM businesses, value chain development and integration are crucial, and this was confirmed by interviewees who forecasted that in the coming years, firms' time and effort would be devoted

Table 1. Effects of nonintegrated value chains and ecosystem vacuum on evolving regenerative medicine business models.

Challenge/Examples	Business Model Effects
Nonintegrated value chains	
Manufacturing	Few cGMP plants and lack of capacity for clinical production
Clinical adoption	Lack of collaborations between therapy manufacturers and clinicians
Translational services	Squeeze on under-resourced start-ups
Technology and delivery gaps	
Autologous versus allogeneic therapy	Product-vs-process approaches to logistics and manufacturing choice
Logistics	Distribution; "stuffing pipe"
Regulators and reimbursement	Large up-front payment for therapies that cure vs longer-term smaller payments for chronic diseases
Disproportionate governance	
First mover disadvantage	Steeper learning curve for pioneers vs followers as regulators learn with pioneer innovators
Limited patients for clinical trials	Clinical trial design challenges as well as the trial expenses bar set higher for small companies

cGMP = current Good Manufacturing Practice.

to developing robust products and processes for clinical trials and marketing authorization.

Manufacturing Gaps—Public Investment in Innovation Infrastructure

In mature technologies, different businesses with different business models link up to form viable value chains. However, in RM value chains, there are still gaps. Certain crucial functions have no players due to market failure, for example, lack of regulatory approved facilities for clinical grade cell manufacture, as the under-resourced SMEs cannot invest in these expensive plants. cGMP clean rooms are key manufacturing cost drivers for SMEs, with basic maintenance costs of around £250,000 (US ~$334,500) per annum. Of the 6 business models, only 2, the manufacturing and scale-up model and the integrated business model, can afford to construct cGMP plants. Since there are yet no integrated business model actors, only a few private sector manufacturing and scale-up business model players are active in this area.

In 2014, the United Kingdom had the following 13 GMP plants with 56 manufacturing clean rooms: Cancer Research UK, Biotherapeutics Development Unit (Hertfordshire); Cellular Therapeutics Ltd (Manchester); Guy's & St Thomas' Hospital, GMP Facility (London); Imperial College London, John Goldman Centre for Cellular Therapy (London); Kings College London, Rayne Cell Therapy Suite (London); King's College London, Cell Therapy Unit, Clinical Research Facility (London); National Health Service (NHS) Blood and Transplant—Speke (Liverpool); Scottish Centre for Regenerative Medicine (Roslin Cells and Scottish National Blood Transfusion Service; Edinburgh); University College London, Great Ormond Street Hospital Cellular Therapy Laboratories (London); Moorfields Eye Hospital, Institute of Ophthalmology, Cells for Sight Advanced Therapy Medicinal Products Manufacturing Unit (London); University of Newcastle Biomanufacturing Facility (Newcastle); Intercytex Ltd (Manchester); and University of Oxford, Clinical Biomanufacturing Facility (Oxford).[12] Of these, at least 8 are public sector or academic based, and Intercytex has now ceased operations.

In response to gaps in the value chain, the UK government set up the Cell and Gene Therapy Catapult (CGTC) with a remit to provide: innovation infrastructure (the new cGMP plant in Stevenage, UK); support for further investment in RM through grants; and advice on regulation, clinical trial design, and business management. A respondent from an immunotherapy development firm noted, "[The CGTC is a] perfect model for us. ... Because [of] what it does, it de-risks the manufacturing for us. ... We do not have to invest in building our own [cGMP] building, so we do not have that cost. ... So you push the risk, the point at which you have to invest your own money in a building, further down the development pathway."

The CGTC's Stevenage plant represents public investment in innovation infrastructure that covers a value chain gap while also de-risking early stage development for under-resourced SMEs. Thus, SMEs delay early risky investment in cGMP plants until they have demonstrated proof of concept, efficacy, and tolerability, making them more attractive to investment by venture capitalists. However, the United Kingdom still has limited capacity for manufacturing cells for clinical use; manufacturers can produce batch sizes for treating only 50 patients at most. Cognizant of this fact, the UK government set up the Advanced Therapies Manufacturing Taskforce, which produced the Advanced Therapies Manufacturing Action Plan, focusing on "retaining and attracting advanced therapies manufacture into the UK."[13] In addition, there are harmonization and collaborative efforts by organizations such as the London Regenerative Medicine Network and the CGTC.

Clinical Adoption Gaps—Public Investment in Trialing Clinical Adoption

There is also a lack of cooperation between therapy manufacturers and end-use clinicians regarding what clinical adoption of the therapy will look like. The level of cooperation depends on therapy type; for example, tissue engineering would need more intimate collaboration between the NHS and the RM therapy provider, as the procedure involves seeding a preprocessed scaffold with autologous cultured cells, and potentially several rounds of surgery, which require the training of surgeons in procedures. A respondent of our survey, from a tissue engineering firm, stated, "We work very closely with the surgeon. So, we are restoring anatomy as well as function. I guess, we have two components we have to fit together; ... it is not just cells, it is not just scaffold. We have to fit them both together in a way that will work."

Immunotherapies may not require the same level of collaboration. However, clinical care is important for managing a potential cytokine storm response in

patients. Figure 2 illustrates, in immunotherapy, the close collaboration between the clinic and manufacturers with regard to scheduling, logistics, testing, and product release activities. The patient goes into the clinic and undergoes leukapheresis for the harvesting of T cells, which are modified and manufactured for delivery to the patient, who may spend, on average, 3 to 7 days in the hospital. Prior to therapy, the patient would have been preconditioned with chemotherapy to down-regulate his or her T cells. The T cells are modified in the manufacturing center, which works in close collaboration with the clinic.

The findings from our study indicate that not all hospitals are able to offer RM therapies. The UK government has, as a result, invested in *advanced therapy clinical centers* to build models on how RM therapy will work in hospital settings. Indications from our interviews are that RM therapies may be offered in regional centers. However, the nature of advanced therapy clinical centers is yet to be established.

Translational Services Gaps—Public Investment in Advisory Service

One firm we studied had identified a need in the industry and had re-engineered its business model from a contract manufacturing organization (CMO) to a translational services business model offering advisory services for RM-related businesses. It had become

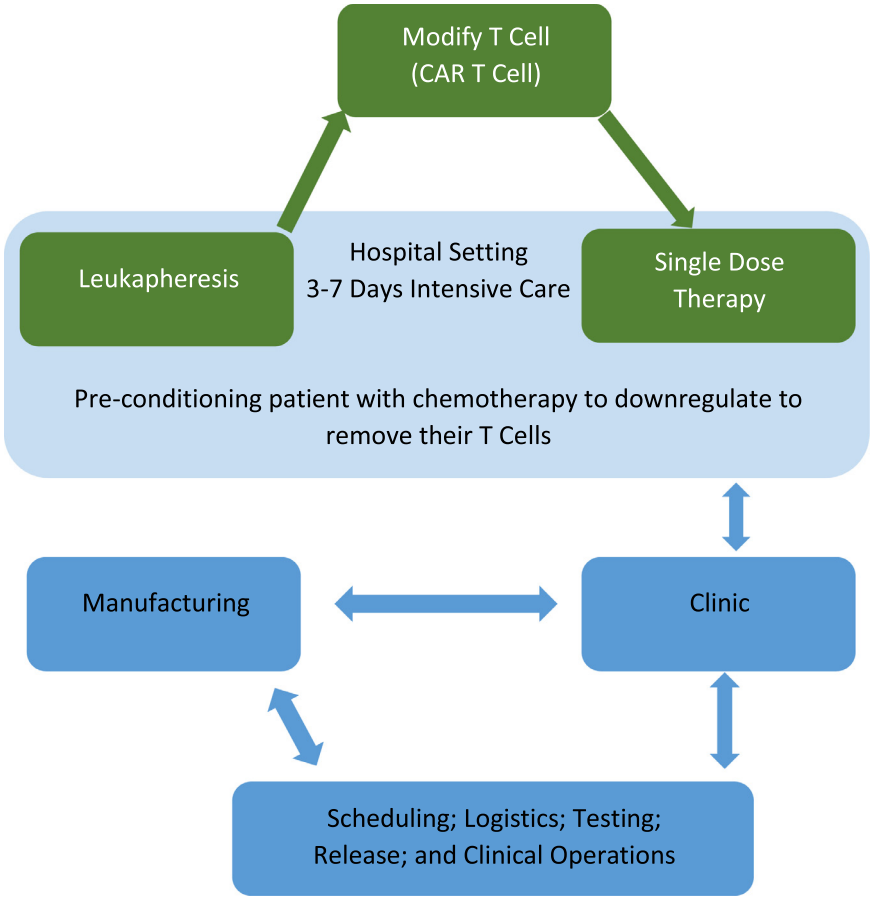

Figure 2. Immunotherapy using chimeric antigen receptor technology (CAR-T) illustrates close cooperation between the clinic and manufacturing with regard to scheduling, logistics, testing, and product release activities (blue arrows and boxes). The patient goes into the clinic and undergoes leukapheresis for the harvesting of T cells, which are modified and manufactured for delivery to the patient, who may spend, on average, 3 to 7 days in the hospital (green arrows and boxes).

cash-neutral but then became unviable when a better-resourced, publicly funded entity, the CGTC, began delivering a similar service. The paradox is that the CGTC, as part of the innovation ecosystem, was set up as a national response to fill gaps in the value chain for RM development. The firm could not compete with a well-funded institution: "The CGTC said, 'We are going to build a manufacturing facility. We are going to be a CMO. We are going to provide regulatory advice; we are providing business development advice. We have research labs.' And they put £100 million ($133.8 million) into it. We could not compete with that."

This example highlights the tension between the innovation ecosystem policy and practice interventions that bridge value chain gaps and the need to balance this with allowing enough "space" for smaller players to operate and provide a variety of actors leading to sustainable value chains. Institutions like the CGTC have a marked effect on at least 2 business models—manufacturing and scale-up, and translational service provision. The crucial question is whether commercial companies will be able to fill the gap when the government eventually withdraws funding from such institutions.

Technology and Delivery Model Gaps

Different Dynamics for Autologous and Allogeneic Therapies

The availability of either an autologous or an allogeneic therapy will influence the manufacturing model, distance of manufacturing sites from the clinic, distribution model, and achievement of economies of scale. Autologous economies of scale can be achieved by what one industry expert termed *scale-out*—processing many autologous samples at the same time; however, scale-out carries the risk for cross-contamination compared to scale-up for allogeneic therapies. Scale-out depends on closed-system automated manufacturing to avoid contamination, which requires timely coevolution of allied technologies/innovations. As a result, allogeneic therapies are deemed more commercially viable; however, some players choose to develop the autologous therapies first because the regulatory and manufacturing routes of autologous therapies are less demanding than are those of allogeneic therapies. An interviewee reported that allogeneic therapy was subject to stricter regulatory processes compared to autologous therapy: "The reason is really learning as we go along, it was always the concept that allogeneic was likely to be the easier way to commercialize to scale up and produce large amounts of drug product and sell drug product at low price or relatively low price and be able to make a big enough profit for the commercial case for investors. But it is a longer route, . . . regulatory approval of an allogeneic product in Europe, and so we decided to start with an autologous product as a proof of concept that this could work. We have done that, we have treated the first 5 patients, and we have collected 2-year data in some cases and 1 year in all cases. And we have enough evidence to say as a product it appears to work; now we want to turn it into a much more commercially viable product. . .. So we have a new Innovate UK grant which is focused on turning the autologous product into an allogeneic product and we have just started that."

Thus, the stringency of a regulatory process can direct innovation into certain directions, which may not be optimal and may be wasteful of resources and time in the early exit Phase I/II or virtual business models. A tissue engineering firm also reported choosing the autologous approach because "the cell therapy guys would say, 'Well, we've got more tolerability and regulatory concerns to deal with because you're giving a cell therapy that's . . . allogeneic rather than autologous.' So, we chose autologous because it is safer, and from a regulatory perspective, as well it is also easier." A CMO pointed out that it can take 6 to 12 months to develop expertise in a new cell therapy manufacture for highly competent and versatile players. Therefore, switching source material results in significant delays in bringing products to market. We discuss issues of regulatory pressure on innovation subsequently.

RM Logistics Issues

The second technology and delivery model issue is the logistics challenge for both autologous and allogeneic therapies. There is a cryopreservation technology challenge as well as working out efficient distribution systems for RM therapies. All respondents identified the need to develop better cryopreservation techniques that enhance long-term cell viability for allogeneic therapies and in some cases for autologous therapies. Thawing procedures also need to be easier for clinical staff. There is a technology limitation, as current state-of-the-art cryopreservation may not be good enough for certain therapies. Also, scheduling and coordination between manufacturers and clinicians need to be optimized. A respondent from a cell therapy firm carrying out clinical

trials spoke of adverse weather affecting their operations: "I remember one winter when all the cells froze in the van we had, the temperature dipped down because the driver parked the car at his house halfway up to Edinburgh overnight and everything just froze because it was −10°C. ...It was the first time I realized how important the logistics are in these things."

Cryopreservation and logistics affect business performance. A respondent with US and UK RM knowledge reported that the dermal substitute Dermagraft (Organogenesis, Canton, Massachusetts), which sold for $1000/unit, was cryopreserved, whereas Appligraf (Organogenesis), which sold for about $800/unit, was not. Shipping and storing a cryopreserved product were more expensive, and the cost of acquiring the −80°C freezer was borne by the cell therapy provider. Clinicians complained of the noise and heat that the freezer generated, and that thawing introduced a risk for mishandling the product. While Dermagraft had a shelf-life of over a year, Appligraf had a shelf-life of 5 days. Consequently, the respondent said, "It was expensive to hold Dermagraft stock for long periods, and accountants were not happy because salesmen were 'stuffing the pipe,' that is, they would buy a year's supply of products now and get a volume discount." The result was that short-term sales went up and long-term sales suffered. This example illustrates some of the systemic technology and delivery challenges that the UK RM sector will need to resolve.

National Regulatory and Reimbursement Systems

The findings from our study show that firms in the RM sector are currently focusing on resolving manufacturing and clinical trial issues but neglecting reimbursement and health care adoption. All of the firms actively developing therapies said that reimbursement is further down the road and that they would consider it more carefully when the time came. A respondent from a cell therapy firm, with UK and US experience, highlighted the health technology assessment and affordability challenge, especially when national health care systems are financially constrained. He cited the example of diabetes and questioned whether the health care system could afford a high upfront payment for a therapy compared to the current small costs spread over the lifetime of a patient.

A shift in the Medicaid reimbursement model in the United States had a negative effect on Organogenesis. The respondent reported that "instead of paying whatever the clinician claimed, they [Medicaid] said treating venous leg ulcer will cost so much; it's up to you how you fix it. This was way less than was being reimbursed for Appligraf and Dermagraft. This example caused huge problems for Organogenesis [and affected their manufacturing capabilities]." Reimbursement of the cost of therapies is a value chain gap that needs to be addressed. One of the firms we interviewed commissioned a reimbursement study in the United Kingdom, considering quality-adjusted life-years and National Institute for Health and Care Excellence guidelines, and preliminary results showed that they could be reimbursed. The National Institute for Health and Care Excellence also commissioned a mock health technology assessment for RM therapies. The conclusion was that existing methods of assessment could be applied to the sector; however, there remain challenges about clinical evidence.[14]

The third innovation ecosystem challenge that the sector faces is different regulators for different markets, especially if they target European and North American markets. Evidence from the field suggests that European regulatory authorities are considered more stringent on cGMP requirements earlier on in development compared with the Food and Drug Administration in the United States. The firms argue that it is possible in the United States to avoid GMP right up to early stage clinical trials, whereas in Europe, that happens much earlier. The second issue highlighted by one of the firms that we studied was that European firms may have to start from scratch with the Food and Drug Administration, and would have to collaborate with an American company to accelerate approval. Turning to the European setting, the firms reported that they get central regulatory approval from the European Medicines Agency (EMA), but they require nation-by-nation reimbursement, with each applying different criteria, making this expensive for under-resourced RM firms. However, in their discussion of regulatory systems in Europe, Japan, and the United States, Milne et al[15] reported that there are attempts at harmonization.

Disproportionate and Nonadaptive Governance Systems

First-Mover Disadvantages of Regulatory Learning and Costs

The findings from our study indicate that some RM pioneering firms face a first-mover disadvantage as

they bear the costs of learning how to manage the regulatory process, and that of helping the regulators to learn, with benefits accruing to follower innovators. According to a pioneering cell therapy firm in the United Kingdom, "Initially, it was very tricky for us, because the regulators hadn't really seen much of this before. So in some senses, we were pioneering the regulatory pathway, by almost being the first in. Certainly, that was the case with some of the interactions we had here in the United Kingdom. So the regulatory system has got a lot easier here in the United Kingdom—or more efficient, would be the better word to use. And the efficiency has led to . . . the process has just become more manageable, in terms of . . . submit[ting] applications for regulatory approval, the . . . number of bodies that . . . [the] application has to go through. It used to be much more cumbersome in the UK than it is now. And I think the UK's definitely got its act together there."

Trust develops as regulators and pioneering innovators work together, a phenomenon that, at a workshop, a representative from the Medicines and Healthcare Products Regulatory Agency called *the fellow traveler concept,* in which regulators acknowledge that they learn from innovators, as it is likely that, in niche areas, innovators know more than do the regulators. Some firms acknowledged that when they started, they did not know what the regulator wanted and they were unsure of the stance they would take on a particular issue, especially in situations without precedents. However, firms pointed out that the regulatory process is still expensive, which can hinder innovation. For example, one firm reported that the regulator informed them that they had to run trials in in vivo animal models, and the trials had serious limitations and did not deliver useful data. They felt that use of in-vivo animal models was wasteful of animals, money, and time, but they had no option because that was the advice from the regulator. Another firm argued that regulators can be accommodative of innovators if one knows what he or she is doing. They sought clinical trial variation for an immunotherapy and obtained it. The accommodation by the regulator may have worked for them because of their extensive in-house regulatory experience and long-term liaison with the regulators, which could have built trust.

Turning to standards, we found that first-movers' advantage could be obtained by "gold-plating" standards or regulations. Pioneers could set higher standards than are required as a competitive tool and barrier for entry (see Tait and Banda[5] for a detailed discussion on standards in cell therapies). Reinforcing this aspect, one respondent reported that in-house regulatory staff have 2 employers: the firm and the regulator. They can change their employer but the regulator remains the same, and as a result, they are motivated to preserve their reputation with the regulator by being overly stringent, thereby gold-plating standards.

Limited Patient Numbers for Clinical Trials

Limited numbers of patients with rare indications lead to challenges in designing clinical trials. For example, epidermolysis bullosa has a prevalence of 1 in 1 million (about 60 patients in the United Kingdom). If 8 clinical trials were required, the RM firms would run out of patients. One firm that was interviewed had only 11 patients and could not proceed further with clinical trials. Small patient numbers are especially difficult for under-resourced SMEs running either the virtual or early exit Phase I/II business models because they cannot afford to recruit patients outside of the United Kingdom. However, Faulkner[16] reported that regulatory systems are now being adapted for rare indications, and Mittra et al[17] argue that the usual approach for indications such as β-thalassemia is to choose a country with a patient population sufficient for the clinical trial.

A related issue is shifting goals for later-comer therapies in clinical trials as standards of care improve. A respondent from a cell therapy firm informed us that the effects of Organogenesis' Appligraf therapy were measured against those of standard therapy for venous leg ulcers at that time, an Unna paste boot (zinc oxide paste, with an elastic wraparound), Appligraf easily passed. On the other hand, a therapy from Advanced BioHealing (La Jolla, California) failed in Phase III clinical trials because its effects did not reach statistical significance compared to those of a 4-layer compression bandage (Smith and Nephew, London, UK), which had become the standard of care and was more efficacious than was the Unna paste boot. In this case, the pioneer had first-mover advantage as the bar was raised for subsequent competing therapies. This experience is common among companies and researchers working on the frontier of innovation when they are unaware of a competing innovation emerging from a different field of science.

DISCUSSION

This article has identified a number of gaps in the value chains required for delivering RM therapies to various markets, and in the innovation ecosystem, that will need to be tailored to more effectively meet the needs of small and large companies innovating in this area. If government supports were removed, current RM value chains would not be viable.

This articles has focused on gaps that are holding back the development of the integrated value chains that will be needed for RM therapies to become independently viable treatments. We have identified 3 value chain–related gaps—manufacturing, translational services, and clinical adoption—and public investment is currently bridging these gaps. Specific areas requiring attention include re-engineering the dynamics of distribution and logistics in cell therapies, the coevolution of supporting expertise (eg, in cryopreservation, surgical and medical skills), increasing the scale and quality of manufacturing facilities, and cultivating and supporting end-user markets.

For issues arising in the innovation ecosystem, we have considered regulation and how it can channel innovation unintentionally in certain directions. Important factors are the first-mover disadvantage, in which pioneers incur severe regulatory learning costs, and the first-mover advantage, in which pioneers are able to gold-plate standards to make life more difficult than necessary for followers. Clinical trials also present problems for innovative companies in terms of the need for recruiting patient numbers large enough to meet the requirements of a regulatory system designed for large-scale medical indications. The different requirements of regulatory systems in different national jurisdictions are also inhibiting international collaboration in RM development.

CONCLUSIONS

The findings from this study highlight the needs for (1) more systemic analyses of the needs of potentially disruptive innovations, in RM and more widely; and (2) policymakers to give greater attention to these insights in planning regulatory and other supporting initiatives, with the promotion of innovation in mind. Some of the general manufacturing and translational challenges are beginning to be addressed by organizations in the United Kingdom, such as the CGTC, London Regenerative Medicine Network, and specific centers that have been set up for this purpose, including, for example, the Engineering and Physical Sciences Research Council's Centre for Innovative Manufacturing in Regenerative Medicine, Loughborough University (Loughborough); the Centre for Regenerative Medicine, University of Bath (Bath); and the UK Regenerative Medicine Platform (https://www.ukrmp.org.uk/hubs).

ACKNOWLEDGMENTS

This work was funded by the UK ESRC Grant Ref ES/L002779/1.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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