Commentary

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Regenerative Medicine

Spatiotemporal readiness is key to preparing regenerative medicine for the clinic

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> "Spatiotemporal readiness is key to the deployment of emergent regenerative medicine therapies in clinical settings and requires ongoing attention."

Tweetable abstract: Successful translation of regenerative medicine projects to the clinic requires attention to the complex interaction of spatial and timing issues from manufacturing to clinical use.

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As regenerative medicine products scale up, researchers turn their attention beyond the ongoing technical challenges of collecting, preserving and delivering gene- and cell-based products to manufacturing and business operations, including process control, automation, supply chain and logistics, and the viability of business model alternatives. Assessing readiness for clinical use, however, requires an integrated assessment across all of these crucial components, including how well they fit together (or not), how synergies might enable platform opportunities and, critically, what kinds of infrastructures should be created to support a range of cell- and tissue-based products and services. Infrastructures reveal the way that futures are anticipated while shaping things in the present [1]. Yet large investments, including major changes to physical facilities, organizational structures and processes, can make it difficult to change things later [2]. There is much at stake, then, for institutional readiness in terms of having robust, yet adaptable, infrastructures.

We suggest that analysis of the spatial and temporal aspects of infrastructure is a useful way to take a more integrated view across all manufacturing phases, participants and components of regenerative medicine when assessing institutional readiness. We use the concept of institutional readiness [3] as a way to frame the interrelation of material technologies, knowledge bases and social and economic factors affecting translation. We focus on the UK and use the term 'advanced therapy medicinal products' to encompass the variety of cell-, tissue- and gene-based therapies that involve altering biological characteristics. Although it is self-evident that there are specific spatial and temporal needs for different cell types and delivery models, we discuss major planning issues that all share.

Our comments derive from an ongoing Wellcome Trust-funded workshop series organized by the authors. The workshops bring together social scientists and biomedical professionals actively developing cell- and tissue-based products with the aim of learning how intended applications and commercialization strategies interact with knowledge production systems and the broader socioeconomic environment. Ongoing workshops center on emerging technological, financial and organizational infrastructures and complex production and scale-up techniques and how these interact with regulatory and policy arenas as well as the development of novel business models and valuation strategies. A core group of seven social scientists, all with expertise in science and technology

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studies, attend all workshops in the series. Each core member has an active portfolio of empirical research regarding cell- and tissue-based products, through which they contribute to the continuing dialogue. Each workshop entails presentations from two invited experts who are actively developing or supporting therapeutic interventions, with in-depth, interactive discussions of specific challenges they face regarding scale-up. We aim to illuminate challenges that may be less discussed, yet are common across various applications, as well as unique issues as new research and production alternatives appear. In this article, the specific contributions and details of individual cases remain anonymous. Our analysis represents the comments of the authors only. This commentary also draws upon related research conducted separately by the individual authors that involves interviews with professionals working on engineered skin, blood and muscle and on clinical translation of gene editing, induced pluripotent stem cells and 3D printing in the UK [4–7]. Signed informed consent was received from all interviewees in these studies prior to interview.

Spatiotemporal readiness

It is important to consider spatiotemporal readiness as a key dimension of overall organizational readiness. Successful translation of regenerative medicine in clinical contexts requires attention to the interrelatedness of the 'where' and 'when' questions with costs, capacities and effective outcomes. A recent collaborative report identifying engineering processes and logistics challenges for cost-effective and reproducible manufacturing highlights how space, speed, cost and quality issues cannot be viewed separately, as they mutually shape and inform each other [8]. This view was echoed in our workshops through examples in which apparently mundane logistical where and when issues, such as the design and layout of laboratory and production spaces and how people, materials and information pass through them, proved non-trivial in the effective delivery of cell- and tissue-based products.

Effectively achieving spatiotemporal readiness is important for the economic and technical success of these endeavors but also has important bioethical implications. Efficient delivery could make therapies available sooner and more cost-effective for end users and, by incorporating a fairness framework for manufacturing capacity allocation, increases the likelihood that the benefits of regenerative medicine will be available for all who need it most [9]. Spatiotemporal readiness enhances product integrity, benefiting manufacturers and human subjects who volunteer for clinical trials. However, appropriate spatiotemporal procedures are highly context-specific and can vary by technology, patient population and economic environment.

Importantly, spatiotemporal readiness encompasses both actual and anticipated where and when issues. Visions of future spatiotemporal infrastructures that later prove inappropriate can impede effective delivery. Multiple potential business models are arising [10,11], each including an anticipated spatiotemporal model. Any business model or manufacturing process that does not accurately account for the spatiotemporal organization of the clinics in which therapeutic products would be applied could face difficulties, especially if the process design has locked-in elements that are poorly aligned with clinical practice. This is further complicated by the diversity of product and patient contexts.

To date, discussion of aligning commercial, regulatory and clinical factors too often implies that commercialization is a linear process, and that readiness will allow an acceleration through various steps [6]. Examining spatiotemporal aspects of translation is one way to show how this linear model can be misleading, as time lines take longer than anticipated and, importantly, become iterative through movements within and between preclinical trials and market authorization. Successful acceleration here requires something other than simply speeding forward toward a chosen goal.

Spatiotemporal readiness before the clinic

International initiatives for manufacturing scale-up are considering multiple levels of scale, from the organization of laboratory space to the geographies of national and international production and use. Although many institutes are offering current GMP facilities for storage, testing and processing, some national-level and government-supported initiatives, such as Canada's Centre for Commercialization of Regenerative Medicine and the UK Cell and Gene Therapy Catapult, offer centralized facilities. Regulatory-compliant modular spaces and consulting services are established to bridge nascent innovations from academic inventors and commercial entities with industrialization expertise. The UK catapult, for example, has both a 1200 m^2 development center with a configurable pod system to replicate users' processes and a 7200 m^2 manufacturing center with GMP-compliant but segregated modules designed for flexible use. In such contexts, companies must decide whether locating their manufacturing work in such sites and utilizing these facilities is preferable to developing and using their own operations. Larger companies

are more likely to use in-house facilitates and acquire technology from start-ups. Product sponsors may be operating out of academic centers or facilities acquired in company purchases and must decide whether and how to reorganize space to meet requirements for the products they intend to make.

Such decisions may be framed by the legacies of previous company acquisitions, as the many takeovers and mergers seen in the sector lead to companies holding a portfolio of spaces and facilities that may or may not map onto their priorities at any particular time. Emerging infrastructures may be built upon existing infrastructure, which possibly brings forward the risk that old constraints may still be in place and can be insufficient to deal with emergent issues and market conditions. Other cases may see the creation of de novo infrastructure or hybrid infrastructures that seek to combine the new with the existing. Such novelty can be costly and more time-consuming. It also retains the risk that the first to create a new mode of operating may or may not be the one who reaps the benefits, as novel radical approaches become reproduced by others once initial problems have been worked through. Alternatively, first movers may not end up developing what becomes the industry standard and be left with outdated legacy infrastructures. As with many therapeutics, first in class is rarely best in class.

The geographical location of these facilities is also important, as locations near major transport links and areas with readily available ancillary services create an advantage. International transportation can also prove burdensome, as logistical boundaries and regulatory jurisdictions provide additional barriers. One eye-catching example occurred when the team producing the first tissue-engineered trachea for transplant was turned away from Bristol Airport in 2008, as easyJet representatives refused to allow the biological material onto the flight, despite assurances in advance it would be allowed, necessitating that £14,000 be spent on a private plane to make the 16 h window for use. Such examples highlight the necessity for regenerative medicine infrastructures to fit within existing infrastructures for transport and other needs. In the UK, future border issues could be exacerbated by the assembly of new administrative borders with EU countries and import and export of biological materials. Even within a single country, deciding how and when to transport material is key. The timing of delivery of a therapeutic product to a patient can be critical, but the appropriate timing of a delivery may be contingent on a patient's complex and variable condition [12]. For example, autologous keratinocyte-based engineered skin should be transplanted within 24 h of leaving the manufacturing facility. But if a patient's condition deteriorates during the transit period such that surgery is not possible within that window, the patient's skin, the company's resources and critical time for healing are all wasted.

Within production facilities, the size and modularity of manufacturing spaces affect workflow, labor, materials and sequencing. For smaller facilities, having fewer higher-grade clean rooms creates problems with scheduling and sequence of events. One workshop attendee described the challenges of deriving GMP induced pluripotent stem cell lines, which necessarily require open cell culture and thus can monopolize a grade B clean room of any size for an extended period. Other issues include mundane but necessary tasks like cleaning and maintenance. Such challenges demand a careful choreography of laboratory space usage in planning sequential and side-by-side activities, which can have significant financial implications when these where and when issues are misaligned. Choice of culture system types and automation also must be considered [13,14]. Closed systems can allow manufacturing to move from grade B to C/D clean rooms, with a likely reduction in cost. Some manufacturing steps can be automated, but there is currently little speed advantage over manual processes. Automated processing still requires skilled operators. As a result, manufacturing remains expensive in terms of high-cost skilled labor time. Many steps still cannot be automated, nor can they be undertaken in fully closed systems, because of the need to feed and sample cells. There is also a relation between closed systems and the cost of labor and reagents.

Spatiotemporal readiness for integrating manufacturing with the clinic

The way existing facilities map onto the anticipated spatiotemporal dimensions of a business model is also important. Such models have clear spatial economics at the core of their vision that frame where and when priorities. Many manufacturers, including large pharmaceutical companies, favor a production model based on conventional pharmaceuticals, with a limited number of manufacturing sites, each supplying a standardized advanced therapy product to a wide territorial range. This keeps the cost of expensive manufacturing equipment and sites (e.g., GMP-compliant) down and allows centralized quality management, batch control and sign-off by qualified persons. This model suits standardized products, whether allogeneic therapies or some autologous therapies where each sample is processed in a comparable way, such as chimeric antigen-receptor T-cell therapies. For many products, localized on-site manufacturing is impractical. The volume and configuration of space would be difficult for many existing facilities; the skills needed for processing, maintenance and even data analytics may not be available; and quality

control capacity in healthcare facilities is not oriented toward this work. Some clinics may have the capacity for tasks like drug compounding or certain forms of chemistry, but fewer could effectively deliver processing and distribution of live biomaterials. Those hospitals with existing capacity in precedent procedures, such as bone marrow transplants, may face less disruption in introducing cell-based transplants. However, in many cases there may not be enough patients at clinical sites to warrant investing in personnel, equipment and meeting GMP requirements to make investment in distributed models viable.

Techniques of additive manufacturing, however, have given a renewed impetus to redistributed manufacturing in health care [15]. One option is highly localized, 'surgeon-led' 3D printing of cellular constructs. This would allow very near-patient manufacturing, which can be important for products with a very short shelf life or those that are not amenable to the freezing and thawing cycles needed for more centralized manufacturing strategies. However, the feasibility depends a great deal on the regulatory classification of such products. If bioprinting can be considered minimal manipulation of the cells, then a bio-printed construct might be regarded as a transplant and its products as the practice of medicine, but it is more probable that regulators will regard the construct as a product under the advanced therapy medicinal product regulations (most likely as either 'tissue-engineered medicines' or combination products) [16]. In this case, the same prohibitive cost implications of localized manufacture discussed earlier are likely to apply, with each clinic counting as a discrete manufacturing site. As a result, this pathway may be restricted to one-off patient-specific implants delivered as 'hospital exemptions' or 'hospital specials.' These bypass the requirement to secure market approval as a medicinal product, but not the requirement for adequate quality management during manufacture, while also limiting the scalability of the technique.

An alternative spatial configuration is the 'hub and spokes' approach where implants are designed, using computer-aided design software, in a centralized facility with centralized quality control and then transmitted to local sites for bioprinting. This looks more like conventional manufacturing in terms of scalability and manufacturing site costs but raises issues regarding the security of transmitted computer-aided design information, which is unavoidably confidential medical data about a patient, and the distribution of liability among the various computer engineers, bioprinter operators, qualified persons, surgeons and manufacturers of components such as bio-inks and scaffolds that may be utilized to create the final implant [16]. In these distrusted manufacturing models, it is not the bio-printed implant that is commercialized but the equipment, protocols and capacity to produce the implant, which is a rather different business model. Readiness here transcends individual institutions and involves a higher-level issue of the capacity of national legal systems (regulation but also issues of manufacturing liability) to support or constrain additive manufacturing.

Another model that could apply to both bioprinting and more conventional regenerative medicines involves the creation of specialist centers of excellence (mainly university hospitals). This approach has (some of) the benefits of centralization but is more distributed. Here it would be important to ensure the physical separation of the hospital from the manufacturing site. This centers-of-excellence model requires less upskilling of healthcare staff than a general distribution model and can be used as a test bed to identify key drivers of institutional readiness and work out how best to align academic, industry and hospital systems, with a view to rolling this knowledge out to other sites in the future. This is the approach currently being pursued by the three advanced therapy treatment centers in the UK that operate within the framework of the National Health Service but span academia, small biotechnology companies and pharmaceutical multinationals [17]. Whatever model is adopted will have profound implications for the development pipeline adopted by companies and their collaborators. As infrastructures become stabilized in particular places, this will dictate the temporal flow of products through these manufacturing systems and place constraints on life cycle management and the creation of next-generation products.

Spatiotemporal readiness and the economics of clinical practice

It is also vital that spatiotemporal aspects of the operations and business models of hospitals are assessed together with those of the product sponsors. Key issues include where procedures will be performed, how much investment will go into adopting new technologies and the burdens of modifying facilities to support them. The high costs associated with one-off complex therapies do not align well with the periodicity of healthcare budgets, which typically have fixed annual limits.

In many countries, hospital cost and revenue models are rapidly changing with the uptake of value-based models. This shift from cost-per-unit thinking to one contingent on clinical outcomes aims to balance healthcare costs with quality, with risk-sharing contracts negotiated between payers and product suppliers. Value-based contracts are being used for high-cost therapies with highly variable outcomes, such as gene therapies [18,19]. Yet this poses

Table 1. Challenges associated with spatiotemporal readiness.

Key planning themes	Core potential issues
Laboratory design and use	Efficient use of space; availability of space at the right time; appropriate sizing for application at hand; maintenance scheduling.
In-house or external manufacturing facilities	Cost; flexibility; speed to start; control and longevity.
Movement between sites	Speed and shelf life; security; border crossings; trade and regulatory hurdles; route reliability.
Adoption of automated systems	Deciding when a process is ready to be locked into automation may sacrifice flexibility; securing regulatory approval; potential for portability of closed systems and required expertise.
Clinic integration and proximity	What level of integration is appropriate for each specific product and each specific clinic; investments and expertise requirements; when to enter the clinic.
Regulatory alignment	Regulatory category fit; timing of submission; proactive actions for undefined future pathways; unique production complexities (e.g., distributed additive manufacturing).
Payment	Structuring reimbursement systems with the rhythms and needs of both companies and clinics; (mis)alignment of therapeutic impact and payment model (e.g., with value-based systems).

particular challenges for regenerative medicine. Outcomes may take considerable time to become apparent for some advanced therapy medicinal product treatments and are more difficult to measure than non-cell-based interventions. This stretches the time line to assess success far beyond the time of treatment, with implications for healthcare institutions and payers as well as product sponsors [7]. Furthermore, recent adoption of alternative 'real-world evidence' (used in review of fast-tracked regenerative medicine advanced therapies in the US and elsewhere) calls for monitoring data through patient registries for years post-treatment. How government and commercial payers will build and utilize such evidentiary alternatives to conventional proofs of efficacy and safety will be key to value-based contract negotiations.

Time lines for fund flows are also affected, with differing implications for various stakeholders. Alternative payment schemes have been proposed for high-cost treatments with potentially highly variable outcomes. Annuity or staggered payments involve an instalment time line that can be preferable from a payer's perspective to spread risk over time [20]. However, such payments may be less amenable to cash–poor small- and mid-size enterprises needing rapid returns to satisfy investors. Value-based payments based on clinical performance also introduce uncertainty for any product sponsor, as the time line and level of payment may be harder to predict and may not meet initial expectations, depending upon outcome. Such possibilities highlight the relationship between business model choices and anticipated payment time lines, as assumptions of future market conditions shape decisions made in the present. Alternative payment schedules may also cause problems for both payer and healthcare facility financial reporting using existing cost accounting infrastructures [18]. Novel infrastructures for tracking patients, monitoring outcomes and distributing financial reward or liability will thus require further analysis, development and investment. At present, it is unclear who should do this and how such infrastructures should be governed. This may require novel forms of public–private partnership.

To address these infrastructure misalignments, both healthcare institutions and innovators need to be resilient, agile and willing to change. However, this may conflict with the need to standardize and build viable platforms and requires attentiveness to what processes or ways of thinking become locked in, for how long and what impact this may have. As such, questions of where and when to standardize or be adaptive arise.

Conclusion

Our discussions with researchers, both in workshops and individual projects, made clear the ways both actual and anticipated spatiotemporal issues shape, enable and constrain actions. We urgently need to take where and when questions seriously and to recognize their complexities as nonlinear processes. In Table 1, we present some of the key themes institutions planning commercialization should consider in relation to spatiotemporal readiness and the issues these provoke.

These and other issues are likely to arise, challenging both actual and anticipated spatiotemporal activities. Focusing on spatiotemporal aspects implies recognizing infrastructure development as a fluid process that requires constant planning, negotiation and maintenance. This attunes us to the interactivity of economic, infrastructural, technical and regulatory aspects, as they influence and shape each other in complex ways across geographies and time lines. It is vital that considerations of spatiotemporal issues are broad and multifaceted, as planning that focuses on phases or processes in isolation misses broader socio-structural issues that affect the infrastructures of regenerative

medicine. Spatiotemporal readiness is key to the deployment of emergent regenerative medicine therapies in clinical settings and requires ongoing attention.

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