BIOENGINEERING

Manufacturing Challenges in Regenerative Medicine

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Along with scientific and regulatory issues, the translation of cell and tissue therapies in the routine clinical practice needs to address standardization and cost-effectiveness through the definition of suitable manufacturing paradigms.

No one will argue the immense potential offered by regenerative medicine. Nevertheless, actual delivery of this potential has proven difficult, with many barriers to commercially viable therapies capable of addressing unmet clinical needs. Some of these barriers have parochial roots—for example, within national regulatory agencies or associated with regional clinical trials governance; others remain to be identified and prioritized as challenges in dire need of addressing globally. Regardless of the reason or the barrier, data collected on the numbers of treated patients indicate an obvious imbalance between scientific innovation and translation to patient benefit (*1*).

In view of this, a small group of experts in regenerative medicine from across the world met in October 2013 in a closed session in Xi'an, China, to discuss these barriers and to recommend ways to move forward. A series of statements from these individuals were compiled before the meeting and produced as "The Xi'an Papers," which are provided here as supplementary file. Several important issues were raised, some more often than others. This Focus article highlights some of the most relevant and pressing challenges in the translation of regenerative medicine approaches and materials, revolved around manufacturing paradigms.

MANUFACTURING, FRONT AND CENTER

The World Summit on Regenerative Medicine in Xi'an, China, covered a wide range of scientific and engineering issues surrounding regenerative medicine, including those related to cell sources, biomaterials, biomolecules, bioreactors, bioprinting, clinical trials, socioeconomic matters, and regulatory processes. From these discussions, a central, recurring theme was identified as a crucial element of any successful paradigm: manufacturing. Although there are some specific differences between the various approaches to regenerative medicine, here we will use the subset of cell/tissue therapies as an appropriate exemplar to summarize the key manufacturing challenges emerged.

From a biological standpoint, achieving a standard potency of cell-based products ideally requires understanding their mechanisms of action. This knowledge should inform the release criteria of the expanded cells or engineered tissues (cell phenotype, stage of cell differentiation, or tissue maturation); the modality of cell delivery; and the factors that control the fate of the implanted cells. From an engineering standpoint, however, one could argue that the target of standardized quality could not be reached without addressing the robustness of the manufacturing processes, in consideration of issues of scale and sustainability. Here, we discuss the main manufacturing-related issues.

The role of bioreactors. The cell-therapy manufacturing processes are expensive. Based on cost, scale-up from limited laboratory facilities to automated systems for bulk production will need to be timed and planned financially. At the phase 1 clinical trial stage, even if only a small number of patients is involved, issues of process scalability need to be already addressed. The number of patients will in fact increase during phases 2 and 3 and, hopefully, further grow with commercialization of approved products.

Similar to other sectors of biotechnology, bioreactors are expected to play a pivotal role to target automation, traceability, and scale-up or scale-out (for allogeneic or autologous products, respectively), as well as efficient monitoring and control of relevant parameters to achieve a standard potency in each manufacturing batch (Fig. 1) (*2*). The required systems and processes will have to be designed based on the expected rate of usage, along with the required number of cells per graft, which in turn will determine the doses prepared per batch. Analysis of production bottlenecks also indicates that more attention has to be paid to streamlining of the different production stages, including downstream processes (such as cell washing, volume reduction, and packaging). Advances in this field require a continuous dialogue between researchers and technology providers in order to combine innovation with practicality. In the field of of cartilage tissue engineering, for example, a European community–funded consortium, BIO-COMET (www.biocomet.eu), is bringing together different core competencies and domains of exploitation to translate a bioreactor-based manufacturing strategy into preclinical and clinical settings.

Quality by design. Bioreactor technologies are typically considered for manufacturing of regenerative medicine products only after evidence of clinical effectiveness, when financial means become copious. At this stage, however, even small changes in the process would require new validation of the product performance. Therefore, if automation is targeted, then it is at best implemented through robotic systems, which merely reproduce the often inefficient manual procedures. As a result, current products are often based on obsolete technologies, and the field misses the opportunity of improving their quality by innovating process design.

The challenge of advancing product and process quality through targeted planning ("quality by design") typically requires fundamental changes in the processes. For example, tissues with higher regenerative potency may have to be engineered by expanding cells directly within three-dimensional (3D) porous scaffolds in perfusion-based bioreactor systems as opposed to 2D petri dishes (*3*), or assembled by using bioprinting devices (*4*). In order to bypass the need for product revalidation, the new technologies will have to be introduced as early as possible during the research and process development stages, before preclinical and clinical tests.

The adopted manufacturing strategy will also critically determine the regulatory requirements of the production facilities and will have profound economic implications.

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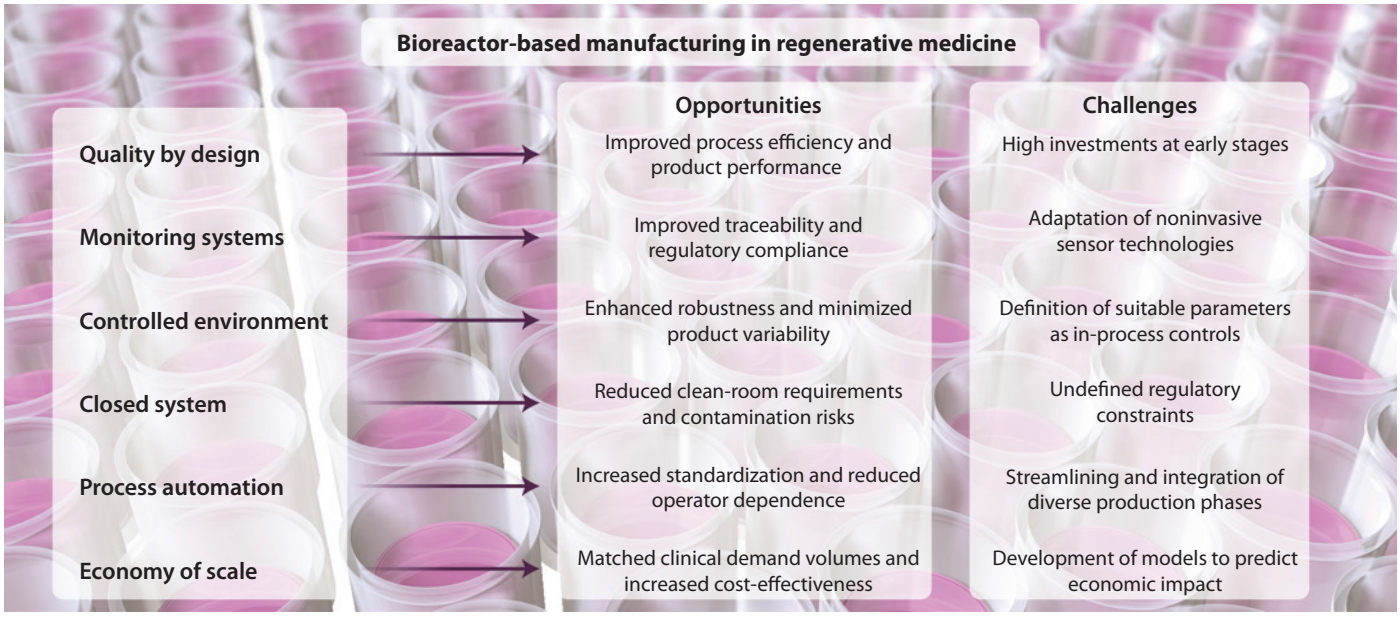

Fig. 1. Manufacturing in cell therapy and tissue engineering. Opportunities and challenges associated with the critical features of bioreactor-based manufacturing paradigms for cell and tissue therapy products. A proposed roadmap to include the described elements into a translational path is outlined in (*2*) and exemplified by BIO-COMET (www.biocomet.eu) in the context of cartilage tissue engineering.

For example, introduction of a controlled and closed manufacturing system for cell culture could imply its possible operation in a Class C clean room. This is different from traditional methods that expose cells to the surrounding environment, which need to be carried out in a Class A room. On the basis of past experiences leading to too high operational expenditures (cash burn rates) immediately after product launch—such as in the case of the pioneer tissue-engineering company Advanced Tissue Sciences (La Jolla, California)—processes would need to be designed as scalable, but should not be effectively scaled until required by sale volumes.

Definition of process end points. In order to be well characterized and reproducible—as is expected for drug products—cell-based regenerative medicine products should be produced based on advanced in-process controls and release criteria specific to the intended clinical use. In the automated manufacturing of cell therapy products, there is thus a need for standardization of assays. Such standardization cannot be directly inferred from those used in the manufacture of biologics and vaccines (for example, where the cell is not the product). Instead, parameters to be measured during and after production of autologous or allogeneic cell-based products need to include biological predictors of batch-to-batch or donor-to-donor variability.

The definition of predictive factors for cell product potency will benefit from smart design of animal studies or clinical trials, addressing not only clinical outcome but also mechanistic questions related to specific features of the final product. This approach can be exemplified by an elegant study on long-term corneal regeneration, by which the percentage of grafted p63-bright cells was identified to predict the clinical outcome of limbal stem-cell cultures (*5*).

Choice of culture media. The supply chain for critical ingredients required for cell culture is not trivial. Several serum-free cell culture media have become available in recent years, which can eliminate well-known difficulties associated with fetal bovine serum (*6*). These media are based on cell attachment factors, growth factors, and other cytokines, the dose of which needs to be optimized for reliable performance while reducing costs. Furthermore, there is a limited number of suppliers of clinically approved materials, and their availability can thus change on short notice, making reproducibility difficult. In order to maintain identity, purity, potency, and safety of a cell therapy product, supply chains need to be secured. Important here are the alternative possibilities to use small molecules, peptides, or synthetic compounds instead of recombinant or purified proteins (for example, human serum albumin).

Biomaterials challenges. The majority of the challenges that concern biomaterials relate more to their selection than to manufacturing, although the trends in materials selection will ultimately have major consequences on manufacturing. The problem is that tissue-engineering processes have largely been based on traditional synthetic biodegradable polymers and a few bioactive ceramics, which have been manufactured by conventional routes. There have been no specifications identified for these so-called scaffolds, and they are far from ideal.

Attention is now being turned toward biomaterials that have more relevant biological properties, which is taking us in the direction of extracellular matrix (ECM)–derived substances, biopolymers, and hydrogels (*7*). These are likely to have critical nanostructural features, and many of them may involve self-assembly and environmental responsiveness. Such characteristics may not be directly compatible with normal top-down manufacturing and therefore could require changes in the production process.

WHEN TO SPIN OFF?

It is apparent from the issues outlined above that establishing a manufacturing process for industrial production in cell/tissue therapy requires large investments. These are difficult to secure because the prospective revenues in regenerative medicine are

considered risky and with uncertain development curves. One way to address the bottleneck is to maintain development as long as necessary within academic walls. This strategy offers the chance not only to reduce the amount of required financial resources and to more directly access public funding, but also to combine the necessary technical advances with the generation of scientific knowledge. The "practicality" in scientific research should not be traded off, but rather enriched with "novelty." Because the latter is often the feature looked for by scientific journals, the combination of approaches will be key for young investigators to progress in their scientific career while fostering an effective development of the field. The new technologies may then be spun off for an industrial exploitation when already validated within preclinical studies and possibly proof-of-principle clinical trials.

A GLOBAL EFFORT

At the Xi'an summit were individuals from countries in Asia, Australasia, Europe, North America, and Africa, and historic differences were clear, especially from a regulatory perspective and the approach to clinical use. Nevertheless, it was apparent that manufacturing issues are at the center of a successful clinical translation of regenerative medicine paradigms, with a pull coming from two ends. At one end, we have the legitimate and ethical creation of wealth; at the other, we have the overwhelming clinical need. The economics of health care are undergoing profound change at the moment, with the two biggest players, the United States and China, both in turmoil with respect to the restructuring (in the former case) and the introduction (in the latter case) of health insurance and reimbursement schemes. The growth of the new and as-yet unproven regime of personalized regenerative medicine sits uneasily in this turmoil, and the business models of the manufacturers—facing huge start-up costs, but with the potential for decreasing the overall cost of health care—need to reflect this niche. It is up to the present generation to elaborate business models that bring together scientific and technical factors with reimbursement and regulatory issues, in a context that will have to evolve toward a global harmonization in order to guarantee the economically critical opportunity of a global commercialization.

SUPPLEMENTARY MATERIALS

http://stm.sciencemag.org/content/6/232/232fs16/suppl/DC1
Supplementary file: TheXianPapers.pdf

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Competing interests: I.M. is President of the Board of Cellec Biotek AG, Basel, Switzerland. P.J.S. is Executive Vice President of Research & New Product Development at Mesoblast, Melbourne, Australia. D.F.W. declares no competing interests of a financial nature; he is Global President of the Tissue Engineering and Regenerative Medicine International Society (TERMIS) and Editor-in-Chief of *Biomaterials*.

10.1126/scitranslmed.3008558

Citation: I. Martin, P. J. Simmons, D. F. Williams, Manufacturing challenges in regenerative medicine. *Sci. Transl. Med.* **6**, 232fs16 (2014).