

EDITORIAL



Cell and gene therapy: scaling up and moving to mass production

Nigel Whittle

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IS CELL THERAPY COMMERCIALY VIABLE?

Cell therapies have huge potential for the treatment of a range of human diseases including cancer, metabolic disorders, tissue degradation and immune deficiencies. Before these therapies can be effectively commercialized for widespread and cost-effective clinical use, however, there is a need to find robust, repeatable and scalable ways to generate large volumes of cells and test to ensure they are a safe and effective therapy.

There are difficulties in commercializing these products so that they are available at an affordable cost to

a great number of patients because of the fragile and individualistic nature of cell therapies. There are two inter-related key requirements: the ability to generate huge quantities of cells (millions, even billions) and the ability to produce small numbers of personalized cells at scale – automating current complex and manually intensive processes.

CELL THERAPY IN ACTION

The basic therapeutic principle of cell therapy is that human cells are administered to patients, where they

migrate to specific target locations, respond to various signals within the body, integrate those diverse signals and generate specific and complex responses in the context of their biological niche. These responses may include stimulation of growth, repair of damaged tissues, restoration of physiological function, elimination of cancer cells or destruction of invading pathogens.

For example, we can administer T cells with the capacity to attack cancer cells via the process of cell-mediated immunity as a course of immunotherapy [1]. Other immunotherapy approaches may

involve administration of NK cells, stem cells, CAR-T cells or various types of lymphocytes. In fact, the most widely used cell therapy is the transplantation of blood stem cells to treat diseases of the blood and immune system, or to restore the blood system after treatments for specific cancers (over 26,000 patients are treated with blood stem cells in Europe each year).

MOVING BEYOND THE LAB

However, the complex nature of living cells and the difficulties inherent in controlling and manipulating their actions in a therapeutic environment provide some of the most daunting challenges in the medical sector. One of the biggest barriers to the more widespread use of cell therapies is the difficulty in scaling up production in order to generate the therapeutic quantities of cells needed, either in dedicated manufacturing facilities or, potentially near to patients, within hospital settings.

ALLOGENEIC VERSUS AUTOLOGOUS: APPROACHES & ECONOMICS

In the case of allogeneic therapies, which use an external donor's cells, it may be possible to use standardized clinical batches of cells for treatment of some common diseases, such as heart failure, vascular conditions, eye diseases and Crohn's disease. Here the challenge is for a dedicated cell manufacturing facility to produce and characterize many millions of identical therapeutic doses

of the cell therapy. Accordingly, the ideal manufacturing process may be a large centralized establishment running at a high capacity, using large-scale manufacturing technology. In the past, industry has favored this approach, as it allows for the scale-up of therapies in much the same way as traditional biotechnological therapeutics, and can form the basis of 'off-the-shelf' products.

However, as these allogeneic approaches use cells from donors, it raises the possibility of significant graft-versus-host disease (GVHD), which could severely limit the efficacy of the treatment. In order to eliminate such concerns, and to produce truly personalized medicines, there is increasing interest in the development of autologous therapies.

REDUCING THE COST OF PATIENT-SPECIFIC THERAPIES

Autologous therapies use the patient's own cells and require the production of one clinical batch for each individual patient. Such personalized processes are currently costly and highly labor intensive. For example, manufacturing a re-engineered cell therapy product such as a CAR-T cell product is particularly complex. Firstly, a patient's own immune cells must be harvested in sufficient quantities, then re-engineered to provide the ability to target specific cancer cells. These engineered cells are then expanded *ex vivo*, characterized and injected back into the patient. Although only a relatively small number of cells may be required for each dose, it may be necessary to set up thousands of small

bioreactor systems, each operating independently and with subtly different operating parameters. And the more operators involved, the greater the cost and the greater the chance of process contamination. The significant quality assurance testing burden, ensuring the cells have been modified as expected, also means a far greater number of re-engineered cells are required than just those for the core therapy itself.

As a result, the cost of production per batch cannot be reduced by exploiting an increasing economy of scale. The cost of such patient-specific cell therapies must therefore be reduced through advances in engineering and manufacturing technology, simplifying and automating wherever possible, to achieve cost-effective production.

AUTOMATING TO INCREASE THROUGHPUT & REDUCE ERROR

Production workflows need to be sufficiently flexible to allow the duration and intensity of T-cell activation steps to be optimized, allowing the proliferative capacity of T cells to be maintained. The benefits of an automated system could potentially include enhanced process and product standardization, effective track and control, higher throughput and ultimately an easier and more manageable process.

DEVELOPING REPEATABLE, SCALABLE PROCESSES

Well-controlled, consistent processes lead to well-understood and

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consistent products and this is particularly apt for cell therapy production. The ability to generate and manufacture well-characterized batches of cells for therapeutic use requires significantly different approaches to those in classical cell culture techniques, where protocols to support the expansion of stem cells are very labor intensive and limited in their scale-up potential. For small biotechnology companies developing a novel process, time and money are of course key constraints, and although scale-up of an existing laboratory platform may be the fastest route, usually a more cost-effective route is the use of bioreactors. This is because small bioreactors require fewer process changes to meet commercialization needs.

PRECISELY MONITORING COMPLEX PARAMETERS

Multiple types of bioreactors have been developed with the ability to grow large numbers of cells, and to monitor and control a number of key operating parameters. The complexity of mammalian cellular growth and its sensitivity to subtle changes in the growth milieu requires in-process monitoring of a range of parameters. These include metabolite concentrations, temperature, pH, O₂ and CO₂ partial pressures, protein concentration,

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and particularly the concentration and viability of cells. Such monitoring could in principle provide precise feedback control through automated systems. Although many developments have been made, current technologies are still limited in their capabilities, either due to their inherent inaccuracy, the need to take repeated samples from the culture or the length of time required for the analysis.

ADVANCED IN-PROCESS MONITORING

Potential technological solutions include the use of analytical technologies that have been developed for other areas, such as impedance spectroscopy techniques that can probe cell composition in-process, measuring parameters such as size, membrane composition or even internal structure. Separately, 1D 1H NMR has been used to quantitate non-protein substrate components and metabolites in mammalian cell cultures, and may represent a possible way to monitor the external cell growth milieu [2].

Advances are being made in the development of systems that can be used to enhance both monitoring and process control, through for example some of the work from our scientists:

- ▶ In-line sensing systems that can potentially monitor the number and percentage of cells with specific characteristics such as expression of high affinity TCRs;
- ▶ Complex modular instrumentation systems that can be combined to create effective work flows;
- ▶ Development of novel manufacturing systems for pharmaceutical companies that combine robustness and consistency with ease of use.

The ability to conduct suitable assays rapidly to monitor all relevant parameters and cell characteristics will be critical factors in the successful industrialization of cell-based therapies (whether autologous or allogeneic).

SAFEGUARDS FOR PRODUCT INTEGRITY

Downstream processing is also a significant concern for cell therapies as the process is complicated by the requirement to maintain the viability of the final product. For example, purification steps will need to be carefully controlled to ensure a safe final therapeutic product. Other steps might include concentration and washing of cells (through tangential flow filtration or continuous centrifugation) before being stored, typically using cryopreservation, for future clinical use. This latter step is critical in generating the final product and needs to be well controlled in order to ensure continued cell viability.

Both upstream and downstream processes will if possible utilize disposable or single-use technologies as well as automation systems to minimize the risks of contamination whilst maintaining reproducibility between clinical batches.

CONCLUSION

There is tremendous clinical promise in the application of therapies based on administering cells to patients to treat a wide range of diseases. In order to fulfil this promise, it is important that manufacture of these therapies can be 'industrialized' through transfer into a commercial setting in a scalable and cost-effective manner. However, the complexity of mammalian cells that yields their great therapeutic potential also dramatically increases the complexity of their production and testing.

A key problem lies in the requirement for robust and reproducible generation of large numbers of cells, which in turn relies on the development of precise monitoring and automated feedback control systems for cell growth. Although the goal of automation is clear, at the moment it is still necessary to utilize the skills of many operators

to effectively carry out those procedures. Analytical and automation systems that have been developed for other sectors may become increasingly useful, and organizations with wide experience in such areas as biosensors, automation and process control are likely to play an increasingly significant role.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The author is an employee of Sagentia. He has no relevant financial involvement with an organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.



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