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Cell Therapy Manufacturing

Addressing the growing pains in cell therapy manufacturing

With a number of therapeutic products finally on the market and several in ongoing clinical trials, cell therapy is gradually taking center stage in immuno-oncology. The focus is now shifting from proving that cell therapy is a vital tool in the fight against cancer, to optimizing the processes of manufacturing products for hundreds of patients, for different conditions and at a reasonable price. Here we discuss some of the growing pains faced by the industry and possible solutions.

In cell therapy, cells are used as a therapeutic agent. In autologous therapies, the cells of interest, collected from the patient, are genetically modified if required, expanded and infused back into the same patient. The same process occurs in allogeneic therapies, but here the cells are collected from a histocompatible healthy donor and infused into a patient.

The first products to reach the market have shown efficacy in liquid cancers. In addition to the products based on chimeric antigen receptor (CAR) T-cells, T-cells, natural killer cells and macrophages can be genetically modified to express T-cell receptors guided to recognize cancer antigens. These products could improve safety and efficacy, whilst also being applicable to solid cancers. However, this approach presents several challenges due to the tridimensional structure and the various mechanisms of immune-evasion developed by the tumor microenvironment. Here, combination therapies, in which cell therapy synergizes with other cancer treatments (e.g. chemotherapy or immune checkpoint inhibitors) are currently being investigated.

To enhance product safety, appropriate protocols to mitigate toxicities related to product administration have been introduced, and cell therapy products with built-in switch-off mechanisms have been generated to prevent graft-versus-host disease. While cell therapy looks to expand its applications beyond immuno-oncology, the field will rely upon systematic approaches and the analysis of large datasets to efficiently support every stage of the product development life cycle.

Autologous therapies have evolved from an academic and clinical setting, with early development taking place in the clinic—often under hospital exemption. As a result, several manufacturing issues were inherited from these settings, such as lack of automation, and an underdeveloped supply chain. By definition, autologous therapies are personalized, and for this reason, the maintenance of the chain of custody and identity is critical throughout the entire manufacturing process as failure to document the identity of the product could be fatal for the patient. This also heightens the need to address any logistical challenges and develop suitable transportation systems.

The industry has developed a *modus operandi* that addresses the new manufacturing needs by scaling out operations. Production is kept in close proximity to the clinic, often with manufacturing suites located at the hospital site or nearby. Close alignment with analytical support is also essential in order to reduce the time spent on chemistry, manufacturing and controls (CMC) activity. To increase time efficiency, automation has now started

to be employed, often with 24-hour production, running seven days a week to keep up with manufacturing output. This requires a different approach to the workforce, moving away from classical work patterns. We expect to see much more innovation going into this sector with the further development of automated and closed modular systems for patient-scale cell therapy manufacturing. Further optimization of the manufacturing processes will overcome the current bottlenecks and reduce the substantial costs currently associated with autologous products.

Scaling out is an alternative to scaling up, where manufacturing is centralized and operated on a large scale. As some companies establish their own manufacturing centers with CMC and quality assurance capabilities in strategic geographical points, others choose to partner with suitable contract manufacturing organizations or access manufacturing centers. Scaling up is a model compatible with allogeneic off-the-shelf products, where large batches are produced to treat hundreds of patients.

At this end, a suitable starting material available in unlimited quantities, compatible with all haplotypes and amenable to any indications will be advantageous. The concept of generating a hypoimmunogenic universal donor cell, to be used as starting material, by differentiating inducible pluripotent stem cells (iPSCs) has been pursued by a number of companies. As iPSCs can divide indefinitely, they could provide the abundant starting material required for the manufacturing of large cell therapy batches.

Alternatively, a source of starting material could come from the process of cellular transdifferentiation. By identifying key regulatory switches, such as transcription factors, it is possible to convert any human cell type into any other without needing to go through a pluripotent stem cell stage.[1] Approaches such this (e.g. Mogrify) systematically identify and rank transcription factors, through large-scale data analysis and next-generation bioinformatics, which can then be virally delivered to drive faster and more efficient cell differentiation or cell conversion (e.g. fibroblasts into T-cells). Optimizing cell conversion in this manner has the potential to provide 'infinite amounts' of starting material suitable for use, not only, as cell therapies but also in regenerative medicine. Computational approaches and analysis of large-scale datasets are an essential asset in the advancement of cell therapy.

It is through innovative solutions that we will see the current growing pains in cell therapy manufacturing overcome and a new generation of products being delivered, offering greater safety and efficacy, for a larger number of patients. **CP**

References

1. *Rackham O.J.L. et al. A predictive computational framework for direct reprogramming between human cell types. Nature Genetics. 2016 Mar;48(3):331-5. doi: 10.1038/ng.3487. Epub 2016 Jan 18.*

Since gaining her PhD in molecular immunology at UCL in 2006, Alessandra has held a variety of positions in both the public and private sectors. She is currently Director of Process Development at Mogrify, a biotech company focused on the development of scalable next-generation cell therapies.

MOGRIFY AND SANGAMO FORM CELL THERAPY PARTNERSHIP

Collaboration and exclusive license agreement for Mogrify's iPSC- and ESC-derived regulatory T cells

The UK-based cell therapy company Mogrify Ltd., and Sangamo Therapeutics, a genomic medicine company, have executed a collaboration and exclusive license agreement for Sangamo to develop allogeneic cell therapies from Mogrify's proprietary induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) and Sangamo's zinc finger protein (ZFP) gene-engineered chimeric antigen receptor regulatory T cell (CAR-Treg) technology.

"Mogrify is delighted to announce its second commercial deal with a U.S. biopharma and the first in the exciting field of T cell immunotherapy," said Darrin Disley, chief executive officer, Mogrify. "The combination of Mogrify's proprietary systematic cell conversion technology and Sangamo's regulatory T cell platform and proprietary ZFP platform is a natural fit. Sangamo is at the forefront of the development of a world-class engineered ZFP genome editing platform and we are very happy to be partnering with such an innovative company."

Jason Fontenot, senior vice president, head of cell therapy, Sangamo, said, "This license agreement provides Sangamo with access to Mogrify's cell conversion technology, which will diversify our options as we develop off-the-shelf allogeneic CAR-Treg cell therapies. We expect this collaboration to accelerate our development of scalable and accessible CAR-Treg cell therapies, so that we can potentially deliver treatments to patients with inflammatory and autoimmune diseases more rapidly."

Mogrify says its technology enables the transformation of any human cell type into any other human cell type. This transformation is achieved using transcription factors or small molecules identified using proprietary big data technologies. iPSCs and ESCs provide an evergreen starting material for the generation of Tregs, and facilitate more complex engineering and greater manufacturing scalability, potentially enabling the resulting therapies to be more cost-effective and thus more accessible to larger patient populations.

Under the terms of the agreement, Mogrify will be responsible for the discovery and optimization of the cell conversion technology from iPSCs or ESCs to regulatory T cells, and Sangamo will be granted exclusive rights to use Mogrify's technology to create Tregs from iPSCs or ESCs. Sangamo expects to then use its ZFP gene-engineering technology and therapeutic development capabilities to transform these Tregs into novel "off-the-shelf" allogeneic CAR-Treg cell therapy candidates and hopes to take them through clinical development through to registration for the treatment of inflammatory and autoimmune diseases.

Original article published in *Contract Pharma* June 2020