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Scanning the horizon for high value-add manufacturing science: Accelerating manufacturing readiness for the next generation of disruptive, high-value curative cell therapeutics

PAUL HOURD & DAVID J. WILLIAMS

Wolfson School for Mechanical, Electrical and Manufacturing Engineering, Centre for Biological Engineering, Loughborough University, Leicestershire, United Kingdom

Abstract

Background. Since the regenerative medicine sector entered the second phase of its development (RegenMed 2.0) more than a decade ago, there is increasing recognition that current technology innovation trajectories will drive the next translational phase toward the production of disruptive, high-value curative cell and gene-based regenerative medicines. *Aim.* To identify the manufacturing science problems that must be addressed to permit translation of these next generation therapeutics. *Method.* In this short report, a long lens look within the pluripotent stem cell therapeutic space, both embryonic and induced, is used to gain early insights on where critical technology and manufacturing challenges may emerge. *Conclusion.* This report offers a future perspective on the development and innovation that will be needed within manufacturing science to add value in the production and commercialization of the next generation of advanced cell therapies and precision medicines.

Key Words: *disruptive, gene editing, induced pluripotent stem cells, manufacturing readiness, manufacturing science, regenerative medicine, technology readiness*

Introduction

Since the regenerative medicine sector entered the second phase of its development (RegenMed 2.0), which marked a step change in translation more than a decade ago [1], there is increasing recognition that current technology innovation trajectories will drive the next phase of the industry toward the production of disruptive cell and gene-based therapies that shift the therapeutic paradigm from symptomatic or disease-modifying treatments to high-value, reimbursable curative medicines [2,3]. In an industrial context, while this transition offers business growth paths with more certainty of high rewards, it may require an equivalent step change in translational capability if the industry is to be ready for the next wave of manufacturing and supply chain challenges that this new generation of regenerative medicines will bring. In this short report a long lens look within the pluripotent stem cell (PSC) therapeutic space is used to gain early strategic insights on where these manufacturing challenges are likely to emerge and to draw future perspectives on the need for reformulated or new manufacturing science.

In the last ten years, significant technological progress has been made in the PSC therapeutic space [4,5], with human induced pluripotent stem cell (iPSC) technology as a new source of patient-specific therapeutic cells, potentially free from the ethical concerns, legislative issues and immune rejection barriers of human embryonic stem cells (hESCs) and their somatic cell nuclear transfer hESC counterparts, beginning to dominate the field [6]. This has been driven by limitations in the availability of most specialist somatic cells and current restrictions in the expansion of adult stem cells together with their associated heterogeneity arising from sources such as bone marrow [7–9].

Advances in iPSC technology, coupled with recent breakthroughs in gene editing and ability to provide highly engineered, developmentally inspired cellular microenvironments (niches) through advances in tissue engineering, by bringing regenerative medicine and gene therapy closer, are expected to substantially broaden the clinical scope of the field over the next decade [3,5,10]. This envisions a natural innovation trajectory toward the development of more precise, highly engineered PSC-derived combination products

Correspondence: **David Williams**, PhD, Wolfson School for Mechanical, Electrical and Manufacturing Engineering, Loughborough University, Leicestershire, LE11 3TU, UK. E-mail: D.J.Williams2@lboro.ac.uk

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and targeted combinatorial therapeutic strategies that have the potential to deliver enhanced safety and efficacy attributes (i.e., by combining cells with other integral or synergistically delivered components that may contribute to the mode of action and the intended therapeutic effect).

Convergent with rapid innovation in pharmacogenomics and molecular diagnostics ('-omics') screening technologies and the impressive momentum in other technology innovation trajectories (e.g. adoptive cancer immunotherapies), this evolution provides general pointers to the core manufacturing and operational innovations that may be needed to underpin the production of the next generation of cell and gene-based regenerative and precision medicines.

By considering approaches to how the convergence of multiple underlying enabling technology options may be brought together for the generation and configuration of the next generation of iPSC-derived cell and gene-based product technology concepts, we summarized the new and emerging manufacturing science challenges that need to be addressed to accelerate their transition from research and development (R&D) to clinical stage bioprocessing. We examined the main scientific/technical challenges related to the intrinsic engineered cellular features of the underlying product technologies and the corresponding risks to manufacturability and producibility. Special attention was given to a broad systems engineering perspective on the maturity of the capability and readiness of the individual underlying product technologies (Technology Readiness Level [TRL]) to deliver their function and the readiness of the corresponding manufacturing systems and/or processes for production (Manufacturing Readiness Level [MRL]). The assignment of TRLs and MRLs is not absolute and is intended to provide a broad indicator of relative maturity to assist a comparison of the challenges associated with technology-manufacturing transitions across multiple product candidates, based on current scientific knowledge, clinical experience and industry practice.

The challenges to advancing product technology maturity within the PSC therapeutic space

The future landscape for candidate iPSC-derived cell and gene-based therapeutic products

The convergence of multiple enabling technology options is providing scope for the development and production of a range of different iPSC-derived cell product technology concepts, applicable to therapeutic modalities ranging from simply transplanting terminally differentiated engineered cells to reseeding decellularized organs or reconstructing 2-dimensional (2D) or 3-dimensional (3D) functional living tissues/organs. Approaches to the generation and configuration of candidate iPSC-derived therapeutic product concepts are shown in Figure 1. This illustrates how the integral functional component parts and their underlying enabling technologies may be brought together and integrated.

Focussed on the derivation of terminally differentiated PSC-derived cells for 2D and 3D cell therapeutic applications rather than on the direct use of undifferentiated PSCs or their cell- free derivatives (e.g., exosomes), this logic imagines five major PSC-derived product technology candidate concept areas: iPSC-derived cell-based technology, gene-modified iPSC-derived cell-based technology, iPSC-derived organoid-based technology, gene-modified iPSC-derived organoid technology and iPSC-derived 3D tissue–engineered technology. These concepts are founded on the manufacture of different cell-based functional elements that comprise [1] the derivation of primed and naïve-state iPSCs from reprogrammed human somatic cells [2], the expansion and terminal differentiation of iPSCs into cell types of interest [3], the genetic engineering or gene editing of iPSCs [4], the encapsulation of iPSC-derived therapeutic cells in fabricated 3D scaffolds for engraftment or cell delivery and [5] the generation of tissue-specific 3D organoids from iPSCs.

Challenges to transitioning product technology maturity

Many of the configurations in Figure 1 are clearly relevant to an array of applications in healthcare, with experimental proof-of-concept having already been achieved pre-clinically for many of the different functional elements. Primed state iPSCs, for example, have been generated from a variety of different human somatic cell types, such as blood cells, fibroblasts and keratinocytes, to derive a range of PSC-derived terminally differentiated cell types, including cardiomyocytes, motor neurons and insulin-producing pancreatic cells. Their therapeutic potential has been evaluated in several pre-clinical animal studies and human disease models [4,5]. *Ex vivo* gene-editing technologies and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology, in particular, have been widely used in iPSCs and PSC-derived organoid cultures, with a growing list of proof-of-concept and pre-clinical studies demonstrating therapeutic potential for single-gene hereditary diseases, such as cystic fibrosis or β-thalassemia [11–15].

However, with little clinical experience using iPSC-derived cells compared with hESCs, significant quality and safety risks related to the asymmetric maturity of the underlying technologies remain [4,5]. An