



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

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## 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

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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 reseeded 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  $\beta$ -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

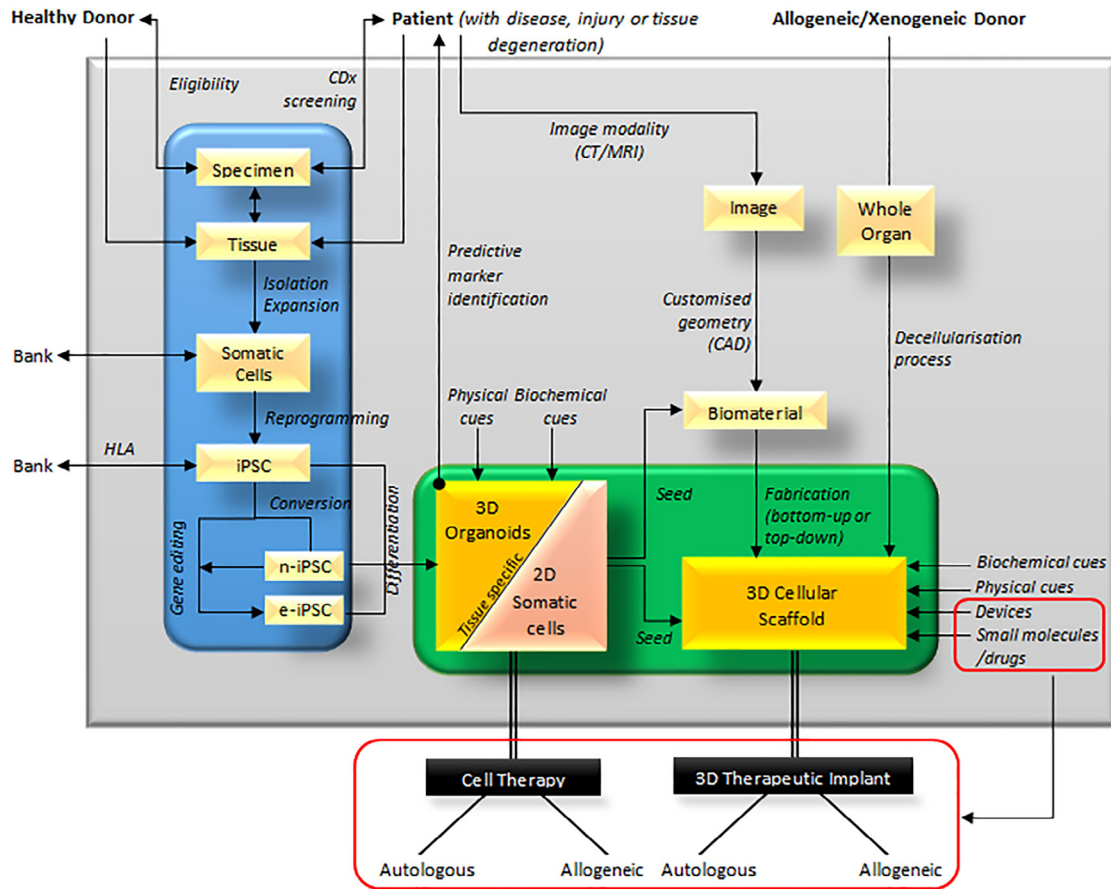


Figure 1. Schematic of approaches to generate candidate iPSC-derived cell and gene-based therapeutic products. Somatic cells isolated from tissue acquired from a patient within a stratified disease subgroup (predictive biomarker(s) identified via a companion diagnostic [CDx]) or from an eligible normal healthy donor are reprogrammed into iPSCs and/or converted to naive state (n-iPSC). Genetic defects in iPSCs or n-iPSCs can be corrected or the cells can be enriched using gene-editing technology (e-iPSC). Subsequently, iPSCs with or without edited modifications are differentiated into multiple target tissue-specific 3D organoids (induced with exogenous self-organization signalling cues) or 2D cell lines before being transferred back to the patient as functional organ-like units or as a cell suspension, respectively. An alternative is to seed biomaterials or acellular pre-formed scaffolds (fabricated from synthetic or naturally derived) with terminally differentiated 3D organoids or 2D cells to form general-form biomimetic structures or customized 3D tissue-engineered constructs for implantation. These constructs can be combined with other integral or synergistically delivered active components or medical device technologies to further refine their development and functionality before, during or after transplantation into the patient.

understanding of these technology-related risks brings into view the technical and scientific challenges that need to be addressed to transition these relatively immature product technologies (TRL 1 to TRL 3) to a level of readiness sufficient for incorporation into a product development program and entry to phase 1 clinical trials in humans (TRL 5). To assist a strategic perspective, the snapshot in Figure 2 provides a high-level view of the level of technology maturity across five major PSC-derived product technology concept areas, based on the intrinsic capability features of the underlying technologies to deliver their function [16]. A consideration of the main quality and safety risks associated with the *ex vivo* manipulation of the cellular component and its niche allows the following future perspectives for transitioning product

technology maturity within the PSC therapeutic space to be drawn.

Persistent risks associated with the unpredictable potential for tumourigenicity and immunogenicity continue to raise challenges for the current generation of cell plasticity (iPSC reprogramming, expansion, terminal differentiation) and gene-editing technologies.

The potential for tumourigenicity primarily arises from random insertion of integrating reprogramming vectors, off-target mutagenesis from gene editing and risk of teratomas arising from transfer of residual undifferentiated or defective iPSCs. The development of second-generation, non-integrating iPSC reprogramming methods has reduced the risk of tumourigenicity arising from the random insertional mutagenesis associated with their integrating

PSC-derived product technology candidates	TRL	TRL	TRL	TRL	TRL	TRL	TRL	TRL	TRL
	1	2	3	4	5	6	7	8	9
ESC-derived cell-based technology	Green	Green	Green	Green	Green	Green	Green	White	White
iPSC-derived cell-based technology	Green	Green	Green	Amber	Amber	White	White	White	White
Gene modified iPSC-derived cell based technology	Green	Green	Amber	White	White	White	White	White	White
iPSC-derived organoid based technology	Green	Green	White	White	White	White	White	White	White
Gene modified iPSC-derived organoid technology	Green	Amber	White	White	White	White	White	White	White
iPSC-derived 3D tissue engineered technology	Green	Green	Green	Amber	White	White	White	White	White

Figure 2. Snapshot of TRLs assessing the maturity of critical technology elements for the development of PSC-derived cell and gene-based product technology candidates. Each box represents the assigned TRL (where technology moves through nine phases: concept exploration [TRL1–2], concept validation [TRL3–4], prototype development [TRL5], pilot production and demonstration [TRL6–7], production and market introduction [TRL8] and production and distribution [TRL9]). Green boxes indicate that all required outputs have been achieved and amber boxes indicate some shortfalls in required outputs. Assignment of TRL is not absolute and is meant as an indicator of the relative product development program risk and need for further development milestones, which may also be application/indication specific. This represents a high-level evaluation of TRLs based on an adaptation of the US Department of Defence TRL scheme [16]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

virus-based predecessors [17,18]. Nevertheless, further technology advances are required to overcome current limitations associated with incomplete reprogramming, as well as low reprogramming and differentiation efficiencies that result in heterogeneous populations and low yields of reprogrammed cells.

Continued improvement in the understanding of the molecular mechanisms underlying reprogramming, expansion and differentiation processes will result in the need to develop better strategies for reducing or eliminating genetic and epigenetic variations that have been observed to change molecular and functional properties of iPSCs and their derivatives. In this regard, naïve-state cell reversion technology has emerged as a promising candidate for resolving these issues, but further advances are needed to improve the efficiency of reversion and stabilization protocols [19].

Despite rapid progress in the gene-editing field, limitations related to gene-editing efficiency and specificity will result in the need to develop more precise *ex vivo* vector delivery systems [12,20,21]. Advances in this area will widen opportunities for reducing the frequency of off-target mutagenesis and cell genotoxicity events and for applying the technology to non-replicating cells (such as iPSC-derived neurons and cardiac myocytes) to extend the application to a broader spectrum of genetic diseases.

Immunogenicity potential in the autologous or allogeneic setting arises from the relative immaturity of PSC-derived somatic cells and changes to epigenetic and protein expression levels in differentiated cells that can arise from reprogramming, culturing and gene editing [5,22,23]. Current challenges are centred on reducing or avoiding the need for immunosuppression and improving the engraftment or persistence of PSC-derived therapeutic cells. Continued expansion in the understanding of the immune response to iPSC

derivatives and to the progeny of gene-corrected iPSCs, in terms of the type and amount of gene expression differences between iPSC-derived cells and their *in vivo* counterparts that can be tolerated after transplantation, will bring the need for further advances in methods for inducing cell maturation *ex vivo* (i.e., for the relevant to disease or organ) and for modifying the immune tolerance of iPSC-derived and gene-edited cells.

### Challenges to advancing the manufacturing maturity within the PSC therapeutic space

As a path to the early market application of these candidate PSC-derived product technology concepts, a necessary level of manufacturing maturity is required to enable the industrialization and transfer of their underlying enabling technologies into a robust, scalable production system design. By enabling the delivery of new product technology capability in a defined sequence of processing events, predictable manufacturing costs and schedules, reproducible levels of performance between manufacturing runs can be achieved.

Supported by an increasing contract manufacturing organization capacity and an expanding number of trade and standards organizations, specialized equipment manufacturers and cell therapy manufacturing and development services (the industrial base), current advances in manufacturing technologies are beginning to demonstrate incremental improvements in manufacturing process maturity and productivity [24,25]. The emergence of a range of closed-system devices and automated modular platforms that can be applied to simplify and automate specific upstream and downstream parts of the manufacturing process (e.g. cell enrichment, expansion, harvesting or purification)

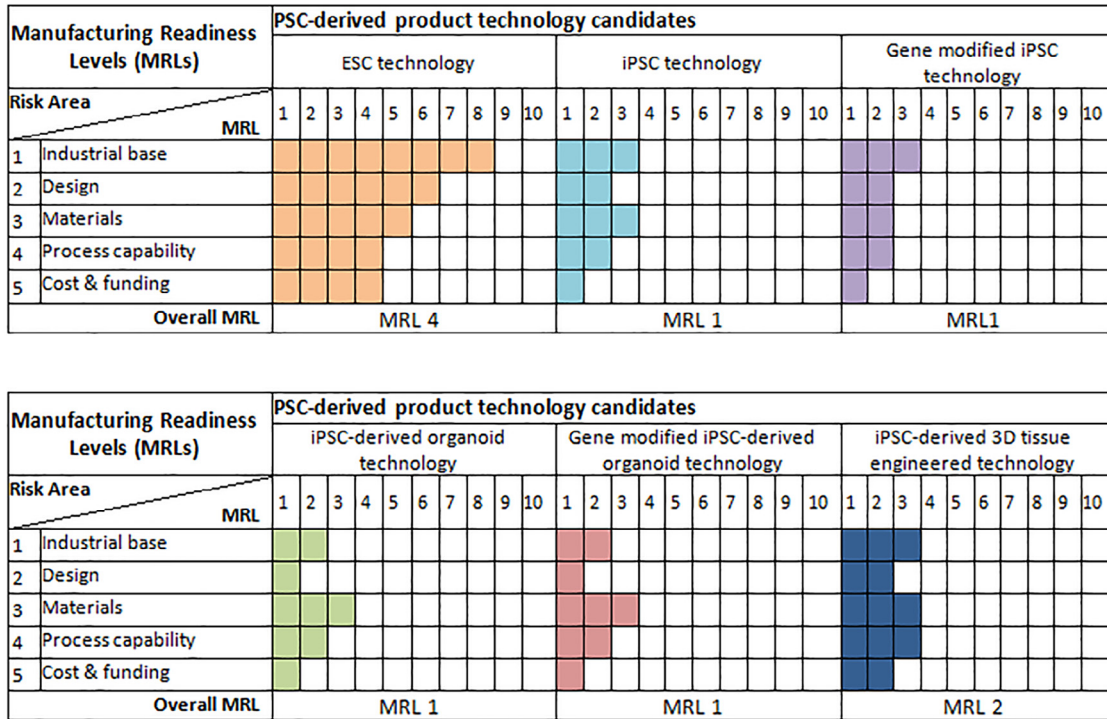


Figure 3. Snapshot of MRLs, assessing manufacturing maturity and the risk for production of the overall PSC-derived cell and gene-based product candidate assemblies. Each box is used to separately trace the maturation progress in each of the cross-cutting risk areas as MRLs increase from MRL1 through MRL10 (concept and feasibility analysis [MRL1–4], technology development [MRL5–6], engineering and manufacturing development [MRL7–8], production and deployment [MRL9] and operations and support [MRL10]). The lowest MRL is used to assign the overall MRL for the identified core processing areas. Assignment of MRL is not absolute and is meant as an indicator of the relative manufacturing risk and need for further development milestones, which may also be application specific (e.g., production of cells or organoids). This represents a high-level evaluation of MRLs based on an adaptation of the US Department of Defence MRL scheme [26].

has gone some way to resolving fundamental manufacturing challenges for the production of somatic cells (i.e., as a cell therapy or starting material for iPSC generation), adult stem cells (relative MRL 7–8) and, to a lesser extent, hESCs (maturity transitioning to MRL 4; Figure 3) [26]. However, as these first-generation cell-based therapies begin to reach the market, the continued pressure to reduce cost of goods (CoGs) and to improve productivity per unit cost remains a key challenge and is the primary current focus of the industry.

For the next wave of potentially personalized, engineered cell-based products that may emerge in the PSC therapeutic space, the transition from a craft phase to an industrial phase of biological engineering, with the convergence of manufacturing system automation, synthetic material discovery and gene/cell state manipulation, is set to challenge the readiness and capability of the existing manufacturing technology and industrial supply chain base. An understanding of the manufacturing risks emerging in this space [3] brings into view a number of new and additional challenges that need to be addressed to transition relatively immature underlying enabling technologies (MRL

1–MRL 2) to a level of readiness sufficient to enable pilot Good Manufacturing Practice (GMP) (pre)production to support phase 1 clinical trials (MRL 5). The snapshot in Figure 3 provides an equivalent high-level view of the level of manufacturing maturity across five major PSC-derived product technology concept areas, based on the intrinsic capability features of the underlying technologies for integration into a system or sub-system for production of the overall product assembly. A consideration of the main manufacturing risks, related to system design, materials manufacturability, process capability, cost and infrastructure, allows the following future perspectives for transitioning manufacturing maturity within the PSC therapeutic space to be drawn.

**Key areas for manufacturing focus**

*Ipsc reprogramming methods and equipment*

Advances in reprogramming methods now provide multiple candidate vectors for gene delivery, with the field shifting toward safer and accelerated chemical and physical non-integrative techniques, under defined xeno-free culture conditions [17,18]. Increasingly, such

scientific advances are yielding commercially available non-integrative reprogramming, kit-based protocols and services. Generally, however, these methods remain highly inefficient and labor-intensive and are often undermined by slow kinetics and poor *ex vivo* control of programming factor presentation and kinetics [18,27].

Continued advances in the mechanistic ‘-omics level’ understanding of the hierarchical events underlying reprogramming processes will extend opportunities for enhancing kinetics and efficiencies [28,29]. Clarification of the metabolites (metabolomics) underlying reprogramming mechanisms, for example, may enable the development of new reprogramming parameters for enhancing the generation of fully reprogrammed human iPSCs [29]. Further advances in the discovery and development of new chemically defined or artificial reprogramming factors and in corresponding 3D biomaterial-based platforms for controlling spatiotemporal precision delivery of reprogramming factors will be needed to improve the scalability and reproducibility of the technology. Enabling the development of simplified iPSC reprogramming methods, this will bring opportunities to make the technology more amenable to automation and to implementation in GMP settings, while driving down the CoGs for vector materials.

Beyond improvements in reprogramming efficiency, continued discovery and understanding of the donor-dependent and patient-specific factors that influence the lineage differentiation propensity, organoid self-assembly and functional capacity of iPSCs and their derivatives [30,31] will result in the need to develop standardized screening and selection criteria for donors and patient-specific starting materials (somatic cells). Further developments in this area are required to improve the ability to consistently produce iPSCs and their terminally differentiated derivatives to the required specifications for allogeneic (e.g., human leukocyte antigen [HLA]-matched iPSC lines) and patient-specific applications [23,32].

Continuing growth in the field will result in the need for extra manufacturing capability and capacity to meet an increasing demand for the cost-effective production and supply of quality-assured viral and non-viral vectors. Up-scaling production and closing the material quality gap will be critical to reducing qualification and validation efforts of cell therapy manufacturers.

#### *Ipsc expansion and differentiation methods and equipment*

The development of the first fully GMP-compliant protocol for manufacturing iPSC lines for potential clinical use represents significant progress in this area [33],

but underscores the need for further advances in technology development to reduce CoGs, exclude heterogeneity in starting materials, improve reprogramming efficiencies, reduce variation between manufacturing runs and improve the resolution of genomic stability testing performed for quality control (QC) and release.

As part of the manufacturing chain, further advances are required in the development of alternative, scalable cold chain and biopreservation methodologies that can be shown to have minimal impact on reprogramming, proliferation and directed differentiation efficiencies, as well as the cellular properties of the final product. This will reinforce the need for technological solutions to maintain and orchestrate complex supply chains and support ‘needle-to-needle’ traceability.

In terms of scalability, the PSC field is progressively moving from 2D flat surfaces (flasks/plates) to suspension cell cultures in stirred-tank/microcarrier-based bioreactors, but the transfer to larger-scale geometries remains a fundamental challenge. Overcoming mass transfer and metabolic constraints, which currently limit the level of cell expansion and differentiation process intensification that can be achieved, will provide a path to reducing the CoGs associated with current craft-based media exchange strategies and to improving industrial scale-up potential [34].

Conventional 2D flask/plate-based protocols are available for the directed differentiation of iPSCs into a wide range of cell lineages and 3D tissue-specific organoid structures. Current iPSC differentiation efficiencies, however, are still highly variable and can produce a heterogeneous mixture of partially reprogrammed ‘defective’ cells and undifferentiated cells. So too are current organoid derivation protocols, which rely on uncontrolled, spontaneous morphogenesis processes at the microscale and yield inconsistencies in macroscale organoid morphology, cyto-architecture and cellular composition. This currently limits their standardization and clinically relevant application [35].

A range of manufacturing techniques, relying on positive and negative selection procedures (e.g. cell sorting), using relevant selective markers or reporter gene expression can be used to enrich for the target phenotype in the final product [21]. However, further technology advances are required to overcome limitations with current analytical techniques and molecular characterization methods, which are not reliably sensitive enough to sufficiently define a heterogeneous cell population that may contain cells in different dynamic states and with tumourigenic or immunogenic potential [36]. Continued development of alternative approaches, such as the use of a suicide gene or other safety checkpoints, will result in the need for the development of more sophisticated, scalable downstream

automated technologies that can be used to detect and selectively eliminate unwanted or transformed cells *ex vivo* in GMP settings [37–39].

Continued advances in the discovery, design and engineering of chemically defined, synthetic biomaterial substrates and soluble morphogenic analogues will result in the need for the development of more dynamic bi-phasic bioreactor systems, which can extend and exploit better control over the behavior of iPSCs during *ex vivo* culture and differentiation. With the ability to rationally tailor chemical and mechanical signals in 3D/4D controllable configurations to maintain self-renewal, to induce cell lineage-specific differentiation or to enhance functional maturation, this will represent a step change toward widening scalable and cost-effective *ex vivo* production options for iPSCs and tissue-specific organoids for clinical application.

#### *Gene-editing methods and equipment for ex vivo modification of iPSCs*

With approximately two dozen tool and kit service companies now offering CRISPR/Cas9-related products, the CRISPR/Cas9 nuclease system is emerging as the most accessible system for precision genome engineering, although there are still uncertainties related to the licensing and commercial use of the technology.

Continued expansion in the mechanistic understanding of the CRISPR/Cas9 nuclease system (as well as the zinc-finger nuclease [ZFN] or transcription activator-like effector nuclease [TALEN] technologies) will widen opportunities for integrating the technology into commercial production systems. However, with a complex mix of active substances, reagents and critical raw materials, further advances in the ability to measure and characterize the process (i.e., critical process parameters and material attributes) and the product output (i.e., critical quality attributes of the genetically modified cell phenotype) are needed. This will drive improvements in the precision and CoGs and enable the development of manufacturing QC and release strategies in GMP settings.

#### *Product and process characterization and control technologies*

At a fundamental level, further advances in validatable measurement and characterization technology are needed to overcome limitations of current analytical methods and approaches for characterizing the functional identity of therapeutically relevant cell populations. Such advances would need to be extended to detecting the level of cellular impurities (residual undifferentiated or partially differentiated iPSCs or partially reprogrammed somatic cells, for example) and to detecting the level and significance

of genetic aberrations at both the level of process development (e.g., to verify integrity of starting materials, intermediates and drug substances) and in the final drug product. These advances will extend the opportunity to develop specifications for cellular starting or input materials that are deterministic of reprogramming, gene editing and expansion or differentiation outcomes, which will be key for establishing comparability parameters and facilitating the mutual recognition of clinical-grade iPSC lines as a starting material for iPSC-derived therapies. This will be a critical first step to reducing the production costs attributed to need for multiple levels of QC and assurance throughout the manufacturing process [40] and for the demonstration of product comparability.

Further advances in 3D manufacturing process technology and continued expansion in the discovery of biomarkers and reporter genes for target or contaminant cells and other potential surrogates of cell quality (e.g., signalling molecule patterns or exosomes into culture media) will result in the need for more sophisticated real-time process analytical technology, non-destructive sampling and test systems as well as quantitated imaging. Such analytical advances will expand opportunities to apply new mechanistic system modelling approaches to the development of feedback-control methods to support data-driven adaptive and automated manufacturing processes. These may rely, for example, on the measurement of variability in gene expression signatures of cell input material, purity ratios of cell populations, cytokine activity patterns, ‘omic’ biomarker levels or rates of biochemical change and their influence on cell identity, purity and potency [34].

Advances in measurement and characterization technologies will reinforce the need for corresponding advances in data analytics and management technology. Combined with the development of more strongly integrated patient registries and standardized data collection infrastructures (including relevant biobanks), this will enhance the scientific and clinical understanding of the safety and effectiveness of these newly emerging products for multiple stakeholders.

#### **Accelerating manufacturing readiness—requirements for manufacturing science**

Anticipation of technology innovation trajectories and their impact on future product development within the PSC therapeutic space has provided a useful future perspective on the readiness of current industrial manufacturing process technology, equipment and operational infrastructure to deal with the longer and more complicated processes that will be involved in the production of the next generation of advanced cell therapies.

This new generation of high-value, disruptive regenerative medicines will demand a higher level of production system efficiency, reliability and operational performance. In the iPSC situation, for example, implementing the multiple technologies and the highly complex sequence of processing steps involved in cellular reprogramming, gene editing, expansion and differentiation into a GMP environment adds a greater level of complexity and lengthens the time required to produce high-quality, functionally mature terminally differentiated cells. With the implicitly sensitive and variable nature of multiple cellular material process inputs, this makes process consistency and product comparability much more difficult to achieve. The need for a specific set of reagents, a different sequence of steps, perhaps exploiting 3D culture settings, a decoupling inventory step or a special final formulation for each terminally differentiated cell type adds significantly to this complexity.

It is this complexity that will drive the need for more flexible or reconfigurable production systems that are able to support long-term and parallel processes for the manufacture of multiple diverse cell types of varying batch sizes. This will result in the need to develop new, more agile and adaptive process technologies and equipment that can deliver new levels of performance and flexibility. Corresponding advances in operational plant design, systems integration and instrumentation will be needed to maintain control and integrity of product and process flows. Simply building bigger and better manufacturing facilities will not be enough. Instead of manufacturing in dedicated facilities (or even designated cleanrooms), advances in the development of closed-processing systems will allow manufacturing to happen in spaces where multiple pieces of equipment can be integrated to manufacture multiple therapies in close physical proximity.

From an engineering standpoint, to take this advance to a greater level of understanding of the manufacturing process and the interplay between the required product specifications and the achievable process capability will be central to developing a scalable production system that can deliver a product with controllable functional metrics. Advances in measurement and characterization technologies, by improving understanding of the increasingly complex product, will be needed to drive an increase in precision and process control. In this context, significant development and innovation within manufacturing science are the only way that the regenerative medicine sector will move from 'the process is your product' paradigm to more certainty in process execution [41].

Putting all these perspectives together, the regenerative medicine sector is beginning to enter the next phase of its development. While the industry has previously focused its attention with respect to

manufacturing on incremental innovation and cost reduction, the hope is that the emphasis of future manufacturing science is targeted at manufacturing and supply chain challenges, not because they are easy but because they are hard and will add value to the industry. Given the leadership, funding, time and commitment, this will be the only way to accelerate technology and manufacturing readiness for the next generation of disruptive, high-value cell therapeutics, recognizing that a significant parallel effort will be needed to transform the organizational and institutional readiness for adopting and implementing these emerging and potentially disruptive therapies.

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