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Patient-specific hiPSC bioprocessing for drug screening: Bioprocess economics and optimisation

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ABSTRACT

This paper describes a decisional tool that is designed to identify cost-effective process designs for drug screening products derived from human induced pluripotent stem cells (hiPSC). The decisional tool comprises a bioprocess economics model linked to a search algorithm to assess the financial impact of manual and automated bioprocessing strategies that use 2D-planar tissue culture technologies. The tool was applied to a case study that examines the production of patient-specific iPSC-derived neurons for drug screening. The production strategies were compared across three analytical drug screening methods, each requiring cell production at a distinct scale (manual patch-clamp analysis, high throughput screening and plate-based pharmacology), as well as different annual cell line utilization requirements ('throughputs') (between 10 and 100 lines) so as to represent different industry scenarios. The tool determined the critical cell line throughput where the most cost-effective production strategy switched from the manual to automated workflow. The key process economics driver was the number of iPSC expansion stages required. Stochastic modelling of the bioprocess illustrated that the automated was more robust than the manual workflow in the scenarios investigated. The tool predicted the level of performance improvements required in iPSC expansion and differentiation as well as reductions in indirect costs and media costs so as to achieve an acceptable cost of goods (COG).

1. Introduction

The advent of hiPSC technology [1] has provided an opportunity to revolutionise modern medicine. Aside from their potential use in the cell therapy sector as clinical grade raw material to produce treatments for a variety of disorders with unmet clinical needs, hiPSCs also offer a more near term application as a tool with which current drug discovery, phenotypic screens, and safety testing programmes might be qualitatively improved [2–5]. This article investigates the production of patient-specific hiPS-cell lines, namely a cell line which is derived from a single patient in order to capture their individual genotype and phenotype. Manufacture of patient-specific cell lines will require scale-out of the process, whereby the manufacturing scale or lot size is kept constant and replicated for each cell line. In contrast, manufacture of non patient-specific cell lines can benefit from scale-up, whereby the manufacturing scale or lot size is increased when larger demands of a cell line are required (see Fig. 1a). Non patient-specific cell lines are more likely to be used for purposes that are independent of the specific genotype or phenotype of a cell.

In drug development, many pre-clinical testing platforms based on animal species prove to be of limited predictive value due to fundamental biochemical, physiological and genomic variations from humans [6–8]. hiPSC-differentiated somatic cells offer an alternative, humanised platform for pre-clinical efficacy and toxicity studies for novel therapeutics in development [9]. They also afford a predictive platform at the preclinical to clinical interface in, for example, safety vigilance of novel therapeutics in development, pinpointing drug responders from non-responders and stratifying patients into treatment groups in patient cohorts. Furthermore, the ability of patient-specific hiPSC-derived cells to model genetic and epigenetic variations of a broad spectrum population may also augment phase I/II clinical trials via the demonstration of a drug's safety

Abbreviations: COG, cost of goods; CTS, CompacT SelecT™ automated cell culture machine; FCI, fixed capital investment; hPSC, human pluripotent stem cell; HTS, high throughput screening; iPSC, induced pluripotent stem cell; PCA, patch-clamp analysis; NCE, novel chemical entity; PBP, plate-based pharmacological analysis; PSC, pluripotent stem cell.

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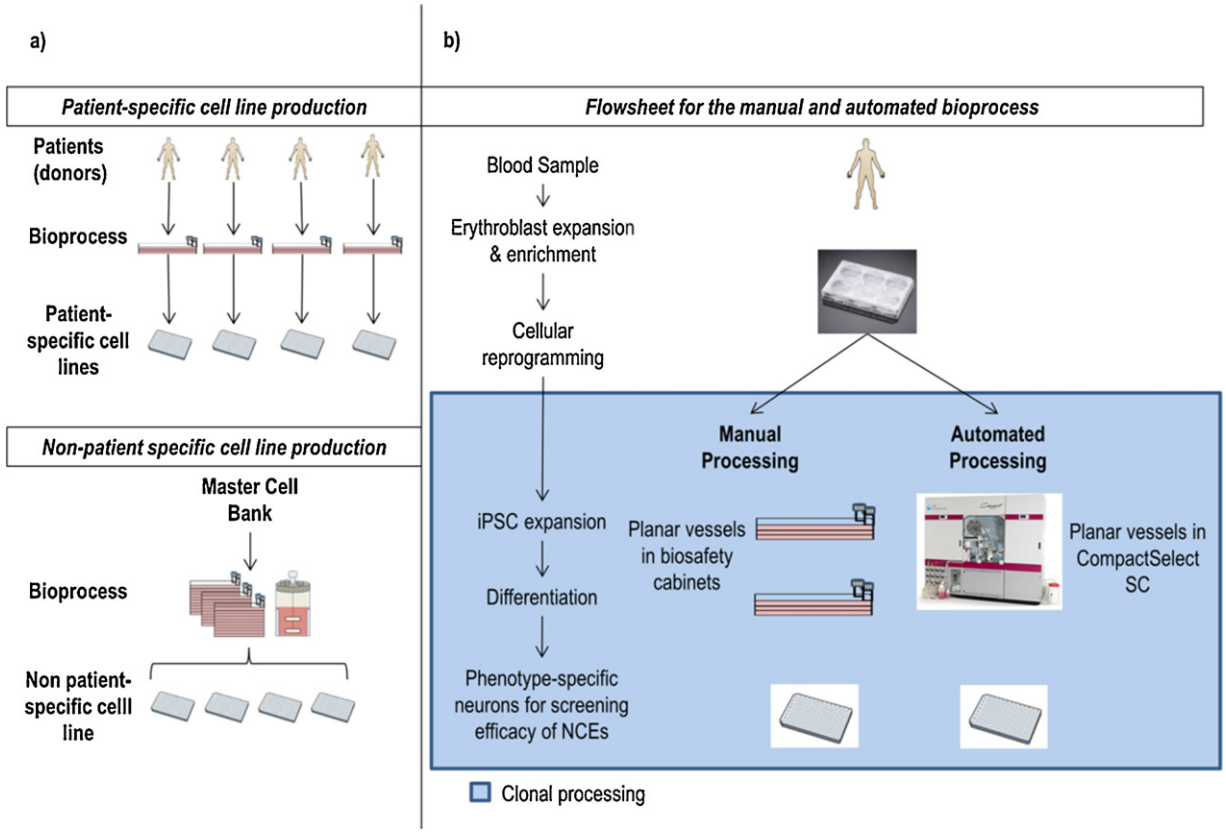

Fig. 1. (a) Outline of process techniques for patient-specific cell lines and non-specific cell lines. The bioprocess for a single patient-specific cell line is scaled-out to achieve a higher throughput. Non-specific bioprocesses are scaled-up to achieve a higher throughput. (b) An overview of the bioprocess strategies considered within this case study. Clonal processing is employed following cellular reprogramming, therefore the technology used to process each donor sample remains constant until this point, regardless of the scale of the bioprocess.

and efficacy within a target population in vitro. Patient-specific hiPSC-derived cells may be of particular use in the assessment of NCEs where the degree of efficacy observed within a cohort may depend upon a specific geno- or phenotype [10]. In this manner they have the potential to lower the time, costs, and risks associated with committing a drug to clinical trials. The cost of bringing a new drug to market is currently estimated to be US$1.2bn—US$1.7bn. When juxtaposed with a clinical attrition rate that can be close to 90% (phase I to approval) [11], such an expensive and complex development cycle has caused drug developers to display caution when committing candidate therapies to clinical trials [12,13].

hiPSC-derived cell types have faced challenges in their implementation owing partly to key issues associated with their production at large scale. Many current iPSC manufacturing protocols are based upon planar, 2-D culture vessels due to their affordability and simplicity [14]. However, lack of scalability owing to limitations in surface area to volume ratio and the inability to conduct online process monitoring are major drawbacks to many 2-D culture systems, as is their labour-intensive nature, which limits their throughput and applicability to larger scale processes [15,16]. Non patient-specific cell processing may benefit from recent iPSC bioprocessing advances, such as single-use bioreactors (SUBs) and microcarriers, which offer both greater potential for scale-up and an enhanced degree of containment in comparison to planar vessels [17–22]. However, patient-specific bioprocesses are not amenable to scale-up and will likely depend upon planar culture technologies, which may be useful when producing cell populations numbering in the low millions [23,24]. Automation systems designed to accommodate planar culture vessels, such as the CompacT SelecT^{TM} (CTS) (Sartorius, Royston, UK), have the potential to reduce the labour requirements, possible points of contamination, and to improve the reliability associated with autologous hiPSC bioprocessing [25–27]. Such systems could be implemented to help achieve large-scale manufacture of patient-specific stem cell products.

The biopharmaceutical sector has benefitted from the use of decisional tools that are able to evaluate alternative process designs in silico in order to achieve cost-effective process design and equipment selection [28–32]. As a nascent field, hiPSC processing is faced with a lack of consensus as to optimal process designs and scale-up/out strategies. Decisional tools similar to those applied to the biopharmaceutical sector can therefore prove useful for identifying key economic drivers and technical innovations required to bridge the gaps constraining widespread application of hiPSC-derived cells. There are only a limited number of studies investigating the impact of process design on manufacturing COG within the stem cell sector. Previous analyses have provided estimates of the current limitations [15,33] and relative cost of PSC processing technologies, including the use of commercially available flow-sheeting software (SuperPro Designer, Intelligen Inc., NJ, USA) to evaluate the economic potential of large-scale iPSC-derived cell bioprocess designs [34]. For other cell types, for example mesenchymal stromal cells for therapy, others have illustrated how a decisional tool can be developed to determine the scales at which microcarriers in SUBs becomes preferable to planar processing platforms during the expansion phase [16].

In this paper, an integrated decisional tool that combines both bioprocess economic modelling and optimisation of the manufacture of patient-specific iPSC-derived neurons for use as a tool in the screening of NCEs is described. The bioprocess economics model and integrated brute-force search algorithm are designed to iden-