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A Benchmark Study

Scalable hiPSC Expansion on Microcarriers with BioThrust's ComfyCell

Authors

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Abstract

This study presents a benchmark evaluation of BioThrust's ComfyCell bioreactor for three-dimensional human induced pluripotent stem cell (hiPSC) expansion on microcarriers under dynamic conditions, demonstrating its suitability for efficient, high-quality, and scalable cell manufacturing. Using the ComfyCell, more than 1.5 × 10^9 hiPSCs were produced, corresponding to a 65-fold expansion within 7 days, while maintaining high viability and preserving cellular identity. Differentiation assays further confirmed the potency of harvested hiPSCs through successful generation of derivatives from all three germ layers. In parallel, dissolved oxygen and key metabolites were closely monitored, providing insights into culture conditions and enabling process optimization. Overall, these results demonstrate the ComfyCell's suitability for scalable hiPSC cultivation under dynamic conditions, supporting the development of advanced biomanufacturing platform solutions for stem cell–based therapeutics.

Objective

The objective of this study was to benchmark the performance of BioThrust's Comfy*Cell* against a commercially available single-use stirred-tank bioreactor (STR_{Ref}) for microcarrier-based expansion of human induced pluripotent stem cells (hiPSCs). The evaluation focused on preserving key biological attributes, cell growth, viability, pluripotency, and differentiation potential, by regulating critical process parameters, such as dissolved oxygen (DO), pH, shear stress, and metabolite levels. Leveraging a novel bionic impeller design in combination with operation in perfusion mode, the study assessed the suitability of the Comfy*Cell* to deliver scalable, robust, and high-quality hiPSCs for the manufacturing of cell therapeutics.

Key Findings

1. The Comfy*Cell* demonstrated its ability to support a viable cell density exceeding 3.7 x 10^6 cells mL^{-1} without the need for direct aeration.
2. When operated in perfusion mode, a single Comfy*Cell* supported the production of more than 1.5 x 10^9 hiPSCs at a fold expansion of 65 in 7 days.
3. The Mem*Stir* impeller facilitated superior DO control at comparatively low agitation rates without the need for direct aeration.
4. The Comfy*Cell* maintained cell quality during expansion, as demonstrated by viability, identity, and differentiation potential evaluations.

Introduction

Human induced pluripotent stem cells (hiPSCs) hold transformative potential for regenerative medicine, disease modeling, and drug discovery due to their unlimited self-renewal capacity and ability to differentiate into any cell type [1-2]. Derived from adult somatic cells such as blood or skin through molecular reprogramming, hiPSCs bypass the ethical concerns associated with embryonic stem cells and enable patient-specific therapies, thereby reducing the risk of immune rejection [3].

Despite this promise, the manufacture of hiPSC-based therapeutics remains challenging. The development of scalable and cost-effective processes is still a major bottleneck preventing next-generation medicines based on these cells from reaching widespread clinical application. A key hurdle in large-scale hiPSC cultivation is their sensitivity to shear stress (τ) generated by bioreactor agitation and bubble rupture, which has been shown to compromise the growth, viability, and potency of these cells [4-5]. Consequently, agitation rates are often kept to a minimum in favor of maintaining cell quality [6].

When working with solid particles such as microcarriers (MCs), the minimum agitation speed required for full suspension was originally defined by Zwietering as the "just-suspended" speed (N_{js}) [7]. This definition was later refined into the N_{s1} and N_{s1u} criteria, which provided more practical and reproducible benchmarks for MC suspension [8-9]. However, reducing agitation inevitably lowers the volumetric mass transfer coefficient (k_La) [10], particularly in the absence of direct or indirect aeration, thereby limiting achievable viable cell yields.

To overcome this trade-off, BioThrust's Comfy*Cell* bioreactor incorporates the Mem*Stir* impeller, a bionic, membrane-based stirring system inspired by the function of the lung. This technology eliminates the need for direct aeration by achieving exceptionally high k_La and oxygen transfer rates through diffusion-based indirect aeration, even at comparatively low agitation rates. As a result, cells are shielded from excessive shear, foam formation is avoided, and the use of antifoam reagents is unnecessary. Together, these features enhance scalability, reduce costs, and simplify downstream processing [11].

In this application note, we present a benchmark evaluation of Mem*Stir*-equipped Comfy*Cell* bioreactors (Figure 1) for the dynamic, microcarrier-based expansion of hiPSCs, highlighting their potential to enable robust and scalable manufacturing of this therapeutically relevant cell type.

Materials & Methods

Figure 1: In the foreground, the ComfyCell reusable bioreactor vessel. In the background, the single-use version of the ComfyCell, referred to as the ComfyCell SU300.

Characterization of the Comfy*Cell* and Reference Bioreactor

Both bioreactors were characterized according to the methods described by Schneider et al. [6]. Briefly, suspension criteria N_{S1} and N_{S1u} were determined visually at MC concentrations of 10–20 g L^{-1} by suspending the MCs (diameter 125–212 µm; density 1022–1030 kg m^{-3}; surface area-to-mass ratio 360 cm^2 g^{-1}) in phosphate-buffered saline [PBS] (Merck, DE) at 50 % and 100 % of each bioreactor's working volume. Visual assessment was supported by placing the vessels above an angled mirror to allow horizontal imaging.

From the agitation rates corresponding to N_{S1} and N_{S1u}, tip speed (U_{tip}), average shear rate (γ), and average shear stress (τ) were calculated based on impeller diameter and geometry, following Wu et al. [12]. Drag coefficients of 0.007 for the STR_{Ref} and 0.0095 for the Comfy*Cell* were estimated. For these calculations, medium properties were assumed equivalent to distilled H_2O at 37 °C, corresponding to a kinematic viscosity of 6.97 × 10^{-7} m^2 s^{-1} and a dynamic viscosity of 6.92 × 10^{-4} kg m^{-1} s^{-1}. The resulting values were then compared with those obtained by computational fluid dynamics (CFD).

Abbreviations

Mem*Stir* = Membrane Stirrer
STR = Stirred-tank Bioreactor
Ref = Reference
hiPSC = human induced Pluripotent Stem Cell
MC = Microcarrier
CFD = Comupational Fluid Dynamics
vvm = Volume of air per working volume per minute
vvd = Vessel volume per day
VCD = Viable cell density
Vb = Cell viability
Glc = Glucose
Lac = Lactate
Gln = Glutamine
rhVTN = recombinant human Vitronectin

Inoculum Production

TMOi001-A hiPSCs (Thermo Fisher, US) were expanded in Essential 8™ medium [E8] (Thermo Fisher, US) at 0.28 mL cm^{-2} over two passages using recombinant human Vitronectin (rhVTN)-coated (Thermo Fisher, US) T-flasks and CellSTACKs (Corning, US). To minimize cell death during replating, cultures were maintained in E8 supplemented with 10 µM Y-27632 (Miltenyi Biotec, DE) for the first 24 h. Thereafter, medium was exchanged daily with fresh E8.
Prior to confluency, the hiPSCs were harvested as single cells by washing with 0.12 mL cm^{-2} PBS (Thermo Fisher, US) and incubating in 0.04 mL cm^{-2} Accutase (Corning, US) for 5–10 min at 37 °C. Detached cells were centrifuged at 300 rcf for 3 min, resuspended in fresh medium, and replated. For cryopreservation following the second passage, cells were instead washed with cooled E8, centrifuged at 300 rcf for 3 min, and resuspended in CryoStor® CS10 (STEMCELL Technologies, US). Aliquots were transferred into cryogenic vials (Simport Scientific, CA), placed in a CoolCell® freezing container (Corning, US), cooled to −80 °C, and subsequently stored in liquid nitrogen for long-term storage.

Evaluation of Cultivation Vessels

To benchmark performance, three cultivation systems were assessed, namely T25 flasks representing static 2D culture, a single-use reference stirred-tank bioreactor (STR_{Ref}) with a pitched-blade impeller representing conventional 3D culture, and BioThrust's Comfy*Cell*, equipped with the innovative Mem*Stir* impeller, as shown in Figure 1. Prior to inoculation, cultivation vessels were filled to 90–95 % of their initial working volume with Essential 8™ Flex [E8F] (Thermo Fisher, US) supplemented with Y-27362. For the dynamic experiments, MCs were added simultaneously. Medium and MCs were then equilibrated to 37 °C, with pH and DO subsequently recalibrated to setpoints of 7.2 and 40 %, respectively. Cells from cryostocks (> 94 % viability, > 5 × 10^7 cells mL^{-1}), resuspended in supplemented E8F were then used to inoculate the T-flasks and stirred bioreactors with 1–2.5 × 10^4 cells cm^{-2} and bring all the cultivation systems to 100 % of their initial working volume.

For the MC-based cultivations, intermittent stirring was applied during the first 6 h post-inoculation following the protocol of Schneider et al. [6], corresponding to 12 cycles of 5 min agitation at N_{S1u} every 25 min. Thereafter, agitation was maintained continuously at N_{S1u}. A more comprehensive summary of the process conditions applied to each cultivation vessel is provided in Table 1.

Table 1: Overview of the cultivation conditions applied to each of the three cultivation vessels assessed..

Parameter	T25 Flask	ComfyCell	Reference STR
Agitation rate (N_{s1u}) [rpm]	-	60 rpm (clockwise)	80 rpm (counterclockwise)
Agitation method	Surface	Indirect membrane aeration	$STR1_{Ref}$: Direct $STR2_{Ref}$: Surface
Aeration rate [vvm]	-	0.1	
DO setpoint [%]	-	40	
pH setpoint [-]	-	7.2	
Medium	Essential 8™ medium (Thermo Fisher, US) Essential 8™ Flex medium kit (Thermo Fisher, US) StemMACS™ Y27632 (Miltenyi BioTec, DE)		
Working volume [mL]	7	275	125-250
Operation mode	Repeated-batch	Perfusion	Perfusion
Microcarrier	-	Synthemax II low-concentration polystyrene (Corning, US)	
Microcarrier concentration [g L^{-1}]	-	10	
Process duration [d]	6	7	
Harvest duration [min]	25		

After a 24 h attachment phase, supplemented E8F was either completely replaced (T-flasks) or diluted with fresh E8 (stirred cultivations). In the STR_{Ref}, cultures were inoculated at 50 % working volume. Therefore, fresh medium was gradually added over 24 h until the final working volume was reached; the fed-batch process then transitioned to perfusion mode via level probe control. In the ComfyCell, cultures were inoculated directly at 100 % working volume, enabling perfusion mode to begin immediately 24 h post-inoculation. In both stirred systems, the perfusion rate was adjusted to maintain the pH setpoint.

At the end of each stirred cultivation, cells were harvested by allowing MCs to settle and replacing the spent medium with TrypLE Select (Thermo Fisher, US). The MCs were resuspended for 20 min at N_{s1u}, followed by 1 min of high-shear agitation at 5–10 × N_{s1u} (corresponding to 400 rpm in the STR_{Ref} and 600 rpm in the ComfyCell). The resulting single-cell suspensions were then collected and analyzed.

Sampling and Analytics

Every 24 h, up to three T25 flasks were harvested and 6 mL samples collected from each stirred bioreactor. To ensure homogeneous distribution of the MCs in the stirred bioreactors, agitation was increased by ≈ 20 % in the STR_{Ref} or direction of agitation changed in the ComfyCell 3 min prior to sampling. Immediately after collection, pH was measured and used to recalibrate the online value if necessary.

For cell concentration measurements in static cultures, T-flasks were harvested by treating adherent cells with 0.04 mL cm^{-2} TrypLE Select (Thermo Fisher, US) for 10 min at 37 °C following the removal of the spent medium. For samples containing MCs, cultures were centrifuged at 200 rcf for 2 min, the supernatant was removed, and the MCs resuspended in TrypLE Select, before incubating the resulting suspension at 37 °C for 10 min to detach cells. In both cases, cell counts and viabilities were determined using the Via1-Cassette™-operated NucleoCounter® NC-200 (Chemometec, DK). In addition to the cell count measurements, 1 mL of the MC suspension was fixed in 10 % formalin (Merck, US) and stored at 4 °C for subsequent imaging of cell distribution with the EVOS 2 fl Auto (Thermo Fisher, US). Finally, following harvest, cell identity and potency were determined using lineage-specific differentiation kits and flow cytometry, as described previously by Teale et. al. [13].

Alongside cell-specific measurements, culture supernatants were analyzed using a Cedex® Bio Analyzer (Roche CustomBiotech, CH) to quantify glucose (Glc), lactate (Lac), glutamine (Gln), and ammonium (Amm) in the dynamic cultivation systems.

Results

Technical characterization of the bioreactors

Initial characterization experiments performed with MCs in PBS showed that the N_{s1u} criterion was met at 70–80 rpm in the STR_{Ref} and at 55–65 rpm in the ComfyCell when agitated in a counter-clockwise and clockwise manner, respectively. In both cases, N_{s1} criterion was met at agitation rates ≈ 25–30 % higher than that required for N_{s1u}. Based on the geometries of the impellers in both bioreactors, the agitation rates required to ensure N_{s1u} was met corresponded to a U_{Tip} of 0.14 m s^{-1} and 0.13 m s^{-1} for the STR_{Ref} and ComfyCell, respectively. When taking into account the properties of the medium and the each impellers drag factor, such tip speeds would theoretically yield average γ of 96 s^{-1} and 47.4 s^{-1}, for either bioreactor, well in alignment with what was observed for the MemStir impeller operated at 60 rpm with CFD (see Figure 2).

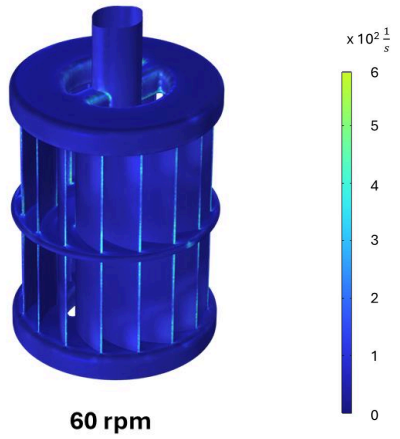

Figure 2: Surface shear rate of the MemStir at 60 rpm in 1^{-s} and a working volume of 275 mL, simulated using COMSOL Multiphysics®.

Shear-stress calculations at N_{s1} and N_{s1u} suggest that operating at N_{s1u} reduced cell exposure to τ by ≈ 25–45 % across both systems (see Figure 3). They further indicated that counter-clockwise agitation when using the STR_{Ref} was preferable, given that it effectively reduced the agitation rate necessary to meet N_{s1u} by 40 % in this bioreactor, reducing average τ by half. This is particularly relevant given the sensitivity of hiPSCs to shear. Interestingly, operating the MemStir-equipped ComfyCell in clock-wise mode produced similar results to the counter clockwise operated STR_{Ref}, indicating its suitability to support hiPSC expansion.

Impact of MemStir impeller on O_2 related parameters

Continuous analysis of DO and O_2 concentration in the gas phase indicated that the MemStir impeller enabled operation at higher volumetric mass transfer rates (k_La) compared to the reference bioreactor when operated under similar conditions (Figure 4).

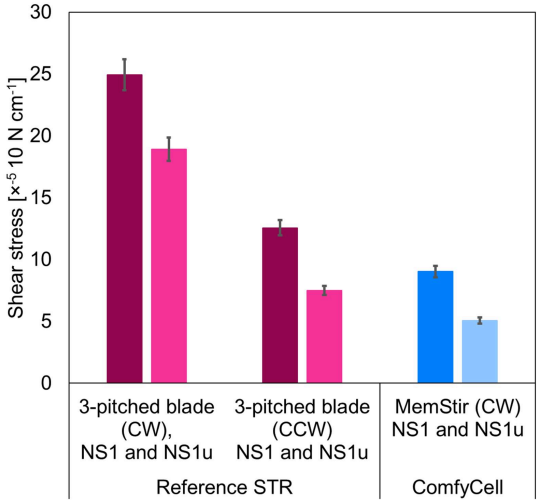

Figure 3: Shear stress calculations at different tip speeds based on the N_{s1} and N_{s1u} criteria. The reference STR was analyzed using a 3-pitched blade impeller with both clockwise and counterclockwise stirring, whereas the MemStir of the ComfyCell was stirred exclusively in a clockwise direction.

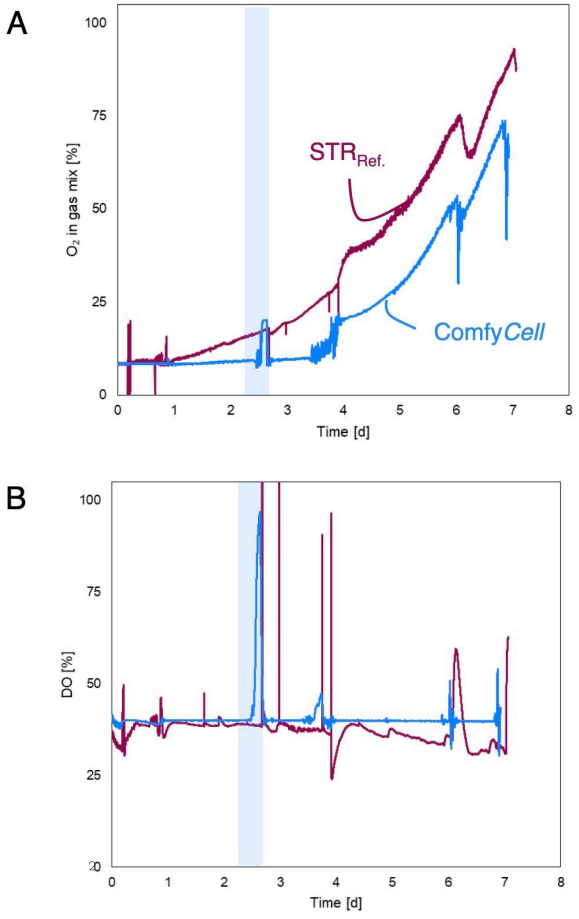

Figure 4: Oxygen concentration kinetics, (A) in gas mix and (B) DO concentration during the 7-day process. The O_2 in the gas mix was deliberately adjusted to 21 % between day 2 and 3 in the ComfyCell experiment (highlighted in a blue vertical stripe) to determine the rate at which the MemStir impeller would correct a deviation in DO from the target setpoint. The STR_{Ref} operated with surface aeration as purple line; and the ComfyCell operated with indirect aeration as blue line.

At N_{s1u} and similar viable cell densities (VCDs), the Comfy*Cell* required ~20 % less O_2 to maintain a 40 % DO setpoint than the reference STR. It also provided more stable DO control, demonstrating superior process regulation. The Mem*Stir* impeller achieved and maintained the target DO setpoint more consistently and faster (within only 10 min) than the reference bioreactor (needing 1-4 hours), indicating superior and time saving process control.

Cellular growth and morphology

Changes in VCDs in cells per mL and cells per cm² of microcarriers (Figure 5A and B), viability (Figure 5C), and specific growth rate (Figure 5D) were determined daily over the entire duration of cultivation. At the end of the bioprocess, microscopic pictures were taken to analyze cell distribution on the MCs (Figure 6). Following cell seeding and the intermittent stirring regime, cell growth was observed across all three controls: a 2D control using a T25 flask, two 3D controls utilizing a conventional STR (one utilizing the sparger: direct aeration and another utilizing headspace aeration only: surface aeration), and the Comfy*Cell* with indirect membrane aeration.

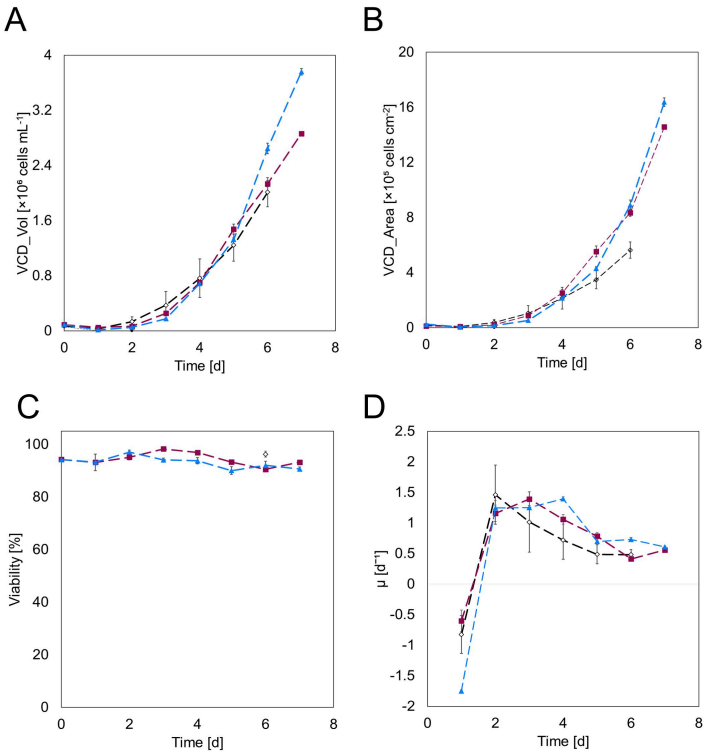

Figure 5: Cell growth and viability across different cultivation vessels. (A) Viable cell density in cells per mL, (B) viable cell density in cells per cm² of microcarriers. (C) Cell viability, and (D) specific growth rate over the 6 to 7-day cultivation period. T25 flask controls are shown as white diamonds with a black dotted line; STR_1_{Ref} operated with direct aeration as black circles with a black dotted line; STR_2_{Ref} operated with surface aeration as purple squares with a purple dotted line; and the Comfy*Cell* operated with indirect aeration as blue triangles with a blue dotted line. Vertical black lines indicate error bars of technical triplicates.

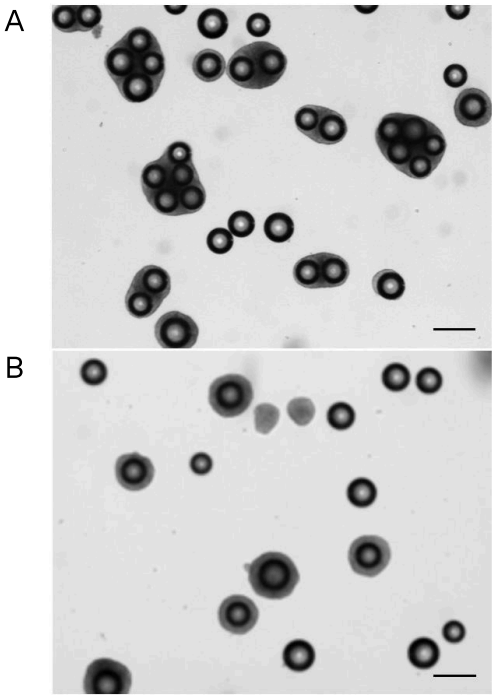

Figure 6: Microscopic images of adherently growing hiPSCs on Synthemax II-coated MCs. The images were taken of the (A) Comfy*Cell* and (B) STR_{Ref} directly prior to harvest. Scale bar in the lower right corner of both images corresponds to 250 µm.

The lag phase lasted one day after which the cells demonstrated typical growth. From day 2 onward, all processes, except for the sparged control, entered the exponential growth phase. In the sparged control, cell density and viability dropped sharply upon the initiation of sparged aeration at 0.1 vvm. In terms of viability, both controls (2D and 3D) and the Comfy*Cell* maintained stable levels above 90 % throughout the 7-day iPSC cultivation. Regarding the specific growth rate (µ; Fig. 5D), the highest overall values were observed in both the STR_{Ref} and Comfy*Cell* conditions. In the STR_{Ref}, the peak growth rate occurred on day 3 with 1.39 d^{-1}, whereas in the Comfy*Cell* it was reached on day 4 with 1.39 d^{-1}, the 2D control peak was on day 1 at 1.46 d^{-1}. All processes exhibited a continuous decline in specific growth rate over the course of the cultivation period.

Metabolic activity

Changes in substrate consumption and metabolite concentrations were analyzed daily over the course of the 7-day bioprocess (Figure 7). In accordance with the approach used for cellular kinetics analysis, the concentration of glucose (Glc, Figure 7A), glutamine (Gln, Figure 7B), lactate (Lac, Figure 7C) and ammonium (NH4, Figure 7D) were monitored in both the 3D control, utilizing the STR_{Ref} with headspace aeration, and the Comfy*Cell* system with membrane aeration. The metabolic kinetics exhibited similar trends across all four parameters, with lactate production levels being slightly lower in the Comfy*Cell*.

Identity and Differentiation Profile

To assess cell quality, viability, pluripotency marker expression, and differentiation capacity into all three germ layers were analyzed at the end of the 7-day bioprocess (Figure 8). All three conditions (Control_T25, STR_{Ref} and Comfy*Cell*) exhibited similar viabilities, exceeding 89 %. Furthermore, iPSCs from all conditions expressed high levels of pluripotency markers, namely Oct3/4, Sox2, Nanog, TRA-1-60 and SSEA-4.

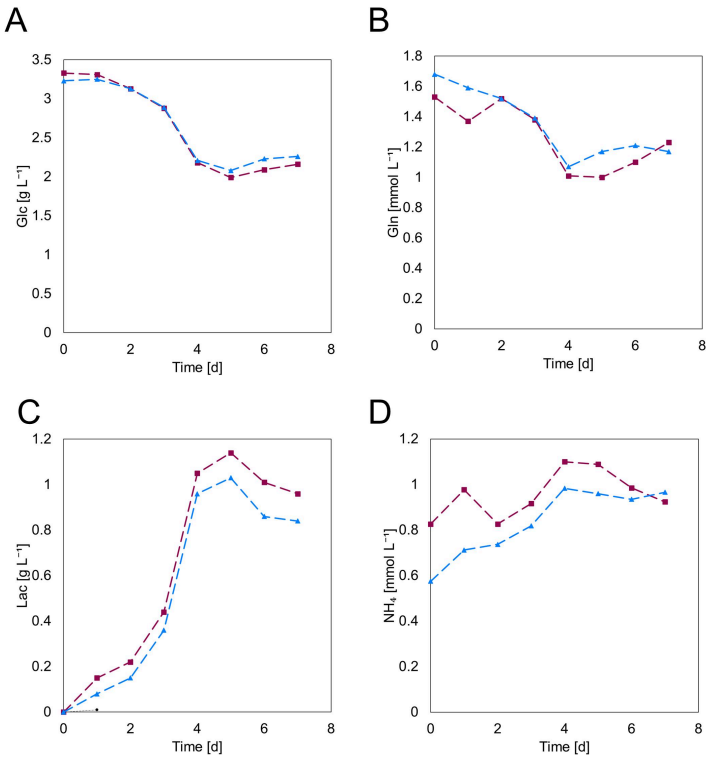

Figure 7: Metabolite kinetics during the 7-day iPSC cultivation. Glucose (A), Glutamine (B), Lactate (C) and Ammonium (D). The reference STR with surface aeration is indicated by purple squares and a purple dotted line, and the Comfy*Cell* by blue triangles and a blue dotted line.

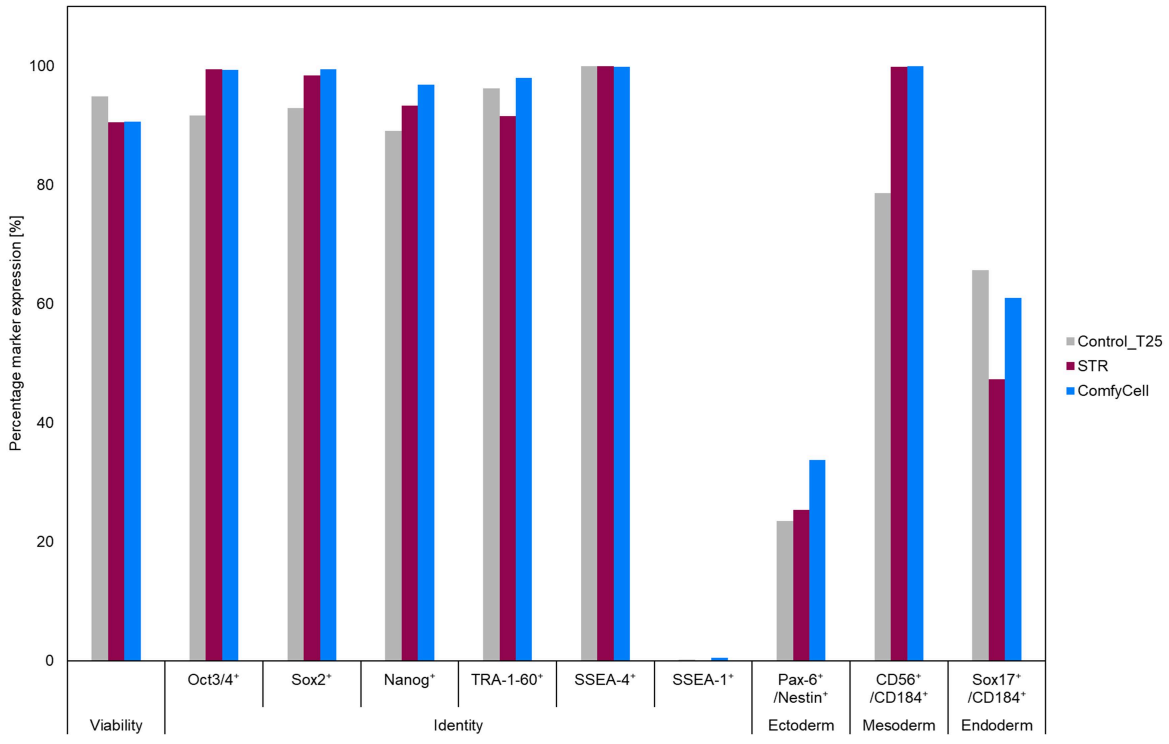

Figure 8: Comparison of hiPSC critical marker expression following bioreactor harvest. Values presented reflect the different pluripotency markers as well as the expression of markers associated to the various germ layers after directed differentiation

The negative marker for differentiation: SSEA-1 was only detected below the critical threshold of 2 %. In addition, the harvested cells were cultured under specific conditions to direct differentiation towards the three germ layers, the ecto-, the meso- and endoderm. Notably, cells cultured using the ComfyCell demonstrated comparable or superior differentiation capacity relative to the two controls.

Discussion

This study benchmarked the performance of BioThrust's ComfyCell against a conventional stirred-tank reactor with a pitched blade impeller and sparger for the expansion of hiPSCs. The ComfyCell demonstrated exceptional performance, achieving a 3-fold increase in total cell yield, surpassing 1.5 billion cells, at an impressive expansion factor of 65 (calculations based on cells per cm^2). In comparison, previous studies have reported lower expansion factors and cell yields. For instance, Borys et al. 2020 achieved a 32-fold expansion over six days using a vertical-wheel bioreactor [14]. Throughout the process, hiPSCs maintained high viability and continued expression of all key pluripotency markers, confirming their suitability for downstream applications and differentiation. Notably, the ComfyCell enabled cultivation without the need for antifoam agents and shear protectants as mentioned by other research groups [15]. Thereby avoiding labor- and cost-intensive downstream purification steps typically required to remove such additives from the final product.

This study incorporated in addition a critical process intensification step through direct, one-step inoculation using high-density cell cryo-stocks (> 50 × 10^6 cells mL^{-1}), reducing upstream processing time and resource requirements [16].

The ComfyCell further demonstrated enhanced process control by achieving faster and more stable DO regulation, while consuming ~20 % less oxygen to maintain DO setpoints. Additionally, shear stress analysis confirmed comparably lower mechanical forces within the ComfyCell, which is crucial for preserving the integrity of shear-sensitive hiPSC cultures.

These findings underscore the ComfyCell's potential as a next-generation platform for scalable, high-quality, and cost-efficient hiPSC manufacturing. Nevertheless, considering the therapeutic demand for >10^9 cells per patient and a target of 2000 doses per batch in allogeneic cell therapies, scaling to larger bioreactor volumes remains a critical next step. The ComfyCell provides a promising foundation for this and has already delivered promising results for the carrier-free cultivation of hiPSCs (data not shown), supporting the development of robust and scalable bioprocesses to advance clinical translation and industrial deployment of hiPSC-based therapies.

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