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Utilizing High-Quality Growth Factors and Cytokines in the Development of iPSC-Derived Hepatic Organoids

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Abstract

The utility of stem cells in laboratory and clinical research has been clearly demonstrated through an extensive number of studies exemplifying them as a model for a multitude of diseases and therapeutic development. The inherent flexibility of stem cells allows for the creation of many different tissue types from a single, highly proliferative base cell type.

Differentiation of induced pluripotent stem cells (iPSCs) into somatic tissues requires specific conditions dependent on the desired tissue type. In this application note, we differentiated human iPSCs into hepatocytes using three distinct media types with their own growth factor and cytokine supplementation at key stages of differentiation, providing a relatively simple method for producing mature hepatic cells. This enabled the production of human hepatic organoids from these source cells, demonstrating a robust method for unlimited organoid development. Here, we outline a simple, standardized, and robust workflow using Sartorius Research Use Only (RUO) Growth Factors and Cytokines in combination with the Incucyte® Live-Cell Analysis System and the iQue® Flow Cytometer for phenotypic characterization and monitoring of growth. This approach simplifies the generation of functional hepatic cells and organoids from iPSCs for drug discovery, development, and toxicity studies.

Introduction

Since they were first generated in 2006, iPSCs have become an integral part of laboratory and clinical *in vitro* research. iPSCs are derived from somatic cells that have undergone a 'reprogramming' process to revert the differentiated cell into a pluripotent stem cell. The pluripotent nature of these cells enables the creation of many different tissue types, providing a model for multiple diseases, including genetic disorders, infectious diseases, and cancer.[1] This has huge potential in the field of personalized medicine, as somatic cells can be taken from a patient and differentiated to produce a tissue specific to the individual.

This iPSC technology can be incorporated into more complex advanced cell models, whereby differentiated iPSCs can be transformed into a miniature version of an organ of interest that emulates the key functional, structural, and biological functions of the *in vivo* counterpart, known as an organoid.[2] This enables individuals with, for example, a genetic disorder to provide a somatic cell which can be reprogrammed into an iPSC, further differentiated into a tissue of interest, and transformed into an organoid with the patient's exact genotype, which can create a model of the disease environment that closely mirrors the *in vivo* environment.[3] This is particularly useful in drug development and safety testing, where hepatic organoids are an effective alternative to *in vivo* cytotoxicity screening.

One group of proteins essential for the maintenance and differentiation of iPSCs is growth factors; the timing and intensity of their release is responsible for determining the success of developmental and differentiation processes. Commercial cell culture media are typically supplemented with growth factors, but their recipes are often unknown, making it difficult to elucidate the contribution of each growth factor. Furthermore, lab-generated growth factors and cytokines have been previously unreliable and inefficacious, thus conditioned media has been typically used to ensure cell lines were correctly supplemented.

In this application note, human derived iPSCs were differentiated into hepatocytes using Sartorius RUO Growth Factors and Cytokines. Morphological changes were monitored using the Incucyte® Live-Cell Analysis System, whilst the changes in cell surface markers associated with the differentiation process were analyzed using the iQue® Flow Cytometry Platform. The iPSC-derived hepatocytes were then further transformed into organoids, the development of which was also monitored.

Assay Principle

Sartorius offers a range of high-quality human RUO Growth Factors and Cytokines that are produced using recombinant DNA technology and do not contain any animal-derived components. These growth factors are of high-purity, low endotoxicity, and can be used for differentiation of iPSCs into mature hepatic cells and hepatic organoids in a non-perturbing and reproducible manner.

The Incucyte® Live-Cell Analysis System and the iQue® Flow Cytometry Platform provide robust solutions for live-monitoring of cells over time and high content phenotyping of marker expression, respectively. They are an ideal pairing for differentiation protocols, where morphological changes and growth accompanying differentiation can be monitored over time and confirmed through the assessment of key differentiation markers.

Methods

The iPSC differentiation workflow schematic (Figure 1) outlines the steps in the differentiation process and highlights key points in the time course for characterization analysis and the development of hepatic organoids.

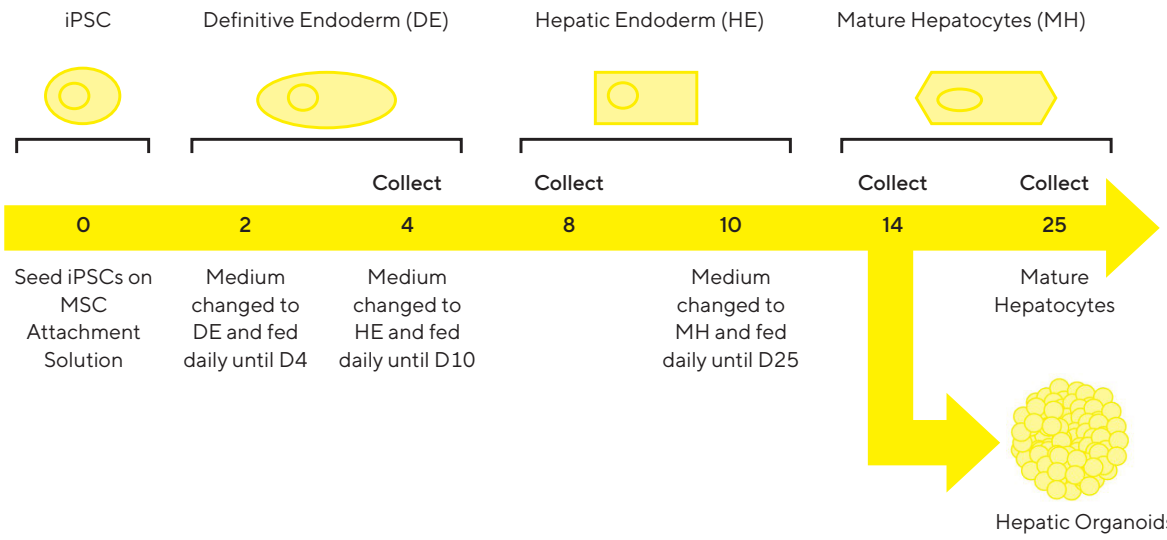

Figure 1. iPSC to hepatocyte cell workflow . *Workflow highlighting the key steps during the differentiation of iPSCs to hepatocytes and hepatic organoids in addition to timepoints for cell collection and analysis.*

Cell culture and maintenance

ATCC DYS 1019 iPS cells were cultured in NutriStem® hPSC XF (Sartorius Cat. No. 05-100-1A) media in 6-well plates coated with vitronectin (10 µg/mL) with daily media changes. Passages were performed using TrypLE every 3-4 days and cells were seeded at 100 K/well. THP-1 cells were grown in RPMI 1640 supplemented with 10% FBS and 1% Penicillin/Streptomycin (P/S). HepG2 cells were grown in DMEM + 10% FBS + 1% P/S.

iPSC differentiation to hepatocytes

iPSCs were seeded in NutriStem® hPSC XF in 6-well plates coated with Sartorius MSC attachment solution (Cat. No. 05-752-1H) at 300 K/well. The following day, cells were fed daily with Definitive Endoderm (DE) medium, at day 5, cells were fed every day with Hepatic Endoderm (HE) medium and from day 10 onwards, cells were fed daily with Mature Hepatocyte (MH) medium (Table 1). Throughout the differentiation process, iPSCs were monitored using the Incucyte® Live-Cell Analysis System.

Media and Supplements	Catalog No.	Definitive Endoderm (DE)	Hepatic Endoderm (HE)	Mature Hepatocyte (MH)
RPMI 1640	-	Base	Base	-
HepatoZYME-SFM	-	-	-	Base
Penicillin/Streptomycin (P/S)	-	1%	1%	-
B27 Supplement	-	1x	-	-
Recombinant Human Activin A	CYK-0100-0007	100 ng/mL	50 ng/mL	-
CHIR99021	-	3 µM	-	-
LY294002	-	10 µM	-	-
Recombinant Human FGF-2 protein 154 aa	CYK-0100-0023	40 ng/mL	-	-
Recombinant Human BMP-4 protein	CYK-0100-0006	10 ng/mL	-	-
Recombinant Human HGF (NK1) protein	CYK-0100-0021	-	-	20 µg/mL
Recombinant Human OSM protein	CYK-0100-0022	-	-	10 µg/mL

Table 1. *iPSC hepatic differentiation media formulations*

iPSC-derived hepatocytes to hepatic organoids

iPSC-derived hepatocytes were collected at day 14 for adaptation into hepatic organoids. Cells were collected, resuspended in Matrigel®, and seeded at 150K in 20 µL domes in 24-well plates. They were cultured in commercially available hepatic organoid growth medium (supplemented with 100 µg/mL P/S) and monitored in the Incucyte® Live-Cell Analysis System until organoids began to form. Media changes were performed twice a week and organoids were passaged at maturity. For validation of Sartorius RUO Growth Factors and Cytokines in supporting human iPSC-derived hepatic organoid expansion, media was formulated as detailed in Table 2.

Surface marker expression analysis

At days 4, 8, 14, and 25, cells were harvested and stained for iPSC markers of pluripotency and non-pluripotency in addition to hepatic markers for DE and MH. Briefly, cells were lifted using Accutase® and reseeded in a 96-well V-bottom plate at 20 K/well, centrifuged at 300g for 5 minutes and washed twice with PBS + 2% FBS before being treated with SSEA-1-FITC (1:50), SSEA-4-APC (1:800), TRA-1-60-PE (1:25), CD99–BV421 (1:50), CD184–BV605 (1:50), and iQue® Cell Membrane Integrity Dye (B/Red) Kit (1:50) (Cat: 90346) and incubated at room temperature in the dark for 30 minutes. The plate was spun at 300g for 5 minutes before analyzing on the iQue® platform. Remaining cells were fixed for intracellular marker staining at all time points.

Intracellular staining

Cells were washed in PBS and fixed using Fixation Buffer (Biolegend) in the dark for 20 minutes at room temperature, washed once in PBS + 2% FBS and stored in PBS + 2% FBS at 4 °C prior to membrane permeabilization and staining. On the day of staining, fixed cells were centrifuged at 300g for 5 minutes and supernatant aspirated, cells were resuspended in Intracellular Staining Permeabilization Wash Buffer (Biolegend) and centrifuged at 300g for 5 minutes, supernatant was then removed, and this step was repeated. After permeabilization, cells were seeded in a 96-well V-bottom plate at 20 K/well before being treated with Albumin-AF405 (1:100) or HNF4a-AF405 (1:100) and incubated at room temperature in the dark for 30 minutes. The plate was spun at 300g for 5 minutes before analyzing on the iQue® platform.

Functional testing of differentiated cells

P450-Glo™ CYP1A2 and CYP3A4 Assays (Promega) were used to assess the hepatocyte-like function of derived cells and organoids, respectively. Substrate was added directly to wells (1:1000 dilution in PBS) alongside CYP inhibitor (α-naphthoflavone, 1 µM – 1A2 and verapamil hydrochloride, 10 µM – 3A4) for 1 hour. Control wells contained no inhibitor. 25 µL/well of the reaction volume was transferred to a white 96-well plate (Thermo Scientific™ 236108) alongside detection reagent for 20 minutes at 37°C. Release of luciferin substrate indicated CYP activity and was detected as an increased luminescent signal as quantified using a CLARIOstar microplate reader (BMG). Wells containing substrate and detection reagent alone were included for background subtraction.

Media component	Supplier	Cat no.	Hepatic organoid media
Advanced DMEM/F12	Gibco	12634010	Base medium
GlutaMAX	Gibco	35050	1%
HEPES	Gibco	15630	10 mM
Penicillin-Streptomycin	Gibco	15140	1%
B27 supplement	Gibco	17504044	1:50
N-acetyl-cysteine	Sigma	A9165	1 mM
Nicotinamide	Sigma	N0636	10 mM
Gastrin I	Sigma	G9020	10 nM
N2 supplement	Gibco	A1370701	1:100
A83-01	Stem Cell Technologies	72022	5 µM
Forskolin	Stem Cell Technologies	72022	10 µM
RUO Growth Factors & Cytokines			
EGF	**Sartorius**	**CYK-0100-0001**	**50 ng/ml**
FGF10	**Sartorius**	**CYK-0100-0017**	**100 ng/ml**
HGF	**Sartorius**	**CYK-0100-0021**	**25 ng/ml**
R-spondin1	**Sartorius**	**CYK-0100-0019**	**1000 ng/ml**

Table 2. *Hepatic organoid growth media formulation*

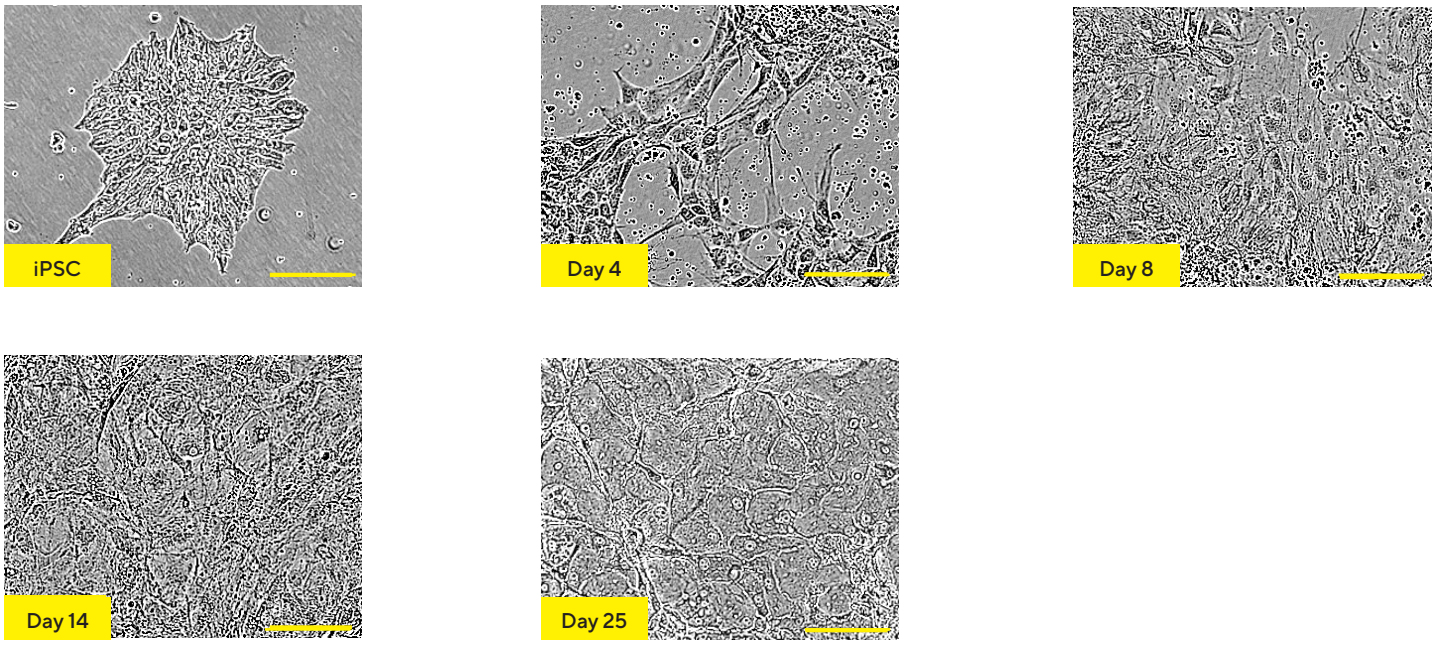

Figure 2. Monitoring iPSC to hepatocyte differentiation using the Incucyte® Live-Cell Analysis System. *iPSCs were differentiated to mature hepatocytes over 25 days using Sartorius RUO growth factors and cytokines. Incucyte® images from representative time points illustrate morphological and spatial changes during differentiation with comparison to iPSCs grown in NutriStem® hPSC XF. Scale bar 100 µm.*

Results

Phenotypic changes during differentiation of iPSCs to hepatocytes

Differentiation of iPSCs into mature hepatocytes was performed over 25 days (Figure 1) and monitored using the Incucyte® Live-Cell Analysis System. High-definition phase-contrast images were acquired throughout, illustrating marked changes in cellular morphology over time (Figure 2). iPSC control cells at the Day 0 timepoint, prior to induction of the hepatic differentiation workflow, formed tightly packed colonies with clearly defined edges, representative of a pluripotent phenotype. Moving through the differentiation process, dramatic changes in the morphology of the iPSC-derived cells were observed. At Day 4, the end of the DE stage of the workflow, cells began to separate from the colonies and spread out across the plate. By Day 8, during the HE stage, the iPSC-derived cells formed a complete monolayer and were progressing towards a hepatic phenotype. Midway through the MH stage of the time course, at Day 14, the cells maintained the monolayer morphology, but became much more tightly packed. Finally, at Day 25, the end of the differentiation workflow, the cells exhibited a large polygonal structure with round nuclei and prominent nucleoli, indicative of mature hepatocytes.

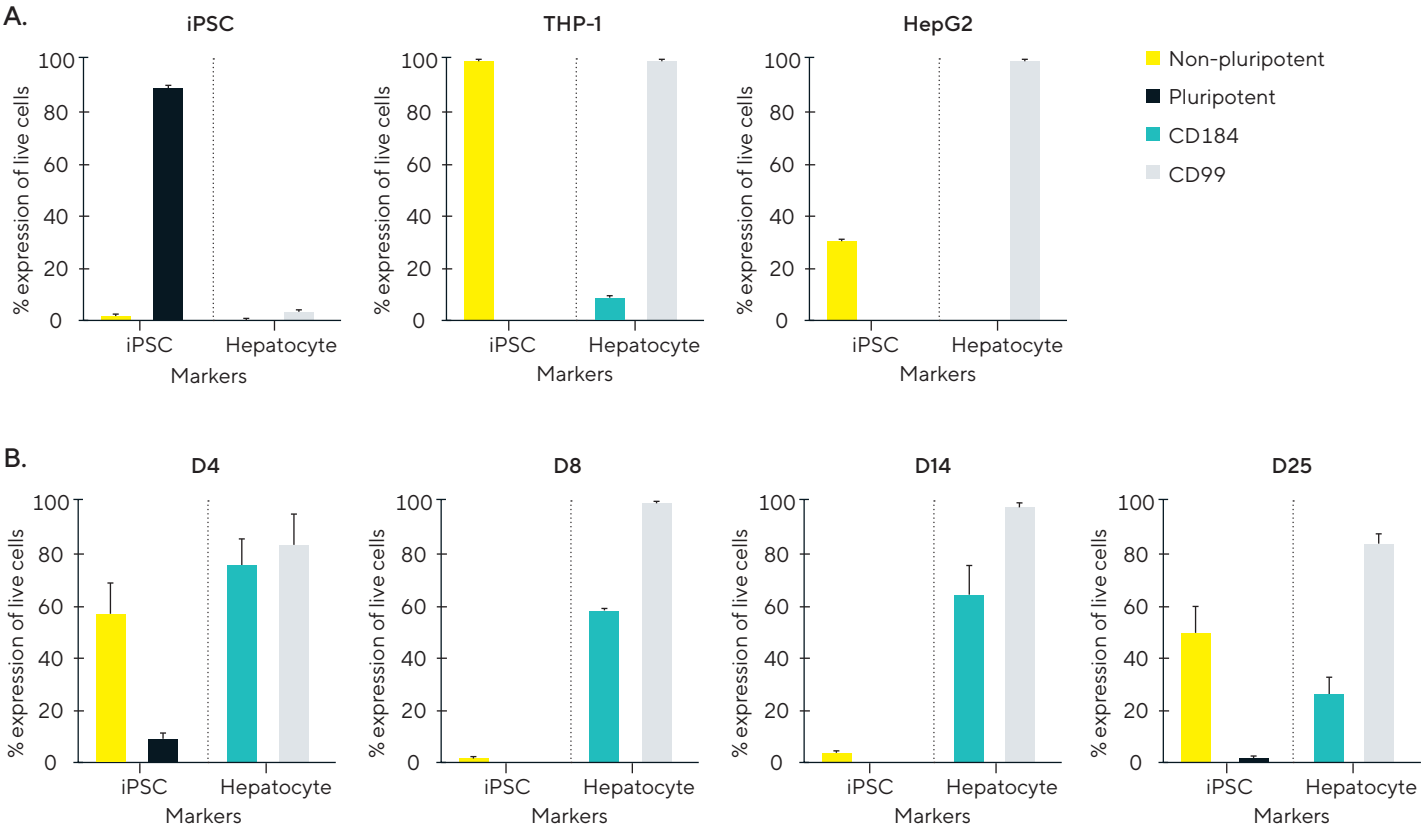

Figure 3. Analysis of surface marker expression changes during differentiation of iPSCs to mature hepatocytes. *iPSCs were differentiated to mature hepatocytes over 25 days using an internally developed protocol with Sartorius RUO Growth Factors and Cytokines. Surface marker expression was characterized using the iQue® Flow Cytometer. Pluripotency was monitored over time by measuring SSEA-1 expression (Non-pluripotent) and SSEA-1-, SSEA-4+, TRA-1-60+ populations (Pluripotent). Hepatocyte differentiation was characterized by monitoring expression of CD184 and CD99 over the time course. A) iPSCs were used as a pluripotent control, THP-1s were used as a differentiated cell line control and HepG2s were used as a control liver cell line. B) Expression profiling of iPSC-derived hepatocytes during differentiation.*

To confirm observed morphological changes, cellular surface marker expression was investigated using the iQue® Flow Cytometer at key timepoints during the differentiation workflow (Figure 3). Three control cell lines were used for baseline expression profiling: iPSCs as a pluripotent phenotype control, THP-1s as a non-pluripotent control, and HepG2s as a hepatocyte-like phenotype control.

The control cell types THP-1 and HepG2 expressed the marker of differentiated cells SSEA-1 and did not express the pluripotency markers (Figure 3A), while both cell types expressed high levels of hepatocyte marker CD99 and no expression of DE marker CD184. Conversely, the undifferentiated iPSC cells did not express SSEA-1, or hepatocyte markers CD99 and CD184, but were highly pluripotent, with > 90% of cells expressing the fully 'pluripotent' phenotype (SSEA-1-/SSEA-4+/TRA-1-60+). Differentiation of iPSCs into the hepatic lineage resulted in an increase in non-pluripotent marker expression (> 50%) during the DE phase at Day 4, while a complete loss of pluripotency marker expression was observed and maintained throughout the differentiation process. Non-pluripotent marker expression was subsequently lost at Days 8 and 14, with an increase at Day 25, indicative of terminal differentiation into mature hepatocytes (Figure 3B).

Hepatocyte marker expression was elevated for both CD184 and CD99 at Day 4, at the end of the DE phase. High levels of CD99 were maintained throughout the differentiation process, indicating a shift towards the hepatic lineage. CD184 expression remained above 50% until Day 25 where it dropped below 30%, while CD99 expression remained high at over 80% indicating a mature hepatocyte phenotype (Figure 3B). This data correlated with Incucyte® images at Day 25, in which cells presented clear hepatocyte morphological features, with corresponding marker expression.

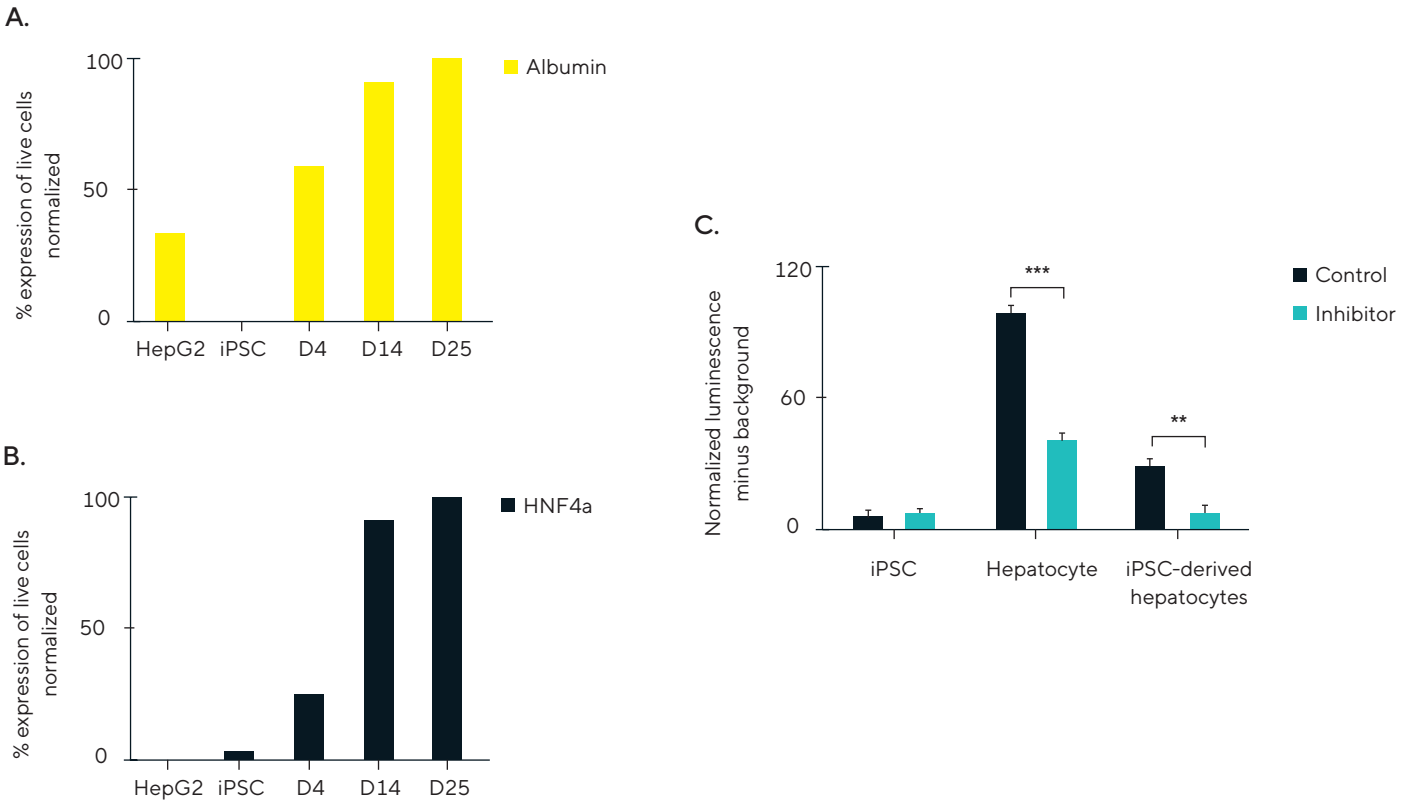

Figure 4. Intracellular marker expression and Cytochrome P450 enzyme activity characterizes successful iPSC to hepatocyte differentiation. *iPSCs differentiated to mature hepatocyte cells over 25 days were characterized by expression of intracellular hepatic markers (Albumin and HNF4a) using the iQue® and by endpoint Cytochrome P450 enzyme assay to analyze functional activity. HepG2s were used as a control liver cell line. A) Expression of Albumin, and B) expression of HNF4a, indicators of mature hepatocyte status, at defined timepoints during iPSC differentiation. C) Endpoint CYP450-Glo luminescence assay comparing CYP1A2 activity in iPSC-derived hepatocytes and iPSC control cells in the presence and absence of CYP1A2 inhibitor α-naphthoflavone (1 µM). Statistical significance analyzed using unpaired t test: p<0.01 (**), p<0.001 (***).*

To determine the success of the Sartorius iPSC hepatic differentiation workflow, further analysis of cellular phenotype and functional activity was essential. iPSC-derived hepatocytes were fixed at each timepoint and stained for the intracellular markers, Albumin and Hepatocyte Nuclear Factor 4a (HNF4a) (Figure 4A and B). The cells were also tested for their functional activity by CYP1A2 cytochrome p450 enzyme assay (Figure 4C).

Intracellular staining of mature hepatocyte markers revealed increased expression at latter stages of the differentiation workflow. Albumin, a secreted protein produced by hepatocytes, was expressed at a maximal level at Day 25, the end of the iPSC-derived hepatocyte differentiation time course (Figure 4A). This level of expression was much higher than in the control cells, HepG2, and dramatically increased compared to iPSC expression, which was undetectable. HNF4a, a marker of mature hepatocytes, was also expressed at the highest level at Day 25, while control cells expressed much lower levels.

CYP1A2 is an enzyme in the CYP450 family and plays a major role in drug metabolism in the liver.[4] Using a CYP1A2 inhibition assay, a Luciferin-1A2 substrate was added to cells, which the CYP1A2 enzyme converts to Luciferin resulting in luminescence of the sample. Endpoint functional analysis of iPSC-derived hepatocytes showed an increase in enzyme activity compared to control iPSCs, however, HepG2 cells showed higher activity (Figure 4C). Significant inhibition of CYP1A2 activity was observed with HepG2 and iPSC-derived hepatocytes when treated with α-naphthoflavone, an inhibitor of CYP1A2.

Development, quantification, and functional analysis of iPSC-derived hepatic organoids

To further characterize iPSC-derived hepatocytes produced during this workflow, it is hypothetically possible to take late-stage cells and develop them into hepatic organoids if differentiation has been successful. To this end, Day 14 cells, prior to terminal differentiation, were harvested and resuspended in Matrigel® domes and treated with commercial hepatic organoid medium while being monitored label-free in the Incucyte® Live-Cell Analysis System.

Representative brightfield (BF) images for the first 5 days of organoid culture, showed the development of 3D structures with organoid morphology that continued to grow through to Day 5 (Figure 5A). Analysis of this data, using the integrated Incucyte® Organoid Software Analysis Module, allowed for easy quantification of key attributes and characterization of organoid growth and morphology. Graphs of organoid object count per image (Figure 5B) and organoid object area (Figure 5C), showed increasing numbers of organoids over time and increasing size of these organoids, respectively, indicating healthy growth. Meanwhile, analysis of eccentricity (Figure 5D) characterized the uniformity of the organoids during monitoring, highlighting a reduction in eccentricity and stabilization of sphericity as organoids formed.

To measure the functional activity of the iPSC-derived hepatic organoids, a CYP3A4 cytochrome p450 enzyme assay was used. CYP3A4 is another enzyme in the CYP450 family involved in liver metabolism and was used for this part of the study because the assay is more compatible with 3D developed hepatocyte cultures, such as hepatic organoids. Functional analysis of iPSC-derived hepatic organoids revealed very high levels of CYP3A4 activity compared to HepG2 and iPSC controls (Figure 5E). CYP3A4 inhibitor, verapamil hydrochloride, induced a significant reduction in enzymatic activity in both HepG2 and iPSC-derived hepatic organoids, evidence that the signal observed was caused by CYP3A4 enzyme activity.

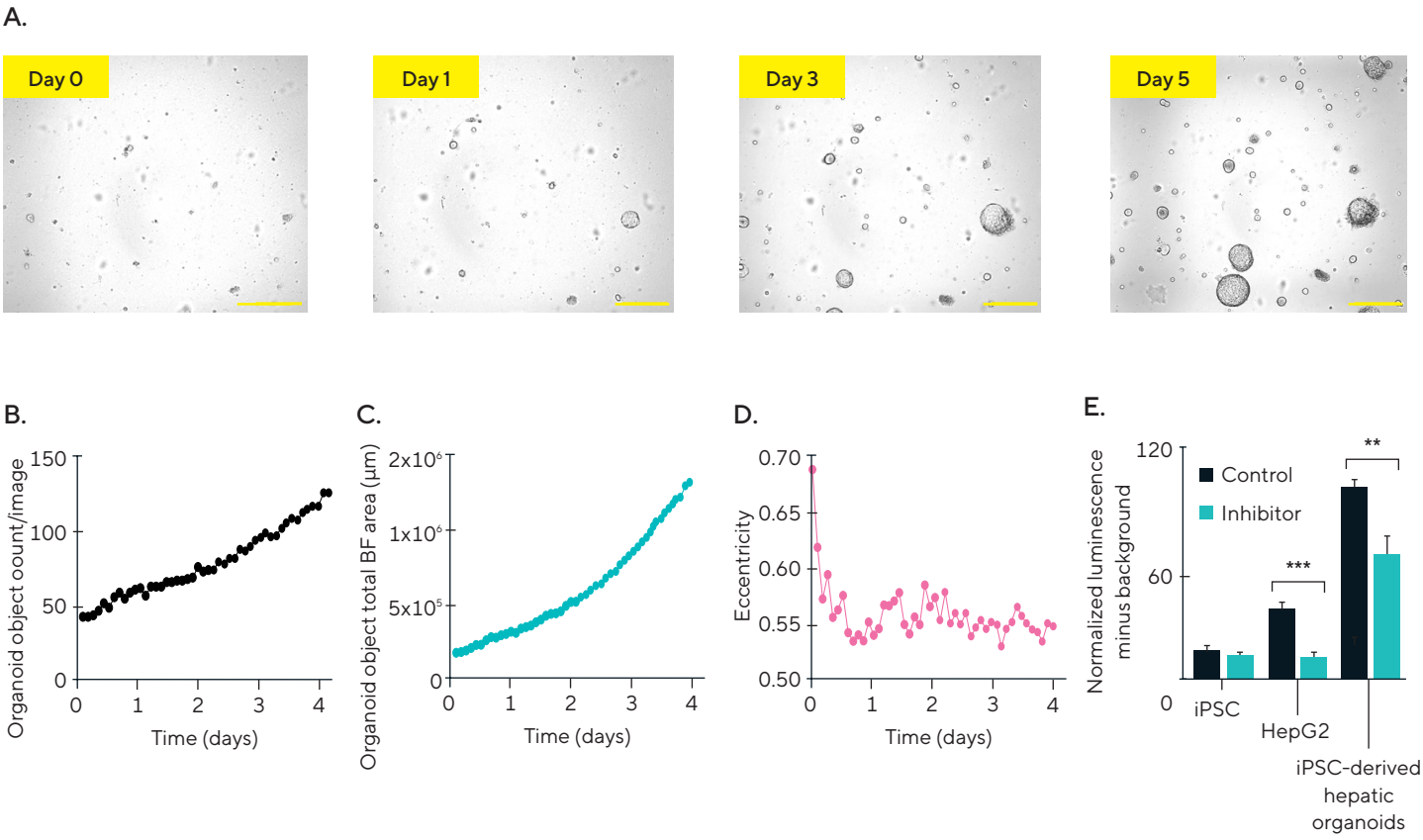

Figure 5. Quantification of iPSC-derived hepatic organoid morphology, growth, and function. *iPSC-derived hepatocytes were collected at Day 14 and transferred to 3D matrix to form hepatic organoids. A) Representative brightfield (BF) images of iPSC-derived hepatic organoids at multiple timepoints. Kinetic Incucyte® quantification of B) organoid object count, C) organoid object total BF area, and D) organoid eccentricity. E) Endpoint CYP450-Glo luminescence assay comparing CYP3A4 activity in iPSC-derived hepatic organoids, iPSC and HepG2 control cells in the presence and absence of CYP3A4 inhibitor verapamil hydrochloride (10 µM). Scale bar 800 µm. Statistical significance analyzed using unpaired t test: p<0.01 (**).*

Finally, it was important to characterize the expression profile of the iPSC-derived hepatic organoids by iQue® Flow Cytometer analysis to further confirm hepatic phenotype. Using the surface marker panel from the hepatocyte characterization experiments, hepatic organoids were dissociated to single cells and stained and analyzed on the iQue® Flow Cytometer. In addition, iPSC-derived hepatic organoids were also analyzed for expression of LGR5, a marker of mature stem cells. LGR5 positive stem cells are an important niche population in organoids, facilitating proliferative capability and differentiation potential, presence of these cells indicates successful organoid development.

iPSC-derived organoids expressed low levels of non-pluripotent marker and no detectable levels of pluripotent markers (Figure 6A) similar to Day 25 late-stage hepatocyte differentiation levels (Figure 6B). These similarities remained consistent upon analysis of hepatocyte marker expression, with high levels of CD99 expressed and levels of CD184 remaining below 50%, indicating a mature hepatic phenotype (Figure 6A).

LGR5 marker analysis was performed to reveal the component stem cell population within the iPSC-derived hepatic organoids. Figure 6C shows that ~25% of the cells within the organoids were positive for LGR5 indicating a high proportion of stem cells, and therefore strong proliferative capabilities. This data also reveals that the organoids produced in this application note are early stage and capable of further differentiation into a mature hepatic phenotype given the right conditions.

This data demonstrates the successful development of proliferative and functional hepatic organoids from source iPSCs using the described workflow and characterization analyses.

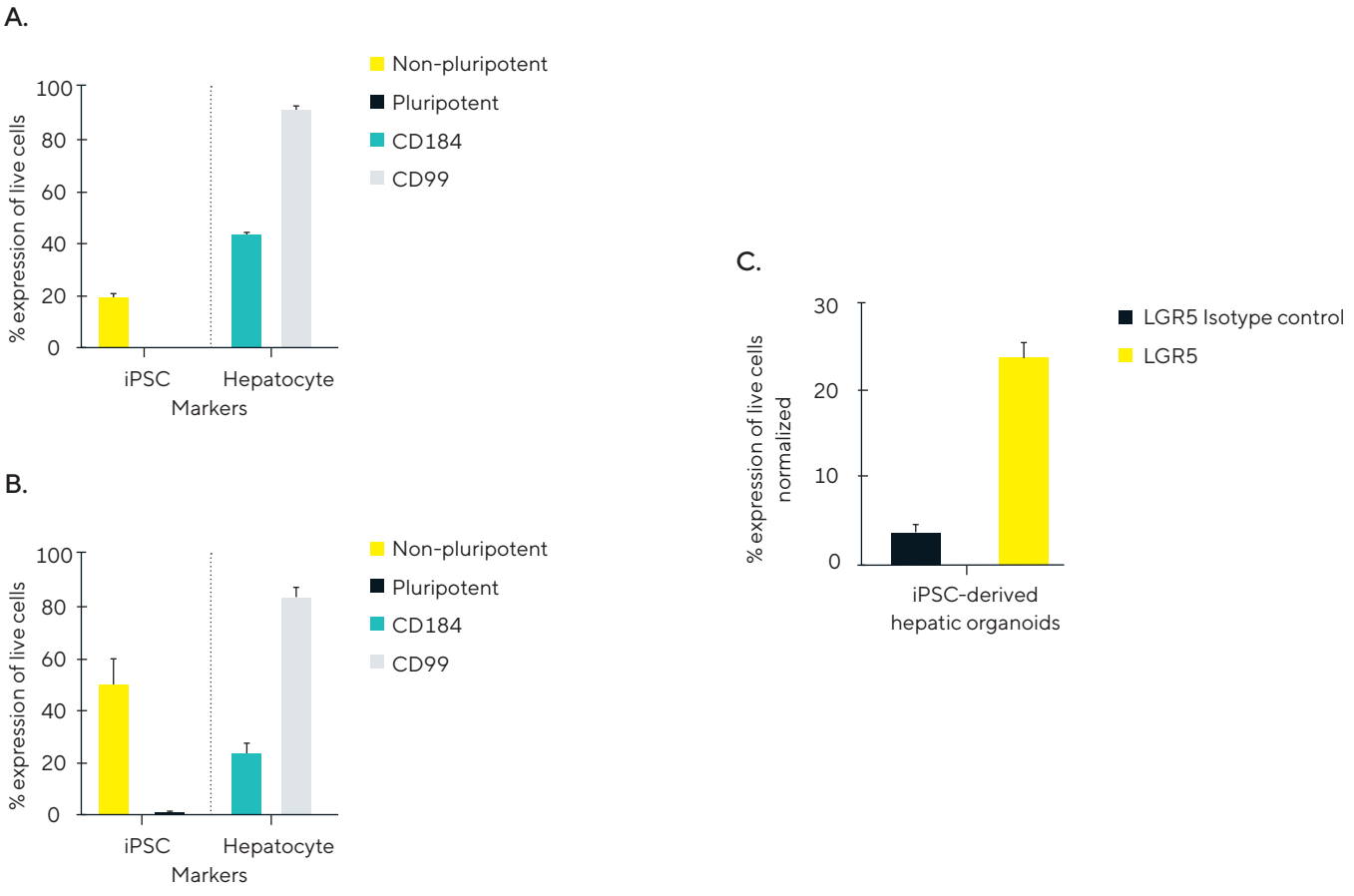

Figure 6. Phenotypic analysis of surface marker expression in iPSC-derived organoids. *iPSCs differentiated to hepatic organoids were further characterized by expression of surface markers using the iQue®. Pluripotency was analyzed by measuring SSEA-1 expression (Non-pluripotent) and SSEA-1-, SSEA-4+, TRA-1-60+ populations (Pluripotent) while hepatic differentiation was characterized by monitoring expression of CD184 and CD99. Expression analysis of iPSC and hepatocyte surface markers in A) iPSC-derived organoids and B) Day 25 iPSC-derived mature hepatocytes. C) Hepatic organoid stem cell composition was measured by LGR5 marker expression.*

To evaluate the ability of Sartorius RUO Growth Factors and Cytokines to support iPSC-derived hepatic organoid growth, organoids were cultured in 100% Matrigel® in 96-well plates with different media formulations. Organoids were automatically located and changes in size (area) were tracked using the Incucyte® Organoid Analysis Software Module. BF area segmentation enabled label-free quantification of organoid growth and automatic generation of metrics describing organoid count, area, darkness, and eccentricity.

Hepatic organoids cultured in basal media without growth factors appeared much smaller than in the other conditions, reaching a maximum diameter of around 600 µm after 10 days of culture (Figure 7A and B). Organoids cultured in media containing Sartorius RUO Growth Factors and Cytokines (RUO GFs) increased in area at a much more rapid rate compared to basal media and commercially available media, reaching a maximum diameter of around 1.2 mm at 7 days, which was maintained for the remainder of the culture period (Figure 7B). In the commercial media the maximum diameter was around 600 µm after 7 days of culture. Organoids cultured in RUO GFs displayed organoid darkness values equivalent to commercial media, but with lower initial darkness (Figure 7C), while organoid counts were conserved across media types (Figure 7D).

Following their use in generation of hepatocytes from iPSCs, Sartorius RUO Growth Factors and Cytokines continue to support organoid development and growth, allowing researchers to have precise control over culture conditions.

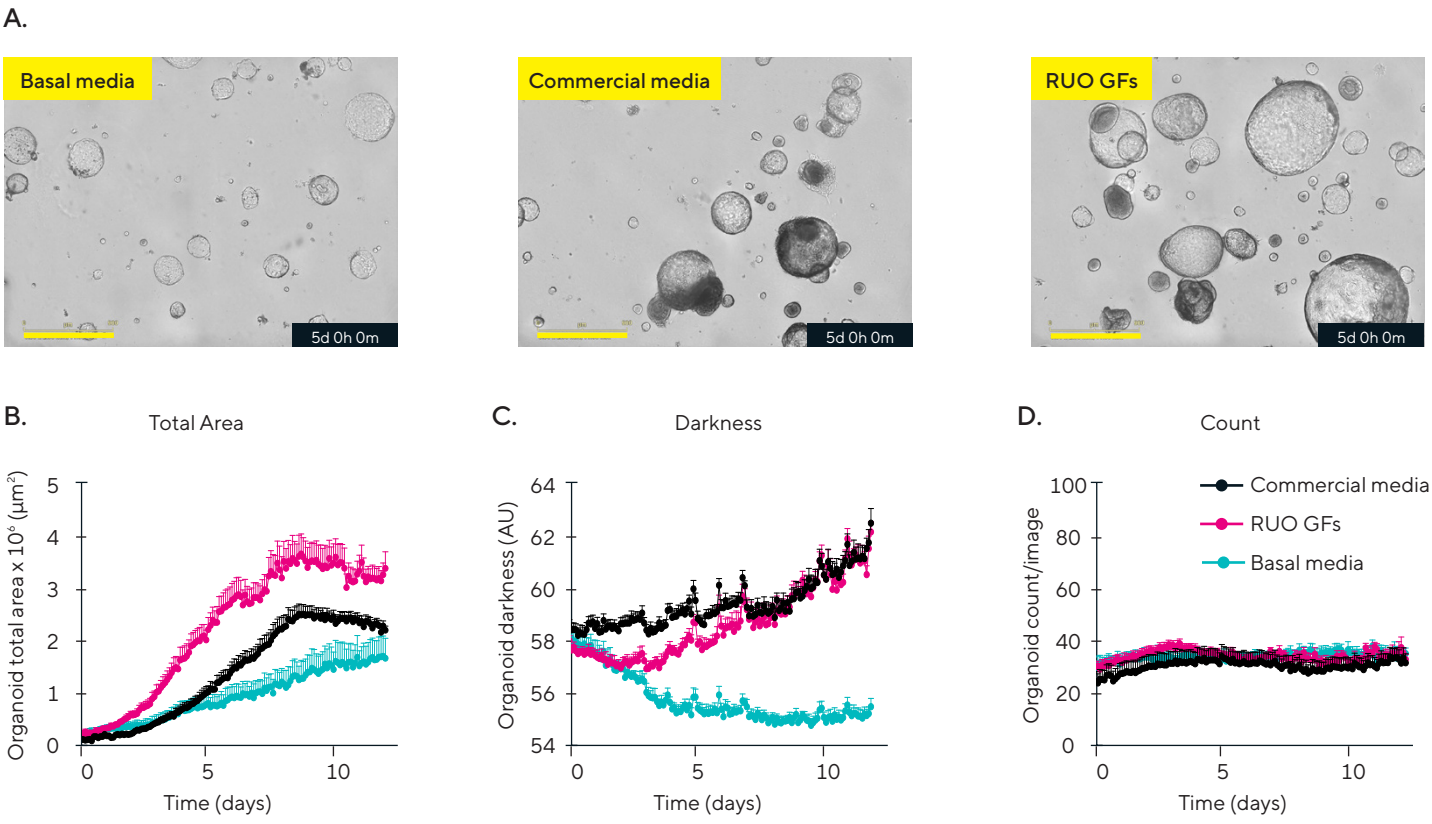

Figure 7. Morphological analysis and quantification of human hepatic organoid growth in different media formulations. *Human iPSC-derived hepatic organoids were cultured in either a commercially available media, basal media without growth factors, or basal media containing 50 ng/ml EGF, 100 ng/ml FGF10, 25 ng/ml HGF, and 1 µg/ml R-spondin1 (RUO GFs). Organoids were monitored over a period of 12 days following culture initiation. (A) Representative 4x brightfield images taken at 5 days post culture initiation. Quantification of organoid growth metrics (B) total area, (C) organoid darkness, and (D) organoid count. Scale bar 900 µm.*

Conclusion

iPSCs are an incredibly flexible potential source of cell types for a multitude of tissue lineages and their use in the development of tissue models for cancer research, disease modelling, and drug discovery is increasing exponentially. However, differentiating iPSCs into specific cell types can be resource-intensive, time-consuming, and unreliable, while the resulting two-dimensional culture is short-lived and non-representative of the *in vivo* niche. Three-dimensional tissue models, such as organoids, bypass some of the limitations of traditional tissue culture, where cells are grown in conditions more closely resembling the physiological environment. Nonetheless, organoids can be difficult to source and develop, often requiring human donor material, or very high initial cost.

In this application note, we have described a simple, standardized, and robust method for differentiating iPSCs into hepatocytes, and ultimately hepatic organoids, using Sartorius RUO Growth Factors and Cytokines in combination with the Incucyte® Live-Cell Analysis System and the iQue® Flow Cytometer for characterization and monitoring of growth and phenotype. In addition, we have also shown the efficacy of Sartorius RUO Growth Factors and Cytokines as media supplementation for the development and culture of human hepatic organoids. These approaches simplify the creation of functional liver tissue lineage cells and organoids from infinitely renewable iPSCs for the derivation of healthy and diseased tissue models for drug discovery, development, and toxicity studies.

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