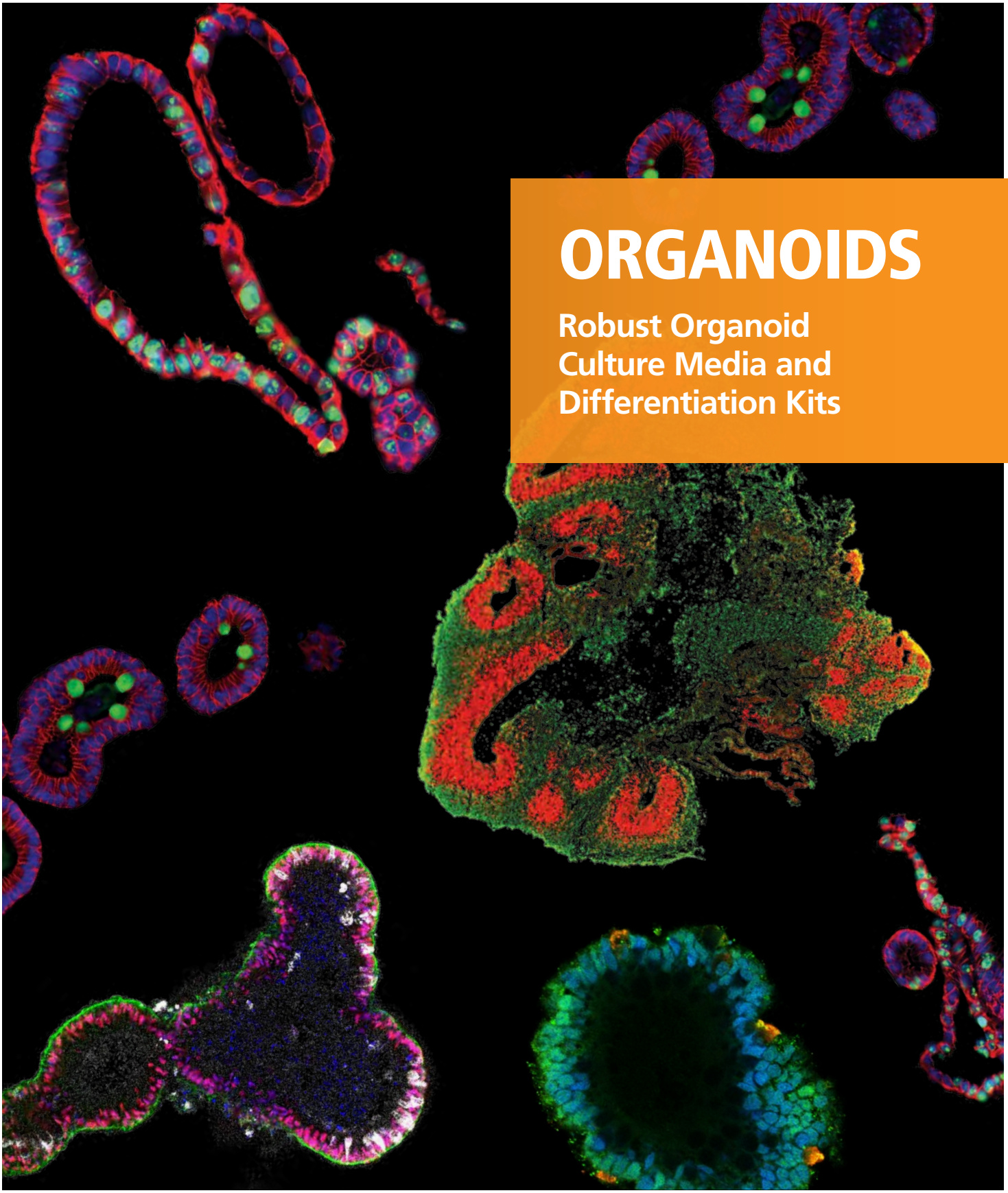

ORGANOIDS

Robust Organoid Culture Media and Differentiation Kits

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TABLE OF CONTENTS

Introduction

Organoids have gained enormous interest as experimental and preclinical models because of their ability to recapitulate some of the key structural and functional features of organs ex vivo. These three-dimensional (3D) tissue cultures make it possible to reproduce many specific aspects of an organ and enable scientists to investigate complex research questions with the convenience of in vitro settings. Since landmark studies describing intestinal[1] and neural organoids[2], culture techniques have been developed for multiple tissues and species to derive organoids from either tissue-resident adult stem cells (ASCs) or from pluripotent stem cells (PSCs), which can be embryonic (ES) or induced (iPS).

While each culture system is distinct, organoids generally contain multiple cell types capable of reproducing some of the structure and functions of their native organ. During organoid culture, stem cells (ASCs or PSCs) are provided with relevant signaling factors that mimic their in vivo stem cell niche. Exposure to these conditions directs stem cells to divide and differentiate into different cell types, which self-organize with complex architecture to resemble the target organ. For example, intestinal organoids exhibit crypt-villus-like patterning with polarized apical-basolateral surfaces similar to the intestinal epithelium. Likewise, cerebral organoids contain multiple representative compartments of the brain that can be observed through fluorescent imaging.

Owing to their cellular organization, organoids exhibit functional features of their native organ; for example, intestinal organoids can secrete mucus, absorb biomolecules, and exhibit epithelial barrier integrity. In epithelial organoid systems, the presence of actively dividing ASCs enables the long-term expansion and maintenance of cultures through serial passaging; organoid cultures can thus provide a valuable source of untransformed primary cells.

Various organoid cultures have received widespread attention for their potential to overcome some of the limitations associated with classical two-dimensional cell cultures and animal model systems. The removal of confounding variables inherent in animal models combined with greater complexity than homogeneous cell cultures gives organoid cultures specific experimental advantages. With their high level of biological relevance and amenability to in vitro manipulation, organoids have the potential to complement or replace primary cells or immortalized cell lines for in vitro experiments. Researchers are also considering organoids for reducing animal experimentation in many circumstances. Additionally, organoids demonstrate high genetic stability in culture, retaining the genotype and phenotype of the source tissue. Organoids, therefore, provide faithful models of disease and can be used to predict patient-specific responses to drug treatment.

Organoids have proven useful for many applications in basic research and have contributed to several biomedical advances. As human organoids recapitulate many of the signaling and cell-cell interactions present in vivo, numerous studies employ this platform to model and investigate infectious diseases, neurological disorders, cancer, and other diseases. Human organoids are also used as a biologically relevant experimental system for drug safety and efficacy testing to bridge the gap between preclinical and clinical studies and make the drug development process faster and more cost-effective. PSC-derived organoids are a particularly effective tool for studying mechanisms underlying human development and organ regeneration and make it possible to model organs from which tissue samples cannot be easily obtained, such as the brain. Combining human PSC-derived organoid technologies with genetic manipulation techniques further broadens the utility of human organoids in scientific research. For instance, CRISPR-Cas9-mediated editing of the *CFTR* gene in gut organoids of cystic fibrosis patients has been shown to correct the CFTR protein sequence, resulting in restoration of CFTR channel activity and reversal of the disease phenotype.

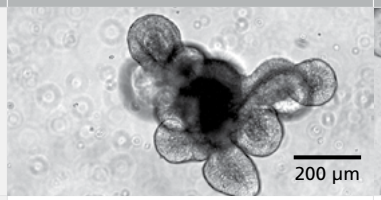
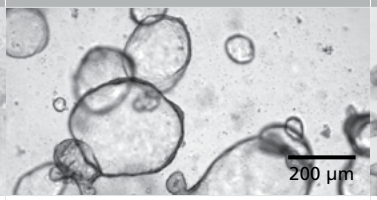
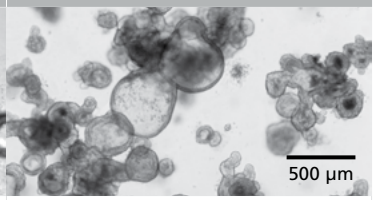
Continued development of organoid methodologies is proving transformative to the biomedical research landscape. In many labs, organoids have complemented model systems already in place, while in others they have enabled investigations previously not possible. Further standardization and optimization of organoid culture techniques will maximize the full benefit of organoids in real-life applications.

Intestinal Organoids

Intestinal organoids incorporate key intestinal cell types, including enterocytes, goblet cells, enteroendocrine cells, and intestinal stem cells, to recapitulate the cellular complement of the intestinal epithelium. The presence of an actively dividing stem cell population enables expansion and maintenance of intestinal organoids in long-term culture.

IntestiCult™ Organoid Growth Medium (Mouse) and IntestiCult™ Organoid Growth Medium (Human) support establishment and long-term maintenance of ASC-derived intestinal organoids from mouse and human cells, respectively. IntestiCult™-SF Organoid Growth Medium (Human) can also be used to initiate human ASC-derived intestinal organoids for a completely serum-free workflow if desired. Human intestinal organoids can be differentiated toward more mature cells of the intestinal epithelium using IntestiCult™ Organoid Differentiation Medium (Human). STEMdiff™ Intestinal Organoid Kit directs human PSCs through a three-stage differentiation process to intestinal organoids that can be maintained and matured in STEMdiff™ Intestinal Organoid Growth Medium. Intestinal organoids grown using these media are convenient, flexible, and relevant intestinal tissue models that can increase experimental impact and reduce laboratory animal use.

Table 1. Comparison of Intestinal Organoid Culture Systems

Intestinal Organoid Type	Mouse (ASC-Derived)	Human (ASC-Derived)	Human (PSC-Derived)
Representative Image			
Organoid Cellular Composition	Organoids simultaneously incorporate an active intestinal stem cell compartment and differentiated cell types in an epithelium that recapitulates the in vivo intestine.	After 1 - 3 passages organoids are composed primarily of cells in a progenitor/stem-like state; organoids can be differentiated to mature intestinal cells in an appropriate medium.	Organoids simultaneously incorporate an active intestinal stem cell compartment, differentiated intestinal epithelial cell types, and associated mesenchymal cells. Organoids are phenotypically fetal.
Starting Material	• Mouse intestinal or colonic crypts • Mouse Intestinal Organoids (Catalog #70931)	• Human intestinal or colonic crypts • Established ASC-derived intestinal organoids	• Human induced pluripotent stem (iPS) or embryonic stem (ES) cell lines • Established PSC-derived intestinal organoids
Organoid Maintenance	Organoids can be maintained through long-term passaging or cryopreserved.	Organoids can be maintained through long-term passaging or cryopreserved.	Organoids can be maintained through long-term passaging or cryopreserved.
Genetic Considerations	• Established common healthy and disease model strains • Tools for in vivo genetic manipulation	• Donor-specific genetic background • Targeted in vitro gene editing possible	• Donor-specific genetic background • Targeted in vitro gene editing possible
Compatible Culture Media	IntestiCult™ Organoid Growth Medium (Mouse) (Catalog #06005)	• IntestiCult™ Organoid Growth Medium (Human) (Catalog #06010) • IntestiCult™-SF Organoid Growth Medium (Human) (Catalog #100-0340) • IntestiCult™ Organoid Differentiation Medium (Human) (Catalog #100-0214)	• STEMdiff™ Intestinal Organoid Kit (Catalog #05140) • STEMdiff™ Intestinal Organoid Growth Medium (Catalog #05145)

IntestiCult™ Organoid Growth Medium (Mouse)

Cell Culture Medium for Establishment and Maintenance of Mouse Intestinal Organoids

IntestiCult™ Organoid Growth Medium (Mouse) is a complete, serum-free organoid growth medium that enables researchers to easily and reproducibly generate experiment-ready organoids in 5 - 7 days.

Why Use IntestiCult™ Organoid Growth Medium (Mouse)?

RELEVANT. Enables generation of intestinal organoid cultures that recapitulate the identity and organization of the adult intestinal epithelium.

ROBUST. Supports efficient establishment of organoids from mouse intestinal crypts in less than one week.

SIMPLE. Generates organoids with a convenient format and easy-to-use protocol.

SERUM-FREE. Reduces experimental variability with optimized formulation.

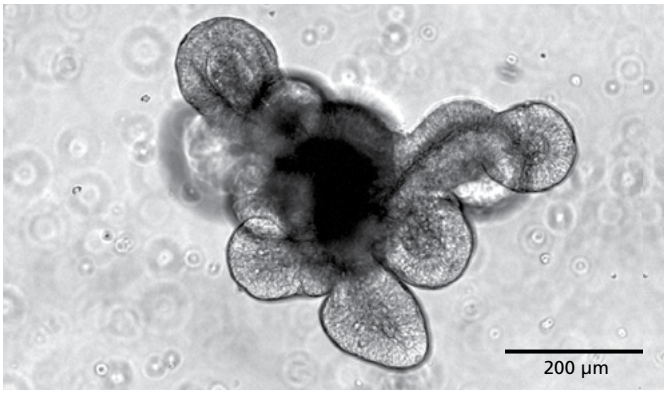


Figure 1. Light Microscope Visualization of a Mouse Intestinal Organoid

Mouse intestinal organoids were cultured in IntestiCult™ Organoid Growth Medium (Mouse) and imaged on Day 5 of passage 0.

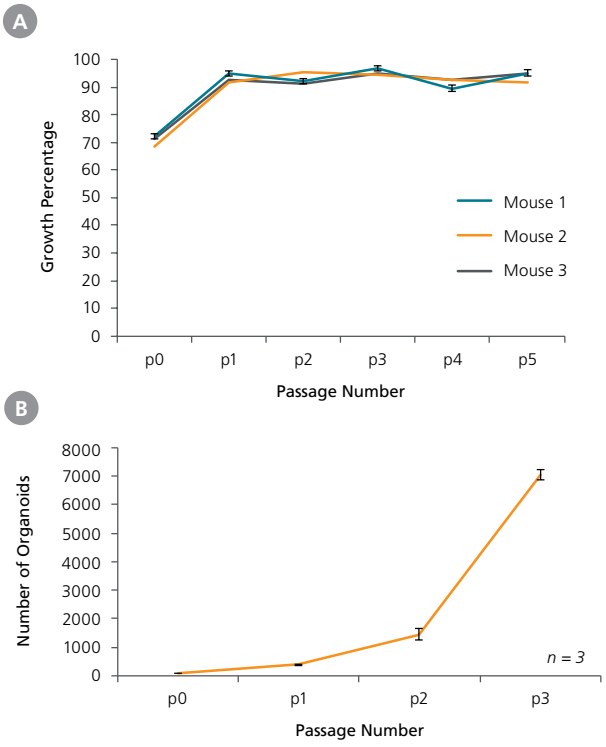


Figure 2. IntestiCult™ Organoid Growth Medium (Mouse) Supports Efficient Organoid Establishment and Expansion

(A) Established organoids can be passaged efficiently over an indefinite number of passages. (B) Starting from a single well containing 100 organoids and passaging at a 1 in 4 split ratio, organoid count increases an average of 4.2-fold per passage.

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Learn More About IntestiCult™ (Mouse)
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IntestiCult™ Organoid Growth Medium (Human)

Cell Culture Medium for Establishment and Maintenance of Human Intestinal Organoids

IntestiCult™ Organoid Growth Medium (Human) is a complete cell culture medium for efficient establishment and long-term maintenance of human intestinal epithelial organoids derived from primary intestinal or colonic crypts or previously frozen colonic organoids.

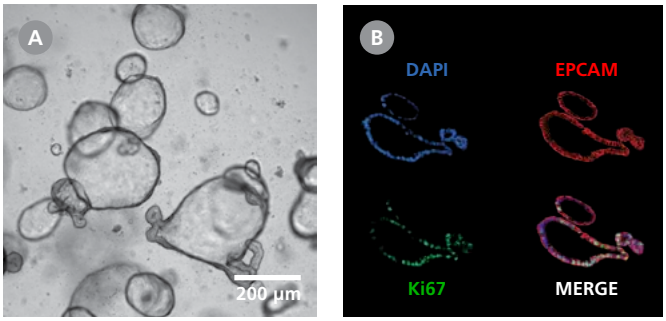

Figure 3. Human Colonic Organoids Grown in IntestiCult™ Organoid Growth Medium (Human)

(A) Colonic organoids grown in IntestiCult™ Organoid Growth Medium (Human) and imaged on Day 7 of passage 0. (B) Immunofluorescence of intestinal organoids showing DAPI (blue), EPCAM (red), Ki67 (green), and the merged image.

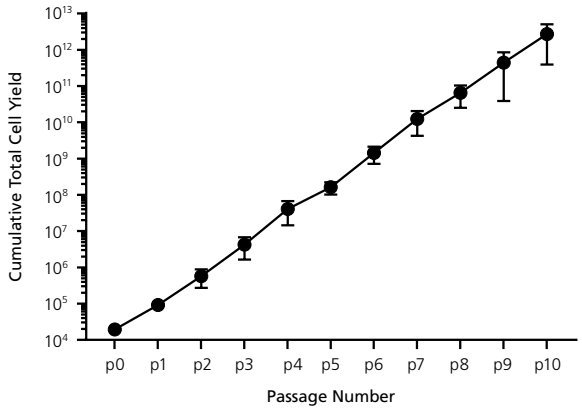

Figure 4. Intestinal Organoids Can Be Maintained in Long-Term Culture Through Passaging

Organoids cultured in IntestiCult™ Organoid Growth Medium (Human) show efficient growth throughout passaging. Cultures were split with an average split ratio of 1 in 6 at each passage. Error bars represent standard error.

Why Use IntestiCult™ Organoid Growth Medium (Human)?

ROBUST. Allows reliable, efficient expansion of intestinal stem cells across donor samples.

RELEVANT. Enables generation of intestinal organoid cultures that can be used to model the adult intestinal epithelium.

COMPLETE. Supports organoid growth without the need for additional growth factors.

CONSISTENT. Generates consistent results between experiments and between laboratories.

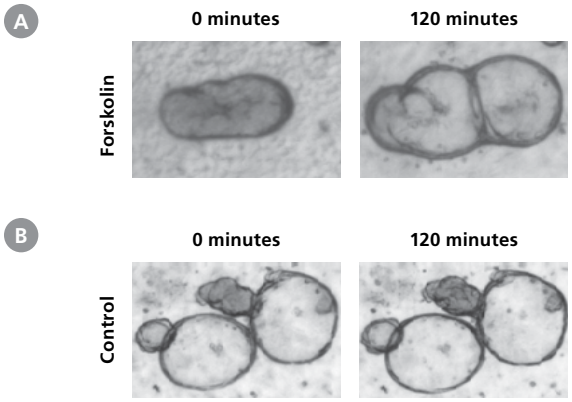

Figure 5. Forskolin-Induced Swelling of Intestinal Organoids

Organoids cultured in IntestiCult™ Organoid Growth Medium (Human) were treated with (A) 5 µM Forskolin or (B) DMSO. Organoid area was measured at 0 minutes and 120 minutes. Forskolin-treated organoids increased in size by 33.5 ± 3.8% in size compared to a 7.5 ± 0.8% increase for control organoids (n = 3). Representative images are shown.

PRODUCT

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IntestiCult™ Organoid-SF Organoid Growth Medium (Human)

Serum- and Conditioned Medium-Free Cell Culture Medium for Establishing and Maintaining Human Intestinal Organoids

IntestiCult™-SF Organoid Growth Medium (Human; OGMH) is a complete serum- and conditioned medium-free cell culture medium that supports the efficient establishment and long-term maintenance of organoids derived from human intestinal crypts. Intestinal organoids grown in IntestiCult™-SF can be further differentiated using IntestiCult™ Organoid Differentiation Medium.

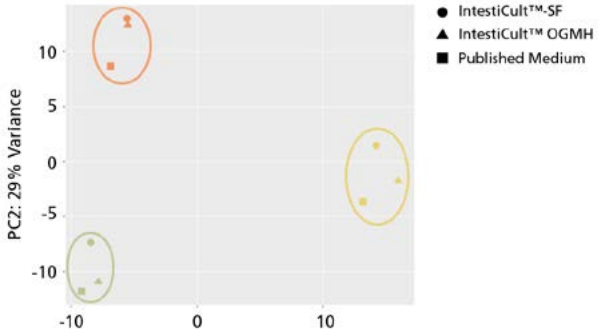

Figure 6. Organoids Grown in IntestiCult™-SF Display Similar Genetic Expression Profiles to Those Grown in IntestiCult™ OGMH

Gene expression analysis of intestinal organoids from three separate donors grown in IntestiCult™-SF (circles), IntestiCult™ OGMH (triangles), and published medium (squares), by principle component analysis, demonstrates that differences between cultures are primarily due to donor variability, with samples forming distinct clusters separated by the donor, rather than by medium.

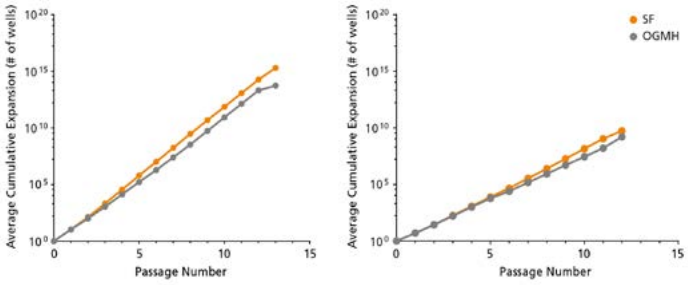

Figure 7. IntestiCult™-SF Provides More Efficient Expansion of Intestinal Organoids Compared to IntestiCult™ OGMH

Human intestinal organoids established from both (A) small intestinal and (B) colonic tissues display more efficient expansion during extended culture when grown in IntestiCult™-SF compared to those grown in IntestiCult™ OGMH. Shown is the cumulative expansion of organoids averaged across two separate donor lines in each medium. IntestiCult™-SF demonstrates more efficient expansion of both small intestinal and colonic organoids during extended culture.

Why Use IntestiCult™ Organoid-SF Growth Medium (Human)?

RELIABLE. Delivers consistent organoid growth, including from degraded tissue samples.

SERUM-FREE. Supports the long-term growth of intestinal organoids in a serum- and conditioned medium-free environment.

OPTIMIZED. Provides lower experimental variability by reducing undefined components.

FLEXIBLE. Generates organoids suitable for a range of applications, including genome editing protocols.

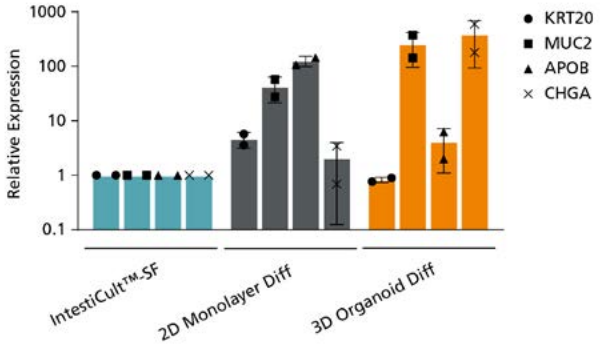

Figure 8. Organoids Grown in IntestiCult™-SF Can Be Further Differentiated Using IntestiCult™ Organoid Differentiation Medium

Further differentiation of organoids in IntestiCult™-SF can be achieved by passaging organoid cultures in IntestiCult™ Organoid Differentiation Medium as organoid-derived monolayers (2D Monolayer Diff) or in 3D organoid culture (3D Organoid Diff). Upon differentiation, markers for enterocytes (KRT20, ApoB), goblet cells (Muc2), and enteroendocrine cells (ChgA) are upregulated in 2D and 3D cultures compared to organoids grown in IntestiCult™-SF.

PRODUCT

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IntestiCult™ Organoid Differentiation Medium (Human)

Complete Culture Medium for the Differentiation of Intestinal Organoids

IntestiCult™ Organoid Differentiation Medium (Human; ODM) is a complete culture medium that supports the further differentiation of intestinal organoids in three dimensions (3D), or in 2D as submerged monolayers or air-liquid interface (ALI) cultures. These cultures can be initiated from intestinal organoids derived from human intestinal crypts, or from passaged organoids that have been cultured with IntestiCult™ Organoid Growth Medium (Human; OGMH; Catalog #06010).

Why Use IntestiCult™ Organoid Differentiation Medium?

RELEVANT. Enables generation of intestinal organoid cultures with physiological proportions of differentiated and stem cell populations.

FLEXIBLE. Allows easy access to the apical surface by transitioning intestinal organoids into monolayer and ALI cultures.

REPRODUCIBLE. Generates consistent results across passages and replicates.

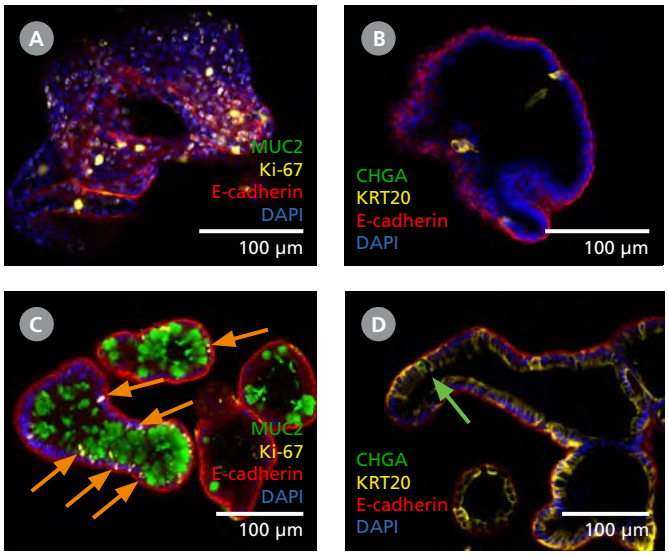

Figure 9. Intestinal Organoids Contain a Higher Proportion of Mature Cell Types Following Differentiation in IntestiCult™ ODM

(A, B) Organoids grown in IntestiCult™ OGM are enriched for Ki-67$^+$ proliferative cells (A), while containing few differentiated cell types such as goblet cells (MUC2, A), enterocytes (KRT20, B), and enteroendocrine cells (CHGA, B). (C, D) When switched to IntestiCult™ ODM, organoids contain a small number of Ki-67$^+$ proliferative cells (C, arrows), with more physiological proportions of goblet cells (MUC2, C), enterocytes (KRT20, D), and chromogranin A- (CHGA-) positive enteroendocrine cells (D, arrow).

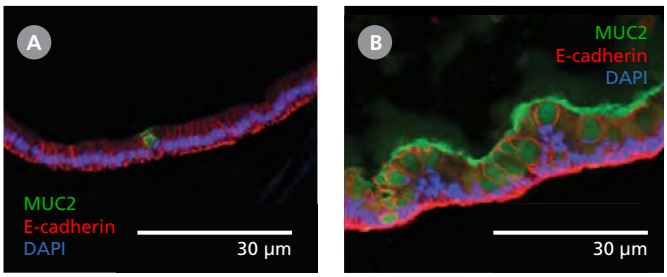

Figure 10. Differentiation of Intestinal Epithelium at the Air-Liquid Interface (ALI) Using IntestiCult™ ODM

(A and B) Comparing cross-sections of organoid monolayers grown in IntestiCult™ ODM as (A) submerged culture or (B) at the ALI shows further differentiation of the intestinal epithelium with an increased proportion of goblet cells and extracellular mucus (MUC2, green).

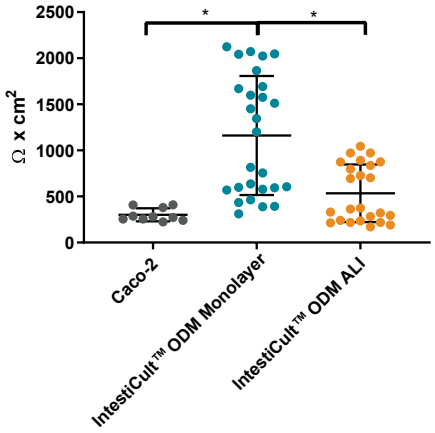

Figure 11. Differentiated Organoid-Derived Monolayers and ALI Cultures Display More Physiological Trans-Epithelial Electrical Resistance (TEER) than Caco-2 Cell

Differentiated organoid-derived monolayers grown as a submerged monolayer (IntestiCult™ ODM Monolayer), or at the ALI (IntestiCult™ ODM ALI), show higher TEER values as compared to Caco-2 cultures. Organoid-derived monolayers grown at the ALI show a loosening of tight junctions due to further differentiation of the brush border, and thus lower TEER values are observed.
* indicates $p < 0.0001$

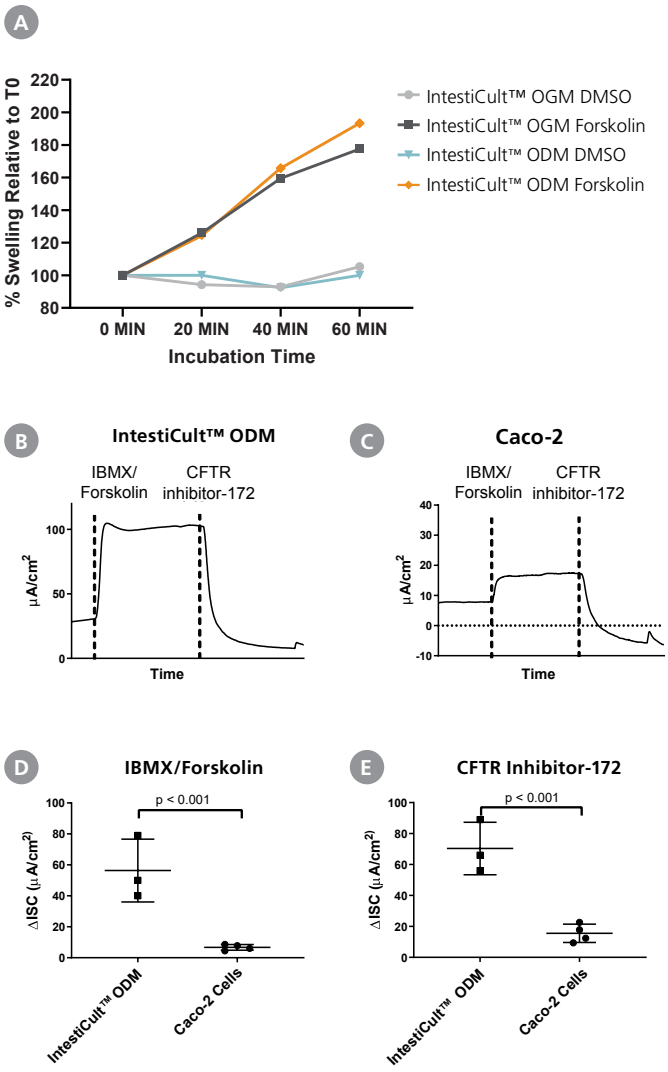

Figure 12. Differentiated Intestinal Organoids Provide a Suitable Model for Studying CFTR Response In Vitro

(A) Organoids differentiated further in IntestiCult™ ODM show a comparable degree of swelling when treated with forskolin as compared to organoids grown in IntestiCult™ OGM, demonstrating suitability for use in forskolin-induced swelling assays. (B,C) Using chamber analysis of submerged (B) organoid-derived monolayers and (C) Caco-2 cultures demonstrate increased sensitivity of organoid-derived monolayers to CFTR activation and inhibition by IBMX/Forskolin and CFTR Inhibitor-172, respectively. (D,E) Analysis of CFTR modulation by IBMX/Forskolin and CFTR Inhibitor-172 show significantly greater (D) activation and (E) inhibition of CFTR activity in organoid-derived monolayers as compared to Caco-2 cultures ($p < 0.001$ for both).

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STEMdiff™ Intestinal Organoid Kit

Differentiate Human ES and iPS Cell Lines to Intestinal Organoids

The STEMdiff™ Intestinal Organoid Kit supports efficient establishment of PSC-derived small intestinal organoid cultures from embryonic stem (ES) cells or induced pluripotent stem (iPS) cells within 30 days. This serum-free medium kit is based on the formulation published by Spence et al.[3] and has been optimized to increase efficiency and reproducibility of organoid formation and expansion.

Why Use STEMdiff™ Intestinal Organoid Kit?

RELEVANT. Enables generation of small intestinal organoid cultures that model the developing intestinal epithelium and associated mesenchyme.

ROBUST. Supports efficient differentiation of human ES and iPS cell lines to intestinal organoids.

CONVENIENT. Allows long-term maintenance of organoids through passaging or cryopreservation for experimental flexibility.

SERUM-FREE. Reduces experimental variability with optimized formulation.

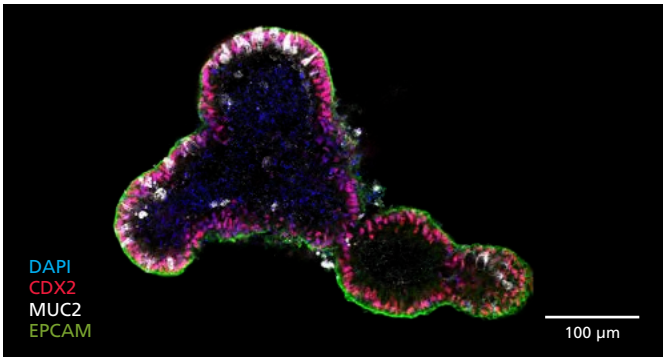

Figure 13. hPSC-Derived Intestinal Organoids Incorporate Features of the Intestinal Epithelium and Mesenchyme

Organoids grown using STEMdiff™ Intestinal Organoid Kit display markers of the intestinal epithelium (EPCAM, CDX2, MUC2). Organoids also exhibit markers for intestinal mesenchyme and intestinal progenitor cells.

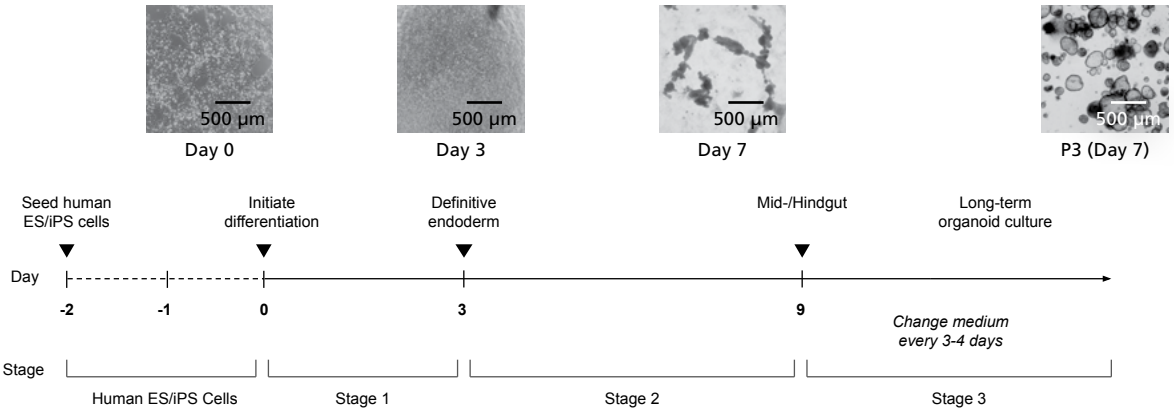

Figure 14. Schematic for Differentiating from hPSCs to Human Intestinal Organoids with the STEMdiff™ Intestinal Organoid Kit

hPSC cultures progress through a three-stage differentiation process to generate human intestinal organoids. By Day 3 of the protocol, cultures exhibit characteristics typical of definitive endoderm and mid-/hindgut differentiation is initiated. During mid-/hindgut differentiation (Days 5 - 7), cells form mid-/hindgut spheroids that are released from the cell monolayer into the culture medium. These spheroids are collected, embedded in extracellular matrix, and cultured in STEMdiff™ Intestinal Organoid Growth Medium to mature into intestinal organoids. Days in parentheses indicate days post-embedding in a given passage.

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Intestinal Organoid Assays

With Contract Assay Services

Organoids provide a convenient and highly predictive model system for studying the effects of novel therapeutic compounds on the intestinal epithelium in vitro. Founded in our expertise from developing IntestiCult™ organoid growth and differentiation media, the intestinal organoid assays offered by Contract Assay Services (CAS) at STEMCELL Technologies are optimized to provide clear read-outs that better represent the effects observed in vivo.

Add the relevance of organoid-based assays to your research in a cost-effective and efficient manner by partnering with CAS.

Intestinal Cytotoxicity Testing

Gastrointestinal toxicity is often one of the dose-limiting factors for new therapeutics. However, compounds that interfere with normal cell growth may not show the same effects when examined in immortalized cell lines or animal model systems.

By maintaining a population of actively dividing stem cells, as well as other differentiated cell types of the human intestine, intestinal organoids are an accurate predictor of intestinal toxicity and provide results that are more predictive of the in vivo response than Caco-2 cells, which are a popular model system for assessing gastrointestinal toxicity.

Like human intestinal organoids, mouse intestinal organoids contain the different cell types of the intestinal epithelium and can serve as a complementary approach to collect high-throughput data without having to sacrifice additional animals.

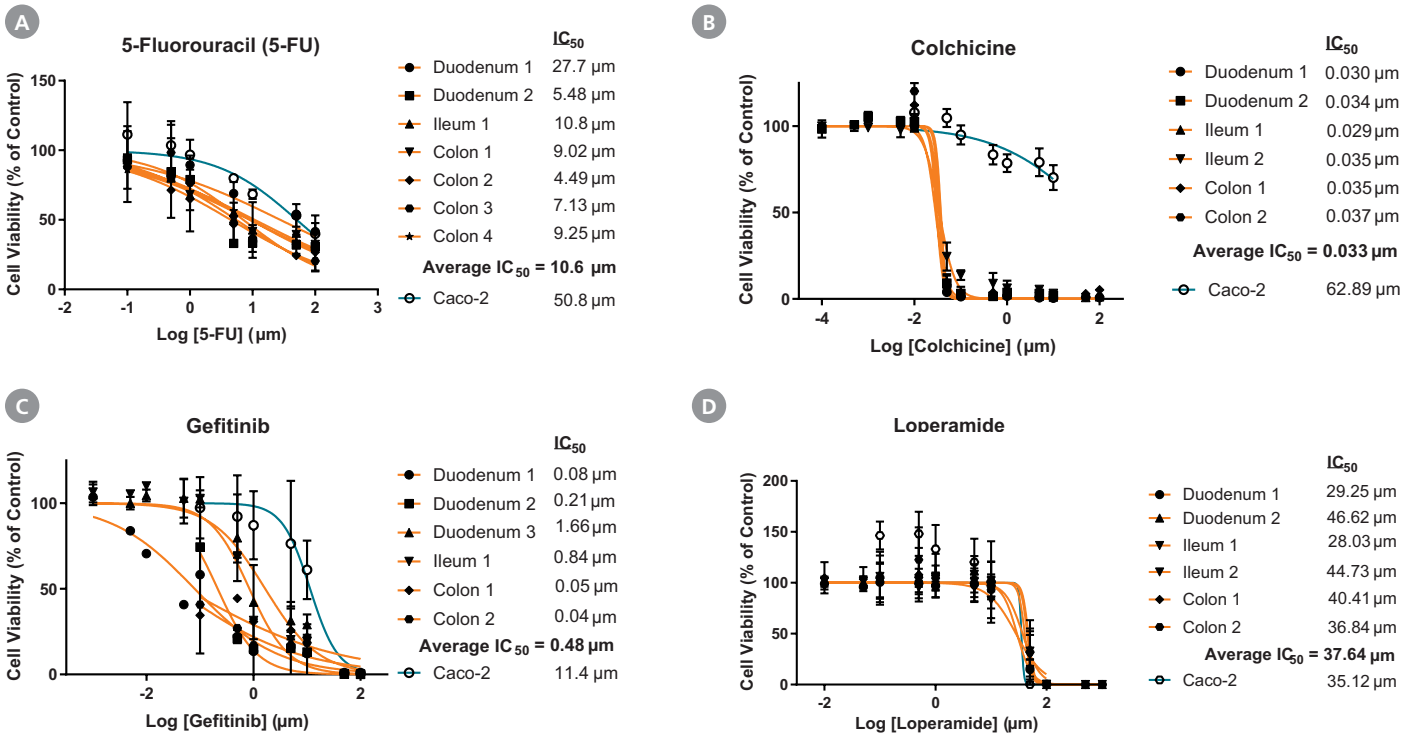

Figure 15. Intestinal Organoids Are a More Sensitive Indicator of Intestinal Toxicity Than Caco-2 Cells

Intestinal organoids provide a better predictor of intestinal cytotoxicity in actively dividing cells. Intestinal organoids were grown from different regions of the intestine and assayed against compounds that primarily affect the growth and cellular division of the intestinal epithelium. Fully grown organoids were treated with (A) 5-fluorouracil (5-FU), (B) Colchicine, and (C) Gefitinib, which demonstrated a higher toxicity against intestinal organoids than is observed in Caco-2 cells, as indicated by a lower IC50. Additionally, organoids do not show sensitivity to nontoxic compounds that do not primarily interfere with cell division processes, such as (D) Loperamide, shown by a significant right shift in IC50 values that reflects the absence of toxicity associated with cell division inhibition.

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Intestinal Barrier Integrity Testing

In addition to interfering with normal turnover of the intestinal epithelium, therapeutic compounds can disrupt the barrier function of the intestinal epithelium. Because organoid-derived intestinal monolayers contain the different cell types of the intestinal epithelium, they provide a convenient system for assessing disruption of the intestinal barrier function in vitro.

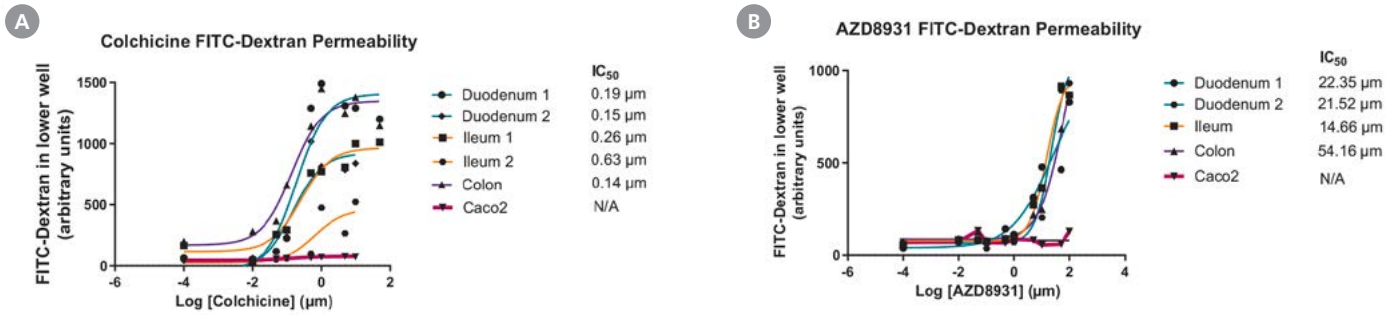

Figure 16. Intestinal Organoids Detect Barrier-Function Disruption Missed By Caco-2 Cells

Organoids are able to detect the barrier function disruption caused by (A) Colchicine and (B) AZD8931, as measured by FITC-Dextran permeability. This barrier disruption is not detected in Caco-2 cells.

CONTRACT ASSAY

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STEMdiff™ Gastric Organoid Differentiation Kit

Culture Medium Kit for Differentiation of Human Gastric Organoids

Reliably generate hPSC-derived gastric organoids for studying gastric development, inflammation, regeneration, microbial interaction, or for disease modeling. With the STEMdiff™ Gastric Organoid Differentiation Kit, you can grow and expand organoids across hPSC lines with high efficiency and reproducibility, to form a convenient model system with direct relevance to the developing stomach.

Why Use the STEMdiff™ Gastric Organoid Differentiation Kit?

RELEVANT. Study the developing gastric epithelium and associated mesenchyme in a human-specific model system.

ROBUST. Efficiently differentiate multiple different human ES and iPS cell lines to gastric organoids.

CONVENIENT. Maintain gastric organoids for long-term through passaging or cryopreservation for experimental flexibility.

SERUM-FREE. Reduce experimental variability with serum-free formulation.

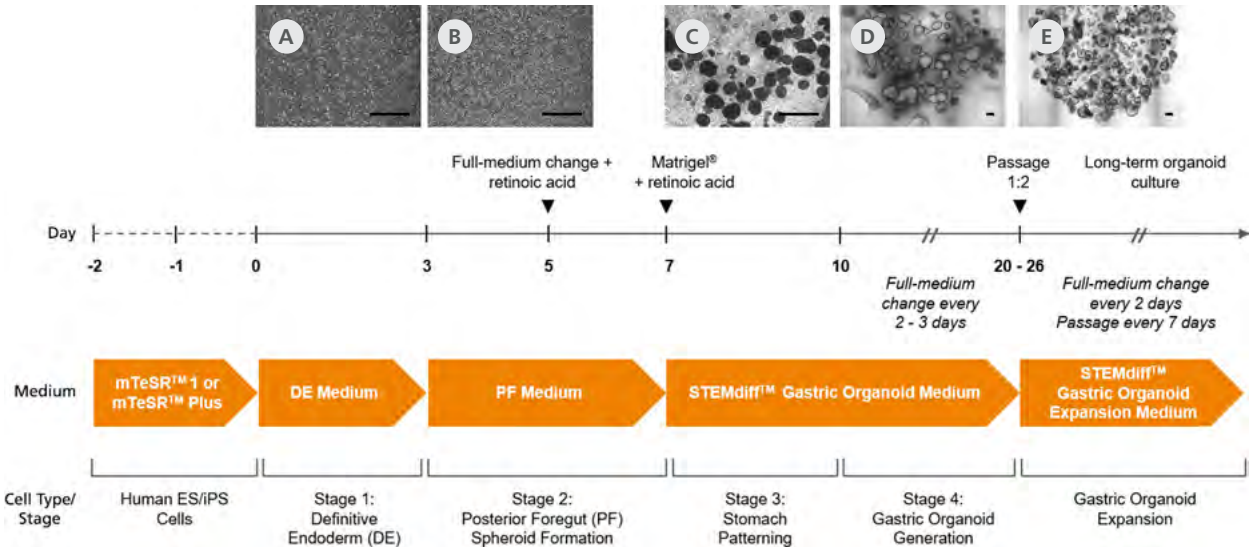


Figure 17. Schematic for Generation of Human Gastric Organoid Cultures Using STEMdiff™ Gastric Organoid Differentiation Kit

hPSCs are seeded as small aggregates (50 - 200 µm) at low density (4000 aggregates/well) in mTeSR™1 or mTeSR™ Plus on Corning® Matrigel®-coated 24-well plates and allowed to attach overnight. Two-dimensional (2D) monolayer cultures are maintained with daily mTeSR™1 medium changes until a near-confluent monolayer (85 - 90%) is achieved. (A) On Day 0, differentiation is initiated by replacing the medium with STEMdiff™ Definitive Endoderm (DE) Medium (Stage 1), then daily medium changes are performed. (B) On Day 3, DE Medium is removed and replaced with STEMdiff™ Gastric Posterior Foregut (PF) Medium (Stage 2). On Day 5, retinoic acid (RA) is added to PF Medium. (C) On Day 7 of differentiation, floating posterior foregut spheroids are harvested from the supernatant and embedded into Corning® Matrigel®. Between Days 7 and 10, embedded PF spheroids are cultured in STEMdiff™ Gastric Organoid Medium + RA (Stage 3). Between Days 10 and 26, spheroids are matured to gastric organoids surrounded by mesenchyme in STEMdiff™ Gastric Organoid Medium. (D) Between Days 20 and 26, gastric organoids are passaged for full differentiation in STEMdiff™ Gastric Organoid Medium until expression of gastric markers is observed (~Day 34) and/or (E) expanded in STEMdiff™ Gastric Organoid Expansion Medium to be used for downstream applications or cryopreserved for future experiments. Scale bars = 500 µm.

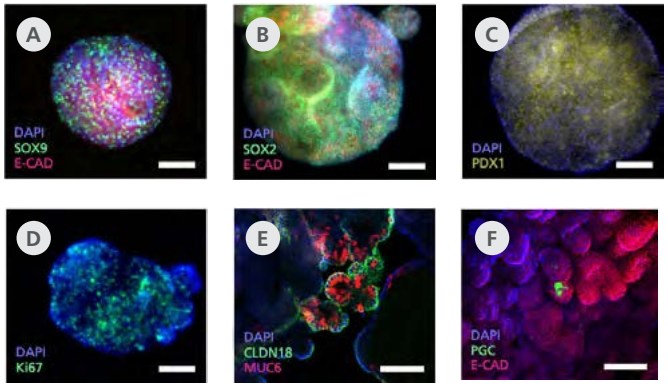


Figure 18. Immunohistochemistry Confirms Expression of Gastric-Specific Markers in Human Gastric Organoids Cultured in Gastric Organoid Expansion Medium

Representative organoids in Expansion Medium at passage 5 expressed progenitor markers (A) SOX9, (B) SOX2, and (C) PDX1; (A, B, F) epithelial marker E-CAD; (D) marker of proliferation Ki67; and (E) gastric tight junction marker CLDN18. (E) Presence of gland cells was detected by expression of MUC6 in the gland regions of the organoids. (F) Detection of scattered expression of PGC indicates differentiation of chief cells (n = 2 - 5). Scale bars = 100 µm.

PRODUCT

Learn More About STEMdiff™ Gastric Organoid Kit

www.stemcell.com/STEMdiff-Gastric

Hepatic Organoids

The development of hepatic organoid culture techniques has provided the hepatic research field with a convenient method for sustained maintenance of liver cells in vitro.[4,5] Hepatic progenitor organoids are cultured by isolating and expanding liver stem and progenitor cells, which are postulated to reside in hepatic ducts. Culture of hepatic progenitor cells as organoids produces spherical organoids consisting primarily of progenitor cells that can be further differentiated to either hepatocytes or cholangiocytes.[6] Compared to traditionally used model systems such as cell lines and animal models, liver organoids provide a more relevant model system for studying hepatic development, regeneration, metabolism, and disease.

HepatiCult™ Organoid Growth Medium (Mouse)

Cell Culture Medium for Establishment and Maintenance of Mouse Hepatic Organoids

Efficiently establish and maintain mouse hepatic progenitor organoid cultures to study hepatic stem and progenitor cells in an in vitro, physiologically relevant system. HepatiCult™ Organoid Growth Medium (Mouse) is a serum-free, defined medium formulation that can generate hepatic progenitor organoids in 4 - 5 days. These organoids are primed for downstream differentiation and can be cryopreserved for a flexible workflow.

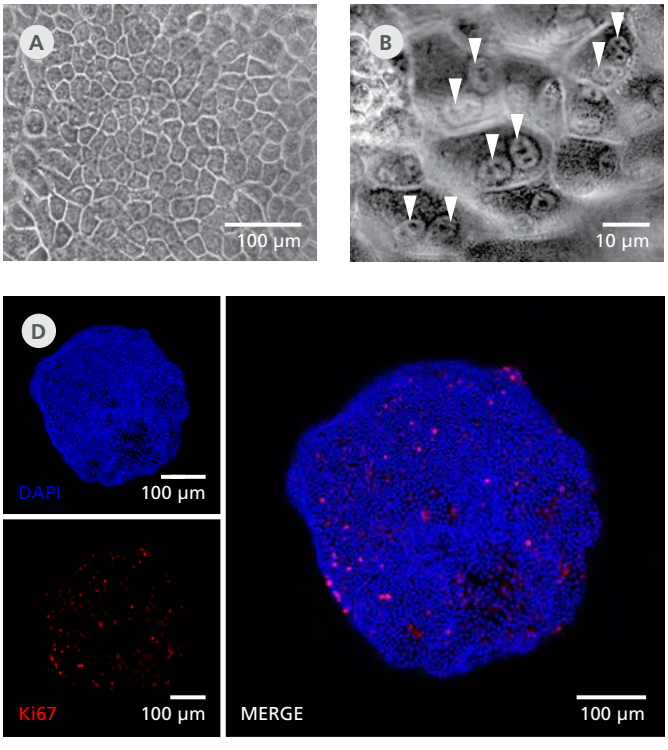
Why Use HepatiCult™ Organoid Growth Medium (Mouse)?

CONVENIENT. Generate organoids in vitro within a week.

STEP-BY-STEP PROTOCOL. Eliminate the need for injury models, hand-picking of ducts, or cell sorting in your workflow.

SIMPLE, TWO-COMPONENT FORMAT. Grow organoids in a simple, serum-free formulation.

FLEXIBLE PROTOCOL. Start with duct fragments or single cells to culture organoids in matrix domes or suspension.



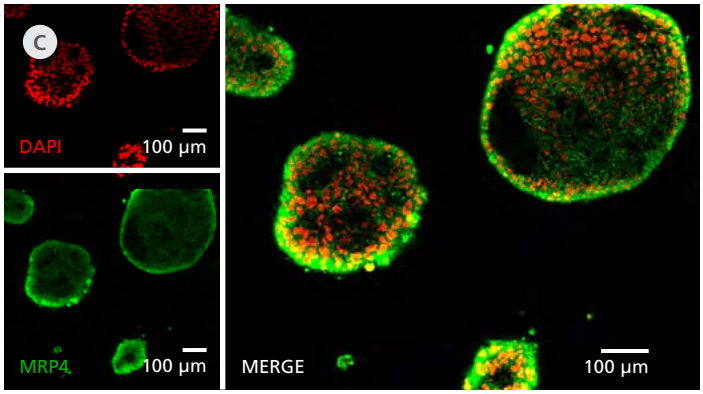


Figure 19. Organoids Grown in HepatiCult™ Organoid Growth Medium (Mouse) Display Some Characteristics Typical of the Mature Hepatic Epithelium

(A) Hepatic progenitor organoids exhibit the polygonal morphology typical of the hepatic epithelium. (B) Hepatic progenitor organoids show binucleation (arrows), a common feature of mature hepatocytes. (C) Immunocytochemistry analysis shows localization of MRP4 (green), a membrane-bound, unidirectional efflux transporter, along the exterior of the organoids and DAPI (red) localized to the cellular nuclei. This indicates cellular polarization of the organoids with the basolateral surface of the epithelium distal from the lumen. (D) Hepatic organoids contain an actively dividing progenitor population, shown by the expression of Ki67 (red). Cell nuclei are stained with DAPI (blue).

PRODUCT
Learn More About HepatiCult™ Mouse
www.stemcell.com/Hepaticult-Mouse

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HepatiCult™ Organoid Kit (Human)

Culture Medium Kit for Initiation, Growth, and Differentiation of Human Liver Organoids

The HepatiCult™ Organoid Kit (Human) contains all the necessary components to culture human liver organoids from fresh or cryopreserved human liver tissue. HepatiCult™ Organoid Initiation Medium (Catalog #100-0384) efficiently generates hepatic organoids across different donor lines, which can be further expanded and maintained in HepatiCult™ Organoid Growth Medium (Catalog #100-0385) for future experimentation or bio-banking. Differentiating these organoids with HepatiCult™ Organoid Differentiation Medium (Catalog #100-0383) generates mature organoids that demonstrate hepatic functionality, including CYP3A4 activity. These organoids can be adapted to a range of culture protocols, including 2D monolayer, suspension cultures, and high-throughput assays.

Why Use HepatiCult™ Organoid Kit (Human)?

COMPLETE. Provides a complete culture system for establishing, maintaining, and differentiating human liver organoids.

ROBUST. Enables efficient organoid initiation across different donor liver tissues.

FUNCTIONAL. Generates mature hepatic organoids that demonstrate CYP3A4 activity.

FLEXIBLE. Allows experimental flexibility with different culture formats.

Table 2. Product Recommendations for Liver Organoid Initiation, Expansion, and Differentiation

Starting Material	Experimental Goal		
	Organoid Initiation	Organoid Expansion	Organoid Differentiation
Human Liver Tissue (fresh or cryopreserved)	**Recommended:** HepatiCult™ Organoid Initiation Medium (Catalog #100-0384) **Serum-Free (Optional):** HepatiCult™ Organoid Growth Medium (100-0385)	HepatiCult™ Organoid Growth Medium (Catalog #100-0385)	HepatiCult™ Organoid Kit (Catalog #100-0386)
Established Liver Organoids (in culture or cryopreserved)	N/A	HepatiCult™ Organoid Growth Medium (Catalog #100-0385)	HepatiCult™ Organoid Differentiation Medium (Catalog #100-0383)

The recommended configuration of the HepatiCult™ Organoid Kit (Human) may differ based on starting material and experimental goals. When establishing liver organoid cultures from human liver tissue, HepatiCult™ Organoid Initiation Medium (OIM; Human) is recommended for efficient organoid initiation. The expansion of established organoids (fresh in culture or cryopreserved) is supported by HepatiCult™ Organoid Growth Medium (OGM; Human). These organoids should be maintained for 2-3 passages before further differentiation using HepatiCult™ Organoid Differentiation Medium (ODM). Refer to the Product Manual (Document #10000008301) for full culturing protocols.

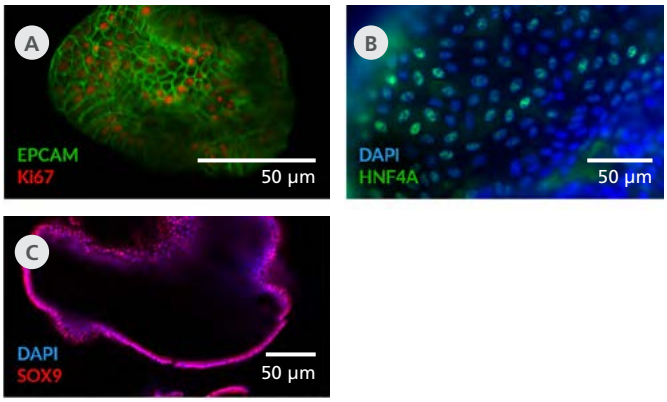

Figure 20. Proliferating Hepatic Organoids Display Characteristics of Hepatic Progenitors

Human liver organoids grown in HepatiCult™ OGM display characteristics of proliferating hepatic progenitors as observed through immunocytochemistry staining of (A) KI67, (B) HNF4A, and (C) SOX9. Proliferating hepatic organoids also display characteristics of the hepatic epithelium, including expression of (A) EPCAM. (B, C) Nuclei are counterstained with DAPI.

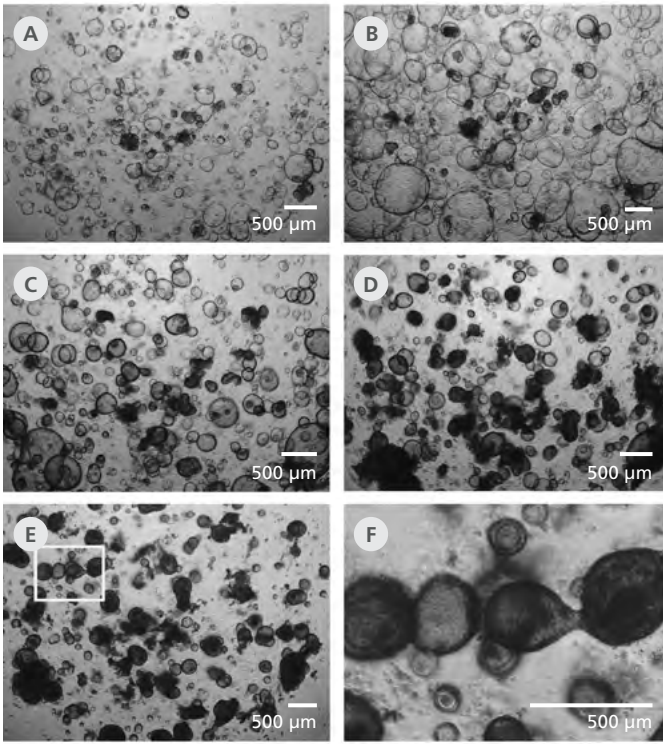

Figure 21. Organoid Differentiation Induces Changes in Organoid Morphology

Organoids exhibit a compact and dense morphology, often comprising thickened epithelia, upon switching cultures to HepatiCult™ ODM. Shown are images of the same culture well over the course of the differentiation, including (A) Day 2 of culture in HepatiCult™ OGM, (B) Day 5 of culture, immediately after switching organoid cultures from HepatiCult™ OGM to HepatiCult™ ODM, (C) Day 7 of culture (two days after switching to ODM), (D) Day 10 of culture (five days after switching to ODM), and (E) Day 15 of culture (ten days after switching to ODM). (F) Magnification of the rectangular section highlighted in (E).

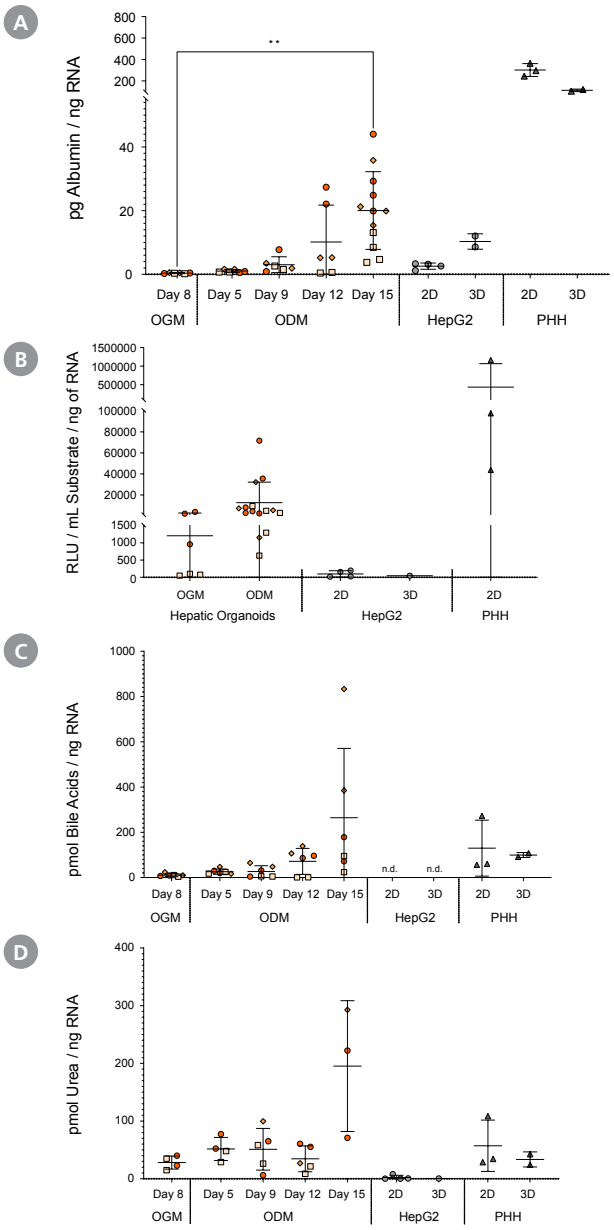

Figure 22. Differentiated Hepatic Organoids Demonstrate Functionality of Mature Hepatocytes

Upon differentiation in HepatiCult™ ODM, liver organoids were assayed for (A) albumin secretion, (B) CYP3A4 activity, (C) total bile acid production, and (D) urea production. Hepatic functionalities were compared to HepG2 cells and primary human hepatocytes (PHH), which were cultured in supplier-recommended media. Albumin secretion was detected using an ELISA kit (Abcam), total bile acid and urea production were analyzed using colorimetric kits (Abcam), and CYP43A4 activity, referring to baseline activity without induction, was determined using the Luciferin-IPA kit (Promega). Values represent the mean ± SD; n = 3 organoid lines derived from different donors across 2 experiments, n = 2 - 3 technical replicates of HepG2 in 1 experiment, and n = 3 cryopreserved PHH donor samples in 1 experiment), * $p < 0.05$; ** $p < 0.01$.

PRODUCT

Learn More About HepatiCult™ Organoid Kit (Human)

www.stemcell.com/Hepaticult-Human

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Pancreatic Organoids

Pancreatic organoids are cultured through isolation and expansion of pancreatic stem and progenitor cells from pancreatic ducts.[7] When cultured with the appropriate growth factors and extracellular matrix, pancreatic progenitor cells form organoids resembling the exocrine component of the pancreas. In addition, isolation of primary tissue from mouse primary tumors and metastases allows for the growth of tumor-derived organoids, providing a model for pancreatic carcinomas and pancreatic ductal adenocarcinoma progression. These organoids retain key characteristics of the parental tumor, including genotype and phenotype, providing a convenient model system for in vitro experimentation.

PancreaCult™ Organoid Growth Medium (Mouse)

Cell Culture Medium for Establishment and Maintenance of Mouse Pancreatic Exocrine Organoids

PancreaCult™ Organoid Growth Medium (Mouse) enables the growth of pancreatic exocrine organoids from pancreatic ducts, duct fragments, single cells, or organoid fragments. Pancreatic organoids can be maintained through extended passaging or cryopreservation, providing a readily available source of cells for future experiments.

Why Use PancreaCult™ Organoid Growth Medium (Mouse)?

CONVENIENT. Generates organoids in vitro within a week.

STEP-BY-STEP PROTOCOL. Eliminates the need for injury models, hand-picking of ducts, or cell sorting.

SIMPLE, TWO-COMPONENT FORMAT. Supports organoid growth in a simple, serum-free formulation.

FLEXIBLE PROTOCOL. Provides flexibility to start with duct fragments or single cells to culture organoids in matrix domes or suspension.

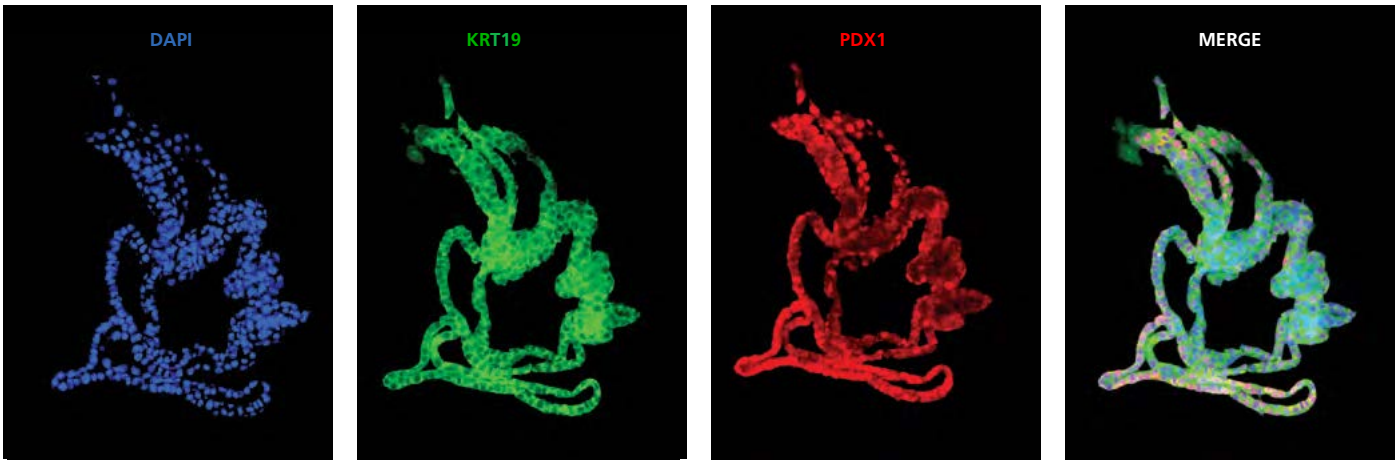

Figure 23. Pancreatic Exocrine Organoids Display Markers of Pancreatic Progenitor and Ductal Cells

Pancreatic exocrine organoids grown in PancreaCult™ Organoid Growth Medium (Mouse) and stained for nuclei (DAPI, blue), ductal marker KRT19 (green), and pancreatic progenitor marker PDX1 (red). Organoids were imaged during passage 12 on Day 5.

Note: The folded appearance of epithelium is a function of cryosectioning and not representative of the shape of proliferating organoids.

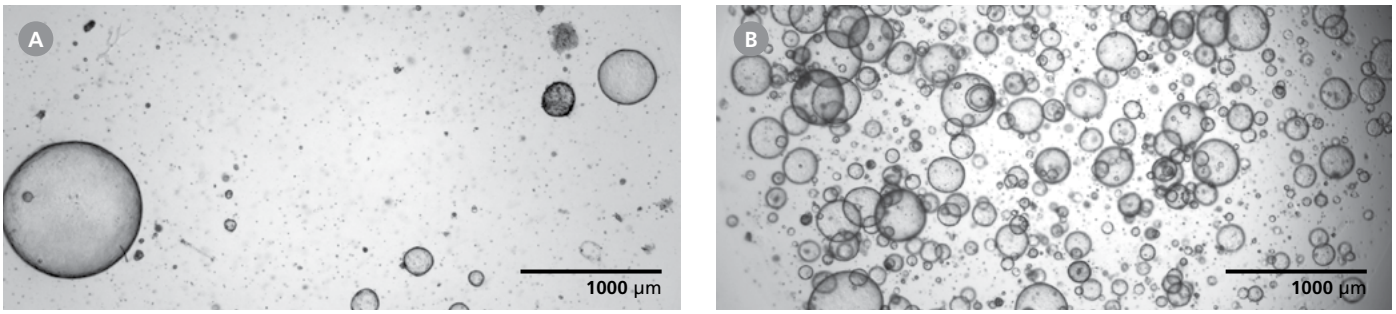

Figure 24. Pancreatic Exocrine Organoids Provide a Model for Pancreatic Carcinomas

PancreaCult™ Organoid Growth Medium (Mouse) supports the growth of organoids from pancreatic carcinomas. Pancreatic ducts were isolated from KPC mice (Kras+/LSL-G12D; Trp53+/LSL-R172H; Pdx1-Cre) and cultured in PancreaCult™ Organoid Growth Medium (Mouse). Organoids were imaged on (A) Day 4 of primary culture and (B) Day 4 after the first passage. An activated KRAS genotype was retained in organoids during culture. Data used with permission from Dr. David Tuveson.

PRODUCT

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PancreaCult™ Organoid Media (Human)

Culture Media Kit for the Initiation, Growth, and Establishment of Human Pancreatic Organoids

Generate robust pancreatic organoid cultures from fresh or cryopreserved islet-depleted pancreatic exocrine fractions for your research. PancreaCult™ (Human) culture media system provides a complete workflow to establish, expand, and maintain pancreatic duct organoids.

Why Use PancreaCult™ Organoid Media (Human)?

CONVENIENT. Recapitulates many key characteristics of adult pancreatic ducts in vitro.

EFFICIENT. Enables organoid initiation and expansion across different pancreatic donor tissues.

FLEXIBLE. Allows expansion of normal and tumor-derived organoids.

RELIABLE. Reduces experimental variability via a serum- and conditioned medium-free formulation.

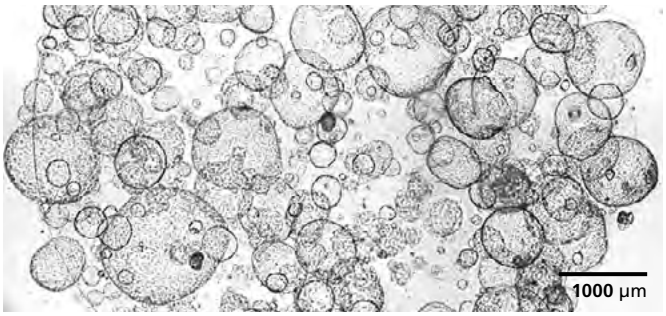

Figure 25. Human Pancreatic Duct Organoids

PancreaCult™ Organoid Initiation Medium (OIM; Human) and Organoid Growth Medium (OGM; Human) support the initiation and expansion of human pancreatic duct organoids from pancreatic tissue or previously established organoid cultures. Shown are organoids grown using PancreaCult™ OIM and OGM and imaged on Day 7 of passage 3.

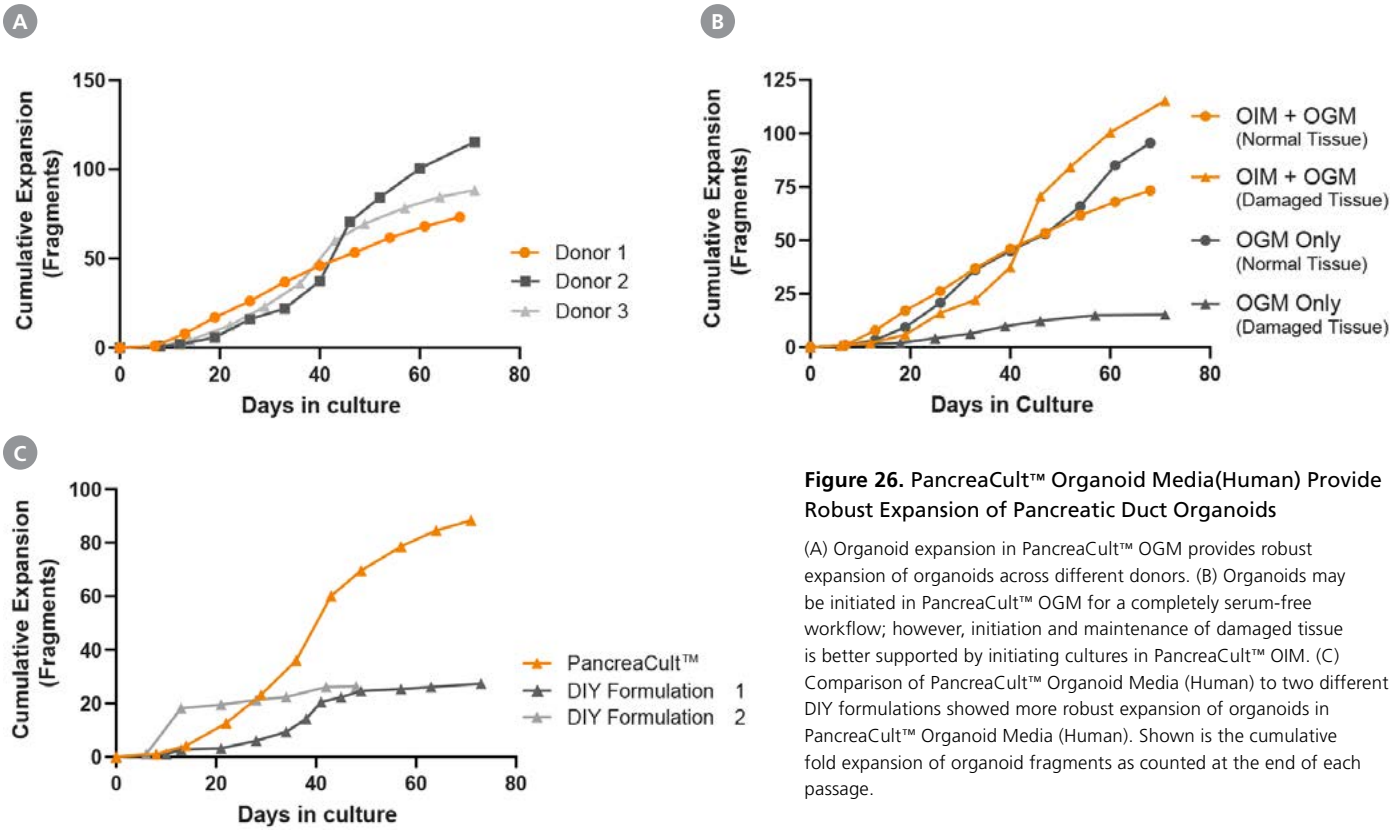

Figure 26. PancreaCult™ Organoid Media(Human) Provide Robust Expansion of Pancreatic Duct Organoids

(A) Organoid expansion in PancreaCult™ OGM provides robust expansion of organoids across different donors. (B) Organoids may be initiated in PancreaCult™ OGM for a completely serum-free workflow; however, initiation and maintenance of damaged tissue is better supported by initiating cultures in PancreaCult™ OIM. (C) Comparison of PancreaCult™ Organoid Media (Human) to two different DIY formulations showed more robust expansion of organoids in PancreaCult™ Organoid Media (Human). Shown is the cumulative fold expansion of organoid fragments as counted at the end of each passage.

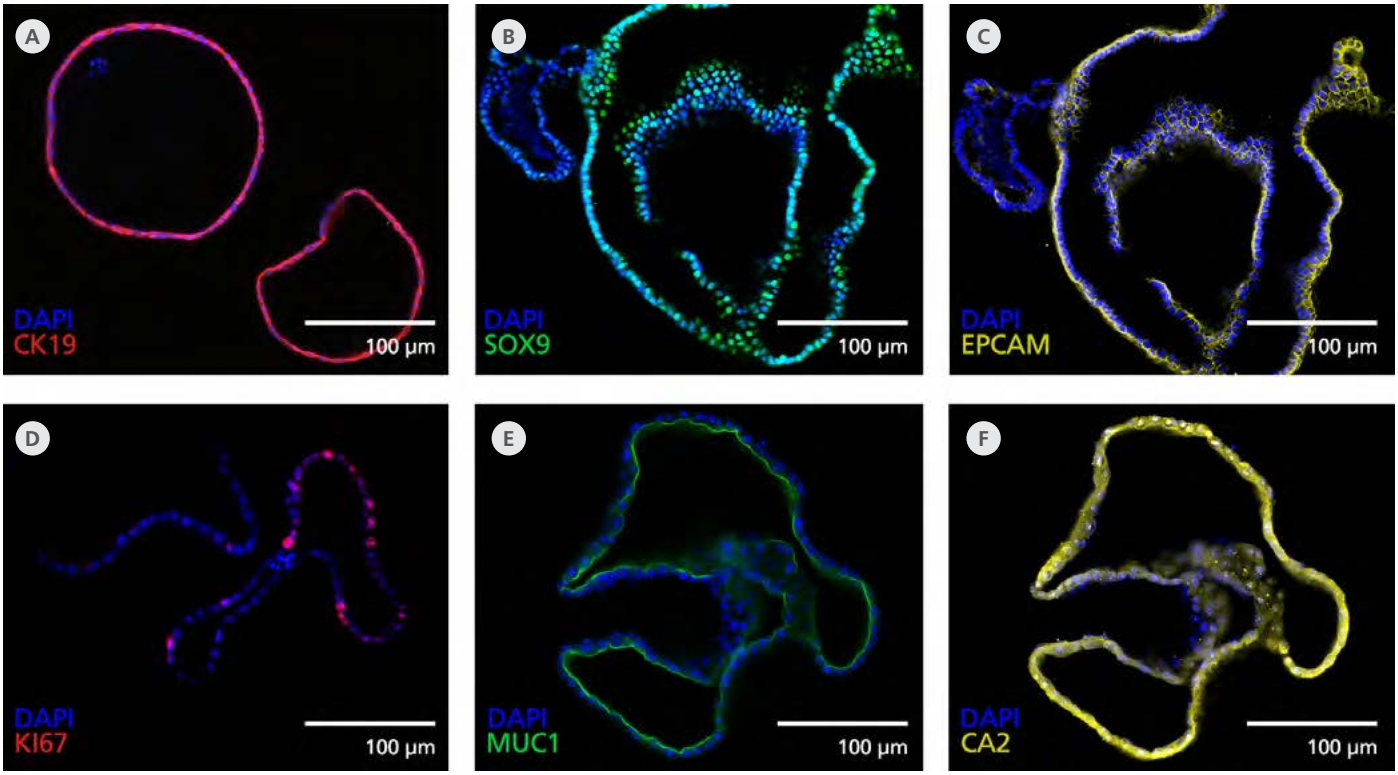

Figure 27. Pancreatic Duct Organoids Display Features of the Pancreatic Ductal Epithelium

Organoids grown using the PancreaCult™ Organoid Media (Human) display marker expression consistent with the pancreatic ductal epithelium when imaged using immunocytochemistry. Shown are organoids grown in PancreaCult™ OGM and stained for (A) pancreatic ductal marker CK19, (B) pancreatic ductal marker SOX9, (C) epithelial marker EPCAM, (D) proliferation marker KI67, (E) apical pancreatic duct marker MUC1, and (F) pancreatic ductal marker CA2. Organoids were imaged on passage 2 (A), passage 3 (B, C) or passage 10 (D-F).

PRODUCT

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Kidney Organoids

The kidney plays an important physiological role in the body, such that nephrotoxicity is a critical consideration during drug screening and development. Despite this, the limited availability of relevant in vitro models has presented challenges for studying kidney health and function. Kidney organoids are addressing this challenge by providing efficient in vitro culture systems that mimic the structure and cellular architecture of the nephron and associated mesenchyme and endothelium.[8] These kidney organoids are composed of convoluted tubular structures with typical nephron-like segmentation marked by the expression of podocyte (podocalyxin [PODXL]), proximal (lotus tetragonolobus lectin [LTL]), and distal tubule (E-cadherin [ECAD]) markers.

STEMdiff™ Kidney Organoid Kit

Serum-Free Medium Kit for the Culture of Kidney Organoids from PSCs

STEMdiff™ Kidney Organoid Kit is a complete, serum-free cell culture medium system that supports highly efficient and reproducible generation of human pluripotent stem cell (PSC)-derived kidney organoids in a simple two-stage differentiation protocol. It has an optimized, quality controlled formulation to increase reproducibility and efficiency across multiple pluripotent cell lines. This kit has been optimized for the differentiation of PSCs previously cultured in mTeSR™1 (Catalog #85850).

Why Use the STEMdiff™ Kidney Organoid Kit?

RELEVANT. Enables generation of human kidney organoids that model the developing nephron and associated endothelium and mesenchyme.

SIMPLE. Minimizes culture manipulations with a two-stage culture system and easy-to-follow protocol.

RELIABLE. Provides low experimental variability through an optimized formulation and rigorous quality controls.

HIGH THROUGHPUT. Generates organoids in 96- and 384-well formats.

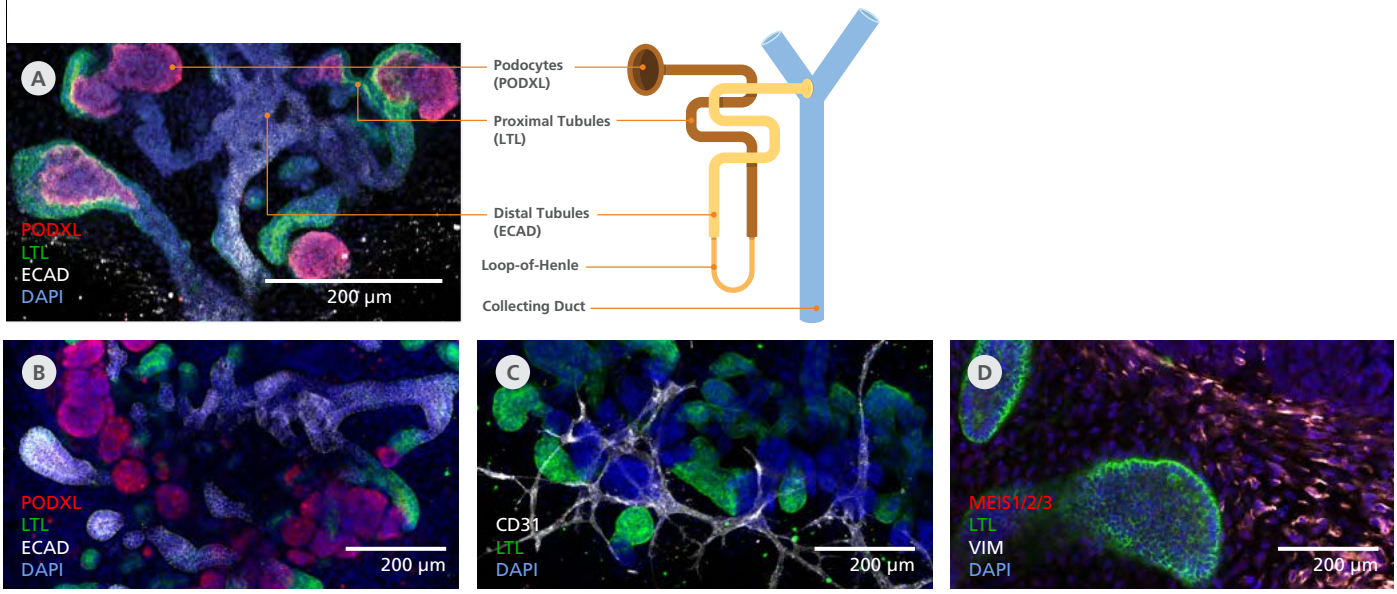

Figure 28. Kidney Organoids Form Convoluted Tubular Structures with Typical Nephron-Like Segmentation

(A) During differentiation, kidney organoids form convoluted tubular structures that resemble the structure and segmentation of the developing nephron. These organoids express markers of the (B) renal epithelium, including podocalyxin (PODXL), lotus tetragonolobus lectin (LTL), and E-cadherin (ECAD), as well as markers of the (C) endothelium (platelet endothelial cell adhesion molecule, CD31), and (D) mesenchyme (vimentin, VIM; Meis homeobox family, MEIS1/2/3).

PRODUCT
Learn More About STEMdiff™ Kidney Organoid Kit
www.stemcell.com/STEMdiff-Kidney

Lung Organoids

Fully differentiated human lung organoids represent versatile and physiologically relevant 3D model systems for studying the in vitro cell biology of the respiratory epithelium and understanding the underlying mechanisms of chronic respiratory diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis (IPF), lung cancer, and infectious diseases. These organoids can also be used for high-throughput screening of efficacy and toxicity of compounds.

PneumaCult™ Airway Organoid Kit

Cell Culture Medium Kit for Generation of Human Airway Organoids

PneumaCult™ Airway Organoid Kit is a serum-free medium kit that supports the efficient generation of fully differentiated and functional airway organoids from both healthy and disease samples. Airway organoid cultures provide an alternative method to ALI-based cultures for in vitro human airway modeling. Since this culture system does not require the use of cell culture inserts, it is amenable to high-throughput drug screening and can be used in large-scale screening for CF transmembrane conductance regulator (CFTR) modulators.

PneumaCult™ Airway Organoid Kit provides the necessary components to prepare PneumaCult™ Airway Organoid Seeding Medium, which allows for initiation of 3D organoid culture, and PneumaCult™ Airway Organoid Differentiation Medium, to further obtain morphologically representative and fully differentiated human airway organoids.

Why Use PneumaCult™ Airway Organoid Kit?

PHYSIOLOGICAL. Model the in vivo human airway with the three-dimensional in vitro system.

OPTIMIZED. Expand and differentiate human airway epithelial cells with this complete media formulation compatible with PneumaCult™-Ex Plus Medium.

RELIABLE. Ensure reproducibility and reduce variability with this rigorously screened and quality control tested media kit.

USER-FRIENDLY. Generate organoids with a convenient format and easy-to-use protocol.

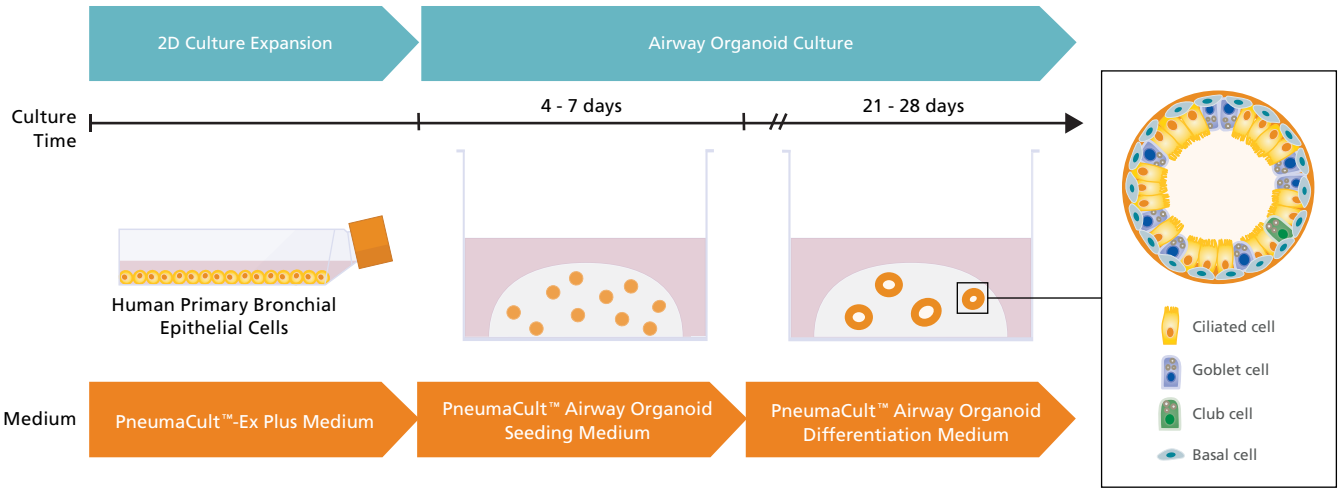

Figure 29. Schematic of Human Airway Organoid Culture Workflow

In the early two-dimensional expansion phase of the human airway organoid culture procedure, human bronchial epithelial cells (HBECs) are expanded using PneumaCult™-Ex Plus Medium. The HBECs are then embedded into a Matrigel® dome and expanded for 4 - 7 days using PneumaCult™ Airway Organoid Seeding Medium. Following the expansion, the HBECs are differentiated using PneumaCult™ Airway Organoid Differentiation Medium for an additional 21+ days.

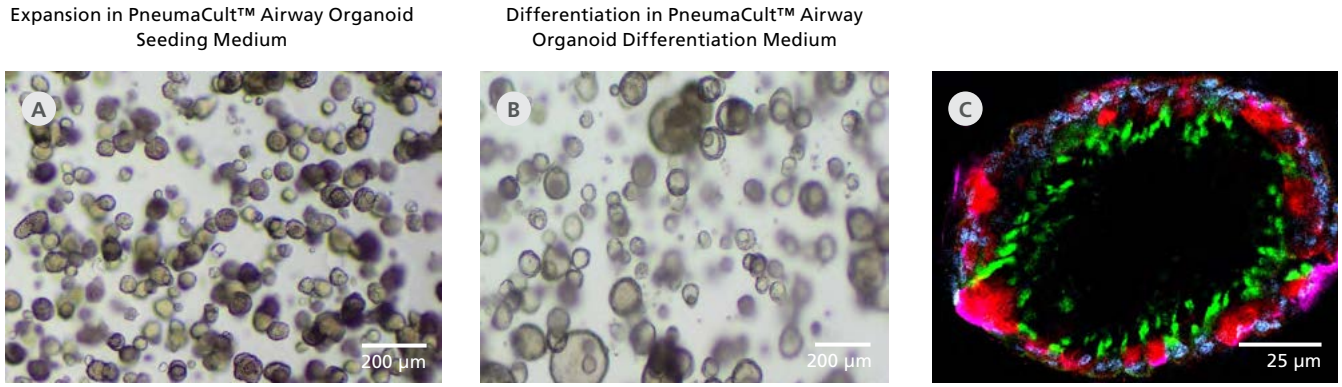

Figure 30. Fully Differentiated Human Airway Organoids Generated Using PneumaCult™ Airway Organoid Kit

(A) Bright-field image of airway organoids growing in PneumaCult™ Airway Organoid Seeding Medium at Day 7 exhibit basal cell spheroid morphology. (B) Bright-field image of airway organoids differentiated in PneumaCult™ Airway Organoid Differentiation Medium at Day 21 exhibit hollow lumens. (C) Airway organoid stained for ZO-1 (junction protein marker, red), MUC5AC (goblet cell marker, purple), AC-Tubulin (ciliated cell marker, green), and DAPI (nuclei, blue).

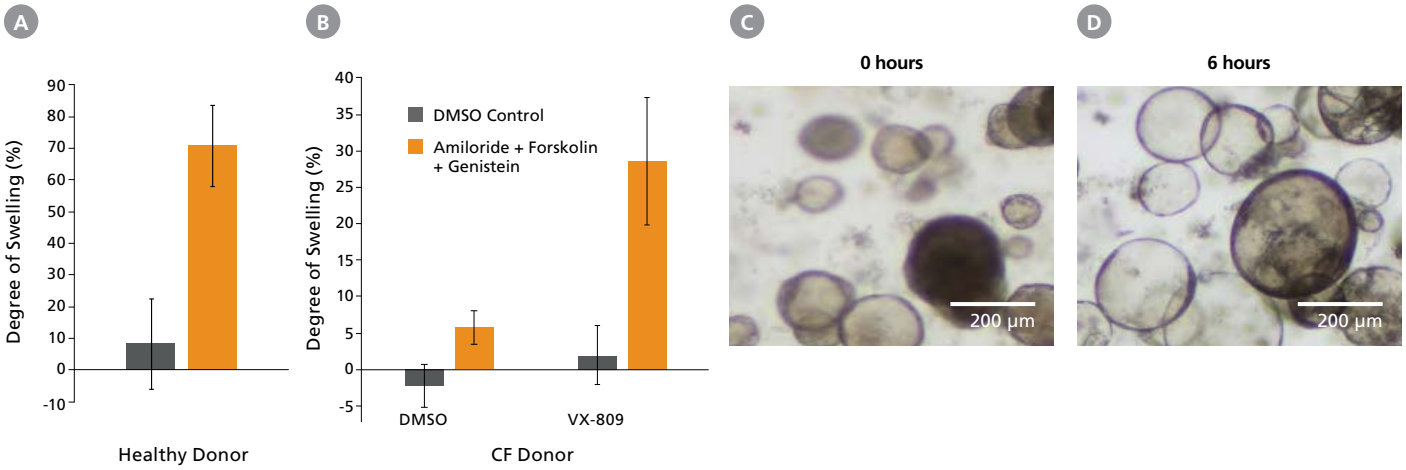

Figure 31. Airway Organoids Are Suitable for Assessing CFTR Protein Expression Using Forskolin-Induced Swelling Assay

(A) Forskolin-treated organoids derived from healthy donors increased in size compared to the DMSO control, indicating functional CFTR protein expression. (B) Forskolin-induced swelling is lost in organoids derived from CF donors but re-established in VX-809-treated airway organoids. Error bars represent ± 95% confidence interval for the mean (n = 3). Bright-field images of airway organoids taken during the Forskolin swelling assay at (C) 0 hours and (D) 6 hours show organoid swelling after treatment.

PRODUCT

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PneumaCult™ Apical-Out Airway Organoid Medium

Cell Culture Medium for Generation and Maturation of Apical-Out Airway Organoids

PneumaCult™ Apical-Out Airway Organoid Medium is a serum- and BPE-free cell culture medium that supports the highly reproducible generation of apical-out airway organoids in 15 days from human bronchial epithelial cells (HBECs) or human airway epithelial cells (HAECs). These polarized airway organoids, with outward-facing, differentiated ciliated cells, provide access to the apical side of the airway epithelium and can be used to perform your infectious disease modeling or high-throughput drug screening. For a complete apical-out airway organoid culture workflow, HBECs or HAECs can be first expanded in PneumaCult™-Ex Plus Medium (Catalog #05040) prior to initiating organoid culture.

Why Use PneumaCult™ Airway Apical-Out Airway Organoid Medium?

CONVENIENT. Access the apical side of the airway epithelium.

MATRIX-FREE. Process organoids for downstream applications seamlessly with a Matrigel®-free protocol.

CONSISTENT. Generate homogeneous organoids across donors.

USER-FRIENDLY. Generate organoids with a convenient, cell culture insert-free format and easy-to-use protocol.

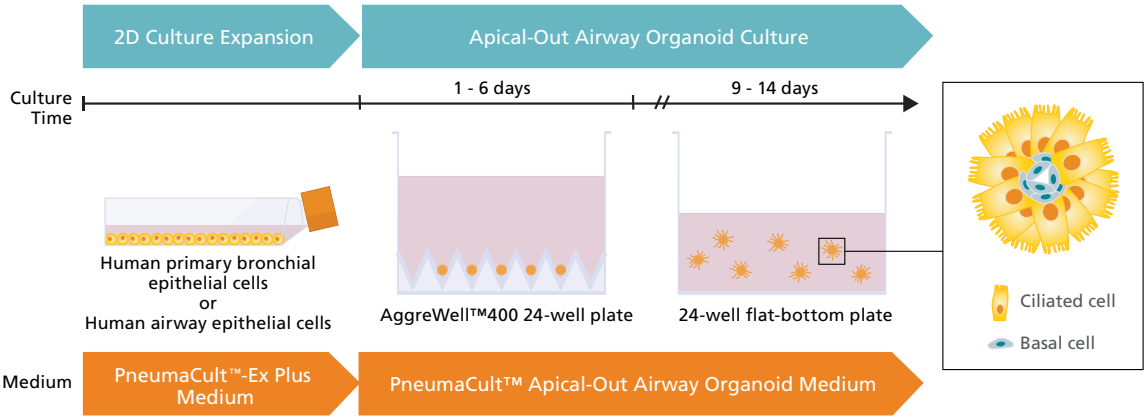


Figure 32. Generation of Apical-Out Airway Organoids Using the PneumaCult™ Apical-Out Airway Organoid Medium

In the two-dimensional expansion phase of the human apical-out airway organoid culture protocol, HBECs or HAECs are expanded using PneumaCult™-Ex Plus Medium. The HBECs or HAECs are then plated into an AggreWell™400 24-well plate and allowed to aggregate for 1 - 6 days using PneumaCult™ Apical-Out Airway Organoid Medium. Following the aggregation, the cells are dislodged from the microwells and the aggregate suspension is transferred to a 24-well flat-bottom plate and differentiated for 9 - 14 days using PneumaCult™ Apical-Out Airway Organoid Medium to generate apical-out airway organoids that display beating cilia.

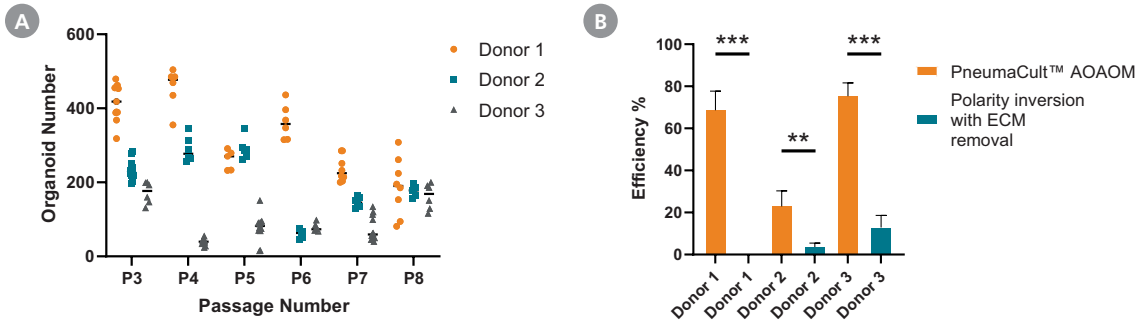


Figure 33. PneumaCult™ Apical-Out Airway Organoid Medium Supports Efficient Generation of Organoids

Apical-out airway organoids were generated by seeding 100 2D-expanded cells derived from 3 donors from passages 3 to 8. (A) Number of generated organoids per well of a 24-well plate at Day 15. Data points represent measurements taken from independent wells of a 24-well plate. (B) The efficiency of two different approaches (ECM-free PneumaCult™ Apical-Out Airway Organoid medium workflow or polarity inversion following ECM removal) is expressed as the percentage of apical-out airway organoids at the end of culture relative to the total number of organoids used to seed the cultures.

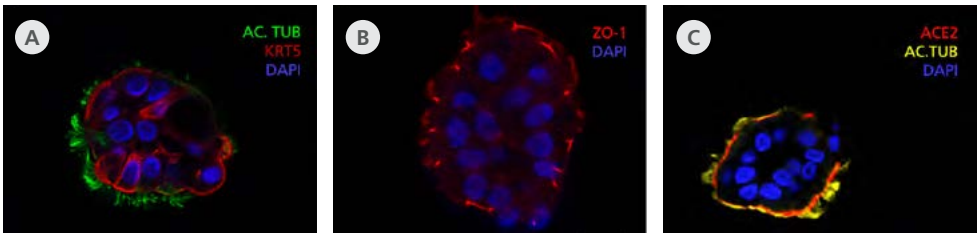


Figure 34. Terminally Differentiated Organoids Exhibit Mature Polarized Airway Epithelium

(A) Day 15 apical-out airway organoids cultured in PneumaCult™ Apical-Out Airway Organoid Medium contain ciliated cells, as confirmed by the presence of acetylated tubulin (AC. TUB; green) on the outward-facing apical cell surface, while keratin 5 (KRT5; red)-expressing basal cells were present alongside ciliated cells. (B) Cell-cell tight junction protein ZO-1 (red) can be readily visualized on the apical side of the organoid. These results indicate efficient generation of organoids across multiple passages with successful apical-out orientation. (C) Presence of ciliated cell marker acetylated tubulin (AC.TUB; yellow) and SARS-CoV-2 key entry marker ACE2 (red) is also shown, suggesting their usefulness for modeling respiratory infection from SARS-CoV-2.

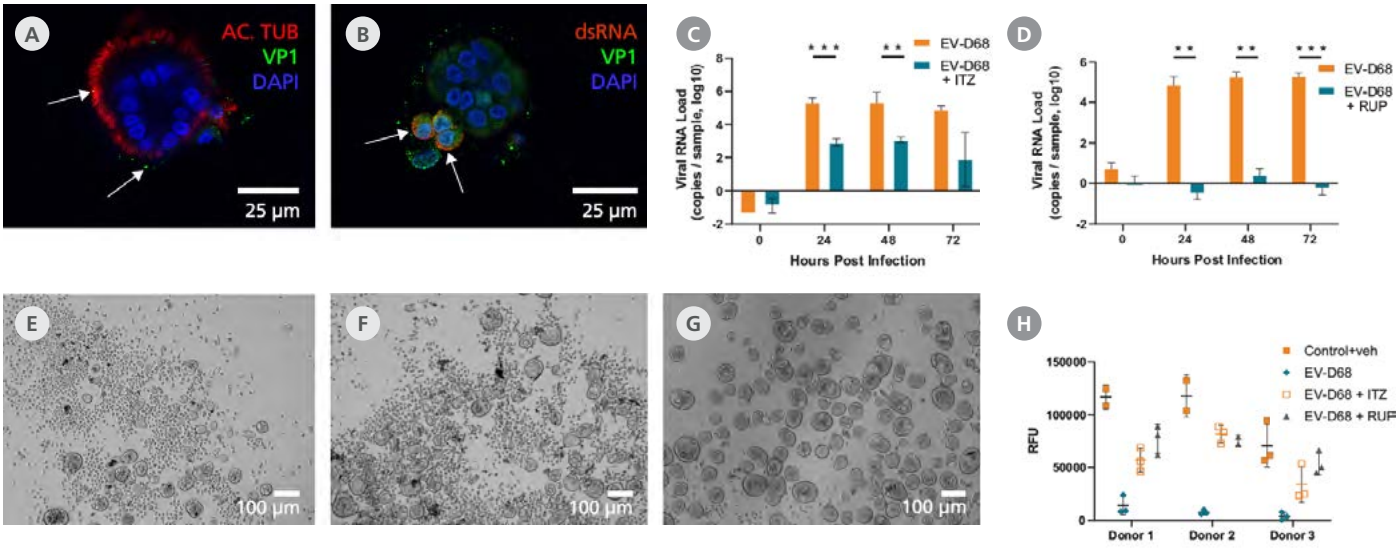


Figure 35. Mature Organoids Were Incubated with Enterovirus-D68 in the Presence or Absence of Itraconazole (ITZ) or Rupintrivir (RUP) to Study Antiviral Effects

To assess whether the PneumaCult™ Apical-Out Airway Organoid system was susceptible with infection to common respiratory viruses, Day 15 differentiated organoids were infected with enterovirus-D68 (EV-D68). (A) At 0 hours post infection, the EV-D68 (VP1, green) could be seen binding to the apical surface (ciliated cells; acetylated tubulin; red). (B) After 6 hours, cells containing double-strand RNA (dsRNA; red), an intermediate stage during the viral replication cycle, can be identified. These cells are also positive for viral protein (VP1, green) and (C and D, orange bars) generate high viral RNA titers, (E) while showing evidence of cytopathogenic effect (CPE). (C, teal bars) Treatment with Itraconazole (ITZ) reduced the viral RNA levels by approximately 2 orders of magnitude and (F) slightly ameliorated the CPE levels. (D, teal bars) Treatment with Rupintrivir (RUP) completely inhibited viral replication, (G) resulting in the absence of any CPE. (H) Measuring the relative fluorescent units (RFU) 72 hours post infection indicated changes in the levels of ATP and viability of the organoids, and revealed a sharp decline in viability following infection with EV-D68. A partial rescue was detected in infected apical-out airway organoids treated with ITZ, whereas those treated with RUP were almost completely rescued.

PRODUCT
Learn More About PneumaCult™ Apical Out Airway
www.stemcell.com/Pneumacult-Apical-Out-Airway

PneumaCult™ Alveolar Organoid Media

Cell Culture Media for Expansion and Differentiation of Human Alveolar Organoids

PneumaCult™ Alveolar Organoid Expansion (AvOE) Medium enables the passage and expansion of human alveolar epithelial type II (ATII) cells long-term as organoids. These alveolar organoids maintain properties indicative of the ATII cell phenotype, including the ability for self-renewal, expected marker expression, and lineage potential for differentiation to alveolar epithelial type I (ATI) cells. PneumaCult™ Alveolar Organoid Differentiation (AvOD) Medium can be used to differentiate the expanded ATII organoids to ATI organoid cultures in as few as 10 days. Differentiated cells show decreased ATII marker expression and strong up-regulation of ATI cell markers. These alveolar organoids are ideally suited for alveolar biology research, infectious disease studies, and drug screening.

PneumaCult™ AvOE and AvOD Media are compatible with primary isolated fresh or cryopreserved ATII cells, as well as high-quality commercially available alveolar epithelial cell sources.

Why Use PneumaCult™ Alveolar Organoid Media?

RELEVANT. Model the human alveolar physiology with an in vitro culture system that recapitulates key features of ATII and ATI cells in vivo.

BIOBANK. Cryopreserve and re-initiate organoid cultures with the biobanking capabilities of the media.

HIGH-YIELD. Maximize yield from the initial sample with a medium that supports passaging and long-term expansion of ATII organoids.

SIMPLE. Generate mature ATII and fully differentiated ATI organoids with a convenient format and easy-to-use protocol.

RELIABLE. Ensure reproducibility with standardized, quality-control tested media.

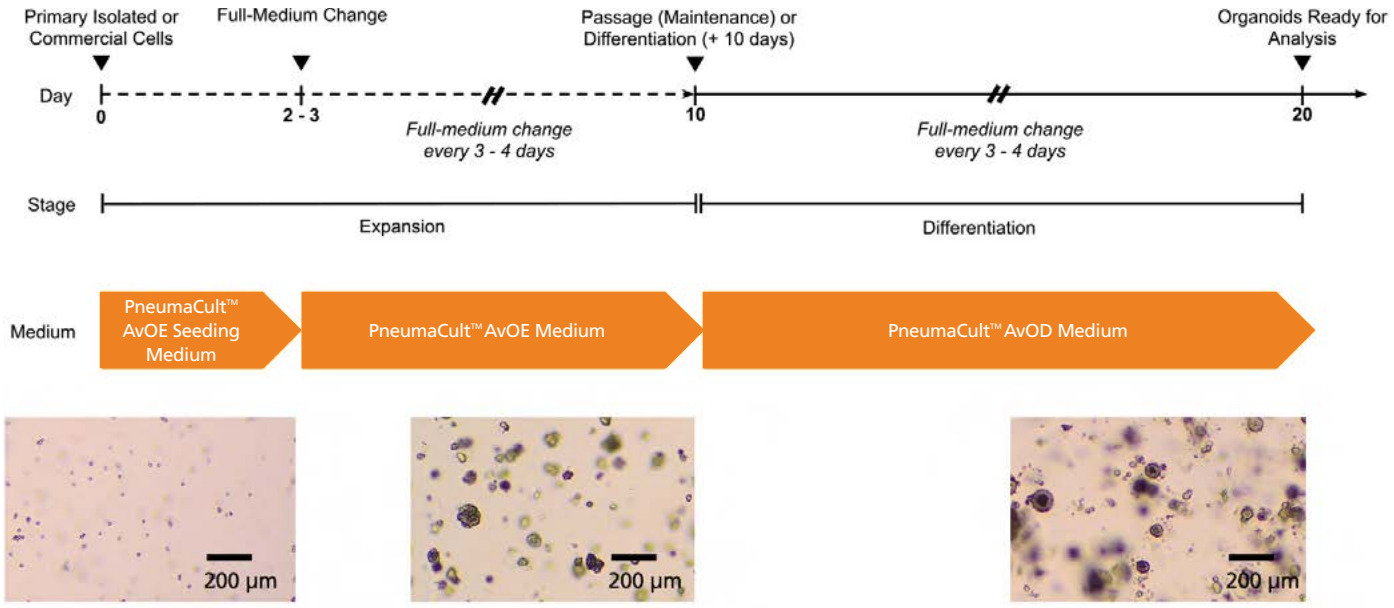


Figure 36. Generation of Alveolar Organoids Using PneumaCult™ Alveolar Organoid Media

The PneumaCult™ Alveolar Organoid Media workflow is a two-stage protocol. During the expansion stage, primary isolated or cryopreserved human ATII single cells are seeded in PneumaCult™ Alveolar Organoid Expansion (AvOE) Seeding Medium. On Day 2 - 3, after a full-media change, cultures are expanded using PneumaCult™ AvOE Medium to obtain mature ATII organoids. In the differentiation stage, ATII organoids are cultured for 10 additional days using PneumaCult™ Alveolar Organoid Differentiation (AvOD) Medium to generate ATI organoids.

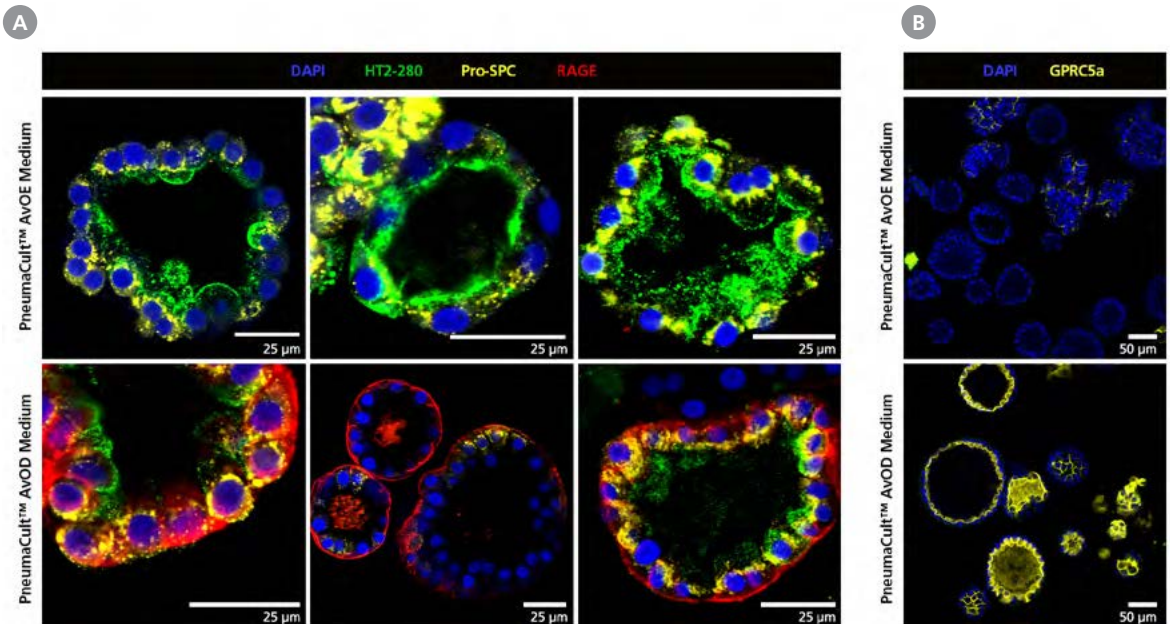


Figure 37. Immunohistochemistry Confirms Expression of ATII and ATI Cell Markers in Alveolar Organoids

(A) Organoids from three donors expanded in PneumaCult™ AvOE Medium (top) express the ATII markers, HT2-280 (green) and pro-surfactant protein C (pro-SPC, yellow). When further differentiated in PneumaCult™ AvOD Medium (bottom), the levels of these ATII markers are down-regulated, while the ATI marker RAGE (red) is upregulated. (B) Differentiated organoids also express high levels of ATI marker GPRC5a (yellow).

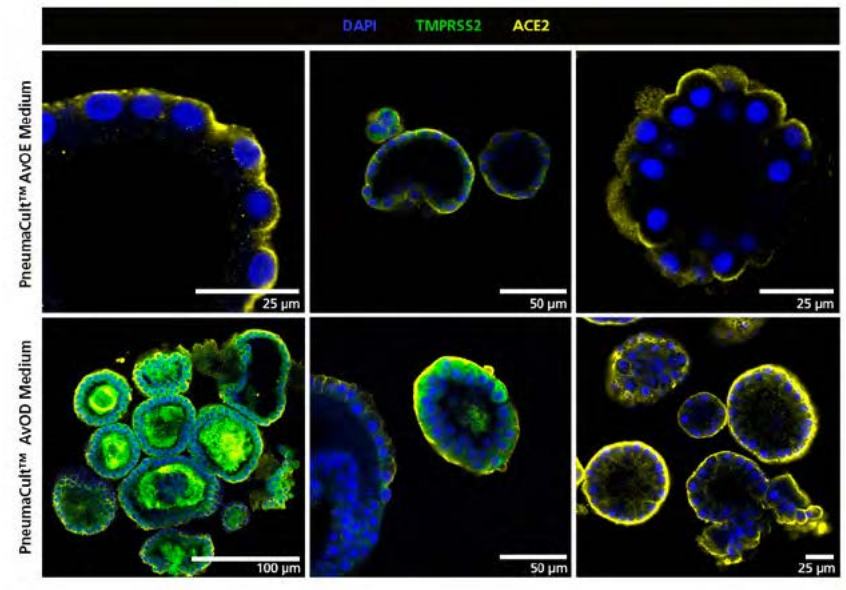


Figure 38. Organoids Cultured in PneumaCult™ Alveolar Organoid Media Express TMPRSS2 and ACE2, Key Markers for SARS-CoV-2 Entry

Organoids from three donors expanded in PneumaCult™ AvOE Medium (top) and differentiated in PneumaCult™ AvOD Medium (bottom) express proteins associated with SARS-CoV-2 entry, TMPRSS2 and ACE2. While ACE2 was expressed in all donors and conditions, TMRPSS2 expression was donor-dependent.

PRODUCT
Learn More About PneumaCult™ Alveolar
www.stemcell.com/Pneumacult-Alveolar

STEMdiff™ Branching Lung Organoid Kit

Cell Culture Medium for Generation and Maturation of Branching Lung Organoids

The STEMdiff™ Branching Lung Organoid Kit (Catalog # 100-0195) supports the efficient and reproducible generation of branching lung organoids from human ES and iPS cells through four stages of differentiation: 1) definitive endoderm, 2) anterior foregut endoderm, 3) lung bud organoid, and 4) branching lung organoids. This serum-free medium system generates organoids that develop proximal and distal-like branching airway epithelial structures, and can be matured for extended periods of organoid culture (> 28 days) using STEMdiff™ Branching Lung Organoid Maturation Kit (Catalog #100-0528).

Why Use STEMdiff™ Branching Lung Organoid Kit?

PHYSIOLOGICALLY RELEVANT. Generate organoids that recapitulate in vivo airway branching morphogenesis and proximo-distal specification.

ROBUST. Efficiently differentiate multiple human ES and iPS cell lines to branching lung organoids.

CONVENIENT. Get experimental flexibility with cryopreservable intermediate stage.

REPRODUCIBLE. Maximize experimental reproducibility with a serum-free, defined formulation.

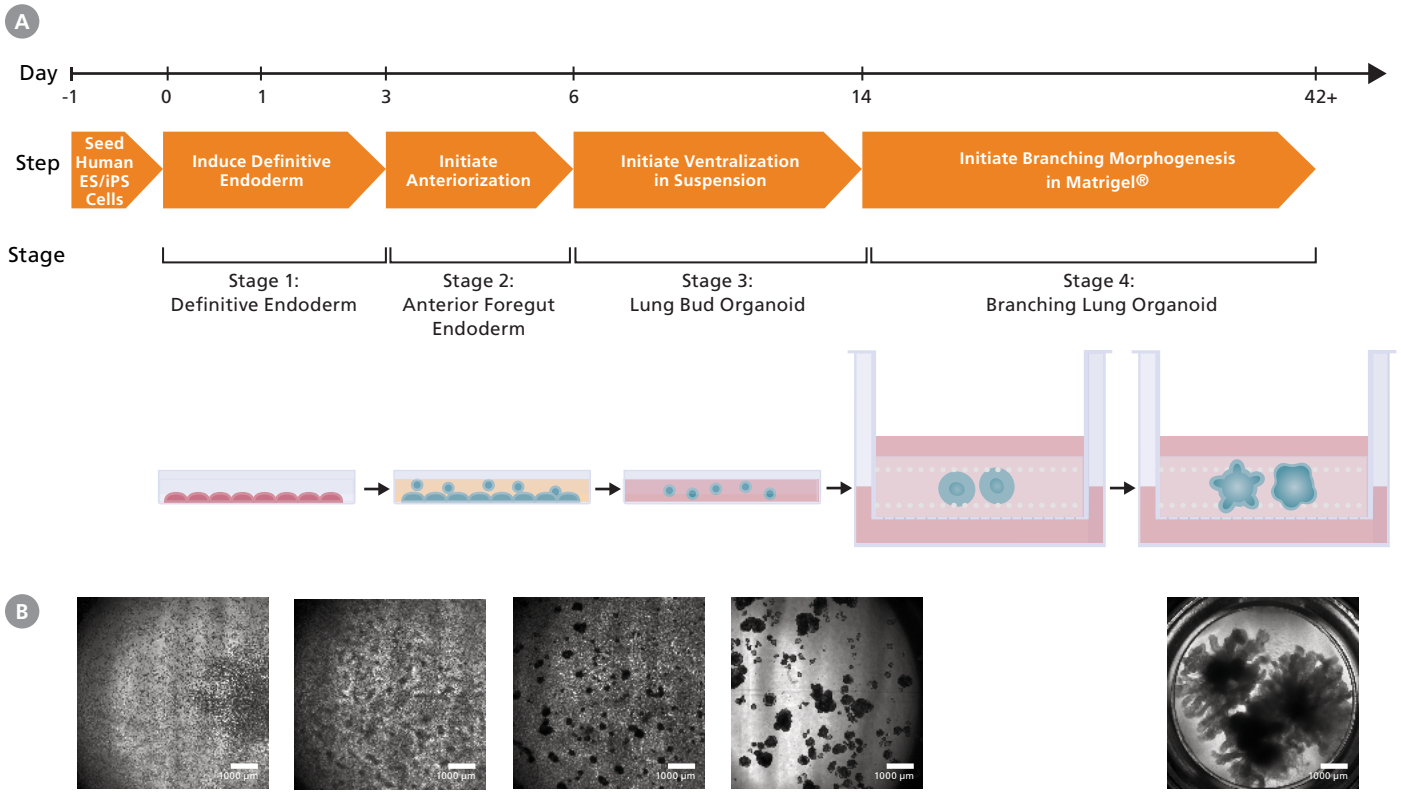


Figure 39. STEMdiff™ Branching Lung Organoid Kit Supports Generation of Branching Lung Organoids

(A) Human PSC cultures progress through a four-stage differentiation process to generate human branching lung organoids. By the end of stage 1 (Day 3), cultures exhibit characteristics typical of definitive endoderm and anterior foregut differentiation is initiated. During stage 2 (Days 3 - 6) anterior foregut endoderm buds are released from the monolayer, and are then suspended to form ventralized lung bud organoids in stage 3 (Days 6 - 14). In stage 4, the lung bud organoids are embedded into Matrigel® sandwich cultures to mature into branching lung organoids. (B) Morphological representation of the culture at different stages.

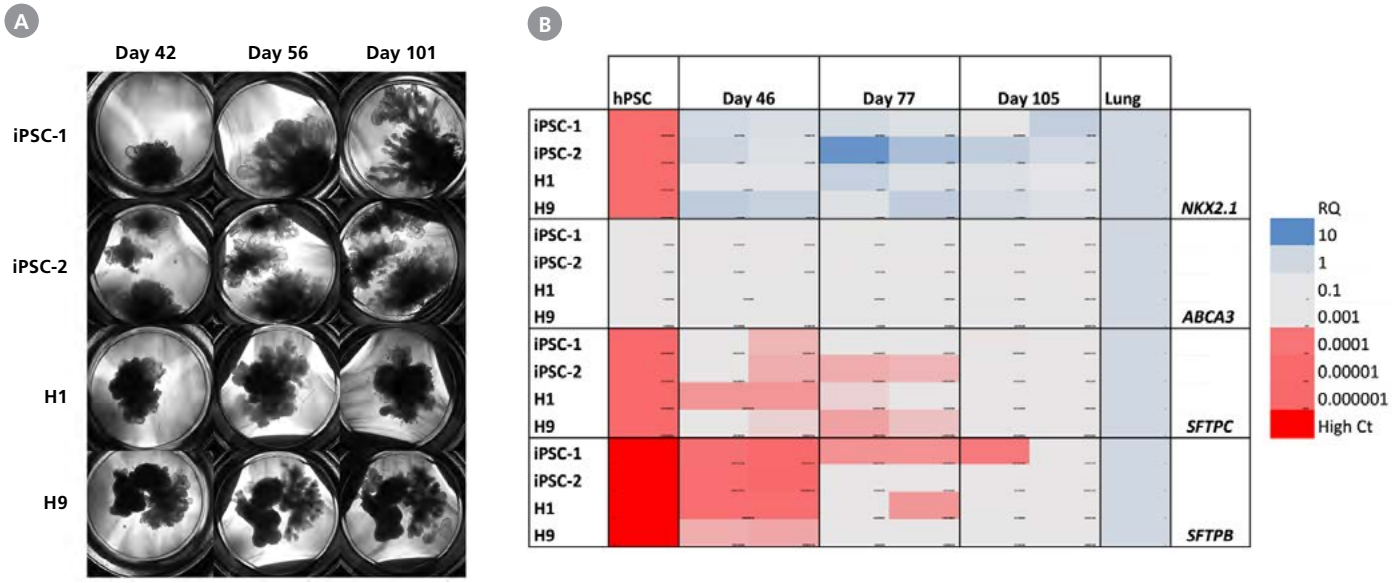


Figure 40. Branching Lung Organoids Cultured in STEMdiff™ Branching Lung Organoid Maturation Kit for Extended Periods Express More Mature Lung Markers

(A) The branching tips of branching lung organoids derived from peripheral blood endothelial progenitor cell-derived iPS cells (iPSC-1), peripheral blood mononuclear cell-derived iPS cells (iPSC-2), or embryonic stem cells (H1 and H9) continue to grow and branch up to Day 101. (B) The expression levels of more mature distal lung markers ABCA3, SFTPC, and SFTPB increase over time. Morphology and gene expression of branching lung organoids cultured up to Day 105 were assessed by RT-qPCR. RQ-values were normalized to TBP and compared to commercially available lung RNA.

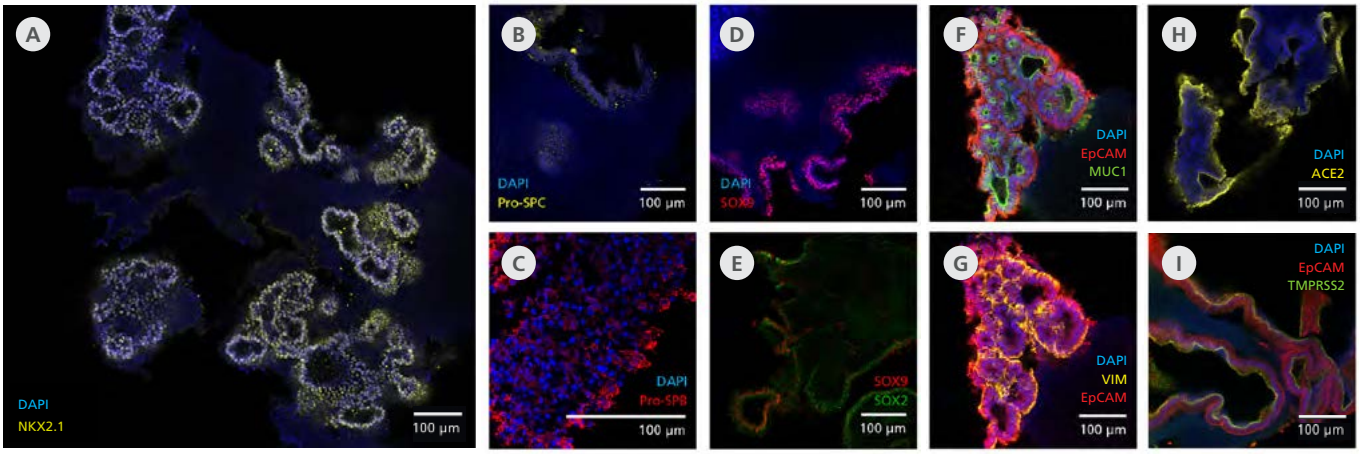


Figure 41. Branching Lung Organoids Cultured in STEMdiff™ Branching Lung Organoid Kit Feature Key Protein Markers and Exhibit Branching Morphogenesis

(A) Branching lung organoids express lung progenitor marker NKX2.1 throughout their branching structures and (B, C) demonstrate the presence of alveolar type II-like cells with pro-surfactant protein B and C expressions. (D, E) These organoids undergo proximodistal differentiation demonstrated by the differential expression of SOX2 and SOX9. (F) MUC1 can be found luminally expressed while the (G) organoids are surrounded by VIM-expressing mesenchyme. (H, I) Branching lung organoids generated with the STEMdiff™ Branching Lung Organoid Kit also express proteins associated with SARS-CoV-2 entry, ACE2 and TMPRSS2. Protein expression was visualized by immunohistochemistry and confocal microscopy of branching lung organoids on Day 63.

PRODUCT
Learn More About STEMdiff™ Branching Lung
www.stemcell.com/STEMdiff-Branching-Lung

Neural Organoids

Differentiation of neural organoids from PSCs generates three-dimensional in vitro cultures that recapitulate the developmental processes and organization of the developing human brain. These organoids provide unique, physiologically relevant in vitro model systems for the study of human neurological development and disease. Neural organoids have important applications in studying human brain development and neurological disorders such as autism and schizophrenia, or brain defects caused by viral infection.

STEMdiff™ Cerebral Organoid Kit

Cell Culture Medium Kit for Establishment and Maturation of Unpatterned Human Cerebral Organoids

Based on the formulation published by Lancaster and Knoblich[11], the STEMdiff™ Cerebral Organoid Kit is a serum-free culture system that is designed to generate cerebral organoids from human ES or iPS cells. Large, optically dense organoids that display multiple cortical-like regions when cryosectioned and immunostained are observed in 40 days, providing relevant models for the early developing human cortex.

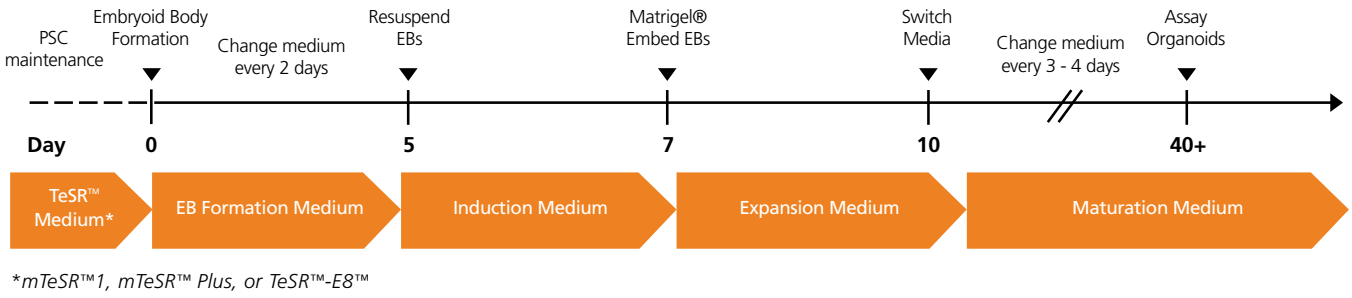
Why Use STEMdiff™ Cerebral Organoid Kit?

UNPATTERNED. Allows differentiation to occur spontaneously to generate multiple brain regions within the same organoid.

FLEXIBLE. Enables culture under matrix droplet embedding or liquid matrix conditions.

OPTIMIZED. Demonstrates increased efficiency of organoid formation with a formulation based on a popular published protocol[11].

COMPATIBLE. Provides a platform for generating new or modified organoid models.



**mTeSR™1, mTeSR™ Plus, or TeSR™-E8™*

Figure 42. Schematic for the STEMdiff™ Cerebral Organoid Kit

Human pluripotent stem cells maintained in mTeSR1™ are dissociated into single-cell suspensions using Gentle Cell Dissociation Reagent (GCDR) and seeded at a density of 9,000 cells/well in a U-Bottom 96-well Ultra-Low Attachment Plate (Corning®) in embryoid body (EB) Formation Medium + 10 µM Rho-Kinase Inhibitor (ROCKi). EBs are fed every 2 days with EB Formation Medium without ROCKi. After 5 days, EBs are transferred to Induction Medium in a 24-well Ultra-Low Attachment Plate (Corning®). EBs are cultured for an additional 2 days and are then embedded in liquid Matrigel® (Growth Factor Reduced, Corning®). They are then transferred to a non-tissue culture treated 6-well plate (12 -16 organoids/well). Embedded organoids are maintained in Expansion Medium for 3 days. On Day 10, organoids are switched to Maturation Medium and cultured on an orbital shaker set at 57 - 95 RPM (Infors HT). Organoids are fed every 3 - 4 days with Maturation Medium. On Day 40, organoids were processed for analysis by RT-qPCR or immunostaining followed by cryosectioning.

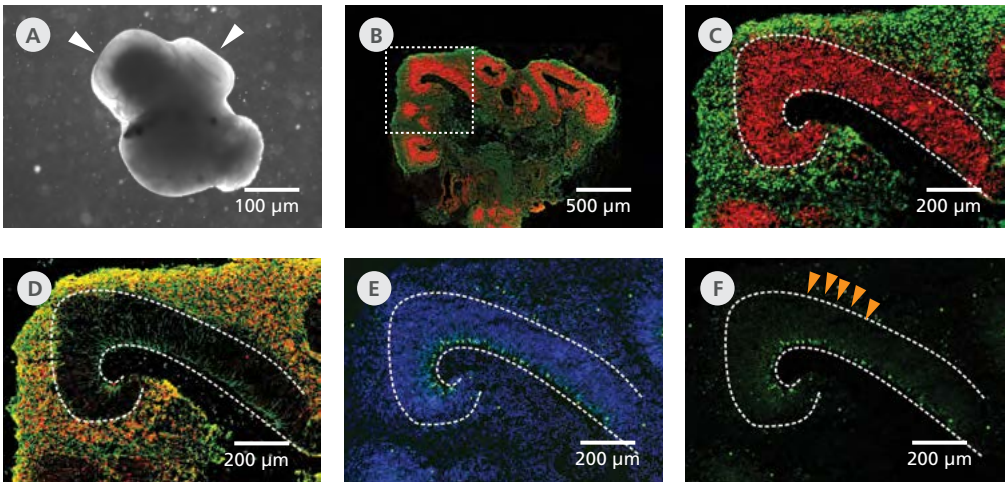


Figure 43. Characterization of Cerebral Organoids Generated Using the STEMdiff™ Cerebral Organoid Kit

(A) A representative phase-contrast image of a whole cerebral organoid at Day 40 generated using the STEMdiff™ Cerebral Organoid Kit. Cerebral organoids at this stage are made up of phase-dark structures that may be surrounded by regions of thinner, more translucent structures that display layering (arrowheads). (B) Immunohistological analysis on cryosections of cerebral organoids reveals cortical regions within the organoid labeled by the apical progenitor marker PAX6 (red) and neuronal marker class III β-tubulin (TUJ-1) (green). (C-F) Inset of boxed region from (B). (C) PAX6$^+$ apical progenitors (red, enclosed by dotted line) are localized to a ventricular zone-like region. Class III β-tubulin$^+$ neurons (green) are adjacent to the ventricular zone. (D) CTIP2, a marker of the developing cortical plate, co-localizes with class III β-tubulin$^+$ neurons in a cortical plate-like region. Organization of the layers recapitulates early corticogenesis observed during human brain development. (E) Proliferating progenitor cells labeled by Ki-67 (green) localize along the ventricle, nuclei are counterstained with DAPI (blue). (F) An additional population of Ki-67$^+$ cells is found in an outer subventricular zone-like region (arrowheads).

PRODUCT
Learn More About STEMdiff™ Cerebral Organoid Kit
www.stemcell.com/COKit

STEMdiff™ Dorsal and Ventral Forebrain Organoid Kits

Cell Culture Medium Kits for Establishment and Maturation of Brain-Region-Specific Organoids

The STEMdiff™ Dorsal and Ventral Forebrain Organoid Differentiation Kits are serum-free cell culture media that work with AggreWell™-generated embryoid bodies to robustly differentiate brain-region-specific organoids that are representative of the developing human forebrain. Using small molecule patterning factors, STEMdiff™ Dorsal Forebrain Organoid Differentiation Kit generates tissue of the early developing dorsal pallium, while STEMdiff™ Ventral Forebrain Organoid Differentiation Kit generates tissue of the early developing ventral subpallium.

For extended periods of organoid culture (> 50 days), the components required for organoid maintenance are available as STEMdiff™ Neural Organoid Maintenance Kit.

Why Use STEMdiff™ Dorsal and Ventral Forebrain Organoid Kits?

PATTERNED. Direct differentiation to brain regions of interest with small molecule patterning factors, based on a popular published protocol[13].

REPRODUCIBLE. Take advantage of reproducible structural morphology between lines and individual organoids to detect subtle disease phenotypes.

SCALABLE. Use with Aggrewell™800 to generate over 500 organoids per kit for screening or more detailed longitudinal study.

MATRIX-FREE. Eliminate embedding steps and reduce handling while preventing organoid fusion.

MODULAR. Combine region-patterned organoid types in culture to generate AssemBloids™ for disease modeling and regenerative applications.

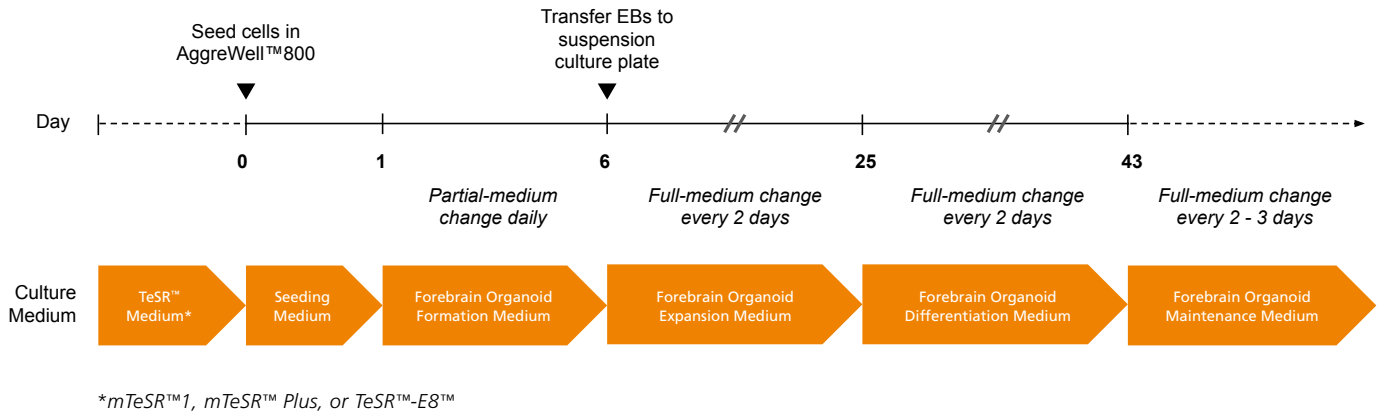


Figure 44. Schematic for the STEMdiff™ Dorsal and Ventral Forebrain Organoid Differentiation Kits

Human ES or iPS cell-derived dorsal or ventral forebrain organoids can be generated in 43 days. Embryoid bodies (EBs) can be created in 6 days with AggreWell™800 plates. The EBs are then cultured in suspension, allowing growth and subsequent patterning to the dorsal forebrain. For patterning to ventral forebrain, the protocol differs only by a supplement added to Forebrain Organoid Expansion Medium. For the long-term maintenance and further maturation of dorsal and forebrain organoids, see the Product Information Sheet. Adapted from protocols by the laboratory of Sergiu Paşca[13].

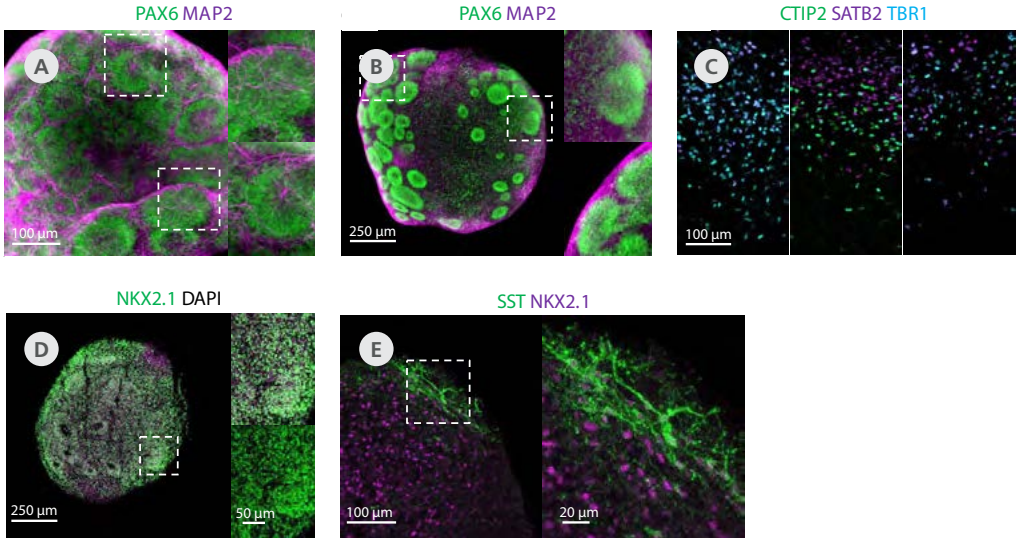


Figure 45. Dorsal Forebrain Organoids Exhibit Cortical Layering, and Both Dorsal and Ventral Organoids Express Markers Characteristic of Their Respective Brain Regions

(A) Day 25 dorsal forebrain organoids display multiple cortical-like regions marked by radialized PAX6$^+$ cells surrounded by MAP2$^+$ neurons. (B) Day 50 dorsal forebrain organoids continue to display multiple cortical-like regions marked by PAX6 and MAP2. (C) Dorsal forebrain organoids (DFO) cultured for 100 - 200 days show increasing separation of deep-layer neurons (CTIP2, TBR1) from upper-layer neurons (SATB2). (D) Ventral forebrain organoids (VFO) at Day 25 exhibit a high level of expression of NKX2.1. (E) Somatostatin (SST)-positive GABAergic interneurons can be seen by Day 75.

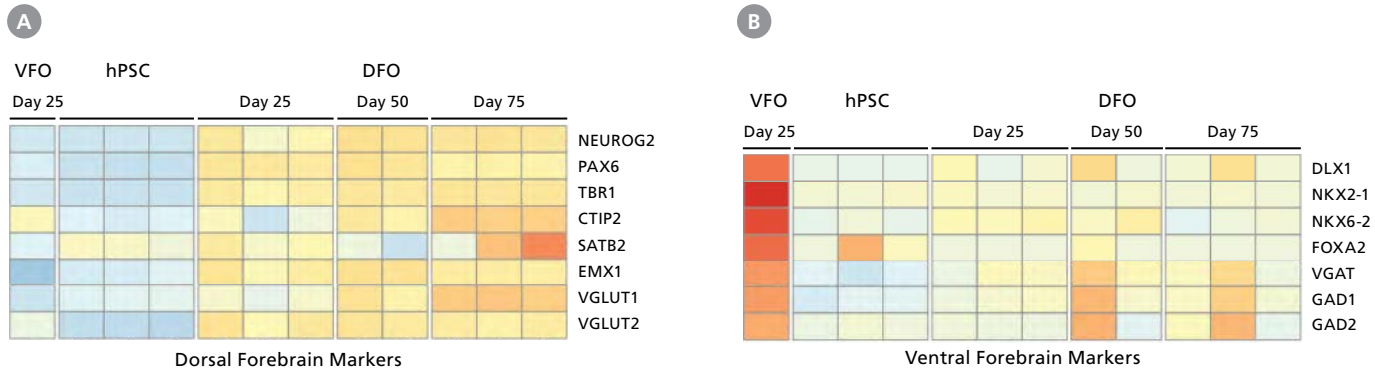


Figure 46. Neural Organoids Generated with STEMdiff™ Dorsal and Ventral Forebrain Organoid Kits Express Key Markers of Brain-Region-Specific Patterning

RNA from single organoids was harvested at each respective time point and subsequently assayed using bulk RNA-seq (1 data column = 1 organoid). (A) Heat map of select genes shows that dorsal forebrain organoids express increasing levels of cortex- and glutaminergic neuron-specific genes from Day 25 to 75. (B) Day 25 ventral forebrain organoids exhibit high expression of markers of the medial ganglionic eminence and of GABAergic neurons. DFO = Dorsal Forebrain Organoids, VFO = Ventral Forebrain Organoids.

STEMdiff™ Choroid Plexus Organoid Kits

Culture Medium Kits for Establishment of Organoids Containing PSC-Derived Choroid Plexus-Like Epithelium and CSF-Like Fluid

Take an in vitro approach to human neural biomarker discovery and CNS permeability with hPSC-derived organoids patterned to the choroid plexus. After a maturation period, organoids generated using STEMdiff™ Choroid Plexus Differentiation Kit feature cystic structures filled with a fluid resembling cerebrospinal fluid (CSF) and surrounded by an epithelial layer expressing ependymal markers (TTR, CLIC6, AQP1).

For extended periods of organoid culture (> 40 days), the components required for organoid maturation can be purchased as STEMdiff™ Choroid Plexus Organoid Maturation Kit.

Why Use STEMdiff™ Choroid Plexus Organoid Kits?

RELEVANT. Adopt a human CNS barrier model for screening and modeling applications with the precise control of an in vitro system.

SIMPLE. Eliminate the need for complex co-cultures or Transwell® systems in your screening pipeline.

PURE. Extract CSF-like fluid to identify human CNS-specific biomarkers in a 100% blood-free system, without requiring a lumbar puncture.

SCALABLE. Obtain 50X more CSF-like fluid from a single kit than obtained from a single mouse, and eliminate the donor-to-donor variability of pooled clinical samples.

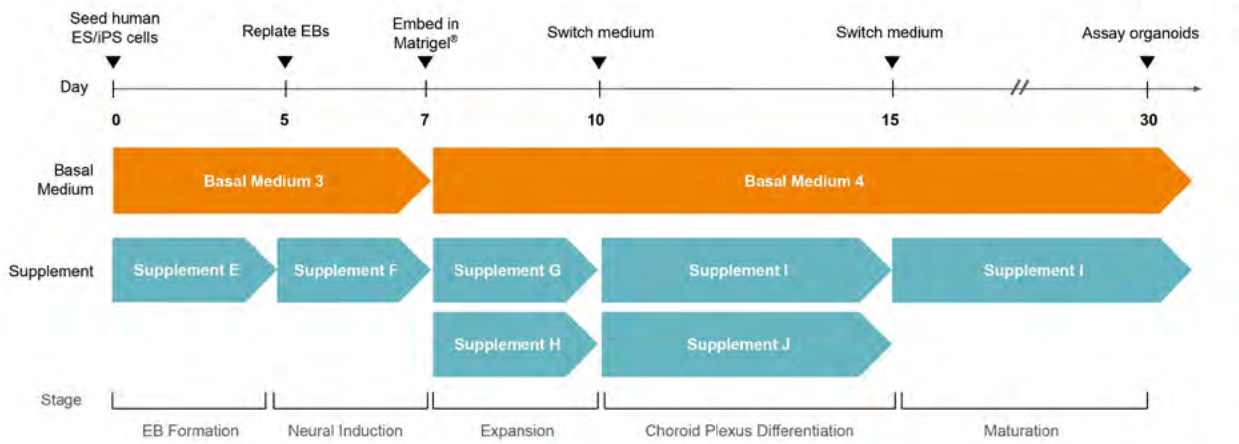


Figure 47. Schematic for the STEMdiff™ Choroid Plexus Organoid Differentiation and Maturation Kits

Choroid plexus organoids can be generated from human embryonic stem (ES) or induced pluripotent stem (iPS) cells in 30 days. The protocol begins with embryoid body (EB) formation, followed by expansion of neuroepithelia and patterning to choroid plexus-like epithelium. After a period of epithelial maturation including extensive bubbling, the organoids develop cystic structures surrounded by an ependymal epithelial layer and filled with a fluid resembling cerebrospinal fluid (CSF). Adapted from protocols published by Pellegrini et al.[14]

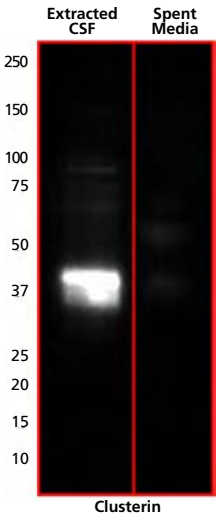


Figure 48. Fluid Extracted from Cysts in Choroid Plexus Organoids Is Enriched with Clusterin Protein, a Marker of CSF

Day 40 choroid plexus organoids were generated from hPSCs using STEMdiff™ Choroid Plexus Organoid Differentiation and Maturation Kits. Cerebrospinal fluid (CSF)-like fluid was extracted from cysts contained in choroid plexus organoids using a 28G syringe. A western blot was performed on the extracted fluid to detect Clusterin and shows a band between the 37 and 50 kDa molecular weight marker. Clusterin is a soluble secreted chaperone protein and biomarker relevant to Alzheimer's disease[15] found in high abundance in CSF.

PRODUCT

Learn More About STEMdiff™ Choroid Plexus Organoid Kits

www.stemcell.com/Choroid-Plexus-Organoid

STEMdiff™ Blood Vessel Organoid Kit

Blood vessels are a fundamental part of all organ systems and have critical roles in multiple diseases, including diabetes, Alzheimer's Disease, and cancer. The blood vasculature is composed of endothelial cells that form luminal tubes and pericytes covering the endothelial wall. In vitro models of vascular biology involve co-culturing endothelial cells with pericytes but do not fully recapitulate their three-dimensional (3D) organization and functionality.

STEMdiff™ Blood Vessel Organoid Kit is a serum-containing kit for differentiation of hPSC-derived blood vessel organoids (BVOs) in a five-stage protocol, with the option to scale up for high-throughput screening in a 96-well format. BVOs generated using this kit have CD31$^+$/CD34$^+$/CD144$^+$/KDR$^+$ endothelial cells and PDGFR-β$^+$/CD146$^+$/SMA$^+$/NG-2$^+$ pericytes. These self-organizing hPSC-derived BVOs are able to form functional, perfusable blood vessels in vivo and can be used to study vascular dysfunction associated with various pathologies. The organoids can also be maintained in STEMdiff™ BVO Maturation Medium for long-term assays*.

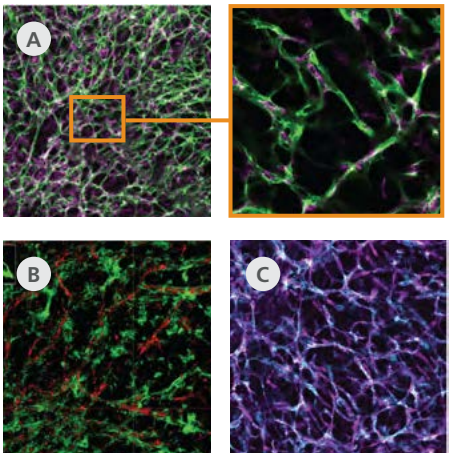


Figure 49. Vascular Networks Mature into Stable Blood Vessels When Cultured Within the Extracellular Matrix in STEMdiff™ Blood Vessel Maturation Medium

(A) hPSC-derived blood vessel organoids are composed of hCD31$^+$ cells (green) and hPDGFRβ$^+$ cells (magenta); small quadrant shows tight endothelial and pericyte interactions. (B) hPSC-derived blood vessel organoids are composed of hCD31$^+$ cells (red) and deposited collagen IV (green; 3D reconstruction of optical Z stacks); small quadrant shows blood vessel lumen. (C) hPSC-derived blood vessel organoids are composed of hCD31$^+$ cells (blue) and alpha-smooth muscle actin cells (magenta).

**STEMdiff™ Blood Vessel Organoid Maturation Medium is available for individual sale.*

WEBINAR

Modeling the Structural and Functional Features of Blood Vasculature with Blood Vessel Organoids

www.stemcell.com/BVO

Why Use STEMdiff™ Blood Vessel Organoid Kit?

PHYSIOLOGICALLY RELEVANT. Generate physiologically relevant 3D blood vessel organoids ideal for disease modeling and drug discovery.

ROBUST. Efficiently develop hPSC-derived organoids with a standardized protocol and optimized reagents.

SCALABLE. Easily scale up your drug discovery or drug testing by using STEMdiff™ Blood Vessel Organoid Kit with a 96-well format.

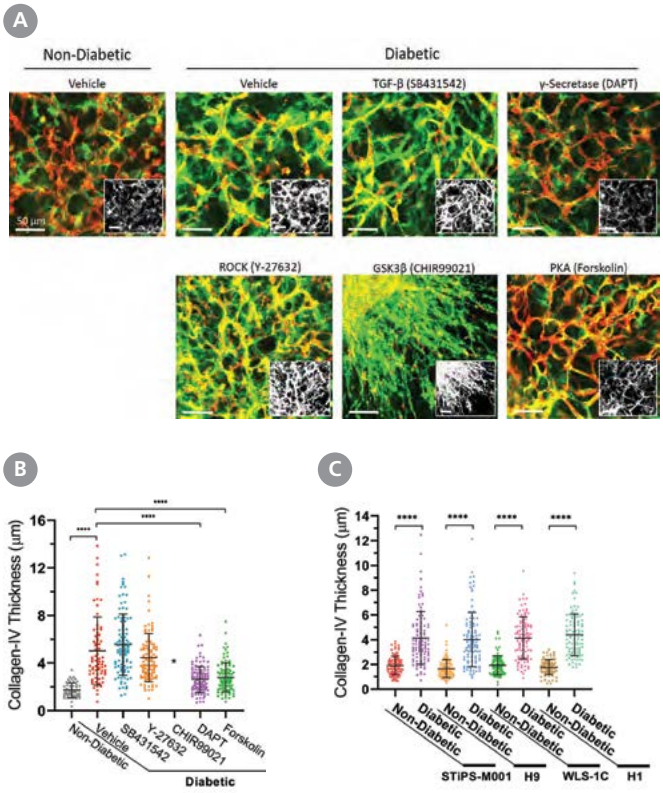


Figure 50. Deposition of Extracellular Matrix

(A) Diabetic conditions were applied to vascular networks, then collagen IV deposition was evaluated. Confocal microscopy revealed the formation of a complex network of tubes composed of CD31$^+$ cells (red). Increased expression of collagen IV (green) was found in diabetic vascular networks compared to non-diabetic. Multiple small molecules were used in diabetic organoids to block signaling pathways involved in diabetic vasculopathies. Only addition of γ-secretase inhibitor DAPT and protein kinase activator (PKA) forskolin significantly reduced expansion of the collagen IV basement membrane. (B) The thickness of the collagen IV coat of individual vessels was measured in optical cross-sections (n = 50 for non-diabetic, n = 73 for diabetic (vehicle) & n = 100 for diabetic (SB431542, Y-27632, CHIR99021, forskolin, and DAPT) blood vessel lumina from one independent experiment. Data expressed as mean ± SD *P indicates < 0.0001; two-tailed Student's t-test). (C) The thickness of the collagen IV coat of individual vessels was measured in optical cross-sections (n = 100 for non-diabetic & n = 100 for diabetic blood vessel lumina from one independent experiment in two iPS cell lines & two ES cell lines. Data are mean ± SD *P indicates < 0.0001; two-tailed Student's t-test).

Product Information

Product	Size	Catalog #
IntestiCult™ Organoid Growth Medium (Mouse)	100 mL	06005
Mouse Intestinal Organoids	200 Organoids	70931
IntestiCult™ Organoid Growth Medium (Human)	100 mL	06010
IntestiCult™ Organoid SF-Growth Medium Human	100 mL	100-0340
IntestiCult™ Organoid Differentiation Medium	100 mL	100-0214
STEMdiff™ Intestinal Organoid Kit	1 Kit	05140
STEMdiff™ Intestinal Organoid Growth Medium	1 Kit	05145
STEMdiff™ Gastric Organoid Differentiation Kit	1 Kit	100-0475
STEMdiff™ Gastric Organoid Expansion Medium	1 Kit	100-0490
HepatiCult™ Organoid Growth Medium (Mouse)	100 mL	06030
Mouse Hepatic Organoids	2 Culture Wells	70932
HepatiCult™ Organoid Kit (Human)	1 Kit	100-0386
PancreaCult™ Organoid Growth Medium (Mouse)	100 mL	06040
Mouse Pancreatic Organoids	200 Organoids	70933
PancreaCult™ Organoid Initiation Medium Human	1 Kit	100-0820
PancreaCult™ Organoid Growth Medium Human	1 Kit	100-0781
STEMdiff™ Kidney Organoid Kit	1 Kit	05160
PneumaCult™ Airway Organoid Kit	1 Kit	05060
PneumaCult™ Apical-Out Airway Organoid Medium	1 Kit	100-0620

Product	Size	Catalog #
PneumaCult™ Alveolar Organoid Expansion Medium	1 Kit	100-0847
PneumaCult™ Alveolar Organoid Differentiation Medium	1 Kit	100-0861
STEMdiff™ Blood Vessel Organoid Kit	1 Kit	100-0651
STEMdiff™ Branching Lung Organoid Kit	1 Kit	100-0195
STEMdiff™ Cerebral Organoid Kit	1 Kit	08570
STEMdiff™ Cerebral Organoid Maturation Kit	1 Kit	08571
STEMdiff™ Choroid Plexus Organoid Differentiation Kit	1 Kit	100-0824
STEMdiff™ Choroid Plexus Organoid Maturation Kit	1 Kit	100-0825
STEMdiff™ Dorsal Forebrain Organoid Kit	1 Kit	08620
STEMdiff™ Ventral Forebrain Organoid Kit	1 Kit	08630
STEMdiff™ Neural Organoid Maintenance Kit	1 Kit	100-0120
mTeSR™1	500 mL	85850
mTeSR™ Plus	1 Kit	05825

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