LIFE SCIENCE

Organoid Research Reagents

Organoid Culture

Organoids are *in vitro* 3D cell aggregates derived from stem cells which are not only capable of self-organization and long term self-renewal, but which also exhibit similar function to the tissues from which they were derived.[1-4] This is achieved through the use of physical and biochemical cues which are able to recapitulate cells' natural environment within living tissue. As such, organoids are able to overcome many of the limitations of existing culture models (2D monolayers, 3D aggregates (such as spheroids), animal models, etc.). Current applications for organoid culture systems include those in:

- **Developmental Biology**[5-9]
- **Disease Pathology**[10-22]
- **Drug Toxicity / Efficacy Testing**[23-26]
- **Regenerative Medicine**[27-30]
- **Personalized Medicine**[15,18,26,31,32]

Organoids can be generated by imbedding either primary tissue (human somatic stem cells (hSSCs)) or pluripotent stem cells (e.g. human induced pluripotent stem cells (hiPSCs)) in the appropriate matrix components and applying appropriate signaling molecules (small molecules / proteins, commonly referred to as niche factors, Table 1).[3] (Figure 1)

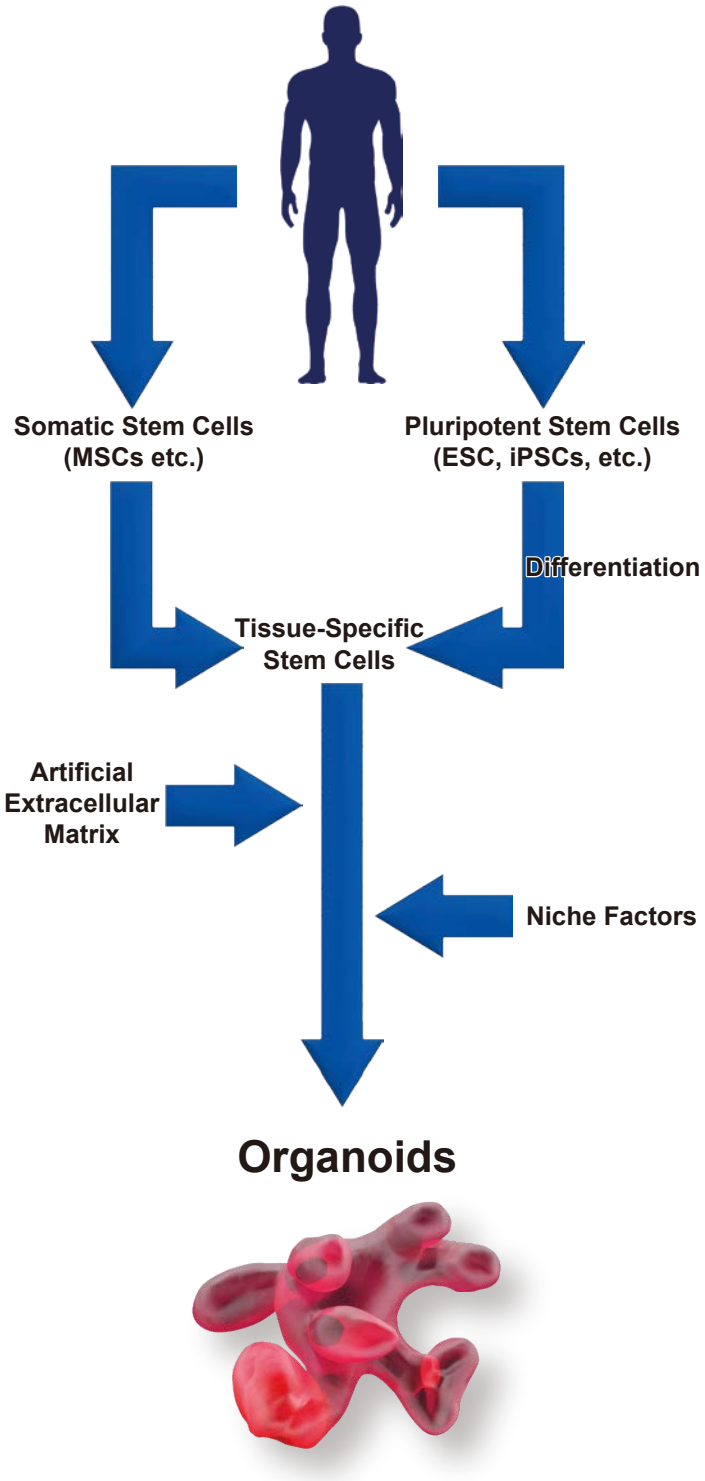

Figure 1. Organoid culture pipeline

Exposure of either somatic stem cells (SSCs) collected directly from tissue samples or differentiated pluripotent stem cells (PCSs) embedded in extracellular matrix with niche factors allows for the production of culturable cell aggregates with a highly similar phenotype to the original cells' tissue-of-origin.

Table 1. Representative niche factors for organoid culture
As summary of niche factors for both hiPSC and hSSC-derived organoids.

Tissue Type	Origin	Culture Conditions	Reference
Small Intestine	hSSCs	A83-01, Nicotinamide, *N*-Acetylcysteine, Y-27623, SB202190, EGF, Rspondin1, Noggin, Wnt-3a	33
	hiPSCs	EGF, Rspondin1, FGF-4, Noggin, Wnt-3a, Activin A	34
Large Intestine	hSSCs	A83-01, Nicotinamide, *N*-Acetylcysteine, Y-27623, SB202190, EGF, Rspondin1, Noggin, Wnt-3a	33
Stomach	hSSCs	A83-01, Nicotinamide, *N*-Acetylcysteine, Y-27623, EGF, Rspondin, FGF-10, Gastrin, Noggin, Wnt-3a	11
	hiPSCs	CHIR 99021, Y-27623, Retinoic Acid, EGF, FGF-4, BMP-4, Noggin, Activin A, Wnt-3a	12
Lung	hSSCs	A83-01, Nicotinamide, Y-27632, SB202190, Rspondin1, FGF-7, FGF-10, Noggin	35
	hiPSCs	[for hSPC Differentiation] SB431542, SANT-2, SU-5402, bFGF, Noggin, SHH, SAG, Activin A [for Organoid Culture] CHIR 99021, SB431542, FGF-4, Noggin	36
Brain	hiPSCs	Y-27632, Heparin, 2-Mercaptoethanol, bFGF, Insulin	37
Liver	hSSCs	[for Organoid Culture] Y-27632, A83-01, Nicotinamide, *N*-Acetylcysteine, Forskolin, EGF, Rspondin1, FGF-10, Gastrin, Noggin, Wnt-3a, HGF [for Hepatocyte Differentiation] A83-01, DAPT, Dexamethasone, EGF, FGF-19, BMP-7, Gastrin, HGF	17
	hiPSCs	bFGF, BMP-4, Activin A, HGF, Oncostatin M	38
Pancreas	hSSCs	A83-01, Nicotinamide, *N*-Acetylcysteine, EGF, Rspondin1, FGF-10, Gastrin, Noggin, Wnt-3a	20
Kidney	hiPSCs	[for Differentiation] CHIR 99021, 2-Mercaptoethanol, Heparin, Retinoic Acid, 1-Thioglycerol, bFGF, FGF-9, BMP-2, BMP-4, Insulin, Activin A, Holo-transferrin [for Organoid Culture] CHIR 99021, Heparin, FGF-9, HGF, GDNF	39, 40
Prostate	hSSCs	Y-27623, A83-01, Nicotinamide, *N*-Acetylcysteine, SB202190, Prostaglandin E2, Testosterone, EGF, Rspondin1, FGF-10, bFGF, Noggin	41
	hiPSCs	[for Differentiation] FGF-10, Activin A, Wnt-10b [for Organoid Culture] Retinoic Acid, Testosterone, EGF, Rspondin1, Noggin	42

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Growth Factors

Characterized as cytokines, growth factors are the name for soluble proteins that initiate signaling cascades in cells related to proliferation, differentiation, survival, inflammation, and tissue repair.

Products

rhEGF	**[EGFR Ligand/Agonist]**	100µg/vial **[R0262]**
rhFGF2	**[FGFR Ligand/Agonist]**	50µg/vial **[R0263]**

References Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways
P. Wee, Z. Wang, *Cancers* **2017**, 9, 52. https://doi.org/10.3390/cancers9050052
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L. Dailey, C. Basilico, *et al.*, *Cytokine Growth Factor Rev.* **2005**, *16*, 233. https://doi.org/10.1016/j.cytogfr.2005.01.007

PI3K/Akt Signaling Pathway

PI3K mediates conversion of PIP2 to PIP3 on the inner leaflet of the cell membrane upon recruitment to the membrane following activation of various receptor proteins including integrin, RTKs, cytokine receptors, B-cell receptors, and GPCRs. PIP3 acts as binding sites for various factors such as PDK1 and mTORC2, as well as Akt, which is activated via phosphorylation by PDK1 and mTORC2. Akt (Protein Kinase B) is a protein kinase which has as target proteins mTORC1, MDM2, Bad, CDK2, Lamin A, IKKα, FOXO1, P27, and GSK-3, among others, giving it an important role in the regulation of such cellular processes as cell growth, survival, motility, metabolism, and protein synthesis.

Products

LY 294002	**[PI3K Inhibitor]**	25mg **[M2410]**
Miltefosine	**[PI3K Inhibitor]**	100mg / 1g **[M2445]**
3-Methyladenine	**[PI3K Inhibitor]**	200mg / 1g **[M2518]**
Quercetin Hydrate	**[PI3K Inhibitor]**	25g **[P0042]**
Wortmannin	**[PI3K Inhibitor]**	20mg **[W0007]**

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References The PI3K/AKT signaling pathway in regulatory T-cell development, stability, and function
S. L. Pompura, M. Dominguez-Villar, *J. Leukoc. Biol.* **2018**, *103*, 1065. https://doi.org/10.1002/JLB.2MIR0817-349R
Targeting PI3K/Akt signal transduction for cancer therapy
Y. He, B. Li, *et al.*, *Signal Transduct. Target. Ther.* **2021**, *6*, 425. https://doi.org/10.1038/s41392-021-00828-5

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MAPK Signaling Pathways

The mammalian MAPK (Mitogen-Activated Protein Kinase) signaling pathways transmit a wide variety of signals from outside the cell through the activation of MAPKs, and are divided into three subgroups based on the specific MAPK at work: ERK, JNK, or p38.

ERK1/2 Signaling Pathway

The ERK/MAPK signaling pathway, playing major roles in cell proliferation and differentiation, begins via extracellular signals received at membrane-embedded receptor proteins such as receptor tyrosine kinases, integrins, and ion channels. Different combinations of ligand/receptor result in the activation of slightly different downstream effectors, but in general, signals from the receptor first reach an adaptor protein such as Shc, GRB2, or Crk, which is then transmitted via activation of a guanine nucleotide exchange factor such as SOS or C3G. This in turn allows for the activation of GTP binding proteins such as Ras and Rap1, which phosphorylate and activate the MAPKKK (MAPK Kinase Kinase) Raf, which phosphorylates and activates the MAPKK (MAPK Kinase) MEK1/2, which finally phosphorylates and activates ERK. Activated ERK dimer is then able to phosphorylate and activate downstream molecules not only in the cytoplasm but also in the nucleus.

p38 Signaling Pathway

As one of the three principal MAPK signaling pathways in mammals, the p38 MAPK signaling pathway plays a similar role as the JNK signaling pathway as a mediator of the cell's response to environmental and genetic stress. In mammals, four isoforms exist (the p38α, p38β, p38γ, and p38δ isoforms), with p38α/β as the main isoforms. Upon direct and indirect activation via Akt, TNFα, Wip1, etc., p38α/β is able to phosphorylate and activate various targets in both the cytoplasm and nucleus, the most prominent of which being p53, MSK1/2, and HBP1. p38α/β activation also results in the downregulation of certain effector molecules such as Cdc25B and CycD1, highlighting the role that p38 plays in the cell cycle.

JNK Signaling Pathway

As one of the three principal MAPK signaling pathways in mammals, the JNK MAPK signaling pathway plays a similar role as the p38 signaling pathway as a mediator of the cell's response to environmental and genetic stress. Upon direct and indirect activation via Akt, Tak1, TNFα, ROS, etc., JNK is able to phosphorylate and activate various targets in both the cytoplasm and nucleus, the most prominent of which being p53, PPARγ, HSP1, c-Jun, and Stat3. JNK activation also results in the downregulation of certain effector molecules such as Bcl2 and Bim, highlighting the role that JNK plays in determination of cell fate.

Products

GW-5074	[c-Raf1 Inhibitor]	100mg	[G0609]
Sorafenib	[Raf1, B-Raf Inhibitor]	500mg	[O0599]
PD 98059	[MEK1/2, AHR Inhibitor]	10mg	[A2529]
SL327	[MEK1/2 Inhibitor]	5mg / 25mg	[L0331]
PD184352	[MEK1/2 Inhibitor]	25mg / 100mg	[P2174]
SP600125	[JNK1/2/3, Aurora A, FLT3, TRKA Inhibitor]	25mg	[A2548]
SU3327	[JNK Inhibitor]	20mg / 100mg	[A2940]
SB239063	[p38α/β Inhibitor]	5mg / 25mg	[B5898]
SB203580	[p38 Inhibitor]	25mg / 100mg	[F0864]
FR180204	[ERK1/2 Inhibitor]	5mg / 25mg	[F1214]
Honokiol	[ERK1/2 Activator, Akt Inhibitor]	200mg / 1g	[H1309]
PD169316	[p38 Inhibitor]	10mg / 50mg	[P2532]
VX-702	[p38α Inhibitor]	25mg / 100mg	[V0147]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

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A Comprehensive Review on MAPK: A Promising Therapeutic Target in Cancer
C. Braicu, *et al., Cancers* **2019**, *11*, 1618. https://doi.org/10.3390/cancers11101618
The p38 Pathway: From Biology to Cancer Therapy
A. Martínez-Limón, *et al., Int. J. Mol. Sci.* **2020**, *21*, 1913. https://doi.org/10.3390/ijms21061913
The JNK Signaling Pathway in Inflammatory Skin Disorders and Cancer
M. B. Hammouda, *et al., Cells* **2020**, *9*, 857. https://doi.org/10.3390/cells9040857

Wnt Signaling Pathway

The Wnt signaling pathway can be divided into the canonical and non-canonical (planar cell polarity and Wnt-calcium) pathways. In the canonical pathway, the Wnt receptor (a dimer of Fz and LRP5/6) sequesters the β-catenin destruction complex upon ligand binding, allowing the build-up of β-catenin in the nucleus. Once in the nucleus, β-catenin complexes with Tcf/Lef transcription factors to control the expression of various downstream genes. The canonical pathway plays major roles in the determination of cell fate during embryonic development, including the determination of body axis, and contributes to the regulation of differentiation and maintenance of stemness.

Products

CHIR99021	[GSK-3α/β Inhibitor]	25mg / 100mg [C2943]
IWP-2	[CK1δ Inhibitor]	10mg / 50mg [I1097]
IWR-1	[Tankyrase Inhibitor]	25mg [I1167]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities
J. Liu, G. Yin, *et al.*, *Signal Transduct. Target. Ther.* **2022**, *7*. https://doi.org/10.1038/s41392-021-00762-6

Notch Signaling Pathway

The notch pathway is highly conserved among multicellular organisms due to its roles in cell-fate determination during early development as a mediator of cell/cell contact. Nascient notch receptor is transported to the cell membrane, where binding with such ligands as Jagged and Dll cause it to be cleaved in turn by the ADAM family proteases and the γ-secretase complex. This results in liberation of notch's intracellular domain (Notch-ICD), which is transported to the nucleus to act as a transcription factor upon complexing with CSL and MAML.

Products

DAPT	[γ-secretase Inhibitor]	25mg [D4257]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Notch signaling at a glance
K. Hori, *et al.*, *J. Cell Sci.* **2013**, *126*, 2135. https://doi.org/10.1242/jcs.127308

Cadherin Signaling Pathway

The cadherin family of genes play critical roles in calcium-dependent cell-cell contact and adhesion, in part mediating contact inhibition and epithelial-to-mesenchymal transition. The canonical cadherins are E-cadherin, N-cadherin, and P-cadherin, which associate with catenins to activate the Wnt, NFκB, Hippo, and RhoA signaling pathways.

Products

DAPT	[γ-secretase Inhibitor]	25mg [D4257]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Cadherin signaling: keeping cells in touch
O. Klezovitch, V. Vasioukhin, *F1000Res.* **2015**, *4*, 550. https://doi.org/10.12688/f1000research.6445.1
Cadherin Signaling in Cancer: Its Functions and Role as a Therapeutic Target
W. Yu, L. Yang, T. Li, Y. Zhangm, *Front. Oncol.* **2019**, *9*, 989. https://doi.org/10.3389/fonc.2019.00989
Cleavage of E-Cadherin by Matrix Metalloproteinase-7 Promotes Cellular Proliferation in Nontransformed Cell Lines via Activation of RhoA
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W. H. Lai, C. W. Siu, *et al.*, *Cell. Reprogram.* **2010**, *12*, 641. https://doi.org/10.1089/cell.2010.0051

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PKC Signaling Pathway

Protein Kinase C (PKC) is a family of serine/threonine-kinases divided into three subfamilies based on associated factors (Ca^{2+}, DAG) which are required for their phosphorylation-mediated activation.

Products

Bisindolylmaleimide I	[PKC Inhibitor]	5mg / 25mg [B5781]
Fasudil Hydrochloride	[PKC Inhibitor]	100mg [F0839]
Staurosporine	[PKC Inhibitor]	10mg [T4000]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Protein kinase C signaling and oxidative stress
R. Gopalakrishna, S. Jaken, *Free Radic. Biol. Med.* **2000**, *28*, 1349. https://doi.org/10.1016/s0891-5849(00)00221-5

Prostaglandin Signaling Pathway

Prostaglandins, a metabolic derivative of arachidonic acid, play key roles in vasodilation and the generation of the inflammatory response.

Products

Prostaglandin E_1	[EP1-4 Ligand / Agonist]	10mg [P1917]
Prostaglandin E_2	[EP1-4 Ligand / Agonist]	1mg / 10mg [P1884]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Pharmacology and signaling of prostaglandin receptors: multiple roles in inflammation and immune modulation
A. N. Hata, R. M. Breyer, *Pharmacol. Ther.* **2004**, *103*, 147. https://doi.org/10.1016/j.pharmthera.2004.06.003

TGFβ Signaling Pathway

The receptors for the TGFβ signaling pathway are single-pass serine/threonine cell surface receptors, and are divided into two groups, type 1 and type 2 receptors. These receptors form a covalent disulfide bond with a receptor of the other type, forming a dimer which then itself dimerizes into a tetramer. The extracellular ligands this tetramer binds to, as well as the affinity and sensitivity of each subunit towards these ligands is used to separate the TGFβ family into three major groups, the TGFβ, BMP (Bone Morphogenic Protein), and Activin subgroups. Upon binding to a ligand, such proteins as Smad2/3, Smad1/5/8, and/or Tak1 are phosphorylated and activated, leading to an increase in the expression of genes related to embryonic development, cell proliferation and apoptosis. The TGFβ pathway is often dysregulated in cancer, and its inhibition is commonly required in organoid culture.

Products

A83-01	[ALK4/5/7 Inhibitor]	25mg [A3324]
SB431542	[ALK4/5/7 Inhibitor]	25mg / 100mg [B4003]
SB525334	[ALK5 Inhibitor]	10mg / 50mg [B5776]
SB505124	[ALK4/7 Inhibitor]	5mg / 25mg [B6056]
SIS3	[SMAD3 Inhibitor]	5mg / 25mg [I1110]
RepSox	[ALK5 Inhibitor]	5mg / 25mg [R0224]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Bone morphogenetic protein receptor signal transduction in human disease
M. C. Gomez-Puerto, *et al., J. Pathol.* **2019**, *247*, 9. https://doi.org/10.1002/path.5170
Opposing roles and potential antagonistic mechanism between TGF-β and BMP pathways: Implications for cancer progression
J. Ning, *et al., eBioMedicine* **2019**, *41*, 702. https://doi.org/10.1016/j.ebiom.2019.02.033

Hedgehog Signaling Pathway

The Hedgehog (Hh) signaling pathway was first discovered due to the essential role it plays in body plan determination during development, but it has also been shown to be important for maintaining stem cell-ness in somatic stem cells. The mammalian Hedgehog ligands comprise three homologues (Desert – DHH, Indian – IHH, Sonic – SHH) with SHH being the most well studied. SHH binding to the Patched-1 (PTCH1) receptor abrogates PTCH1's repressive effect on Smoothened (SMO), which can then activate members of the GLI family of transcription factors, which go on to promote transcription of downstream factors.

Products

Jervine	[Smoothened Inhibitor]	10mg [J0009]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

References Hedgehog Signaling in Development and Cancer
J. Jiang, C. C. Hui, *Dev. Cell* **2008**, 15, 801. https://doi.org/10.1016/j.devcel.2008.11.010

Other Organoid Culture Additives

Products

***N*-Acetyl-L-cysteine**	25g / 250g [A0905]
Dexamethasone	1g [D1961]
Forskolin	10mg / 50mg [F0855]
L-Glutamine	25g / 100g / 500g [G0063]
Heparin Sodium Salt from Hog intestine	100mg / 1g [H0393]
2-Mercaptoethanol	25g / 500g [M0058]
Nicotinamide	25g / 500g [N0078]
Penicillin G Potassium Salt	25g [P1772]
Prostaglandin E_2	1mg / 10mg [P1884]
Retinoic Acid	1g / 5g [R0064]
Streptomycin	25g / 500g [S0585]
Testosterone	1g / 10g [T0027]

‡These products are not guaranteed for cell culture applications. They are not sterilized, and should be passed through a sterile filter before use.

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