

# Maintenance of Pluripotent Stem Cells

Xeno-Free, Serum-Free Systems  
for the Culture, Reprogramming  
and Differentiation of Pluripotent  
Stem Cells

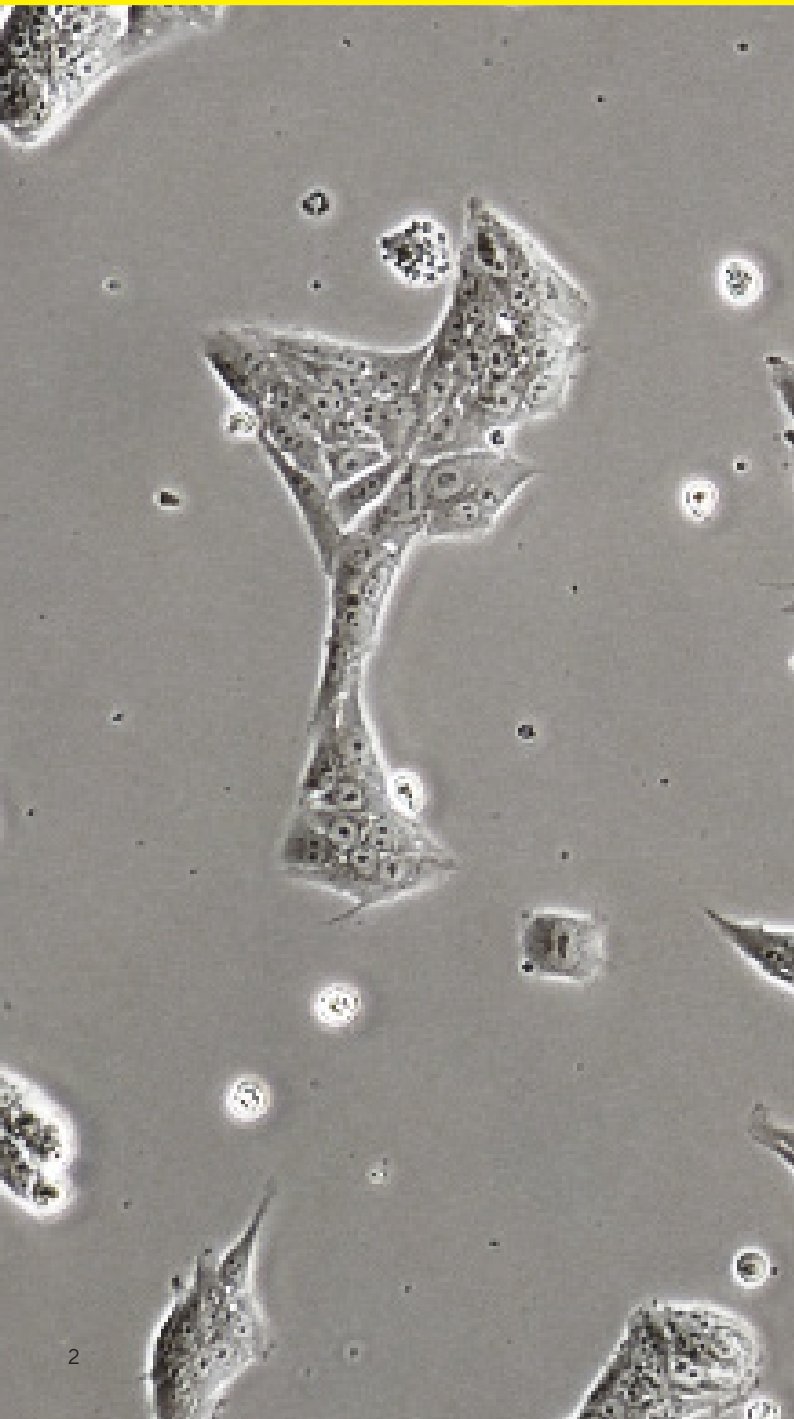
Simplifying Progress

**SARTORIUS**

# From Research to Cell Based Therapies

The transition from stem cell culture research models to clinical applications requires the design and implementation of qualified processes. Defined, high-quality culture systems and appropriate documentation are therefore an essential element in the development of regenerative stem cell therapies, where implantation in humans is the desired outcome.

We provide an optimized cell culture environment for human pluripotent stem cell research, including the NutriStem® defined, serum free (SF), xeno-free (XF) media family and its auxiliary reagents, manufactured in a cGMP compliant facility. In addition, a Drug Master File (DMF) registered at the FDA is available.



## Product Overview

### Media

#### **NutriStem® hPSC XF**

Defined, xeno-free, serum-free medium for optimal growth and expansion of hPSC on feeder or feeder-free conditions, using laminin or Matrigel.

#### **NutriStem® hPSC XF Medium (Growth Factor-Free)**

A modified composition of the complete NutriStem® hPSC XF Medium. Contains no bFGF or TGF $\beta$ , making it an ideal medium for many experimental assays, such as reprogramming (including mRNA reprogramming), embryoid body (EB) formation, and various differentiation assays.

#### **NutriStem® hPSC XF with +20 ng/ml bFGF**

A modified composition of the complete NutriStem® hPSC XF Medium. Contains additional bFGF, making it an ideal medium for adaptation of hPSC from serum-containing or other commercial serum-free media

## Attachment

### **LaminStem™ 521**

Chemically defined, recombinant Laminin-521 for the attachment of human pluripotent stem cells in a feeder-free culture system.

### **Vitronectin ACF**

Chemically defined, animal component-free (ACF) human recombinant lyophilized vitronectin protein for the attachment of human pluripotent stem cells in a feeder-free culture system.

## Dissociation

### **Recombinant Trypsin EDTA Solution**

ACF recombinant trypsin solution with EDTA for efficient single cell dissociation of adherent cell types from surfaces and tissues.

### **EDTA Solution 0.5M**

Enzyme-free, chemically defined, ACF dissociation solution.

## Cryopreservation

### **NutriFreez® D10**

#### **Cryopreservation Medium**

ACF, protein-free and chemically defined freezing medium, for hPSC cryopreservation both as single cells and aggregates.

# hPSC Proliferation With NutriStem<sup>®</sup> hPSC XF

## Products

Product Name	Cat. #	Storage
NutriStem <sup>®</sup> hPSC XF	05-100-1	-20 °C
NutriStem <sup>®</sup> hPSC XF Medium (Modified, GF-free, bFGF-free)	06-5100-01-1	-20 °C
NutriStem <sup>®</sup> hPSC XF with +20 ng/ml bFGF	06-5100-11-1	-20 °C

Defined, xeno-free, serum-free medium designed to support the growth and expansion of hESCs and hPSCs.

## Advantages

### Excellent performance

- Superior cell proliferation (low doubling time)
- Maintenance of pluripotent stem cell characteristics and stable karyotype over long term passages (> 50 passages)

### User-friendly

- One bottle formulation, ready-to-use
- Weekend-free feeding regime
- Straightforward adaptation protocol

### Flexible

- Versatile coating and culture methods
- Flexible packaging
- Custom modifications

### Defined, xeno-free, serum-free medium

- Reproducible and consistent results throughout experiments
- Batch-to-batch consistency

### cGMP medium

- Complete product dossier
- Available DMF
- Produced under cGMP conditions

### Low growth factor concentrations (bFGF, TGF Beta)

- Improves cell quality, reprogramming and differentiation capabilities

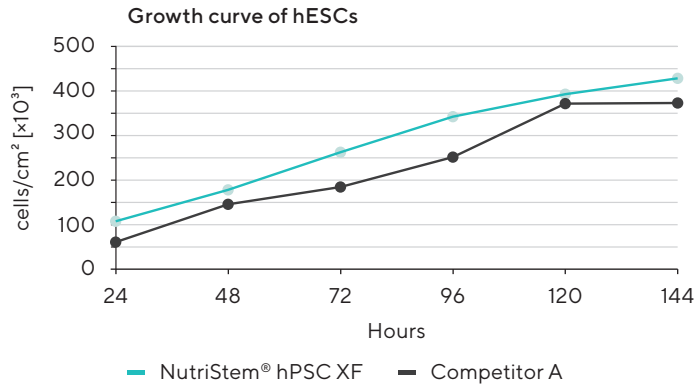
### Widely referenced in publications

- Feel confident in your research

# Excellent Proliferation of Undifferentiated hPSCs

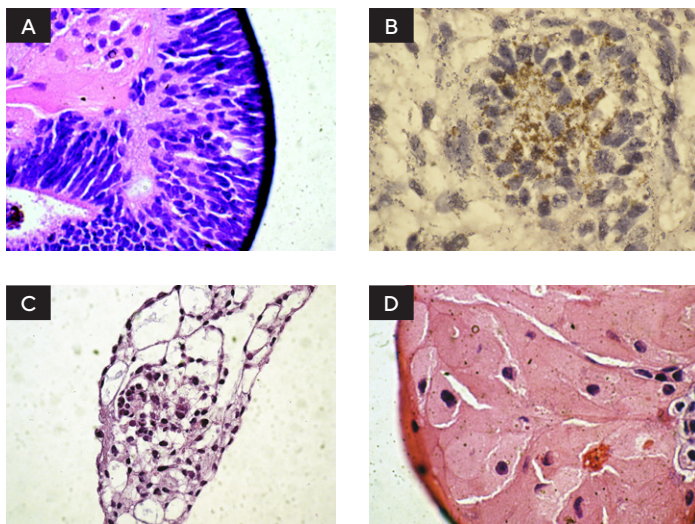
NutriStem® hPSC XF Medium enables excellent proliferation of undifferentiated hESCs and hPSCs.

**Figure 1:** H1 cells (passage 6) were seeded in 96 well plates (Matrigel-coated) in various media. Media were changed every 24 hours. The number of cells was determined using a CyQuant cell proliferation assay kit.



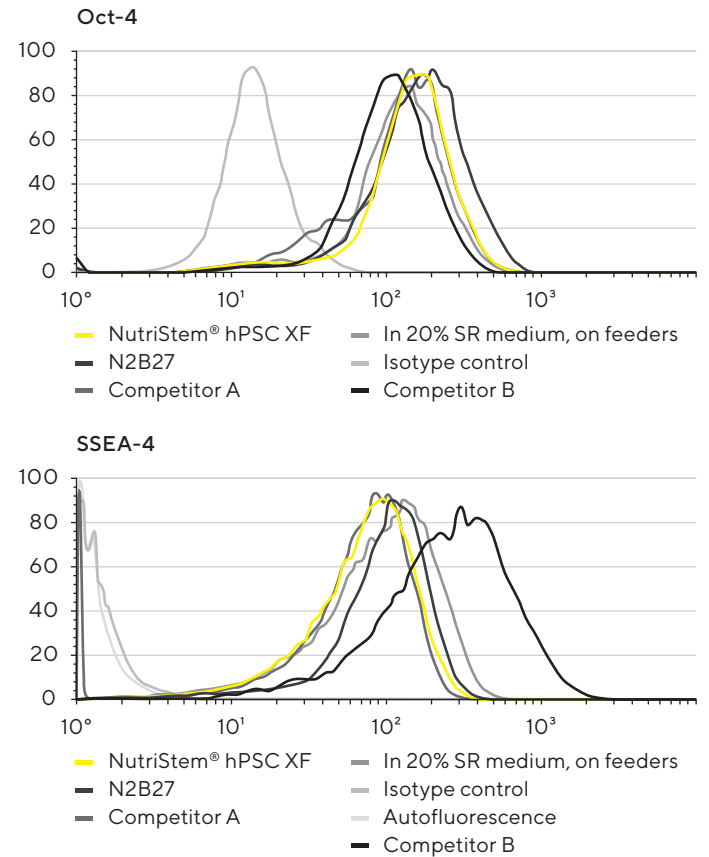
# Embryoid Body (EB) Formation

**Figure 2:** hESCs from cell line H9.2 were cultured for 16 passages in NutriStem® hPSC XF Medium using a Matrigel matrix and tested in vitro for pluripotency by EB formation. After suspension in serum supplemented medium the cells spontaneously formed embryoid bodies containing embryonic germ layers. Examining the histological sections of 14-day-old EBs, the following cell types were identified; (A) Neural rosette (ectoderm), (B) Neural rosette stained with Tubulin, (C) Primitive blood vessels (mesoderm) and (D) Megakaryocytes (mesoderm). Stained with H&E.

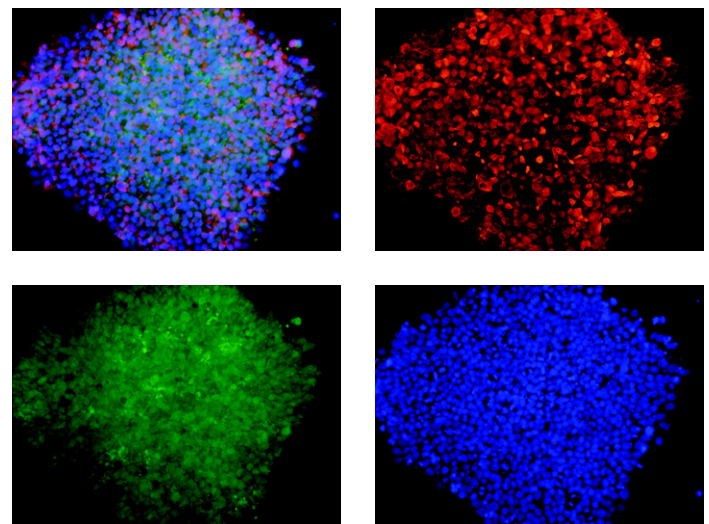


# High Expression of Pluripotent Stem Cell Markers

**Figure 3:** H1 cells cultured in different media for 6 passages were analyzed and compared using flow cytometry and gene expression. Cells cultured in NutriStem® hPSC XF Medium were found to be >90% positive for SSEA-4 and Oct-4.



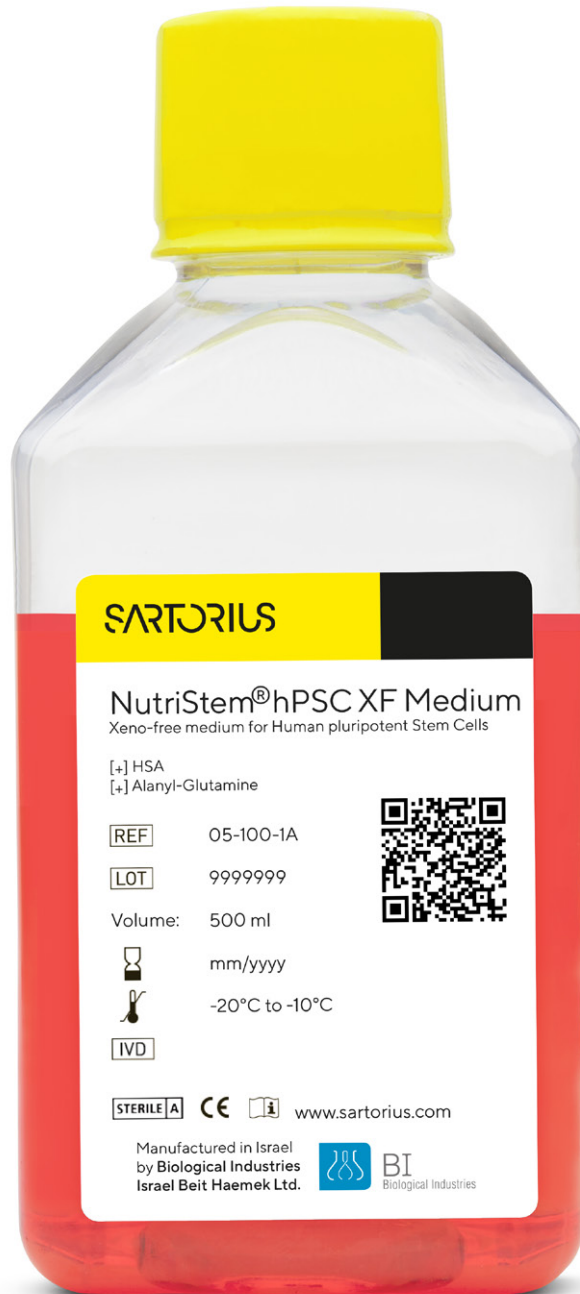
**Figure 4:** H1 cell morphology and immunofluorescence analysis of hESC markers: red SSEA-4, green OCT4 and blue DAPI. H1 cells stained positive for the expression of pluripotency markers.



# NutriStem<sup>®</sup> hPSC XF Medium

## Gives You the Freedom and Versatility to Derive and Culture Pluripotent Stem Cells in a Variety of Methods

NutriStem<sup>®</sup> hPSC XF Medium supports both feeder-dependent and feeder-free culture systems. The medium is also suitable for culture as colonies or monolayer, and supports single cell applications.



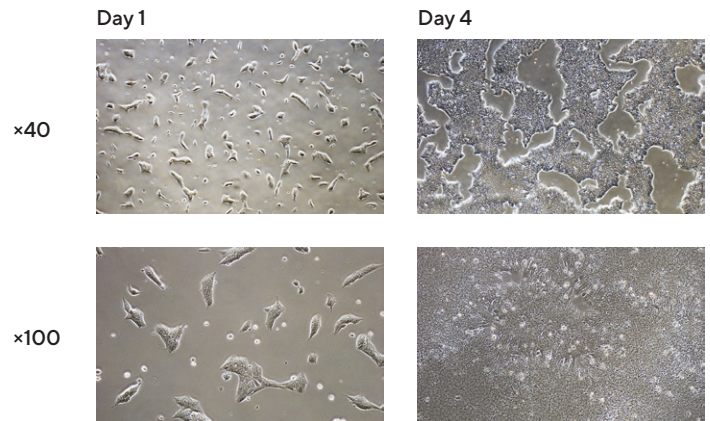
# Laminin-Based Culture System

LaminStem™ 521 with NutriStem® hPSC XF Medium provide an optimal culture environment for undifferentiated expansion and growth of hES and hPS cells in a defined, feeder-free culture system as a monolayer, while maintaining proper phenotype and genetic stability. Studies have shown that efficient clonal derivation of hES cell lines is possible with the combined use of NutriStem® hPSC XF medium and LaminStem™ 521 substrate, finding that the cells grew better in NutriStem® hPSC XF than any other defined medium tested, and that hESCs can be passaged and maintained using a single-cell expansion protocol (Rodin, S. et al. 2014).

## Single cell passaging using LaminStem™ 521 and Recombinant Trypsin EDTA Solution

Culturing of hPSCs using NutriStem® hPSC XF Medium with LaminStem™ 521 enables easy and reliable single-cell passaging without artificial apoptosis inhibitors, such as ROCK inhibitor (Y-27632). This provides standardized procedures that are fast and easy to use. For the efficient dissociation and passaging Recombinant Trypsin EDTA Solution should be used.

**Figure 5:** Typical recovery of H1 (61) hESCs from single-cell passage using Recombinant Trypsin EDTA Solution and NutriStem® hPSC XF medium on 0.5µg/cm<sup>2</sup> LaminStem™ 521. Representative images for colony morphology one day and 4 days post-passage.



*“hES cells grew better in the xeno-free chemically defined NutriStem® hPSC XF Medium”*

(Rodin et al. 2014)

## Key References

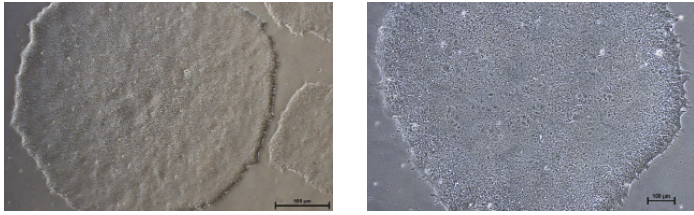
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- S. Rodin et al., Monolayer culturing and cloning of human pluripotent stem cells on laminin-521-based matrices under xeno-free and chemically defined conditions. *Nature Protocols* 9, 2354-2368 (2014) doi:10.1038/nprot.2014.15
- Rodin S, et al. Clonal culturing of human embryonic stem cells on laminin-521|E-cadherin matrix in defined and xeno-free environment. *Nat Commun.* 5:3195. doi: 10.1038/ncomms4195, 2014

## Clinical Applications

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## Matrigel™-Based Culture System

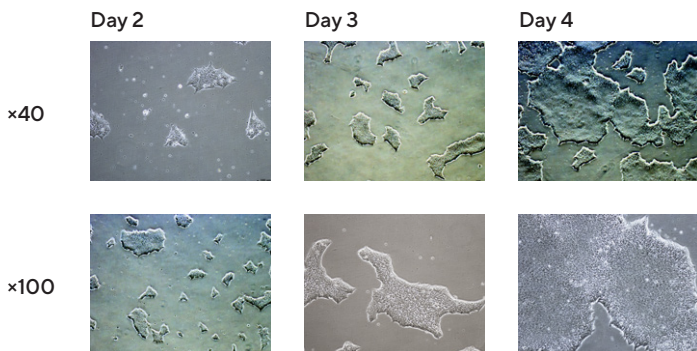
**Figure 6:** H1 hESCs cultured in NutriStem® hPSC XF Medium on Matrigel™ display compact colonies and distinct colony morphology typical of hPSCs.



### Enzyme-free passaging with EDTA

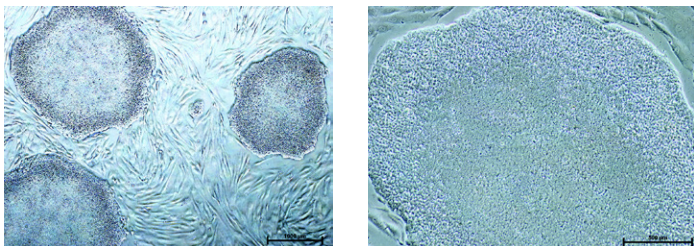
Small aggregate dissociation using EDTA is a gentle, enzyme-free method of passaging cells grown in feeder-free conditions.

**Figure 7:** Typical recovery of hESCs from enzyme-free passage (0.5mM EDTA) using NutriStem® hPSC XF medium on Matrigel™. Representative results for colony morphology of H1 hESC 2-4 days post-passage.



## Feeder-Dependent Culture (MEF|HFF)

**Figure 8:** H1 hESC colonies on MEF feeder layer display compact colonies and distinct colony morphology typical of hPSCs.



*“NutriStem appears to support iPSC culture on feeders better than E8”*

(T. Cerbini et al., 2015)

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## Gene Editing

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- C.L. Sweeney et al. Targeted Repair of CYBB in X-CGD iPSCs Requires Retention of Intronic Sequences for Expression and Functional Correction. *Molecular Therapy*, 2017
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## Clinical Applications

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- Q. Gu et al. Accreditation of Biosafe Clinical-Grade Human Embryonic Stem Cells According to Chinese Regulations. *Stem Cell Reports*. 2017 Jul 11; 9(1): 366–380.
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## Key References

### Gene Editing

- T. Cerbini et al., Transfection, Selection, and Colony-picking of Human Induced Pluripotent Stem Cells TALEN-targeted with a GFP Gene into the AAVS1 Safe Harbor, *JoVE (Journal of Visualized Experiments)*, 2015

### Clinical Applications

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# Auxiliary Products

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Product Name	Cat. #	Storage
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EDTA Solution 0.5M	01-862-1	RT
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Diluted EDTA Solution 0.5mM is an enzyme-free, chemically defined, Animal Component Free (ACF) solution, suitable for the dissociation of human pluripotent stem cells. EDTA Solution 0.5mM mediates rapid cell dissociation by chelating calcium and magnesium ions that facilitate cell adhesion

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Product Name	Cat. #	Storage
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LaminStem™ 521	05-753-1	-20 °C
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LaminStem™ 521 facilitates self-renewal hPSC in a chemically defined, feeder-free cell culture system. LaminStem™ 521 is composed of purified laminin-521, a cell-type specific basement membrane protein proven to support excellent attachment proliferation of hES and hPS cells.

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Product Name	Cat. #	Storage
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Recombinant Trypsin EDTA Solution	03-079-1	RT
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Recombinant Trypsin EDTA Solution was developed for efficient single cell dissociation of adherent cell types from surfaces and tissues and were optimized for sensitive cells, such as hPSCs.

Recombinant Trypsin EDTA Solution is ready-to-use and animal component free. The addition of EDTA accelerates the dissociation phase. The solution does not contain any chymotrypsin, carboxypeptidase A, or other protease contaminants.

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Product Name	Cat. #	Storage
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Vitronectin ACF	05-754-0002	-20 ° to -80 °C
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Vitronectin is a secreted glycoprotein that supports cell adhesion through binding to various integrins and proteoglycans. Vitronectin ACF (Animal Component Free) can function as a chemically-defined matrix component for the attachment of human embryonic and induced pluripotent stem cells in a feeder-free culture system. Vitronectin ACF is a 459 amino acid, single-chain, monomeric recombinant protein, which migrates at an apparent molecular weight of 75 kDa by SDS-PAGE under reducing conditions. The calculated molecular weight of Vitronectin ACF is 52.2 kDa.

# hPSC Cryopreservation

## Products

Product Name	Cat. #	Storage
NutriFreez® D10 Cryopreservation Medium	05-713-1	2-8 °C

NutriFreez® D10 Cryopreservation Medium is an animal component-free, ready-to-use solution for the cryopreservation of animal cells.

NutriFreez® D10 Cryopreservation Medium was developed to maintain ACF conditions during cryopreservation when culturing cells in a XF culture system, and has been extensively validated with human ES cells (H1, H9 and HuES9). NutriFreez® D10 Cryopreservation Medium has shown to be very effective for the cryopreservation of hPSCs as single cells and cell aggregates.

Cells preserved with NutriFreez® D10 Cryopreservation Medium show high viability, attachment, growth performance, and maintenance of pluripotency markers after thawing (Figure 1), with superior results compared to both serum-containing freezing media and other serum-free solutions.

## Advantages

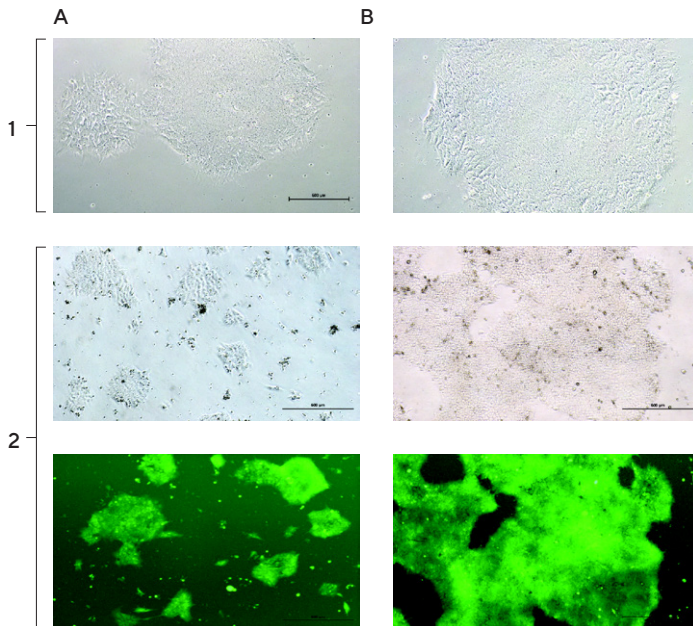
- Chemically defined, Animal component-free (ACF), Protein-free
- Works with various media
- Suitable for freezing hESCs and hPSCs cultured in both feeder and feeder-free conditions
- High recovery efficiency: maintains excellent attachment ability as well as growth performance
- Maintains hESC and hPSC pluripotency
- Complete formulation; Ready-to-use at 2-8°C
- For cryopreservation of hPSC clumps or single cells
- DMF available

**Figure 9:** H1 hES cells (1) and BGO1V|hOG (2) GFP reporter cells frozen in NutriFreez® D10 Cryopreservation Medium. Cryopreserved hES cells were thawed into NutriStem® hPSC Medium on Matrigel-coated plates. Cells show high viability at day 1 (A) and at day 4 post-thaw (B).

*“...cryopreservation with CryoStem\* showed the best recovery rate for hPSCs after thawing”*

(Nishishita N, et al., 2015)

\*NutriFreez® replaces the brand name “CryoStem”



## Key References

### Pluripotent Stem Cells

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### Mesenchymal Stem Cells

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# Key References for Derivation, Reprogramming and Differentiation

## hESC Derivation

NutriStem® hPSC XF medium enables successful derivation of new hESC lines, as well as long-term genetically stable growth of the clonal hESC lines in chemically defined, xeno-free environment.

### Key References

- M.V. Krivega et al. Cyclin E1 plays a key role in balancing between totipotency and differentiation in human embryonic cells. *MHR: Basic science of reproductive medicine*, Volume 21, Issue 12, 1 December 2015
- S. Rodin et al., Monolayer culturing and cloning of human pluripotent stem cells on laminin-521-based matrices under xeno-free and chemically defined conditions. *Nature Protocols* 9, 2354-2368 (2014) doi:10.1038/nprot.2014.159

## hPSC Reprogramming

NutriStem® hPSC XF medium supports mRNA-based cellular reprogramming of human cells. mRNA reprogramming is a fast, safe and efficient method for generating integration-free, virus-free, clinically relevant iPSC cell lines from mature human cells.

We also offer the possibility for modified NutriStem® hPSC XF Medium without growth factors.

Clonal mRNA reprogrammed iPSC lines can be expanded and maintained in NutriStem® hPSC XF Medium.

### Key References

- Protocol describes using laminin substrate and NutriStem™ hPSC XF Culture Medium to provide a complete xeno-free reprogramming environment:  
Protocol: Stemgent® StemRNA™-NM Reprogramming Kit for Reprogramming Adult and Neonatal Human Fibroblasts, ReproCell
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X. Gao et. al. Comparative transcriptomic analysis of endothelial progenitor cells derived from umbilical cord blood and adult peripheral blood: Implications for the generation of induced pluripotent stem cells. *Stem Cell Research*, 2017
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- Reprogramming of human and mouse adipose-derived stem cells into iPSC:
- S. Sugii et al., Human and mouse adipose-derived cells support feeder-independent induction of pluripotent stem cells. *PNAS* February 23, 2010 vol. 107 no. 8 3558-3563

# hPSC Differentiation

NutriStem® hPSC XF Medium is widely referenced in publications, showing effective differentiation of hPSCs into variety of cell types.

## Key References

### Cardiomyocyte differentiation

- R. Ophir et al. Inflammation And Contractility Are Altered By Obstructive Sleep Apnea Children's Serum, In Human Embryonic Stem Cell Derived Cardiomyocytes. American Journal of Respiratory and Critical Care Medicine 2017
- J. KRISTENSSON, Optimization of Growth Conditions for Expansion of Cardiac Stem Cells Resident in the Adult Human Heart. Master's thesis in Biotechnology, Department of Physics, Division of Biological Physics, Chalmers University of Technology, Gothenburg, Sweden 2016
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- E. Di Pasquale et al. Generation of human cardiomyocytes: a differentiation protocol from feeder-free human-induced pluripotent stem cells. JoVE (Journal of Visualized Experiments) 76 (2013): e50429-e50429
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### Retinal differentiation

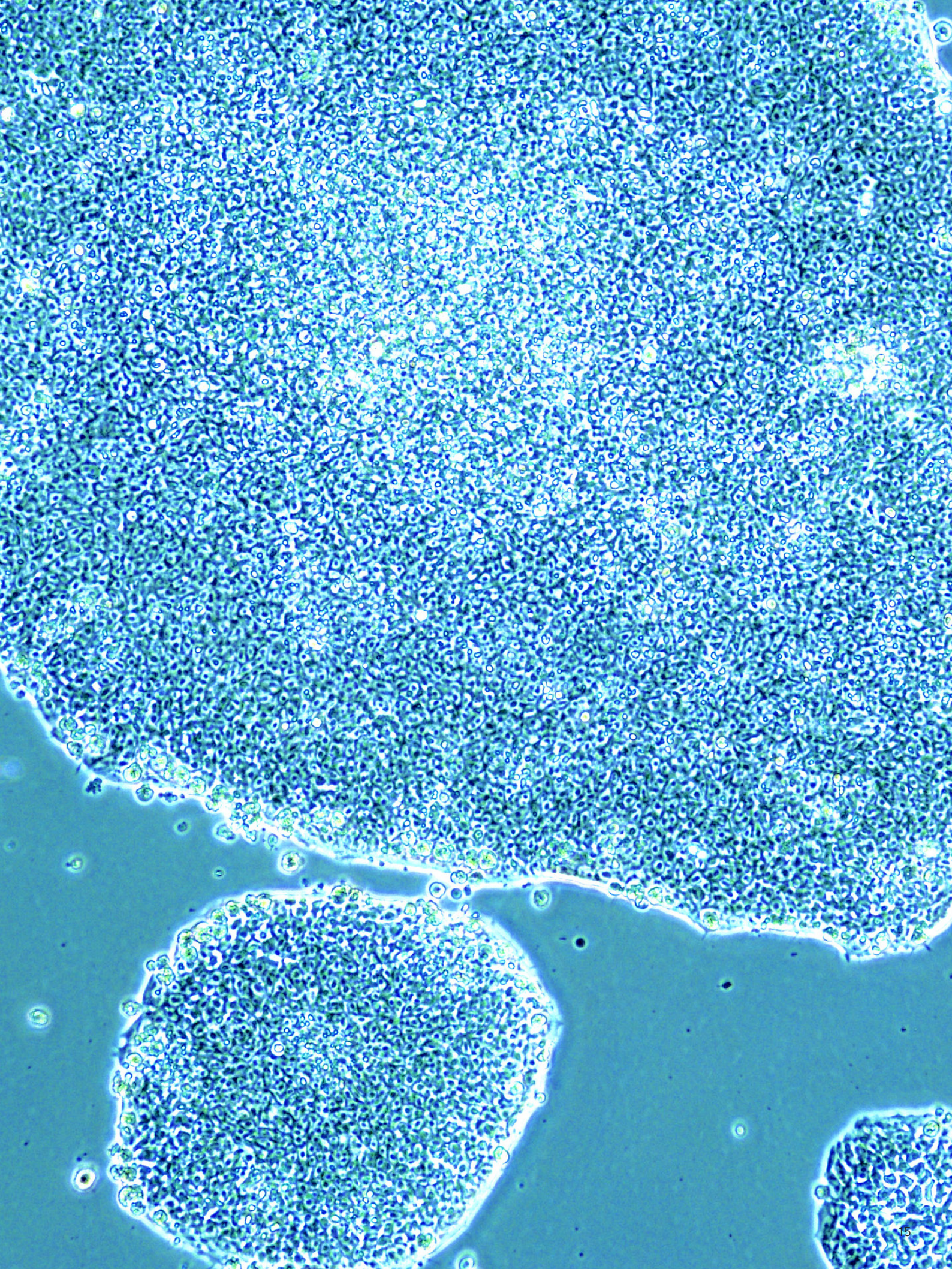
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- D. VOULGARIS, Evaluation of Small Molecules for Neuroectoderm differentiation & patterning using Factorial Experimental Design. Master Thesis in Applied Physics, Department of Physics, Division of Biological Physics, Chalmers University of Technology, Göteborg, Sweden 2016
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# Ordering Information

Product Name	Cat. #	Size	Storage
NutriStem® hPSC XF Medium	05-100-1A	500 ml	-20 °C
	05-100-1B	100 ml	
NutriStem® hPSC XF Medium (Modified, GF-free, bFGF-free)	06-5100-01-1A	500 ml	-20 °C
NutriStem® hPSC XF with +20 ng/ml bFGF	06-5100-11-1A	500 ml	-20 °C
LaminStem™	05-753-1F	1 ml	-20 °C
Vitronectin ACF	05-754-0002	1 ml	-20 °C to -80 °C
Recombinant Trypsin Solution	03-078-1A	500 ml	RT
	03-078-1B	100 ml	
Recombinant Trypsin EDTA Solution	03-079-1A	500 ml	RT
	03-079-1B	100 ml	
EDTA Solution 0.5M	01-862-1B	100 ml	RT
Accutase Solution	03-073-1B	100 ml	-20 °C
NutriFreez® D10 Cryopreservation Medium	05-713-1A	500 ml	2-8 °C
	05-713-1B	100 ml	
	05-713-1C	20 ml	
	05-713-1D	10 ml	
	05-713-1E	50 ml	



# Sartorius and Biological Industries

Biological Industries (BI) is part of the Sartorius group. Based in Israel, we have been committed for 40 years to provide optimal and innovative solutions for cell culture practice. We manufacture and supply life science products to biopharmaceutical, academic, and government research facilities, as well as to biopharma companies.

## Our diverse portfolio of products and services includes:

- Liquid and powdered cell culture media
- Novel serum-free and animal component-free media and supplements
- Products for stem cell research and cell-based therapies
- Products for mycoplasma detection and treatment
- Disinfectants
- Products for molecular biology
- Custom formulations and contract manufacturing services

All our products are manufactured via a quality management system ISO 9001:2015 and in regards to medical devices ISO 13485:2016. All aspects of the product's life cycle fall under the QMS procedures. The set-up of clean zone and clean room facilities for manufacturing are following ISO 14644, whereas the production rooms are ISO 8, storage of sterile accessories ISO 7, and filling rooms ISO 5. Aseptic filling and validation are performed according to ISO 13408.

From the outset, our policy has been based on the need to maintain an active Research and Development program in all facets of company activities. The company has its own in-house R&D department, and in addition, maintains active contact with science-based companies and research institutions in Israel and abroad, including know-how agreements with several such institutions. These ongoing efforts have led to the introduction of a series of serum-free medium products, as well as many other products for cell culture and molecular biology.

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