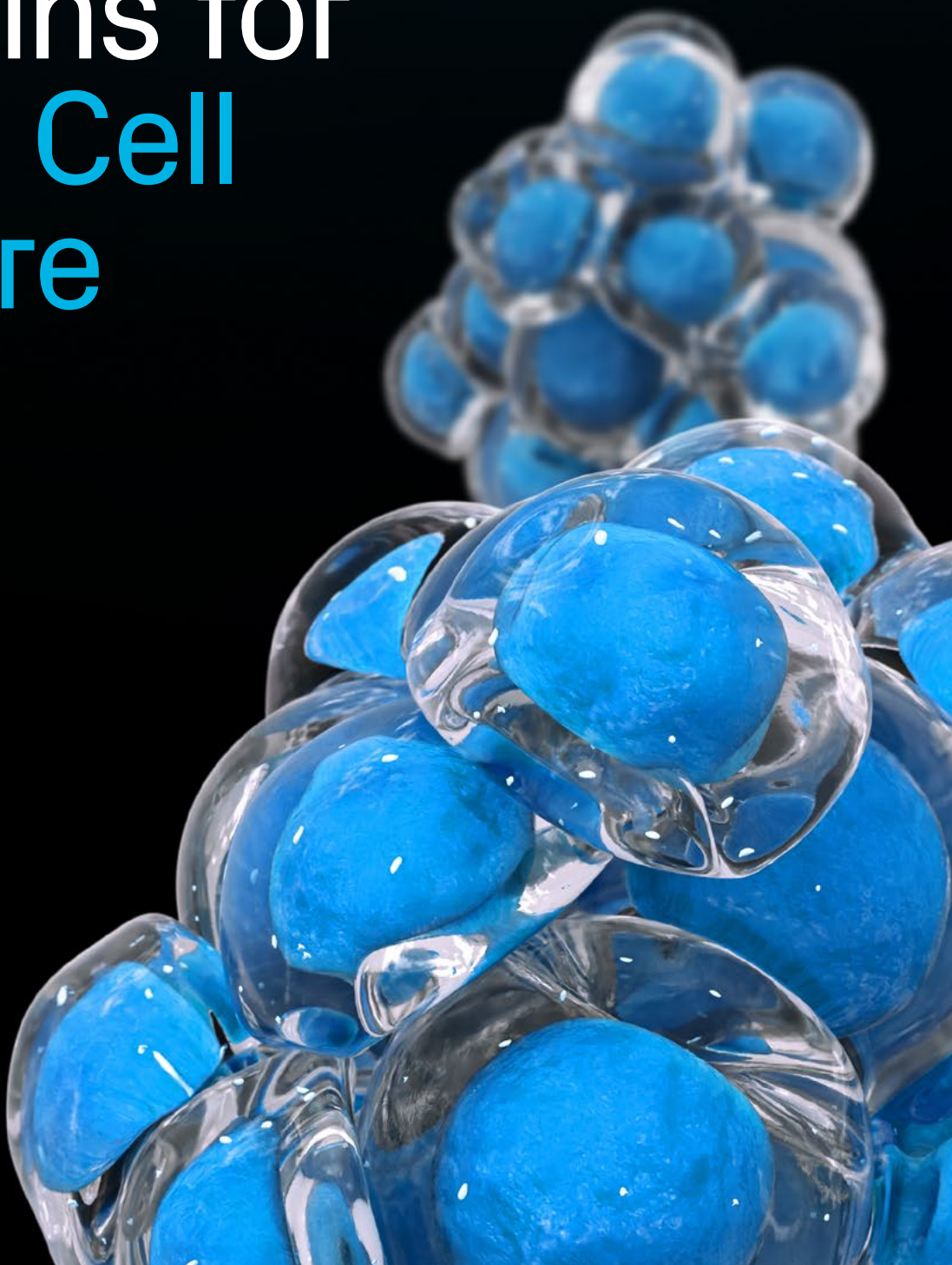
bio-techne® | R&D SYSTEMS

STEM CELL CULTURE

Proteins for Stem Cell Culture



Optimize your stem cell cultures with R&D Systems™ cytokines and growth factors. Our proteins provide high levels of bioactivity and lot-to-lot consistency so you can have confidence in their ability to promote robust stem cell expansion and differentiation with minimal variability between cultures. From basic research to preclinical applications, we offer research-grade, Animal-free, and GMP proteins to meet all your experimental needs.

Key Benefits of Using R&D Systems Proteins for Stem Cell Culture

- High Levels of Biological Activity: The biological activity of every protein we offer is tested in an appropriate bioassay to confirm that it meets our strict QC activity parameters.
- Lot-to-Lot Consistency: Minimal lot-to-lot variability is ensured by testing each new lot side-by-side with previous lots, so you don't have to worry whether results will be reproducible over time.
- High Purity and Low Endotoxin Levels: Our proteins are typically over 95% pure and have a guaranteed industry-leading endotoxin level of <0.1 EU/ug by the LAL method.
- Highly Cited: R&D Systems proteins commonly used for culturing stem cells and organoids are highly cited in the scientific literature.
- Seamless Transition from Preclinical Research to Clinical Manufacturing: R&D Systems Animal-free Preclinical and Animal-free GMP proteins frequently originate from the same clone, sequence, and expression system to make the transition from preclinical research into clinical manufacturing as seamless as possible.
- Supply Chain Reliability: Our team has the experience and the capacity to ensure that we can provide you with a stable supply of the proteins needed for your research now and into the future.
- Bulk Proteins at Discounted Prices: We have the ability to scale up the production of any protein and we offer economical pricing on bulk orders.
- Custom Protein Capabilities: For specialized protein requests, you can always contact our Custom Protein Services team. Whether you are looking for a different formulation of a protein, incorporation of a non-standard label, or custom bottling, we have the capabilities and the team to develop the protein that you need.
- Comprehensive Portfolio of Reagents for Your Entire Stem Cell and Organoid Culture Workflows: Along with our proteins, we also offer a wide range of other products for stem cell and organoid culture and characterization, including Cultrex™ Basement Membrane Extracts, media supplements, Tocris™ small molecules, antibodies, ELISA Kits, RNAscope™ ISH assays, and analytical instruments to automate different steps of your workflow.

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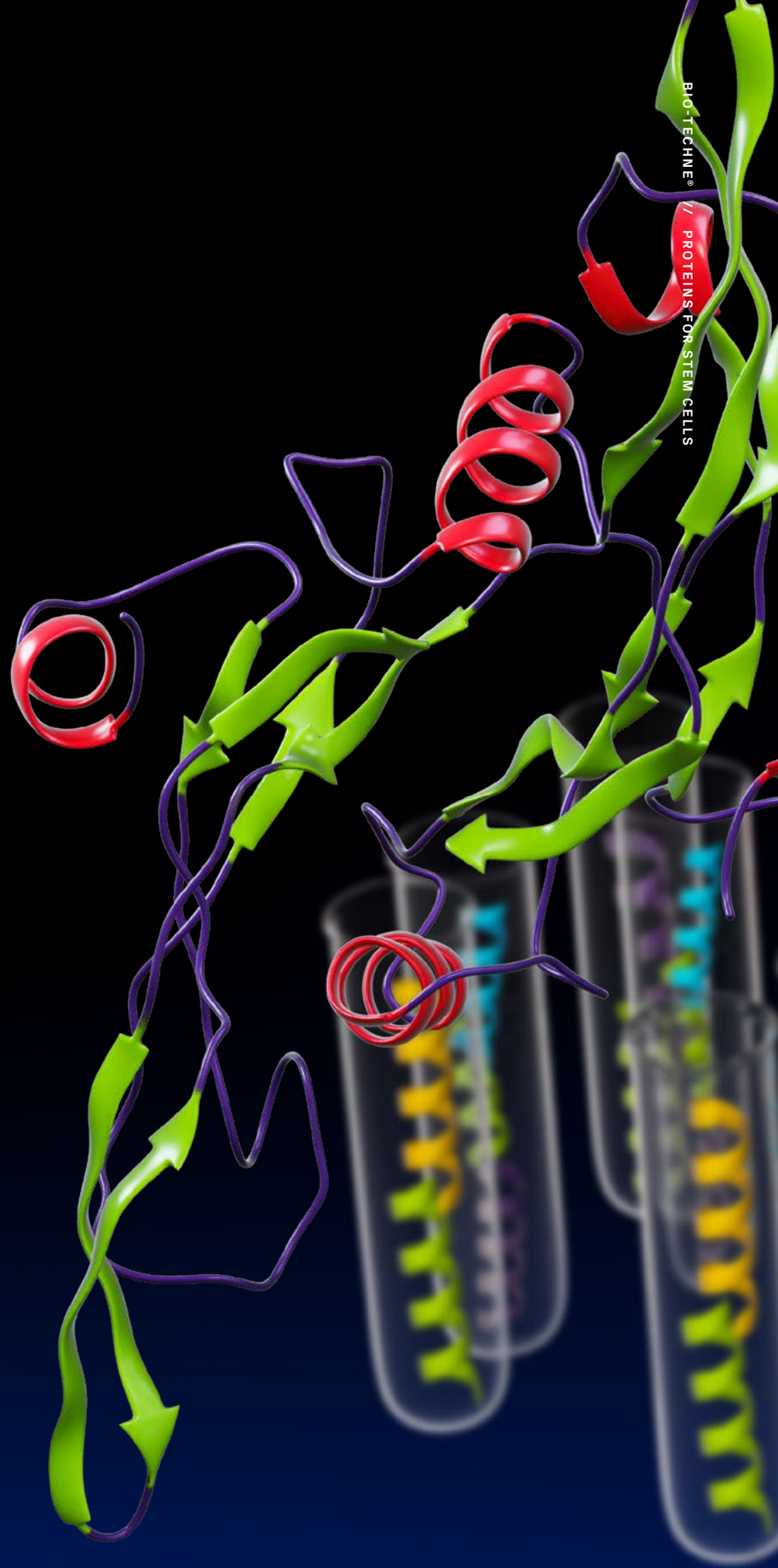

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TABLE // 01

Proteins for Stem Cell and Organoid Culture				
Molecule	**Species**	**Source**	**Catalog #**	**Stem Cell Type**
Activin A*	Human/Mouse	CHO	11348-AC	ESC, iPSC,
BDNF	Human	CHO	11166-BD	NSC
BMP-2*	Human/Mouse	*E. coli*	355-BEC	ESC, iPSC, MSC, NSC
		CHO	355-BM	
BMP-4*	Human	*E. coli*	314-BPE	ESC, iPSC, HSC, MSC, NSC
	Human	NS0	314-BP	
BMP-6	Human	NS0	507-BP	MSC
BMP-7	Human	CHO	354-BP	ESC, iPSC
CNTF	Human	*E. coli*	257-NT	NSC
Dkk-1	Human	HEK293	11387-DK	ESC, iPSC
EGF*	Human	*E. coli*	236-EG	ESC, iPSC, MSC, NSC
Erythropoietin	Human	CHO	287-TC	HSC
FGF basic/FGF2/ bFGF*	Human	*E. coli*	BT-FGFB	ESC, iPSC, MSC, NSC
	Human	*E. coli*	4114-TC	
FGF-3	Human	*E. coli*	1206-F3	ESC, iPSC
FGF-4	Human	*E. coli*	7460-F4	ESC, iPSC, MSC, NSC
FGF-7/KGF*	Human	*E. coli*	251-KG	ESC, iPSC
FGF-8	Human	*E. coli*	4745-F8	NSC
	Human/Mouse	*E. coli*	423-F8	
FGF-9	Human	*Sf21 (baculovirus)*	273-F9	ESC, iPSC
	Human	HEK293	11233-F9	ESC, iPSC
FGF-10	Human	*E. coli*	345-FG	ESC, iPSC, NSC
FGF-17	Human	*E. coli*	319-FG	ESC, iPSC
FGF-18	Human	*E. coli*	8988-F18	ESC, iPSC
FGF-19	Human	*E. coli*	969-FG	ESC, iPSC
Flt-3 Ligand/FLT3L*	Human	HEK293	308-FKHB	ESC, iPSC, HSC
	Human	NS0	308-FKN	
	Human	*E. coli*	BT-FT3L	
G-CSF	Human	*E. coli*	214-CS	HSC
GDF-5/BMP-14	Human	*E. coli*	8340-G5	MSC
GDNF*	Human	NS0	212-GD	NSC
GM-CSF*	Human	*E. coli*	215-GM	HSC
	Human	CHO	7954-GM	
HB-EGF	Human	*Sf21 (baculovirus)*	259-HE	MSC
HGF*	Human	NS0	294-HGN	ESC, iPSC
IFN-γ*	Human	*E. coli*	285-IF	HSC
	Human	HEK293	10067-IF	
IGF-I/IGF-1*	Human	*E. coli*	291-G1	ESC, iPSC, MSC, NSC

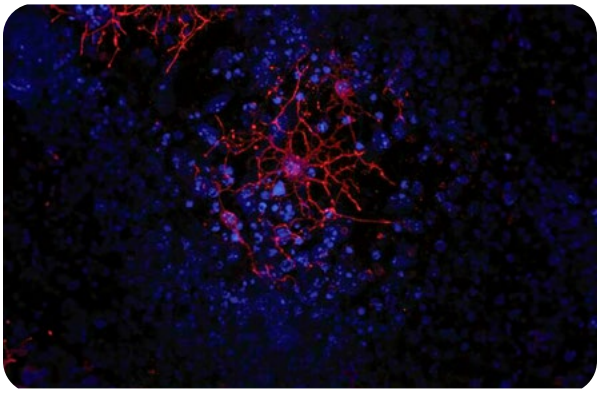
* GMP-grade proteins are available for these molecules.

Molecule	Species	Source	Catalog #	Stem Cell Type
IL-2*	Human	*E. coli*	BT-002	HSC
	Human	CHO	10453-IL	
IL-3*	Human	*E. coli*	203-IL	ESC, iPSC, HSC
IL-4*	Human	*E. coli*	BT-004	HSC
	Human	CHO	6507-IL	
IL-6*	Human	*E. coli*	206-IL	ESC, iPSC, HSC, MSC
	Human	HEK293	7270-IL	
IL-7*	Human	*E. coli*	BT-007	HSC
	Human	HEK293	11089-IL	
IL-10*	Human	*E. coli*	1064-ILB	HSC
	Human	*Sf*21 (stably transfected)	217-ILB	
	Human	HEK293	11178-IL	
IL-11	Human	CHO	10836-IL	ESC, iPSC, HSC
IL-15*	Human	*E. coli*	BT-015	HSC
IL-21*	Human	*E. coli*	8879-IL	HSC
	Human	HEK293	11393-IL	
M-CSF*	Human	*E. coli*	216-MC	HSC
	Human	CHO	216-MCC	
beta-NGF	Human	NS0	256-GF	NSC
Nodal	Human	*E. coli*	3218-ND	ESC, iPSC
Noggin*	Human	NS0	6057-NG	ESC, iPSC, NSC
NT-4	Human	*Sf*21 (baculovirus)	268-N4	NSC
PDGF-AA*	Human	*E. coli*	221-AA	ESC, iPSC, MSC, NSC
PDGF-BB*	Human	*E. coli*	220-BB	ESC, iPSC, MSC, NSC
R-Spondin 1	Human	CHO	4645-RS	ESC, iPSC
R-Spondin 3	Human	CHO	3500-RS	ESC, iPSC
SCF*	Human	*E. coli*	BT-SCF	ESC, iPSC, HSC
	Human	HEK293	11010-SC	
Sonic Hedgehog/ Shh*	Human	HEK293	8908-SH	ESC, iPSC, MSC, NSC
	Human	*E. coli*	1845-SH	
TGF-β1*	Human	HEK293	7754-BH	ESC, iPSC, MSC
TGF-β2	Human	NS0	302-B2	MSC
TGF-β3	Human	CHO	8420-B3	MSC
Thrombopoietin*	Human	*E. coli*	288-TPE	ESC, iPSC, HSC
	Human	NS0	288-TPN	
VEGF*	Human	*E. coli*	BT-VEGF	ESC, iPSC, HSC, NSC
	Human	*Sf*21 (baculovirus)	293-VE	
Wnt-3a*	Human	CHO	5036-WN	ESC, iPSC, HSC
Wnt-5a	Human/Mouse	CHO	645-WN	ESC, iPSC
Wnt-5b	Human	CHO	7347-WN	MSC
Wnt-10b	Human	CHO	7196-WN	MSC

* GMP-grade proteins are available for these molecules.

Key: **ESC** Embryonic Stem Cells **iPSC** Induced Pluripotent Stem Cells **HSC** Hematopoietic Stem Cells **MSC** Mesenchymal Stem Cells **NSC** Neural Stem Cells

Optimize Your Stem Cell Cultures with R&D Systems Proteins



Oligodendrocyte Marker 04/DAPI

Figure 1. Culture and Characterization of Mouse Oligodendrocytes. D3 mouse embryonic stem cells were expanded in KO-ES Media supplemented with Bovine Fibronectin Protein (R&D Systems, Catalog # 1030-FN) to support cell attachment and spreading, ITS Media Supplement (R&D Systems, Catalog # AR013) and N-2 Plus Media Supplement (R&D Systems, Catalog # AR003), and a panel of growth factors for effective oligodendrocyte differentiation, including Recombinant Human FGF-basic, Recombinant Human EGF (R&D Systems, Catalog # 236-EG), and Recombinant Human PDGF-AA (R&D Systems, Catalog # 221-AA). Oligodendrocytes were detected using a Mouse Anti-Human/Mouse/Rat/Chicken Oligodendrocyte Marker O4 Monoclonal Antibody (R&D Systems, Catalog # MAB1326). The cells were stained with the NorthernLights™-557 Affinity-purified Goat Anti-Mouse Secondary Antibody (R&D Systems, Catalog # NL019; red). The nuclei were counterstained with DAPI (Tocris Bioscience, Catalog # 5748; blue).

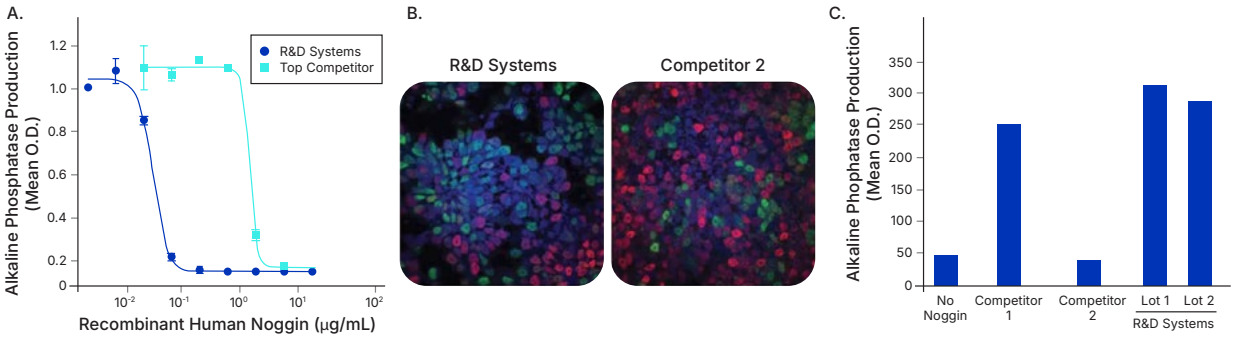


Figure 2. R&D Systems Recombinant Human Noggin Displays Higher Activity than Leading Competitors' Noggin Proteins and Minimal Lot-to-Lot Variability. (A) The bioactivity of R&D Systems Recombinant Human Noggin (Catalog # 6057-NG; dark blue line) or recombinant human Noggin from a top competitor (light blue line) was determined by assessing the ability of the proteins to inhibit alkaline phosphatase production induced by 50 ng/mL Recombinant Human BMP-4 (R&D Systems, Catalog # 314-BP) in the ATDC5 mouse chondrogenic cell line. In the presence of 50 ng/mL Recombinant Human BMP-4, the ED_{50} for this effect for R&D Systems Recombinant Human Noggin was approximately 30-fold greater than the top competitor's Noggin protein. (B, C) BG01V human embryonic stem cells were cultured in Mouse Embryonic Fibroblast Conditioned Media supplemented with FGF basic (5 ng/mL). Stem cells were driven into early cells of the neuroectoderm using a 3-day incubation in 25 ug/mL of R&D Systems Recombinant Human Noggin (Lot 1, Lot 2; Catalog # 6057-NG) or recombinant human Noggin from two different competitors (Competitor 1, Competitor 2). Control cells were incubated in media without Noggin (No Noggin). The cells were stained for the early ectoderm marker, Otx2, and the neuroectoderm marker, SOX1. (B) Representative images of Otx2 (red), SOX1 (green), and DAPI (blue) staining in embryonic stem cells differentiated with Noggin from R&D Systems or Noggin from Competitor 2. (C) SOX1+ clusters were quantified under each of the indicated culture conditions. Cells treated with R&D Systems Recombinant Human Noggin showed an increase in SOX1+ cells compared to both the untreated and competitor-treated cells. R&D Systems Recombinant Human Noggin showed consistent differentiation across the lots tested.

BG01V human embryonic stem cells were licensed from ViaCyte, Inc.

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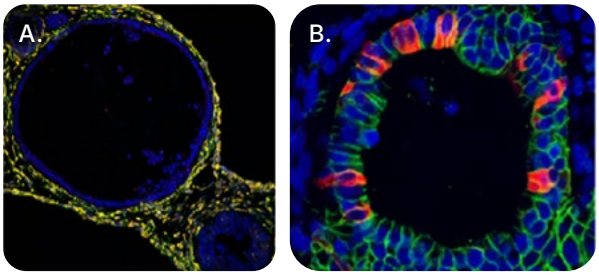

Figure 3. Culture and Characterization of iPSC-derived Human Intestinal Organoids. iPSC-derived human intestinal organoids were embedded in Cultrex™ UltiMatrix RGF Basement Membrane Extract (R&D Systems, Catalog # BME001-05) and cultured in intestinal organoid culture medium, which includes Recombinant Human Wnt-3a (R&D Systems, Catalog # 5036-WN), Recombinant Human Noggin (R&D Systems, Catalog # 6057-NG), Recombinant Human R-Spondin 1 (R&D Systems, Catalog # 4645-RS), Recombinant Human EGF (R&D Systems, Catalog # 236-EG), along with the other reagents listed in the intestinal organoid culture medium recipe in the human intestinal organoid culture protocol. (A) Human intestinal organoids were stained using a Rat Anti-Human/Mouse/Rat Vimentin Monoclonal Antibody (R&D Systems, Catalog # MAB2105; green) and a Goat Anti-Human/Mouse Desmin Antigen Affinity-purified Polyclonal Antibody (R&D Systems, Catalog # AF3844; red) to visualize myofibroblast cells and counterstained with DAPI (Tocris Bioscience, Catalog # 5748; blue). (B) Human intestinal organoids were stained using a Goat Anti-Human/Mouse E-Cadherin Antigen Affinity-purified Polyclonal Antibody (R&D Systems, Catalog # AF748; green) and a Mouse Anti-Human MUC2 Monoclonal Antibody (Novus Biologicals, Catalog # NBP2-44431; red) and counterstained with DAPI (Tocris Bioscience, Catalog # 5748; blue).

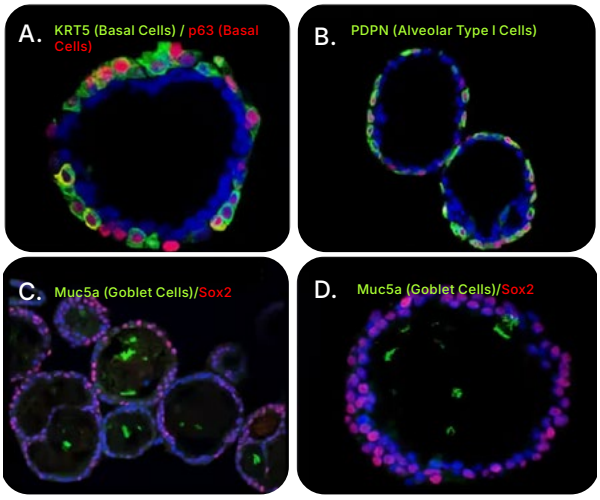

Figure 4. Culture and Characterization of Adult Stem Cell-derived Human Lung Organoids. Adult stem cells isolated from human lung biopsy tissue were embedded in Cultrex UltiMatrix RGF Basement Membrane Extract (R&D Systems, Catalog # BME001-05) and cultured for 20-60 days in lung organoid expansion medium, which includes Recombinant Human R-Spondin 1 (R&D Systems, Catalog # 4645-RS), Recombinant Human Noggin (R&D Systems, Catalog # 6057-NG), Recombinant Human FGF-7 (R&D Systems, Catalog # 251-KG), and Recombinant Human FGF-10 (R&D Systems, Catalog # 345-FG), along with the other reagents listed in the lung organoid expansion medium recipe in the human lung organoid culture protocol. Lung organoids were able to differentiate and exhibit markers for various cell types of the lung. Lung organoids were stained with (A) a rabbit anti-human Cytokeratin 5 (KRT5) monoclonal antibody (green) and a Goat Anti-Human p63/TP73L Polyclonal Antibody (R&D Systems, Catalog # AF1916; red) to visualize basal cells, (B) a Hamster Anti-Mouse Podoplanin (PDPN) Monoclonal Antibody (Novus Biologicals, Catalog # NB600-1015; green) to visualize alveolar type I cells and a Goat Anti-Human p63/TP73L Polyclonal Antibody (R&D Systems, Catalog # AF1916; red) to visualize basal cells, and (C, D) a Mouse Anti-MUC5AC Monoclonal Antibody (Novus Biologicals, Catalog # NBP2-15196; green) to visualize Goblet cells and a Mouse Anti-Human/Mouse/Rat SOX2 Monoclonal Antibody (R&D Systems, Catalog # MAB2018; red). All samples were counterstained with DAPI (Tocris Bioscience, Catalog # 5748; blue).

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Animal-Free Preclinical Proteins

In addition to our research-grade proteins, Bio-Techne also offers Animal-free preclinical proteins and GMP-grade proteins. Our Animal-free preclinical proteins are made in the same facility using the same processes as our GMP-grade proteins. Since the proteins are the same, they make excellent reagents for research and process development and allow for a smooth transition from preclinical work to clinical manufacturing. Animal-free proteins are purified and manufactured in dedicated, controlled access, animal-free laboratories using equipment and media that are certified as animal-free. We have a strict definition of animal-free and at no point in the production process are these proteins exposed to any animal components or byproducts. The catalog numbers for our Animal-free preclinical proteins are listed in the product table alongside the corresponding GMP-grade proteins.

GMP-Grade Proteins for Regenerative Medicine and Cell Therapies

GMP-grade proteins are manufactured under guidelines that allow for their use as ancillary materials in cell therapy manufacturing processes. They undergo extensive quality control testing and come with comprehensive documentation and full transparency and traceability of source and manufacturing system. This allows cell therapy manufacturers to be confident that they are using a consistent, safe, and traceable supply of reagents.

Documentation

GMP products manufactured, tested, and released under an ISO 9001:2015 and ISO 13485:2016 certified quality management system, lot-to-lot consistency, materials traceability, employee training and documentation, equipment maintenance and monitoring records, Drug Master Files, and more.

Satisfied Clients

Clients include more than 300 pharmaceutical and biotech companies and we regularly welcome audits of our facilities.

Quality Control Testing

Mass spectrometry, HPLC, SDS-PAGE, endotoxin, presence of host cell content, adventitious agents, and more.

Regulatory Guidelines Followed

GMP proteins are manufactured in compliance of the applicable sections of the World Health Organization:

1. USP Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products.
2. Ph. Eur. General Chapter 5.2.12, Raw Materials of Biological Origin for the Production of Cell-base and Gene Therapy Medicinal Products.

Animal-Free Preclinical and GMP-Grade Proteins

TABLE // 02

Protein (Human; Source: *E. coli*)	Animal-Free GMP-Grade Protein (Catalog #)	Animal-Free Preclinical Protein (Catalog #)
Betacellulin	BT-BTC-GMP*	BT-BTC-AFL
BMP-4	314E-GMP	AFL314E
EGF	236-GMP*	AFL236
FGF basic (145 aa)	BT-FGFB-GMP	BT-FGFB-AFL
Flt-3 Ligand/FLT3L	BT-FT3L-GMP	BT-FT3L-AFL
GM-CSF	215-GMP	AFL215
IFN-γ	285-GMP*	AFL285
IGF-I	291-GMP*	AFL291
LR3 IGF-I	8335D-GMP	
IL-1β/IL-1F2	201-GMP	AFL201
IL-2	BT-002-GMP*	BT-002-AFL
IL-3	203-GMP	AFL203
IL-4	BT-004-GMP*	BT-004-AFL
IL-6	206-GMP*	AFL206
IL-7	BT-007-GMP*	BT-007-AFL
IL-10	1064-GMP	AFL1064
IL-15	BT-015-GMP*	BT-015-AFL
IL-21	8879-GMP*	AFL8879
M-CSF	216-GMP	AFL216
PDGF-AA	221-GMP	AFL221
PDGF-BB	220-GMP	AFL220
SCF/c-kit Ligand	BT-SCF-GMP*	BT-SCF-AFL
Shh N-terminus	1314-GMP	
Shh (C2411) N-terminus	1845-GMP	AFL1845
Thrombopoietin	288E-GMP*	
TNF-α	210-GMP	AFL210
VEGF	BT-VEGF-GMP*	BT-VEGF-AFL

* DMF have been filed for these GMP Proteins. GMP-grade IL-2, IL-7, and IL-15 are available through our joint venture partnership with ScaleReady // scaleready.com

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Additional GMP-Grade Proteins Available from R&D Systems

There are some instances when a protein requires production in a eukaryotic system to maintain activity. This may be due to protein folding or post-translational modifications that can only be accomplished by making the protein in a eukaryotic cell line. These GMP-grade proteins, which are not considered to be animal-free, are listed in the table below. Whenever a GMP-grade protein cannot be produced in an animal-free process, it is always clearly indicated on our website.

TABLE // 03

Protein (Human)	Source	Catalog #
Activin A	CHO	338-GMP*
BMP-2	CHO	355-GMP
GDF-8/Myostatin	NS0	788-GMP
GDNF	NS0	212-GMP
HGF	NS0	294-GMP
KGF/FGF-7	*E.coli*	251-GMP
Noggin	NS0	3344-GMP
TGF-β1	CHO	240-GMP
Wnt-3a	CHO	5036-GMP

R&D Systems GMP-grade proteins are intended for use as ancillary materials in GMP manufacturing of investigational or marketed clinical products, such as cell therapy, gene therapy, tissue-engineered products, combination products, or other Advanced Therapy Medicinal Products. They are not therapeutic products or excipient and are not suitable for direct administration to humans.

* DMF have been filed for these GMP Proteins.

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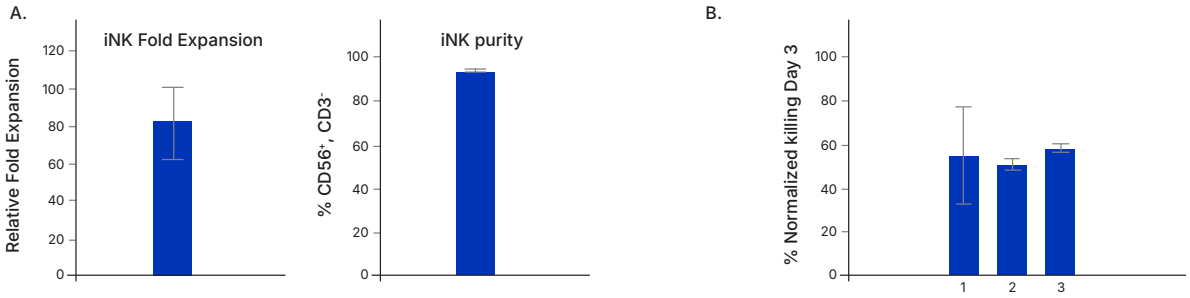

Figure 5. Assessment of the Expansion, Purity, and Killing Capacity of Human iPSC-derived Natural Killer Cells Differentiated with R&D Systems GMP-grade Cytokines. Based on a protocol by Zhu, H. and D. Kaufman (2019) Methods Mol. Biol., human induced pluripotent stem cells (iPSCs) were grown in the presence of R&D Systems GMP-grade Recombinant Human $VEGF_{165}$ (Catalog # BT-VEGF-GMP), GMP-grade Recombinant Human SCF (Catalog # 255B-GMP), GMP-grade Recombinant Human BMP-4 (Catalog # 314E-GMP), and GMP Y-27632 dihydrochloride (Tocris Bioscience, Catalog # TB1254-GMP) and then differentiated in the presence of GMP-grade Recombinant Human IL-3 (Catalog # 203-GMP), GMP-grade Recombinant Human IL-7 (Catalog # BT-007-GMP), GMP-grade Recombinant Human IL-15 (Catalog # BT-015-GMP), GMP-grade Recombinant Human SCF (Catalog # 255B-GMP), and GMP-grade Recombinant Human Flt-3 Ligand (Catalog # 308E-GMP). (A) Thirty days after initiating cell differentiation from iPSCs, the average fold expansion and purity of iNK cells were respectively determined by hemacytometer and flow cytometry using an Alexa Fluor® 405-conjugated Mouse Anti-Human CD3 epsilon Monoclonal Antibody (R&D Systems, Catalog # FAB100V) and an Alexa Fluor® 647-conjugated Rabbit Anti-Human NCAM-1/CD56 Monoclonal Antibody (R&D Systems, Catalog # FAB24086R). The experiment was performed in triplicate. (B) To assess iNK cell functionality, the cells were expanded for three days and a killing assay was performed by adding the iNK cells to fluorescently-labeled K-562 target cells at a 2:1 effector:target ratio. Loss of fluorescence, indicative of target cell killing, was quantitatively measured after three more days using an Incucyte® Live Cell Analysis System. The killing assay was performed in triplicate. The x-axis shows biological replicates (N=3) and the error bars show technical replicates (N=3).

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North America TEL 800 343 7475
Europe // Middle East // Africa TEL +44 (0)1235 529449
China info.cn@bio-techne.com, TEL 400.821.3475

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