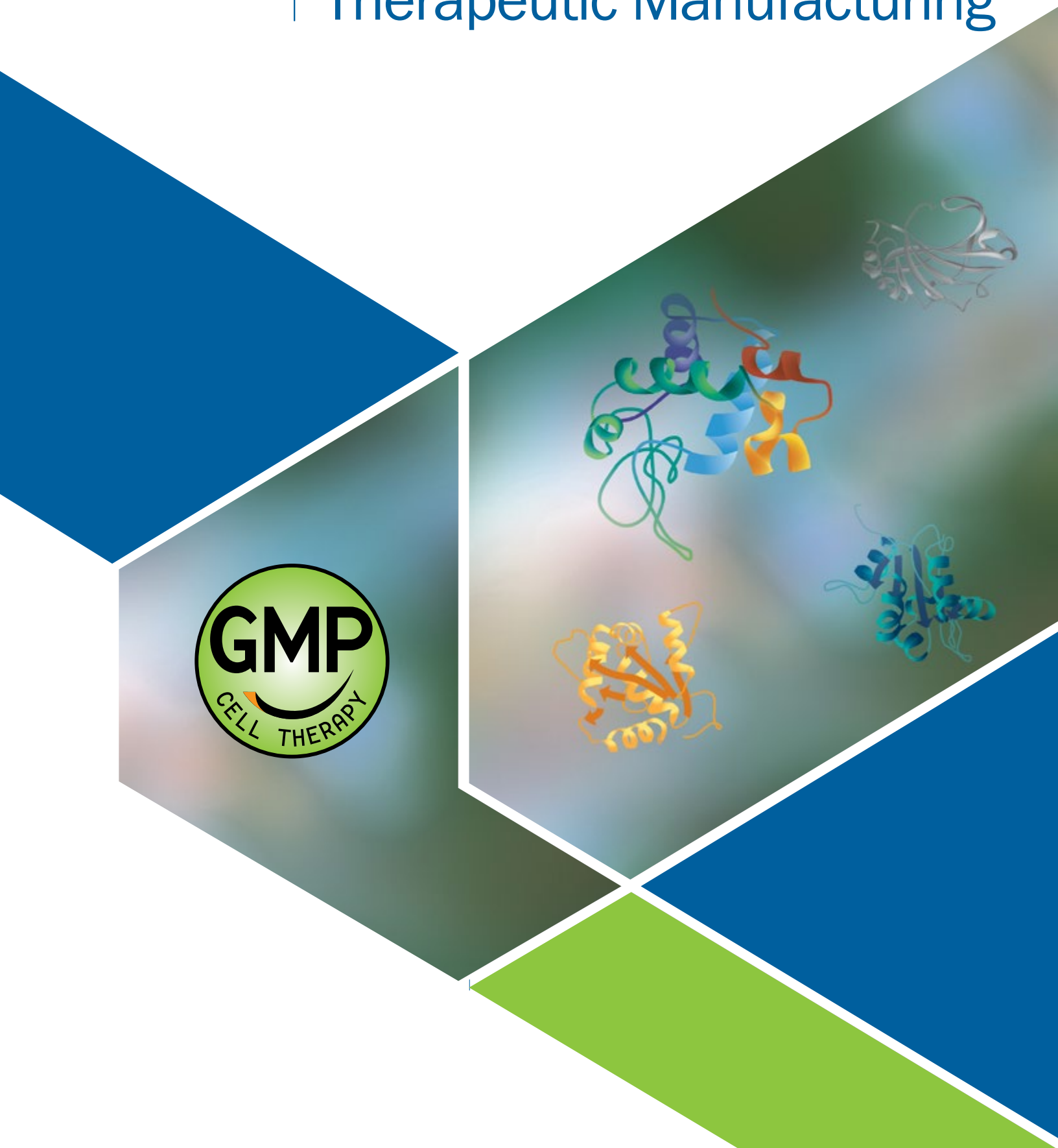
R&D SYSTEMS
a bio-techne brand

GMP Proteins for Therapeutic Manufacturing



R&D Systems® GMP* Proteins for Therapeutic Manufacturing

Immune cell therapies, stem cell therapies, and regenerative medicine, often grouped into the category of advanced therapy medicinal products (ATMPs), offer some of the most revolutionary and exciting new approaches for treating human disease. Because they utilize living cells or tissues as the therapeutic, the manufacturing process is vastly more complex than those of more traditional treatment methods. The use of high-quality media supplements such as growth factors and cytokines is paramount to ensuring safety, efficacy, and minimizing batch-to-batch variability.

R&D Systems has a rich history of producing the most widely used proteins in the world. Our expertise in protein development and manufacturing, combined with stringent quality control and experienced regulatory support, allows us to offer industry-leading GMP proteins for cell therapy manufacturing.

Ensuring Consistency

Regulatory Certifications and Support:

GMP products manufactured, tested, and released under an ISO 9001:2015 and ISO 13485:2016 certified quality management system

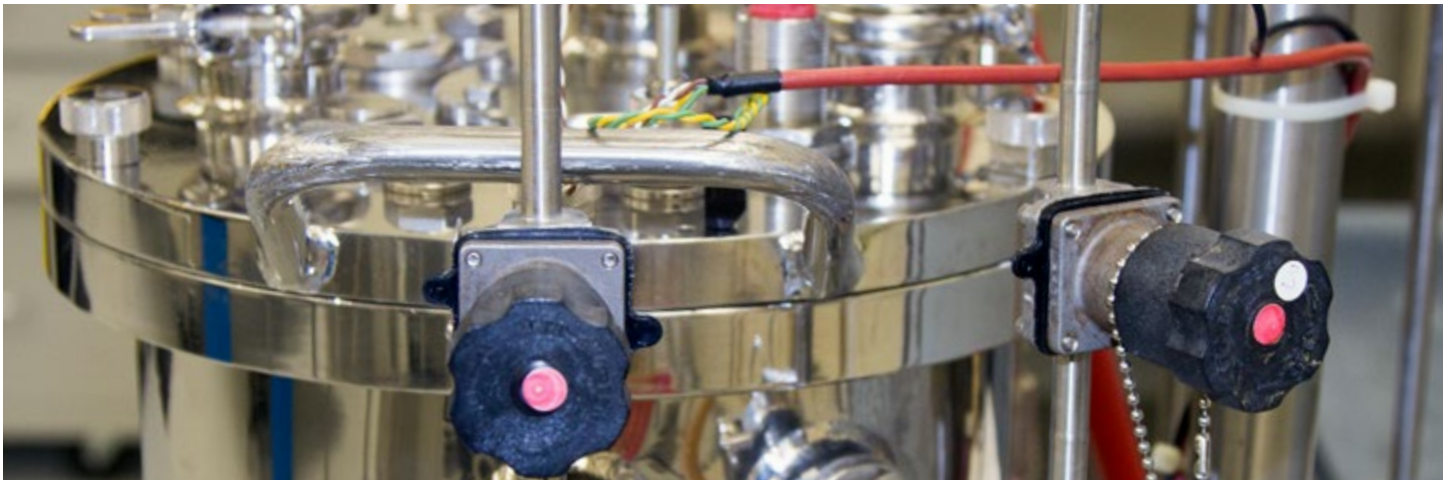
- A full Quality Assurance (QA) review of all batch and bottling records is done before any material is shipped
- Individual specification sheets with all testing results are reviewed by both our Quality Control (QC) and QA departments.
- Documented processes and QA control of documentation and process changes
- Personnel training program
- Raw material testing, tracing, and vendor qualification/monitoring
- Fully validated equipment, processes, and test methods
- Equipment calibration schedules using a computerized calibration program
- Facility maintenance, safety programs, and pest control
- Material review board for variances
- Monitoring of stability over product shelf-life
- Product change notifications

*R&D Systems GMP 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 excipients, and are not suitable for direct administration to humans.

Ensuring Safety and Efficacy

Guidelines and Quality Control:

- USP Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Product
- Ph. Eur. General Chapter 5.2.12, Raw Materials of Biological Origin for the Production of Cell-based and Gene Therapy Medicinal Products
- Lot-specific Certificate of Analysis
- Certificates of Origin
- Animal-free capabilities
- Defined endotoxin specifications
- N-terminal sequencing for first 10 amino acids
- Defined purity specifications
- Mycoplasma testing
- Host cell protein testing
- Bioburden/Sterility testing in accordance to USP
- Validated activity testing
- Formal stability testing program
- Viral testing of cell banks available



Combining Purity, Bioactivity, and Consistency

As growth factors and cytokines are produced in biological systems, they are inherently susceptible to variability. To maximize efficacy and safety, a supplier should have a quality management system in place to ensure lot-to-lot consistency and highly-purified formulations. A highly potent cytokine or growth factor can also lower the amount needed for use and in turn lower costs.

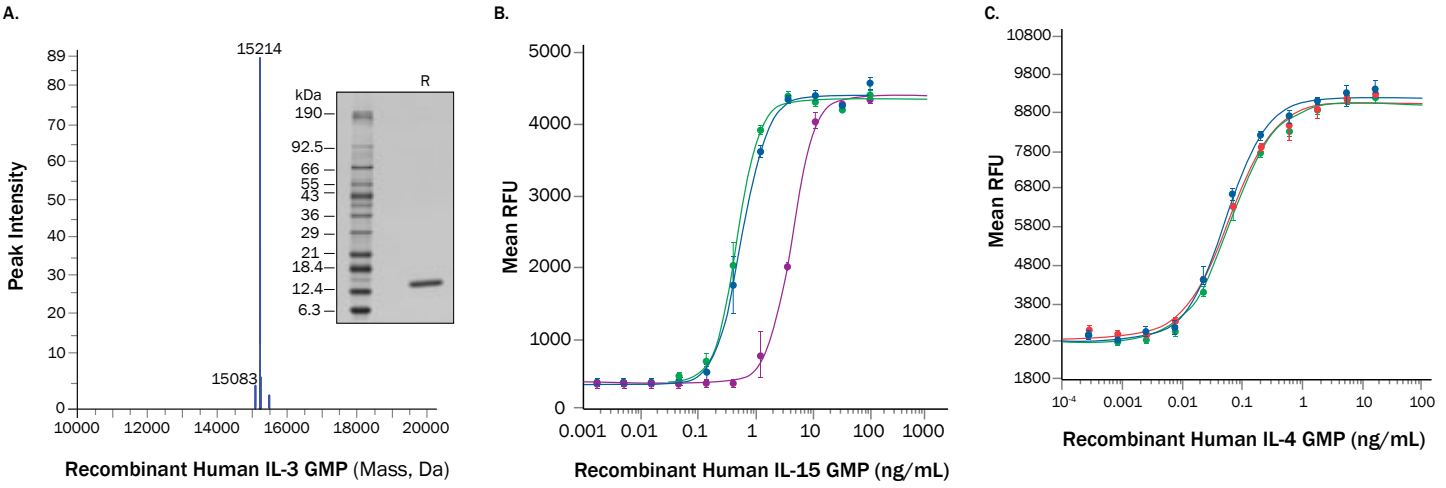
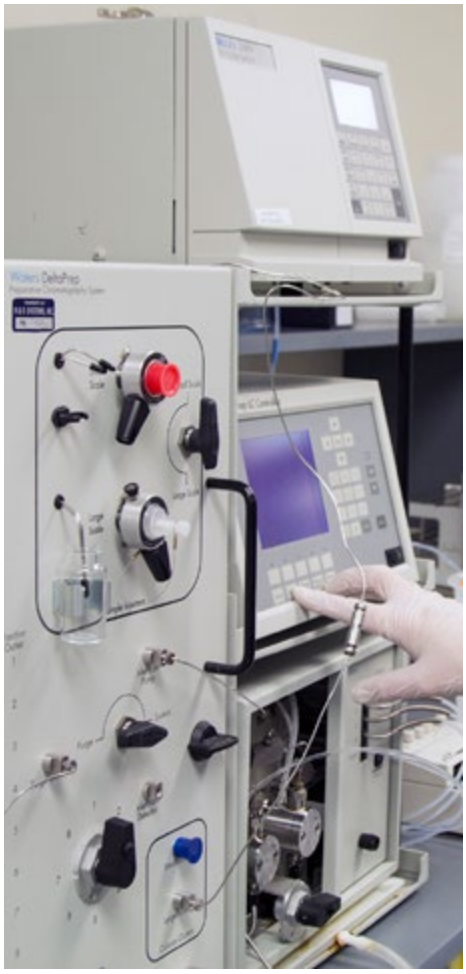


Figure 1. Characterization of Purity, Bioactive Potency and Lot-to-Lot Consistency. A. Electrospray Ionization mass spectrometry (ESI-MS) analysis of GMP Recombinant Human IL-3 (Catalog # 203-GMP). The labeled peaks at 15214 Da and 15083 Da correspond to the calculated molecular mass with the N-terminal Met, and without the N-terminal Met, respectively. Greater than 97% purity is also seen using SDS-PAGE under reducing (R) conditions (inset). **B.** Two lots of GMP Recombinant Human IL-15 (Catalog # 247-GMP; green and blue) exhibit 10-fold greater activity in a proliferation assay using MO7e human megakaryocytic leukemic cells than the equivalent cytokine from another supplier (magenta). **C.** GMP Recombinant Human IL-4 (Catalog # 204-GMP) stimulates the proliferation of TF-1 human erythroleukemic cells. Overlapping curves highlight reproducible bioactivity over three different lots. The specific activity of recombinant human IL-4 is ~2.9 x 10^4 IU/µg, calibrated against human IL-4 WHO International Standard (NIBSC code: 88/656).

Unparalleled Combination of Protein and Regulatory Experience



- Developing and manufacturing proteins since 1985
- Clients from more than 35 countries around the world
- R&D Systems® GMP products are used in the manufacture of numerous clinical trial candidates
- Regular client audits of our facilities
- Confidentiality assured
- More than 100 protein scientists dedicated to development and manufacturing
- More than 90 employees in quality and regulatory roles

Other On-Site Capabilities for Enhanced QC Testing: Meeting Additional Customer Needs

- **Gel permeation chromatography/size exclusion chromatography (GPC/SEC):**
  Aggregation assessment
- **Reverse phase HPLC:**
  Purity assessment can reveal truncations, mixed disulfide patterns, and more
- **Light scattering analysis (SLS, DLS):**
  Aggregation, oligomer analysis, and molecular weight determination when used in tandem with analytical sizing aggregation, oligomer analysis, and molecular weight determination
- **Advanced HPLC testing:**
  Homogeneity
- **Surface plasmon resonance:**
  Binding kinetics
- **Differential scanning fluorimetry (DSF):**
  Protein stability and protein-ligand interactions

Animal-Free and Animal Component-Free Manufacturing

Animal-free proteins are particularly important to researchers concerned with experimental variables caused by trace animal components or mammalian pathogens. When possible, R&D Systems® GMP proteins are made in an entirely animal-free process.

Animal-Free

Our dedicated controlled-access animal-free laboratories ensure that at no point in production are these products exposed to potential contamination by animal components or animal byproducts. Every stage of manufacturing is conducted in compliance with R&D Systems stringent standard operating procedures. Production and purification procedures use equipment and media that are confirmed as animal-free.

Animal Component-Free Process (ACFP)

There are some proteins that exhibit greater activity and consistency when they are produced in eukaryotic systems. This may be due to protein folding or post-translational modifications. However for some GMP proteins, we offer animal component-free process (ACFP) manufacturing using an animal free-certified Sf 9 insect cell line.

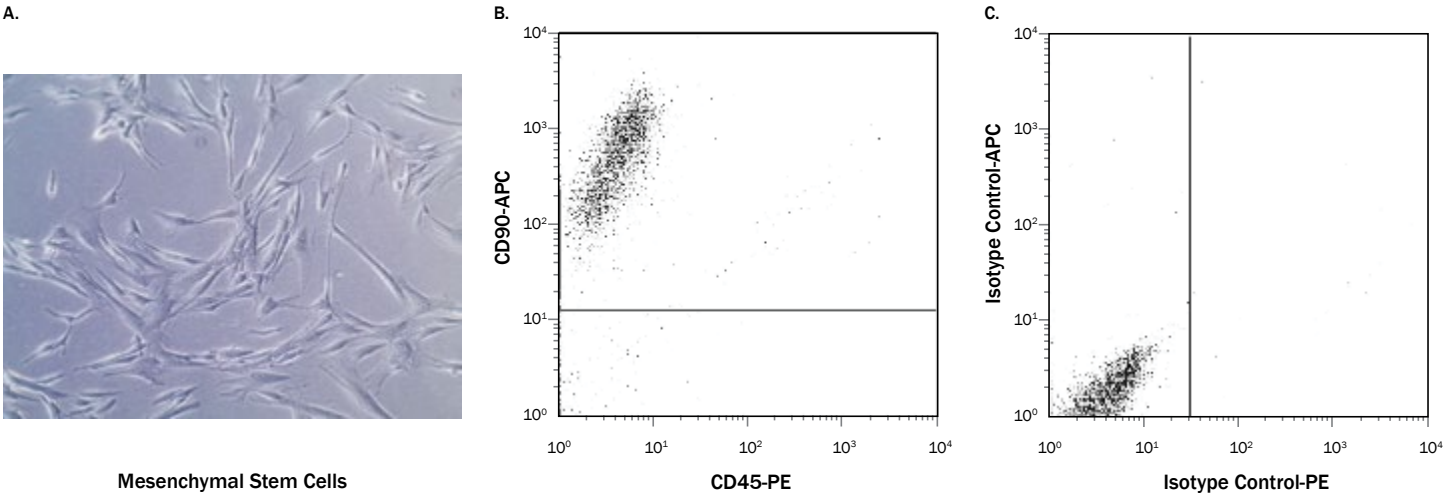
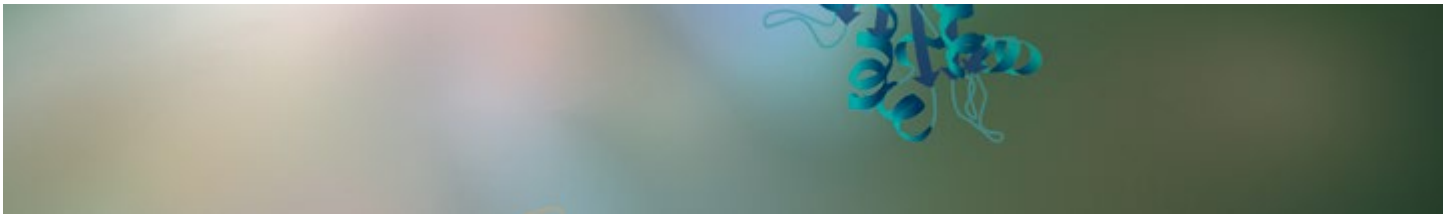


Figure 3. MSC expansion using GMP Recombinant Fibronectin. A. Mesenchymal stem cells (MSCs) cultured on GMP/ACFP Recombinant Human Fibronectin (4305B-GMP) and expanded in StemXVivo® Xeno-Free Human MSC Expansion Media maintain a characteristic fibroblast-like morphology and remain in an undifferentiated state over 5 passages. **B.** The positive MSC marker CD90 was detected with APC-conjugated Mouse Anti Human CD90/Thy1 Monoclonal Antibody (Clone Thy-1A1; Catalog # FAB2067A). Expression of the negative MSC marker was detected with PE-conjugated Mouse Anti-Human Monoclonal Antibody (Clone 2D1; Catalog # FAB1430P). **C.** Quadrants were set based on isotype controls.



GMP Proteins Available from R&D Systems

GMP Protein	Animal Free	ACFP	GMP Protein	Animal Free	ACFP	GMP Protein	Animal Free	ACFP
Activin A			IFN-γ	✓		M-CSF	✓	
BDNF			IGF-I	✓		Noggin		
BMP-2			IL-1β	✓		NRG1-b1		
BMP-4			IL-2	✓		NT-3		
BMP-7			IL-3	✓		NT-4		
EGF	✓		IL-4	✓		PDGF-BB	✓	
Dkk-1			IL-6	✓		Periostin		
FGF basic	✓		IL-7	✓		SCF/c-kit Ligand	✓	
Fibronectin		✓	IL-11		✓	Sonic Hedgehog	✓	
Flt-3 Ligand		✓	IL-12			TGF-β1		✓
GDF-8/Myostatin			IL-15	✓		TGF-β3		✓
GDF-11			IL-17E	✓		TNF-α	✓	
GDNF			KGF/FGF-7			VEGF		✓
GM-CSF	✓		LR3 IGF-I	✓		Wnt-3a		
HGF								

Custom Manufacturing

At times raw materials needed for therapeutic manufacturing are available for research use only (RUO). We can help you navigate regulatory hurdles by manufacturing RUO proteins using GMP guidelines. Custom development teams include dedicated project managers, regulatory experts, and world class protein scientists to ensure that the materials meet your specifications and facilitate transition from pre-clinical to clinical applications.

Learn more | rndsystems.com/gmp

Partnering with you to meet your regulatory requirements

As the demand for biopharmaceuticals and the promise of cellular therapies grow, so does the need for high-quality growth factors and cytokines used for cell culture. Our experienced Quality and Manufacturing teams will partner with you to ensure we meet all of the requirements necessary to instill confidence as your reagent supplier.

Learn more | rndsystems.com/gmp

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