REPLIGEN

Breaking Productivity Barriers in Upstream Bioprocessing

XCell® ATF SYSTEM

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Better Economics, Productivity, and Sustainability

Upstream Process Intensification

The increasing global demand for advanced biotherapeutics is creating an imperative for disruptive technologies that enhance manufacturing output. Traditional fed-batch processes are unable to meet the need due to their limited productivity and excessive resource requirements that result in higher costs.

Upstream process intensification can reduce manufacturing costs, boost productivity, and reduce the waste and energy consumption required for production.

Adopting perfusion using cell retention devices is the ideal method for upstream process intensification. It allows for continuous bioprocessing with longer run times than traditional batch or fed-batch operations, resulting in higher product yields and reduced cost of goods (COGS). Perfusion cell culture offers the significant economic, productivity, and sustainability benefits that manufacturers need to meet the global demand for advanced biotherapeutics.

ECONOMIC BENEFITS

- Lower cost of goods
- Reduce capital expenses
- Distribute manufacturing
- Reach the market faster

PRODUCTIVITY BENEFITS

- Reach 10X higher viable cell density
- Gain 20X increased yield
- Scale linearly
- Achieve continuous bioprocessing

SUSTAINABILITY BENEFITS

- Reduce energy use
- Reduce waste
- Reduce bioreactor size
- Reduce facillity footprint

Longer run times and higher viable cell density

The Key Advantage of Alternating Tangential Flow

The XCell ATF System is an advanced cell retention device and controller that enables continuous bioprocessing through perfusion cell culture. At the heart of the XCell ATF device is Alternating Tangential Flow (ATF) that works as follows:

(1) The core of the ATF device is a hollow fiber filter module that allows selective passage of media components and product while retaining the cells within the bioreactor.

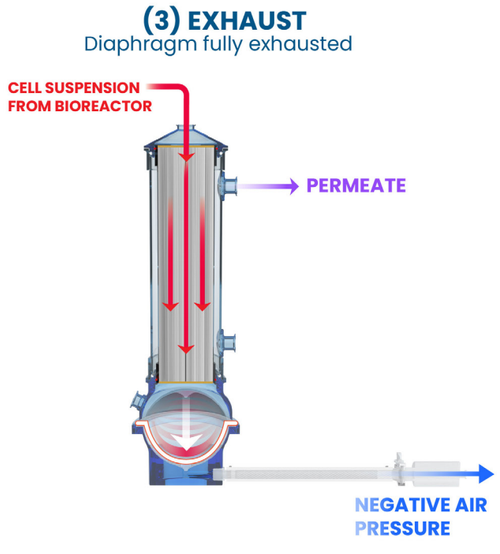
(2) A specialized diaphragm pump cycles the flow of cell suspension between the bioreactor and the cell retention device.

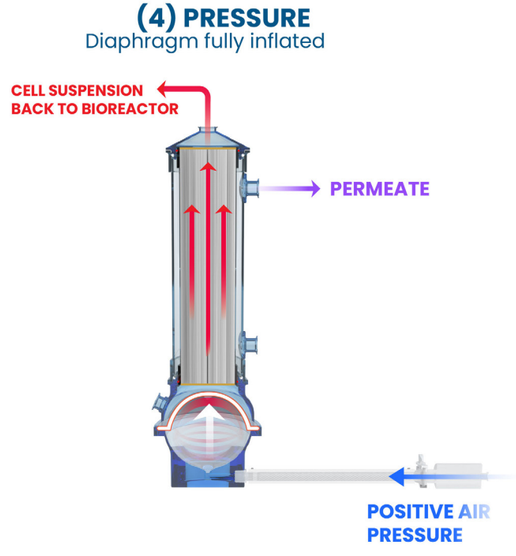
(3) In the exhaust mode, spent media components, cellular debris, and product in suspension are drawn from the bioreactor into the cell retention device.

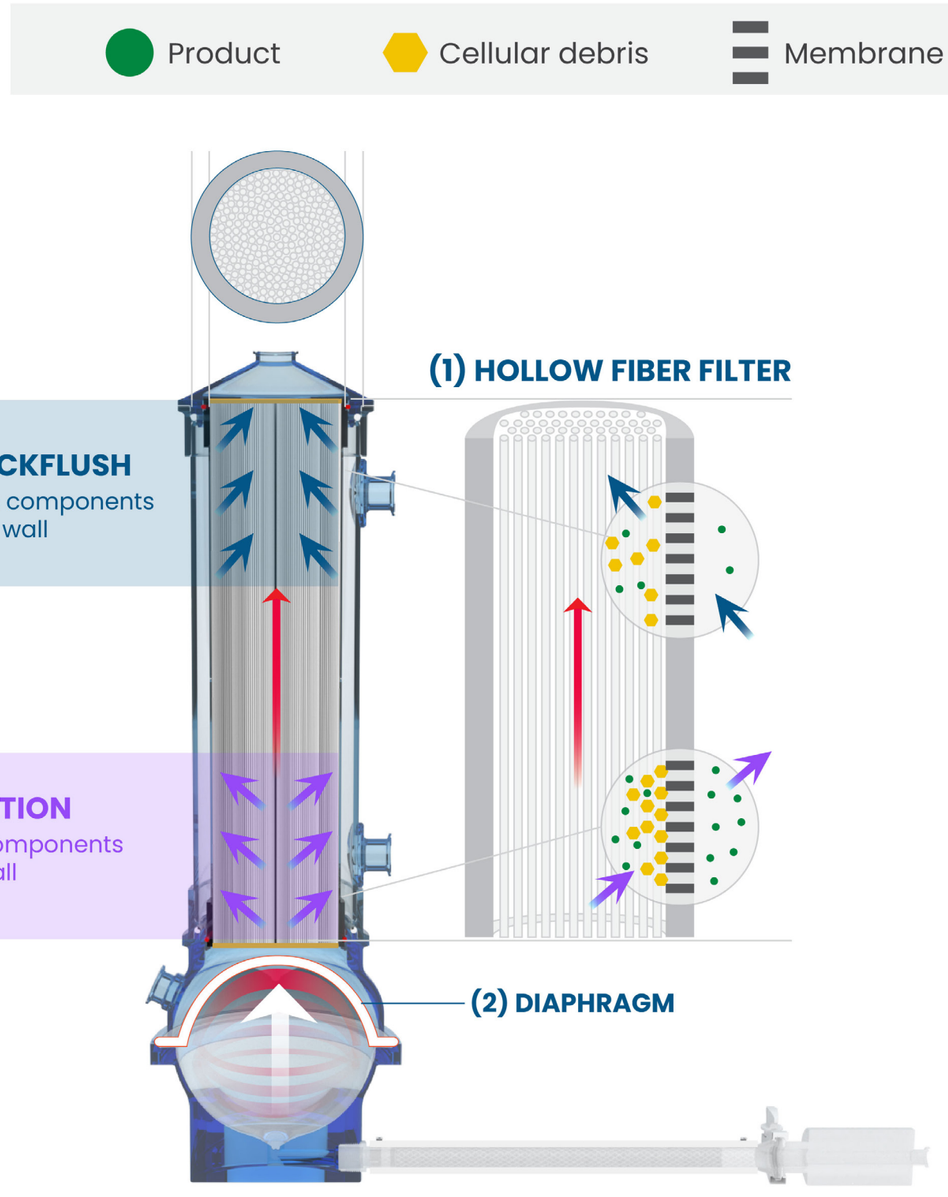
(4) Then in the reverse pressure mode, the flow direction is switched, and the cell suspension is returned back to the bioreactor.

(5) During this upward and downard action, the ATF generates backflush action that dislodges any foulants accumulated on the filter surface, cleaning the filter. This alternating bidirectional flow of the ATF technology reduces filter fouling and clogging that would otherwise limit run duration and reduce cell viability.

The extended run time and higher viable cell density ensures increased bioreactor productivity and improved unit economics in bioprocessing.

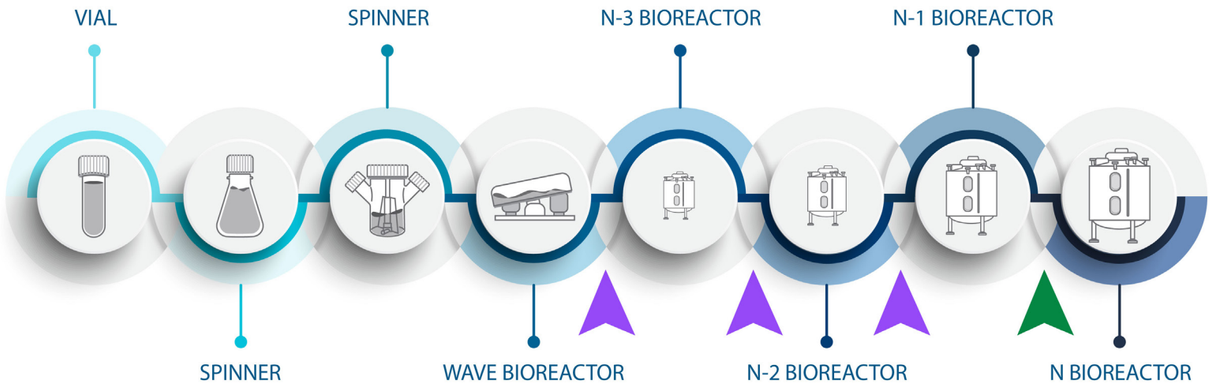






XCell ATF System
Applications in Process Intensification

Intensified Seed Train Workflow



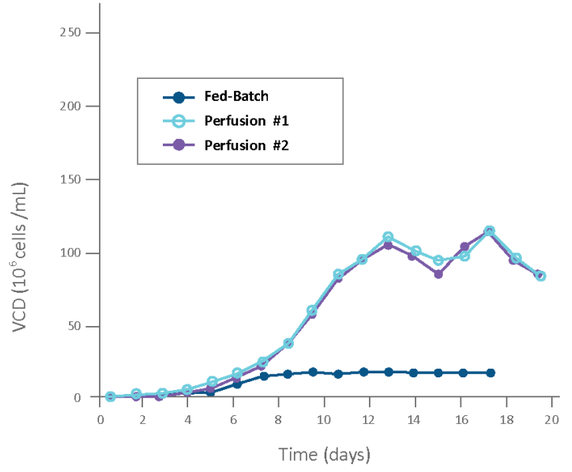


Figure 1: Long-term perfusion with the XCell ATF System achieved 100-130 million viable cell density (VCD) compared to 13 million for Fed-Batch.

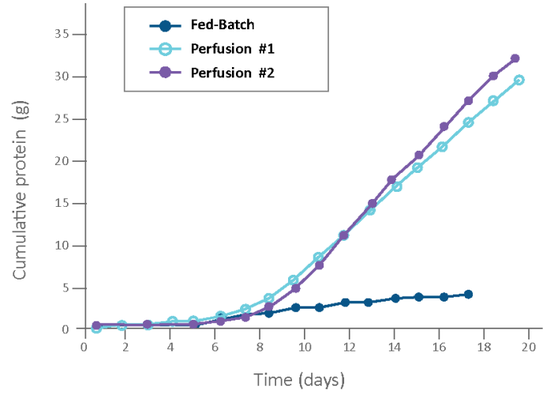


Figure 2: Higher VCD of perfusion cultures translated to an increase in total product yield. The perfusion process yielded approximately 30-35 g, while the Fed-Batch process achieved only 3 g in approximately 15 days.

Seed train intensification with XCell ATF system

Generating a high-density inoculum to effectively seed production bioreactors is a critical initial step in successful bioprocessing. Traditional seed trains are often challenged by limited nutrient availability, waste accumulation, and the physical constraints of scaling.

The XCell ATF System overcomes these limitations by integrating into the N-1 or earlier bioreactors, elevating cell densities 5-10x over conventional methods. Purple arrows in the seed train diagram indicate key stages where intensification can be implemented.

Through concentrated fed-batch or perfusion mode, the system can readily attain densities over 100 million cells/mL in the seed reactor providing a superior inoculum for the production scale and saving both costs and space.

Long-Term Perfusion in N-Stage Production

Long-term perfusion maintains a steady viable cell density (Figure 1) at the N-stage production (green arrow in the workflow diagram) to significantly boost product yield compared to traditional fed-batch culture (Figure 2). The XCell ATF System supports this through robust cell retention, controlled nutrient addition, and continuous waste removal, sustaining prolific cell growth for days or weeks at densities exceeding 100 million cells/mL, enabling truly continuous bioprocessing.

Benefits of Long Term Perfusion:

Increased productivity: Achieves 20X volumetric productivity compared to fed-batch operation.

Efficient process: Higher productivity leads to fewer runs and reduced footprint.

Reduced risk and cost: Run continuous perfusion for two weeks to 60+ days, minimizing downtime and cost.

With over 500+ global adoptions across diverse therapeutic modalities including in the production of monoclonal antibodies, vaccines, and recombinant proteins, the XCell ATF System has significantly expanded capacity, lowered costs of goods, and increased productivity wherever there is a need for more cells across these diverse applications.

XCell ATF Devices
Linearly Scalable Cell Retention

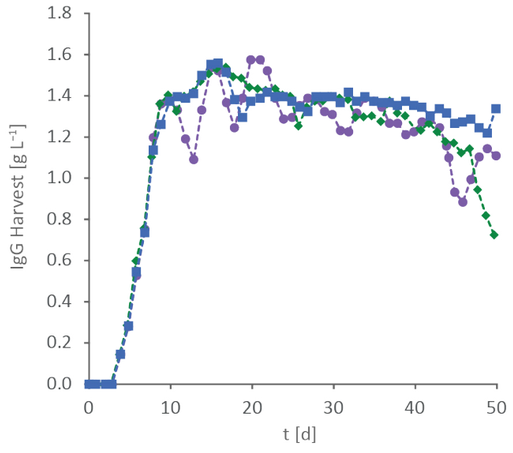


Figure 3: Scientists at Zurich University of Applied Sciences published an industry-leading 50-day perfusion process developed at 2L and scaled to 50L using an XCell ATF 2 Device and an XCell ATF 6 Device respectively that achieved consistent viable cell densities of over 100 million cells/mL and harvested more than 1 g/L/day of antibody (IgG harvest) using a CHO cell line expressing trastuzumab. The consistency and linear scalability of XCell ATF Technology resulted in comparable harvest yields between the 2L and 50L processes as well as between the two 50L processes.

Adapted from Ott, V, et al. Processes. 2024, 12(4), 806, licensed under CC BY.

The XCell ATF Device is a cell retention system that enables perfusion cell culture by removing waste while keeping cells in the bioreactor, supporting high-density cultures from 0.5 to 5000 L across various scales. It is adaptable for N-stage or seed train applications, whether at process development, pilot, clinical, or commercial production scales.

Stainless Steel or Single-Use: Available in single-use versions for faster implementation (reducing time by over 80%) or stainless steel for long-term durability.

Linear Scalability: Uniform linear height across the range of devices* ensures consistent flow rates and uniform conditions as volume increases (Figure 3).

Gentle, Low-Shear Operation: Diaphragm pumping action minimizes shear stress, preserving cell viability.

Automated Performance: Integrates seamlessly with the XCell Lab or XCell LS controllers for precise operation, advanced monitoring, and intuitive control.

Easy Integration: Industry-standard connectivity facilitates straightforward integration with bioreactors.

**Except ATF 4 Device, which is half-height.*

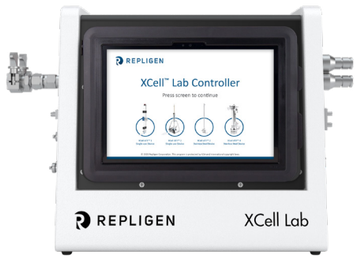
PILOT-SCALE DEVELOPMENT | PILOT-SCALE DEVELOPMENT | CLINICAL TO COMMERCIAL PRODUCTION

ATF 1 Device *Single Use*	**ATF 2 Device** *Single Use and Stainless Steel*	**ATF 4 Device** *Stainless Steel (Half-Height)*	**ATF 6 Device** *Single Use and Stainless Steel*	**ATF 10 Device** *Single Use and Stainless Steel*
0.5 – 2 L Culture Volume	**2 – 10 L** Culture Volume	**10 – 50 L** Culture Volume	**50 – 200 L** Culture Volume	**200 – 5000 L** Culture Volume
0.017 L Volume Exchanged	**0.1 L** Volume Exchanged	**0.4 L** Volume Exchanged	**1.3 L** Volume Exchanged	**6 L** Volume Exchanged
0.022 m2 Filter Surface Area	**0.13 m2** Filter Surface Area	**0.77 m2** Filter Surface Area	**2.5 m2** Filter Surface Area	**11 m2** Filter Surface Area

XCell Lab Controller | XCell LS Controller

XCell ATF Controllers
Precise, Reliable Operation from PD to Commercial Scale

The XCell Lab and XCell LS Controllers are part of the XCell ATF System of integrated devices, controllers, and software that deliver optimized upstream process intensification across process development to clinical and commercial scale bioprocessing. The XCell ATF controllers ensure consistent performance and precision by sharing a framework of critical components that include flow and permeate pressure sensors that provide real-time monitoring and control, and a simple and intuitive HMI for ease of operation.

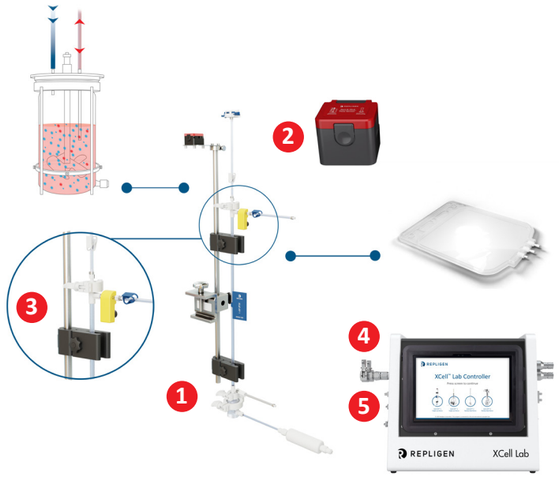


The XCell Lab Controller is a precision-engineered system designed specifically for upstream process development. It simplifies, accelerates, and scales intensification efforts by maintaining precise control of flow rates, even in high cell density environments, making it ideal for small-scale experiments that drive process optimization.

Scalable design: Optimized for small-scale intensification, the system prepares processes for seamless scale-up to larger production systems.

Flexible setup: Supports up to two devices per controller and integrates with bioreactors, offering high throughput and versatility.

Real-time monitoring: Integrated pressure sensors and permeate pressure data provide enhanced process insights and optimization.



The XCell LS Controller is built for large-scale clinical and commercial production. Designed for integration into regulated facilities, it offers advanced control features and handles the higher operational demands of large-scale manufacturing.

High-capacity operation: Supports larger bioreactor volumes (10-5000 L) for clinical and commercial production.

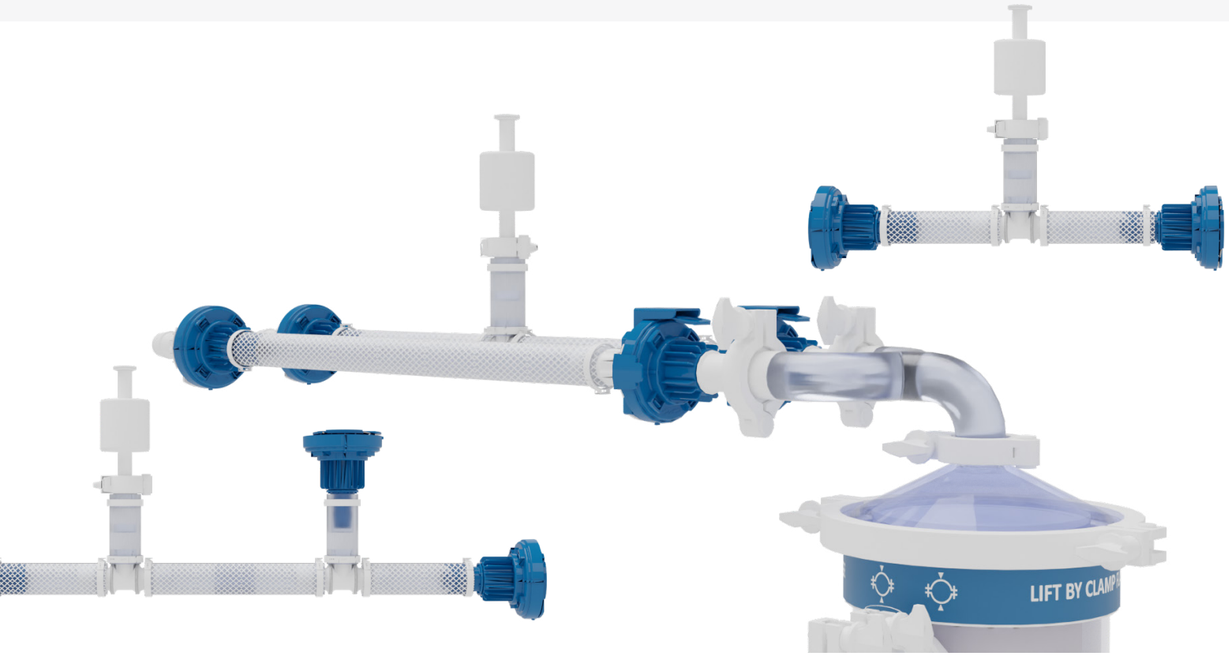
Commercial-grade features: Includes a robust touchscreen HMI or headless option, built for continuous, long-term operation.

Advanced integration: Offers remote control via DeltaV/DCS for integration with facility-wide automation and control systems.

Regulatory compliance: Fully 21 CFR Part 11 compliant, meeting the stringent standards required for GMP-regulated production.

	XCell Lab Controller	XCell LS Controller
1 XCell ATF Devices	Supports ATF 1, ATF 2, and ATF 4	Supports ATF 4, ATF 6, and ATF 10
2 Flow Sensor	Clamp-on flow-based feedback of ATF Rate for precision pumping	
3 Permeate Pressure Sensor	In line sensor monitors filter health throughout the process giving operators valuable information to change filter when it is needed	
4 HMI	User-friendly interface for process development	Industrial touchscreen with headless option available
5 Controller	Engineered for process development with flexibility for scale-up	Built for large-scale production, fully 21 CFR Part 11 compliant, with Delta V/DCS integration

Critical Components to Maximize Performance



A range of single-use connectors, tube sets, and fluid management components are available for seamless integration with XCell ATF Systems:

Sterile and ready-to-use: Pre-sterilized single-use components minimize setup time while reducing contamination risks.

Customizable flow paths and overmolded tubing connections: Secure overmolding optimizes fluid transfer by eliminating leak-prone fasteners and reducing the number of connections required. XCell ATF Devices are dead-ended using GE Readymate or AseptiQuik X connectors.

ProConnex® silicone tubing: Engineered to elevate your operations while shortening and de-risking your supply chain with in-house extrusion and assembly in a controlled cleanroom environment.

Cell culture supplements – Boost your productivity

Optimizing cell culture performance without using animal-derived products like serum presents challenges. Cell culture supplements are designed to enhance growth and productivity in chemically-defined media:

LONG® R3-IGF-I: a recombinant analog of human insulin-like growth factor-I boosts cell culture performance.

LONG® EGF: a recombinant analog of human epidermal growth factor used in regulatory-approved cell-based therapies.

Contact your technical sales specialist to learn more and request samples.

Support

Repligen provides complete implementation support and services to ensure success with the XCell ATF System. As a trusted partner, we offer guidance from initial theory to execution and long-term performance.

Our field applications team supports you with:

- **Technology fit assessments**
- **Evaluation planning**
- **Data analysis**
- **Scale-up guidance**

Scan the QR code to learn more about the complete workflow solutions offered by Repligen.

REPLIGEN

ABOUT US

Since 1981 Repligen has been inspiring advances in bioprocessing through the development of flexible, single-use manufacturing solutions. As an innovation leader and driver of disruptive technologies, we have an established track record of providing first-to-market solutions coupled with unparalleled expertise across workflows.