



iCELLis® Single-Use Fixed-Bed Bioreactor Systems



Productivity and reduced footprint for industrialization of animal cell culture processes in a fixed-bed bioreactor

The iCELLis bioreactor system is an automated, single-use, fixed-bed bioreactor, that provides excellent cell growth conditions for adherent cells.

The bioreactors system main features include:

- ▶ Cell culture process simplification, from vial to product
- ▶ Fully-integrated, single-use iCELLis 500+ bioreactor with disposable, pre-installed calibrated probes
- ▶ Unique waterfall system for optimal oxygenation and CO₂ stripping
- ▶ Compact high-cell-density, fixed-bed bioreactor providing a significant increase in volumetric productivity vs. traditional stirred tanks
- ▶ Predictable scalability from R&D to manufacturing
- ▶ Significant decrease in operational costs and capital investments vs. classical 2D flatware

Central to the iCELLis bioreactor technology is the use of a compact fixed-bed, filled with proprietary macrocarriers. This matrix is made of class VI⁽¹⁾ polyester microfibers and provides a surface area for cell growth up to 500 m². This is the surface-equivalent of 3,000 roller bottles (at 1700 cm² each) (Figure 1). The iCELLis bioreactor comes pre-packed with macrocarriers.

Because of the cell to cell interactions within the 3D environment of the fixed-bed, iCELLis bioreactors can be inoculated at very low density, 3,000 cells per cm² and even lower points. The seed train can as such be streamlined and simplified, leading to less manual operations and a reduction of associated costs.

Evenly-distributed media circulation is achieved by a built-in magnetic drive impeller, ensuring low shear stress and high cell viability (Figure 2). The cell culture medium flows through the fixed-bed from the bottom to the top. At the top, the medium falls as a thin film down the outer wall where it takes up O₂ to maintain high k_La in the bioreactor. This unique waterfall oxygenation, together with a gentle agitation and biomass immobilization, enables the compact iCELLis system to achieve and maintain high cell densities – equaling the productivity of much larger stirred-tank units.

Process simplification, from vial thawing to final product, is at the heart of the iCELLis platform. As cells are immobilized in the fixed-bed (Figure 3), and the iCELLis system operates in perfusion / recirculation mode, no centrifugation is needed to harvest the cells. This benefit further simplifies the downstream process.

Figure 1

The iCELLis 500+ bioreactor (500 m²) is equivalent to 3,000 roller bottles (1700 cm² each)

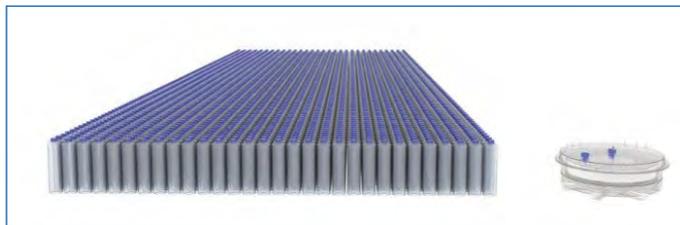


Figure 2

Media flow in the iCELLis 500+ bioreactor (60 - 70 L)

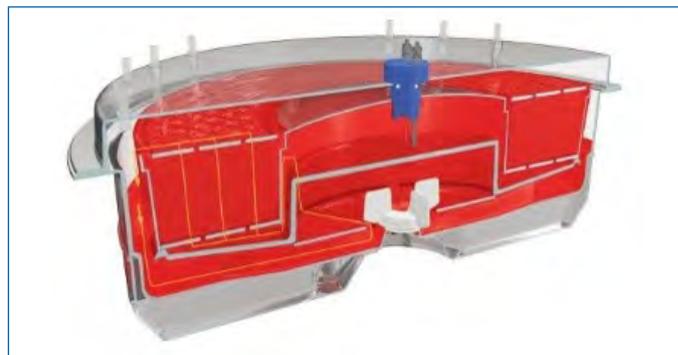
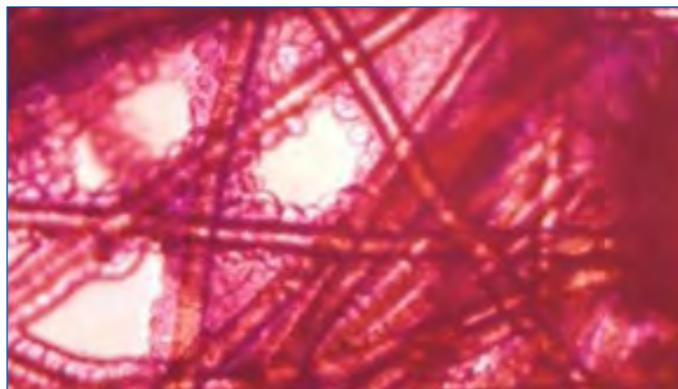


Figure 3

Microscopy view of MDCK cells immobilized on iCELLis system carriers



System Overview, Features and Benefits

The iCELLis bioreactor system is available in two formats (Table 1 and Figure 5):

- ▶ The iCELLis Nano system for feasibility studies and small-scale production (up to 4 m²)
- ▶ The iCELLis 500+ system for industrial scale manufacturing (up to 500 m²)

Table 1

Configurations of iCELLis bioreactors at small and manufacturing scale

Bioreactor	Bioreactor Diameter (mm)	Fixed-Bed Height (mm)	Fixed-Bed Volume (L)	Bioreactor Volume (L)	Surface Area (m ²)	
					Low Compaction	High Compaction
iCELLis Nano	110	20	0.04	1	0.53	0.8
iCELLis Nano	110	40	0.08	1	1.06	1.6
iCELLis Nano	110	100	0.2	1	2.65	4
iCELLis 500+/100	860	20	5	70	66	100
iCELLis 500+/200	860	40	10	70	133	200
iCELLis 500+/500	860	100	25	70	333	500

Both systems have an integrated mixing system for evenly-distributed media circulation and low shear stress, waterfall media oxygenation for high oxygen transfer and use the same macrocarriers specifically adapted to adherent cell cultures. The height of fixed-bed can be varied – from 2 cm to 10 cm – offering several configurations of small and large scale. The scaling from the small bioreactor to the large one is straightforward, and typically based on retention of compaction and fixed-bed height (Figure 4).

Figure 4
iCELLis bioreactor bench (Nano) and manufacturing (500+) scales and their modular size fixed-bed. LC = low compaction; HC = high compaction

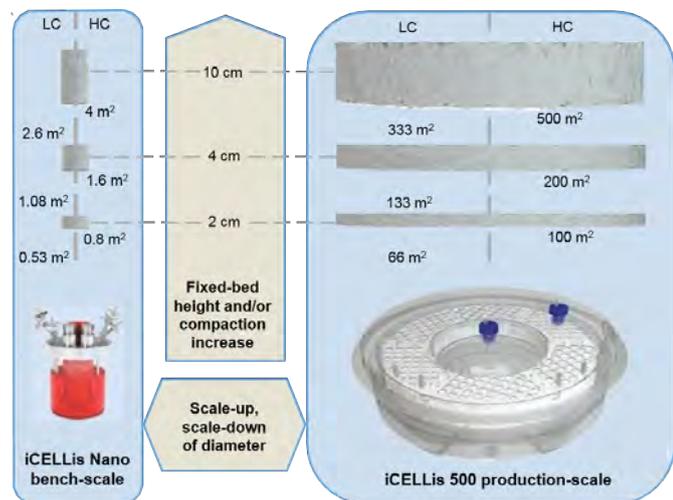


Figure 5
iCELLis Nano bioreactor (left) and iCELLis 500+ bioreactor (right)

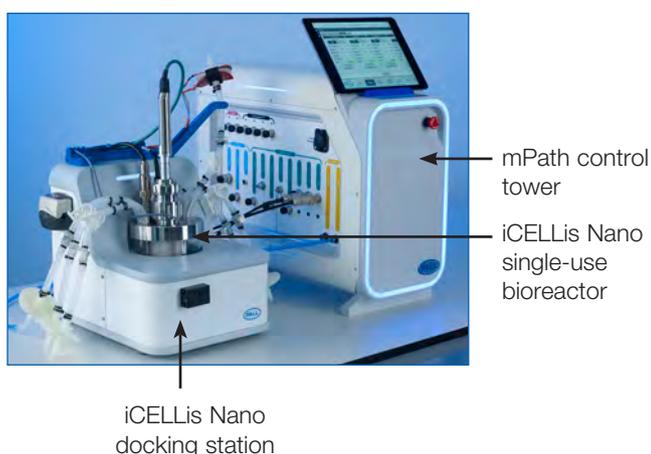


Table 2
iCELLis Nano bioreactor system

Feature	Benefit
Bioreactor with re-usable electrochemical sensors	Monitoring of DO, pH ⁽²⁾ , temperature and biomass possible
Hardware features docking station with perfusion integrated and mPath™ control tower and Link Server	Ergonomic and robust industrial design, using same controller as all other Pall benchtop bioreactor systems
IP54 rated hardware	Ready for use in cleanrooms
Advanced alarming	Color coded illumination allows identification of operating state from distance
Overflow control and internal bioreactor pressure measurement	Prevents spill
Temperature control and advanced heating through resistors	Maintain temperature and heat from 20 to 37 °C within 1 hour
Gas handling by six oxygen-rated thermal mass flow controllers (TMFCs)	Accurate gas mixing enabling accurate parameter control
Integrated cable management tools	Ease-of-use and ergonomics
mPath control tower designed for operation with Pall Link SCADA software package	See Pall publication USD 3220 for more information
	<ul style="list-style-type: none"> ▶ Allows access data anywhere on any networked device including laboratory workstations, desktop computers or remote devices such as laptops or mobile phones ▶ Intuitive visual displays for easy interaction with the bioreactor ▶ Advanced trending capability ▶ Database centric design supports naming, logging and exporting experiments for traceability and data analysis ▶ Management features for user-definable recipes including scheduling, version control and retirement for recipes no longer in use ▶ PLC based and designed for operation following 21 CFR Part 11/Annex 11 regulations

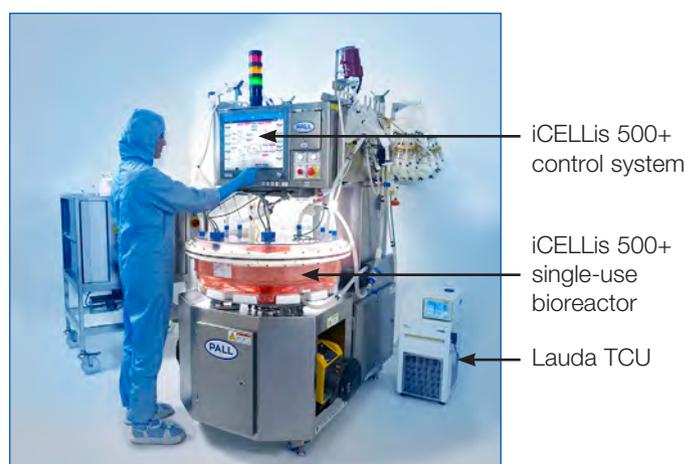


Table 3*iCELLis 500+ bioreactor system*

Single-use bioreactor made of material free of animal origin components and tested for Class VI USP⁽¹⁾ compliance. The bioreactor is set on a fully integrated system including docking station, perfusion pumps and controller. The iCELLis 500+ bioreactor has an integrated SCADA 21 CFR Part 11 compliant software that will control all process parameters – pH⁽²⁾, dissolved oxygen (DO), gas flow, temperature, stirring speed, biomass – throughout the duration of the culture.

Feature	Benefit
Single-use bioreactor made of USP Class VI ⁽¹⁾ materials free of animal origin components and supplied gamma-irradiated	Ease-of-use, plug and play concept, with no cleaning validation for product contact components required
Bioreactor with single-use sensors and Kleenpak® Presto aseptic connectors	Monitoring of DO, pH ⁽²⁾ , temp and biomass possible, in addition to bioreactor pressure
Hardware features docking station with perfusion integrated and controller	Ergonomic and robust industrial design
Overflow control and internal bioreactor pressure measurement	Prevents spill
Temperature control and heating through temperature control unit and integrated double jacket	Robust temperature control
Integrated tubing management tools	Ease-of-use and ergonomics
Process control	<ul style="list-style-type: none"> ▶ Designed in accordance to Good Automated Manufacturing Practice (GAMP) and for operation following 21 CFR Part 11/Annex 11 regulation ▶ Recipe manager plus to create recipes, controlling automatically the system and generating batch reports for audits ▶ SCADA system based on Wonderware♦ ArchestrA which offers maximum functionality for process control and data acquisition and recipe management ▶ The data and alarms generated during the cell culture batch are stored on a local SSD drive in a secured database ▶ An ethernet port is included in the system to connect it to the user's network and enable custom data history

Performance and Applications

The fixed-bed design of the iCELLis system makes it the perfect solution for industrialization of adherent cell processes and virus production for both gene therapy and vaccines, providing a large cell growth surface area while keeping the footprint very small. The iCELLis system accommodates up to 500 m² of growth area, which, when compared with available surfaces of multitray systems and roller bottles, corresponds to a huge reduction in volumes. Table 4 illustrates the iCELLis 500+/500 m² system is equivalent to 794 cell stacks with 10 trays and 5,882 roller bottles at 850 cm² each.

Table 4

Available surface area in an iCELLis 500+ system and comparison with multitray cell factory systems (CF)/roller bottles (RB)

	Fixed-Bed Volume (L)	Equivalent Culture Surface (m ²)	Equivalent CF10 (6,300 cm ²)	Equivalent Roller Bottles (850 cm ²)
iCELLis Nano fixed-bed height 10 cm	0.2	4	6	47
iCELLis 500/500 fixed-bed height 10 cm	25	500	794	5,882

In addition to volume reduction, the use of a filled, fixed-bed in the iCELLis system enables higher specific productivity than in other culture systems. Table 5 below shows data on yield achieved for most common vectors. Results clearly highlight that the growth matrix inside the iCELLis system is a favored growth environment which, together with controlled cell culture parameters, can significantly increase the biomass amplification, as well as the number of viral particles produced by each cell (specific productivity). Additional experiments demonstrated that iCELLis bioreactors require limited adaptation protocols and enable easy, straightforward scale-up for the majority of mammalian cell lines.

Table 5

Specific productivities achieved with iCELLis systems with several kinds of vectors produced from different mammalian cell lines

Vector	Cell	Size	Yield/cm ²	Unit	Extrapolated to 500 m ²	Source
Adeno-Associated Virus (AAV)	HEK 293T	0.53 m ²	4.7 x 10 ¹⁰ (transient)	VG	2.3 x 10 ¹⁷	University of Ulm Biotechnology Journal – 2015
	HEK 293T/17	0.53 m ²	3.6 x 10 ¹⁰ (transient)	VG	1.8 x 10 ¹⁷	St Jude Human Gene Therapy Methods – 2016
Lentivirus	HEK 293T	0.53 m ²	5.1 x 10 ⁶ (transient)	TU	2.5 x 10 ¹³	MolMed♦ Vector manufacturing production using disposable fixed-bed bioreactors iCELLis Nano. Cell and Gene Therapy Manufacturing conference, 2016
Retrovirus	AM12	1.06 m ²	7.3 x 10 ⁵ (stable)	TU	3.6 x 10 ¹²	MolMed Vector manufacturing production using disposable fixed-bed bioreactors iCELLis Nano. Cell and Gene Therapy Manufacturing conference, 2016
	HEK 293Vec	2.65 m ²	9.26 x 10 ⁷ (stable)	VT	4.6 x 10 ¹⁴	Memorial Sloan Kettering Journal of Immunotherapy – 2015
Adenovirus	HEK 293	100 m ²	6.1 x 10 ⁹ (infection)	VP	3.0 x 10 ¹⁶	FinVector Human Gene Therapy – 2015

VG = viral genomes, TU = transducing units, VT = viral titer, VP = viral particles

Documentation and Certificates

The iCELLis bioreactors are delivered with complete documentation that qualifies the system. All units are tested prior to shipment and witnessed factory acceptance testing (FAT) is available on request. The biocontainers are delivered with all the batch specific certificates and calibration information for the included single-use sensors. Pall also can assist with hardware qualification, and standard installation verification (IV), operational verification (OV), and site acceptance test (SAT) test protocols are available.

Preventive Maintenance and Service Packages

The iCELLis systems are supported with extensive maintenance and service packages. Pall has a global network of technicians and engineers available to assist with installation, qualification, training, technical support, preventive maintenance and on-site repairs. Contact Pall to discuss any of these services. Pall Accelerator process development services provide customers with expert advice and support for the implementation of fully integrated single-use processing solutions into new or existing processes, including process optimization, equipment selection, transfer of existing processes, scale-up and troubleshooting advice. Details can be found in the Accelerator Process Development Services brochure (USD 3079). Preventive maintenance packages are available to ensure the continuous reliable operation of the iCELLis bioreactor and to minimize downtime. Preventive maintenance typically includes a full functional test, exchange of wear parts, and calibration of all sensors. Details can be found in Maintenance Services brochure (USD 3078).

General System Specifications

	iCELLis Nano System	iCELLis 500+ System
Dimensions (W x D x H) (mm)		
Controller	230 x 600 x 450	1038 x 1609 x 2122
Docking station	340 x 360 x 290	
Weight (kg)		
Controller	20 kg	650 kg (without TCU)
Docking station	6.7 kg	
Gases		
Connections	Quick connectors 6 mm	Male Swagelock ¼ in. connector
Control	TMFC	TMFC
O ₂	0 - 2000 mL/min	0 - 7000 mL/min
CO ₂	0 - 2000 mL/min	0 - 1500 mL/min
N ₂	0 - 2000 mL/min	0 - 1500 mL/min
Air	0 - 2000 mL/min	0 - 3000 mL/min
Pumps	1 x fixed speed (base addition); 2 x variable speed (perfusion in-out)	5 x (perfusion in-out, base addition, sampling and inoculation), (7 if optional fill and drain pumps are ordered)
Agitation control and range	Magnetic drive impeller (100 - 1500 rpm)	Magnetic drive impeller (0 - 450 rpm)
Temperature control and range	Resistors – Peltier elements 20 - 40 °C	Double jacket – TCU 25 - 40 °C
pH ⁽²⁾ control	Electrochemical, re-use 0 - 14	Single-use, optical 6.5 - 8.5 ⁽²⁾
DO control	Electrochemical, re-use 0 - 150% air saturation	Single-use, optical 0 - 150% air saturation
Control architecture	PLC	PLC
SCADA	Pall Link – any device connected	Wonderware

Ordering Information

iCELLis Nano hardware

Description	Part Number
iCELLis Nano bioreactor system	ICLNANOBRS
Pall Link server and SCADA software	MPATHLINK

iCELLis Nano single-use bioreactors

Part Number	Part Number (Biomass Compatible)	Surface Area for Cell Growth (m ²)
810039NS	810124NS	0.53
810040NS	810125NS	0.80
810061NS	810126NS	1.06
810041NS	810127NS	1.60
810206NS	810128NS	2.65
810042NS	810129NS	4.00

iCELLis Nano single-use manifolds

Part Number	Description
6415-0474M	Base manifold (gamma irradiated)
6415-0474N	Sampling manifold 1 L (gamma irradiated – manifold for sampling, feeding, harvesting)
6415-0473U	Recirculation loop manifold 2 L (gamma irradiated)
6415-0474V	Lid tubing (non sterile – 6 tubing with CPC and vent filter for bioreactor assembly autoclaving)
6415-0454E	Recirculation loop manifold 10 L (gamma irradiated)

iCELLis 500+ hardware

Part Number	Description
ICL500CSSSIP	iCELLis 500+ process control system (universal)
ICL500HFLPUMP	iCELLis 500 high flow pumps (optional)
ICL500LTCU120	iCELLis 500 Lauda TCU 120 V
ICL500LTCU230	iCELLis 500 Lauda TCU 230 V

iCELLis 500+ single-use (SU) bioreactors 10 cm falling film

Part Number	Description
4415-I500V66	iCELLis 500+ SU vessel 66 m ² with Kleenpak aseptic connectors
4415-I500V133	iCELLis 500+ SU vessel 133 m ² with Kleenpak aseptic connectors
4415-I500V333	iCELLis 500+ SU vessel 333 m ² with Kleenpak aseptic connectors
4415-I500V100	iCELLis 500+ SU vessel 100 m ² with Kleenpak aseptic connectors
4415-I500V200	iCELLis 500+ SU vessel 200 m ² with Kleenpak aseptic connectors
4415-I500V500	iCELLis 500+ SU vessel 500 m ² with Kleenpak aseptic connectors
4415-I500V133BM	iCELLis 500+ SU vessel 133 m ² with Kleenpak aseptic connectors and biomass probe
4415-I500V333BM	iCELLis 500+ SU vessel 333 m ² with Kleenpak aseptic connectors and biomass probe
4415-I500V100BM	iCELLis 500+ SU vessel 100 m ² with Kleenpak aseptic connectors and biomass probe
4415-I500V200BM	iCELLis 500+ SU vessel 200 m ² with Kleenpak aseptic connectors and biomass probe
4415-I500V500BM	iCELLis 500+ SU vessel 500 m ² with Kleenpak aseptic connectors and biomass probe
4415-I500V66BM	iCELLis 500+ SU vessel 66 m ² with Kleenpak aseptic connectors and biomass probe

All iCELLis 500+ single-use bioreactors exist in 6 cm falling film version – contact your Pall representative for references.

iCELLis 500+ single-use manifolds

Part Number	Description
6415-I500MFLA	iCELLis 500+ starter kit low flow Allegro™ film

Contains

		Qty
6415-0615S	iCELLis 500+ manifold inoculum 2 and 10 L biocontainer	1
6415-0615T	iCELLis 500+ manifold base addition	2
6415-0464F	iCELLis 500+ manifold feed in 2 low flow	1
6415-0464G	iCELLis 500+ manifold harvest and feed out low flow	1
6415-0615V	iCELLis 500+ manifold feed in 1 for heating module low flow	1
6415-0615U	iCELLis 500+ manifold sampling with Kleenpak sterile disconnecter	1

Part Number Description

6415-I500MFHA	iCELLis 500+ starter kit high flow Allegro film
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iCELLis 500 starter kit low flow Allegro film contains

		Qty
6415-0458Z	iCELLis 500+ manifold harvest and feed out high flow	1
6415-0615S	iCELLis 500+ manifold inoculum 2 L and 10 L biocontainer	1
6415-0615T	iCELLis 500+ manifold base addition	2
6415-0464C	iCELLis 500+ manifold feed in 2 high flow	1
6415-0615R	iCELLis 500+ manifold feed in 1 for heating module high flow	1
6415-0615U	iCELLis 500+ manifold sampling with Kleenpak sterile disconnecter	1

Figure 6

iCELLis Nano bioreactor and mPath control tower



The iCELLis bioreactors are available as standard models and both the bioreactor hardware and consumables can be customized. Please contact a Pall representative to find the ideal solution for your application. Our teams are specialized in upstream and downstream processing and will gladly help find the right technology for any part of your manufacturing process. It is possible to combine products to meet any requirement in the upstream part of the process:

- ▶ Media preparation
- ▶ Buffer preparation
- ▶ Media sterilization and aseptic transfer liquid transfer into the bioreactor (e.g. glucose, anti-foam, base, etc.)
- ▶ Seed train solutions
- ▶ Cell harvest and separation

Please contact Pall for a total solution discussion on your process.

(1) As per standards USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity; USP <88> Biological Reactivity Tests *In Vivo*, for Class VI - 50 °C Plastics; and USP <661> Containers - Plastic.

(2) The correct level of accuracy can only be expected at the pH value at which the 1-point calibration is performed. The greater the distance from the point of calibration, the lower the probability that the accuracy will be within specification. Therefore, if these bioreactors demonstrate a greater distance, then Pall's recommendation is that the bioreactors can only be used under mitigation actions, specifically manual pH control. Pall's dedicated application team can provide support for these mitigation actions.

Figure 7

iCELLis 500+ bioreactor



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