iCELLis™

SINGLE-USE FIXED-BED BIOREACTOR SYSTEMS

Speed to clinic and market is crucial when making advanced therapies. iCELLis™ fixed-bed bioreactors are a robust, compact adherent cell culture solution delivering scalable performance from 0.5 to 500 m^2 to support process development through clinical and commercial production. These bioreactors can reduce space demands by up to 65% and labor costs by up to 67% when compared to traditional flatware solutions (1). iCELLis bioreactors are fully closed systems, capable of maintaining low shear environments. They come integrated with pH, dissolved oxygen (DO), and biomass sensors, and they are supplied with U.S. Code of Federal Regulations (CFR) Title 21, Part 11 (21 CFR Part 11) compatible software. They deliver consistent high cell density, product titer, and vector quality to enable speed to your next milestone, and they offer intrinsic readiness for proven industrial-scale success. The newest member of the family – the intermediate-scale iCELLis 50 bioreactor – provides a geometrically similar scale-down model to the iCELLis 500+ bioreactor. It's also well-suited to manufacture small Phase 1 and Phase 2 clinical batches.

Performance and scale-up

While flatware is the go-to format during R&D and preclinical process development, it has severe limitations as scales increase, and the need to produce efficiently under good manufacture practice (GMP) conditions becomes a priority. Planning for an intrinsically industrializable manufacturing process early in development reduces delays and risks associated with technology transfer.

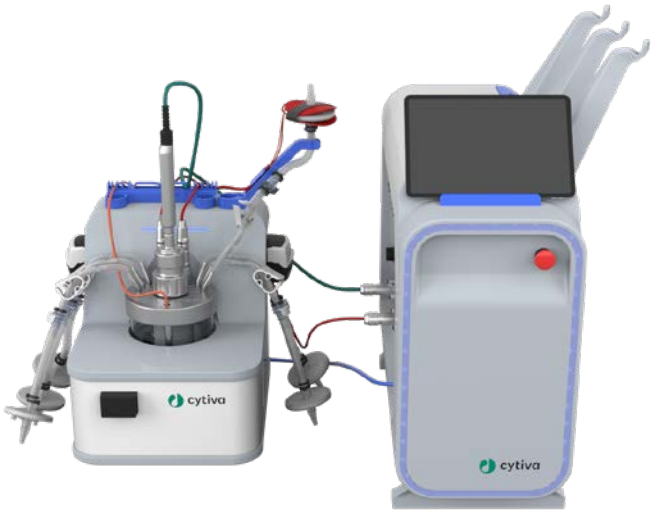

Fig 1. iCELLis Nano bioreactor with mPath™ control tower.

The iCELLis bioreactor technology also provides opportunities for process optimization and simplification that can make the difference between commercial viability and costly process inefficiency.

- Large volume production achieving high cell density and high yield in a small footprint
- Closed, automated operation minimizing risk and maximizing ease of use
- Seed cell densities as low as 3000 cells/cm^2 to simplify the seed train demands and streamline the upstream process
- Capable of supporting continuous perfusion processes without modification

Table 1. Comparison of largest available iCELLis bioreactor surface areas to other 2D cell culture technologies

	Fixed-bed volume (L)	Equivalent culture surface (m^2)	Equivalent Nunc Cell Factory 10-layer systems (6300 cm^2)	Equivalent roller bottles (850 cm^2)	Equivalent Corning HyperStack systems (18 000 cm^2)
iCELLis Nano bioreactor (4 m^2)	0.2	4.0	6	47	2
iCELLis 50 bioreactor (50 m^2)	2.5	50	79	588	27
iCELLis 500+ bioreactor (500 m^2)	25	500	794	5882	277

Together, the fixed-bed system design, integrated process monitoring, and control features enable higher specific productivity compared to other culture systems.

Table 2 shows published data for some common applications across a range of cell lines and vector types that exceed the published value for 2D flatware.

Table 2. Specific productivities achieved using iCELLis bioreactor systems with several types of vectors produced from different mammalian cell lines.

Vector	Cell	Size	Yield/cm²	Unit	Yield extrapolated to 500 m²	Reference
Adeno-associated virus (AAV)	HEK293T	0.53 m^2	2.15 × 10^{10}	VG	1.08 × 10^{17}	(2)
	HEK293T/17	0.53 m^2	9.06 × 10^{10}	VP	4.53 × 10^{17}	(3)
	HEK293	333 m^2	3.00 × 10^{9}	VG	>1.00 × 10^{16}	(4)
Lentiviral	HEK293T	133 m^2	4.14 × 10^{7}	pfu	2.07 × 10^{14}	(5)
	HEK293T	2.7 m^2	1.05 × 10^{6}	TU	5.25 × 10^{12}	(6)
Retroviral	AM12	1.06 m^2	9.9 × 10^{6} (stable)	TU	4.95× 10^{12}	(7)
	HEK293-Vec	2.7 m^2	9.38 × 10^{7} (stable)	TU	4.69 × 10^{14}	(8)
Adenoviral	HEK293	100 m^2	6.10 × 10^{9}	VP	3.05 × 10^{16}	(9)
	HEK293	66 m^2	1.57 × 10^{10}	VP	7.85 × 10^{18}	(10)

VG = viral genomes, TU = transducing units, pfu = plaque forming units, VP = viral particles

Scalability

The iCELLis bioreactor is currently available in three formats, each with three bed heights to provide a range of surface areas (Table 3):

- The iCELLis Nano bioreactor is optimized for process development but is also suitable for small-scale clinical production (~ 0.5 to 4 m^2). It mirrors the iCELLis 500+ bioreactors characteristics and can be used to predict process performance at larger scales.
- The iCELLis 50 bioreactor is designed for intermediate and pilot-scale operations (6 to 50 m^2). It is a 1/10th geometric scale down model of the iCELLis 500+ bioreactor. It can be used for process development, derisking scale-up, medium-scale clinical production, and troubleshooting commercial processes.
- The iCELLis 500+ bioreactor is optimized for the large-scale production (66 to 500 m^2) and delivers a robust automated platform for the production of high-quality viral vectors.

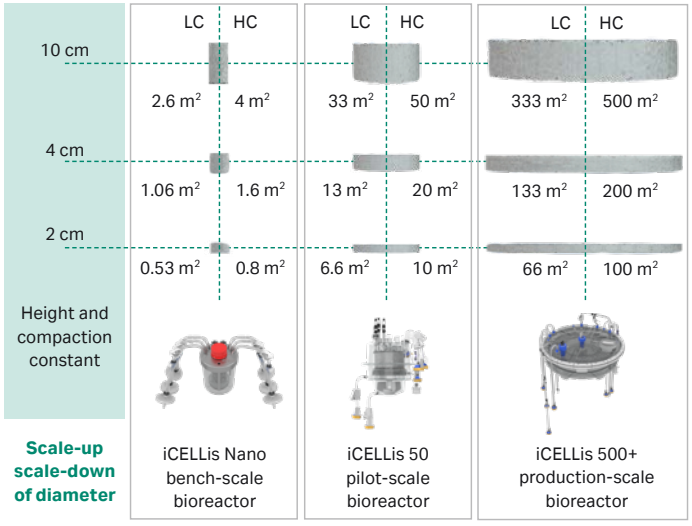

Fig 2. Scale-up options strategy between the iCELLis Nano (bench-scale), iCELLis 50 (pilot-scale), and iCELLis 500+ (production-scale) bioreactors. LC = low compaction, HC = high compaction.

User software and automation

The iCELLis bioreactor family is built with our innovative mPath™ Link user interface, which has become an integral part of our Cytiva automation platform. It focuses on supervisory control and data acquisition with recipe management, aiming to provide an automation ecosystem for bioprocess scientists and engineers.

The mPath™ Link software was designed for use in both GMP-regulated and process development environments, meeting all the requirements of an industrial manufacturing environment, including compliance with 21 CFR Part 11 or EudraLex Annex 11 (Computerised Systems). mPath Link software includes tools such as real-time data trending, customizable control loops, on screen operational instructions, recipe management, and reporting. These features make it a powerful tool to help you quickly understand and scale up your process.

For more detailed information, please visit http://www.cytiva.com/mpathlink.

Table 3. Configuration of iCELLis bioreactors

Bioreactor	Diameter (cm)	Bed height (cm)	Bed volume (L)	Volume (L)	Low compaction surface area (m^2)	High compaction surface area (m^2)
iCELLis Nano bioreactor	11	2	0.04	1.0	0.53	0.8
	11	4	0.08	1.0	1.06	1.6
	11	10	0.20	1.0	2.6	4.0
iCELLis 50 bioreactor	28	2	0.50	11	6.6	10
	28	4	1.0	11	13	20
	28	10	2.5	11	33	50
iCELLis 500+ bioreactor	86	2	5	70	66	100
	86	4	10	70	133	200
	86	10	25	70	333	500

Platform overview

1) The fixed-bed substrate uses USP class VI polyethylene terephthalate (PET) carriers that are common to all iCELLis bioreactors. The iCELLis Nano, iCELLis 50, and iCELLis 500+ bioreactors include three bed heights and two compaction factors to deliver scalability across a range of surface areas (Table 3).
2) Agitation of the culture media and reagents is driven with a magnetically coupled impeller isolated from the carriers, minimizing any shear on the cell culture.
3) After passing through the carriers, media overflows the outer wall of the fixed-bed, creating a falling film. This generates high rates of bubble-free oxygen transfer and CO_2 stripping, allowing the iCELLis bioreactor to maintain high cell densities.
4) Integrated DO, pH, and biomass sensors continuously measure critical culture conditions and cell density.
5) The iCELLis Nano permits the extraction of sample carriers to measure cell density directly.

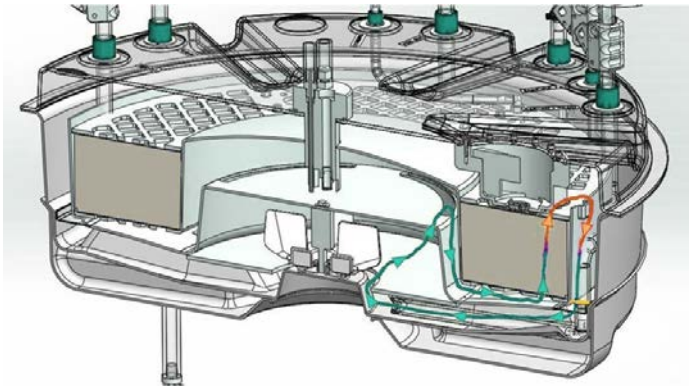

Fig 3. The flow path of media illustrated in the iCELLis 500+ bioreactor.

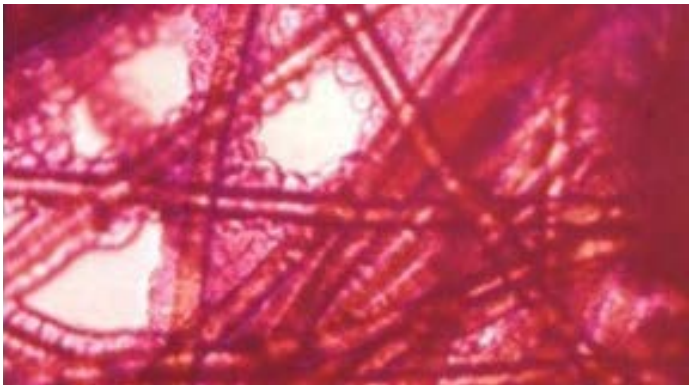

Fig 4. Madin-Darby canine kidney (MDCK) cells attached to iCELLis bioreactor carriers.

System overview

Name	iCELLis Nano bioreactor	iCELLis 50 bioreactor	iCELLis 500+ bioreactor
Components	Docking station mPath control tower iCELLis Nano bioreactor vessel Tubing manifolds mPath Link server	Docking station Integrated mPath control tower iCELLis 50 bioreactor vessel Tubing manifolds mPath Link server	Integrated skid with docking station and control tower Temperature control unit (TCU) iCELLis 500+ bioreactor vessel Tubing manifolds
Surface area range	0.5 to 4 m^2	6.6 to 50 m^2	66 to 500 m^2
Sensors	pH, DO, temperature, and biomass	pH, DO, temperature, biomass, weight, and pressure	pH, DO, temperature, biomass, weight, and pressure
Gas handling	Six thermal mass flow controllers (TMFCs) Custom gas blends for precise pH and DO control	Four TMFCs Custom gas blends for precise pH and DO control	Four TMFCs Custom gas blends for precise pH and DO control
Enhanced process analytical technology (PAT)	Biomass probe for cell density	Biomass probe for cell density	Biomass probe for cell density
21 CFR Part 11 compatible software	Suitable for the manufacture of small batches in a GMP environment	Bioreactor can be easily used to manufacture in a GMP environment	Bioreactor can be easily used to manufacture in a GMP environment
Fill and drain time	< 1 min	< 40 min	< 20 min
Control tower and supervisory control and data acquisition	mPath Link tower + mPath Link network	Integrated or network mPath Link	AVEVA ArchestrA (integrated with equipment)
Other	iOS and Android phone app: users can control their iCELLis Nano bioreactor from anywhere, and can receive email or text message alerts when the bioreactor is in alarm, or another critical event has occurred	iOS and Android phone app: users can control their iCELLis 50 bioreactor from anywhere, and can receive email or text message alerts when the bioreactor is in alarm, or another critical event has occurred	

General system specifications

	iCELLis Nano bioreactor system	**iCELLis 50 bioreactor system**	**iCELLis 500+ bioreactor system**
Dimensions (W × D × H)	230 × 600 × 450 mm (controller) 340 × 360 × 290 mm (docking station)	820 × 1050 × 1800 mm	1038 × 1609 × 2122 mm
Weight	20 kg (controller) 6.7 kg (docking station)	450 kg	650 kg (without TCU)
Gases connections	Quick connectors 6 mm	Male swagelock ¼" connector	Male swagelock ¼" connector
Control	TMFC	TMFC	TMFC
O_2	0 to 1000 mL/min	0 to 700 mL/min	0 to 7000 mL/min
CO_2	0 to 1000 mL/min	0 to 150 mL/min	0 to 1500 mL/min
N_2	0 to 1000 mL/min	0 to 150 mL/min	0 to 1500 mL/min
Air	0 to 1000 mL/min	0 to 300 mL/min	0 to 3000 mL/min
Pumps	3 × (base, perfusion in-out)	4 × (feed in, feed out, base, sampling)	5 × (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 to 1500 rpm)	Magnetic drive impeller (0 to 450 rpm)	Magnetic drive impeller (0 to 450 rpm)
Temperature control and range	Resistors – Peltier elements 20°C to 40°C	Silicon heater jacket – 30°C to 37°C	Double jacket – TCU 25°C to 40°C
pH control	Electrochemical, re-use 0 to 14	Single-use, optical 3 to 10	Single-use, optical 3 to 10
DO control	Electrochemical, re-use 0% to 150% air saturation	Single-use, optical 0% to 300% air saturation	Single-use, optical 0% to 300% air saturation
Control architecture	Programmable logic controller (PLC)	PLC	PLC
Supervisory control and data acquistion (SCADA) software	mPath Link software – any device connected	mPath Link software	WONDERWARE
Electrical requirements	110/230 V AC, 50/60Hz, 700W, 3x EU/US/UK socket	110/220/230 V AC, 50/60 Hz, 4000W, 1x L6-30R socket	230 V AC, 50 Hz, 4200W (skid) + 4600W (TCU), 1x 2P+E 32A socket and 1x EU/US socket

Ordering information

Please contact us to receive a quote for any materials

iCELLis bioreactor system hardware

Material description	Product code
iCELLis Nano bioreactor control system	ICLNANOBRS-FULL
iCELLis 50 bioreactor control system (with touchscreen)	ICL50BRS-HMI
mPath Link server and SCADA software	MPATHLINKV3
iCELLis 500+ bioreactor control system	ICL500CSSSIPH
iCELLis 500+ high speed pumps (optional)	ICL500HFPUMP
iCELLis 500+ TCU – 120 volts	ICL500LTCU120
iCELLis 500+ TCU – 230 volts	ICL500LTCU230

iCELLis Nano bioreactor single-use vessels

Surface area (m²)	Fixed-bed height (cm)	Compaction	Product code
0.53	2	Low (1×)	4415-40-LC-BM
0.80	2	High (1.5×)	4415-40-HC-BM
1.06	4	Low (1×)	4415-80-LC-BM
1.60	4	High (1.5×)	4415-80-HC-BM
2.65	10	Low (1×)	4415-200-LC-BM
4.0	10	High (1.5×)	4415-200-HC-BM

iCELLis Nano bioreactor single-use tubing manifolds

Tubing type	Material description	Product code
Weldable AdvantaFlex with MPC connectors	Lid tubing manifolds	6415-1384W
Weldable AdvantaFlex with MPC connectors	Base addition manifold	6415-1384T
Weldable AdvantaFlex with MPC connectors	Sampling and 1 L seeding manifold	6415-1384U
Weldable AdvantaFlex with MPC connectors	2 L recirculation manifold	6415-1384S
Weldable AdvantaFlex with MPC connectors	5 L recirculation manifold	6415-1540F
Weldable AdvantaFlex with MPC connectors	10 L recirculation manifold	6415-1540G

All iCELLis Nano bioreactor manifolds are supplied gamma irradiated.

iCELLis 50 bioreactor single-use vessels

Surface area (m²)	Fixed-bed height (cm)	Compaction	Product code
6.6	2	Low (1×)	4415-I50-6BM
10	2	High (1.5×)	4415-I50-10BM
13	4	Low (1×)	4415-I50-13BM
20	4	High (1.5×)	4415-I50-20BM
33	10	Low (1×)	4415-I50-33BM
50	10	High (1.5×)	4415-I50-50BM

All iCELLis 50 bioreactor vessels are equipped with weldable tubing, Kleenpak™ Presto sterile connectors, and are supplied gamma irradiated.

iCELLis 50 bioreactor single-use tubing manifolds

Material description	Product code
iCELLis 50 base manifold	4415-1937L
iCELLis 50 inoculum bag manifold 2 L	4415-1938E
iCELLis 50 inoculum bottle manifold 2 L	4415-1938M
iCELLis 50 500 mL flush bag	4415-1938J
iCELLis 50 feed out manifold	4415-1938F
iCELLis 50 feed in manifold	4415-1939N
iCELLis 50 sampling manifold	4415-1933V

All iCELLis 50 bioreactor manifolds are supplied gamma irradiated.

iCELLis 500+ bioreactor single-use vessels

Surface area (m^2)	Fixed-bed height (cm)	Compaction	Product code
66	2	Low (1×)	4415-S66BM
100	2	High (1.5×)	4415-S100BM
133	4	Low (1×)	4415-S133BM
200	4	High (1.5×)	4415-S200BM
333	10	Low (1×)	4415-S333BM
500	10	High (1.5×)	4415-S500BM

All iCELLis 500+ bioreactor vessels are equipped with weldable tubing, Kleenpak™ Presto sterile connectors, and are supplied gamma irradiated.

iCELLis 500+ bioreactor single-use tubing manifolds

Material description	Flow rate	Comments	Product code
High flow starter kit	High flow (⅜" internal diameter (i.d.) × ½" outer diameter (o.d.) pump tubing) – for recirculation	Includes feed-in 1/preheater, feed-in 2, harvest/feed-out, inoculum, base, and sampling manifolds	6415-I500MFHA
Low flow starter kit	Low flow (¼" i.d. × ⅜" o.d. pump tubing) – for perfusion	Includes feed-in 1/preheater, feed-in 2, harvest/feed-out, inoculum, base, and sampling manifolds	6415-I500MFLA
Feed-in 1 – preheater manifold	High flow	N/A	6415-0615R
Feed-in 1 – preheater manifold	Low flow	N/A	6415-0615V
Feed-in 2 manifold	High flow	N/A	6415-0464C
Feed-in 2 manifold	Low flow	N/A	6415-0464F
Harvest/feed-out manifold	High flow	N/A	6415-0458Z
Harvest/feed-out manifold	Low flow	N/A	6415-0464G
Inoculum manifold	N/A	N/A	6415-0615S
Base manifold	N/A	N/A	6415-0615T
Sampling manifold	N/A	N/A	6415-0615U

All iCELLis 500+ bioreactor manifolds are supplied gamma irradiated.

The iCELLis bioreactors are available as standard models and both the bioreactor hardware and consumables can be customized. Please contact a representative to find the optimal 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 us for a total solution discussion on your process.

Servicing

All iCELLis bioreactors are serviced by a highly trained team of field service engineers. Servicing packages include:

EssentialCare: Proactive approach to prevent instrument failure, reduce unscheduled downtime, and enable you to perform your daily workflow with confidence. The scheduled maintenance includes inspection, cleaning, and adjustments needed to maintain high performance.

FullCare: All-inclusive package including an annual preventive maintenance visit, labor, travel, and spare part costs to maximize uptime and productivity and provide peace-of-mind allowing you to focus on your core competencies and let us take care of your critical assets. The plan allows you to experience our worry-free contract support, including predictable ownership costs, simplified budget planning, and priority scheduling.

References

1. Cameau E and Laskowski A. Cost Modeling Comparison of 2D Flatware and iCELLis Bioreactors to Produce Adherent Cell Products. Poster reformatted, ASGCT, 2020
2. Emmerling VV, Pegel A, Milian EG, Venereo-Sanchez A, et al. Rational plasmid design and bioprocess optimization to enhance recombinant adeno associated virus (AAV) productivity in mammalian cells. *Biotechnology Journal.* 2016;11(2):290-297. https://doi.org/10.1002/biot.201500176
3. Powers A, Piras BA, Clark RK, Lockey TD, Meagher MM. Development and optimization of AAV hFIX particles by transient transfection in an iCELLis fixed-bed bioreactor. *Human Gene Therapy Methods.* 2016 (Jun); 27(3):112-21. https://doi.org/10.1089/hgtb.2016.021
4. Powers A, Drury JE, Hoehamer CF, Lockey TD, Meagher MM. Lentiviral vector production from a stable packaging cell line using a packed bed bioreactor, *Molecular Therapy*. 2020; 19:1-3. https://doi.org/10.1016/j.omtm.2020.08.010
5. Wang X, Olszewska M, Qu J, et al. Large-scale clinical-grade retroviral vector production in a fixed-bed bioreactor. *Journal Immunotherapy.* 2015; 38(3):127-135. https://doi.org/10.1097/CJI.0000000000000072
6. Lesch HP, Heikkilä KM, Lipponen EM, et al. Process development of Adenoviral vector production in fixed-bed bioreactor – from bench to commercial scale, *Human Gene Therapy.* 2015; 26(8): 560-71. https://doi.org/10.1089/hum.2015.081
7. Neri et al., Vector manufacturing production using disposable fixed-bed bioreactors iCELLis Nano, Cell Therapy Manufacturing & Gene Therapy Congress, 2018 (presentation)
8. Wang X, Olszewska M, Qu J, et al. Large-scale clinical-grade retroviral vector production in a fixed-bed bioreactor. Journal Immunotherapy. 2015; 38(3):127–135.
9. Lesch et al., Process development of Adenoviral vector production in fixed-bed bioreactor – from bench to commercial scale, Human Gene Therapy, 2015, 26(8): 560-71
10. Legman et al., Development and Optimization of Large Scale Production of Adenoviral Vector and Autologous Insulin Producing Cells Using iCELLis® 500 and Xpansion® 200 Single-Use Bioreactors, BioCan 2017 (poster)

cytiva.com/iCELLis

CY48658-10Oct25-DF